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CHAPTER **16**

# Acidity of alkenes and polyenes

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## I. INTRODUCTION

Little quantitative data, either experimental or theoretical, are available on the acidities of dienes and polyenes. Accordingly, this chapter will review recent work on the acidities of alkenes and the data available on dienes and polyenes will be placed in this context.

Alkenes frequently have two kinds of C−H bonds, vinyl and allyl, that are generally more acidic than the C−H bonds of saturated alkanes. Quantitative measures of acidity are related to the chemistry of the corresponding carbanions and carbanion salts or organometallic compounds. Several methods have been used for the study of anions in the gas phase[1]. For many acids it is possible to measure equilibrium constants for equilibria of the type in equation 1. From such equilibrium constants with compounds RH of independently known gas-phase acidity, it has been possible to determine the acidities of a wide range of compounds[2].

$$RH + R'^{-} \rightleftharpoons R^{-} + R'H \tag{1}$$

An alternative approach to acidities is via a thermodynamic cycle using the bond dissociation energy ($DH^{\circ}$), electron affinity (EA) and ionization potential (IP) as follows:

$$\begin{array}{ll} AH \longrightarrow A^{\bullet} + H^{\bullet} & DH^{\circ} \\ A^{\bullet} + e^{-} \longrightarrow A^{-} & -EA \\ H^{\bullet} \longrightarrow H^{+} + e^{-} & IP \\ \hline AH \longrightarrow A^{-} + H^{+} & \Delta H^{\circ} = \text{Acidity} \end{array}$$

$$\therefore \Delta H^{\circ}_{\text{acid}} = DH^{\circ}(\text{A}{-}\text{H}) + \text{IP}(\text{H}^{\bullet}) - \text{EA}(\text{A}^{\bullet})$$

Thus, acidity can be determined from independent measures of the bond dissociation energy and electron affinity, or the acidity provides a measure of the electron affinity of the corresponding radical if the bond dissociation energy is known.

Alkenes are not acidic enough for their acidities to be measured in terms of the usual solution definition of dissociation into anion and proton (equation 2).

$$\text{RH} \rightleftharpoons \text{R}^{-} + \text{H}^{+} \tag{2}$$

$$K_{\text{eq}} = [\text{R}^{-}][\text{H}^{+}]/[\text{RH}]$$

Such equilibrium constants, $K_{\text{eq}}$, are known only for highly conjugated carbanions, such as in cyclopentadienyl anion in water or triphenylallyl anion in DMSO[3]. Some values are known for equilibrium constants and enthalpies of equation 1 in the gas phase. Additional energies are available for many compounds by computation — with modern methods, computed energies for equation 2 are reliable to a few kcal mol$^{-1}$.

Other experimental values are available for *ion pair acidities* defined by the transmetallation reaction of equation 3, where the acid R′H of known p$K_{\text{a}}$ serves as a reference, and are thermodynamic in nature.

$$\text{RH} + \text{R}'^{-}\text{M}^{+} \rightleftharpoons \text{R}^{-}\text{M}^{+} + \text{R}'\text{H} \tag{3}$$

$$-\log K = \text{p}K_{\text{RH}} - \text{p}K_{\text{R}'\text{H}}$$

These equilibria give directly only acidity differences between RH and R′H and can vary with solvent and counterion. The corresponding $-\log K$ values have been converted to p$K$ scales by choosing one compound as the standard and referring others to it. The standard chosen for tetrahydrofuran (THF) solutions is fluorene and it is assigned a p$K$ of 22.9, its value in the DMSO scale (statistically corrected per hydrogen; for fluorene the measured p$K$ is 22.6)[3,4].

Finally, in many cases the acidity equilibria cannot be measured but the *rate* of proton transfer or transmetallation can be measured to give an *ionic* or *ion pair kinetic acidity*. Studies using the rates of proton transfer have included the use of isotopes such as tritium and deuterium[5,6]. The rate is then used to calculate the Brønsted slope, $\alpha$, by plotting the logarithm of the proton transfer rate against the p$K_{\text{a}}$, as determined by the equilibrium acidity, for a series of compounds. From this plot, the approximate p$K_{\text{a}}$ of an unknown compound can be determined by comparison of the same type of compounds.

Alkenes and polyalkenes have two fundamentally different types of relatively acidic protons, the vinyl and allylic hydrogens. Vinyl hydrogens are bound by approximately sp$^2$ hybrid orbitals on carbon and the corresponding carbanions are relatively localized; their relative acidity is due in part to the higher degree of s-character in the carbon orbital of the vinyl C−H bond. The allylic C−H bond is conjugated to the double bond and the corresponding carbanions are delocalized; the higher acidity of these protons stems primarily from such charge delocalization in the corresponding carbanion. These two types of protons will be treated separately in the following sections.

## II. VINYL HYDROGENS

### A. Gas-phase Acidities

Acetylene is sufficiently acidic to allow application of the gas-phase proton transfer equilibrium method described in equation 1[7]. For ethylene, the equilibrium constant was determined from the kinetics of reaction in both directions with $NH_2^-$[8]. Since the acidity of ammonia is known accurately, that of ethylene can be determined. This method actually gives $\Delta G_{acid}$ at the temperature of the measurement. Use of known entropies allows the calculation of $\Delta H_{acid}$ from $\Delta G = \Delta H - T\Delta S$. The value of $\Delta H_{acid}$ found for ethylene is $409.4 \pm 0.6$ kcal mol$^{-1}$. But hydrocarbons in general, and ethylene in particular, are so weakly acidic that such equilibria are generally not observable. From net proton transfers that are observed it is possible sometimes to put limits on the acidity range. Thus, ethylene is not deprotonated by hydroxide ion whereas allene and propene are[9]; consequently, ethylene is less acidic than water and allene and propene (undoubtedly the allylic proton) are more acidic. Unfortunately, the acidity of no other alkene is known as precisely as that of ethylene.

A further measure of acidity is provided by rates of deuterium exchange between a labeled base such as $DO^-$ and a proton acid. The mechanism involves exchange within weak ion–molecule encounter complexes as shown in equation 4.

$$RH + DO^- \rightleftharpoons RH \cdot DO^- \rightleftharpoons R^- \cdot DOH \rightleftharpoons RD \cdot HO^- \rightleftharpoons RD + HO^- \quad (4)$$

Using a selected ion flow tube (SIFT) technique, DePuy and coworkers studied such rates of deuterium–hydrogen exchange for a series of neutral carbon acids[10]. Table 1 contains some selected rates of exchange with $DO^-$ from DePuy's work; these rates are approximate measures of relative acidity in the gas phase.

Accurate values of these acidities are not known experimentally because these compounds are in the weakly acidic range, but some qualitative conclusions can be made. For example, on bombardment of butadiene or methyl vinyl ether with $NH_2^-$, the corresponding deprotonated anions ($R^-$) were present but not in the case of *tert*-butylethylene. Butadiene and methyl vinyl ether are therefore more acidic than *tert*-butylethylene. The

TABLE 1. Selected rate constants for the deuterium isotope exchange reactions, $DO^- + MH \longrightarrow HO^- + RD$ at 299 ($\pm$1) K

| RH | $k_{obsd}$[a] | $\Delta[\Delta H_{acid}]$[b] kcal mol$^{-1}$ |
|---|---|---|
| $H_2C{=}CHCH{=}CH_2$ | 9.6 | <12.8 |
| $H_2C{=}CHOCH_3$ | 10 | <12.8 |
| Norbornadiene | 10 | 11.2[c] |
| $C_6H_5C(CH_3)_3$ | 19 | <12.8 |
| $H_2C{=}CHC(CH_3)_3$ | 1.1 | <12.8 |
| $CH_4$ | $\leqslant$0.002 | 25.8[d] |
| $CH_3OCH_3$ | $\leqslant$0.003 | >12.8 |
| $H_2C{=}CH_2$ | $\leqslant$0.002 | >12.8 |
| $H_2C{=}O$ | exchange observed | <12.8 |

[a] In units of $10^{-10}$cm$^3$ particle$^{-1}$ s$^{-1}$.
[b] Relative value to that in water.
[c] Reference 11.
[d] Reference 12.

protons at the 2- (or $\beta$) C positions of butadiene and the proton on the carbon adjacent to the oxygen of methyl vinyl ether were found to be kinetically more acidic than the protons at other positions by labeling experiments. The greater acidity observed for *tert*-butylethylene relative to ethylene was attributed to the charge stabilizing polarization effect of the *tert*-butyl group. Further investigation of the mechanism for isotope exchange showed that the acidity of ethylene is close to that of ammonia ($\Delta H_{\text{acid}} = 403.6$ kcal mol$^{-1}$) because the vinyl anion is detected in other SIFT experiments but is produced at a slow rate.

Alternatively, some conclusions can be derived from the relative reactivities of carbanions. For example, DePuy and colleagues[13] made use of a clever method involving reactions of silanes with hydroxide ion to deduce acidities of such weak acids as alkanes and ethylene. The silane reacts with hydroxide ion to form a pentacoordinate anion that ejects a carbanion held as a complex with the hydroxysilane; rapid proton transfer gives the stable silanoxide ion and the carbon acid (equation 5).

$$HO^- + (CH_3)_3SiR \longrightarrow [(CH_3)_3SiOH \cdots R]^- \longrightarrow (CH_3)_3SiO^- + RH \qquad (5)$$

The relative amounts of $(CH_3)_3SiO^-$ or $R(CH_3)_2SiO^-$ produced were assumed to be inversely proportional to the basicities of $R^-$ and $CH_3{}^-$ and were used to determine acidities of RH by comparison with the known p$K_a$ values of methane and benzene. Some derived values are summarized in Table 2. The reliability of this method can be judged by noting that the value for ethylene differs by only 2 kcal mol$^{-1}$ from the more accurate value described above. The methyl hydrogen in 1-butene is 8 kcal mol$^{-1}$ more acidic than ethane, undoubtedly because of the electron-attracting inductive effect of the vinyl group. The 2-H in propene is also found to be more acidic than the hydrogen of ethylene, showing again that polarizable alkyl groups appear to stabilize carbanions in the gas phase. The DePuy group points out that one possible problem with this method is that the carbanions are not formed free but rather within a complex with the silanol, and are essentially solvated by the silanol[13].

Another measurement of the p$K_a$ for ethylene comes from the formation of carbanions in the gas phase by decarboxylation of carboxylate anions[14]. Carbanions that are too basic will not form in this way; the corresponding carboxylates do not decarboxylate. From the energy thresholds of such decarboxylations Graul and Squires estimated $\Delta H_{\text{acid}}$ of ethylene <401 kcal mol$^{-1}$, but this value differs substantially from the accepted value of 409.4 kcal mol$^{-1}$.

Few other alkenes have been studied. Norbornadiene is deprotonated by $NH_2{}^-$ but not by $H^-$[11]. Additional bracketing experiments by Lee and Squires provided estimates

TABLE 2. Acidities of RH from reaction of $(CH_3)_3SiR$ with $OH^-$[13a]

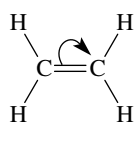
| MH | $\Delta H^\circ_{\text{acid}}$ (kcal mol$^{-1}$) |
|---|---|
| $CH_4$ | 416.6 |
| $C_6H_6$ | 400.7 |
| $C_2H_6$ | 420.1 |
| $n$-$C_4H_{10}$($CH_3-H$) | 412.0 |
| $C_2H_4$ | 407.5 |
| $CH_2{=}CHCH_3$($CH_3-H$) | 405.8 |

[a]The known acidities of benzene and methane are used as standards for the others.

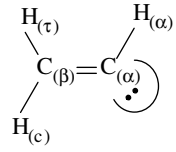
of $\Delta H_{acid}$ of norbornene equal to 401 kcal mol$^{-1}$ and of norbornadiene equal to 398 kcal mol$^{-1}$[15].

## B. Theory

Scheiner and Wang have calculated the geometries of ethylene **1** and vinyl anion **2** at the Self-Consistent Field (SCF) Hartree–Fock level with a 6-31+G** basis set[16]. Both structures are planar (Table 3). Their results differ little from much earlier calculations of Williams and Streitwieser[17]. The $\beta$-methylene group of ethylene is almost unchanged on deprotonation. The $C_{(\beta)}-H$ bond lengths elongate by only 0.01–0.02 Å and only one angle changes by as much as 4° ($\beta = \angle C_{(\alpha)}C_{(\beta)}H_{(c)}$). The elongation of the double bond of the vinyl anion is also quite small, 0.034 Å. The largest changes are with the $C_{(\alpha)}-H_{(\alpha)}$ bond length and the $\angle C_{(\alpha)}C_{(\beta)}H_{(\alpha)}$ angle, 0.031 Å and 13°, respectively. According to Mulliken populations, the negative charge is divided almost equally between the $\alpha$ and $\beta$ positions; however, there is a difference between the $\sigma$ and $\pi$ electronic populations. $C_{(\alpha)}$ has a higher $\sigma$ charge than in ethylene but has a low $\pi$ electron population; the reverse is true for $C_{(\beta)}$. The electron density function shows that removal of the vinyl proton and formation of the lone pair on carbon polarizes the electrons in the double bond, an effect that can be symbolized as **3**. Much of the increased electron density, however, is associated with the hydrogens[18], a polarization effect that is also symbolized in **3**. Williams and Streitwieser accordingly suggested that the relative acidities of $sp^n$ localized systems (i.e. ethane, ethylene and acetylene) might be due not only to the amount of s-character of the lone pair, but also to the polarizability of the $\pi$ electrons[17].




**(1)**

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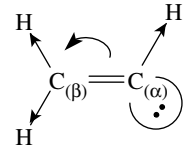



**(3)**

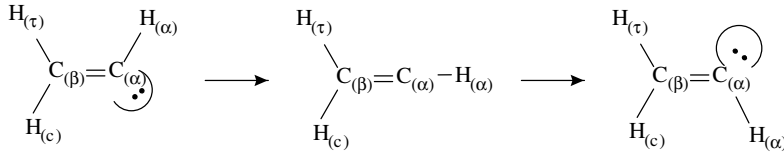
The energy barrier calculated for inversion of the vinyl anion (**2** ⟶ **2′**) by changing ($C_{(\beta)}C_{(\alpha)}H_{(\alpha)}$) through 180° in its linear transition state (**2a**), 34 kcal mol$^{-1}$, is in good agreement with the previously calculated value (SCF-LCAO-MO) of 39 kcal mol$^{-1}$ by Lehn and coworkers[19]. The corresponding SCF and MP2 energies for the optimized geometries at 6-31+G** as well as the corresponding deprotonation energies are given in Table 4.

The calculated deprotonation energies of ethane, ethylene and acetylene by SCF Hartree–Fock (HF) and MP2 methods follow the expected order: 456, 455 (basis

TABLE 3. Bond distances (in Å) and angles (in degrees) in ethylene, **1**, and vinyl anion, **2**[a]

| Compounds | C–H bond distances | C=C bond distances | ∠CCH angles |
|---|---|---|---|
| **1** | 1.076 | 1.321 | 121.7 |
| **2** | $C_{(\beta)}-H_{(\tau)}$ 1.087 | $C_{(\alpha)}-C_{(\beta)}$ 1.354 | $\angle C_{(\alpha)}C_{(\beta)}H_{(\tau)}$ 121.6 |
| | $C_{(\beta)}-H_{(c)}$ 1.096 | | $\angle C_{(\alpha)}C_{(\beta)}H_{(c)}$ 125.5 |
| | $C_{(\alpha)}-H_{(\alpha)}$ 1.107 | | $\angle C_{(\alpha)}C_{(\beta)}H_{(\alpha)}$ 108.6 |

[a]Reference 16.



**(2)** **(2a)** **(2′)**

TABLE 4. SCF and MP2 energies for ethylene and vinyl anion and the deprotonation energy ($\Delta E_{acid}$) for ethylene[a,b]

| | Absolute SCF energy[c,d] | Absolute MP2 energy[c,d] | G2 total energy[d,e,f] | SCF $\Delta E_{acid}$[g] | MP2 $\Delta E_{acid}$[g] | G2 $\Delta E_{acid}$[b] | expt[h] |
|---|---|---|---|---|---|---|---|
| $H_2C{=}CH_2$ | −78.04307 | −78.32274 | (−78.41593)<br>−78.41193 | 422.0 | 410.8[i] | (407.0)<br>409.0 | 409.4 |
| $H_2C{=}CH^-$ | −77.36881 | −77.65292 | (−77.76722)<br>−77.76326 | | | | |

[a] Reference 16.
[b] Reference 20.
[c] 6-31+G** basis set.
[d] Energy in Hartrees.
[e] Corrected for basis set superposition error (BSSE).
[f] Energy in parentheses is calculated at 0 K, the other at 298 K.
[g] Energy in kcal mol$^{-1}$.
[h] Reference 8.
[i] Calculated value at MP2/6-31+G* = 407.7 kcal mol$^{-1}$; the corresponding MP4 value is 408.7 kcal mol$^{-1}$[21].

set 6-31+G*)[22]; 422, 410.8 (6-31+G**)[16]; and 380.3, 384.8 (6-31+G**) kcal mol$^{-1}$[23], respectively. The added correlation energy of the MP2 method has a variable effect on these energies. Saunders[24] tested a number of theoretical levels and found best overall agreement with the 6-31+G* + MP2 level. This method gave $\Delta H^\circ_{acid} = 408.6$ kcal mol$^{-1}$ for ethylene, in good agreement with the experimental values. Smith and Radom[20] used G2 theory to calculate the absolute acidity resulting in $\Delta H^\circ_{acid} = 409.0$ kcal mol$^{-1}$ and $\Delta H^\circ_{acid} = 378.0$ kcal mol$^{-1}$ for ethylene and acetylene, respectively. These theoretical results are in excellent agreement with experiment[8].

## C. Vinylic Anions in Solution

A few measurements are available that relate to the ion pair acidity of ethylene and some other alkenes. Ethylene is difficult to metallate directly, but vinyl bromides and iodides undergo facile transmetallation with alkyllithium reagents. Applequist and O'Brien determined the equilibrium constants of transmetallation exchange reactions as a measure of relative acidity (equations 6 and 7)[25].

$$RLi + R'I \overset{K_{obsd}}{\rightleftharpoons} RI + R'Li \tag{6}$$

$$K_{obsd} = [RI][R'Li]/[RLi][R'I] \tag{7}$$

For R′ = phenyl and R = vinyl, the corresponding $\log K_{obsd}$ is $-2.41 \pm 0.92$; that is, by this measure ethylene is more acidic than benzene with ether as the solvent. It should be

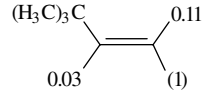



FIGURE 1. Relative rates of tritium exchange with cesium cyclohexylamide in cyclohexylamine[31]

noted that measurements of ion pair acidities may be complicated by aggregation of the phenyllithium and vinyllithium ion pairs which was not taken into account, although the equilibrium constants measured were not sensitive to solvent.

Cram[26] had developed an acidity scale based on the ion pair acidity and used this and other measures (such as the acidity function technique) in compiling his so-called MSAD acidity scale, named after W. K. McEwen, A. Streitwieser, D. E. Applequist and R. E. Dessy. The scale used 9-phenylfluorene ($pK_a = 18.5$) as its standard and is considered at least approximately to refer to the dilute aqueous solution as the standard state. On this scale ethylene is assigned a p$K$ value 0.5 units lower than benzene; however, in another early compilation[27] ethylene is 1 p$K$ unit higher than benzene. In an updated MSAD scale, ethylene was found to be 1 p$K$ unit less acidic than benzene[6,28,29].

Kinetic acidities provide another measure. The rate of isotope exchange of ethylene-$d_4$ with cesium cyclohexylamide (CsCHA) in cyclohexylamine (CHA)[6] is about 0.1 the rate of exchange of benzene. The corresponding exchange of *trans*-3,3-dimethyl-1-butene-1-d is about 0.02 that of benzene-d, and shows that the *β-tert*-butyl group exerts an electron-donating inductive effect[5,30]. Other positions in *tert*-butylethylene show the effects of steric hindrance to exchange (Figure 1)[31]. Note that this effect differs from that in the gas phase (*vide supra*).

Norbornadiene is readily metallated by butyllithium, in agreement with its higher gas-phase acidity than ethylene (*vide supra*)[32].

## III. ALLYL HYDROGENS

Vinyl C−H bonds are more acidic than the C−H bonds in saturated hydrocarbons because of their higher s-character and the polarizability of the double bond, but the corresponding carbanions are essentially localized. Allylic C−H bonds have the s-character of saturated hydrocarbons, but the resulting carbanions now have the possibility of additional stabilization by delocalization. Allylic positions are thus generally the most acidic in alkenes.

### A. Gas-phase Acidities

One of the earliest measurements of the gas-phase equilibrium acidity of propene involved measuring the rates of reaction of propene with hydroxide ion in both directions[33]. The resulting equilibrium constant gave $\Delta H_{acid} = 391 \pm 1$ kcal mol$^{-1}$. In the case of ethylene, the acidity and independently measured electron affinity of vinyl radical were used to determine the bond dissociation energy, a quantity difficult to obtain accurately by other means[8].

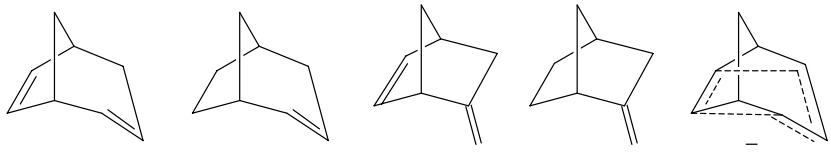
Another early acidity investigation of propene by the thermodynamic method involved the determination of the electron affinity of allyl radical by photodetachment from allyl anion[34]. Extrapolation of the data to a photodetachment threshold gave an electron affinity (EA) of allyl radical of 0.55 eV which, combined with a bond dissociation energy of allyl-H of 89 kcal mol$^{-1}$, gave $\Delta H_{acid} = 390$ kcal mol$^{-1}$.

The same method was used to determine the electron affinities of pentadienyl radical (0.91 eV) and heptatrienyl radical (1.27 eV)[35]. The corresponding bond dissociation

energies are not known accurately. Using a reasonable value of 76 kcal mol$^{-1}$ for $CH_2{=}CHCH{=}CHCH_2{-}H$ gives a corresponding $\Delta H_{acid} = 368$ kcal mol$^{-1}$.

In studies of substituent effects, Bartmess and Burnham measured the acidities of several 2-substituted propenes in the gas phase[36]. Electron-attracting groups have the expected acidity-enhancing effect. 2-Methylpropene was found to be 0.6 kcal mol$^{-1}$ more acidic than propene. Isoprene (2-methylbutadiene) was found to be 6 kcal mol$^{-1}$ more acidic than propene but the experimental error was almost as large. The acidity of isoprene of 385 kcal mol$^{-1}$ is substantially higher than that of its conjugated isomer, 1,3-pentadiene, quoted above as 368 kcal mol$^{-1}$. Dahlke and Kass studied 3-fluoro-, 3-methoxy- and 3-(dimethylamino)-propene and found almost no change in the acidity of propene within their experimental uncertainty of $\pm 4$ kcal mol$^{-1}$[37].

Lee and Squires determined the gas-phase acidities of a number of cyclic alkenes and dienes including the bicyclic compounds **4**, **5**, **6** and **7**[15]. Their values are summarized in Table 5 and have estimated uncertainties of 1–2 kcal mol$^{-1}$. The relatively high acidity of **4** was attributed to bishomoconjugation of the double bond with the allyl anion, as shown in **8**[15].



**(4)** **(5)** **(6)** **(7)** **(8)**

## B. Theory

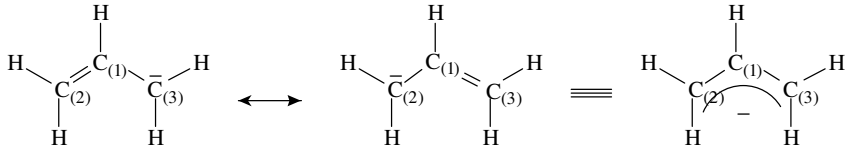
Extensive theoretical studies have been carried out to probe the nature of the allyl anion. These studies supplement and extend the experimental results. Allyl anion is of special interest because it is the simplest $\pi$-delocalized carbanion with 4 electrons and 3 $p_\pi$-centers. Much recent theoretical discussion has concerned the role of resonance in the stabilization of such conjugated systems, a stabilization defined as the enthalpy difference between the localized double-bonded system and its conjugated state. The stabilization of allyl anion has generally been attributed to the delocalization of charge associated

TABLE 5. Gas-phase acidities of some cyclic and bicyclic unsaturated hydrocarbons[a]

| Compound | $\Delta H_{acid}$ (kcal mol$^{-1}$) |
|---|---|
| **4** | 380 |
| **5** | 389 |
| **6** | 389 |
| **7** | 389 |
| Cyclohexene | $\geqslant$387 |
| 1,3-Cyclohexadiene | 372 |
| Cyclooctene | $\leqslant$386 |
| 1,3-Cyclooctadiene | 375 |
| 1,5-Cyclooctadiene | 375 |

[a]Reference 15.

with the resonance structures **9a** and **9b.** A recent argument based on the magnitudes of stretching vibrations has nevertheless supported some new concepts, namely that it is the $\sigma$-system which imposes the equal CC bond lengths[38]. The asymmetric stretching modes of benzene and allyl cation and anion to give alternating double and single bonds are enhanced by the $\pi$-electronic systems.



**(9a)** **(9b)**

In an attempt to assess the importance of the delocalization energies in the allyl system, Gobbi and Frenking have computed various distorted structures of allyl anion and rotational transition states, such as **11a–11d**, and have compared the relative energies with the corresponding allyl cations, **10a–10c**[39]. The structures are shown in Figure 2 and the energies are summarized in Table 6.

The allyl anion ground-state conformation is $C_{2v}$ at 6-31G HF and $C_2$ at MP2. The energy difference, however, is only 0.2 kcal mol$^{-1}$ and when the zero-point energy (ZPE)

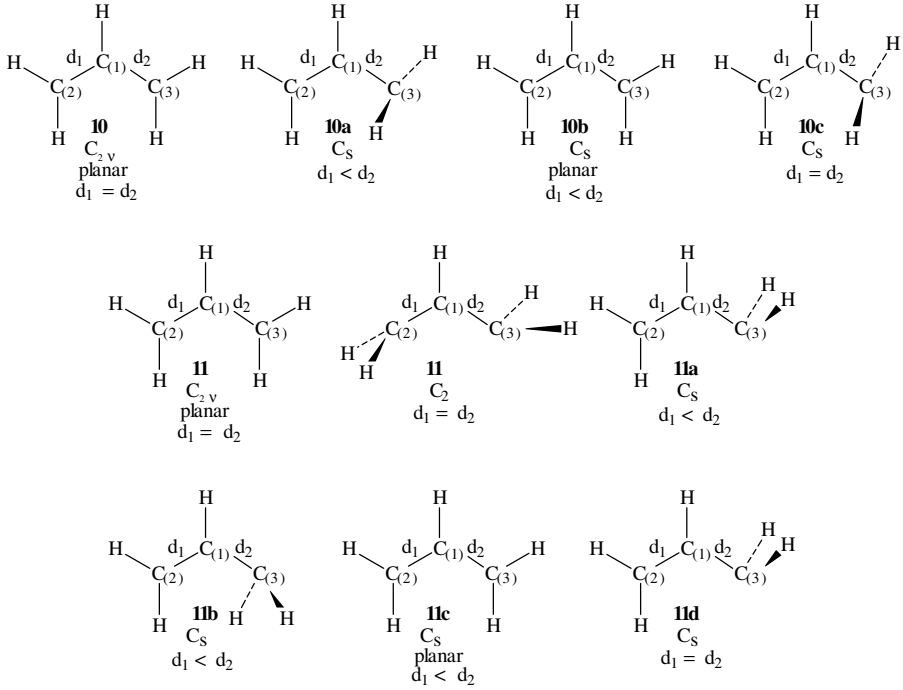



FIGURE 2. Structures of calculated allyl cations, **10**, and allyl anions, **11**

TABLE 6. Calculated results for allyl cations, **10**, and allyl anions, **11**[a]

| | **10** | **10a** | **10b** | **10c** | **11** | **11a** | **11b** | **11c** | **11d** |
|---|---|---|---|---|---|---|---|---|---|
| Symmetry | $C_{2v}$ | $C_s$ | $C_s$ | $C_s$ | $C_2$ ($C_{2v}$) | $C_s$ | $C_s$ | $C_s$ | $C_s$ |
| $E_{rel}$ | (0.0) | (34.0) | (4.0) | (38.3) | 0.0 | 22.8 | 25.3 | (7.7) | (27.9) |
| | *0.0* | *37.8* | *4.4* | *38.7* | (0.0) | (20.4) | (22.7) | *7.4* | *28.0* |
| | | | | | *0.0* | *23.1* | *25.4* | | |
| $C_{(1)}-C_{(2)}$ | 1.382 | (1.318) | (1.318) | (1.373) | 1.393 | 1.348 | 1.351 | (1.331) | (1.382) |
| ($d_1$) | (1.373) | | | | (1.382) | (1.331) | (1.334) | | |
| $C_{(1)}-C_{(3)}$ | 1.382 | (1.445) | (1.445) | (1.373) | 1.393 | 1.493 | 1.503 | (1.508) | (1.382) |
| ($d_2$) | (1.373) | | | | (1.382) | (1.508) | (1.518) | | |

[a] $E_{rel}$ is the energy relative to the lowest-energy conformation (in kcal mol$^{-1}$); $d_1$ and $d_2$ are calculated bond lengths (in Å). Energies and geometries are given at MP2/6-31G(d); in parentheses for HF/6-31G(d); in italics for MP2/6-31G(d)//HF/6-31G(d).

correction is taken into account, the $C_{2v}$ structure is the minimum. Rotation of the methylene group can proceed through either the **11a** or **11b** transition states. The inward rotation **(11b)** is energetically more favored by 2.3 kcal mol$^{-1}$ with an increase in the negative charge on $C_{(3)}$ of 0.162 *e* (topological analysis) and 0.274 *e* (NBO) accompanying the localization of bonds. For $C_{(1)}-C_{(2)}$ and $C_{(1)}-C_{(3)}$ using the numbering scheme of Frenking, the bond order $P_{CC}$ is 1.832 (more double bond-like) and 1.102 (more single bond-like), respectively. Although the barrier to rotation about the $C_{(1)}-C_{(3)}$ bond in allyl anion is quite large, the distortion energy of the planar structures is relatively small (7.4 kcal mol$^{-1}$) but higher than in allyl cation by 3.1 kcal mol$^{-1}$.

With respect to the $\sigma$ and $\pi$ interactions towards the geometry in the allyl system, Frenking separated the distortions into the rotation of the methylene group and bond distances. The former 'turns off' $\pi$-conjugation while bond-length distortion only changes the $\pi$-interactions. From both the topological[40] and Natural Bond Orbital (NBO)[41] analysis, the negative charge resides mostly on the terminal carbons: $q(\rho(\mathbf{r}))$ and $q$(NBO) for $C_{(2)}$ and $C_{(3)}$ in reference to Frenking's numbering scheme (as pictured in Figure 2) are $-0.328$ and $-0.817$, respectively; and including the hydrogens, the charge for $C_{(2)}$ and $C_{(3)}$ is $-0.446$ and $-0.512$. Note that the two methods give reasonable agreement for the $CH_2$ groups but differ in the distribution of charge between C and H.

A second argument concerning resonance stabilization centered on a stabilizing effect in the allyl anion. Wiberg and coworkers challenged the generally accepted point that allyl anion is stabilized by electron delocalization[42]. Their approach is based on large basis-set calculations of allyl cation and anion and their localized counterparts (see Table 7). The reaction of hydride transfer from propene to propyl cation to form the unconjugated allyl cation was computed to be endothermic. The corresponding proton transfer from propene to give unconjugated allyl anion, however, was found to be exothermic. Both effects were attributed to the electron-attracting inductive effect of the C−C double bond. The calculated rotational barrier of allyl anion of 19 kcal mol$^{-1}$ is 17 kcal mol$^{-1}$ lower than for allyl cation. The cation has a calculated barrier of 36 kcal mol$^{-1}$, but the experimentally approximated barrier is 25 kcal mol$^{-1}$ with a resonance energy stabilization range of 8–18 kcal mol$^{-1}$[43].

Wiberg split the stabilization of the energy barrier into two parts: (a) electrostatic energy in the planar form and (b) delocalization. Electrostatic stabilization lowers the energy of the planar form because the charge is spread over three atoms rather than being localized on one carbon in the rotated form. An estimation of the electrostatic stabilization was made by calculating a model, methane, for the localized anion and yielded a 23 kcal mol$^{-1}$

TABLE 7. Calculated ionization energies[a] and energy changes for several reactions[b]

| Reaction | $\Delta E$ (kcal mol$^{-1}$) | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 6-311++G**//6-31G* | | | | | |
| | 6-31G*//6-31G* | RHF | MP2 | MP3 | MP4 | $\Delta H_{calc}$ | $\Delta H_{obs}$ |
| propane ⟶ propyl$^+$ + H$^-$ | 307.5 | 267.3 | 288.3 | 285.8 | 284.8 | 276 | 274 ± 3[c] |
| propene ⟶ allyl$^+$ + H$^-$ | 286.0 | 248.7 | 268.1 | 266.9 | 265.1 | 258 | 256 ± 3 |
| propane ⟶ propyl$^-$ + H$^+$ | 452.6 | 436.1 | 425.9 | 430.1 | 426.9 | 417 | 419 ± 3 |
| propene ⟶ allyl$^-$ + H$^+$ | 425.4 | 408.0 | 399.8 | 405.2 | 402.8 | 392 | 390 ± 3 |
| propyl$^+$ + propene ⟶ unconj allyl$^+$ + propane | +12.5 | +14.5 | +16.3 | +15.5 | +15.9 | | |
| propyl$^-$ + propene ⟶ uncon allyl$^-$ + propane | −6.7 | −6.8 | −5.4 | −5.5 | −5.1 | | |
| unconj allyl$^+$ ⟶ conj allyl$^+$ | −34.0 | −33.1 | −36.5 | −34.4 | −35.6 | | |
| unconj allyl$^-$ ⟶ conj allyl$^-$ | −20.4 | −21.3 | −20.8 | −19.4 | −19.0 | | |

[a]In kcal mol$^{-1}$.
[b]Abbreviations: unconj stands for unconjugated and conj stands for conjugated.
[c]The experimental value given for 1-propyl cation is actually that for the ethyl cation. The values should not be much different, for the open propyl cation will receive a small stabilization because of its greater size, but the experimentally studied ethyl cation has a small stabilization from bridging.

difference between the planar and rotated forms, which is close to the observed energy difference between the above two forms. Therefore, he attributed the rotational barrier in the allyl anion to the change in electrostatic energy rather than to resonance stabilization, and concluded: 'whereas the cation has significant resonance stabilization, the anion has little stabilization'[42].

Frenking argued with Wiberg's conclusion that electrostatic effects dominate the barrier in allyl anion rather than resonance stabilization. Among allyl systems, the highest barrier to rotation is that of the allyl cation with the largest change in the charge differences on the $CH_2$ group in the rotated form (see Table 8). The lowest rotational barrier is that of the allyl radical with basically no change in charge distribution. The barrier for allyl anion lies between that of the cation and radical, but with a significant amount of charge redistribution.

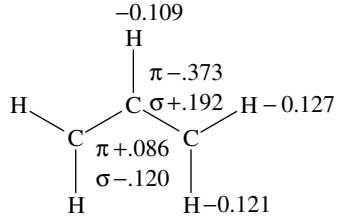
How does this address the difference in the barrier to rotation between allyl cation and anion? The $CH_2$ methylene group is planar in the transition state in the case of the cation **(10c)** but pyramidal in the anion **(11a)**. Frenking calculated the energy for the transition state of the anion with a planar $CH_2$ group at the MP2/6-31G(d)//HF/6-31G(d) level to be 9.8 kcal mol$^{-1}$ higher than the pyramidal $CH_2$ group in **11a**, but 32.9 kcal mol$^{-1}$ higher than the ground-state structure, **11**. Therefore, the total energy for the rotation of the allyl anion with a planar $CH_2$ group is quite comparable to that of allyl cation. Pyramidalization clearly stabilizes the anion transition state and lowers the rotational barrier.

TABLE 8. Calculated energies ($\Delta E$) for barrier to rotation in the allyl systems and charge differences ($\Delta q$) for the $CH_2$ groups[a]

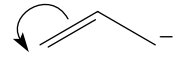
| | Allyl cation, **10** | Allyl radical | Allyl anion, **11** |
|---|---|---|---|
| $\Delta E$ (kcal mol$^{-1}$) | 37.8 | 12.6 | 23.1 |
| $\Delta q$(NBO) | 0.33 | 0.02 | 0.27 |
| $\Delta q(\rho(\mathbf{r}))$ | 0.17 | 0.02 | 0.16 |

[a]Reference 39.

The actual charge distribution in the allyl anion is of further interest in this connection. The simple resonance structures (**9a** and **9b**) suggest that the negative charge is solely on the two terminal carbons. The actual charge distribution as given by Bader's topological analysis[42] shown in **12** gives a much different picture: the $\pi$ and $\sigma$ charges are shown for carbon. Note that 60% of the negative charge is carried by the hydrogens[18]. The terminal carbons have negative charge in the $\pi$-system, but the $\sigma$-system is positive; the reverse is true for the central carbon. This observation, that charge in one system polarizes the other, is becoming more common. Note also that even a classical electrostatic picture of $\pi$-polarization, as in **13**, would leave the central position with a positive charge.




**(12)**



**(13)**

The theoretical studies of allyl anion lead naturally to those of metal salts and, in particular, allyllithium. Hommes and colleagues considered the effect of the metal on the structure of the allyl ion pair[44]. They calculated the energies of a series of alkali metals for the $C_s$ symmetric bridged ('ion-pair') and $C_s$ symmetric planar (covalent) species at the 6-31G** for C, H, Li and Na and at 6-31G* for Rb and Cs. The optimized structure of the allyl alkali metal is the bridged $\eta^3$ ion pair species (Table 9). As one proceeds down the Group I alkali metal column, the natural charge on the metal as well as $C_{(2)}$ becomes more positive and the charge on $C_{(1)}$ and $C_{(3)}$ becomes more negative, with the exception of the carbons in allylcesium. The structural features change as well; the M−C bond length and the CCC bond angle increases as the metal becomes larger. The structure of the metal salt is important because it will influence its behavior in reactions.

The rotational barriers increase from sodium to cesium to yield an estimate of the 'free' allyl anion barrier to rotation. The calculated barrier is higher than that determined experimentally. Hommes and colleagues proposed that the decrease could be due to solvation or dimerization. Considering both dimerization and solvation, the calculated barrier decreases by 5.5 and 0.5 kcal mol$^{-1}$, respectively.

The theoretical study of the structure of propene was then used as a model to calculate the effect of the structure on the proton affinity, and later to predict the acidity of similar systems such as cycloalkenes[46]. Deformation of the CCC angle as a function of the stability of the anion was probed, and the results were in agreement with the acidities of the hydrogens of propene. The allylic protons were found to be more acidic than the vinylic ones, which is in contrast to the results of Gründler[47].

### C. Allylic Anions in Solution

Allyl anion is too strongly basic to be studied as the free anion in solution. Bordwell developed an acidity scale based on equation 1 in dimethyl sulfoxide (DMSO) at 25 °C[3] and applied the method to a number of more acidic substituted allylic systems. A summary of some results is shown in Table 10. DMSO is sufficiently polar that there is little ion

TABLE 9. Calculated energies and rotational barriers of $\eta^3$ and $\eta^1$ allyllithium and allylalkali metal compounds

| Compound | | Absolute energies[a] | ZPE[b,h] | rotational barriers | |
|---|---|---|---|---|---|
| | | | | (calcd $\Delta E$)[c] | (expl $\Delta G^{\ddagger}$)[c] |
| $C_3H_5Li$ | $\eta^3$ | 124.32623[d] | 45.8(0) | | |
| | $\eta^1$ | 124.29554[d] | 45.0(1) | 18.5[d] | 10.7[i] |
| $C_3H_5Li{-}OH_2$ | $\eta^3$ | 200.56745[d] | 61.9(0) | | |
| | $\eta^1$ | 200.53708[d] | 61.0(2) | 18.2[d] | |
| $(C_3H_5Li)_2$ | $\eta^3$ | 246.52231 | 93.9(0)[g] | | |
| | $\eta^1$ | 246.50063 | 93.1(1)[g] | 13.0[f] | |
| $C_3H_5Na$ | $\eta^3$ | 278.70629[d] | 44.6(0) | | |
| | $\eta^1$ | 278.68461[d] | 44.4(1) | 13.4[d] | 11.5[j] |
| $C_3H_5K$ | $\eta^3$ | 715.42691[d,f] | 44.3(0) | | |
| | $\eta^1$ | 715.39919[d,f] | 43.8(1) | 17.4[d] | 14.3, 16.7[i] |
| $C_3H_5Rb$ | $\eta^3$ | 3052.62835[d,f] | 44.2(0) | | |
| | $\eta^1$ | 3052.59752[d,f] | 43.8(1) | 19.0[d] | 18.1[j] |
| $C_3H_5Cs$ | $\eta^3$ | 7665.39864[d,f] | 44.0(0) | | |
| | $\eta^1$ | 7665.36314[d,f] | 43.5(1) | 21.8[d] | 18.0[i] |
| $C_3H_5^-$ | $\eta^1$ | 116.88560[e] | 39.9(0)[f] | | |
| | *syn* | 116.85163[e] | 40.2(1)[f] | 21.7[h] | |
| | *anti* | 116.84806[e] | 40.3(1)[f] | 24.0[h] | |

[a] Absolute energies in au.
[b] Zero-point energies.
[c] In kcal mol$^{-1}$.
[d] MP2(fc)/(6-31+G*).
[e] MP2(fu)/(6-31G*) (fu = full) with 6-31+G** basis sets on C used for $C_3H_5^-$.
[f] 3-21G.
[g] 6-31G* and Huzinaga basis sets used for K, Rb and Cs, 6-31+G* and 6-31+G** on C used for $C_3H_5^-$.
[h] 6-31+G**. Number of imaginary frequencies is given in parentheses: (1) a transition state; (2) a second-order saddle point.
[i] Reference 45.
[j] Reference 71.

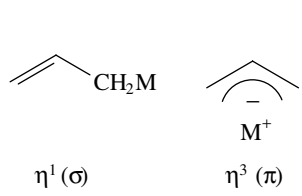
TABLE 10. Equilibrium acidities of selected allylic compounds in dimethyl sulfoxide at 25 °C[a]

| Acid | p$K_a$[b] |
|---|---|
| $CH_2{=}CHCH_2NO_2$ | 7.7 |
| $PhCH{=}CHCH_2SO_2Ph$ | 20.2 |
| $CH_2{=}CHCH_2SO_2Ph$ | 22.5 |
| $Ph_2C{=}CHCH_2Ph$ | 25.6[c] |
| $Ph_2C{=}CHCHPh_2$ | 25.8 |
| $CH_2{=}CHCH_3$ | (44)[d,e] |

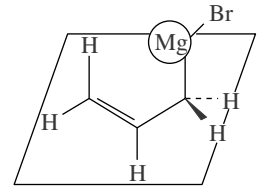
[a] Reference 3.
[b] p$K_a$ values of acids forming chelating anions have been corrected for ion-pairing with $K^+$. Most p$K_a$ values were measured by using two or more indicators or standard acids and are believed to be accurate to 0.1 unit.
[c] This number is comparable (26.76) to the cesium ion-pair acidity for the same compound measured in THF at 25 °C[49].
[d] Reference 50.
[e] Reference 48.

pairing and the results pertain to the ionic p$K$ values with the dilute DMSO solution as the standard state. The results were extrapolated to give the approximate corresponding p$K_a$ of propene[48]. The derived value of 44 is comparable to that of toluene.

With less polar solvents and more basic allyl anions the compounds are present as ion pairs. The carbon–metal bond with the alkali and alkaline earth metals are known to have high ionic character. The allyl compounds behave accordingly as salts. The structures of allyl compounds of the alkali and alkaline earth metals are of two fundamental types, a $\eta^1$ (or $\sigma$) type, **14**, in which the metal cation is associated closely with a single terminal allylic carbon, and the $\eta^3$ (or $\pi$) type, **15**, in which the cation bridges the two terminal allylic positions.



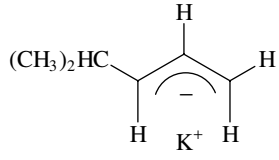

**(14)** **(15)**



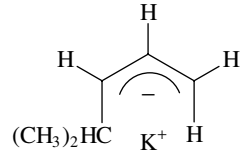

**(16)**

Early NMR work by Roberts and coworkers[51–53] showed that allyl Grignard reagents **(16)** are of the $\sigma$ type in which the metal migrates rapidly from one terminus to the other. This result was confirmed by more recent high resolution $^{13}$C NMR work of Schlosser and Stähle[54].

In the case of allylpotassium, the metal complex exists as a symmetric $\pi$ structure. No temperature dependence was shown by either $^{13}$C NMR for $\Delta\delta[C_{(1)}-C_{(3)}]$ or by $^1$H NMR for substitution with deuterium at $C_{(3)}$. Thompson and Ford measured experimentally a variety of allylalkali metal compounds using variable-temperature NMR in THF-$d_8$[45]. Addends such as TMEDA, hexamethylphosphoric triamide (HMPA), 15-crown-5-ether, [2.1.1]cryptand and $n$-butyllithium showed either no change in the spectrum or rapid decomposition of the complexing agent. Measurement of the populations of $E$ **(17)** and $Z$ **(18)** isomers of 1-isopropylallylpotassium showed the $Z$ isomer to be more stable (Table 11).




**(17)**



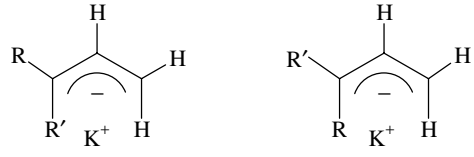

**(18)**

Further investigation of allylpotassium complexes have shown that 2-isopropylallyl potassium does not show diastereotopism of the methyl groups at temperatures as low as $-155\,^{\circ}$C[54,59]. Therefore, the activation barrier for interconversion is on the order of 4 kcal mol$^{-1}$ or lower. Both crotyl **(19)** and prenyl **(20)** potassium complexes are further examples of the preference for allylpotassium compounds to exist as symmetric $\pi$ species. The potassium has the appropriate atomic radius to 'reach' both $C_{(1)}$ and $C_{(3)}$. No increase in stabilization is gained upon addition of solvent. Allylcesium behaves in the same manner. In general, the theoretically calculated rotational barriers (Table 9) are higher

TABLE 11. Experimental barriers to rotation

| Compound | | $\Delta G^{\neq}_c(T_c, {}^\circ C)$ (kcal mol$^{-1}$) |
|---|---|---|
| Allyllithium | | $10.7 \pm 0.2$ (−51) |
| Allylpotassium | | $16.7 \pm 0.2$ (68) |
| Allylcesium | | $18.0 \pm 0.3$ (68) |
| 2-Methylallylpotassium | | $15.9 \pm 0.3$ (51) |
| (*Z*)-1-Methylallylpotassium | $(C_{(1)}-C_{(2)})$ | 18–22[a] |
| | $(C_{(2)}-C_{(3)})$ | $17.0 \pm 0.3$ (68) |
| (*Z*)-1-Isopropylallylpotassium | $(C_{(1)}-C_{(2)})$ | > 19.3 (68) |
| | $(C_{(2)}-C_{(3)})$ | $17.0 \pm 0.3$ (47) |
| (*E*)-1-Isopropylallylpotassium | $(C_{(2)}-C_{(3)})$ | ⩽ 14.0 (28) |
| 2-Isopropylallylpotassium | | < 4[b] |
| 2-Isopropyl-1,3-diphenylallyl potassium | | 12.5[c] |
| (1,1,3,3-Tetramethylallyl)lithium | | 14[d] |
| *exo*-[1,1,3-Tris(trimethylsilyl)allyl]lithium | | 17[e] |
| 1,3-Diphenylallylsodium | | $16.5 \pm 0.2$[f] |

[a] Estimated; Reference 45.
[b] Reference 54.
[c] Reference 55.
[d] Reference 56.
[e] Reference 57.
[f] Reference 58.




**(19)** R = H, R′ = $CH_3$
**(20)** R = R′ = $CH_3$

than the experimentally determined ones. The discrepancy ranges from 0.9 kcal mol$^{-1}$ for allylrubidium up to 7.8 kcal mol$^{-1}$ for allyllithium.

Allyllithium is one of the most important complexes but is also more difficult to study. Schleyer and coworkers have shown recently that dynamic NMR studies of allyllithiums are complicated by aggregation[60]. As a result, the difference in the carbon signals from the isotopically labeled species is smaller than expected for two rapidly equilibrating nonsymmetric structures. The resulting variable-temperature NMR investigation also revealed that the lithium complex is unsymmetric with a low barrier to interconversion, but the disymmetry was attributed to aggregation. Allyllithium exists as a dimer at 165 K in tetrahydrofuran and becomes more aggregated at higher temperatures. Such aggregation also provides an explanation for the discrepancy between the calculated (17.7 kcal mol$^{-1}$)[61] and experimental ($10.7 \pm 0.2$[45] and $10.5 \pm 0.2$[62] kcal mol$^{-1}$) energies of activation for rotation of a terminal $CH_2$ group.

On substitution of allyllithium with methyl groups, the structures are distorted $\pi$ complexes becoming more $\eta^1$-like. The previously described allyllithiums are contact ion pairs (CIP) whose dissociation is too low to permit study of the free carbanion. However, this is not the case for a more delocalized system such as 1,3-diphenylallyl whose lithium salts can exist as solvent separated ion pairs (SSIP) in ethereal solutions for which the organic moiety could be treated essentially as a free carbanion[55]; Boche and coworkers studied the effect of substitution at $C_{(2)}$ in their 1,3-diphenylallyl lithiums on the rotational barriers

and conformational preferences[55]. In the parent system, the more stable conformation of the allyl anion is the *exo,exo*-conformer. Upon substitution of larger groups such as phenyl and isopropyl at $C_{(2)}$, the *exo,endo*-conformer becomes more favorable. At the sterically demanding extreme where R = *tert*-butyl, the only conformer present is the *endo,endo*-structure. Therefore, the equilibrium of the interconversion is determined by the steric interaction between the R group at $C_{(2)}$ and the phenyl groups. The rotational energy barrier reflects the steric congestion upon substitution, increasing the ground-state energy conformation and decreasing the barrier, such as in the *tert*-butyl case (12.5 kcal mol$^{-1}$). The addition of HMPA has little effect and rules out ion pairing effects. In conclusion, these allyl anions are essentially SSIP or 'naked' in nature because there is little if no difference between the $\Delta G^{\ddagger}$ for 2-cyano-1,3-diphenylallyl anion in this study and of the lithium, sodium and potassium salts in DMSO[63,64]. In earlier experimental work of the rotational processes in these systems, Burley and Young found not only hindered rotation about the C−C bond of the allyl group in 2-methyl-1,3-diphenylallyl carbanion, but also about the C−ph bond in 2-methyl-1,3-diphenylallyl, 1,3-diphenylallyl and 1-methyl-1,3-diphenylallyl carbanions[65]. These interconversions are illustrated in Figure 3.

Streitwieser and Boerth studied the kinetic acidities of cycloalkenes with lithium cyclohexylamide (LiCHA) in cyclohexylamine for comparison with those of benzene and toluene[66]. The relative rates of deprotonation and the corresponding equilibrium p*K* values are tabulated in Table 12. These proton transfer transition states are stabilized by conjugation of the reacting C−H bond with the double bond.

In order to investigate the effect of chain length of alkenes upon acidity and aggregation, Thiele and Streitwieser probed the equilibrium acidity of a series of polyenes using UV VIS-spectroscopy in THF at 25 °C: Ph(CH=CH)$_n$CH$_2$Ph ($n$ = 1, DP3; $n$ = 2, DP5; $n$ = 3, DP7; $n$ = 4, DP9)[70]. The equilibrium acidity was determined using the transmetallation reaction of equation 3 with $Cs^+$ as the counterion. The results were consistent with

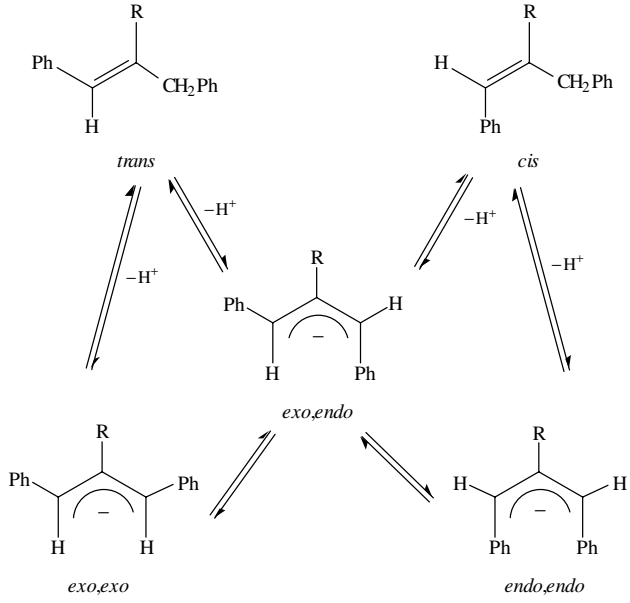



FIGURE 3. The proposed interconversion scheme for substituted 1,3-diphenylallyl anions

TABLE 12. Relative rates of deprotonation at 50 °C in cyclohexylamine, dihedral angle (C=C−C−H) as determined from force field calculations, and deduced equilibrium $pK_{CsCHA}$ values for several carbon acids[a]

| Compound | Relative rates | C=C−C−H[b] | $pK_{CsCHA}$ |
|---|---|---|---|
| Cycloheptene | 1 | 58.5° | |
| Cyclopentene | 0.063 | 13.1° | 44 |
| Cyclohexene | 0.193 | 123.5° | 46 |
| Cyclooctene | 0.206 | 78.8° | |
| Benzene | 0.505 | | 43[c] |
| Toluene | 119 | | 41.2[d] |

[a]Reference 66.
[b]Reference 67.
[c]Reference 68.
[d]Reference 69.

formation of monomers rather than higher-order aggregates. The increasing delocalization of charge was used to explain the decrease in $pK_a$ with respect to chain length. These highly delocalized carbanions have less electrostatic attraction to cations and are more highly dissociated to the free ions in THF. The free anions have significantly different UV-VIS spectra and permitted the determination of the dissociation constants and the corresponding ionic p$K$ values given in Table 13. These values are expected to apply to the DMSO solutions as well. The p$K$ values correlate with various theoretical measures but also give a simple 'electron-in-a-box' type of correlation with the function $(n+8)^{-1}$, where $n$ is the chain length and the '8' accounts for the effect of the phenyls on the size of the 'box'.

In the above work the available evidence suggests that the carbanions are in the fully extended conformation. Tolbert and Ogle[72] studied the same series of carbanions in DMSO solution by $^{13}C$ NMR spectroscopy and found only the fully extended conformations. This is the expected result on the basis of electron repulsion within the anions.

The unsubstituted pentadienyl anion also appears generally to be in the fully extended form, the so-called W-structure (Figure 4); examples are pentadienyllithium in THF[73]

TABLE 13. Compilation of the p$K$ values for the cesium ion pair and free ion of polyenes in THF at 25 °C[a]

| Compound | Cs ion pair p$K$ | Free ion p$K$ |
|---|---|---|
| DP3 | 27.85 | 26.17 |
| DP5 | 25.62 | 23.79 |
| DP7 | 24.14 | 21.91 |
| DP9 | 23.01 | 20.46 |

[a]Reference 70.

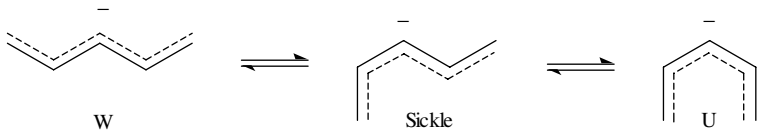



FIGURE 4. Stereoisomers of pentadienyl anion

and pentadienylpotassium in liquid ammonia[74]. In substituted pentadienyl systems, steric effects involving the substituents favor formation of the alternative S (Sickle) and U stereoisomers (Figure 4)[75].

## IV. ACKNOWLEDGMENTS

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## V. REFERENCES

1. C. R. Moylan and J. I. Brauman, *Ann. Rev. Phys. Chem.*, **34**, 187 (1983).
2. S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, *J. Phys. Chem. Ref. Data.*, **17**, 861 (1988).
3. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
4. A. Streitwieser, J. C. Ciula, J. A. Krom and G. Thiele, *J. Org. Chem.*, **56**, 1074 (1991).
5. M. J. Maskornick, Ph.D., University of California, Berkeley. 1969.
6. M. J. Maskornick and A. Streitwieser Jr., *Tetrahedron Lett.*, **17**, 1625 (1972).
7. D. K. Bohme, G. I. Mackay, H. I. Schiff and R. S. Hemsworth, *J. Chem. Phys.*, **61**, 2175 (1974).
8. K. M. Ervin, S. Gronert, S. E. Barlow, M. K. Gilles, A. G. Harrison, V. M. Bierbaum, C. H. DePuy, W. C. Lineberger and G. B. Ellison, *J. Am. Chem. Soc.*, **112**, 5750 (1990).
9. D. K. Bohme and L. B. Young, *J. Am. Chem. Soc.*, **92**, 3301 (1970).
10. J. J. Grabowski, C. H. DePuy and V. M. Bierbaum, *J. Am. Chem. Soc.*, **105**, 2565 (1983).
11. C. A. Wight and J. L. Beauchamp, *J. Am. Chem. Soc.*, **103**, 6499 (1981).
12. J. E. Bartmess, J. A. Scott and R. T. J. McIver, *J. Am. Chem. Soc.*, **101**, 6046 (1979).
13. C. H. DePuy, S. Gronert, S. E. Barlow, V. M. Bierbaum and R. Damrauer, *J. Am. Chem. Soc.*, **111**, 1968 (1989).
14. S. T. Graul and R. R. Squires, *J. Am. Chem. Soc.*, **110**, 607 (1988).
15. R. E. Lee and R. R. Squires, *J. Am. Chem. Soc.*, **108**, 5078 (1986).
16. S. Scheiner and L. Wang, *J. Am. Chem. Soc.*, **114**, 3650 (1992).
17. J. E. Williams Jr. and A. Streitwieser Jr., *J. Am. Chem. Soc.*, **97**, 2634 (1975).
18. K. B. Wiberg, P. v. R. Schleyer and A. Streitwieser, *Can. J. Chem.*, in press.
19. J. M. Lehn, B. Munsch and P. Millie, *Theor. Chim. Acta*, **16**, 351 (1970).
20. B. J. Smith and L. Radom, *J. Phys. Chem.*, **95**, 10549 (1991).
21. W. H. Saunders Jr. and J. E. Van Verth, *J. Org. Chem.*, **60**, 3452 (1995).
22. A. Pross, D. J. DeFrees, B. A. Levi, S. K. Pollack, L. Radom and W. J. Hehre, *J. Org. Chem.*, **46**, 1693 (1981).
23. S. M. Cybulski and S. Scheiner, *J. Am. Chem. Soc.*, **109**, 4199 (1987).
24. W. H. Saunders Jr., *J. Phys. Org. Chem.*, **7**, 268 (1994).
25. E. Applequist and D. F. O'Brien, *J. Am. Chem. Soc.*, **85**, 743 (1963).
26. D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York, 1965.
27. E. M. Kosower, *An Introduction to Physical Organic Chemistry*; Wiley, New York, 1968.
28. A. Streitwieser Jr., P. J. Scannon and H. M. Neimeyer, *J. Am. Chem. Soc.*, **94**, 7936 (1972).
29. T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper Collins, New York, 1987.
30. B. P. Hepp, Ph.D. Thesis, University of California, Berkeley, 1990.
31. L. Xie, P. Speers and A. Streitwieser, unpublished results.
32. A. Streitwieser Jr. and R. A. Caldwell, *J. Org. Chem.*, **27**, 3360 (1962).
33. G. I. Mackay, M. H. Lien, A. C. Hopkinson and D. K. Bohme, *Can. J. Chem.*, **56**, 131 (1978).
34. A. H. Zimmerman and J. I. Brauman, *J. Am. Chem. Soc.*, **99**, 3565 (1977).
35. A. H. Zimmerman, R. Gygax and J. I. Brauman, *J. Am. Chem. Soc.*, **100**, 5595 (1978).
36. J. E. Bartmess and R. D. Burnham, *J. Org. Chem.*, **49**, 1382 (1984).
37. G. D. Dahlke and S. R. Kass, *J. Am. Chem. Soc.*, **113**, 5566 (1991).
38. A. Gobbi, Y. Yamaguchi, G. Frenking and H. F. Schaefer, III, *Chem. Phys., Lett.*, **244**, 27 (1995).
39. A. Gobbi and G. Frenking, *J. Am. Chem. Soc.*, **116**, 9275 (1994).
40. R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, New York, 1994.
41. A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, **83**, 735 (1985).

42. K. B. Wiberg, C. M. Breneman and T. J. LePage, *J. Am. Chem. Soc.*, **112**, 61 (1990).
43. H. Mayr, W. Forner and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **101**, 6032 (1979).
44. N. J. R. v. E. Hommes, M. Buhl and P. v. R. Schleyer, *J. Organomet. Chem.*, **409**, 307 (1991).
45. T. B. Thompson and W. T. Ford, *J. Am. Chem. Soc.*, **101**, 5459 (1979).
46. D. W. Boerth and A. Streitwieser Jr., *J. Am. Chem. Soc.*, **100**, 750 (1978).
47. W. Gründler, *Tetrahedron Lett.*, 2291 (1970).
48. F. G. Bordwell and D. J. Algrim, *J. Am. Chem. Soc.*, **110**, 2964 (1988).
49. D. A. Bors, M. J. Kaufman and A. Streitwieser, *J. Am. Chem. Soc.*, **107**, 6975 (1985).
50. O. P. Shkurko, M. J. Terekhova, E. S. Petrov, V. P. Mamaev and A. J. Shatenshtein, *J. Org. Chem. USSR (Engl. Transl.)*, **17**, 260 (1981).
51. J. E. Nordlander and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 1769 (1959).
52. J. E. Nordlander, W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 494 (1961).
53. G. M. Whitesides, J. E. Nordlander and J. D. Roberts, *J. Am. Chem. Soc.*, **84**, 2010 (1962).
54. M. Schlosser and M. Stähle, *Angew. Chem., Int. Ed. Engl.*, **19**, 487 (1980).
55. G. Boche, K. Buckl, D. Martens and D. R. Schneider, *Tetrahedron Lett.*, **51**, 4967 (1979).
56. J. Cabral and G. Fraenkel, *J. Am. Chem. Soc.*, **114**, 9067 (1992).
57. G. Fraenkel, A. Chow and W. R. Winchester, *J. Am. Chem. Soc.*, **112**, 2582 (1990).
58. R. J. Bushby, *J. Chem. Soc., Perkin Trans. 2*, 1419 (1980).
59. M. Schlosser and G. Rauchschwalbe, *J. Am. Chem. Soc.*, **100**, 3258 (1978).
60. W. R. Winchester, W. Bauer and P. v. R. Schleyer, *J. Chem. Soc., Chem. Commun.*, 177 (1987).
61. T. Clark, E. D. Jemmis, P. v. R. Schleyer, J. S. Binkley and J. A. Pople, *J. Organomet. Chem.*, **150**, 1 (1978).
62. P. West, J. I. Purmort and S. V. McKinley, *J. Am. Chem. Soc.*, **90**, 797 (1968).
63. G. Boche, K. Buckl, D. Martens, D. R. Schneider and H.-U. Wagner, *Chem. Ber.*, **112**, 2961 (1979).
64. G. Boche, D. Martens and H.-U. Wagner, *J. Am. Chem. Soc.*, **98**, 2668 (1976).
65. J. W. Burley and R. N. Young, *J. Chem. Soc., Perkin Trans. 2*, 835 (1972).
66. A. Streitwieser Jr. and D. W. Boerth, *J. Am. Chem. Soc.*, **100**, 755 (1978).
67. N. Allinger and J. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972).
68. A. Streitwieser Jr., P. J. Scannon and H. M. Niemeyer, *J. Am. Chem. Soc.*, **94**, 7936 (1972).
69. A. Streitwieser Jr., M. Granger, F. Mares and R. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973).
70. G. Thiele and A. Streitwieser, *J. Am. Chem. Soc.*, **116**, 446 (1994).
71. S. Brownstein, S. Bywater and D. J. Worsefold, *J. Organometal. Chem.*, **199**, 1 (1980).
72. L. M. Tolbert and M. E. Ogle, *J. Am. Chem. Soc.*, **112**, 9519 (1990).
73. R. B. Bates, D. W. Gosselink and J. A. Kaczynski, *Tetrahedron Lett.*, 205 (1967).
74. G. J. Heiszwolf and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **86**, 807 (1967).
75. M. Schlosser and G. Rauchschwalbe, *J. Am. Chem. Soc.*, **100**, 3258 (1978).

*The Chemistry of Dienes and Polyenes.* Volume 1
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CHAPTER **17**

# The electrochemistry of dienes and polyenes

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## I. INTRODUCTION

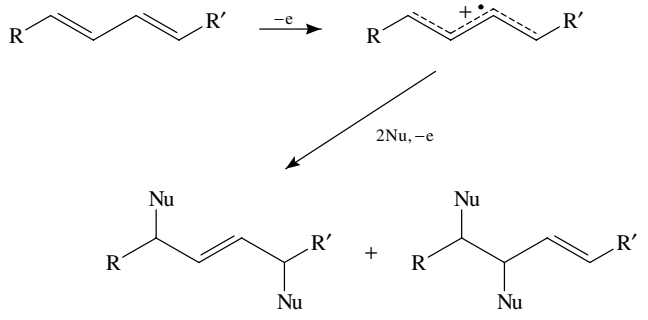
The electrochemical oxidation or reduction of dienes and polyenes is generally more useful than the corresponding reaction of monoolefins which is not substituted with activating groups, since the electrode potentials required in the reaction of dienes and polyenes are generally much lower than the potentials necessary in the reaction of monoolefins.

## II. ANODIC OXIDATION

### A. Conjugated Dienes

The anodic oxidation of conjugated dienes is much more easily achieved than the oxidation of monoolefins since the conjugation of the $\pi$-electron system lowers the oxidation potentials of the dienes. Several peak potentials for dienes are summarized in Table 1[1].

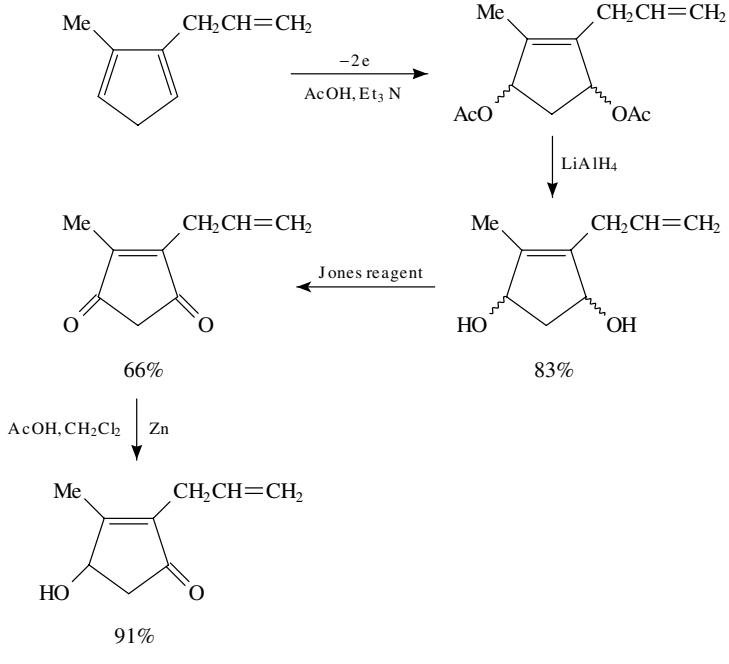
The typical pattern of anodic oxidation of conjugated dienes is oxidative 1,2- or 1,4-addition of nucleophiles, though the selectivity usually depends on the structure of the diene and the reaction conditions (equation 1).




(1)

Some typical results are shown in Table 2. The table shows that oxidation of conjugated dienes such as isoprene, piperylene (1,3-pentadiene), cyclopentadiene and 1,3-cyclohexadiene with a carbon anode in methanol or in acetic acid containing tetraethylammonium *p*-toluenesulfonate ($Et_4NOTs$) as the supporting electrolyte yields mainly 1,4-addition products[2]. 1,3-Cyclooctadiene yields a considerable amount of the allylically substituted product.

The product, 1,4-diacetoxy-2-allyl-3-methyl-2-cyclopentene, obtained (45% current efficiency) from 2-allyl-3-methyl-1,3-cyclopentadiene through anodic oxidation with carbon rod anode in acetic acid is successfully used as a starting compound in the synthesis of allethrolone as shown in equation 2[3].




(2)

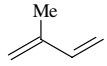
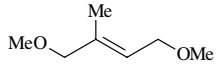
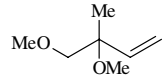
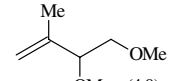
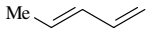
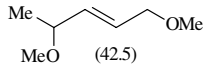
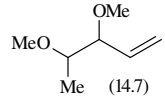
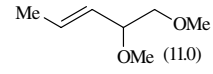
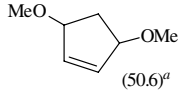
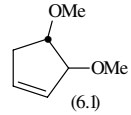
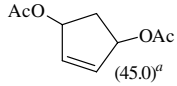
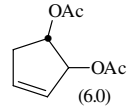
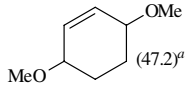
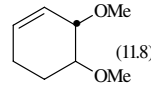
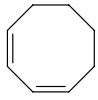
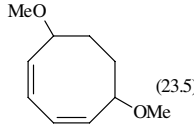
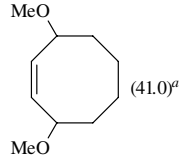
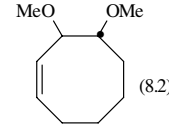
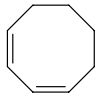
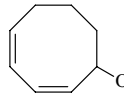
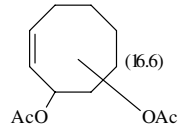
When a palladium(II)–hydroquinone system is used as the mediator[4] in the anodic oxidation of 1,3-cyclohexadiene in acetic acid, either *trans*- or *cis*-1,4-diacetoxy-2-cyclohexene is formed with rather high selectivity, though the possible formation of 1,2-diacetoxylated compound is not discussed.

TABLE 1. Peak oxidation potentials ($E_p$)[a] of dienes[b]

| Diene | $E_p$ | Diene | $E_p$ |
|---|---|---|---|
| Butadiene | 2.0 | 1,3-Cyclooctadiene | 1.55; 1.70 |
| Isoprene | 1.75 | 1,3-Pentadiene | 1.48 |
| Cyclopentadiene | 1.50 | 1,3-Cyclohexadiene | 1.36 |

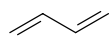
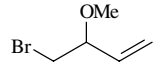
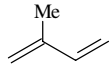
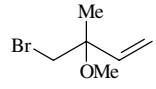
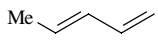
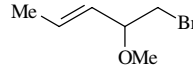
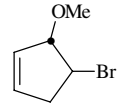
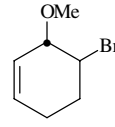
[a] V vs $Ag/Ag^+$.
[b] Glassy carbon; solvent, methanol; supporting electrolyte, 0.5 M $NaClO_4$

TABLE 2. Oxidation of conjugated dienes

| 1,3-Diene | Solvent | Product (current efficiency %) | | |
|---|---|---|---|---|
|  | MeOH |  (18.6) |  (12.5) |  (4.0) |
|  | MeOH |  (42.5) |  (14.7) |  (11.0) |
|  | MeOH |  (50.6)[a] |  (6.1) | |
|  | AcOH |  (45.0)[a] |  (6.0) | |
|  | MeOH |  (47.2)[a] |  (11.8) |  (2.8) |
|  | MeOH |  (23.5) |  (41.0)[a] |  (8.2) |
|  | AcOH |  (53.6) |  (16.6) | |

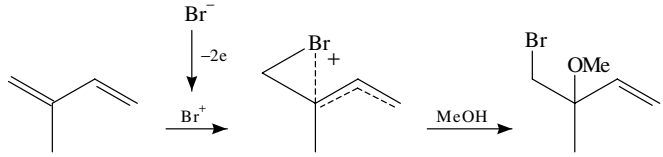
[a] Mixture (1:1) of *cis* and *trans* isomers

TABLE 3. Bromomethoxylation of 1,3-dienes

| 1,3-Diene | Products | Yield (%) |
|---|---|---|
|  |  | 40 |
|  |  | 64 |
|  |  | 66 |
|  |  | 41 |
|  |  | 45 |

In this reaction, the redox couple hydroquinone/benzoquinone promotes the second redox couple Pd(0) $\rightleftharpoons$ Pd(II) and Pd(II) causes the oxidative transformation of the diene to the 1,4-diacetoxylated compound. The most remarkable characteristic of this reaction
is that the oxidation takes place at anode potential lower than 1 V vs SCE. In a typical case, the yield of 1,4-diacetoxy-2-cyclohexene is 61% with a *trans*:*cis* ratio of 86:14. On the other hand, the ratio is 10:90 (34% yield) when the reaction is carried out in the presence of chloride anion[5].

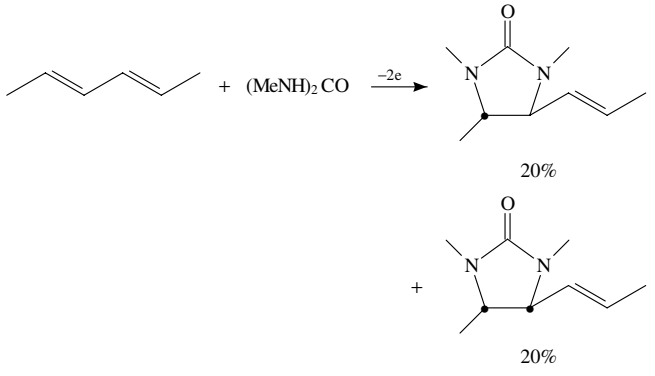
1,2-Addition takes place selectively when the reaction is carried out in methanol by using the redox couple of $Br^-/Br^+$ as the mediator as shown by some typical examples in Table 3[6]. The mechanism of this 1,2-addition may be as shown in equation 3 on the basis that it is regio- and stereoselective and follows the Markovnikov rule.




(3)

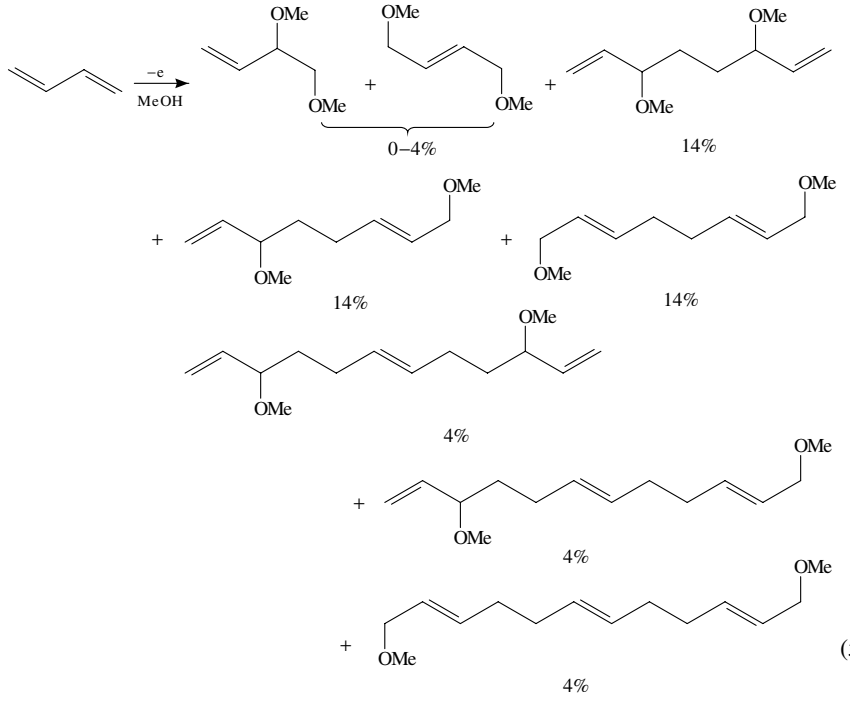
The electrophilic bromonium ion adds to the diene at the position which yields the most stable cationic intermediate and the stereochemical relation of the Br and the MeO group in the product is always *trans* when the diene system is cyclic. The fact that 1,2-addition takes place selectively but 1,4-addition does not occur is explained by the formation of the bridged bromonium ion as the intermediate.

When conjugated dienes are anodically oxidized with a graphite anode in MeCN in the presence of $NaClO_4$ and *N*,*N*′-dimethylurea, a variety of 2-imidazolidinones are formed though the yields are not always high as exemplified in equation 4[7].



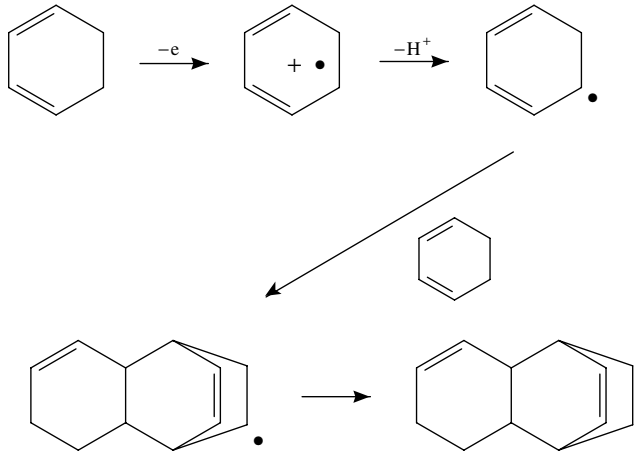

(4)

The products of electrochemical oxidation of conjugated dienes are considerably affected by the reaction conditions such as the material of the electrode, the supporting electrolyte and the solvent. The oxidation of butadiene with a graphite or carbon-cloth anode in 0.5 M methanolic solution of $NaClO_4$ mainly yields dimerized products along with small amounts of monomeric and trimeric compounds (equation 5)[1]. The use of platinum or glassy carbon mainly gives monomeric products. Other dienes such as isoprene, 1,3-cyclohexadiene, 2,4-hexadiene, 1,3-pentadiene and 2,3-dimethyl-1,3-butadiene yield complex mixtures of isomers of monomeric, dimeric and trimeric compounds, in which the dimeric products are the main products.



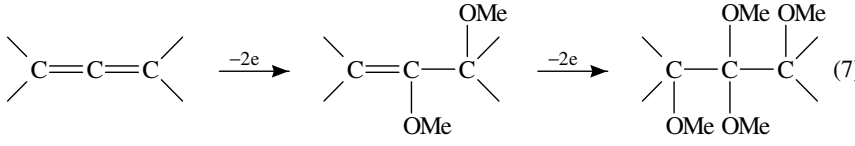

(5)

As mentioned above, the electrochemical oxidation of a diene yields 1,2- and 1,4-addition products when the reaction is carried out in the presence of a nucleophile such as methanol or acetic acid. When the oxidation is carried out in the absence of the nucleophile it usually yields a polymeric compound as the major product. The formation of a small amount of the Diels-Alder adduct is, however, observed when the reaction is carried out in $CH_2Cl_2$ with graphite anode. One of the proposed reaction pathways is shown in equation 6[8], though it is not clear whether the cyclohexadienyl radical serves as a diene (as shown in equation 6) or a dienophile in the Diels-Alder reaction.




(6)

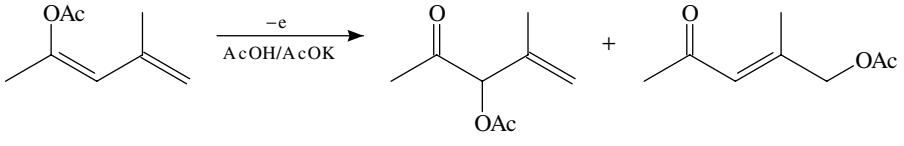
The anodic oxidation of 1,2-dienes in methanol takes place stepwise at each double bond yielding a tetramethoxylated compound as one of the products (equation 7)[9]. This result is reasonable since a 1,2-diene is not a conjugated diene.



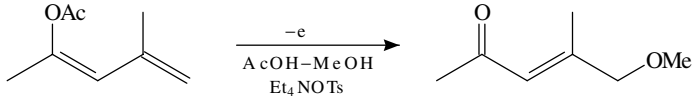

(7)

The electrochemical oxidation of monoolefins bearing electron-donating substituents such as alkoxy, acyloxy or dialkylamino group takes place more easily than that of simple monoolefins, and products formed by the addition of a nucleophile to the double bond are obtained with satisfactory yields[4].

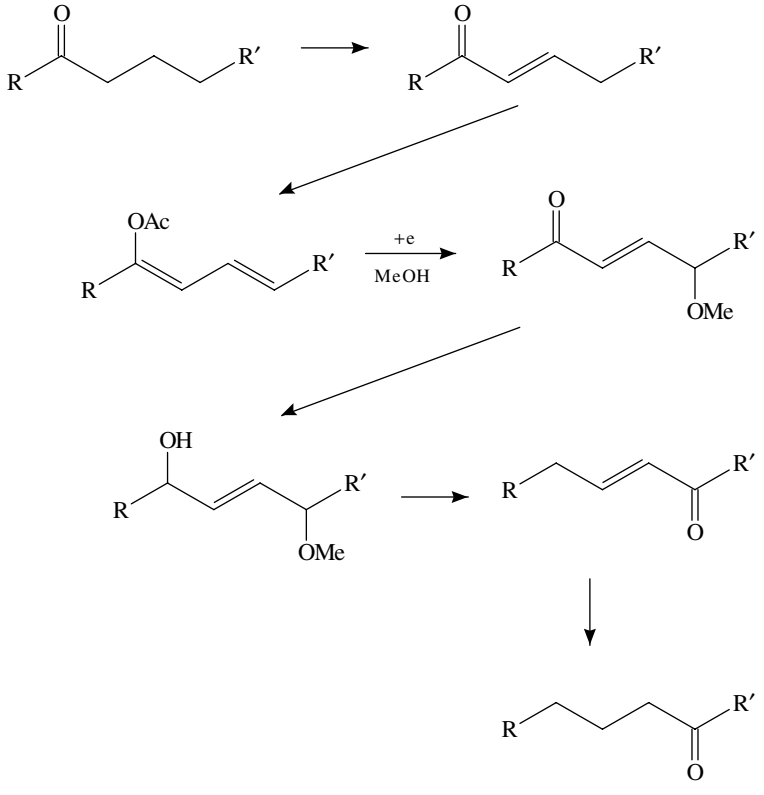
In the case of the anodic acetoxylation of a 1-acetoxy-1,3-diene, however, the addition of the acetoxyl group to the diene is usually not regioselective, and a mixture of the two positional isomers is yielded (equation 8). On the other hand, the anodic methoxylation of the same diene gives a 4-methoxy-enone with high regioselectivity when the reaction is carried out in methanol containing 10% acetic acid (equation 9)[10]. Some typical results are summarized in Table 4. This anodic and regioselective methoxylation is an effective key reaction for the transposition of a carbonyl group from the original position to the $\gamma$-position (1,4-transposition) as shown schematically in equation 10.




(8)




(9)

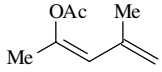
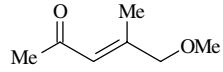
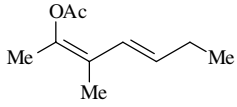
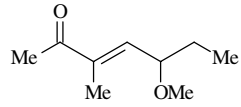
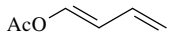
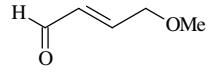
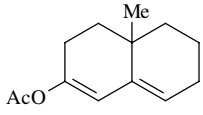
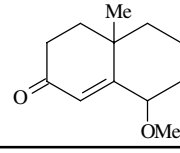



(10)

## B. Nonconjugated Dienes

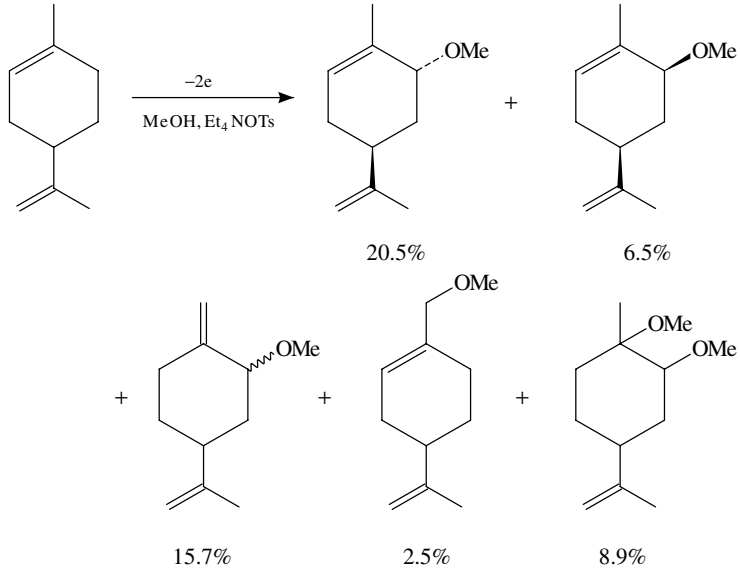
Compared with conjugated dienes, the electrochemistry of nonconjugated dienes is classified into two types, A and B[11,12]. In type A, the double bond of the diene behaves essentially the same as the double bond of a monoolefin in the anodic oxidation. A typical

TABLE 4. Anodic oxidation of enol acetates

| Dienol acetate | γ-Methoxy Carbonyl Product | Yield (%)[a, b] |
|---|---|---|
|  |  | 81 |
|  |  | 74 |
|  |  | 76 |
|  |  | 66 |

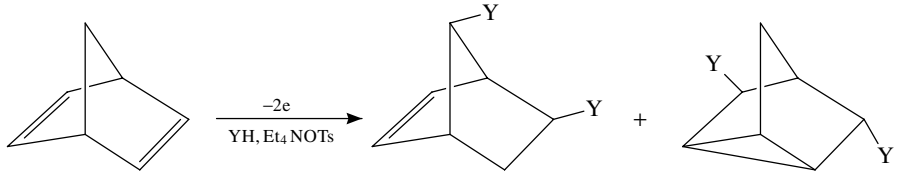
[a] Isolated yields.
[b] The yields were obtained at the stage when 2 F/mol of electricity was passed.

example is the oxidation of limonene in methanol (equation 11) in which the reaction which actually takes place is the oxidation of the double bond located in the cyclohexene ring, followed by allylic substitution and ring contraction, whereas the isopropenyl group is retained intact. These patterns of reaction are similar to those observed in the anodic oxidation of monoolefins.



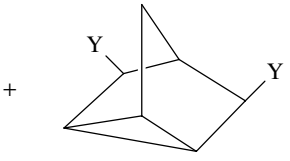

(11)

On the other hand, the electrooxidation of norbornadiene or bicyclo[2.2.2]octa-2,5-diene shows a different electrochemistry (type B) and yields a mixture of some unique products as shown in equations 12 and 13.

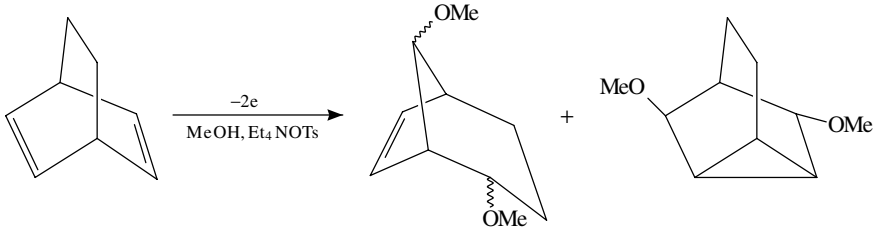



Y = OAc 6.2% 14.1%
Y = OMe 8.8% 16.5%

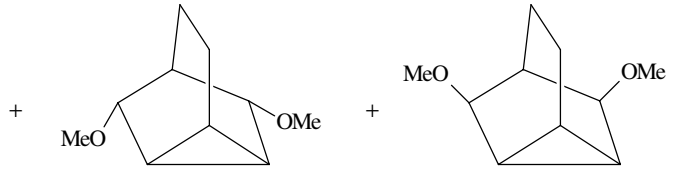
(12)




15.4%
18.4%

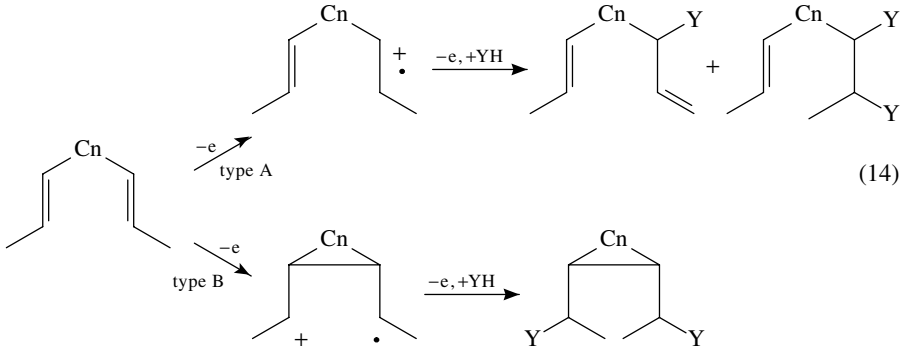



23.8% 22.5% (13)




9.1% 5.3%

These results clearly show that in type B reactions the electrooxidation pattern is remarkably different from that of the corresponding monoolefin. The types A and B are summarized schematically in equation 14.




(14)

In type A reactions one electron is removed from one of the two double bonds to form a cation radical, and allylic substitution and oxidative addition take place as the following reactions. On the other hand, in type B reactions the initial electron transfer from the double bond is accompanied by a transannular reaction between the two double bonds.

The difference between dienes reacting according to type A and those according to type B is clearly reflected in their oxidation potentials (Table 5).

Thus, the oxidation potential of the former type of diene (limonene) is substantially the same as that of the corresponding monoolefin (1-Me-cyclohexene), whereas norbornadiene and bicyclo[2.2.2]octadiene show much lower oxidation potentials than those of norbornene and cyclohexene.

This result suggests that in the anodic oxidation of type B, the cation radical formed from one of the two double bonds is stabilized through transannular interaction with another double bond.

As shown in Table 6 and Figure 1, the oxidation potentials of 2-substituted norbornadienes (1), 2-substituted bicyclo[2.2.2]octa-2,5-dienes (2) and 4-substituted [2.2]paracyclophanes (3) clearly indicate that the transannular interaction between two double bonds contributes already at the stage of the first electron transfer. Namely, in compounds 1−3, the electron is transferred from the unsaturated bond which is not substituted by the electron-withdrawing group, Figure 1 shows the

TABLE 5. Oxidation potentials of dienes and the corresponding monoolefins (V vs SCE)[a]

| | | | | | |
|---|---|---|---|---|---|
| Norbornene | 2.02 | Cyclohexene | 2.14 | 1-Me-Cyclohexene | 1.70 |
| Norbornadiene | 1.54 | Bicyclo[2.2.2]octadiene | 1.82 | Limonene | 1.67 |

[a]Solvent: MeCN; supporting electrolyte, 0.1 M $LiClO_4$.

TABLE 6. Oxidation potentials of **1**, **2** and **3**

| Substituent X | Oxidation potential (V vs. SCE) | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| H | 1.54 | 1.82 | 1.47 |
| $CO_2Me$ | | | 1.61 |
| $CO_2Et$ | 1.85 | 2.11 | |
| COMe | 1.85 | 2.07 | 1.57 |
| CN | 1.99 | 2.22 | 1.65 |
| $NO_2$ | | | 1.72 |

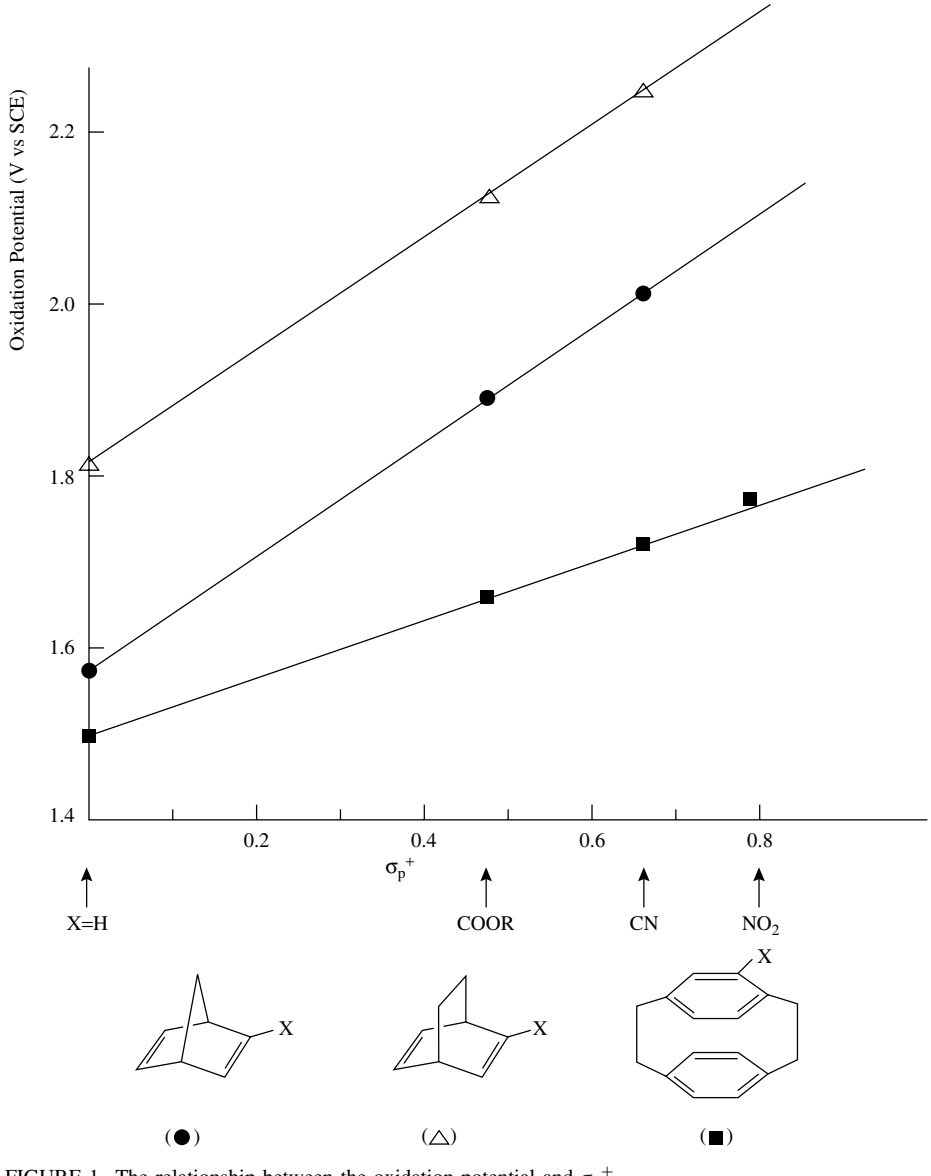



FIGURE 1. The relationship between the oxidation potential and $\sigma_p^+$

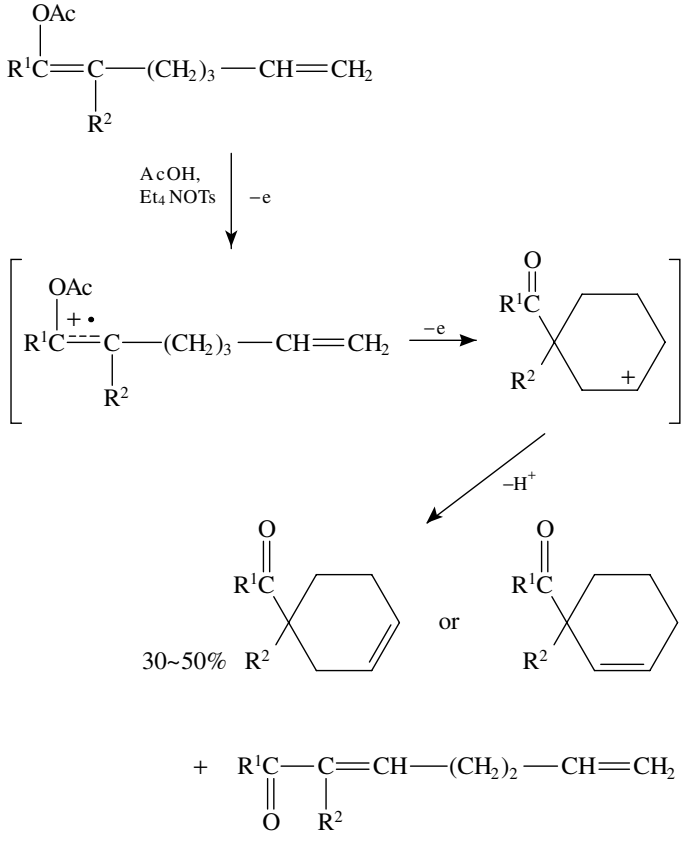
linear free energy correlations between the oxidation potentials which are required to remove an electron from the double bond not bearing the substituents and the $\sigma_p^+$ parameter.

This result indicates that the substituent located on one bond affects electronically the process of electron removal from the other double bond which is not bearing the substituent.

If the substituents are, however, electron-donating, the first electron transfer must take place at the double bond bearing the substituents. Hence, it is impossible to observe the transannular effect in this case.

Although it is unclear what type of $\sigma$ value is the most suitable to use with a cation radical system, it is reasonable that the best linear relationship is given with $\sigma^+$, although for the substituents investigated $\sigma_p^+ \approx \sigma_p$.

Despite the fact that the electrochemical oxidation of most of the nonconjugated dienes generally does not give products which result from interaction of the double bonds with one another, the anodic oxidation 1-acetoxy-1,6-heptadienes gives intramolecularly cyclized products, that is, the cyclohexenyl ketones (equation 15)[13]. The cyclization takes place through the electrophilic attack of the cation generated from enol ester moiety to the double bond.




(15)

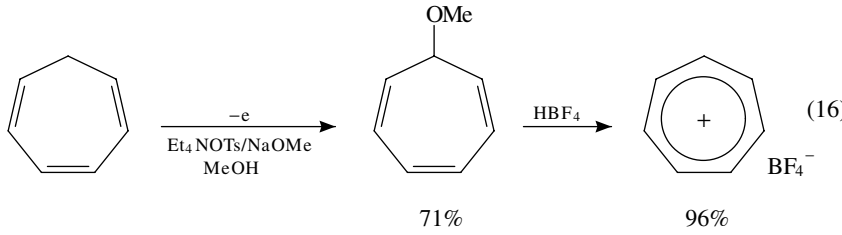
$R^1$=Me, $R^2$=Me, Et

## C. Trienes

The anodic oxidation of acyclic polyenes is practically useless, since the control of the reaction site is usually difficult and hence the product is often a mixture of isomers which are not always easily isolable.

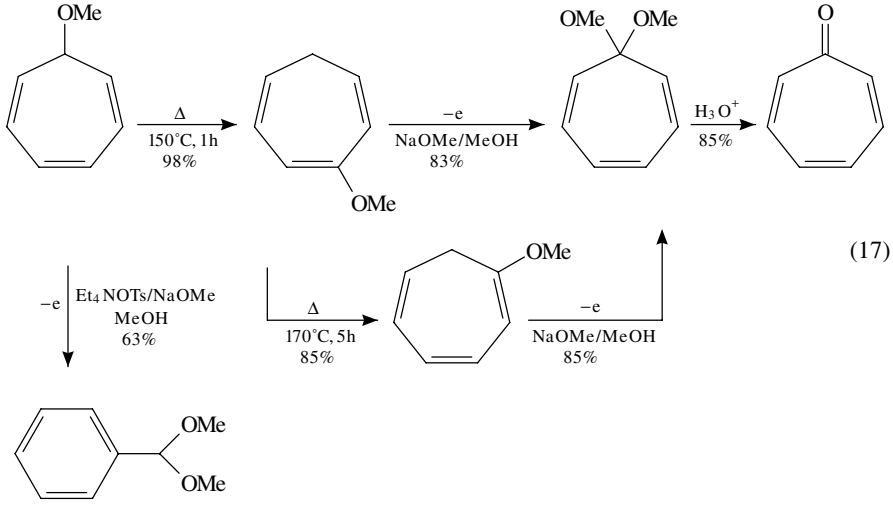
On the other hand, the anodic oxidation of 1,3,5-cycloheptatrienes is one of the most powerful key tools for the preparation of a variety of non-benzenoid aromatic compounds such as tropylium salts, tropones, tropolones, 2*H*-cyclohepta[*b*]furan-2-ones and azulenes[14].

The anodic oxidation of 1,3,5-cycloheptatriene in MeOH, however, gives the product 7-methoxy-1,3,5-cycloheptatriene (7-MeO-CHT) in a rather low yield when the reaction is carried out by using $Et_4NOTs$, NaOMe, $Bu_4NBF_4$ or $H_2SO_4$ as the supporting electrolyte. On the other hand, the use of a mixture of $Et_4NOTs$ and NaOMe as the supporting electrolyte dramatically increases the yield (equation 16).



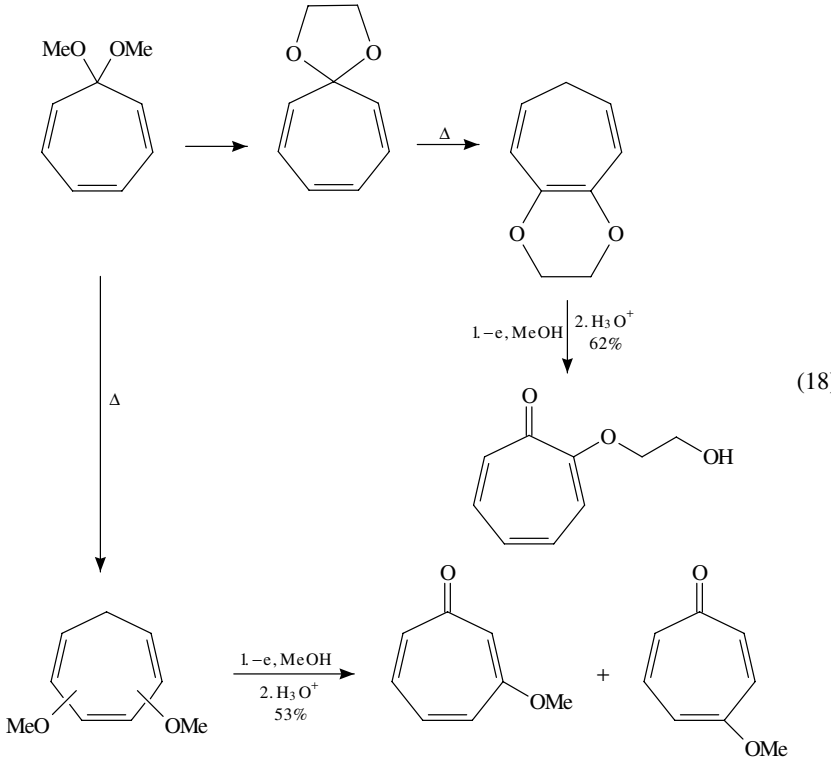
(16)

The anodic oxidation of 7-MeO-CHT in MeOH results in the formation of benzaldehyde dimethyl acetal through a ring contracting rearrangement, whereas 3-MeO-CHT and 1-MeO-CHT are prepared by thermal rearrangement of 7-MeO-CHT and afford 7,7-diMeO-CHT in 83% and 85% yields, respectively, upon the anodic oxidation. The hydrolysis of 7,7-diMeO-CHT in 5% aqueous $H_2SO_4$ gives tropone in 85% yield (equation 17).



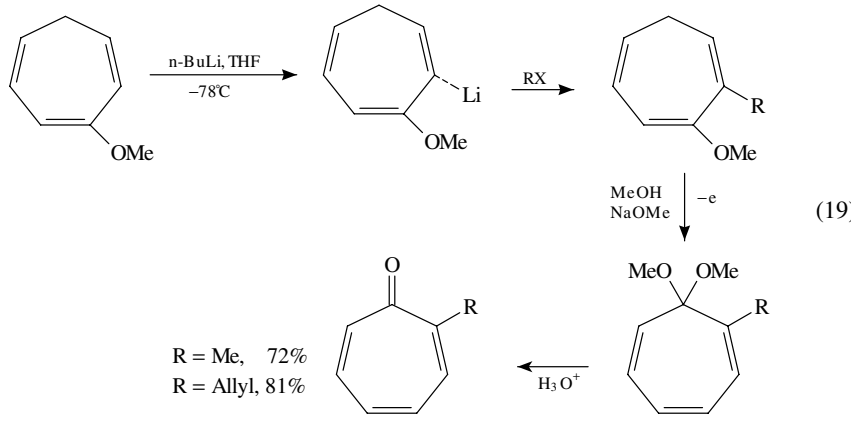
(17)

The transformation of 7,7-diMeO-CHT to $\alpha$-, $\beta$- and $\gamma$-tropolones is also achievable by using anodic oxidation in the key step (equation 18), namely the electrochemical oxidation of an isomeric mixture of diMeO-CHTs prepared by the thermal rearrangement of 7,7-diMeO-CHT yields a mixture of methyl ethers of $\beta$- and $\gamma$-tropolones. On the other hand, the thermal rearrangement of the ethylene acetal of tropone gives 3,4-dioxyethylene-CHT as a single product due to the difficulty of formation of other isomers, and it yields the ether of $\alpha$-tropolone upon anodic oxidation.

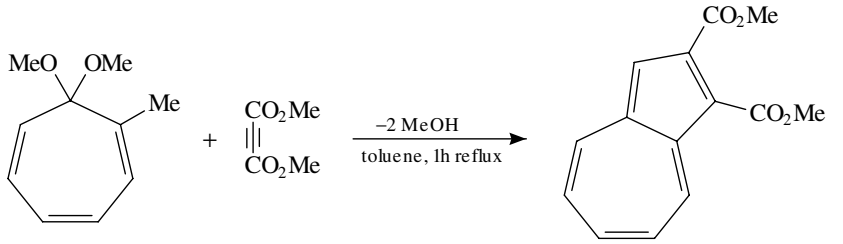



(18)

The anodic oxidation of 2-alkyl-3-MeO-CHT followed by hydrolysis of the intermediate 1-alkyl-7,7-diMeO-CHT gives 2-alkyltropones in high yields (equation 19). The precursor 2-alkyl-3-MeO-CHT is synthesized by the alkylation of 2-lithio-3-MeO-CHT prepared by the regioselective lithiation of 3-MeO-CHT with BuLi. The intermediate 1-alkyl-7,7-diMeO-CHT is highly useful for the synthesis of the azulene skeleton through its reaction with dimethyl acetylenedicarboxylate (equation 20).




(19)

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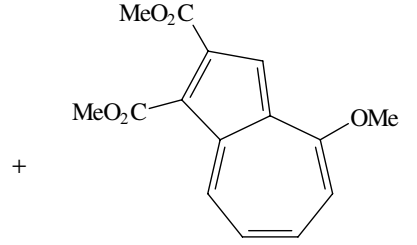
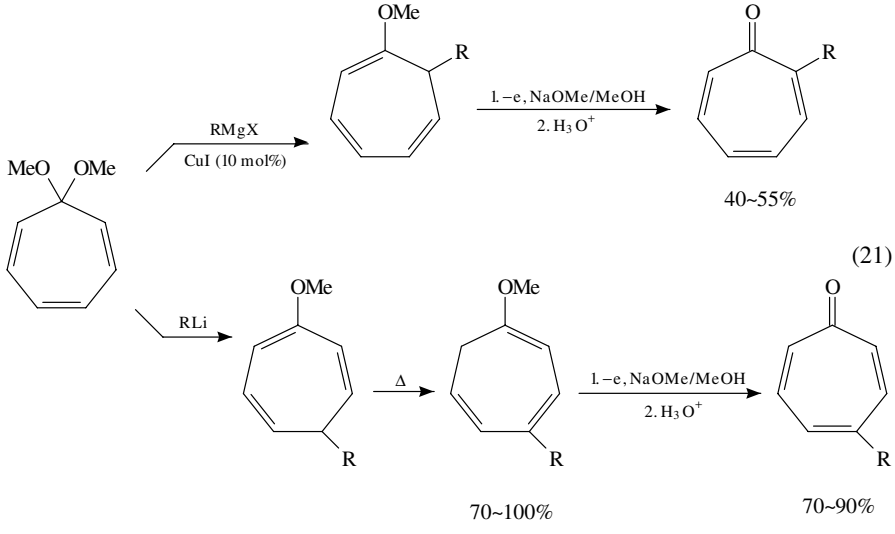



The electrochemical oxidation of 1-MeO-7-alkyl-CHT in MeOH yields 2-alkyltropones, while the thermal rearrangement of 3-MeO-7-alkyl-CHT to 1-MeO-4-alkyl-CHT followed by its anodic oxidation in MeOH affords 4-alkyltropones (equation 21). 1-MeO-7-alkyl-CHT is prepared by the regioselective alkylation of 7,7-diMeO-CHT with a Grignard reagent and CuI, while 3-MeO-7-alkyl-CHT is also regioselectively prepared by alkylation of 7,7-diMeO-CHT with an alkyl lithium.




(21)

## III. CATHODIC REDUCTION

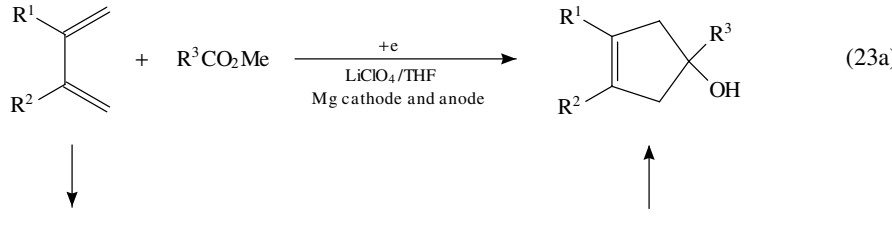
### A. Dienes

Compared with the anodic oxidation of a 1,3-diene, the cathodic reduction of a 1,3-diene may be less interesting since the resulting simple transformation to monoolefin and alkane is more conveniently achieved by a chemical method than by the electrochemical method. So far, only few reactions which are synthetically interesting have been studied[15]. The typical pattern of the reaction is the formation of an anion radical from 1,3-diene followed by its reaction with two molecules of electrophile as exemplified by the formation of the dicarboxylic acid from butadiene (equation 22)[16].

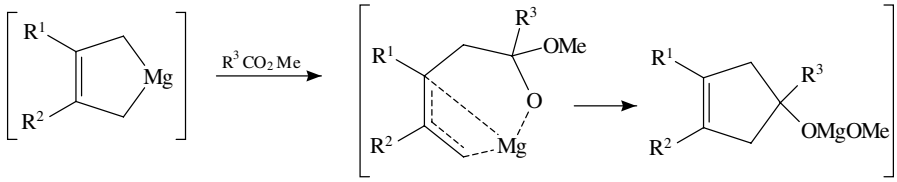
$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[CO_2]{+e} \xrightarrow{H^+} HO_2C{-}CH_2{-}CH{=}CH{-}CH_2CO_2H \quad (22)$$

50%

On the other hand, it has been found that the electrochemical reduction is a very unique and useful tool in synthetic organic chemistry when magnesium is used as the material of the electrode. The cathodic reduction of 1,3-dienes with magnesium electrode gives very unique products, i.e. 3-cyclopentenol derivatives when it is carried out in the presence of a carboxylic acid ester (equation 23)[17].




(23a)




(23b)

This novel electroreductive cyclocoupling corresponds to a 1,4-addition of a one-carbon unit to the 1,3-diene, and does not take place without using magnesium electrode. The first step in this coupling reaction is the cathodic reduction of 1,3-diene to an anion radical, and the second step is the formation of a Mg-diene complex, which thereafter reacts with the ester to yield the coupling product as shown in equation 23b.

The intermediary formation of the Mg-diene complex is confirmed by a two-step reaction method, namely in the first step a solution of 1,3-diene is electrochemically reduced with magnesium electrode in the absence of the ester. After a sufficient amount of electricity is passed, the current is terminated and the ester is added to the solution. The fact that the coupling product is also formed by this two-step method strongly supports the formation of the intermediate Mg-diene complex.

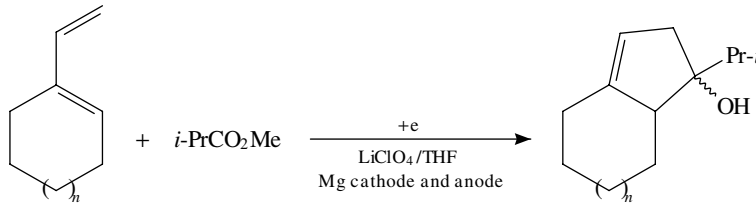
Some of the typical results are shown in Table 7. The aromatic ester does not give the cyclized product but other products were not identified.

This cyclocoupling reaction is not limited to acyclic dienes. Both 1-vinylcyclohexene and 1-vinylcycloheptene give the cyclized products in good yields (equation 24).

TABLE 7. Cathodic coupling of 1,3-dienes with esters

| Diene | | Ester | Product |
|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | Yield (%)[a] |
| Me | H | *n*-Bu | 76 |
| Me | H | *i*-Pr | 71 |
| Me | H | $PhCH_2CH_2$ | 56 |
| $(CH_3)_2C{=}CHCH_2CH_2$ | H | Et | 63 |
| Me | Me | *i*-Pr | 88 |
| Me | H | Ph | 0 |

[a]Isolated yields.

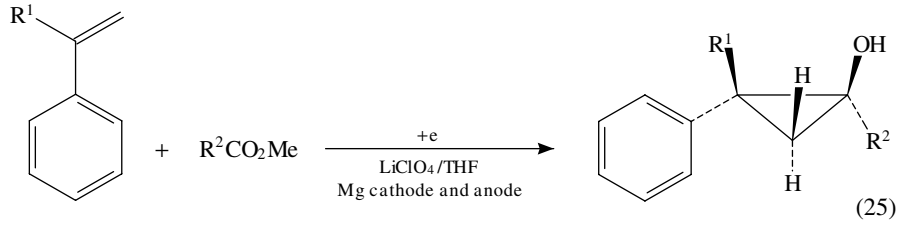



(24)

($n = 1$)
($n = 2$)

($n = 1$) 62%
($n = 2$) 72%

Although styrene is not a 1,3-diene, the cathodic reduction of a solution containing styrene and an ester with magnesium electrode interestingly affords a single stereoisomer of 2-phenylcyclopropanol derivative in which the phenyl and the alkyl ($R^2$) groups are stereoselectively located in a *cis* relationship on the cyclopropane ring (equation 25).




(25)

$R^1 = H$
$R^1 = Me$

Yield (%)

| | | |
|---|---|---|
| $R^1 = H$, $R^2 = Me$ | 71 | |
| $R^1 = H$, $R^2 = Et$ | 67 | *cis* |
| $R^1 = H$, $R^2 = i$-Pr | 55 | |
| $R^1 = R^2 = Me$ | 94 | |

Although a 1,2-diene is not a conjugated diene, it is also electrochemically reducible with platinized platinum electrode in acidic solution to the monoolefin and a saturated alkane[18].

In contrast with oxidation, clear reduction wave is not observed in the electrochemical reduction of cyclopentadiene[19].

### B. Trienes and Polyenes

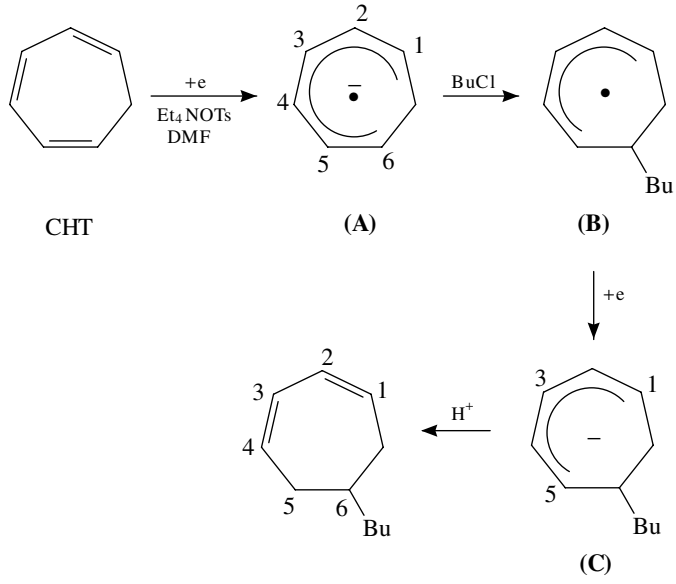
The electrochemical reduction of cycloheptatriene (CHT) in liquid ammonia takes place at about −2.5 V vs SCE and forms the radical anion of CHT. The radical anion is stable in ammonia on the voltammetric time scale but decays slowly by disproportionation and coupling reaction pathways to give respectively 1,3- and 1,4-cycloheptadienes (total yield 34–39%) and $C_{14}H_{18}$ (in yields of 55–58%) isomers which incorporate the bitropyl carbon skeleta[20].

The anionic intermediates generated by the cathodic reduction of CHT and some of its derivatives such as 1-MeO- and 3-MeO-CHTs are regioselectively alkylated with alkyl halides to give 6-alkyl-1,3-cycloheptadiene and 1-MeO-6-alkyl-1,3-cycloheptadiene as the main products, respectively[21].

The electroreduction of CHT in DMF in the presence of *n*-butyl chloride gives, for example, 6-butyl-1,3-cycloheptadiene as the main product (equation 26). This selectivity in alkylation is interesting, since it is also known that the reductive butylation of CHT using $Li/NH_3$ as the reducing agent gives a mixture of 5-butyl-1,3-cycloheptadiene and 3-butyl-1,4-cycloheptadiene in which the latter is the main product[22,23].

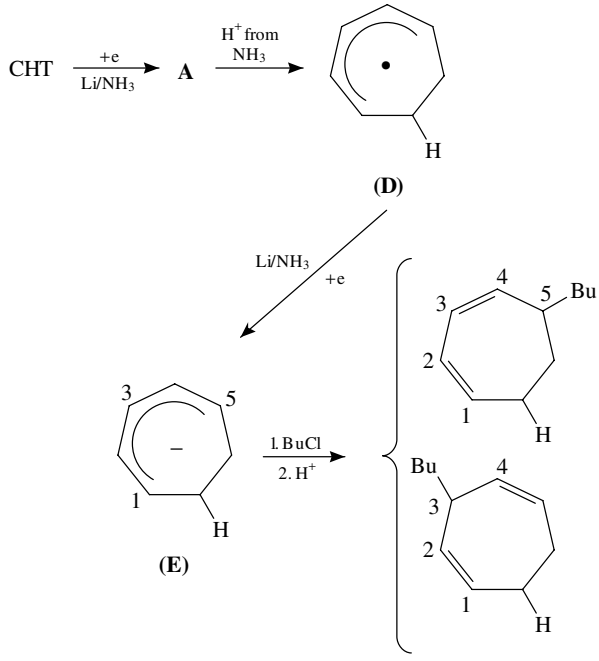
This difference of regioselectivity in alkylation of CHT is explained by the difference of the electrophile which reacts with the first active intermediate formed from CHT. Thus, the first active intermediate formed by one-electron transfer to CHT is an anion radical species **(A)** in both the electrochemical and the Li-metal reduction.

Since the electroreduction is carried out in the presence of BuCl in aprotic solvent (DMF), **A** reacts with BuCl before it is protonated by the solvent to give a radical species **(B)** as the second intermediate. It is reasonable that **A** reacts with BuCl at its 1- and 6-positions since the negative charge density is the highest at these two positions. In the third intermediate **C**, formed by one-electron reduction of **B**, the negative charge is mainly located at the 1-, 3- and 5-positions. The counter cation of the anion **C** is, however, the bulky $Et_4N^+$. Hence, anion **C** is most reactive at its 5-position and gives the 6-butyl derivative upon protonation at the 5-position[21] (equation 26).



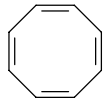
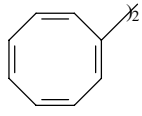
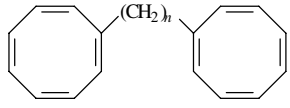

(26)

On the other hand, in the reduction of CHT with $Li/NH_3$, butyl chloride is absent when **A** is formed and hence **A** is protonated by $NH_3$ at its 1- and 6-positions to yield a radical intermediate **D**. In the anionic intermediate **(E)**, formed by one-electron reduction of **D**, the negative charge is mostly located at the 1-, 3- and 5-positions. Hence, the butylation takes place at these positions to give 5-butyl-1,3-cycloheptadiene and 3-butyl-1,4-cycloheptadiene as the final products (equation 27).




(27)

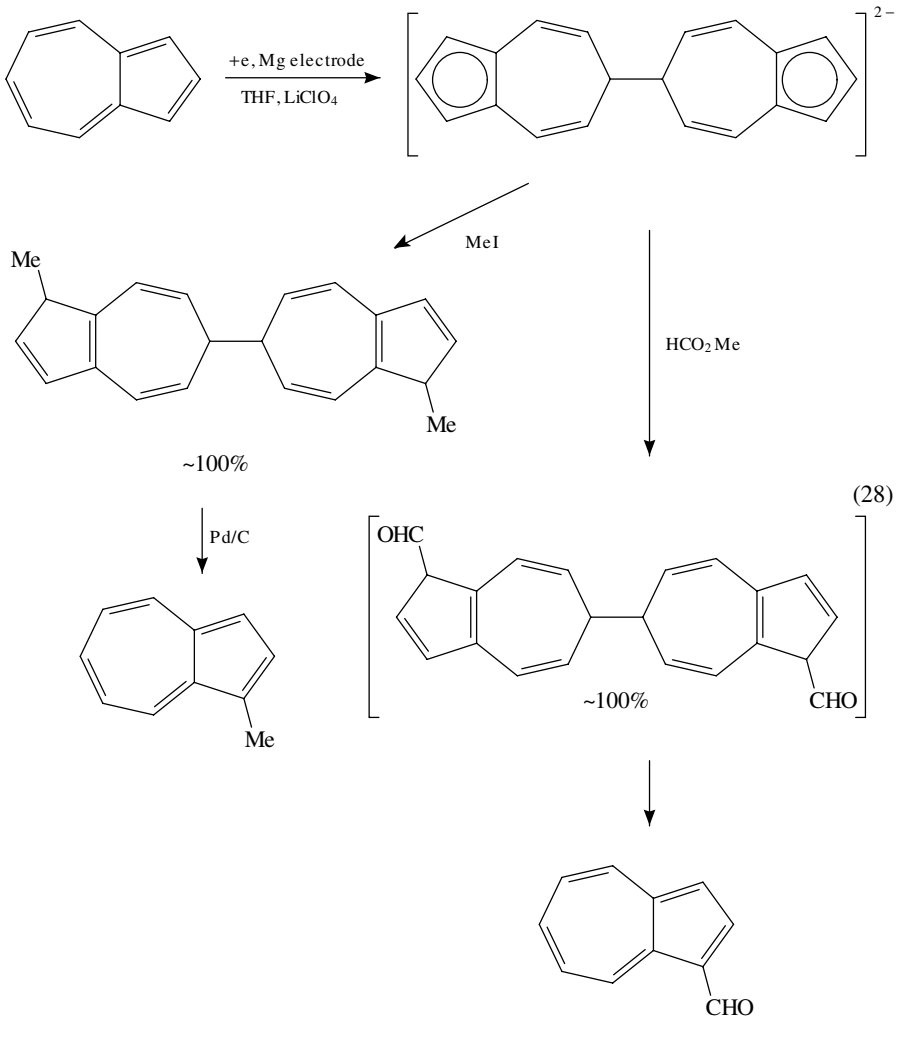
TABLE 8. Reduction peak potentials for some derivatives of cyclooctatetraene

| | | Ep (V vs SCE) |
|---|---|---|
|  | | −1.62 |
|  | | −1.66 |
|  | $n=1$ | −1.62 |
| | $n=2$ | −1.66 |
| | $n=3$ | −1.68 |

This electroreductive alkylation is successfully applied to the synthesis of $\beta$-thujaplicin.

Cyclooctatetraene and some of its derivatives are electrochemically reducible in dry degassed DMF containing $Bu_4NClO_4$ as the supporting electrolyte. The first reduction peak potentials which are required to form the corresponding anion radical are shown in Table 8[24], though a further reaction of the intermediates is not known.

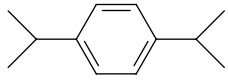
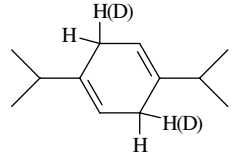
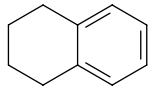
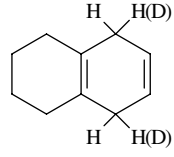
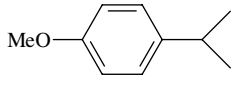
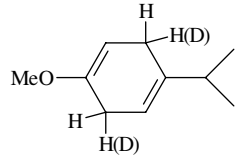
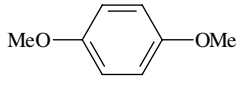
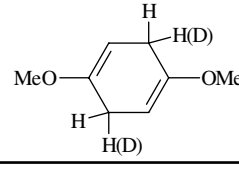
The electrochemical reduction of azulene with carbon, platinum, lead or zinc cathode does not give any product, whereas that with magnesium electrode yields a dimeric compound as the only reduction product, though the dimeric compound is easily transformed to the corresponding monomeric compound by a mild oxidation as shown in equation 28[25].




(28)

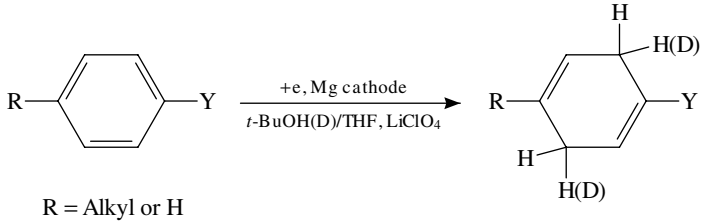
Although benzene is not a triene and its electrochemical reduction is not always practically facile, the benzenoid ring has been found to be easily reduced by the electrochemical method when magnesium is used as cathode[26] (equation 29). As some of the typical

TABLE 9. Electroreductive synthesis of dienes from benzenoid compounds

| Benzenoid compound | Diene | Yield (%)[a] |
|---|---|---|
|  |  | 83 (80) |
|  |  | 94 (70) |
|  |  | 91(79) |
|  |  | 80 (67) |

[a] Yields shown in parentheses are those for deuteriated products.

results summarized in Table 9 show, this electrochemical method is practically useful for the synthesis of dienes and especially of deuteriated dienes.




(29)

R = Alkyl or H
Y = Alkyl or MeO

## IV. REFERENCES

1. H. Baltes, E. Steckhan and H. J. Schäfer, *Chem. Ber.* **111**, 1294 (1978).
2. T. Shono and A. Ikeda, *Chem. Lett.*, 311 (1976).
3. T. Shono, I. Nishiguchi and M. Ohkawa, *Chem. Lett.*, 573 (1976).
4. T. Shono, *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer-Verlag, Heidelberg, 1984.

5. J-E. Bäckvall and A. Gogoll, *J. Chem. Soc., Chem. Commun.*, 1236 (1987).
6. T. Shono, K. Tsubata and Y. Nakamura, *Nippon Kagaku Kaishi*, 1794 (1984); *Chem. Abstr.*, **102**, 112834 (1985).
7. H. Baltes, L. Stork and H. J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, **16**, 413 (1977).
8. S. E. Nigenda, D. M. Schleich, S. C. Narang and T. Keumi, *J. Electrochem. Soc.*, **134**, 2465 (1987).
9. B. Zinger and J. Y. Becker, *Electrochim. Acta*, **25**, 791 (1980).
10. T. Shono and S. Kashimura, *J. Org. Chem*., **48**, 1939 (1983).
11. T. Shono, A. Ikeda, J. Hayashi and S. Hakozaki, *J. Am. Chem. Soc.*, **97**, 4261 (1975).
12. T. Shono, A. Ikeda and S. Hakozaki, *Tetrahedron Lett.*, 4511 (1972).
13. T. Shono, I. Nishiguchi, S. Kashimura and M. Okawa, *Bull. Chem. Soc. Jpn.*, **51**, 2181 (1978).
14. T. Shono, T. Nozoe, H. Maekawa, Y. Yamaguchi, S. Kanetaka, H. Masuda, T. Okada and S. Kashimura, *Tetrahedron*, **47**, 593 (1991).
15. A. J. Fry, *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, New York, 1989.
16. J. W. Loveland, U. S. Patent No. 3032489; *Chem. Abstr.*, **57**, 4470 (1962).
17. T. Shono, M. Ishifune, H. Kinugasa and S. Kashimura, *J. Org. Chem.*, **57**, 5561 (1992).
18. H. Nakajima and H. Kita, *J. Chem. Soc., Faraday Trans. 1*, **79**, 1027 (1983).
19. R. D. Moulton, R. Farid and A. J. Bard, *J. Electroanal. Chem.*, **256**, 309 (1988).
20. M. A. Fox, K. -ud-Din, D. Bixler and W. S. Allen, *J. Org. Chem.*, **44**, 3208 (1979).
21. T. Shono, T. Nozoe, Y. Yamaguchi, M. Ishifune, M. Sakaguchi, H. Masuda and S. Kashimura, *Tetrahedron Lett.*, **32**, 1051 (1991).
22. H. Dirkzwager, Th. J. Nieuwstad, A. M. Van Wijk and H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **92**, 35 (1973).
23. K. Hafner and W. Rellensmann, *Chem. Ber.*, **95**, 2567 (1962).
24. M. A. Fox, K. A. Colapret, J. R. Hurst, R. L. Soulen, R. Maldonado and L. Echegoyen, *J. Org. Chem.*, **57**, 3728 (1992).
25. T. Shono, M. Ishifune and S. Kashimura, 67th Annual Meeting of The Chemical Society of Japan, Tokyo, March 1994 Abstract, 1994, p. 1334.
26. T. Shono, and S. Kashimura, 65th Annual Meeting of The Chemical Society of Japan. Tokyo, March 1993, Abstract, 1993, p. 70.

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CHAPTER **18**

# Syntheses and uses of isotopically labelled dienes and polyenes

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## I. INTRODUCTION

Sections I–V of this chapter deal with the syntheses of unsaturated organic compounds playing an essential role in biochemical processes of life. Numerous polyunsaturated compounds have been synthesized in order to elucidate their physiological role, for instance in brain. However, the main impact on permanent searches for new improved methods of synthesis of isotopically labelled dienes and polyenes comes from nuclear medicine and nuclear pharmacy. The deuterium and carbon-13 labelled polyunsaturated compounds are needed as internal standards in mass spectral determinations of very low concentrations of biologically active substances in biological fluids.

The mechanism of protective action of some unsaturated compounds against cancer and the mechanism of reactions of compounds possessing cytoprotective activity, of compounds needed for treatment of cardiovascular diseases, of gastrointestinal ulcers in man, of neonatal hyperbilirubinemia, or of breast carcinoma, unsaturated inducers of colon cancer, receptor interactions in biological membranes, etc, are the frequent topics addressed by the isotopic chemical synthetic papers reviewed in Sections II–V of this chapter. Sections III and IV deal with isotopically labelled prostaglandins which are the object of synthetic studies and with the impressive progress which has been made in the synthesis of $^{11}$C-labelled compounds of very high specific activity, applied in non-invasive PET methods in diagnosis and treatment.

A large number of papers are published annually on isotopic studies of the mechanisms of chemical reactions of unsaturated compounds. In spite of the large efforts of theoretical chemists and isotope physical chemists the mechanism of two important classes of organic reactions, namely Diels-Alder addition reactions and thermal aliphatic Claisen rearrangements, opening the route to the synthesis of unsaturated carbonyl compounds, has not been clarified satisfactorily. Experimental studies of the elementary acts in these organic reactions by the methodology of carbon and hydrogen isotope effects are difficult, time consuming and expensive and the examples presented in Section VI of kinetic isotope effect (KIE) investigations are very fragmentary. In many cases one can consider them rather as a more or less important introduction, but not a complete solution of the problem. They inform the reader about the contemporary state of fundamental studies in this field.

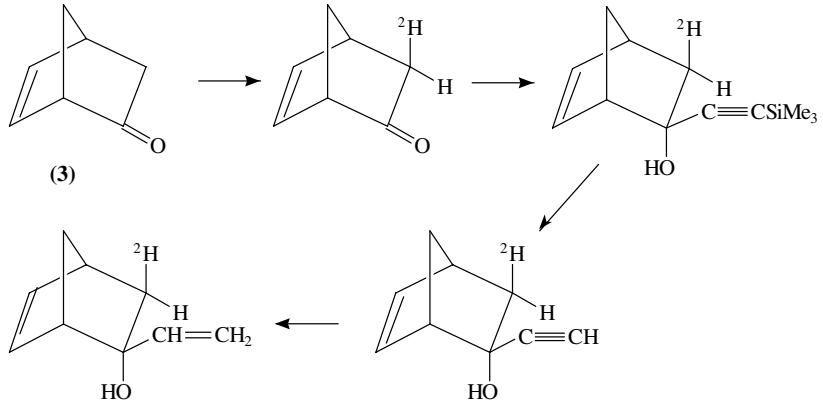
## II. SYNTHESIS OF DIENES AND POLYENES LABELLED WITH STABLE ISOTOPES

### A. Synthesis of Deuterium-labelled Compounds

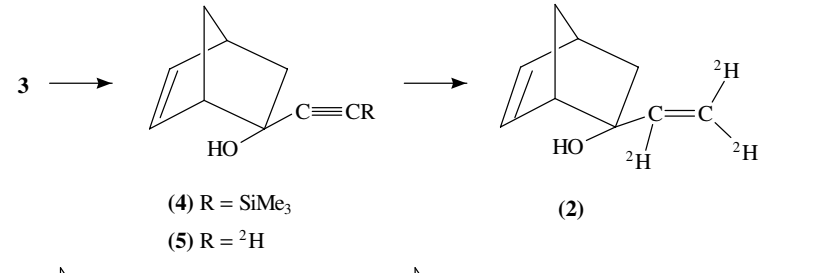
#### *1. Synthesis of the deuterium-labelled 2-exo-vinylbicyclo[2.2.1]hept-5-en-2-ols*

The title compound has been deuterium labelled[1] with $^2$H at $C_{(3)}$ **(1)**, and in the vinyl group **(2)** by deuterium exchange of the enolizable hydrogen atoms in **3** followed by

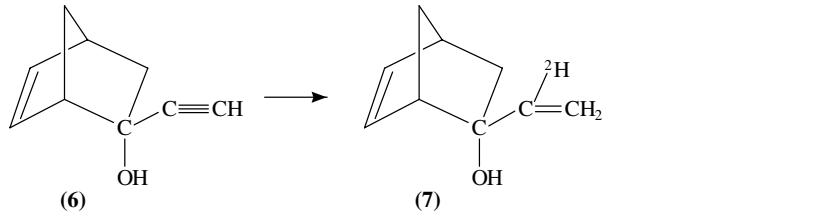
the reaction sequence shown in equation 1, and by desilylation of the intermediate **4** with $NaO^2H$ in $MeO^2H$ followed by reduction of the labelled alcohol **5** with lithium aluminium deuteride in THF, respectively (equation 2). The reduction of **6** with $LiAl^2H_4$, followed by quenching with a protic solvent, gave mainly (in 89% yield) the labelled alcohol **7** (equation 3). These deuteriated compounds were needed for elucidating the mechanism of the mass spectral fragmentation of the 2-hydroxy-1,3-butadiene formed upon electron-impact ionization.




(1)




(2)

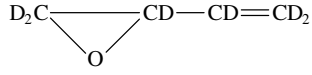



(3)

## *2. Synthesis of [$D_6$]-butadiene monoepoxide*

[$D_6$]-butadiene monoepoxide, **8**, has been synthesized[2] by treating the water solution (pH 5.5) of magnesium monoperoxyphthalate hexahydrate at room temperature with [$D_6$]-1,3-butadiene at 1 atmosphere in 94% yield after 50 min reaction time. Under these conditions less than 1% of butadiene diepoxide has been formed as determined by GC/MS. The concentration of the [$D_6$]-butadiene monoepoxide in the aqueous reaction mixture at various reaction times has been determined by selective ion monitoring of ions with $m/z$

of 42, 48 and 74 for [$D_6$]-butadiene monooxide and of ions with $m/z$ of 30, 58 and 90 for [$D_6$]-butadiene diepoxide, respectively.

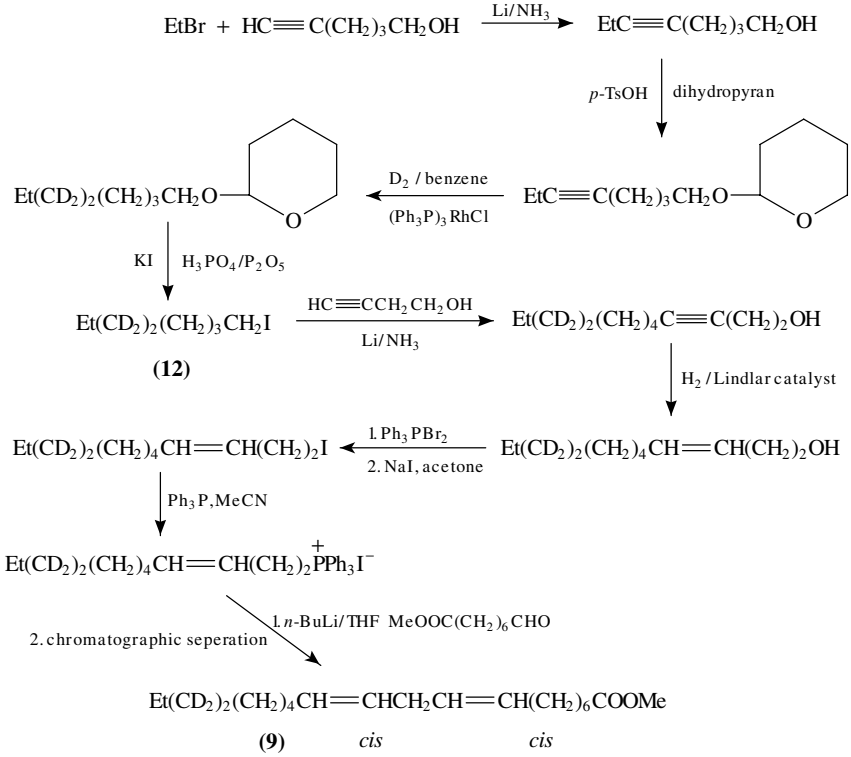


**(8)**

The epoxide metabolites of inhaled 1,3-butadiene, used in industry[3], are reported to be carcinogenic and mutagenic in rodents, and their *in vivo* concentration following inhalation exposure to butadiene has to be determined[4] by gas chromatography/mass spectroscopy, the isotope dilution method utilizing **8** as an internal standard. Commercially available [$D_6$]-propylene oxide has been used previously as an internal standard to monitor *in vivo* blood propylene oxide levels following inhalation exposure to propylene[5].

### *3. Synthesis of methyl 8c,11c-eicosadienoate-17,17,18,18-$D_4$, **9**, methyl 8c,11c,14c-eicosatrienoate-17,17,18,18-$D_4$, **10** and methyl 5c,8c,11c-eicosatrienoate-17,17,18,18-$D_4$, **11***

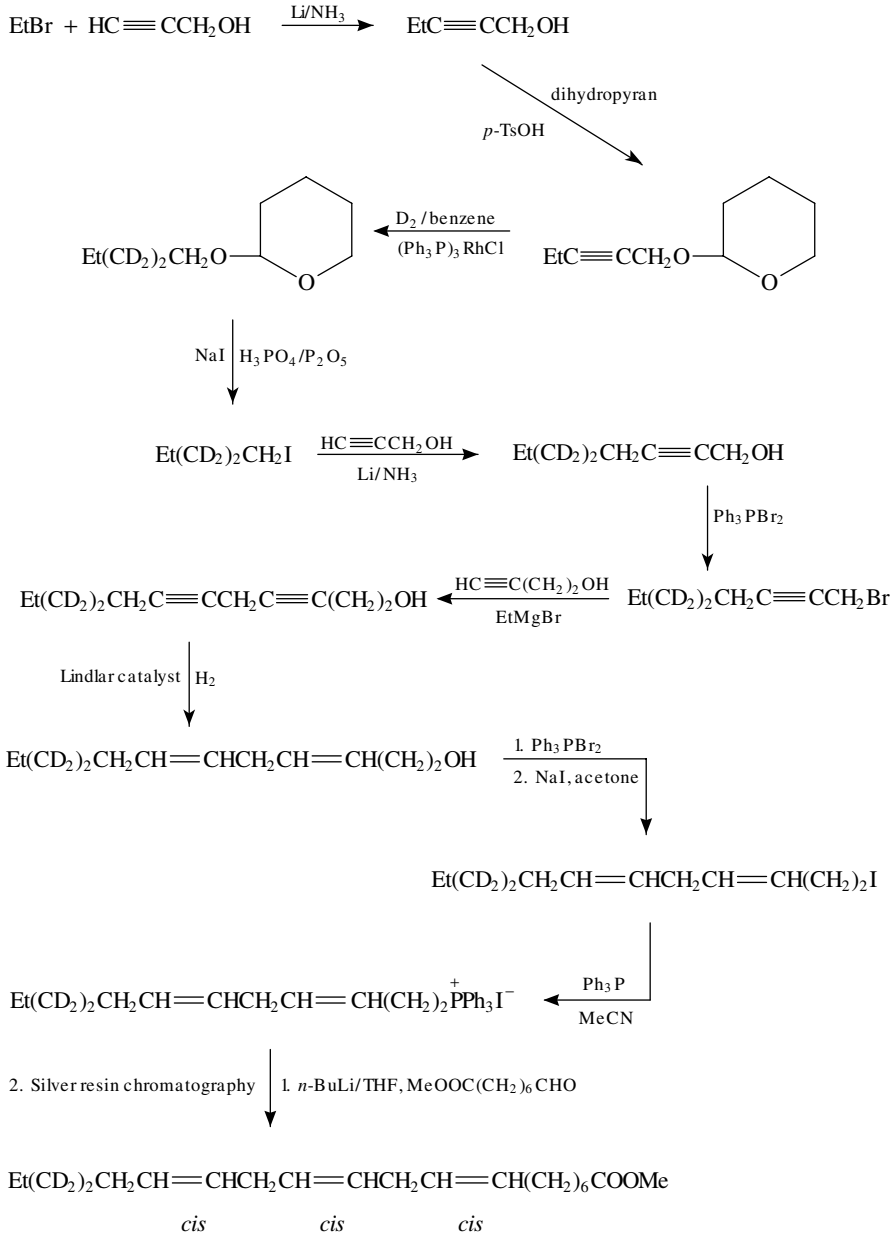
The deuteriated title compounds **9**, **10** and **11** have been synthesized[6] in multigram quantities in order to investigate the fatty acid metabolism in humans[7–9] (equations 4–6).




41% total combined yields, step yields 82–96%

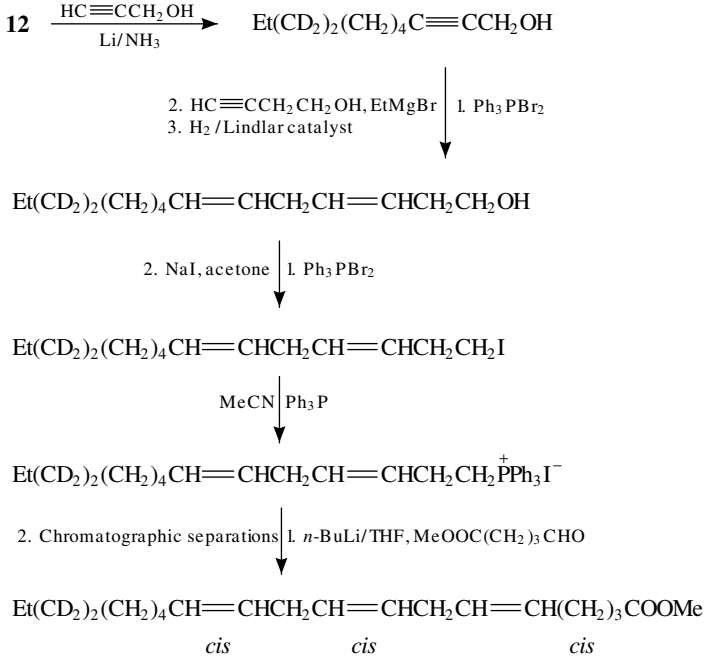
(4)

The reaction sequences shown in equations 4 and 5 involve the reduction of the appropriate acetylenic tetrahydropyranyl (THP) ethers with $(Ph_3P)_3RhCl$ and deuterium gas.




**(10)** 25% combined yield

(5)

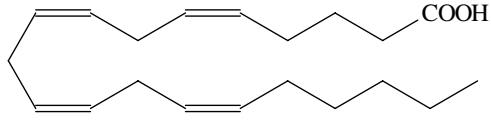



(6)

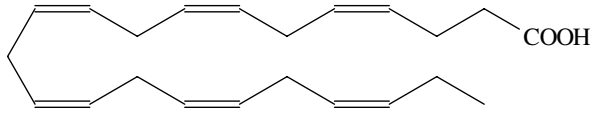
**(11)** 40% combined yield

### *4. Synthesis of ethyl ω-$^2H_5$-decosa-4,7,10,13,16,19-hexaenoate,* ***16***

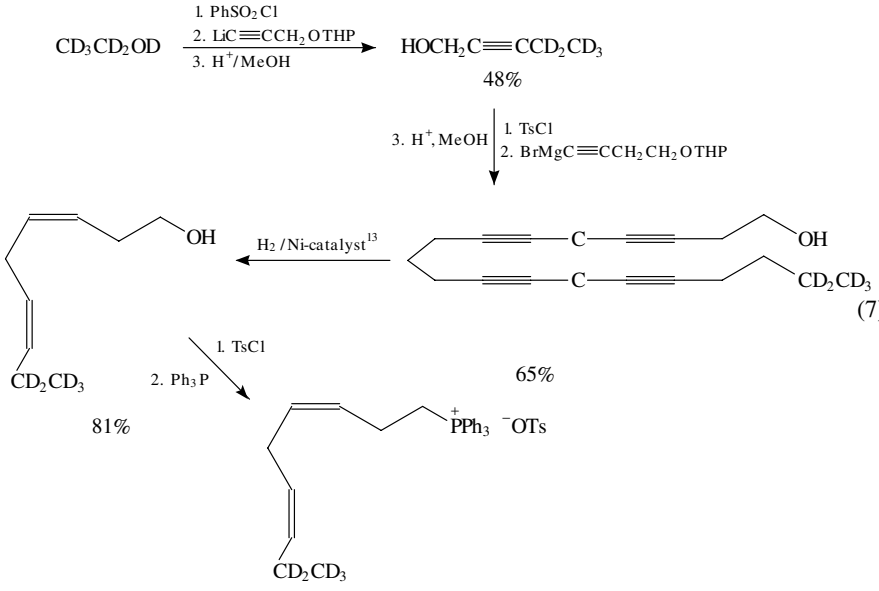
Elucidation of the physiological role of arachidonic acid **13** and other polyunsaturated fatty acids, particularly the role of all *Z*-4,7,10,13,16,19-decosahexaenoic acid **14**, found in brain, required the corresponding stable-isotope labelled material[10,11]. The deuteriated phosphonium salt **15**, the key intermediate used in the synthesis of title compound **16** (equation 8), has been prepared in 19% overall yield[12] starting with ethanol-$D_6$ (equation 7).



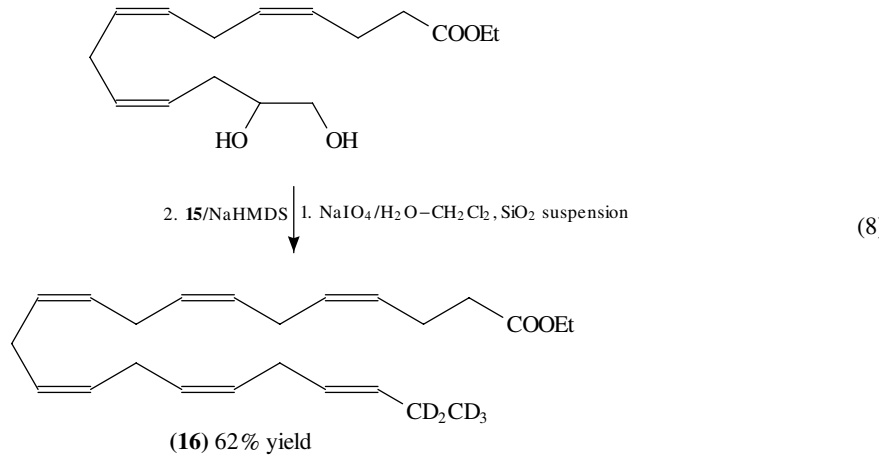

**(13)**




**(14)**



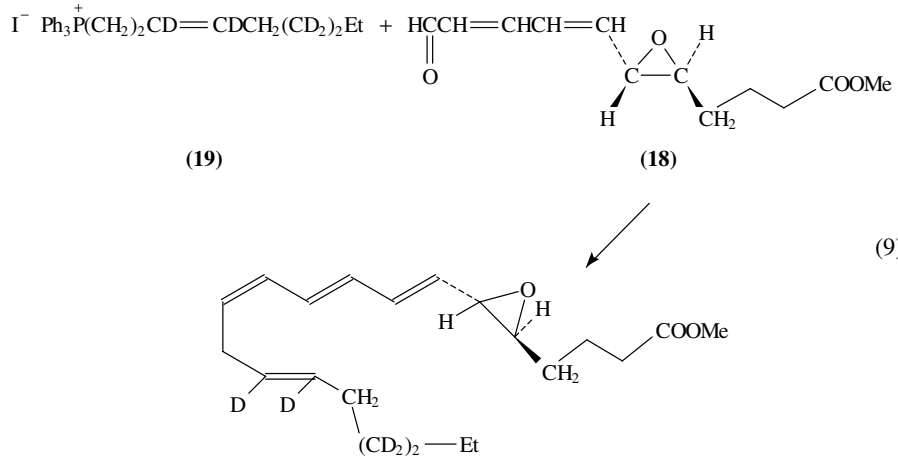

**(15)** 76% step yield, 19% overall yield




**(16)** 62% yield

### *5. Synthesis of deuteriated leukotriene $A_4$ methyl ester*

14,15,17,17,18,18-[$^2H_6$]-Leukotriene $A_4$ methyl ester, **17**, has been synthesized[14] by Wittig olefination of epoxy dienal **18** with the key reagent 3,4,6,6,7,7-[$^2H_6$]-(*Z*)-(3-nonen-1-yl)triphenylphosphonium iodide, **19** (equation 9). **17** is employed as stable isotope internal standard for the MS trace analysis of eicosanoids[15–17].

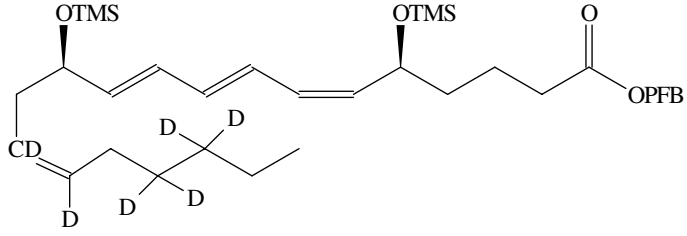



(9)

**(17)** [$^2H_6$]-LTA$_4$ methyl ester, 78%

### *6. Synthesis of [14,15,17,17,18,18-$^2H_6$]-leukotriene-B$_4$*

The deuteriated title compound **20**, needed for quantitative determination of endogenous LTB$_4$ in various biological fluids by GC/MS[18,19], has been obtained[20] by enzymatic hydration with human monocytes of D$_6$-LTA$_4$ precursor[14,21]. Leukotriene D$_6$-LTB$_4$ has been separated from its *trans* isomers, 6-*trans*-D$_6$-LTB$_4$ and 12-epi-6-*trans*-D$_6$-LTB$_4$, in high isotopic purity (99.4%) by reversed-phase HPLC and identified by GC/MS. Leukotrienes B$_4$ and C$_4$ are potent inflammatory mediators[22].

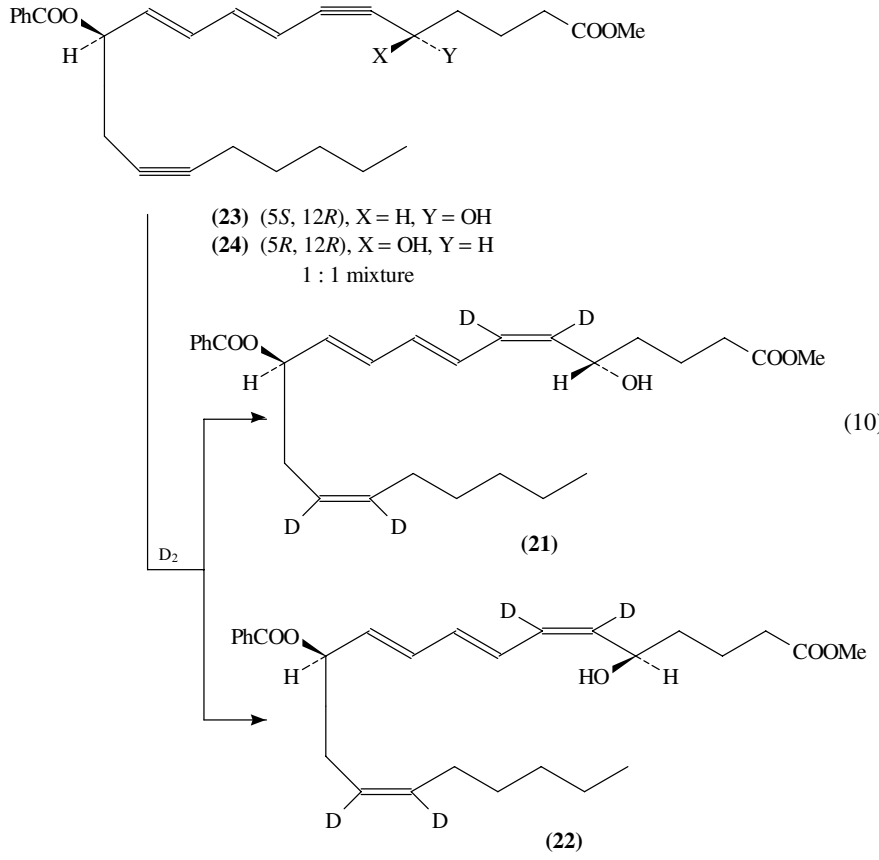



**(20)** pentafluorobenzyl (PFB) - TMS derivative of the enzymatic product used in SIM (selected ion monitoring) GC/MS analysis of the title compound

### *7. Synthesis of [6,7,14,15-$^2H_4$]-leukotriene B$_4$ methyl ester*

The title compounds LTB$_4$, **21** (*Z*) and **22** (*Z*), have been synthesized[23] by stereoselective reduction with deuterium gas of a 1:1 mixture of the suitable diacetylenic precursors **23** and **24** using Lindlar catalyst or palladium on barium sulphate catalyst (equation 10). Leukotriene B$_4$, a 5-lipoxygenase metabolite of arachidonic acid, playing

a major role in allergic, inflammatory and immunological states[24], had to be deuterium labelled for its quantification in biological samples[25,26] and for defining its physiological role.



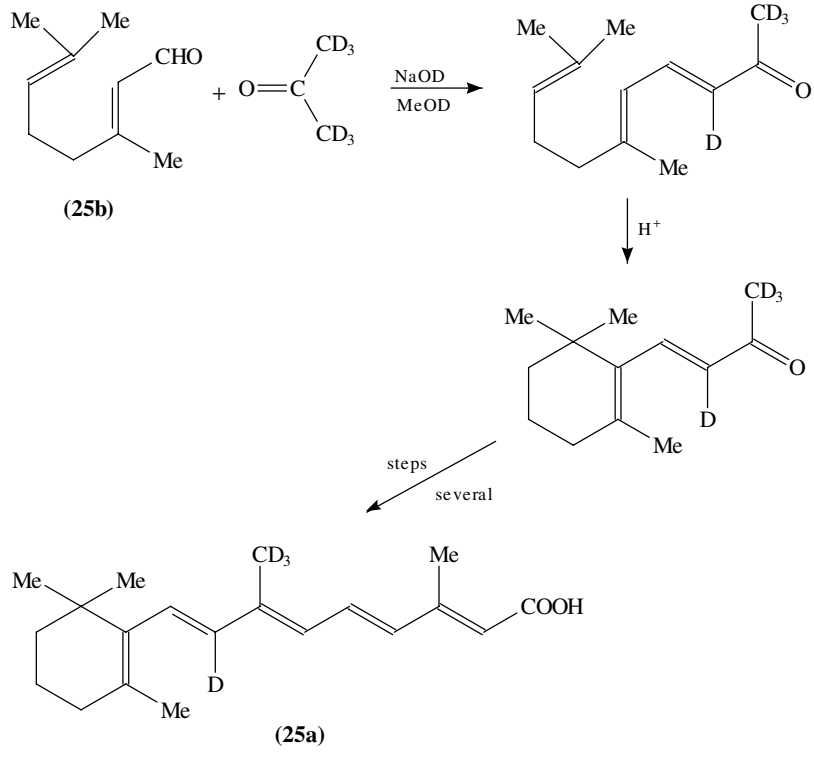

(10)

### 8. Synthesis of 13-cis-retinoic 8,(9,9,9-methyl)-$D_4$ acid

The $D_4$ acid **25a**, which according to MS had 94% of $D_4$, has been prepared[27] from citral **25b** and acetone-$D_6$ as before[28] (equation 11).

### 9. Synthesis of tri-, tetra- and penta-deuteriated forms of vitamin A

Four deuteriated retinols, **26–29**, with 3 to 5 deuterium atoms have been synthesized[29] for metabolism of vitamin A studies in humans[30]. Deuterium has been introduced into appropriate intermediates, used in the reaction scheme shown in equation 12, by base-catalysed exchange with $^2H_2O$ or perdeuterioacetone. The numbering system for retinol (vitamin A alcohol) is shown in equation 12.




(11)

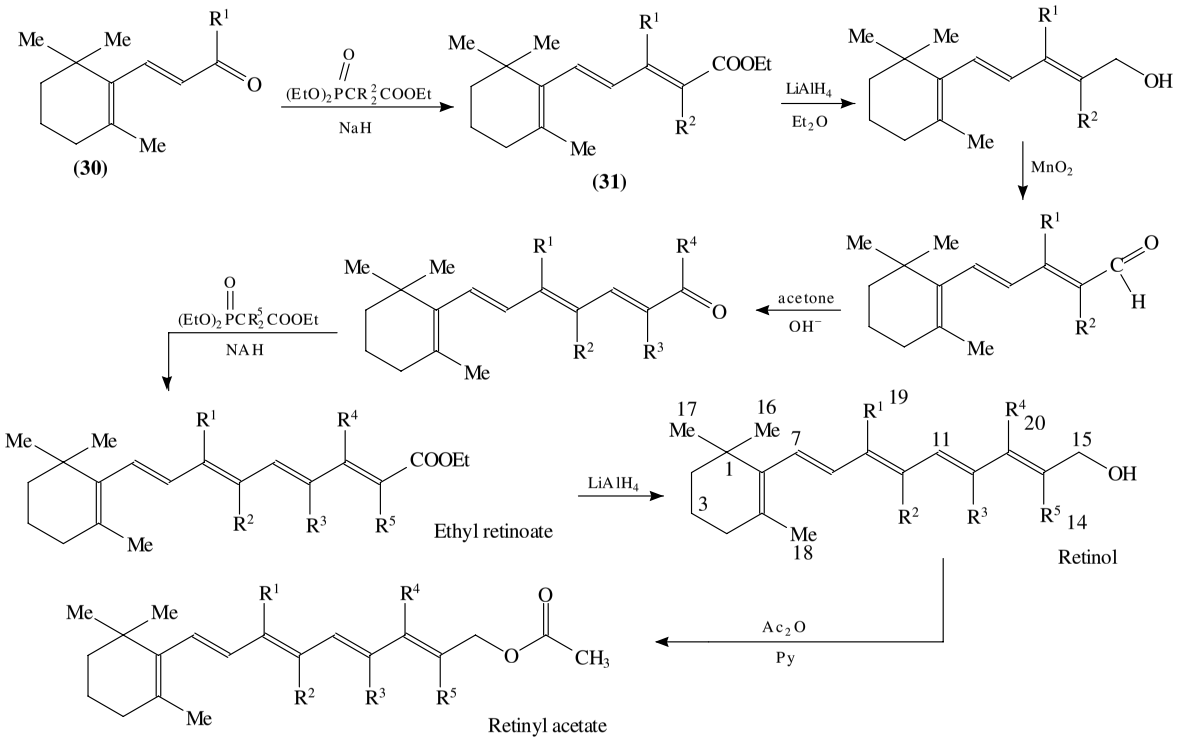
In the case of the synthesis of 10,19,19,19-$^2H_4$-vitamin A, the most useful for biological studies, three deuterium atoms were incorporated into $\beta$-ionone **30**, in >98% by deuterium exchange with excess $D_2O$ in the presence of $NaO^2H$ (and pyridine). The tri-deuteriated **30**, utilized in Wittig–Horner reaction with dideuterio triethyl phosphonate, provided tetradeuteriated ethyl $\beta$-ionilidene acetate **31** with more than 98% $^2H_4$ (by NMR). No deuterium loss in the subsequent synthetic steps was observed as evidenced by MS and NMR analysis.

### *10. Synthesis of deuteriated $^2H_8$-$\beta$-carotene*

Dietary $\beta$-carotene, a nutritionally important source of vitamin A, exhibits a protective effect against cancer risk[31,32]. The deuteriated compound, 10,10′,19,19,19,19′,19′,19′-$^2H_8$-$\beta$-carotene, **32**, has been obtained[33] by double condensation of the C-15 Wittig salt **33** with the symmetrical $C_{10}$ dial 2,7-dimethyl-2,4,6-octatrienedial, **34** (equation 13) for the study of $\beta$-carotene metabolism in humans.

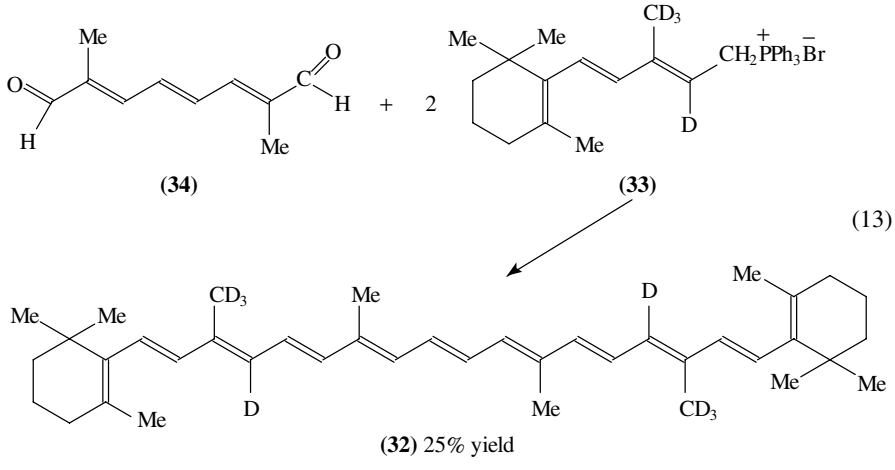
### *11. Synthesis of (±)-16,17,18,19-[$^2H_4$]-prostaglandin $D_2$, **35***

Using dimethyl 3,4,5,6-[$^2H_4$]-2-oxoheptylphosphonate, **36**, prepared in two steps as shown in equation 14, the title prostaglandin $D_2$, **35**, has been synthesized[34] in thirteen steps (equation 15).

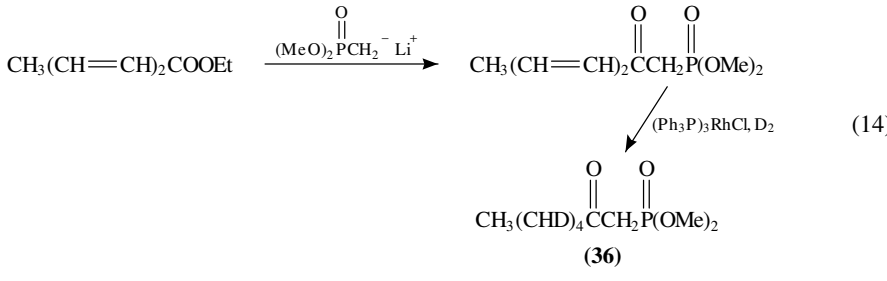



(12)

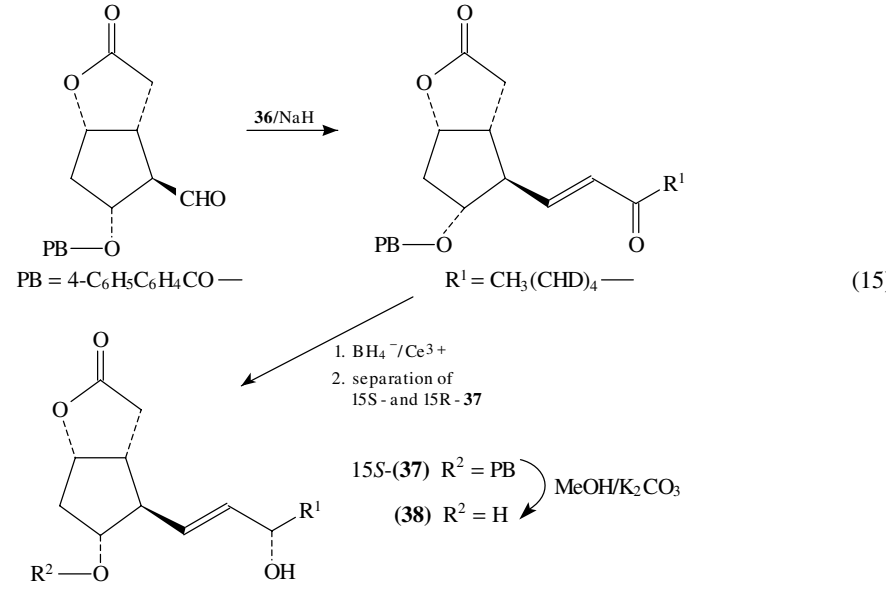
**(26)** 20, 20, 20- $^2H_3$ -retinoic acid ethyl ester ($R^1$ = Me, $R^4$ = $C^2H_3$)
**(27)** 14, 20, 20, 20 - $^2H_4$-retinoic acid ethyl ester ($R^1$ = Me, $R^4$ = $C^2H_3$, $R^5$ = $^2H$)
**(28)** 12, 14, 20, 20, 20 - $^2H_5$-retinyl acetate ($R^1$ = Me, $R^3$ = $R^5$ = $^2H$, $R^4$ = $C^2H_3$)
**(29)** 10, 19, 19, 19 - $^2H_4$-retinyl acetate ($R^1$ = $C^2H_3$, $R^2$ = $^2H$, $R^4$ = Me)



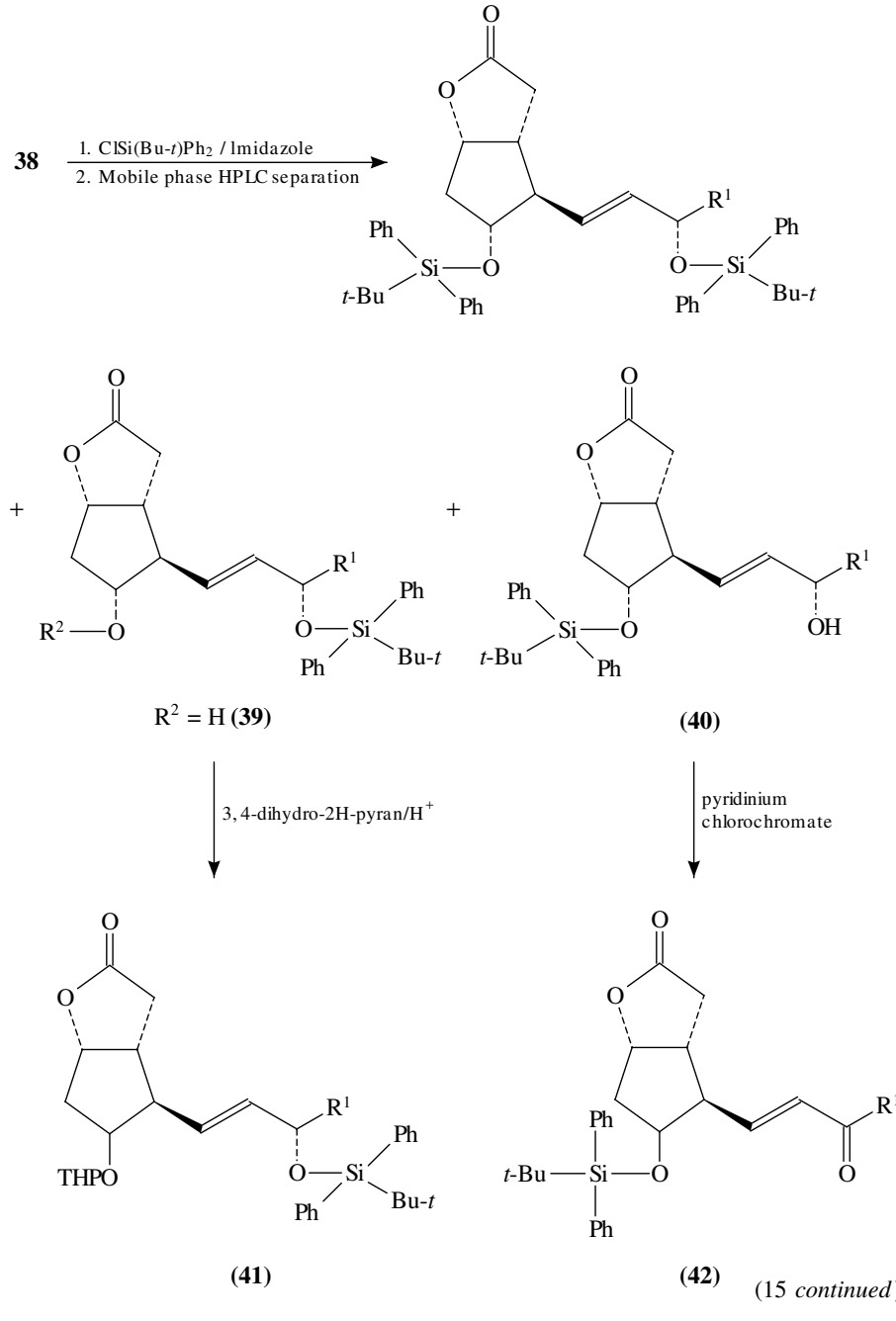
**(34)** **(33)** **(32)** 25% yield (13)



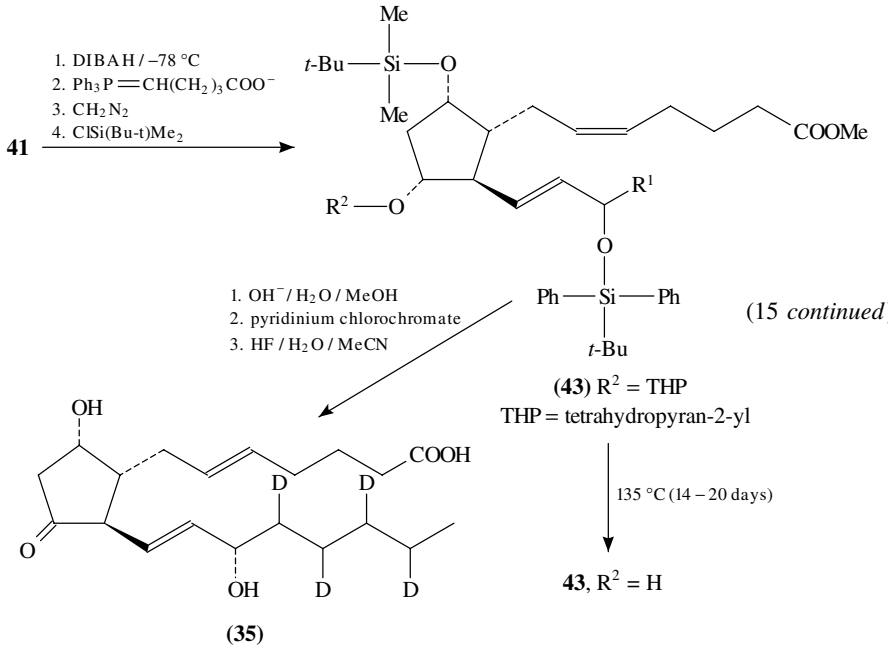
**(36)** (14)



(15)




(15 *continued*)



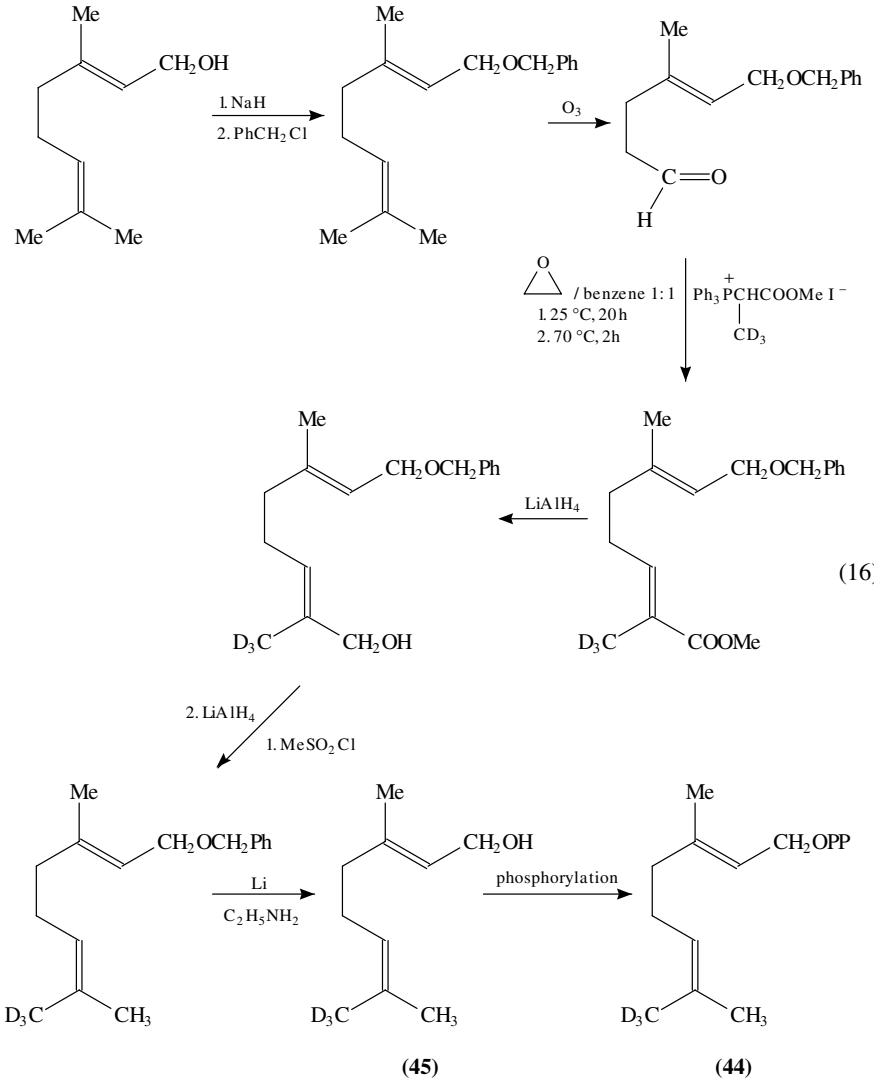

### *12. Synthesis of [10,10,10-$^2H_3$]-geranyl diphosphate*

The title compound **44**, [10,10,10-$^2H_3$]-3,7-dimethyl-2(*E*)-6-octadienyl diphosphate, has been obtained[35] as in equation 16, in order to investigate the mechanism of biosynthesis of limonene[36]. In the last step the diphosphate ester **44** was obtained as the trilithium salt in 47% yield by converting [10,10,10-$^2H_3$]-geraniol **45** into [10,10,10-$^2H_3$]-geranyl chloride with *N*-chlorosuccinimide, treating the chloride with tris(tetra-*n*-butyl)ammonium hydrogen diphosphate, and converting the product into the ammonium salt with cation exchange resin. The resulting triammonium salt of the diphosphate ester was converted into the trilithium salt with lithium chloride.

### *13. Synthesis of 4- and 10-deuteriated neryl and geranyl-β-D-glucosides and their use in tandem MS studies*

*a*. The title compounds, **46** (*Z*) and **47** (*E*), have been synthesized[37] starting with the deuteriated ketone **48**, prepared in >99% isotopic abundance by base-catalysed exchange with [$^2H_2$]-water. Reaction of **48** under Wittig–Horner conditions furnished the unsaturated esters **49** and **50** which, after chromatographic separation, have been reduced selectively with diisobutyl aluminium hydride (DIBAH), avoiding the reduction of C=C double bond. Modifying the published procedure[38] for the β-D-glucosidation of alcohols, **46** and **47** have been obtained under optimized reaction conditions[37] (equation 17).

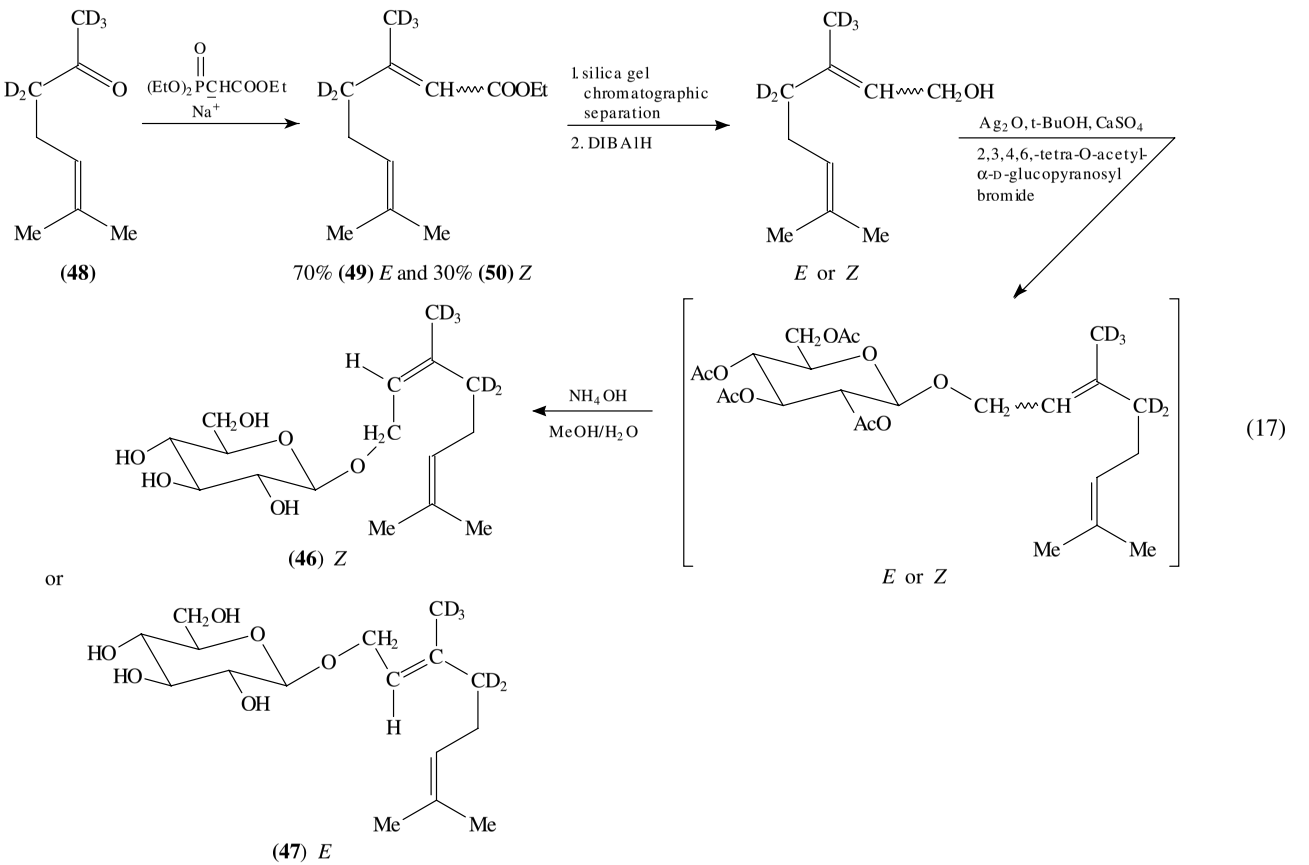
*b*. Tandem MS comparison of the low-energy CAD collision spectra of (M − H) ion, generated in ammonia NICl (triple quadrupole MS[37]) from geranyl, 4-[$^2H_2$]-10-[$^2H_3$]-geranyl, neryl and 4-[$^2H_2$]-10-[$^2H_3$]-neryl-β-D-glucosides, revealed the formation of the



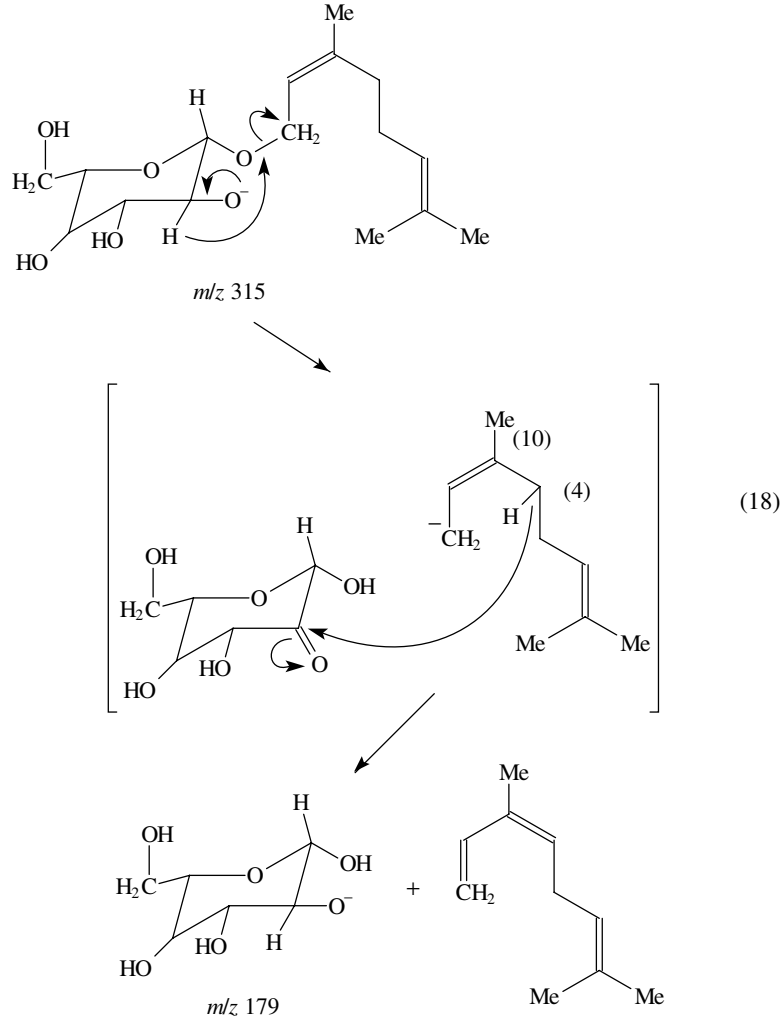

(16)

99.4% deuterium enrichment at C-10
20% overall yield

daughter $m/z$ 179 $(C_6H_{11}O_6)^-$ ion and $m/z$ 180 $(C_6H_{10}{}^2H_1O_6)^-$ ion from parent 315 $(M-H)^-$ and parent 320 $(M-H)^-$ ion, respectively, of the above glucosides. This confirmed the mechanism of the fragmentation of **46** and **47**, exemplified for decomposition of $m/z$ 315 $(M-H)^-$ ion of neryl-$\beta$-D-glucoside. The formation of the $m/z$ 179 ion is the result of hydride migration from position 4 (and 10) of the aglycone unit to the osidic part taking place in the intermediate 'anionic ketonic complex' (equation 18). The molecular ion $(M-H)^-$ arises from the osidic part, whereas the aglycone is eliminated as a neutral fragment.


CD3
D2C
O
Me
Me
(48)
(EtO)2PCHCOOEt
Na+
CD3
D2C
CH COOEt
Me
Me
70% (49) E and 30% (50) Z
1. silica gel chromatographic separation
2. DIBAlH
CD3
D2C
CH CH2OH
Me
Me
E or Z
Ag2O, t-BuOH, CaSO4
2,3,4,6,-tetra-O-acetyl-α-D-glucopyranosyl bromide
CH2OAc
AcO
AcO
AcO
O
O
CH2 CH
CD3
CD2
Me
Me
E or Z
NH4OH
MeOH/H2O
CD3
H
C
CD2
CH2OH
O
H2C
HO
HO
O
OH
Me
Me
(46) Z
or
CH2OH
O
HO
HO
OH
O
CH2
C
CD3
CD2
C
H
Me
Me
(47) E

(17)



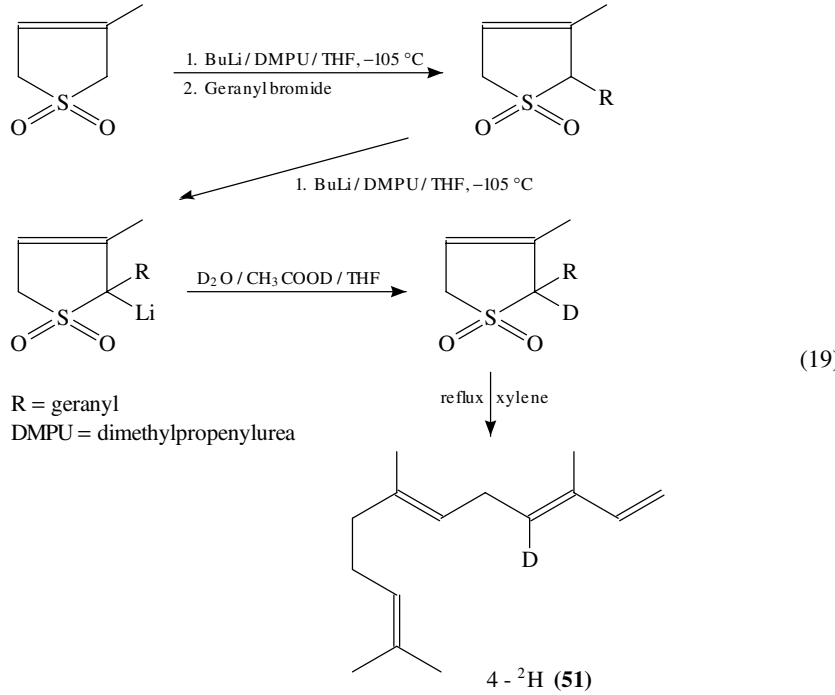

(18)

### *14. Synthesis of 4-$^2$H-α-farnesene and 1-$^2$H-α-farnesene*

The sesquiterpene α-farnesene, **51**, a primary aroma component which occurs in the skin of apples[39] and other fruits[40], attractant and oviposition stimulant to *Laspeyresia pomonella*[41,42], has been deuteriated at $C_{(1)}$ and at $C_{(4)}$ (equations 19 and 20), for study of the induction of superficial scald of apples[43].

### *15. Synthesis of $D_6$-α-farnesene*

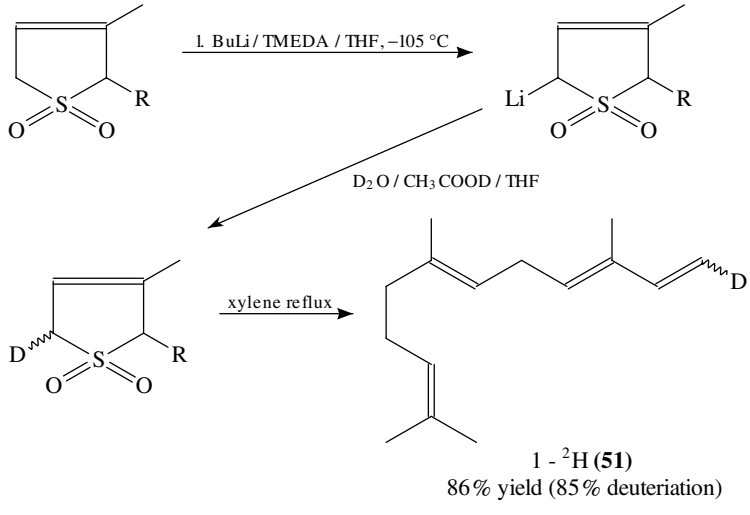
The title compound, **52**, 3,7-dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3*E*,6*E*,10-tetraene, bearing a higher proportion of deuterium, was needed for continuing studies of the induction of superficial scald of apples. It has been synthesized[44] by two parallel




(19)

R = geranyl
DMPU = dimethylpropenylurea

4 - $^2$H **(51)**
85% yield (60% deuteration)



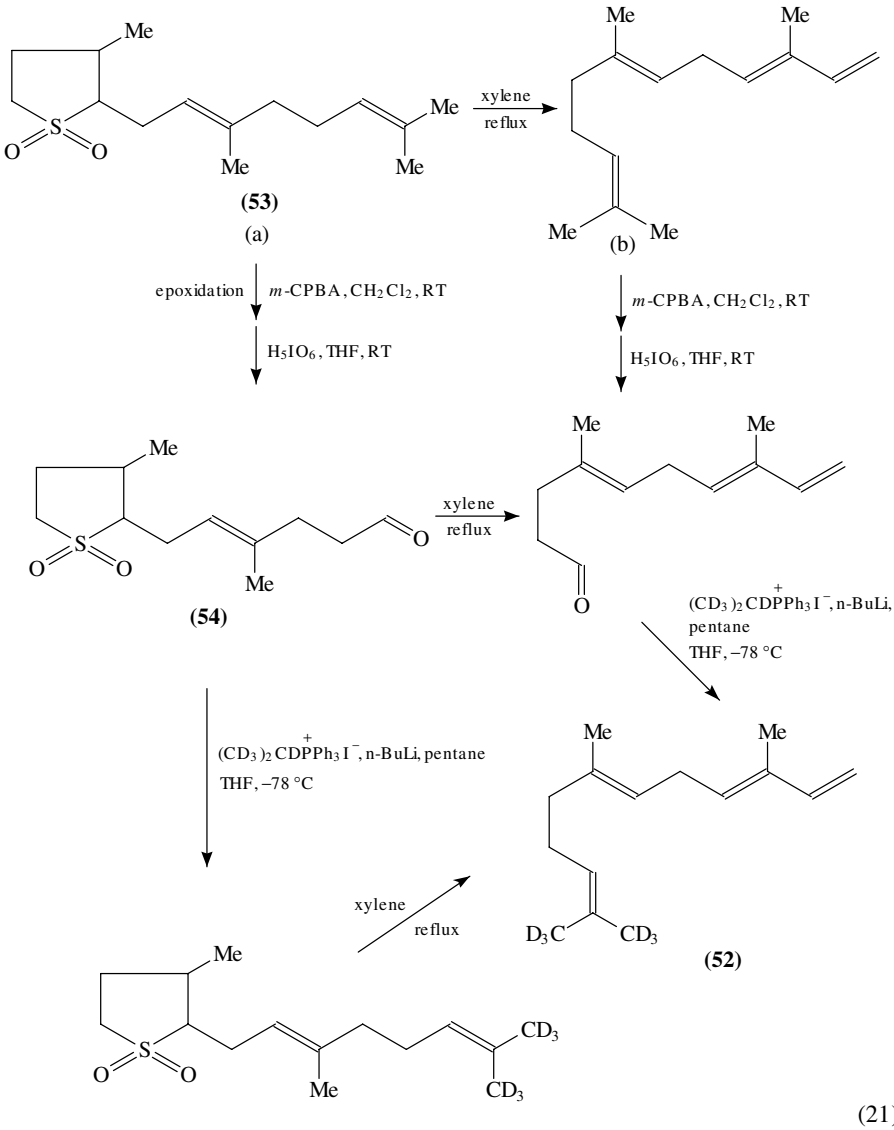

(20)

1 - $^2$H **(51)**
86% yield (85% deuteration)

TMEDA = *N*, *N*, *N*′, *N*′ - tetramethylethylenediamine

routes a and b (equation 21), starting from the common substrate 2-geranyl-methyl-sulpholene, **53**. Route b gave product **52** in only 9% yield. The overall yield in the synthesis

carried out according to route a, which involves the Wittig reaction of aldehyde **54** with $^2H_7$-isopropyl triphenylphosphonium iodide, followed by thermal elimination of sulphur dioxide, was better (23%).

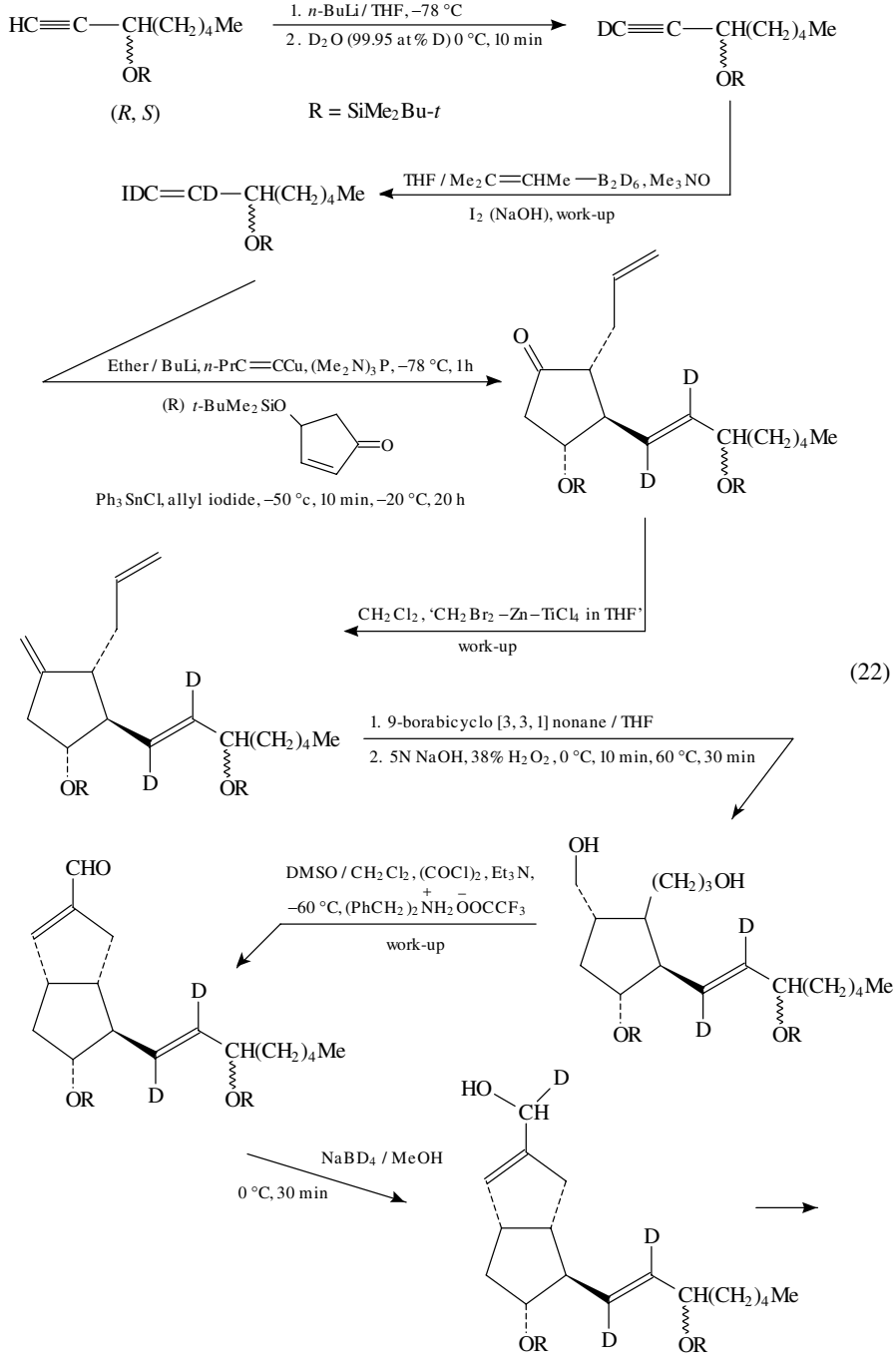



(21)

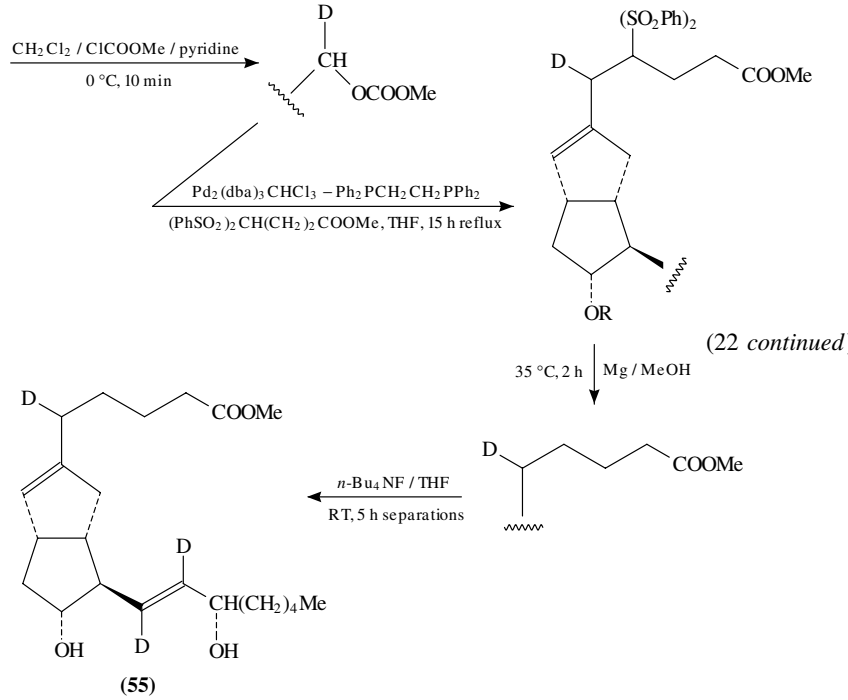
### *16. Synthesis of polydeuteriated 9 (O)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$ methyl esters*

*a*. Synthesis of [5,13,14)-$^2H_3$], of the title derivative, **55**, a promising therapeutic agent for cardiovascular diseases[45–47], has been carried out via H/D exchange, deuterioboration

and sodium borodeuteride reduction[48] as shown in equation 22.

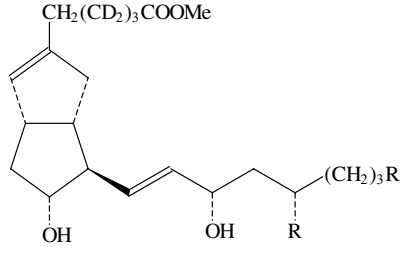



(22)

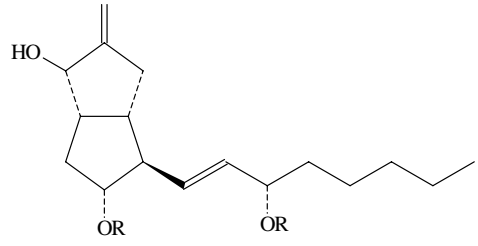



**(55)**

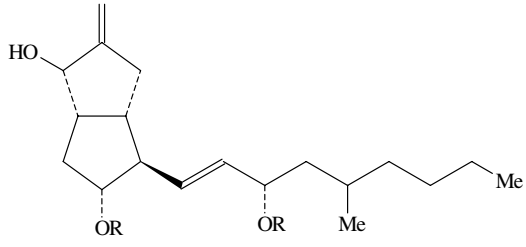
*b*. The [2,2,3,3,4,4-$^{2}H_6$] derivative **56** has been prepared[48] starting with tetrahydrofuran-$D_8$ (equation 23). Similarly, the derivatives **57** and **60** have been prepared as shown in




**(56)** R = H, **(57)** R = Me

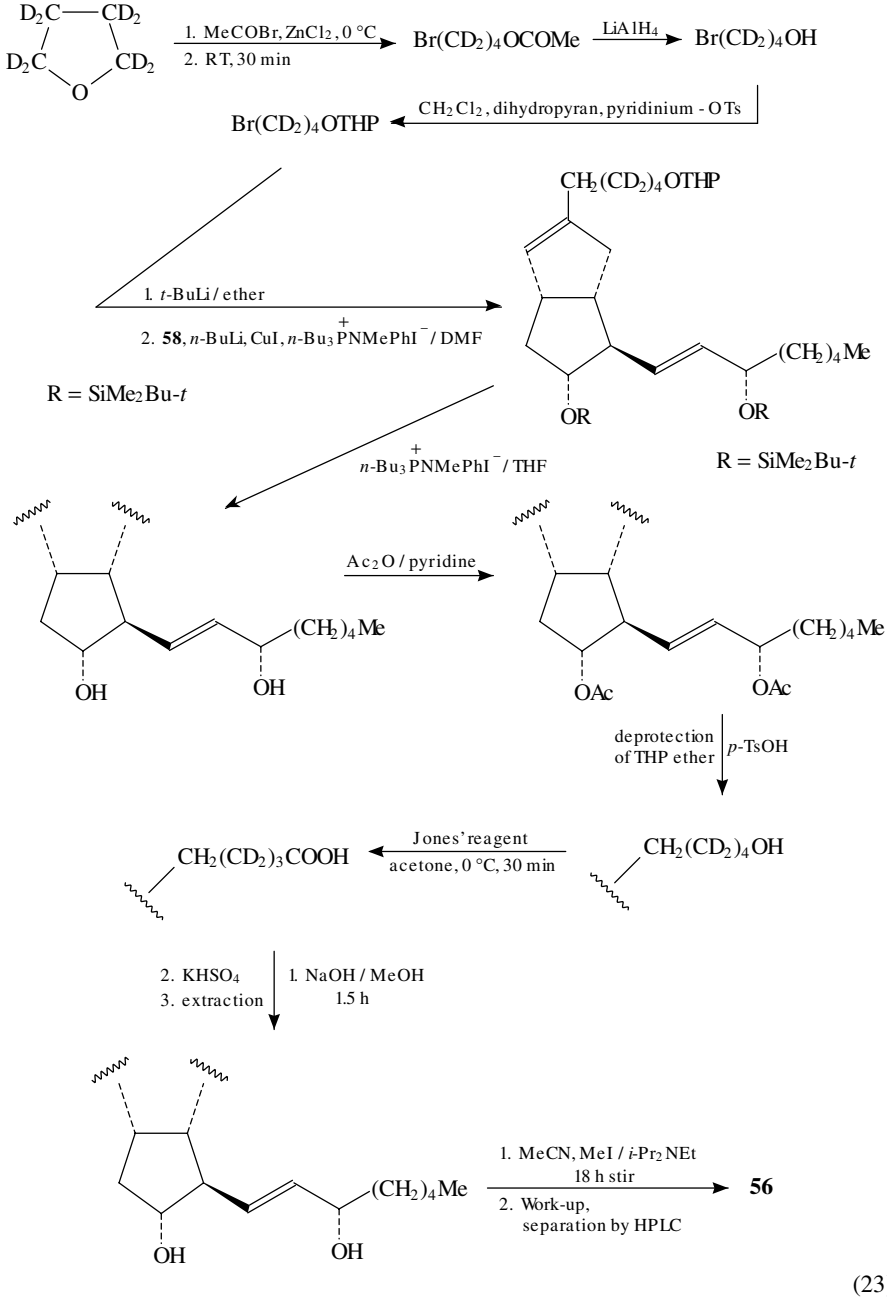



**(58)** R = $SiMe_2Bu$-*t*

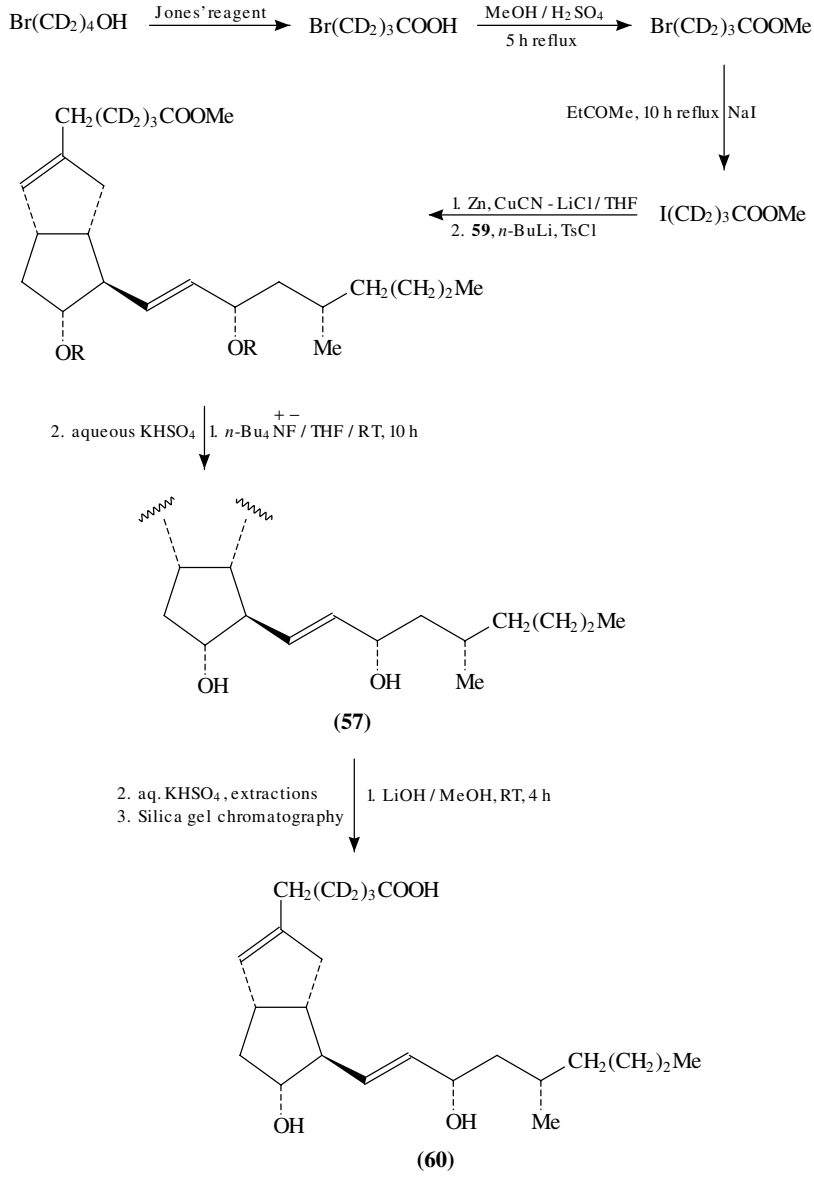



**(59)**

equation 24. The polydeuteriated isocarbacyclin derivatives **55**, **56** and **57** have been obtained for use as internal standards in GC/MS quantitative analysis and for use as substrates in metabolic studies.




(23)

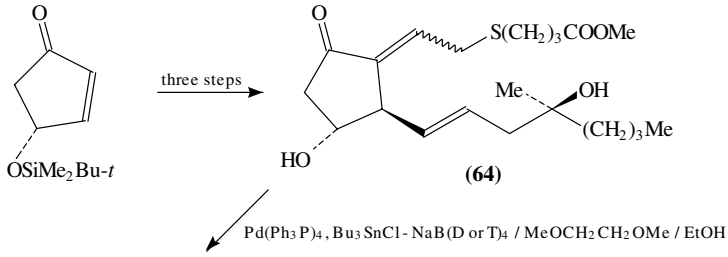



(24)

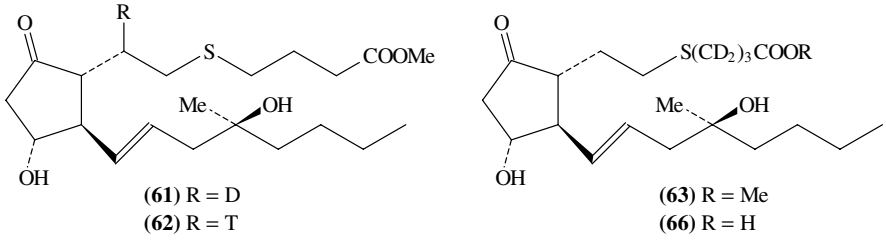
### *17. Synthesis of [7-$^2$H]-, [7-$^3$H]- and [2,2,3,3,4,4-$^2H_6$]-(16S)-15-deoxy-16-hydroxy-16-methyl-5-thiaprostaglandin $E_1$ methyl ester,* ***61****,* ***62*** *and* ***63***

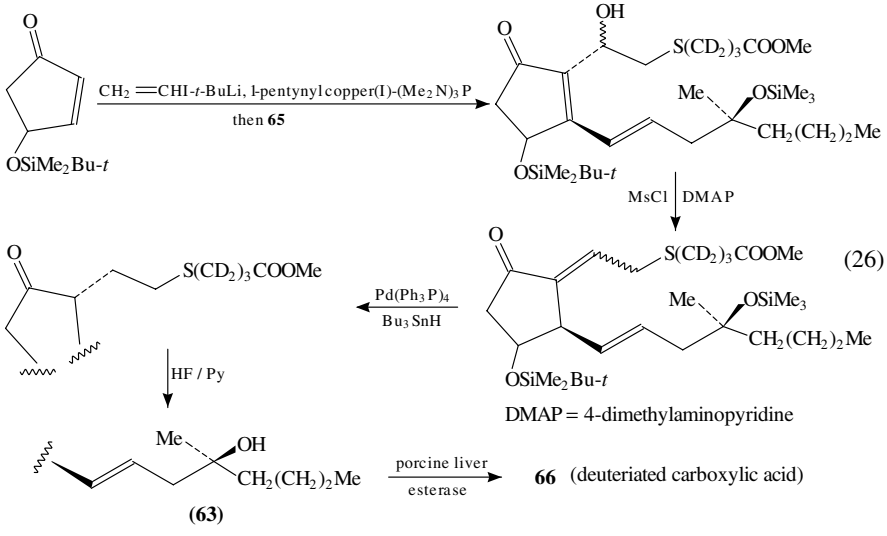
The prostaglandin $E_1$ and $E_2$ analogues showing antisecretory and cytoprotective activities[49,50] had to be deuterium or tritium labelled for preclinical studies. The tritiated or deuteriated title compounds **61**, **62** and **63** have been synthesized[51] by the methods outlined in equations 25, 26 and 27. Compounds **61** and **62**, with hydrogen at 7-position

substituted by deuterium or tritium atoms, have been obtained by conjugate reduction of the enone function of the $\Delta^7$ olefinic precursor **64** with *in situ* generated tributyltin[$^2$H]- or [$^3$H]hydride in the presence of palladium(0) catalyst (equation 25). Compound **63** with hydrogen atoms at the 2,3,4-positions substituted by deuterium atoms has been synthesized[51] as shown in equation 26, using the hexadeuteriated aldehyde **65** prepared in three steps (equation 27). Compound **63** has been used[51] as internal standard in GC/MS analysis.

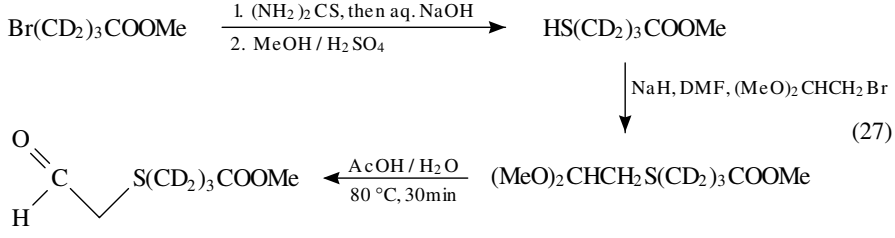



**61**, 85% deuterium (by MS)
**62**, 146.8 mCi, 15% yield, specific activity 13.8 mCi/mmol, 95% radiochemical purity (25)



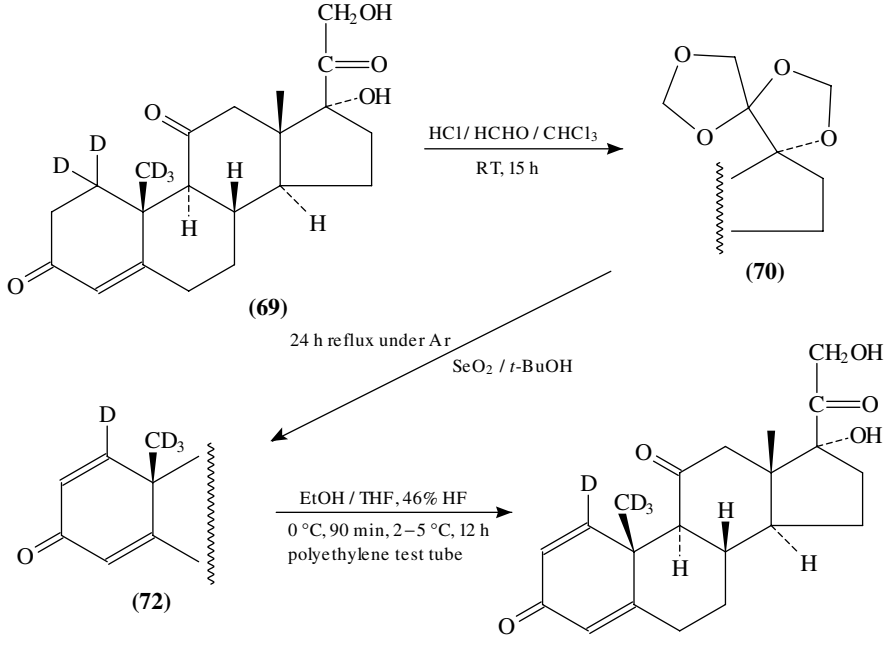

(26)



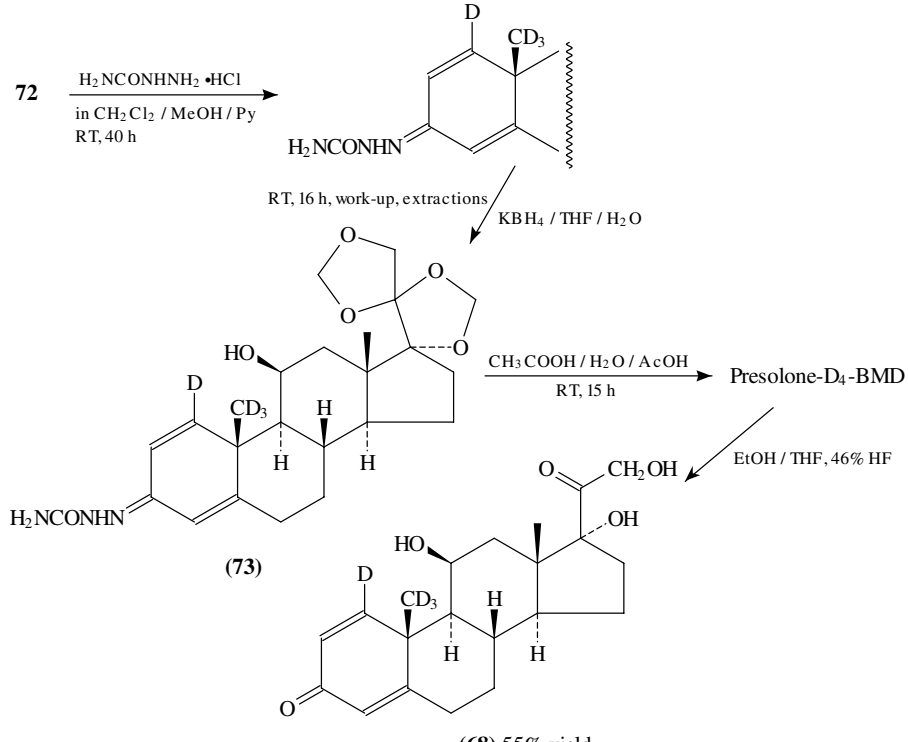

(27)

*18. Synthesis of multiply deuterium labelled prednisone and prednisolone*

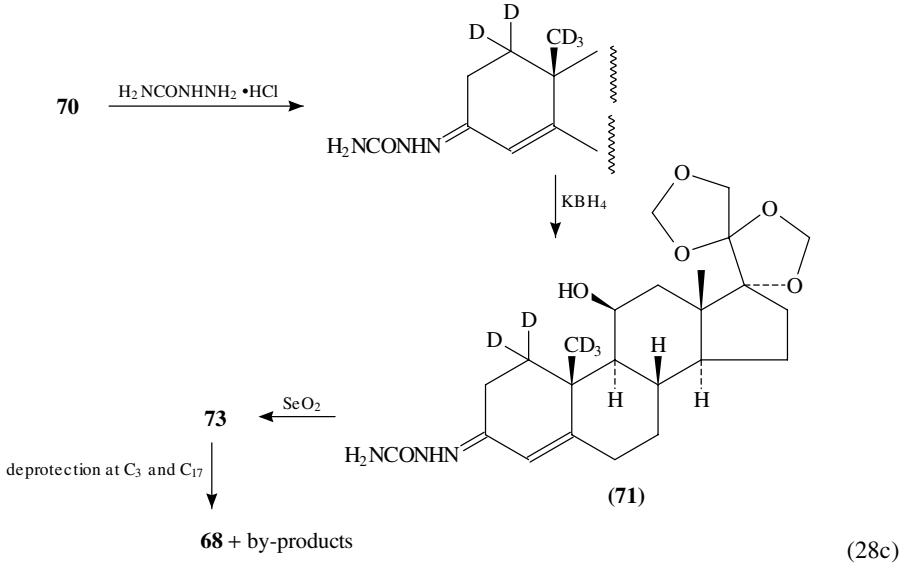
[1,19,19,19-$^2H_4$]Prednisone, **67**, and [1,19,19,19-$^2H_4$]prednisolone, **68**, containing four deuterium atoms at chemically stable sites, have been synthesized[52] starting from [1,1,19,19,19-$^2H_5$]cortisone, **69** (equations 28a, 28b and 28c). No loss of deuterium from the $C_{(19)}$ and $C_{(1)}$ positions has been observed in the course of a synthetic sequence which involved the oxidation of the intermediates **70** and **71** with selenium dioxide in *t*-butanol. Route 28c has been less satisfactory because of the formation of by-products, especially in the oxidation of **71**. Compounds **67** and **68** with $^2H$-label in chemically and biologically stable $C_{(1)}$ and $C_{(19)}$ positions are suitable for use in stable isotope methodology (coupled with GC/MS[53,54]) of investigations on steroid hormones in humans[55].




**(67)** [1, 19, 19, 19 - $^2H_4$]-17α, 21-Dihydroxypregna-1,4-diene-3,11,20-trione (prednisone-$D_4$) (28a)


72
H2NCONHNH2 •HCl
in CH2Cl2 / MeOH / Py
RT, 40 h
RT, 16 h, work-up, extractions
KBH4 / THF / H2O
CH3COOH / H2O / AcOH
RT, 15 h
Presolone-D4-BMD
EtOH / THF, 46% HF
(73)
(68) 55% yield

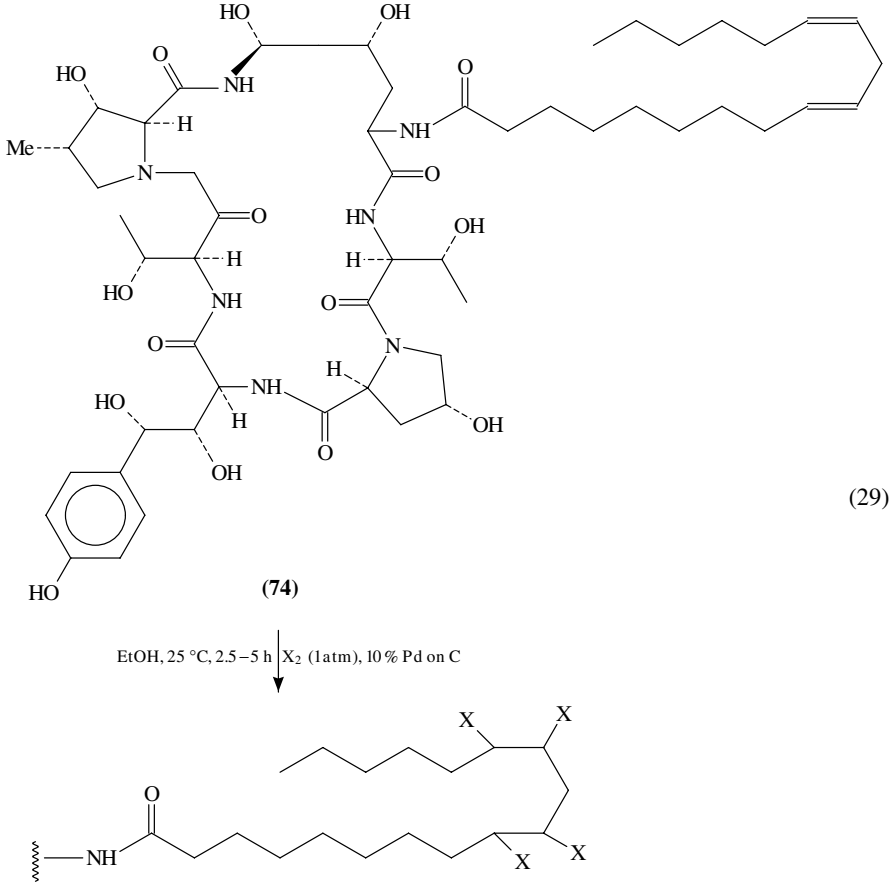
(28b)


70
H2NCONHNH2 •HCl
KBH4
SeO2
73
deprotection at C3 and C17
(71)
68 + by-products

(28c)

### *19. Synthesis of deuteriated and tritiated echinocandin B and anilinostearamide and the problem of HPLC isotope effects*

Echinocandin B, **74**, a macrocyclic peptide possessing antibiotic and antifungal properties[56], has been catalytically reduced with hydrogen, deuterium or tritium[57] (equation 29). The proton NMR and mass spectra of the reduction product **76** indicated that incorporation of deuterium exceeded saturation of double bonds. Four to ten deuterium atoms (with eight predominating) had been incorporated. This means that under the experimental conditions employed allylic labelling took place and a double-bond isomerization occurred during the reaction. Hydrogen–deuterium exchange might be also occurring[58].




(29)

**(75)** tetrahydroechinocandin B, 20% yield (in EtOH, 2.5 h reaction time)

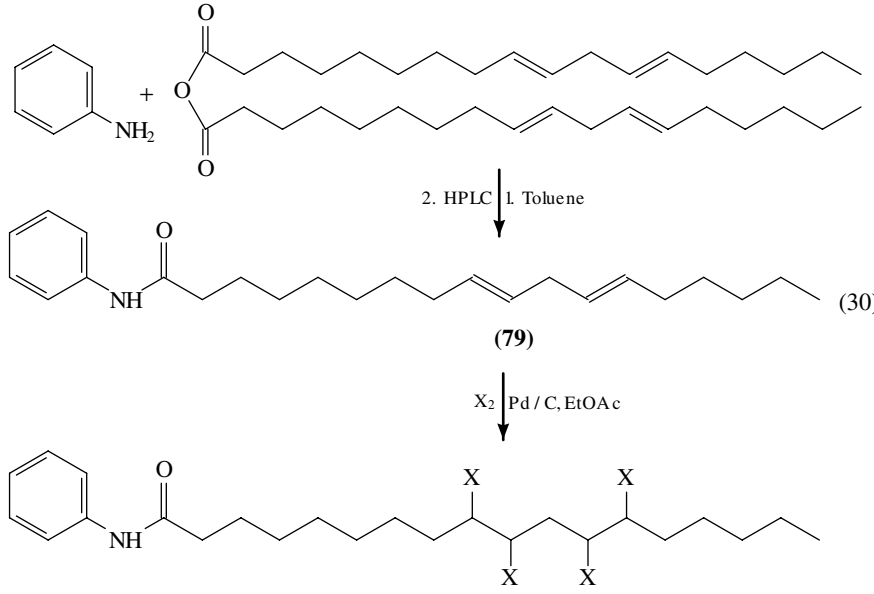
**(76)** X = $^{2}$H, 30% yield (5 h reaction time in DMF)

**(77)** X = $^{3}$H, 5.41 mCi, specific activity 129.0 Ci mmol$^{-1}$, 97.6% radiochemical purity by HPLC

During the reversed phase HPLC analysis of the tritiated echinocandin **77** it has been observed that the radioactivity of **77** has been detected prior to the UV absorbance of the

reference compound. This chromatographic isotope effect has been also observed in the case of deuteriated analogue and the elution order tritiated < deuteriated < hydrogenated has been established.

The model compound anilinostearamide **78**, labelled in the aliphatic chain only, prepared subsequently by the reduction of linoleic precursor **79** with hydrogen or deuterium (equation 30), exhibited a chromatographic isotope effect of similar magnitude. The labelled compound elutes on the reversed-phase HPLC prior to the unlabelled one.




(30)

**(78)** X = H (100% yield); X = $^{2}$H (100% yield)

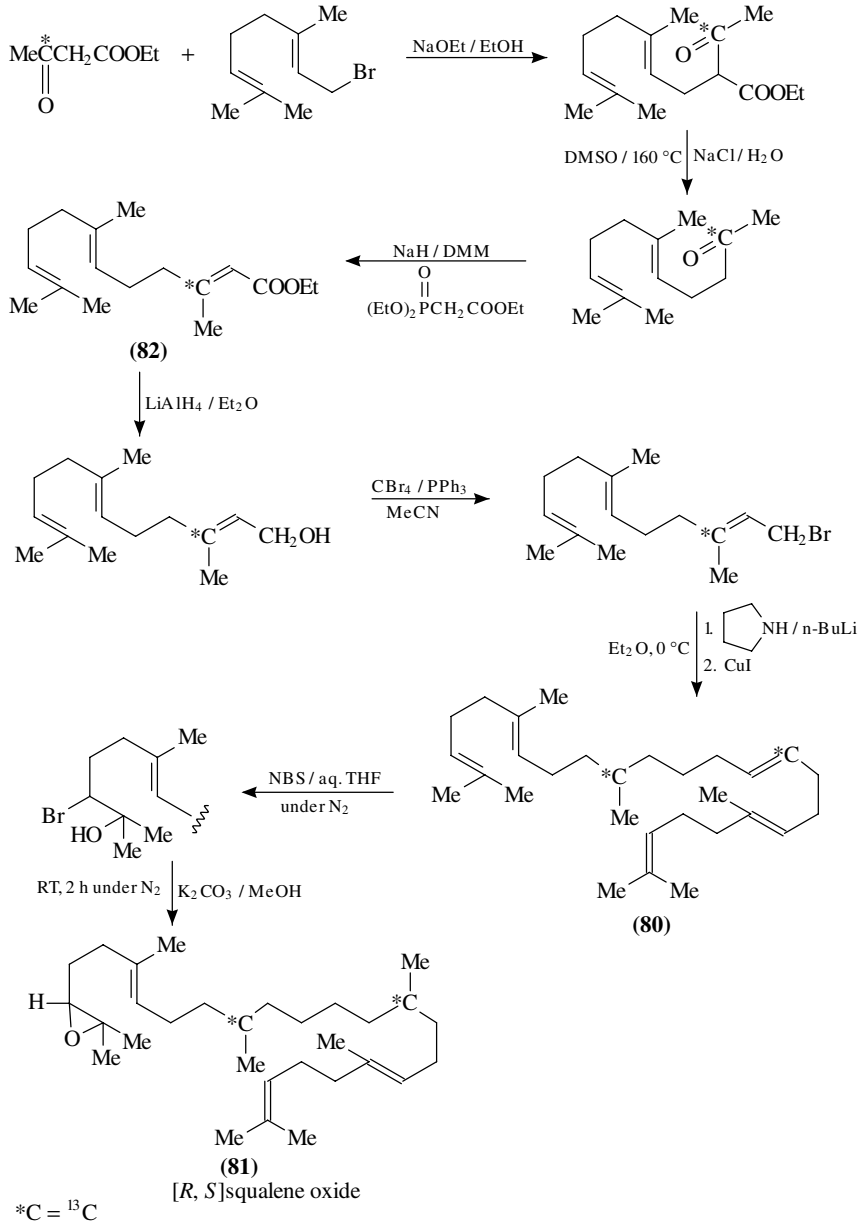
It has been suggested[57] that the observed isotope effect arises from the differences in interaction between the C−H and C−D bonds and the stationary phase. The deuteriated compounds are less lipophilic than the unlabelled ones. The C−D bonds are shorter, exhibit lower polarizabilities and have lower vibrational frequencies. The deuterium atoms behave as being smaller than hydrogen atoms. The C−D bonds do not have as strong an attractive force to the stationary phase as do the C−H bonds and therefore the deuteriated species are eluted faster on reversed-phase HPLC than the hydrogenated species[59−64]. The rigorous treatment of Vapour Pressure Isotope Effects (VPIE) and Chromatographic Isotope Effects developed by Bigeleisen[65], van Hook[66] and Devyatykh[67] is presented in review articles and monograph chapters[68−70].

## B. Synthesis of Carbon-13-labelled Compounds

### *1. Synthesis of 10,15-[$^{13}C_2$]-Squalene, **80**, and -DL-squalene oxide **81***

10,15-[$^{13}C_2$]-Squalene, **80**, has been produced[71] in the reaction sequence shown in equation 31 which involves alkylation of 3-$^{13}$C-ethyl acetoacetate with geranyl bromide, followed by hydrolysis, decarboxylation and treatment with triethyl phosphonoacetate and then reduction of the ester **82** with $LiAlH_4$, bromination with $CBr_4/PPh_3$ and coupling the farnesyl bromide with CuI/Li-pyrrolidine. Epoxidation of **80** has been effected by

treatment with NBS in aqueous THF followed by elimination of HBr with $K_2CO_3$.



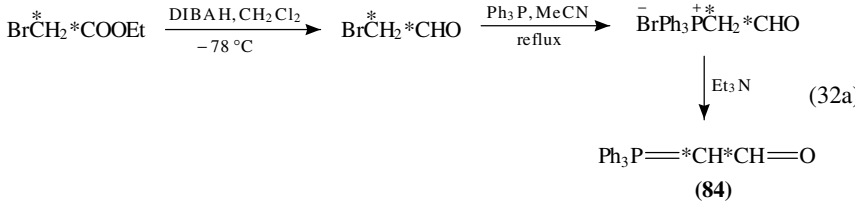

(31)

The $^{13}C$-labelled squalene has been used[71] to study the mechanism of its enzymatic conversion to lanosterol (3-$\beta$-hydroxy-8,24-lanostadiene[72]) by yeast squalene-oxide lanosterol

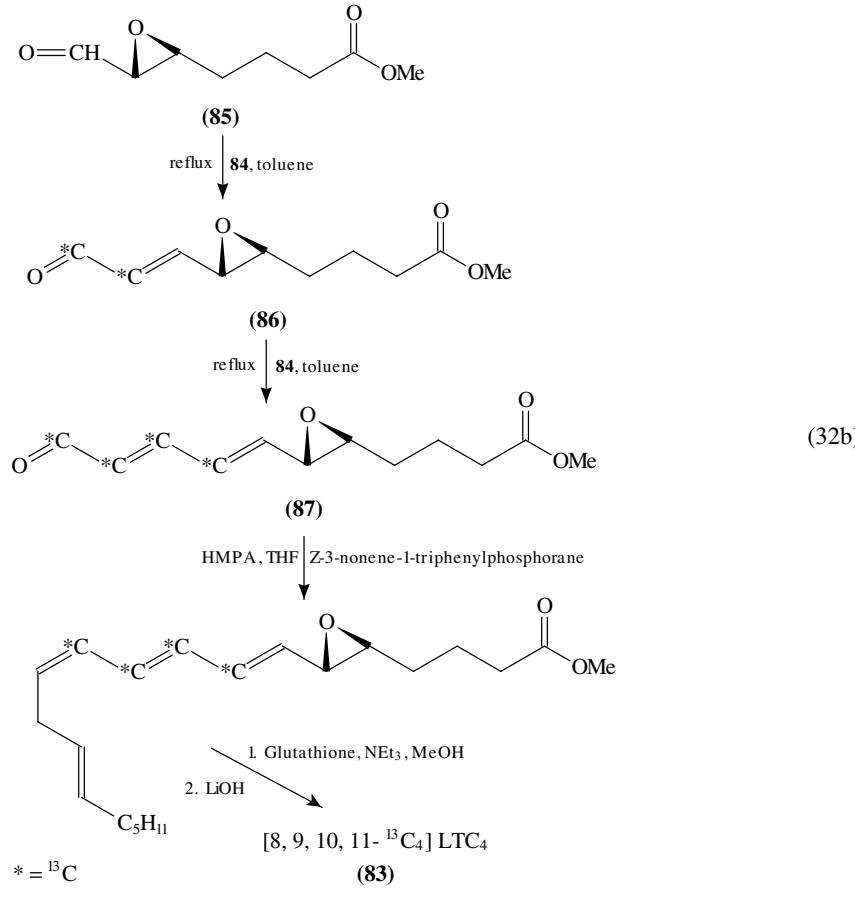
cyclase and it will be utilized in the future for preparations of labelled steroid analogues commercially unavailable.

### *2. Synthesis of [8,9,10,11-$^{13}C_4$]leukotriene $C_4$*

The title compound, [8,9,10,11-$^{13}C_4$]$LTC_4$, **83**, an ideal internal standard for GC/MS and other MS determinations of cysteine containing leukotrienes which show biological effects at very low concentration, such as smooth muscle contraction and hypersensitivity reactions[73], has been obtained[74] in a reaction sequence shown in equations 32a and b.




(32a)

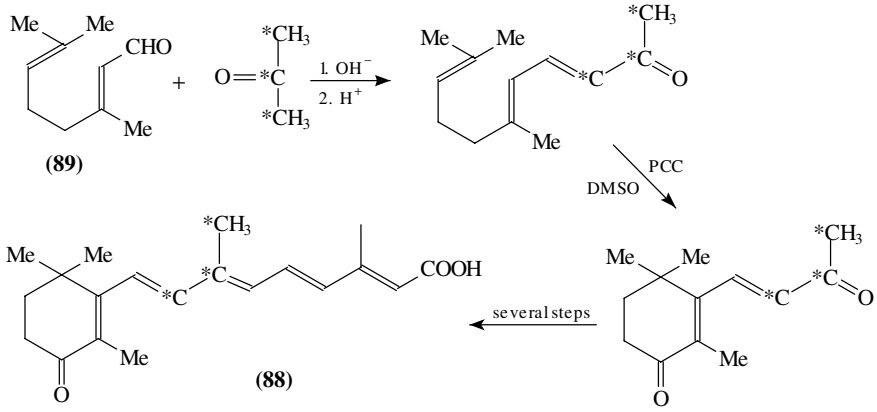



(32b)

Wittig reaction of [1,2-$^{13}C_2$]formylmethylenetriphenylphosphorane, **84**, with **85** and subsequent Wittig reaction of **86** with **84** yielded [8,9,10,11-$^{13}C_4$]LTA$_4$ methyl ester, **87**, which in the last step was converted to **83** in 12% yield.

### *3. Synthesis of 4-oxo-13-cis-retinoic-8,9,19-$^{13}C_3$ acid*

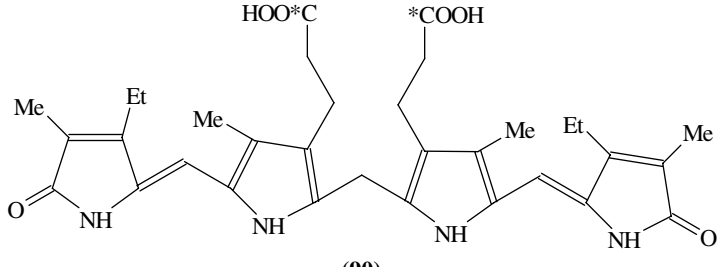
The title compound, **88**, the main metabolite of 13-*cis*-retinoic acid in mammals, has been synthesized[27] as before via condensation of acetone-1,2,3-$^{13}C_3$ with 3,7-dimethyl-2,6-octadienal (citral), **89** (equation 33).




(33)

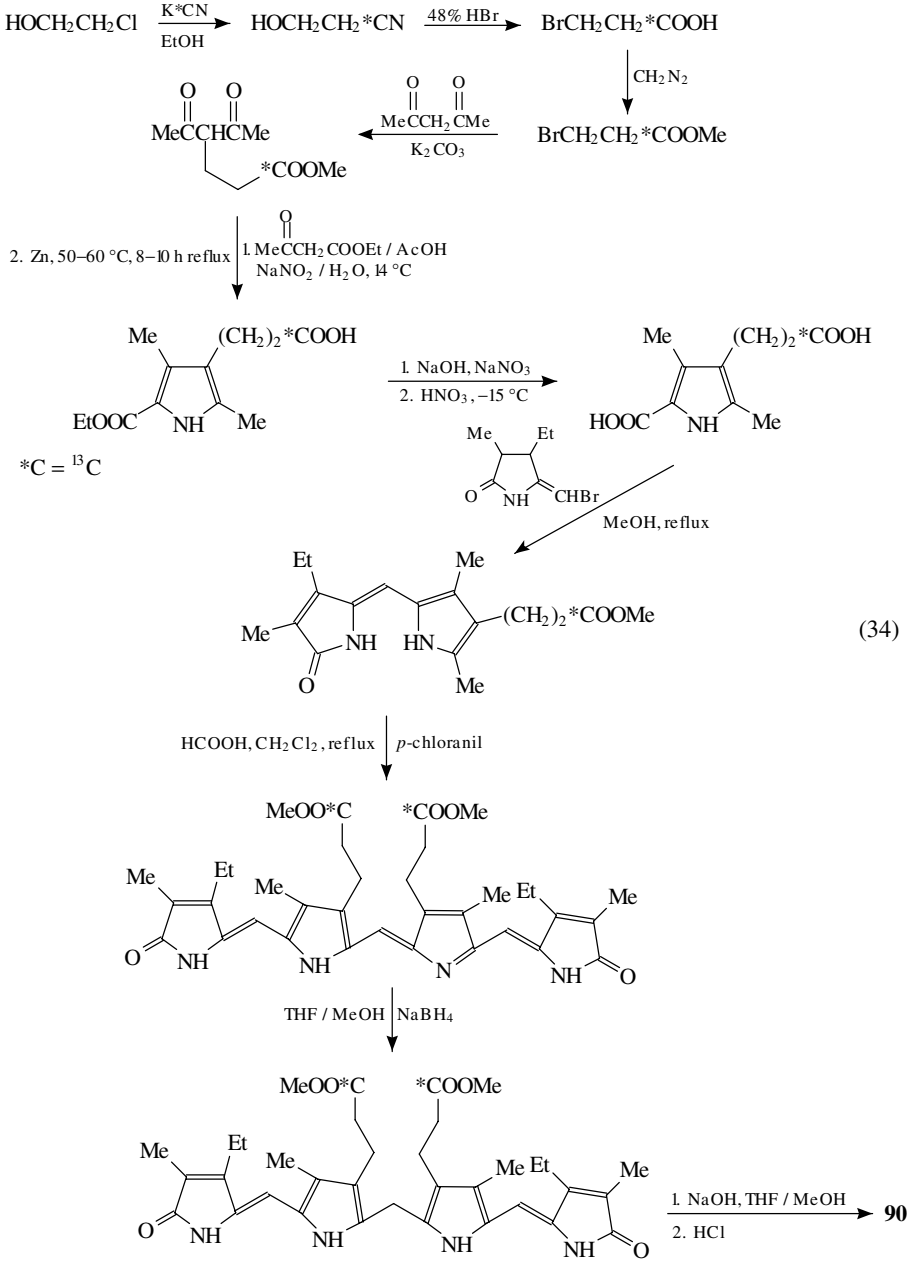
### *4. Synthesis of bis-[$^{13}$COOH]-mesobilirubin-XIII$\alpha$*

Mesobilirubin-XIII$\alpha$ labelled with $^{13}$C in two propionic acid $^{13}$COOH groups, **90**, has been synthesized[75] in 11% overall yield from K$^{13}$CN in 10 steps shown in equation 34. **90**, a model compound not found in nature, is to be used to study the conformation of bilirubin in solution[76] or when bound to proteins or in membranes to understand its ability to cross several selective physiological barriers such as placenta and blood–brain barrier




**(90)**

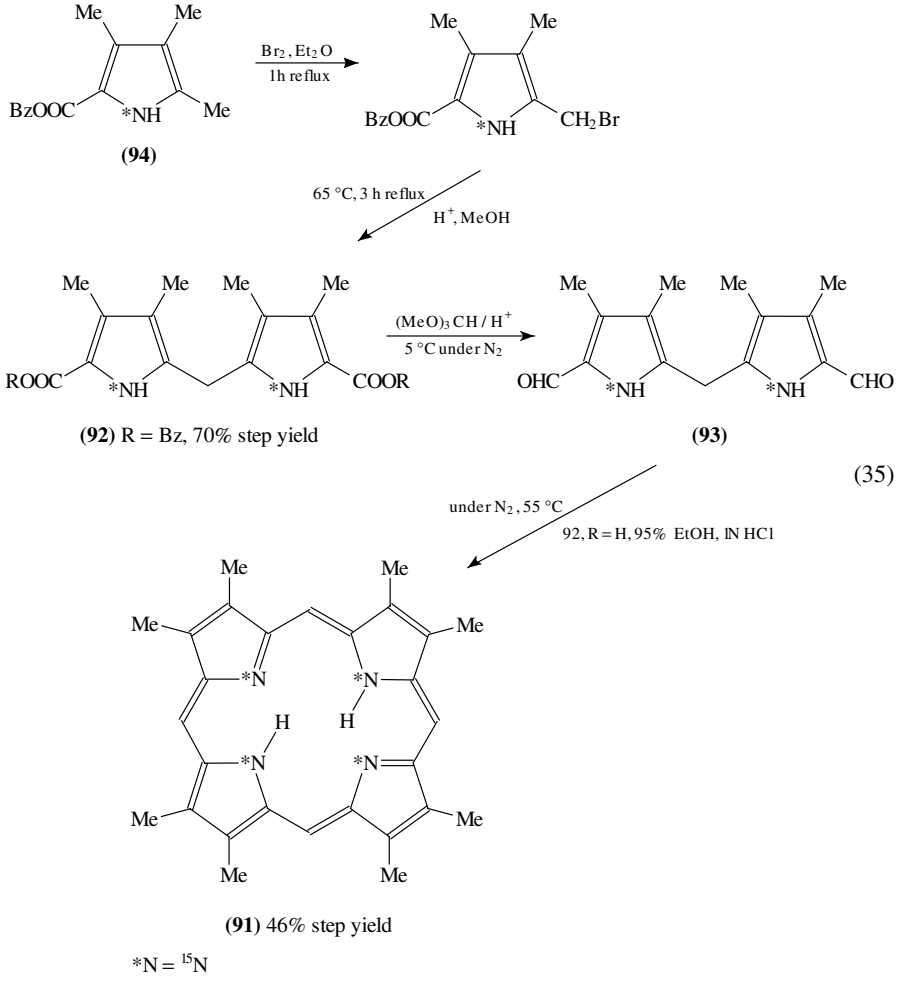
(BBB). It is suggested[75] that conformation-stabilizing intramolecularly hydrogen-bonded bilirubin is involved in transport of **90**.



## C. Synthesis of Nitrogen-15-labelled Compounds

### *1. Synthesis of [$^{15}N_4$]-octamethylporphyrin*

[$^{15}N_4$]-octamethylporphyrin **91** has been synthesized[77] for solid state NMR studies by condensation of [$^{15}N_2$]-5,5′-dicarboxy-3,4,3′,4′-tetramethyldipyrrylmethane **92** with [$^{15}N_2$]-5,5′-diformyl-3,4,3′,4′-tetramethyldipyrrylmethane, **93**, in 46% yield as outlined in equation 35, which follows from the previously described synthetic procedure[78,79].




(35)

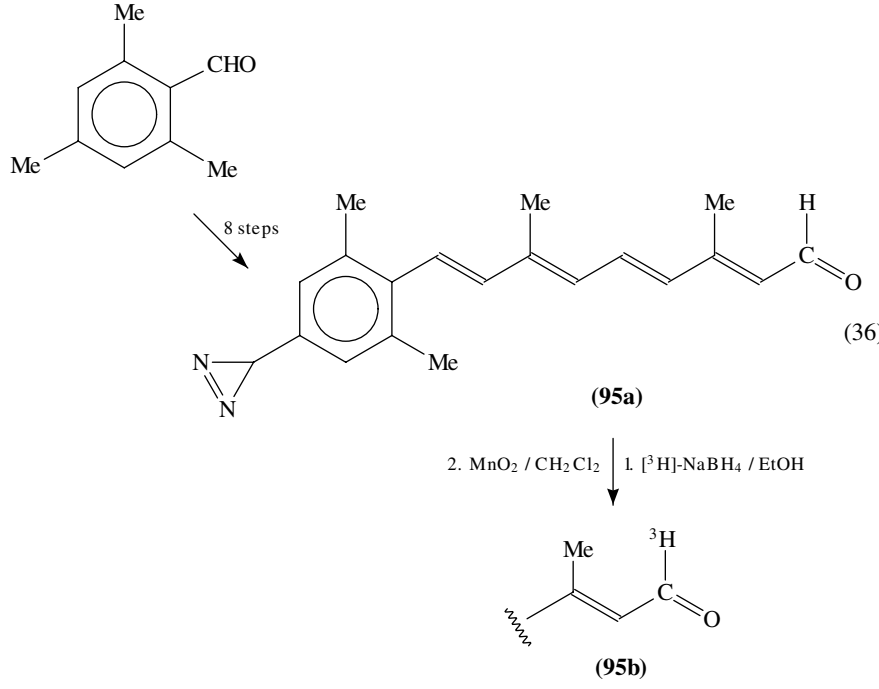
Benzyl [$^{15}$N]-3,4,5-trimethylpyrrol-2-carboxylate, **94**, has been obtained[77,79] in 38% yield in the reaction of [$^{15}$N]-sodium nitrite with benzyl acetoacetate in AcOH at 10–5 °C, during 18 h, followed by addition of 3-methyl-2,4-pentanedione, AcONa, powdered zinc in AcOH, heating the suspension at 60 °C during 1 h, pouring the suspension over ice-water (5 °C, 18 h) and recrystallization (MeOH–$H_2O$).

## III. SYNTHESIS AND USES OF DIENES AND POLYENES LABELLED WITH TRITIUM

### A. Synthesis of Tritium-labelled Retinol and Retinoic Acid Analogues

#### *1. Synthesis of 3,7-dimethyl-9-[4′-(3H-diazirinyl)-2′,6′-dimethylphenyl]-2E,4E,6E,8E-nonatetraenal-1-$^3$H,* ***95b***

This photoaffinity labelling analogue of all-*trans*-retinal, **95b**, has been tritium labelled[80] by reduction of unlabelled aldehyde **95a** with [$^3$H]-$NaBH_4$ and subsequent oxidation of the obtained tritium-labelled retinol with activated manganese dioxide. The product **95b** (specific activity 38.3 mCi mmol$^{-1}$) has been isolated by preparative TLC (equation 36).

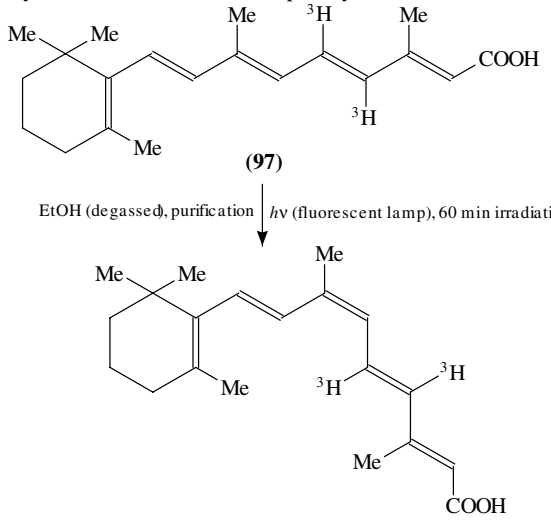



(36)

**95b** has been used to investigate the mechanism of the light-driven proton pumping activity taking place in purple membranes[81,82] of halobacteria living in water of very high salt concentration, which they utilize as energy transducers. The purple membrane contains a single protein *bacteriorhodopsin*, folded into its lipid bilayer. The colour is caused by the presence of one equivalent of retinal, 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenal covalently bound to the protein through the protonated Schiff base linkage[81,82].

#### *2. Synthesis of 9-cis-retinoic acid [11,12-$^3H_2$(N)] by photochemical isomerization*

The tritium-labelled 9-*cis*-retinoic acid [11,12-$^3H_2$], **96**, the natural ligand for retinoid X receptor (RXR)[83], has been produced[84] by small-scale photoisomerization of all-*trans*-retinoic acid [11,12-$^3H_2$(N)], **97**, followed by HPLC purification (equation 37).




(37)

**(96)** specific activity of 48.7 Ci mmol$^{-1}$, radiochemical purity > 96%

### *3. Synthesis of isotopically labelled retinoids*

*a. Synthesis of tritium-labelled retinyl acetate*. Retinyl acetate, **98**, labelled with tritium at the $C_{(11)}$ and $C_{(12)}$ positions, has been obtained[27] by partial reduction of oxenin **99** with tritium gas to hydroxenin [11,12-$^3H_2$], **100**, and subsequent acetylation and rearrangement (equation 38). The phase transfer 'rearrangement solvent' is 10 mg of acetyl trimethylammonium bromide (CETAB) + 10 $\mu$L pyridine in 100 mL of $CH_2Cl_2$.

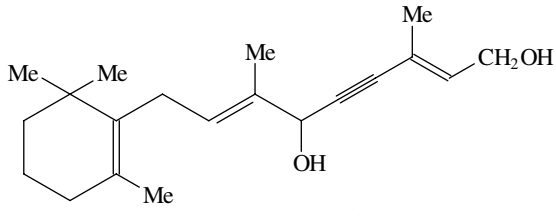
*b. Synthesis of tritium-labelled [11,12-$^3H_2$] retinol, **101**, retinyl ester, **102**, and all-trans retinoic acid, **103***. Retinol-[11,12-$^3H_2$], **101**, was obtained[27] by alkaline hydrolysis of **98**, retinoic-[11,12-$^3H_2$] acid, **103**, was obtained by oxidation of **101** with manganese dioxide and silver oxide, retinyl-[11,12-$^3H_2$] propionate, **102a**, retinyl [11,12-$^3H_2$]-myristate, **102b**, and retinyl-[11,12-$^3H_2$] palmitate, **102c**, have been obtained by treatment of **101** with propionic anhydride and myristoyl chloride or palmitoyl chloride, respectively (equation 39).

Retinyl esters **102a–c** (1 mCi ml$^{-1}$) stored under argon at $-60\,^{\circ}$C in toluene containing 40 $\mu$g of 2-*t*-butyl-4-methoxyphenol and 4 $\mu$L of pyridine are quite stable. After 1 year about 60% decomposition was noted, due to radiolysis in the case of **102c**. Retinoic acid **103** under similar conditions is also radiochemically stable, but after 4 months the material has to be repurified[85]. Specific activities of tritium-labelled retinoids in the 10–40 Ci mmol$^{-1}$ range have been found necessary in view of the discovery and use of cellular retinoid binding proteins[86].

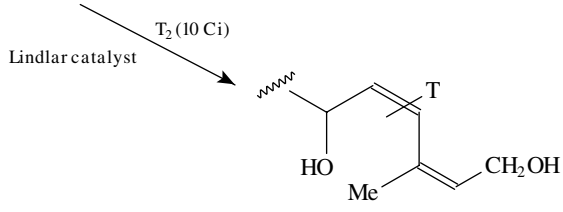
## B. Synthesis of Tritium-labelled Analogues of Juvenile Insect Hormones

### *1. Synthesis of tritium-labelled photoaffinity analogues of natural hormones*

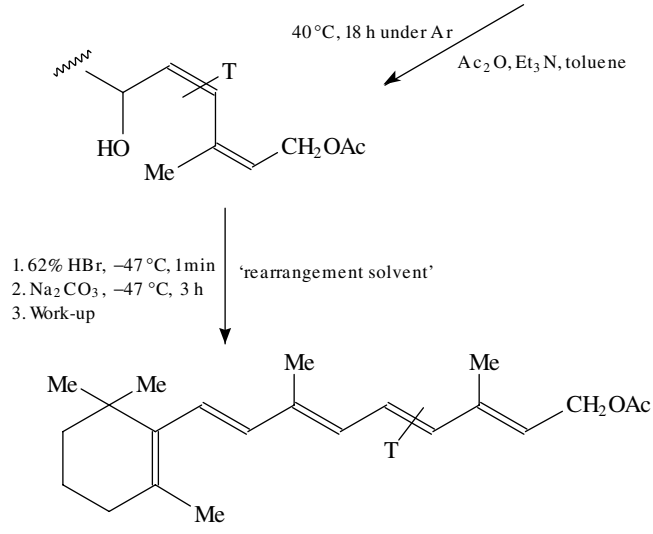
The tritium-labelled diazoacetates **107**, **108** and **109** have been obtained[87a] from the corresponding tritiated[87b] juvenile hormones (JH), JHI, JHII and JHIII (**104–106**), by




**(99)**




**(100)** 40% yield, radiation purity of 90%, specific activity 40–50 Ci mmol$^{-1}$



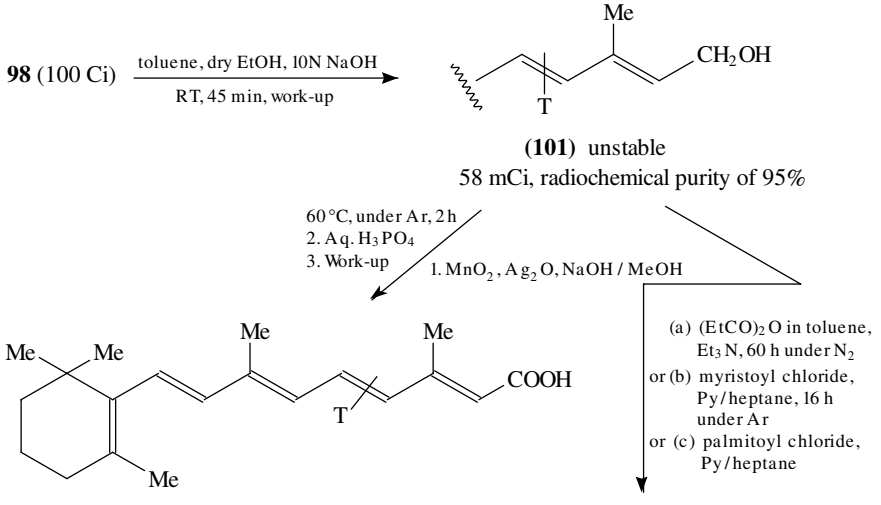

(38)

**(98)** specific activity 22.7 Ci mmol$^{-1}$, 69 mCi mg$^{-1}$; radiochemical purity of 91%

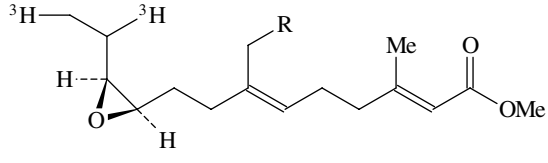
selective reduction of the ester group, followed by acylation of the corresponding alcohols with glyoxylic acid chloride tosylhydrazone **110**[88] and subsequent treatment with *N*,*N*-dimethylaniline and triethylamine[89] (equations 40 and 41). **107**, **108** and **109** are used for photoaffinity labelling of extracellular and cellular JH binding proteins[87].

### *2. Synthesis of [12-$^3$H]-farnesoic acid and [13-$^3$H]-farnesyl diazomethyl ketone*

The tritium-labelled farnesoic acid [$^3$H]-MF, **111**, and its diazomethyl ketone analogue, [$^3$H]-FDK, **112**, which can be used for the photoaffinity labelling of MF binding

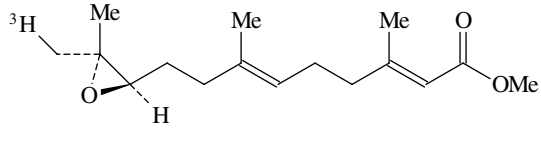



(39)

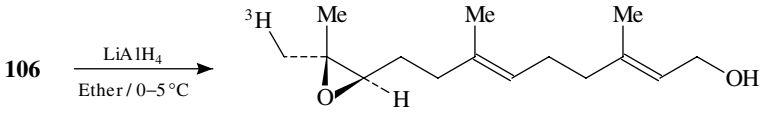



**(104)** JHI; R = Me
specific activity 58 Ci mmol$^{-1}$

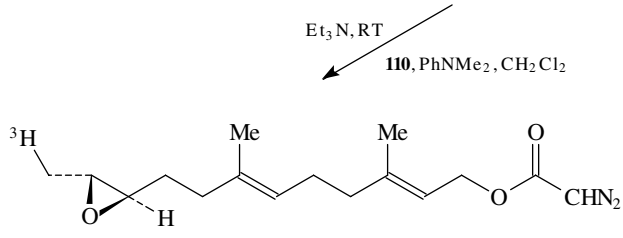
**(105)** JHII; R = H
specific activity 58 Ci mmol$^{-1}$




**(106)** JHIII, specific activity 15 Ci mmol$^{-1}$

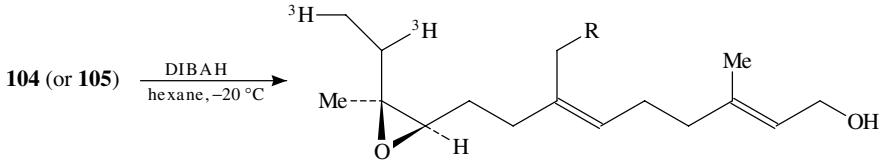



43% radiochemical yield

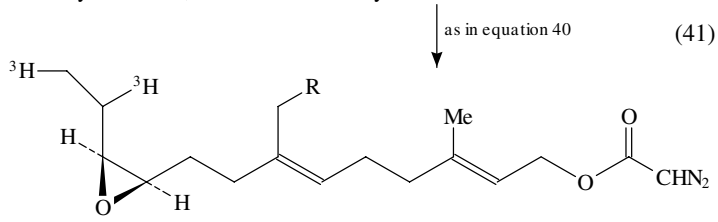



(40)

**(107)** 52% radiochemical yield




R = Me, 72% radiochemical yield R = H; 62% radiochemical yield




(41)

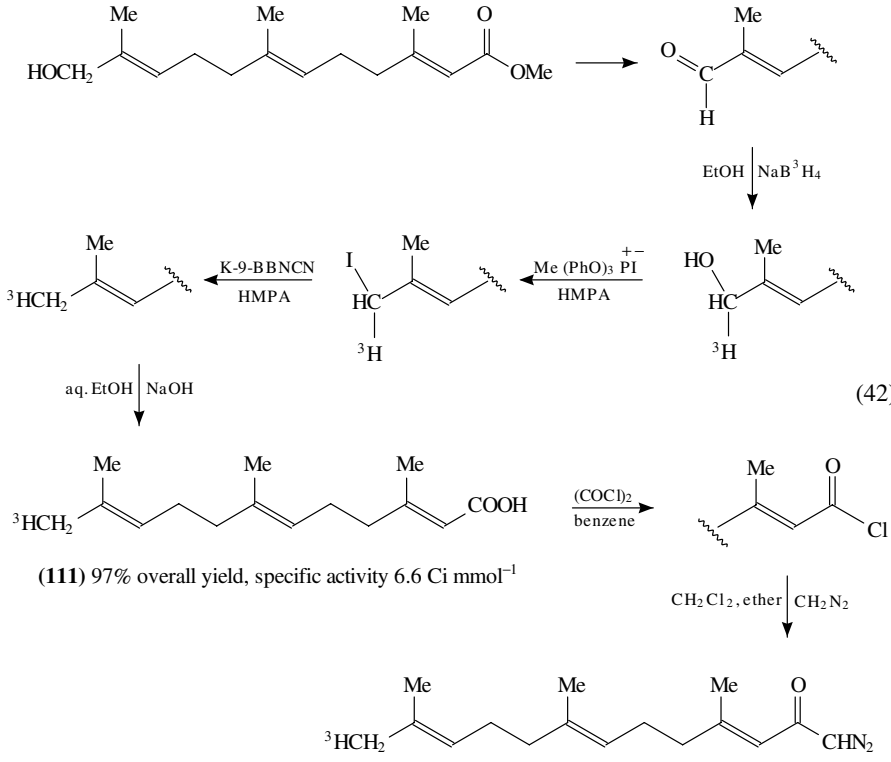
**(108)** R = Me, 65% radiochemical yield
**(109)** R = H, 58% radiochemical yield

proteins, have been synthesized[90] in the procedure presented in equation 42, to examine the biochemical role of MF in crustacean physiology[91].

## C. Synthesis of Tritium-labelled Prostaglandin Analogues

### *1. Synthesis of enprostil-[13,14-$^3$H]*

Enprostil, **113**, antisecretory prostaglandin (PG) analogue, containing tritium in the metabolically stable 13,14-positions and having a high specific activity of 41 Ci mmol$^{-1}$, has been prepared[92] in a fifteen-step microscale synthesis (equation 43). The tritium-labelled **113** was required for use in absorption, distribution, metabolism and excretion studies before the development of this substance for treatment of gastrointestinal ulcers in man[93]. Labelled prostaglandins having specific activity in excess of 100 Ci mmol$^{-1}$ are to be developed[92].




(42)

**(111)** 97% overall yield, specific activity 6.6 Ci mmol$^{-1}$

**(112)** specific activity 6.6 Ci mmol$^{-1}$ (24% radiochemical yield) + **(111)** 72% radiochemical yield

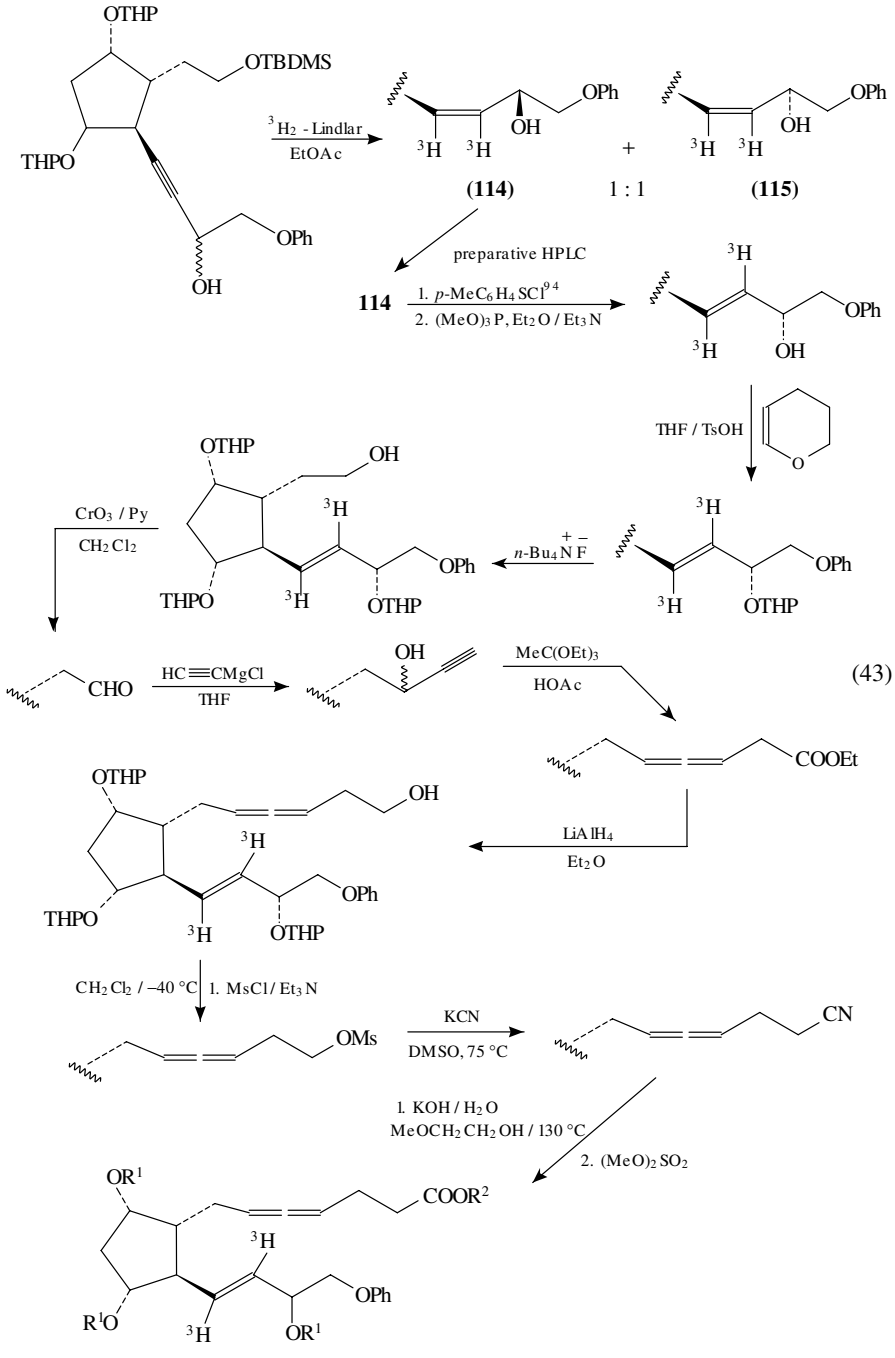
### *2. Synthesis of di-tritiated 9-(O)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$ methyl esters*

Two di-tritiated isocarbacyclin methyl esters **116** and **117** in the title have been synthesized[95] from (*Z*)-olefinic precursors **118** and **119** at the $\omega$-side chain by catalytic hydrogenation with tritium gas (equations 44 and 45). The therapeutic candidates for cardiovascular deseases[96], **116** and **117**, were required for preclinical studies and for use in RIA analysis.

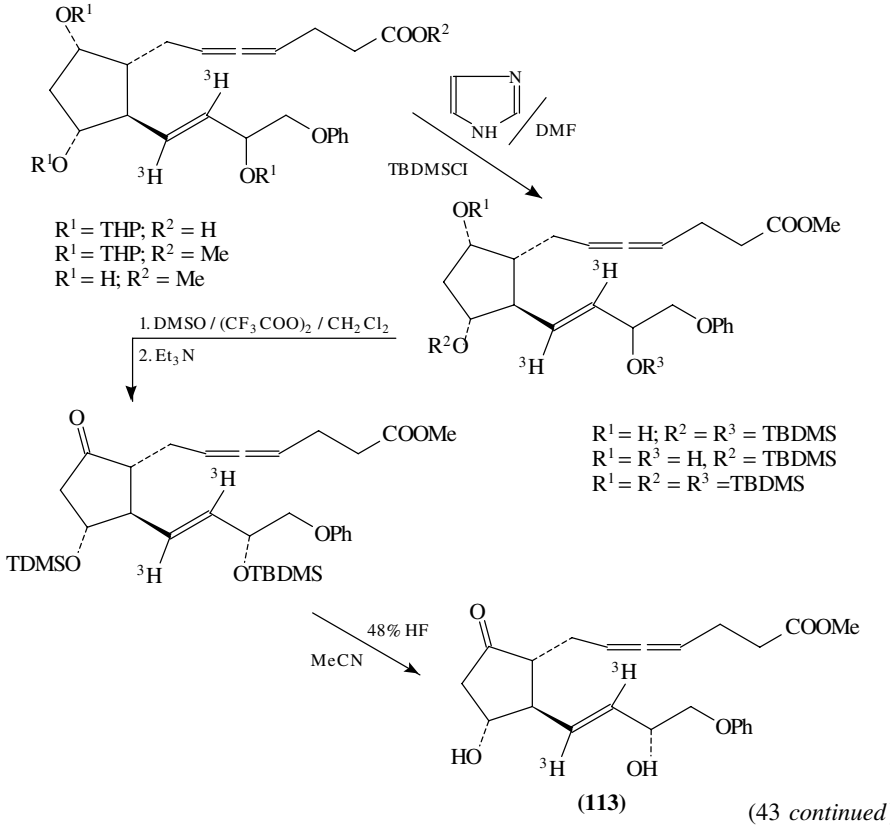
### *3. Enzymatic synthesis of tritium-labelled prostaglandin $D_2$ and other prostaglandins*

Tritium-labelled [5,6,8,9,12,14,15(*n*)-$^3$H]PGD$_2$ **120**, prepared in one-stage enzymatic synthesis, using PGH-synthetase/PGH-PGD-isomerase[97], from tritium-labelled [5,6,8,9,11,12,14,15(*n*)]arachidonic acid, produced previously[98], has been converted[97] by enzymatic and chemical transformations into 15-keto-13, 14-dihydro-[$^3$H]PGD$_2$, **121**, 9$\alpha$, 11$\beta$-[$^3$H]PGF$_2$, **122**, 9-deoxy-$\Delta^9$-[$^3$H]PGD$_2${[$^3$H]PGJ$_2$}, **123**, and 9-deoxy-$\Delta^{9,12}$-13,14-dihydro-[$^3$H]PGJ$_2$, **124**.

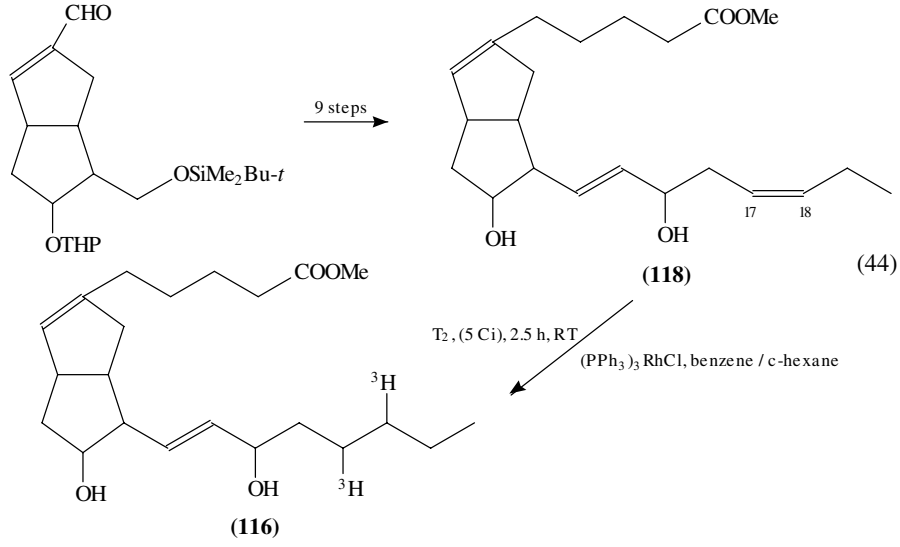
L-Selectride, LiB[CH(Me)Et]$_3$H, was found to be a more effective reducing agent than $NaBH_4$ in the synthesis of compound **122**. Specific activities of starting **120** and **121** were 120 Ci mmol$^{-1}$, and that of arachidonic acid was 180 Ci mmol$^{-1}$.


OTHP
OTBDMS
THPO
OPh
OH
$^3H_2$ - Lindlar
EtOAc
$^3H$ $^3H$
OPh
OH
+
(114)
1 : 1
(115)
preparative HPLC
114
1. p-MeC6H4SCl[94]
2. (MeO)3P, Et2O / Et3N
THF / TsOH
O
CrO3 / Py
CH2Cl2
n-Bu4N+ F−
THPO
OTHP
CHO
HC≡CMgCl
THF
MeC(OEt)3
HOAc
COOEt
LiAlH4
Et2O
CH2Cl2 / –40 °C
1. MsCl / Et3N
OMs
KCN
DMSO, 75 °C
CN
1. KOH / H2O
MeOCH2CH2OH / 130 °C
2. (MeO)2SO2
OR1
COOR2
R1O

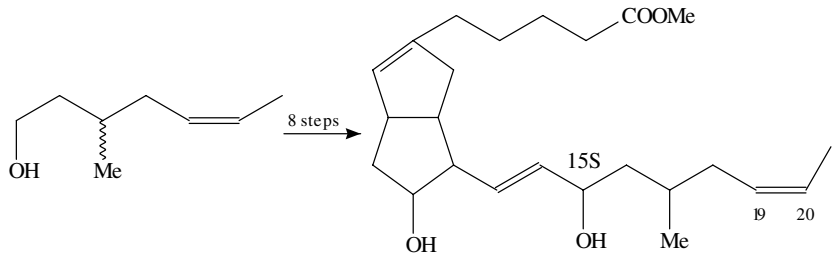
(43)




(43 *continued*)

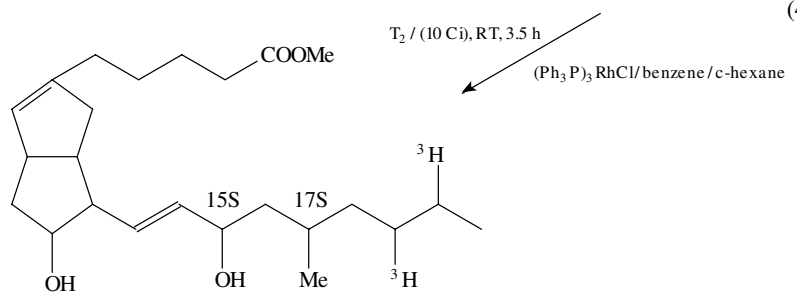



(44)

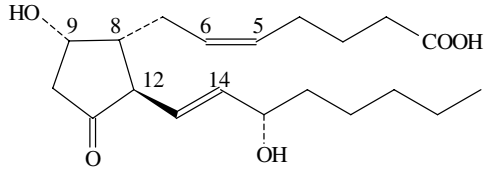



**(119)**

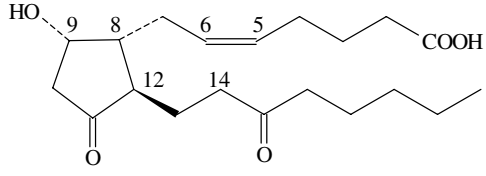
(45)



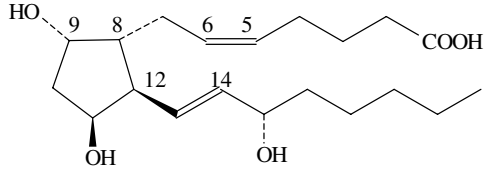

**(117)** specific activity 50 Ci mmol$^{-1}$



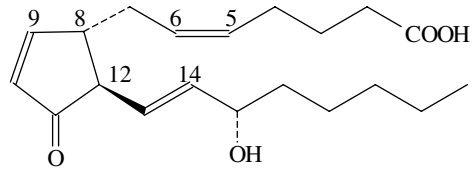

**(120)**



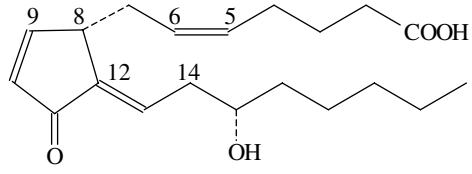

**(121)**



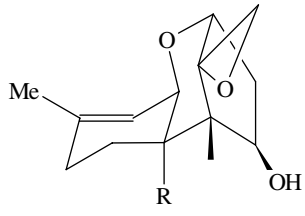

**(122)**

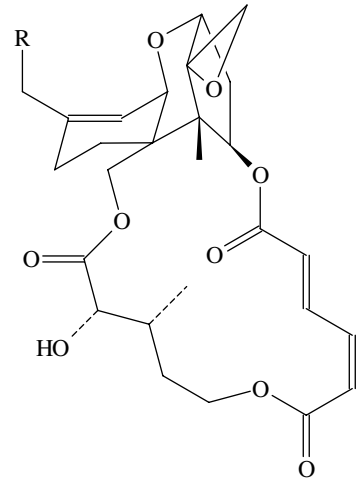



**(123)**




**(124)**




**(125)** R = CHTOH. 32% yield, specific activity 266 mCi mmol$^{-1}$

**(126)** R = T, specific activity 130 mCi mmol$^{-1}$, 4% yield

**(127)** R = $CH_2OH$

**(128)** R = CHO

**(129)** R = OH

**(130)** R = $OSO_2Me$

### *4. Synthesis of tritium-labelled [15-$^3$H]-verrucarol, **125**, and [16-$^3$H]-verrucarin A, **126***

The naturally occurring mycotoxins, **125** and **126**, produced mainly by fungi[99] and implicated in the variety of toxicoses in man and animals[99,100], have been tritium labelled[101] (equations 46 and 47) for use in toxicology metabolism and pharmacokinetic studies. Position 15 in verrucarol and position 16 in verrucarin A have been tritium-labelled, because they should not suffer from the loss of labelling protons during the

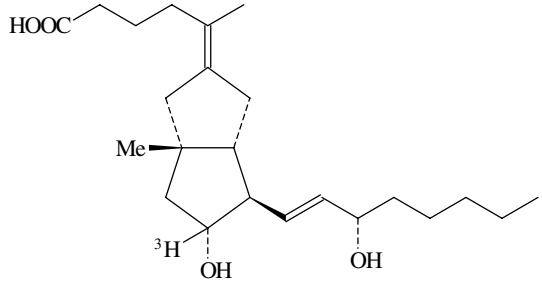
metabolic studies in animals.

$$\mathbf{127} \xrightarrow{RuCl_2(Ph_3P)_3} \mathbf{128} \xrightarrow[\text{overnight}]{[^3H]NaBH_4,\ THF,\ RT} \mathbf{125} \quad (46)$$

$$\mathbf{129} \xrightarrow[Et_3N\ /\ CH_2Cl_2,\ 0\ ^\circ C]{MeSO_2Cl} \mathbf{130} \xrightarrow[CH_2Cl_2,\ C_{16}H_{33}\overset{+}{P}(C_4H_9)_3Br^-]{[^3H]NaBH_4,\ 200\ mCi,\ \text{specific activity } 11.4\ Ci\ mmol^{-1}} \mathbf{126} \quad (47)$$

### *5. Synthesis of tritium-labelled ciprostene*

The tritium-labelled title compound, (U-3H)-61,431, **131**, has been synthesized[102] by treating the free acid with methyl iodide and diisopropylethylamine, reaction of the U-61,431 methyl ester with *t*-butyldimethylsilyl chloride, separation of the 11-*O*-silyl and 15-*O*-silyl derivatives by column chromatography, oxidation of the 15-*t*-butyldimethylsilyl ether, methyl ester to 11-keto derivative with chromium trioxide and stereoselective reduction of the 11-keto group with sodium borotritide, to give the 11-$\alpha$-hydroxy epimer. Deprotection of the (U-3H)-15-silyl methyl ester with $Bu_4NF$, followed by washing out the labile tritium by aqueous KOH/MeOH, gave (11-3H)-U-61, 431, which after semi-preparative HPLC has been injected subcutaneously into rats. During the first 24 h about 40% of dose radioactivity was found in the urine, and about 50% of dose in faeces 72 h after dosing. Less than 1% of tritiated water were excreted in urine, faeces and expired air.




**(131)**

### *6. Synthesis of tritium-labelled fluorescent derivatives of prostaglandins*

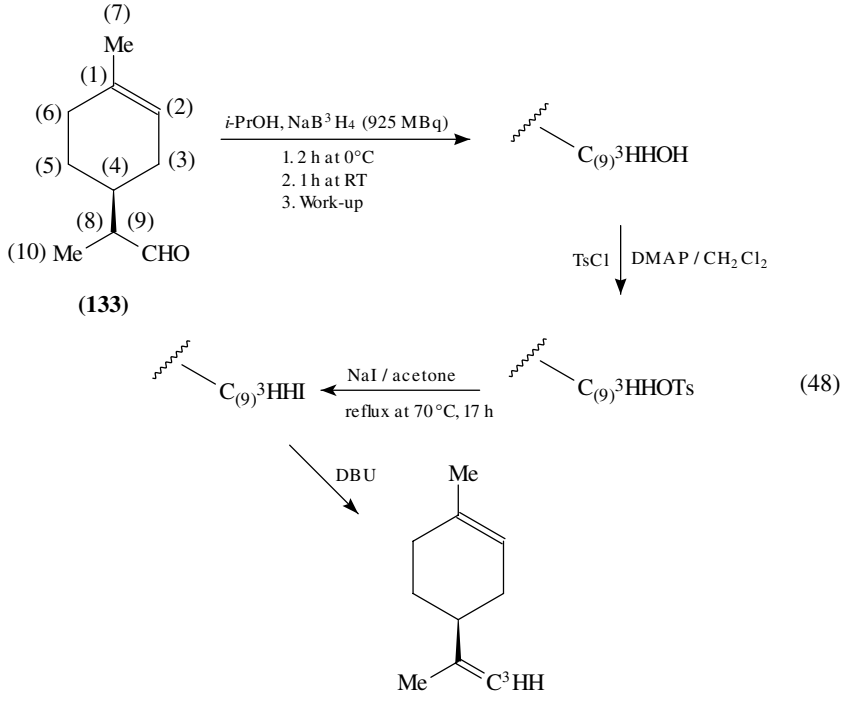
Tritium-labelled $PGE_1$ (50 Ci mmol$^{-1}$), $PGF_{2\alpha}$ (150 Ci mmol$^{-1}$) and $PGE_2$ (180 Ci mmol$^{-1}$) have been converted[103] into 1,5-DNS derivative, 1,5-DNS-1-(dimethylamino)-5-naphthalenesulphonic acid hydrate, $Me_2NC_{10}H_5SO_3H{\bullet}xH_2O$, a highly sensitive fluorescent probe for proteins[104–106]. The doubly labelled [$^3$H]-DNS-PGs could therefore be used as a radioactive fluorescent probe for liquid receptor interactions in biological membranes and also for determination of the molar radioactivity isotopically labelled PGs, when the amount of the labelled compound is very small.

## D. Synthesis of Limonene

### *1. Synthesis of (4S)-(−)-[9-$^3$H]-limonene*

The title compound, **132**, (4*S*)-[9-$^3$H]-1-methyl-4-(1′-methylethenyl)cyclohexene, has been synthesized[107] from (1′*S*,2*R*,*S*)-2-(4′-methylcyclohex-3′-enyl)propanal [(4*S*,8*R*,*S*)-(−)-1-*p*-menthen-9-al, **133**], via a route shown in equation 48 in 55% overall yield

and improved enantiomeric purity (72% ee, compared with the literature method[108] of 38% ee). The radioactive (4*S*)-(−)-limonene, **132**, was needed as substrate in the course of studies of the biosynthesis[107] of carvone in *Mentha spicata* (spearmint).




**(133)**

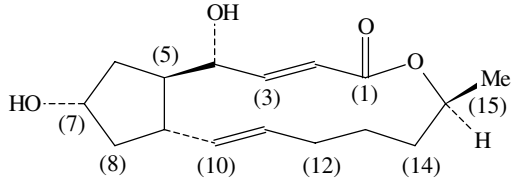
[9-$^3$H]-(**132**)
specific activity 629 MBq mmol$^{-1}$

(48)

## E. Synthesis of Dienes by Catalytic and Radiochemical Methods

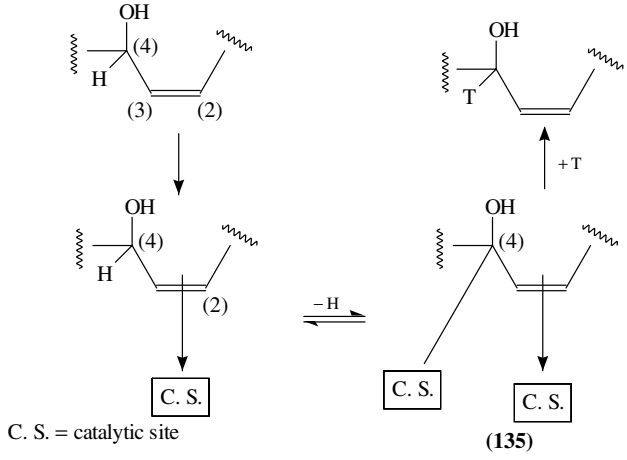
### *1. Synthesis of tritium-labelled brefeldin-A by catalytic isotope exchange with tritium gas*

The title compound BFA, **134**, has a profound effect on the Golgi apparatus and can alter the membrane traffic. Tritium-labelled **134** should help to understand its biological action. **134** has been labelled with tritium[109] at positions $\alpha/\beta$ to both double bonds (whereas the

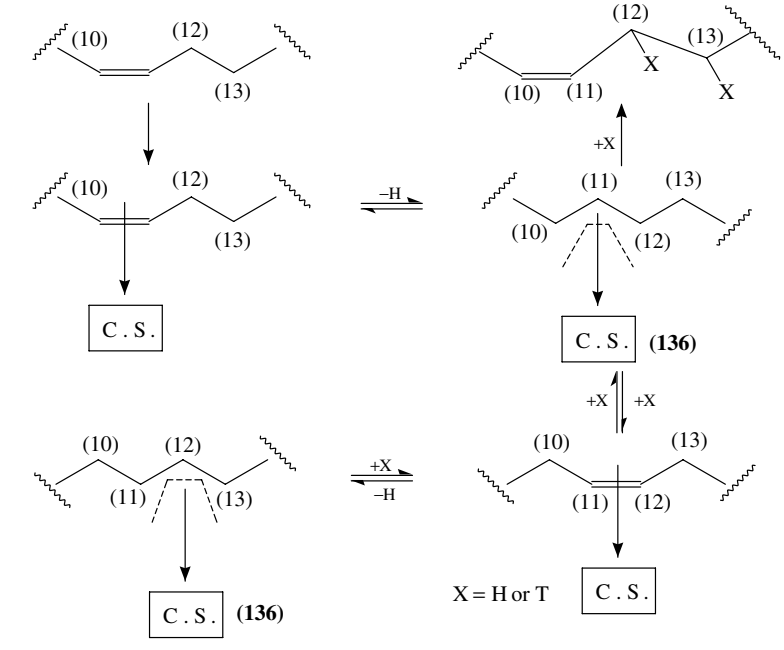



**(134)** Brefeldin A

labelling on the double bond was of minor importance) by hydrogen isotope exchange of **134** with tritium gas ($T_2$) in 1,4-dioxane over a commercial palladium catalyst supported on diatomaceous earth (5% metallic weight). The addition of air in the gas phase increased the catalytic activity. The exchange has been considerably enhanced when the air/$T_2$ ratio was about four. The specific activities of **134** were up to 2.8 Ci mmol$^{-1}$. Two mechanisms for tritium incorporation into **134**, involving two different adsorbed species, '$\sigma-\pi$', **135**, and '$\pi-$allylic', **136**, on the catalyst surface have been proposed[110] (equations 49 and 50, respectively) and discussed[109]. The investigation of all factors governing the exchange reaction should result in obtaining higher tritium specific activities of **134**.



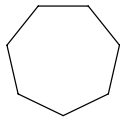

(49)



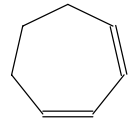

(50)

### *2. Synthesis of simple seven-membered ring compounds labelled with tritium*

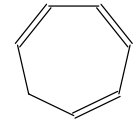
The following 14 seven-membered ring compounds, increasing in complexity from cycloheptane to complicated benzodiazepine systems, have been labelled with tritium[111] using 'activated tritium' (AcT method) employing a microwave power generator[112], 'adsorbed tritium' at RT (AdT method[113]) and high-temperature tritium ion ('HTI' method[111]): cycloheptane, **137**, 1,3-cycloheptadiene, **138**, 1,3,5-cycloheptatriene, **139**, 2-cyclohepten-1-one, **140**, (*t*)-3,3,5-trimethylhexahydroazepine, **141**, 2-oxohexamethyleneimine (caprolactam), **142**, 1-aza-2-methoxy-1-cycloheptene, **143**, 1,4-diazacycloheptane (homopiperazine), **144**, azulene, **145**, 1-benzosuberone, **146**, 1,8-diazabicyclo-[5.4.0]undec-7-ene, **147**, 5*H*-dibenzo[*b*,*f*]azepine (iminostilbene), **148**, *trans*-10,11-dibromodibenzosuberone, **149**, and 8-chloro-11-(4-methyl-1-piperazinyl)5*H*-dibenzo[*b*,*e*]diazepine (clozepine), **150**.



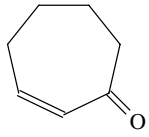
**(137)** 10.5 mCi yield, specific activity 31.8 mCi mmol$^{-1}$



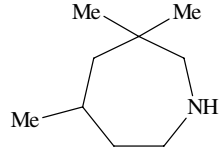
**(138)** 8.6 mCi yield specific activity 8.9 mCi mmol$^{-1}$



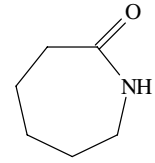
**(139)** 6.8 mCi yield specific activity 17 mCi mmol$^{-1}$



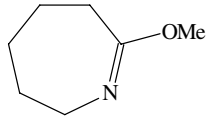

**(140)** 134 mCi yield specific activity 157 mCi mmol$^{-1}$



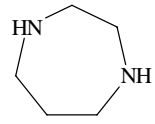

**(141)** 2.4 mCi yield specific activity 16 mCi mmol$^{-1}$



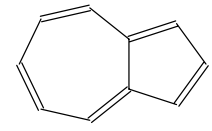

**(142)** 166 mCi yield specific activity 107 mCi mmol$^{-1}$



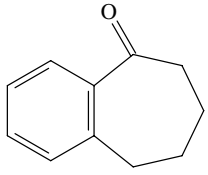

**(143)** 299 mCi yield specific activity 428 mCi mmol$^{-1}$



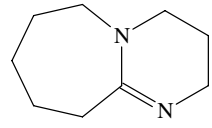

**(144)** 32 mCi yield specific activity 48 mCi mmol$^{-1}$



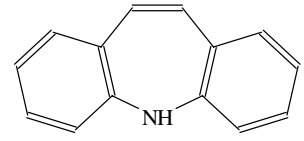
**(145)** 48 mCi yield specific activity 185 mCi mmol$^{-1}$




**(146)** 172 mCi yield specific activity 1833 mCi mmol$^{-1}$

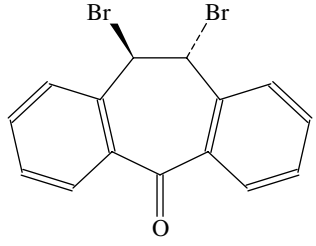



**(147)** 101 mCi yield specific activity 151 mCi mmol$^{-1}$

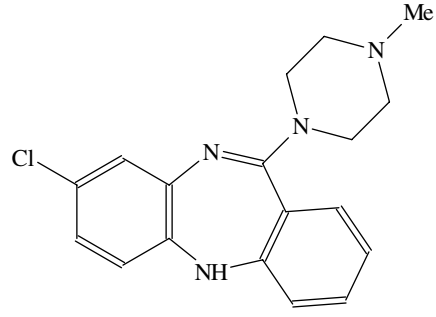



**(148)** 117 mCi yield specific activity 238 mCi mmol$^{-1}$

Many biologically active substances and neuroleptic drugs have a seven-membered ring in their structure. Benzodizapines of extremely high specific activity used in receptor binding studies are isotopically labelled by synthesis[114]. The specific activities of compounds **137–150** are sufficiently high for *in vitro* metabolic and radiotracer studies.




**(149)** 17 mCi yield
specific activity 43 mCi mmol$^{-1}$




**(150)** 2 mCi yield
specific activity 562 mCi mmol$^{-1}$

The distribution of tritium in compounds **137–150** can be determined by tritium NMR spectroscopy without chemical manipulations[115]. The structure retention index relationship (SR IR)[116] has been used for identification of unknown radioactive peaks and to differentiate by-products from radioimpurities from extraneous sources.

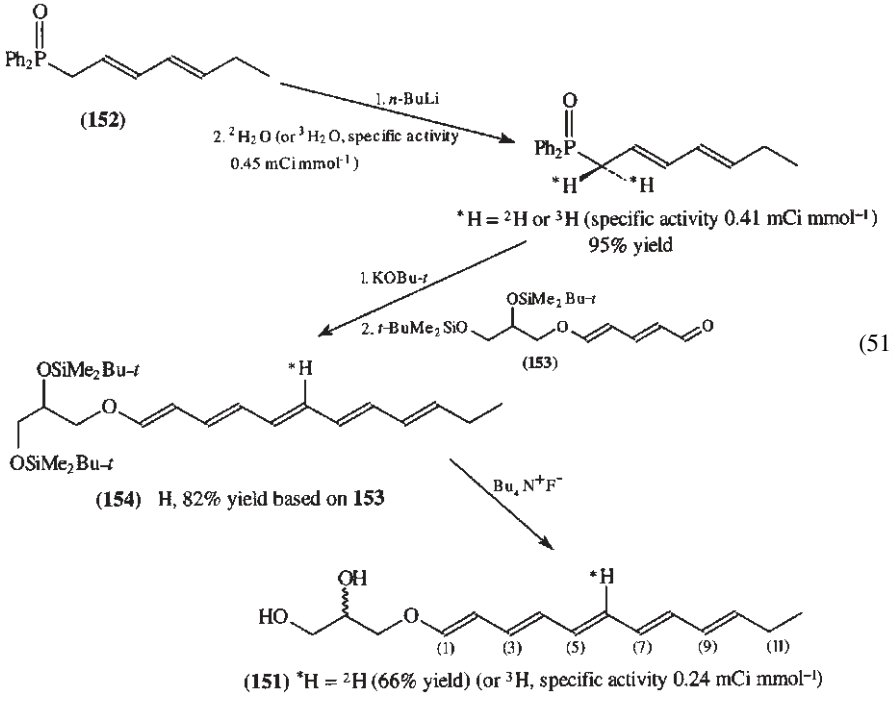
## F. Tritium Isotope Effects in Synthesis of Polyenes

### *1. Synthesis of [6-$^2$H] and [6-$^3$H] fecapentaene*

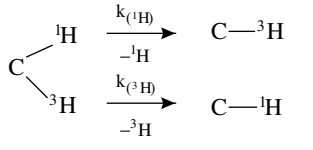
Fecapentaene **151**, a potent mutagen, potential inducer of colon cancer, first isolated from human feces[117,118], has been deuterium and tritium labelled[119] by exchange of the $\alpha$-protons of (*E*,-*E*)-2,4-heptadienyldiphenylphosphine oxide, **152**, with $^2H_2O$ or $^3H_2O$, followed by Wittig–Horner condensation with aldehyde **153**, and deprotection of the silylated derivative **154** with fluoride (equation 51), **151** is used in the study of its interactions with DNA[119].

The maximum specific activity of tritium[120] ($I_{1/2} = 12.33$ years) equals 9664 Ci g$^{-1}$.

Tritium specific activity of the product **151** [$^3$H] indicates a slightly higher retention of $^3$H relative to $^1$H in the coupling second step. No tritium, deuterium and carbon-14 KIE and exchange systematic study of the mechanism of the Wittig–Horner coupling reaction[119] has been carried out. The determined specific activities of the $\alpha$-tritiated 2,4-heptadienyldiphenylphosphine oxide **152** (0.41 mCi mmol$^{-1}$) and of the product **151** (equation 52) (0.24 mCi mmol$^{-1}$) indicate a rather small intramolecular C$-^1$H/C$-^3$H KIE in the rupture of one of the two $\alpha$-carbon–hydrogen bonds in the coupling reaction above. This is characteristic for highly asymmetrical transition states if the rupture of the C–H bond takes place in the rate-determining step and the double $C_{(5)}$=$C_{(6)}$ bond formation occurs in the subsequent fast product **154** formation step. We assume also that silylated derivative **154** and product **151** are tritium-labelled in non-labile $C_{(6)}$ position. Silylated derivative **153** tritium-labelled at the terminal keto group has not been investigated. $^{14}$C KIE have also not been studied. The interpretation of the small $k_H/k_T$ value of 1.4 should therefore be postponed. We note that no yield of **154** with respect to the tritiated precursor **152**, which is needed for intermolecular $^3$H KIE estimation, was given.




(51)

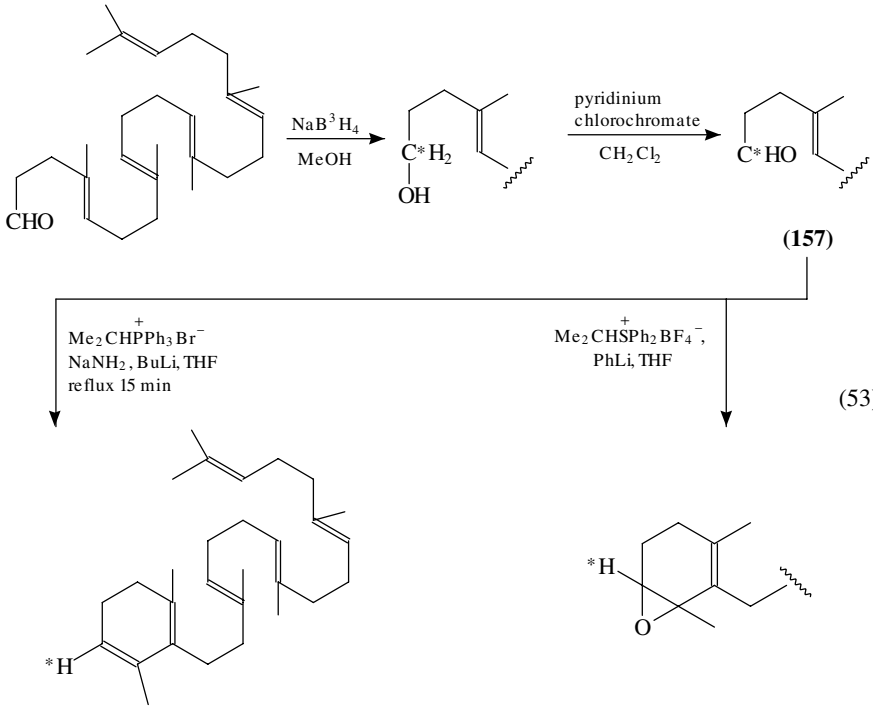


$$k_{(^1H)} \Big/ k_{(^3H)} \cong 1.412 \qquad (52)$$

### *2. Synthesis of [3-$^3$H] squalene and [3-$^3$H]-2,3-oxidosqualene*

[3-$^3$H]Squalene, **155**, and [3-$^3$H]-2,3-oxidosqualene, **156**, the key compounds in studies of the biosynthesis of sterols[121], have been obtained[122] according to the route shown in equation 53, which involves the modified Wittig reaction of [1-$^3$H]trisnorsqualene aldehyde **157** with phosphorus ylide to give **155** or with sulphur ylide to give **156** in high radiochemical yield and high purity.

At room temperature the chemical and radiochemical yields of **155** were different. The chemical yields were in the 30–40% range, while the radiochemical, not very reproducible yields were in the 6–15% range. Cattel and coworkers[122] assigned these differences to tritium isotope effect in the Wittig reaction. No correlation between the specific activity of **155** and the degree of chemical conversion of **157** into **155** has been presented. The temperature dependence of the observed secondary tritium isotope effect has also not been




(53)

**(155)** [3-$^3$H] squalene, 84% radiochemical yield

*H = $^3$H

**(156)** 77% chemical yield

26 mCi, specific activity 1.9 Ci mmol$^{-1}$

studied. The C—*H bond at the aldehyde carbon is not broken in the course of Wittig reaction but the vibrational motion of the aldehyde hydrogen should be less constrained in the transition state corresponding to formation of **155** from **157**.

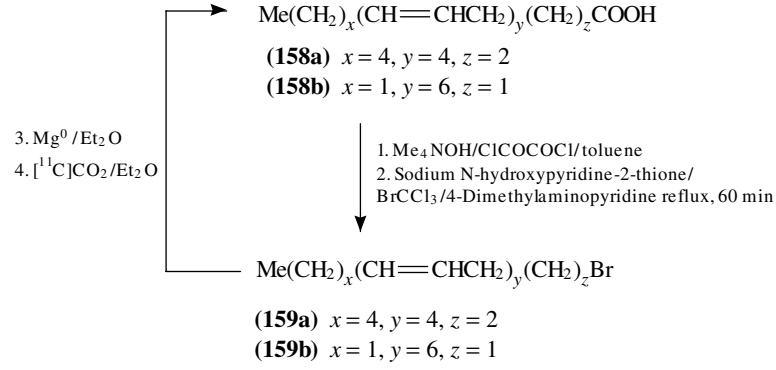
## IV. SYNTHESIS AND USES OF DIENES AND POLYENES LABELLED WITH RADIOISOTOPES OF CARBON

### A. Synthesis and Uses of Dienes and Polyenes Labelled with Carbon-11

#### *1. Remote radiosynthesis of 1-[$^{14}$C]polyhomoallylic fatty acids*

1-[$^{11}$C]arachidonic acid, **158a-$^{11}$C** and 1-[$^{11}$C]docosahexaenoic acid, **158b-$^{11}$C**, have been prepared[123] applying a retro-synthesis involving a radical decarboxylation of *N*-hydroxypyridine-2-thione esters[124] of both arachidonic and docosahexaenoic acid, formation of the polyhomoallylic magnesium bromide from the corresponding (all-*Z*)-1-bromononadeca-4,7,10,13-tetraene, **159a**, and (all-*Z*)-1-bromoheneicosa-3,6,9,12,15,18-hexaene, **159b**, and subsequent carbonylation of the Grignard reagents with [$^{11}$C]$CO_2$ (equation 54). The final radiochemical purities of **158a-$^{11}$C** and **158b-$^{11}$C** were in excess of 95% by radio-HPLC. **158a-$^{11}$C** and **158b-$^{11}$C** were used[123,125] for *in vivo* evaluation of regional brain phospholipid metabolism by PET. Both **158a-$^{11}$C** and **158b-$^{11}$C** are

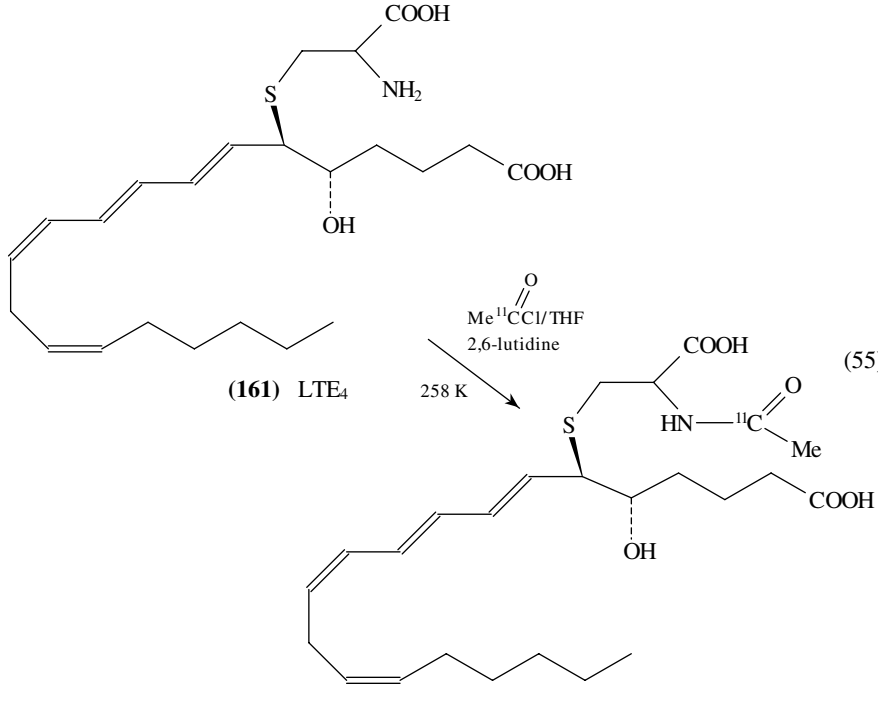
rapidly and selectively incorporated into brain phospholipids[126].




(54)

### *2. Synthesis of 5(S)-hydroxy-6(R)-(N-[1-$^{11}$C]acetyl)cysteinyl-7, 9-trans-11, 14-cis-eicosatetraenoic acid*

The title compound **160**, a biologically potent metabolite of arachidonic acid metabolism, produced in the 5-lipoxygenase pathway in some mammalian cells[127,128], has been synthesized[129–131] by the reaction of leukotriene $E_4$, **161**, with [1-$^{11}$C[acetyl chloride in 1.3% yield based on [1-$^{11}$C] acetyl chloride[129] (equation 55).

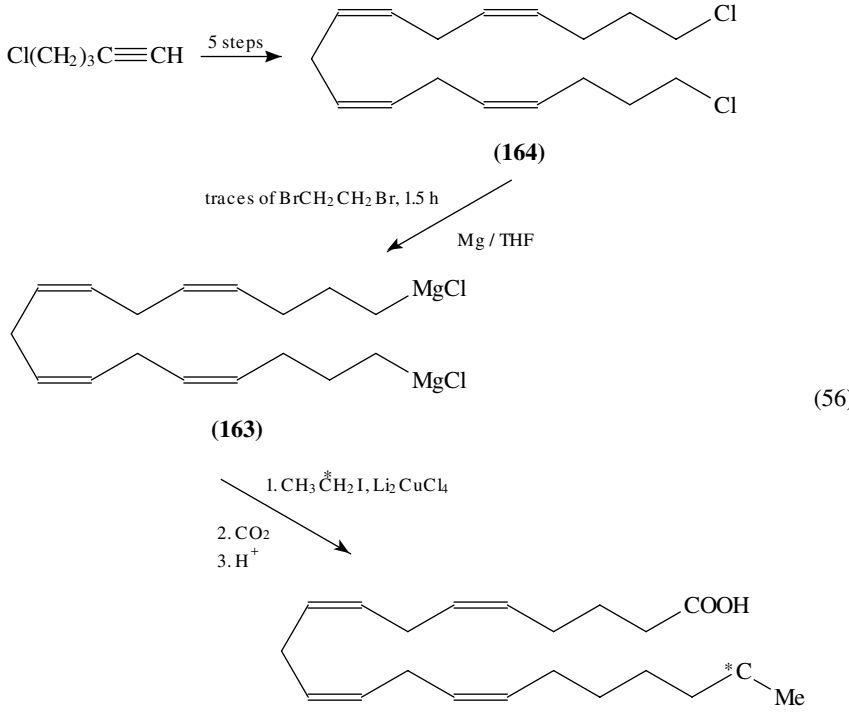



(55)

The complete preparation required 50 min. The PET scans with **160**, performed in normal and mutant rats, showed[129,132] that N-[1-$^{11}$C]acetyl-LTE$_4$ may be used to study various human diseases with impaired bile flow and reduced liver function.

### *3. Synthesis of [19-$^{11}$C]arachidonic acid*

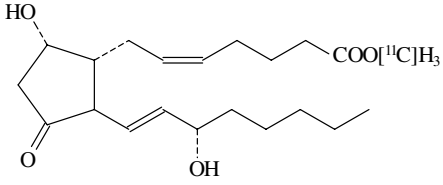
[19-$^{11}$C]Arachidonic acid **162** has been prepared[123,133,134] in 23% decay corrected radiochemical yield within 52 min in a coupling reaction of *bis*-Grignard reagent **163** of (all-*Z*)-1,17-dichloro-4,7,10,13-heptadecatetraene, **164**, with [1-$^{11}$C] ethyl iodide followed by carbonation with $CO_2$ (equation 56). Starting with 20 GBq $^{11}CO_2$, 760 MBq of **162** has been obtained with a specific activity 1.6 GBq μmol$^{-1}$. [19-$^{13}$C]Arachidonic acid, **164**, has been synthesized by trapping the mixture of $^{13}CO_2$ and [$^{11}$C]carbon dioxide in methyl magnesium bromide in THF. The subsequent steps were carried out in an analogous manner to that in equation 56.



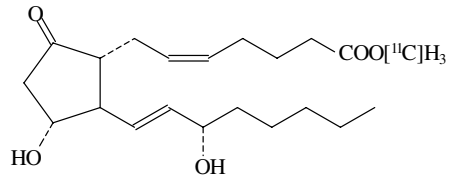

(56)

**(162)** *C = $^{11}$C (98% radiochemical purity)
or **(164)** *C = $^{13}$C

The authors have also synthesized[134] fatty acids labelled with deuterium and carbon-11 in order to investigate if kinetic isotope effects related to fatty acid metabolism can be observed *in vivo* by PET[133,135–137]. *In vitro*, the large kinetic deuterium isotope effects are observed in the oxidation of deuteriated aliphatic carboxylic acids with alkaline permanganate and manganate[135–139].



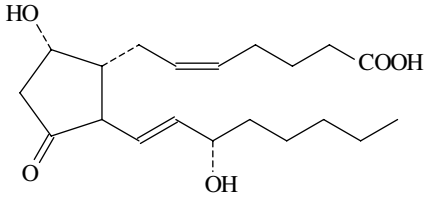

**(165)** $PGD_2$[$^{11}$C]Me




**(166)** $PGE_2$[$^{11}$C]Me

### *4. Synthesis of [$^{11}$C]methyl esters of prostaglandins $D_2$ and $E_2$*

$^{11}$C-Labelled methyl esters of prostaglandin $PGD_2$, **165** and prostaglandin $PGE_2$, **166**, for PET investigations, have been synthesized[140] with the use of [$^{11}$C]methyl iodide via direct estrification of their carboxylate anion, generated *in situ* by the use of tetramethylpiperidine (TMP), to avoid rapid degradation of the prostaglandin when treated with aqueous NaOH in DMF (equation 57).




$PGD_2$

1. TMP, DMSO / DMF
2. [$^{11}$C]$H_3$I, –78 °C
3. 42 °C, 5 min

**165** specific activity 0.9 GBq μmol$^{-1}$ (57)

Starting with 3 GBq [$^{11}$C]carbon dioxide produced in a $^{14}$N($p,\alpha$)$^{11}$C nuclear reaction, the radiochemical yield of **165** was 0.5 GBq at the end of preparative purification performed in *Sep-Pak C18* columns. The methyl esters of prostaglandins have a high affinity for the specific binding sites[141].

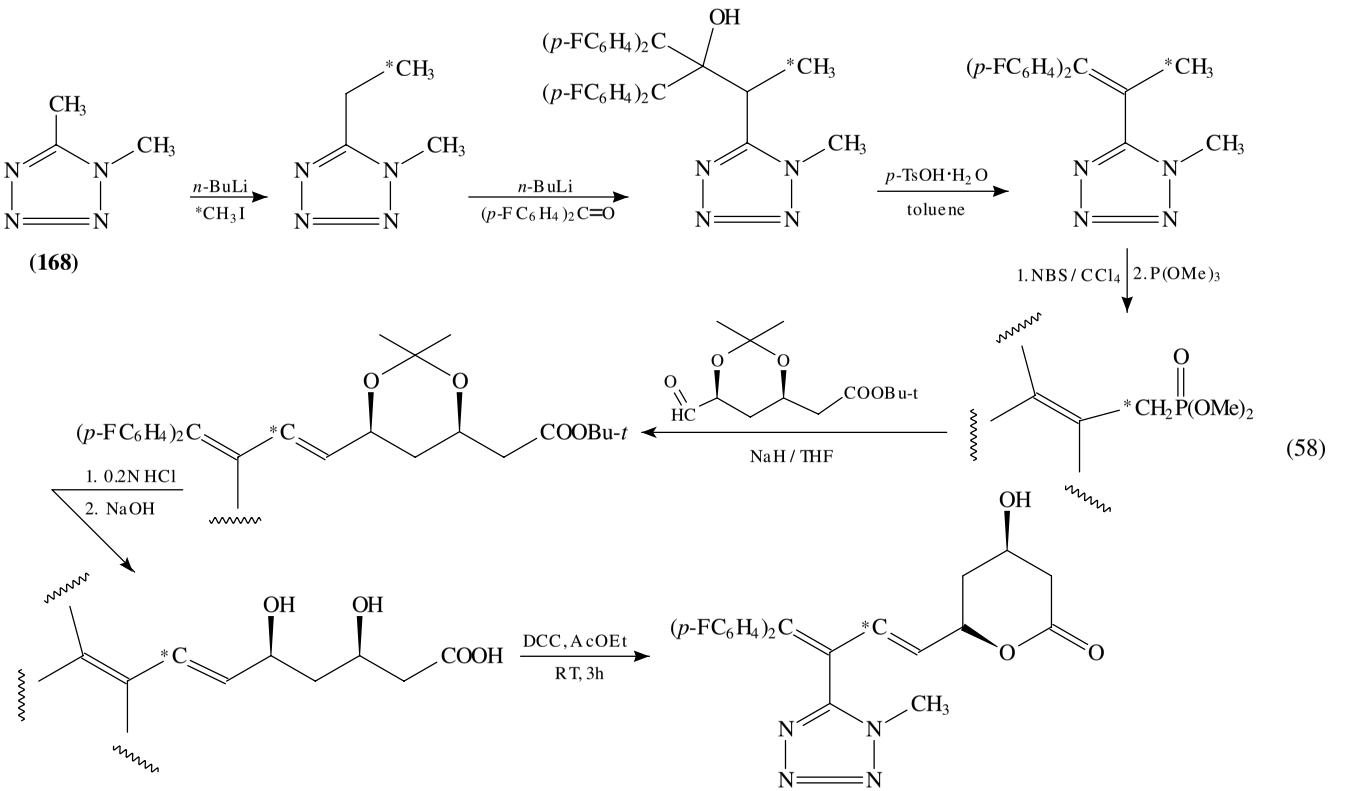
## B. Synthesis and Uses of Dienes and Polyenes Labelled with Carbon-14

### *1. Synthesis of (±)-trans-6-[4,4-bis(4-fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)-1(E),3-[2-$^{14}$C]butadienyl-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one*

The recently discovered[142] title compound BMY-22089, **167**, is more potent than the natural products compactin and mevinolin[143] in lowering the serum cholesterol levels in both animals and man by inhibiting the action of enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) which determines the biosynthesis of cholesterol[144]. It has been prepared[143] in 20% overall yield in various steps starting with the tetrazol **168** (equation 58), for pharmacokinetic and drug distribution studies.

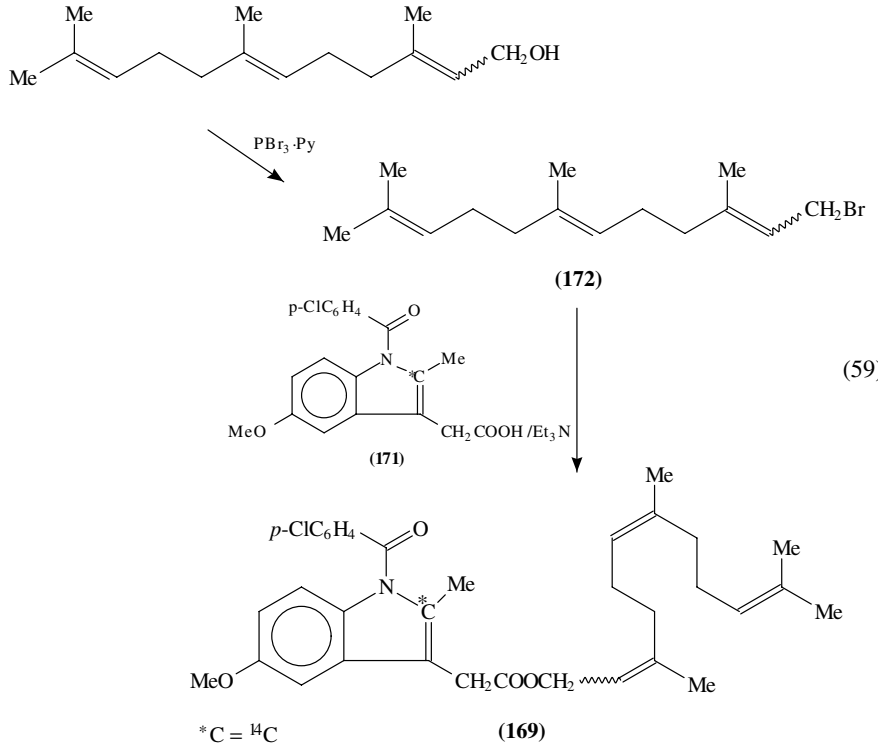
### *2. Synthesis of $^{14}$C-labelled indometacin farnesil*

E-0710 (IMF), the farnesil esters of indometacin[145], **169** and **170**, prodrugs showing anti-inflammatory activity with diminished gastro-intensinal irritation, have been synthesized[146] according to two schemes shown in equations 59 and 60. $^{14}$C-IMF- **169** has been obtained by esterification of commercially available $^{14}$C-IND, **171**, with farnesyl


(168)
n-BuLi
*CH3I
n-BuLi
(p-FC6H4)2C=O
p-TsOH·H2O
toluene
1. NBS / CCl4
2. P(OMe)3
NaH / THF
1. 0.2N HCl
2. NaOH
DCC, AcOEt
RT, 3h
(167) specific activity 31.4 μCi mg–1
DCC = Dicyclohexylcarbodiimide
*C = 14C

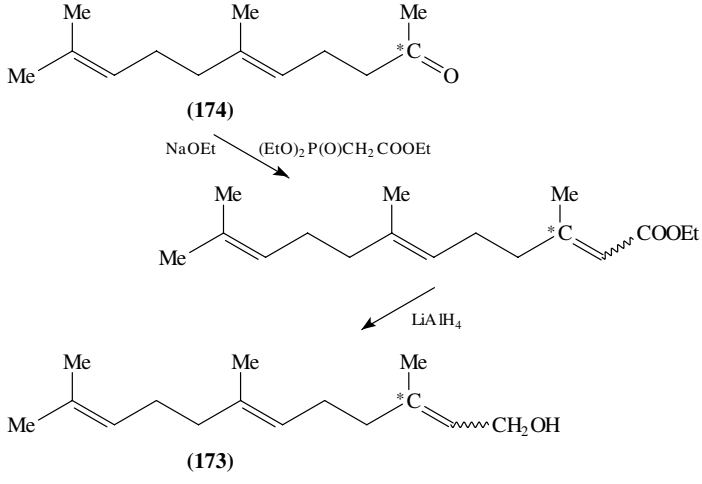
(58)

bromide **172** in the presence of triethylamine (equation 59).

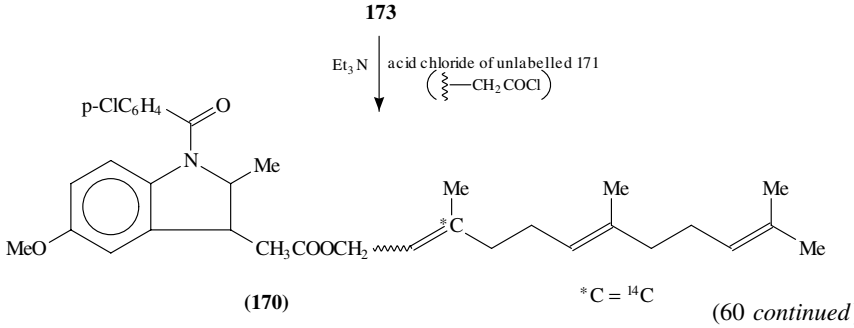



(59)

$^{14}$C-F-IMF, **170**, containing farnesyl moiety labelled with $^{14}$C, has been obtained involving the synthesis of $^{14}$C-labelled farnesol [$^{14}$C-F, **173**] from ketone **174** (equation 60). **169** and **170** have been synthesized in order to clear the pharmacokinetic profile of these drugs *in vivo* and *in vitro*.



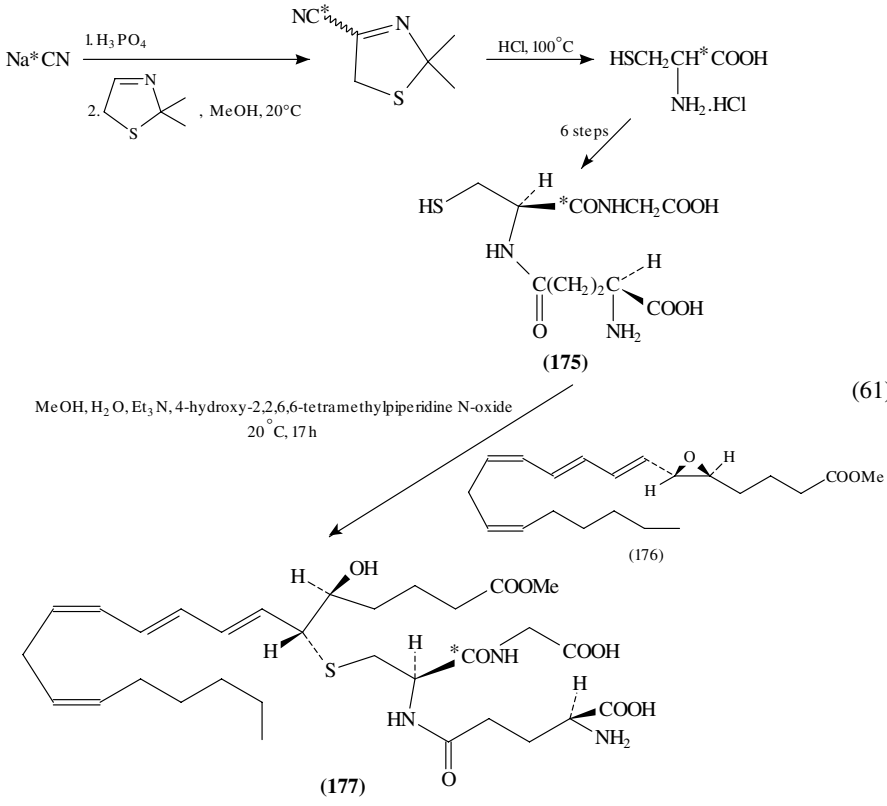

(60)



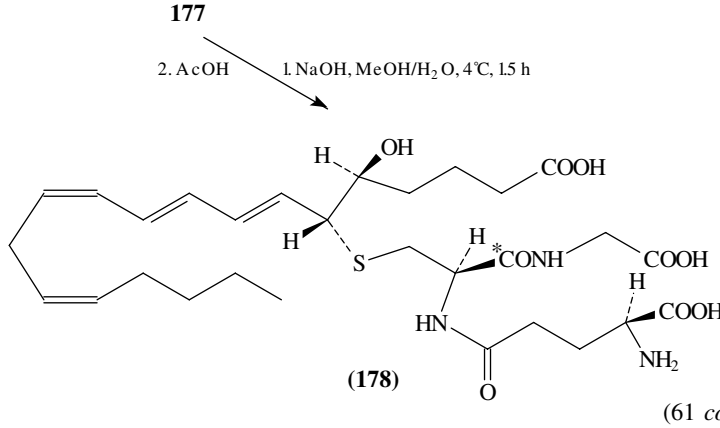

(60 *continued*)

### *3. Synthesis of [5S,6S]-[Cys-$^{14}$CO]-LTC$_4$*

The labelled tripeptide (L,L)-glutathione-$^{14}$C, **175**, prepared in an eight-step chemical synthesis[147] starting with Na$^{14}$CN, has been coupled with (5*S*,6*S*)-LTA$_4$ methyl ester, **176**, yielding (5*S*,6*R*)-[Cys-$^{14}$CO]-LTC$_4$ methyl ester, **177**, which after hydrolysis (NaOH/MeOH/$H_2O$) and neutralization by acetic acid provided *N*-{*S*-[1-(4-carboxy-1-hydroxybutyl)pentadeca-(2*E*,4*E*,6*Z*,9*Z*)-tetraenyl]-*N*-λ-L-glutamyl-L-[1-$^{14}$C]}cysteinyl glycine, **178**, in 74% yield (specific activity 50 mCi mmol$^{-1}$, 3.88 MBq) (equation 61).




(61)



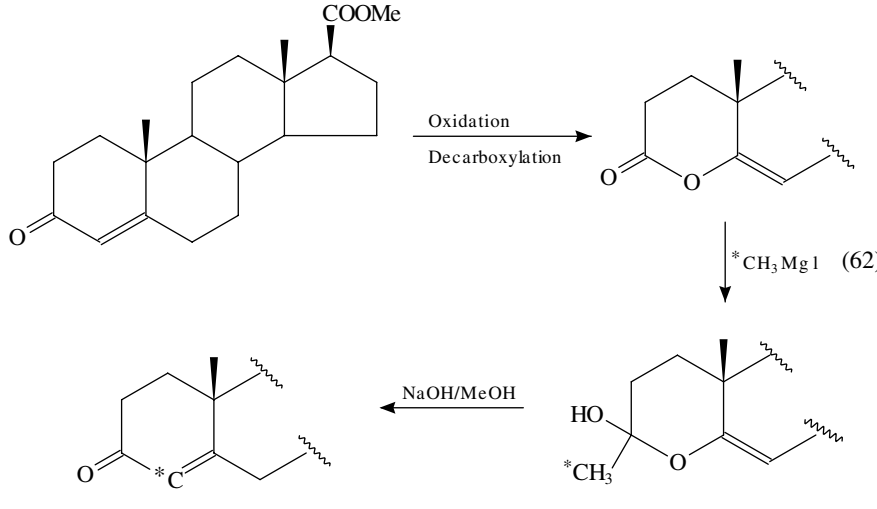

**(178)**

(61 *continued*)

**178** is used in the study of peptidoleukotrienes biosynthesis and metabolism[147] in view of their biological activities, like contraction of smooth muscles or vasodilatation, and in asthma-related diseases[148].

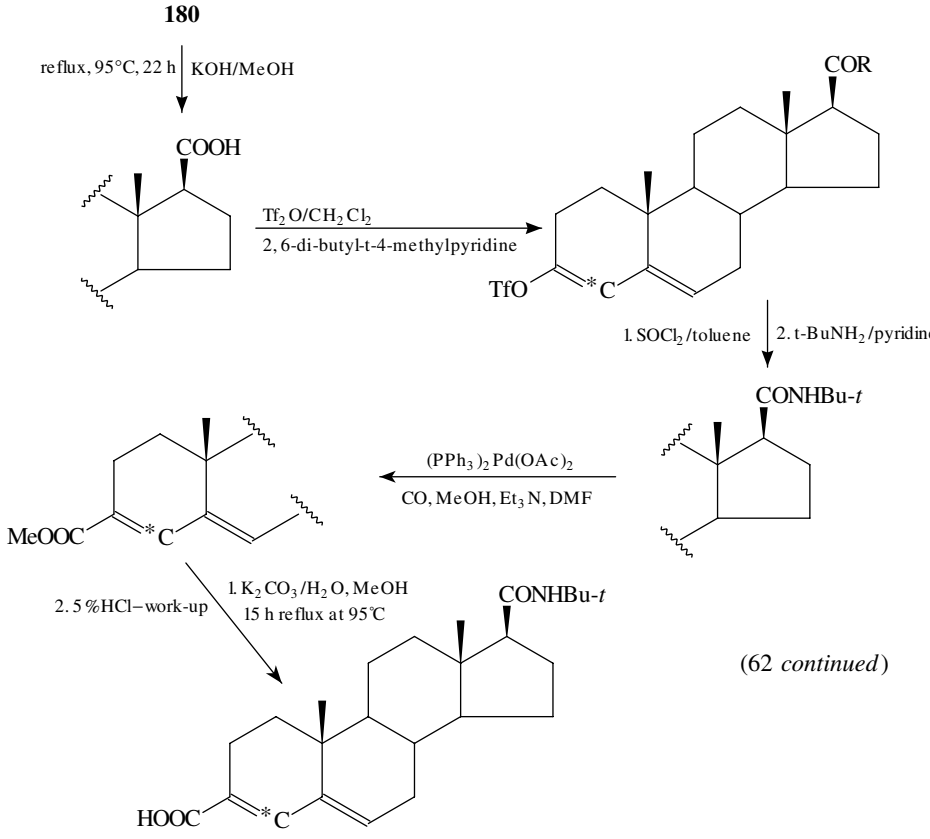
### *4. Synthesis of [$^{14}$C]SK and F 105657 and tritiated SK and F 105656, the prostatic steroidal 5α-reductase inhibitors*

*a*, 17β-[*N*-(1,1-Dimethylethyl)carbamoyl]androsta-3,5-diene-4-$^{14}$C-3-carboxylic acid ([$^{14}$C]SK and F 105657), **179**, suppressing the human biosynthesis of 5α-dihydrotestosterone, essential for normal prostatic growth to reach puberty, but causing the benign prostatic hyperplasia (BPH) at the later age[149], has been synthesized[150,151] in the sequence shown in equation 62 involving *t*-butyl amidation, triflation and carbomethoxylation.




(62)

**(180)**




(62 *continued*)

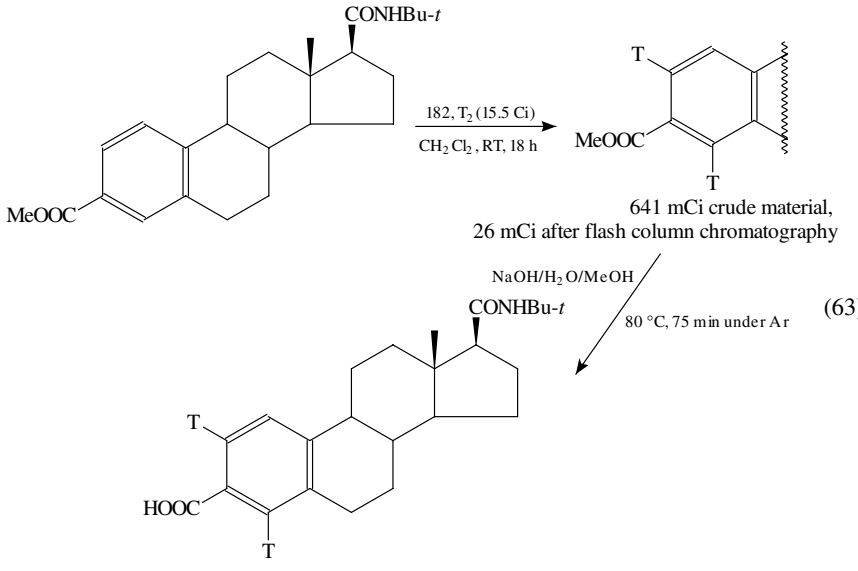
**(179)** 98% radiochemical purity,
47% yield from **180**

*b*. Synthesis of 17$\beta$-[*N*-(1,1-dimethylethyl)carbamoyl]estra-1,3,5(10)-triene-2,4-$^3H_2$-3-carboxylic acid, **181**. The A-ring aromatic analogue SK and F, 105656, **181**, has been tritium-labelled[150] (equation 63) by iridium-mediated exchange methodology[150,152] using $[IrH_2(Me_2CO)_2(PPh_3)_2]$ $BF_4$, **182**.

Both **179** and **181**, therapeutic agents for treatment of BPH, have been prepared to profile their pharmacokinetic and binding characteristic in various biomedia[150]. Tritium labels were incorporated exclusively into $C_{(2)}$ and $C_{(4)}$ positions of the A ring as observed by the $^3H$ NMR spectra[150]. It has been suggested that the isotopically labelled hydrogen is channeled into the *ortho* positions of the A aromatic ring through the catalytic cycle[150,153] shown in equation 64.

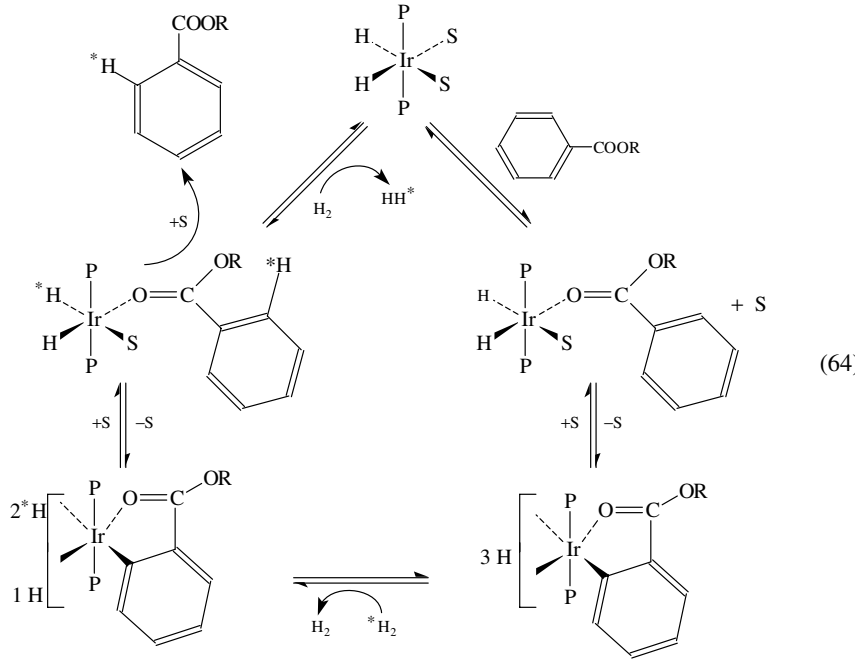
### *5. Synthesis of sodium 3-[1-$^{14}$C]-ethyl-7-isopropyl-1-azulenesulphonate*

The title compound **183**, a new therapeutic agent[154] for stomatitis, pharyngitis and ophthalmia, has been labelled[155] with $^{14}C$ in the ethyl group attached to the azulene ring (equation 65) for the study of metabolism in animals.



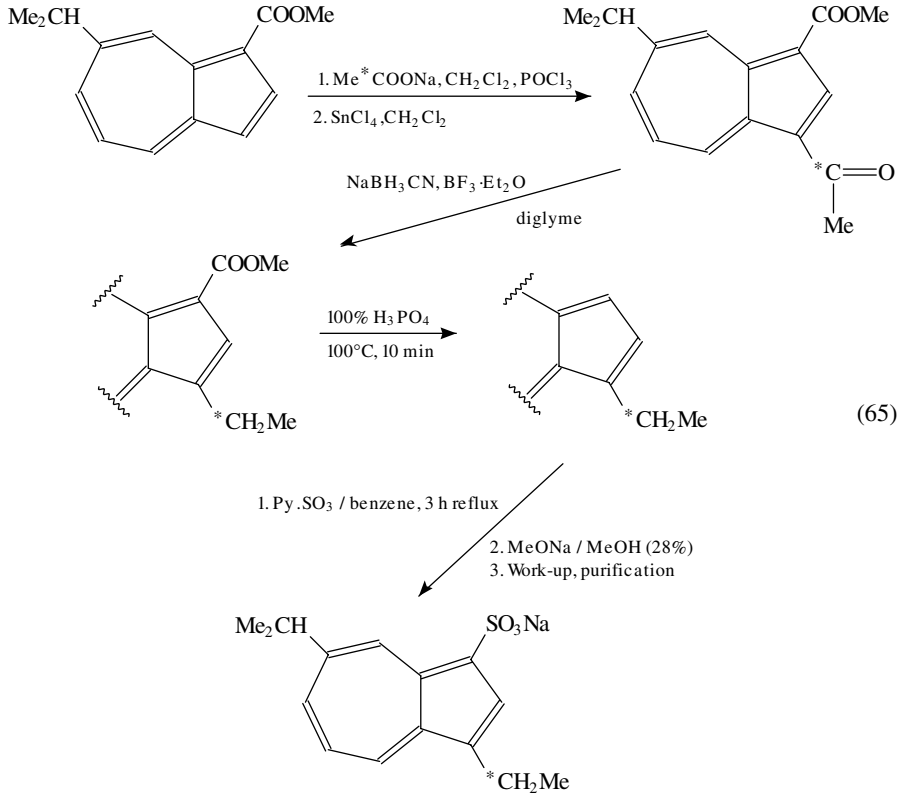

(63)

**(181)** 17 mCi, radiochemical puity > 99 %
specific activity 774 mCi mmol$^{-1}$




(64)

P = Triphenylphosphine
S = Acetone
*H = $^{3}$H or $^{2}$H




(65)

**(183)** 93.4% step yield, specific activity 1.98 GBq mmol$^{-1}$

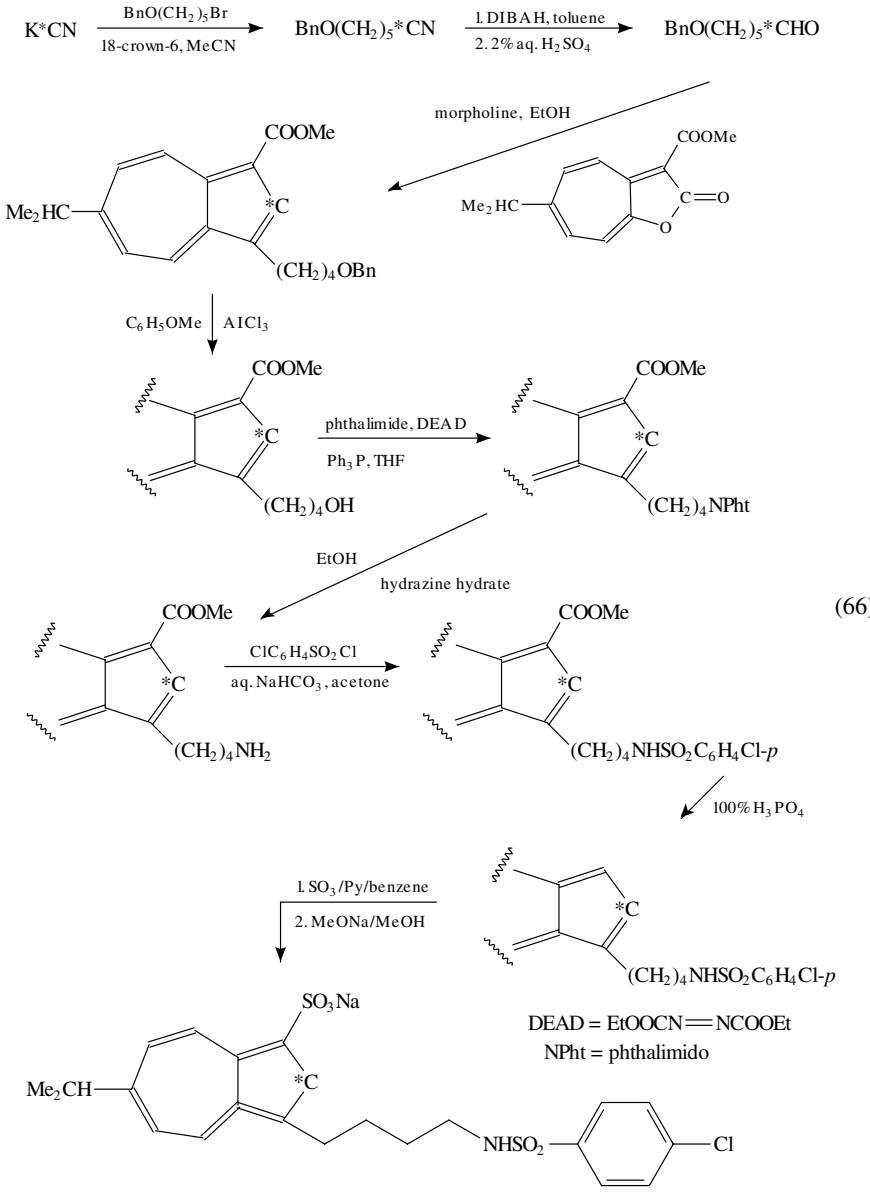
The Friedel-Crafts acylation at the 3-position of the azulene ring was possible due to the effect of the electron-withdrawing 1-methoxycarbonyl group. **183** has been prepared previously in an eight-step synthetic route in an unsatisfactory reaction yield[156].

### *6. Synthesis of sodium 6-isopropyl-3-[4-(p-chlorobenzenesulphonylamino)butyl]-[2-$^{14}$C] azulene-1-sulphonate*

The title compound, KT2-962, **184**, possessing excellent $TXA_2$ receptor antagonistic activity[157] (Thromboxane $A_2$ is the vasoconstricting and platelet-aggregating agent[158]), has been labelled with carbon-14 at the 2-position of the azulene ring[159] in a nine-step procedure using potassium [$^{14}$C]-cyanide (equation 66) in 64% overall radiochemical yield in NCA (non-carrier added) form for metabolism and disposition studies.

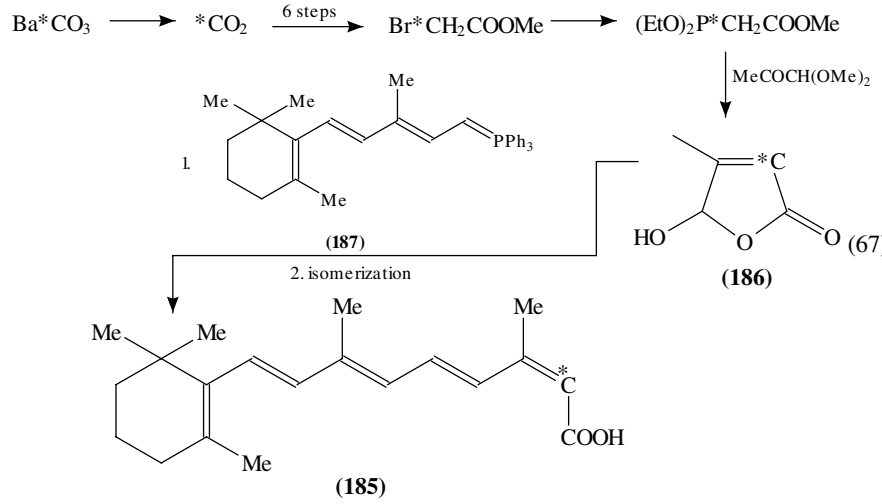
### *7. Synthesis of 13-cis retinoic [14-$^{14}$C] acid*

13-*Cis* retinoic acid **185**, labelled with carbon-14 at the 14 position, has been obtained[27,100] in the reaction of $^{14}$C-labelled butenolide **186** with C-15 Wittig reagent **187** (equation 67).



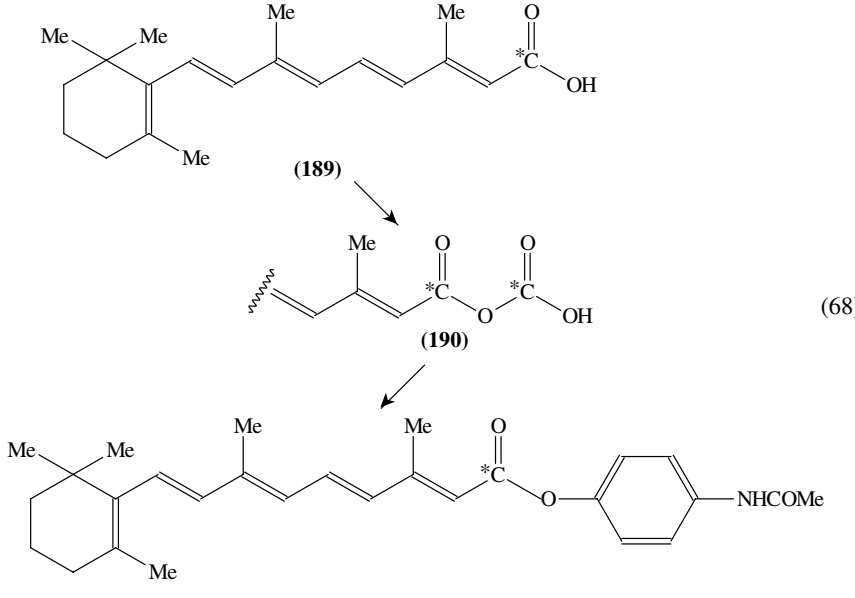

(66)

**(184)** 1.9 GBq, specific activity 2.36 GBq mmol$^{-1}$, 85% step yield, 99% HPLC purity




### *8. Synthesis of 4-(N-acetylamino)phenyl-1-[$^{14}$C] retinoate*

The title compound **188**, currently under development for the treatment of acne, psoriasis and photoaging via a topical application, has been synthesized[161] in two steps by reacting carboxyl-[$^{14}$C]vitamin A, **189**, with ethyl chloroformate and subsequent treatment of the mixed anhydride **190** with acetamidophenol in the presence of a catalytic amount of 4-dimethylaminopyridine (equation 68), Carbon-14-labelled compound was needed to investigate its metabolism and the extent of systematic adsorption of **188** after dermal application.

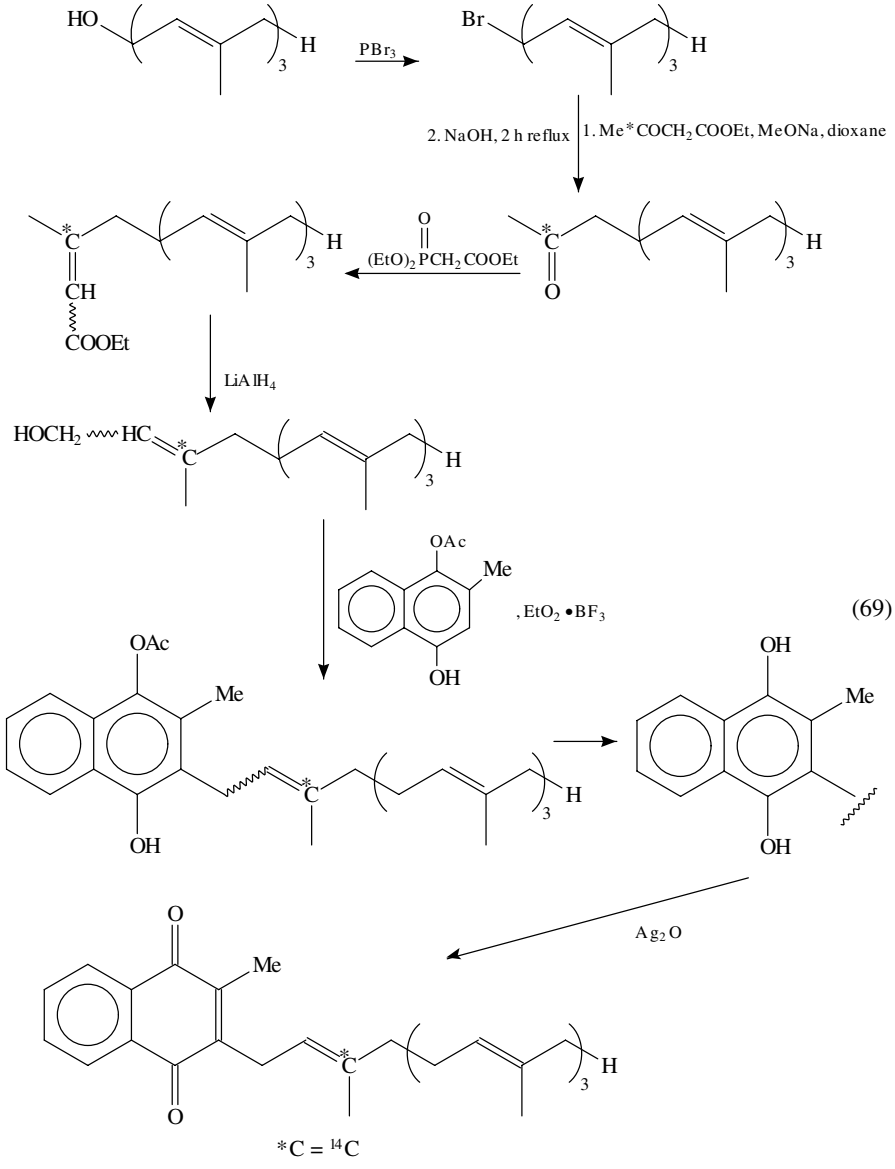



(68)

**(188)** 42% overall yield, 97.5% radiochemical purity, specific activity 23 μCi mg$^{-1}$

### *9. Synthesis of all-trans-[3-$^{14}$C]menaqinone-4*

All-*trans*-menaquinone-4, **191**, potentially useful for therapy of hypoprothrombinemia due to vitamin K deficiency, has been synthesized[162] using ethyl [3-$^{14}$C]acetoacetate as shown in equation 69, for drug disposition studies in animals.

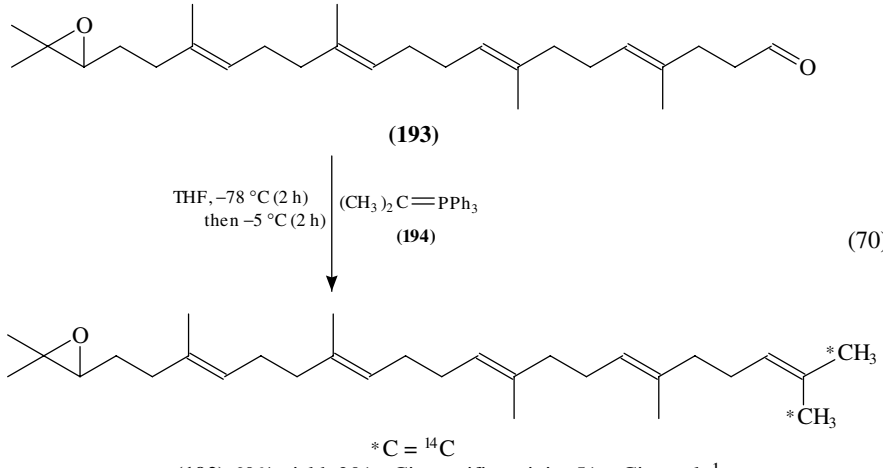



(69)

**(191)** overall radiochemical yield 12%, specific activity 669 MBq mmol$^{-1}$, *trans* isomer ≥ 96% after chromatography and recrystallization

### *10. Synthesis of [24,30-$^{14}$C]-labelled-2,3-epoxysqualene*

[24,30-$^{14}$C]-(3*S*)-2,3-epoxysqualene and its racemate have been prepared by two routes in a metabolically non-labile position relative to the demethylation of lanosterol to cholesterol (equation 70 and 71). The racemic [24,30-$^{14}$C]-2,3-epoxysqualene, **192**, has been obtained[163] by condensation of (3*S*, 3*R*)-2,3-epoxytrisnorsqualene aldehyde **193** with freshly prepared $^{14}$C-labelled isopropylidenephosphorane, **194** (equation 70).




(70)

**(192)** 60% yield, 301 μCi, specific activity 51 mCi mmol$^{-1}$

The optically active (3*S*)-$^{14}$C-labelled 2,3-epoxysqualene **195** has been prepared[163] by treating (3*S*)-2,3-epoxytrisnorsqualene aldehyde **196** with $(^{14}CH_3)_2C{=}PPh_3$ in THF solution as shown in equation 70. The (20*S*)-(4*E*,8*E*,12*E*,16*E*)-20,21-epoxy-4,8,13,17,21-pentamethyl-4,8,12,16-decosatetraen-1-al, **196**, has been synthesized in six steps as shown in equation 71.

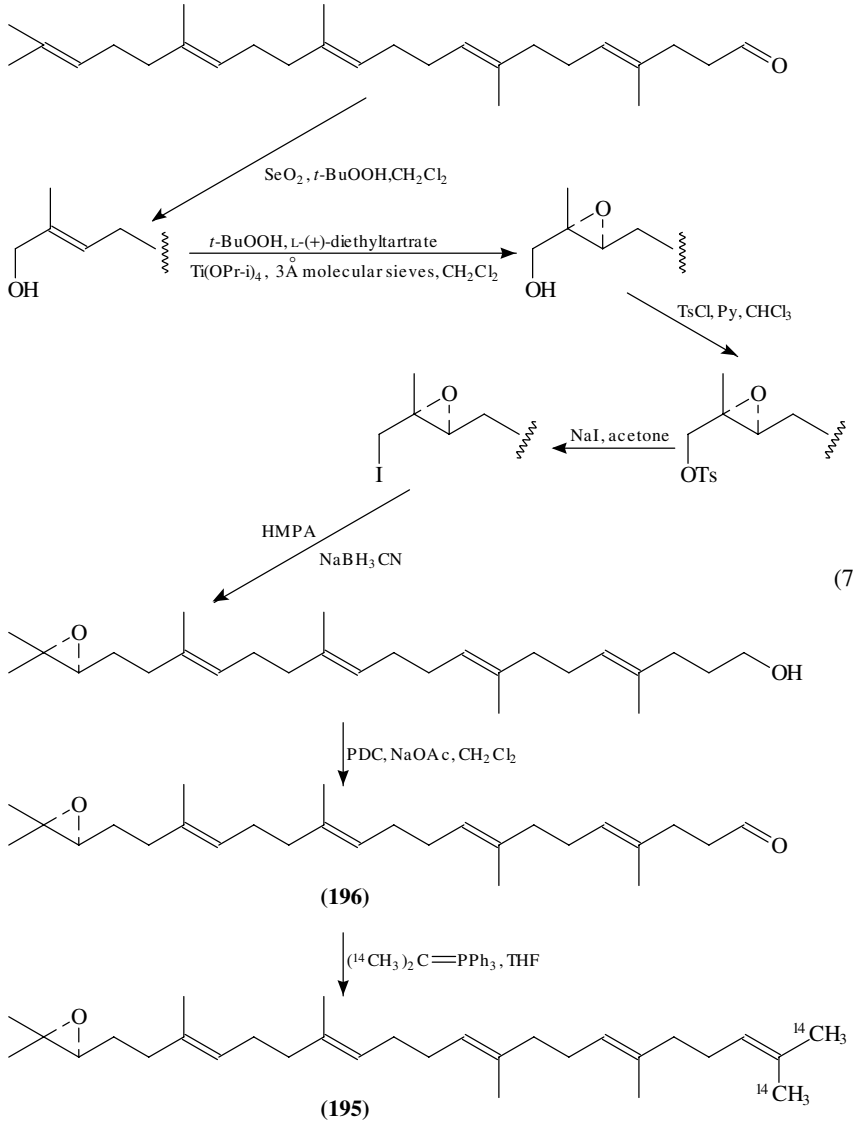
Optically active (3*S*)-form, **195**, is a key intermediate in the biochemical synthesis of triterpenes and sterols in vertebrates, plants and fungi[164].

### *11. Synthesis of $^{14}$C-chloroacetates of 2-demethylthiocolchicine, **197**, of 3-demethylthiocolchicine, **198**, of N-acetylcolchinol, **199**, and of the $^{14}$C-9-isocyanato-9-deoxy-N-acetylcolchinol, **200***

The title compounds **197** and **198**, covalently binding with high specificity to the β-subunit of tubulin[165,166,169], have been obtained[167] by treating 2-demethylthiocolchinine, **201**, and 3-demethylthiocolchinine, **202**, respectively with $ClCH_2{}^{14}COCl$ in $CH_2Cl_2$ solution containing triethylamine.

The radiolabelled 9-chloroacetoxy-*N*-acetylcolchinol, **199**, has been prepared[167] by reacting *N*-acetylcolchinol **203** dissolved in $CH_2Cl_2$ and containing $Et_3N$, with $ClCH_2{}^{14}COCl$ during 24 h at 55 °C.

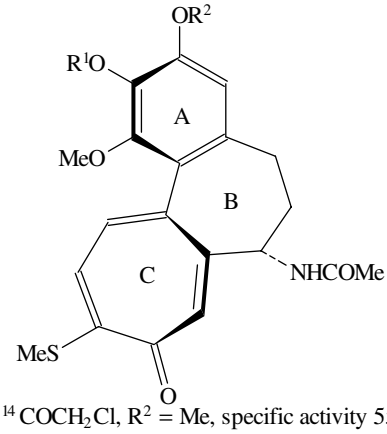
The radiolabelled isothiocyanate **200** has been prepared[167] by an early published procedure[168] using radiolabelled $^{14}CH_3I$ (50 mCi mmol$^{-1}$, 2 mCi, 0.04 mmol).




(71)

PDC = Pyridinium dichromate

The $^{14}$C-chloroacetate of *N*-acetylcolchinol **199** and the $^{14}$C-isothiocyanate **200** were also found to react covalently with tubulin, but in a non-specific manner[167], contrary to compounds **197** and **198** which react covalently with the colchicine binding site on tubulin with a $\beta$-subunit: $\alpha$-subunit marking ratio[169] of about 4:1.

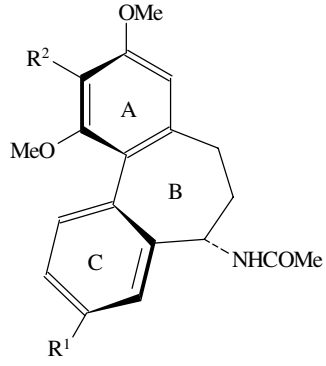



**(197)** $R^1 = {}^{14}COCH_2Cl$, $R^2$ = Me, specific activity 55 mCi mmol$^{-1}$, radiochemical yield 26.1%

**(198)** $R^1$ = Me, $R^2 = {}^{14}COCH_2Cl$, specific activity 55 mCi mmol$^{-1}$, radiochemical yield 5.7%

**(201)** $R^1$ = H, $R^2$ = Me

**(202)** $R^1$ = Me, $R^2$ = H



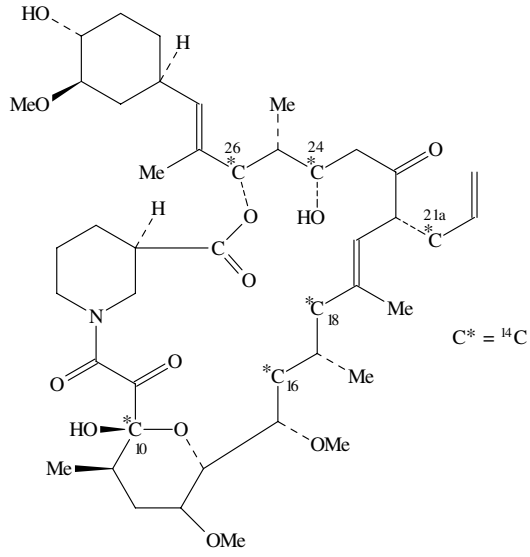

**(199)** $R^1 = O{}^{14}COCH_2Cl$, $R^2$ = OMe, specific activity 56 mCi mmol$^{-1}$, radiochemical yield 7.8%

**(200)** $R^1$ = NCS, $R^2 = O{}^{14}CH_3$, specific activity 50.0 mCi mmol$^{-1}$, radiochemical yield 32%

**(203)** $R^1$ = OH, $R^2$ = MeO

### *12. Synthesis of $^{14}$C-labelled FK-506,* ***204***

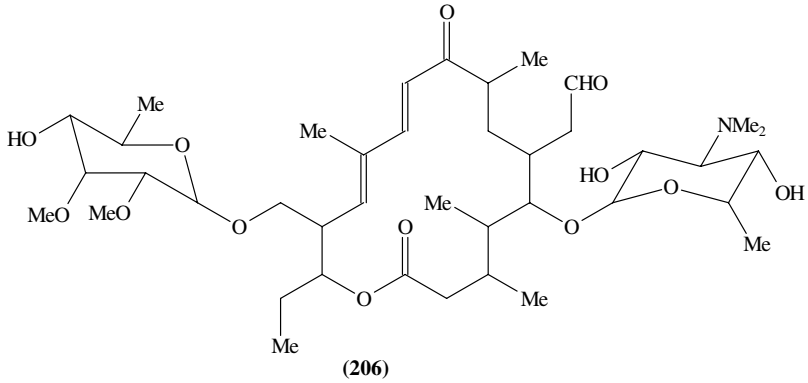
The immunosuppressant compound[170] FK-506, similar in effect to cyclosporin A, the leading drug for use in immune system suppression to prevent rejection of transplanted organs[171], has been labelled at carbon atoms 10, 16, 18, 21*a*, 24 and 26 by fermentative biosynthesis using sodium [1-$^{14}$C]propionate as a precursor[172]. The same $^{13}$C-labelled positions were derived from [1-$^{13}$C]propionate. FK-506 producing culture *Streptomyces tsukubaenis* no 9993 has been utilized in this biosynthesis (120 h incubation at 29 °C).




(**204**) FK-506, 3.6 mCi after HPLC, 0.6% from 614 mCi of [1-$^{14}$C]propionate (specific activity 57.7 mCi (mmol$^{-1}$).

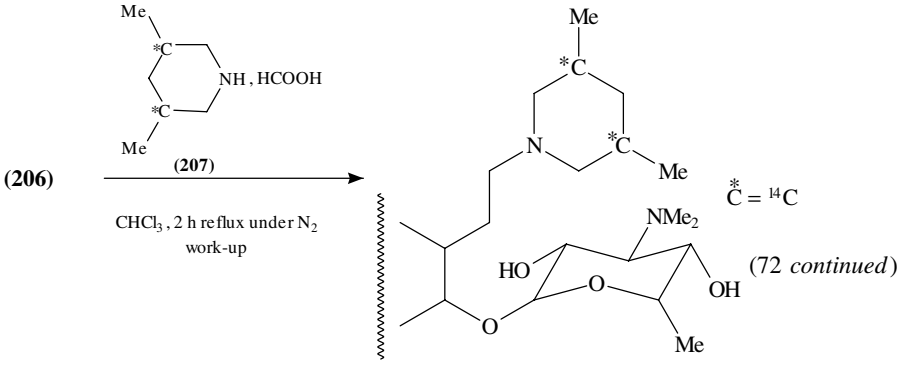
### *13. Synthesis of $^{14}$C-radiolabelled tilmicosin*

Tilmicosin **205** has been $^{14}$C-labelled on the 3,5-dimethylpiperidinyl side chain[173] by reductive amination of the C-20 aldehyde of desmycosin **206** with 3,5-dimethylpiperidine hydrochloride-3,5-$^{14}$C, **207**, using 95–97% formic acid in boiling chloroform (equation 72). The required 3,5-lutidine radiolabelled in the piperidine ring, has been prepared in a six-step radiosynthetic route starting with 2-$^{14}$C-diethyl malonate as shown in equation 73. **205** (EL-870) is an antibacterial[174] used in treating respiratory diseases in cattle and swine. Radiolabelled EL-870 was required for biochemical studies. It is currently under development as a parenterally administered antibacterial agent for treatment of pneumonic pasteurellosis in calves and for use in feed for the control of pasteurella pneunomia in pigs.

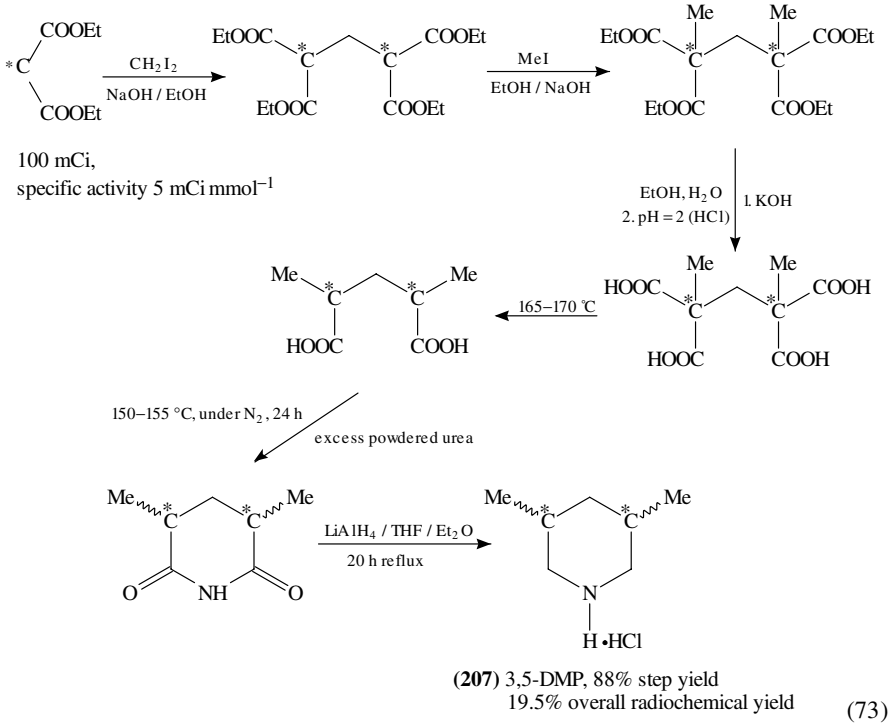



**(206)**

(72)



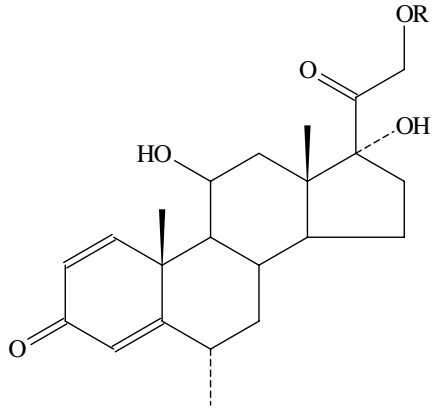

**(205)** EL 870, 97% yield, total activity 19.5 mCi, specific activity 6.48 mCi mmol$^{-1}$

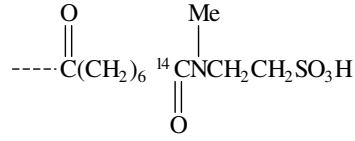



**(207)** 3,5-DMP, 88% step yield
19.5% overall radiochemical yield (73)

### *14. Synthesis of $^{14}$C-labelled methylprednisolone suleptanate*

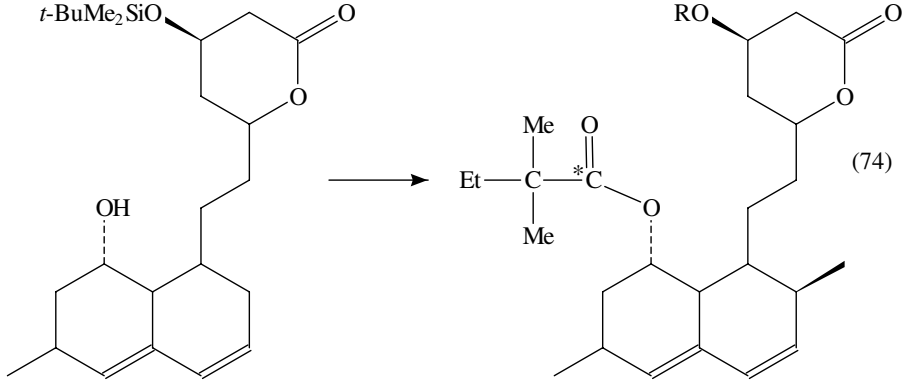
The methylprednisolone suleptanate **208b**, the water-soluble prodrug of the methylprednisolone corticosteroid **208a**, has been labelled with $^{14}$C exclusively at the carboxamide carbon[175] which was found to be metabolically stable with no loss of $^{14}CO_2$ after administration to test animals and man.




**(208a)** R = H, **(208b)** R = 

### *15. Synthesis of $^{14}$C-labelled simvastatin, **209***

This potent inhibitor of cholesterol biosynthesis has been synthesized[178] by one-pot esterification of the alcohol **210** with the acid chloride of 2,2-dimethylbutanoic[1-$^{14}$C] acid, obtained by carbonation of the Grignard reagent prepared from 2-chloro-2-methylbutane (equation 74). Desilylation of **211** afforded [$^{14}$C]simvastatin **209** in 29% radiochemical yield from $^{14}$C-labelled $CO_2$. This $^{14}$C-labelled drug was needed for elucidation of its metabolic fate in experimental animals.




(74)

**(210)**

**(209)** R = H
**(211)** R = $SiMe_2Bu$-*t*

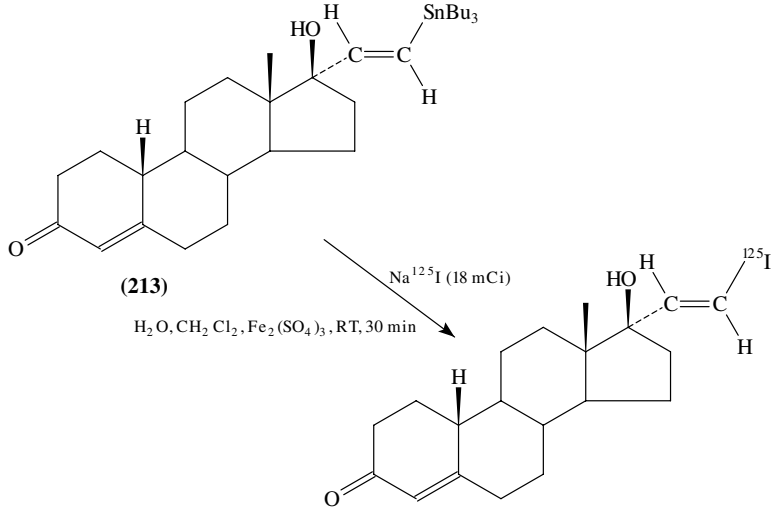
*C = $^{14}$C

## V. SYNTHESIS AND USES OF DIENES AND POLYENES LABELLED WITH HEAVY RADIOISOTOPES

### A. Synthesis of Iodine-125-labelled Compounds

#### *1. Synthesis of NCA 17α{2-(E)-[$^{125}$I]-iodovinyl}-19-nortestosterone*

This $^{125}$I-labelled steroid hormone (E-$^{125}$I VNNT), **212**, needed for human breast cancer therapy, has been synthesized[177] by [$^{125}$I]-iododestannylation of 17α-[2-(*E*)-tri-*n*-butylstannylvinyl]-19-nortestosterone (E-TBS VNNT), **213**, using [$^{125}$I]-sodium iodide/ferric sulphate in mixed $CH_2Cl_2$ water solvent, as the iodinating agent (equation 75). This avoided standard oxidants like $KMnO_4$, $KlO_4$, $K_2CrO_4$ or $H_2O_2$, chloramine-T and *N*-chlorosuccinimide which can oxidize the stannyl steroid substrate.




(75)

**(212)** 10 mCi,
specific activity 2200 Ci mmol$^{-1}$

Ferric sulphate is a mild oxidant and is non-reactive with the steroid substrate. It liberates iodine quantitatively (equation 76), and the iodine is extracted into $CH_2Cl_2$ and consumed as in equation 75.

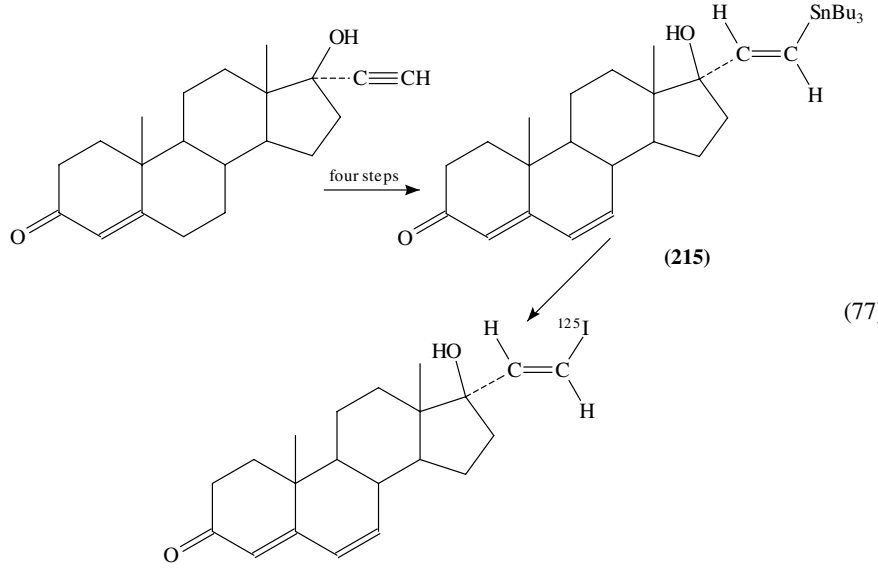
$$Fe_2(SO_4)_3 + 2Na^*I \xrightarrow[\text{or neutral solvent}]{H^+} 2FeSO_4 + Na_2SO_4 + {}^*I_2 \qquad (76)$$

In the non-labelled reaction, **213** reacts with excess of iodine and quantitative yield of E-IVNNT is obtained[177,178]. The formation of E-$^{125}$IVNNT, **212**, is ascribed to the generation of a four-membered transition state, formed by two polarized bonds, $C^--Sn^+$ and $I^+-I^-$, in which the two radioiodine atoms are shared by the two reactive centres, carbon and tin. The reaction leads to the formation of steroid-CH=CH$^{125}$I and of iodostannyl compound, $^{125}ISnBu_3$, which is lost during the evaporation and/or during chromatography lowering the yield of **212** to about 50% radioactive yield. The 30–90% radiochemical yield observed in $^{125}$I-iododestannylation[179], using CAT or $H_2O_2$, are caused by formation of an HO–I species and the product 'C–I' and by-product 'HO–Sn' formation (little or no iodine is captured by tin).

The cultures of T47D human breast ductal carcinoma ($2 \times 10^5$ cells) have been used to determine the uptake of E-$^{125}$IVNNT and specific progesterone receptor binding *in vitro*[177]. Cell binding assays demonstrated that **212** binding to T47D breast carcinoma was specific and saturable with an affinity for the progesterone receptor 10-fold greater than that of commercially available PgR ligand $^3$H-R5020. E-$^{125}$IVNNT should be useful for determining PgR + tumors and for measuring the number of progesterone receptors in these tumors[177].

### *2. Synthesis of 17α-{(E)-2-[$^{125}$I]iodoethenyl} androsta-4,6-dien-17β-ol-3-one*

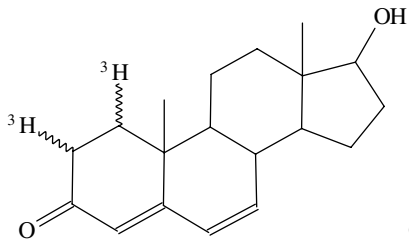
The synthesis of the title compound, **214**, the active-site-directed photoaffinity radiolabel for androgen-binding proteins ('ABP'), has been accomplished[180,181] by treatment of excess 17α-[(*E*)-2-tributyltin(IV)ethenyl]androsta-4,6-dien-17β-ol-3-one, **215**, with sodium iodide-125 of specific activity 27 Ci mmol$^{-1}$ in a sodium acetate–AcOH buffered solution and a solution of 30% $H_2O_2$ in glacial AcOH (equation 77).



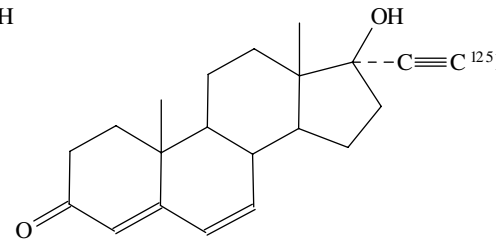

(77)

([$^{125}$I] **214**) 52% radiochemical yield after HPLC, specific activity 27 Ci mmol$^{-1}$, 100% radiochemical purity

The ability of [$^{125}$I] **214** as well as of the previously prepared[182] [$^3$H]Δ$^6$-testosterone, **216**, and 17α-[$^{125}$I]iodoethynylandrosta-4,6-dien-17β-ol-3-one[183], [$^{125}$I] **217**, to serve as photoaffinity labelled reagents, resides in the excitation of the conjugated dienone system to an excited singlet state, which then undergoes intersystem crossing to a triplet state in which the excited steroids abstract hydrogen from the protein. The recombination of the resultant steroid-protein radical pair leads to formation of the covalent bond[184]. The extended conjugation of Δ$^6$-testosterone results in the shift of the carbonyl absorption band from 305 nm to 345 nm. The last absorption band is beyond the absorption band of cytosol and consequently a photoactivation of the unsaturated carbonyl group and subsequent covalent bond formation with the protein is possible. The decomposition of [$^{125}$I] **217** and its protein complex in the presence of β-mercaptoethanol makes the utility of [$^{125}$I] **217** very limited.



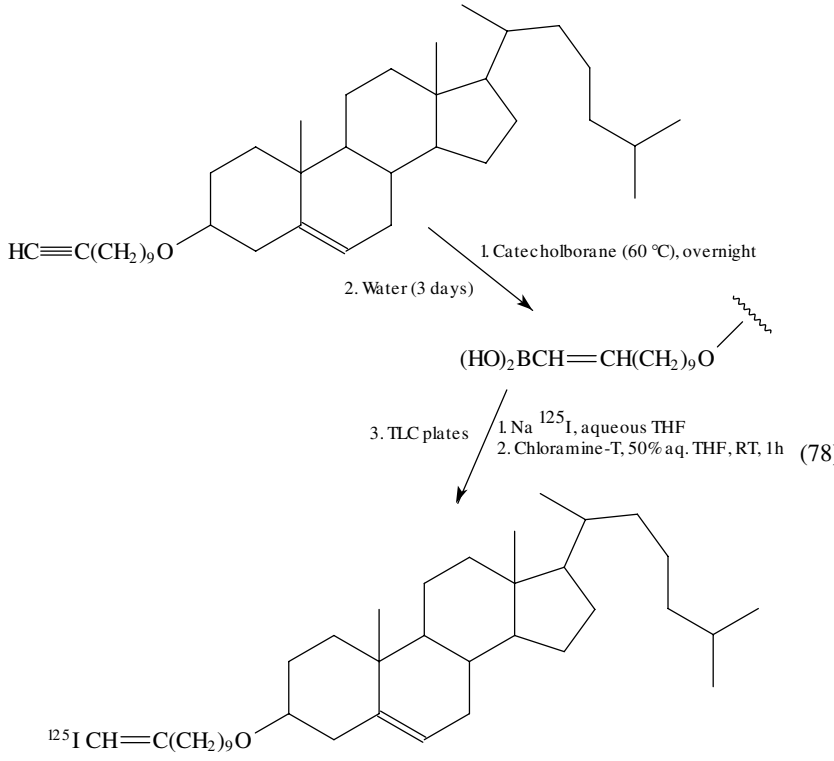

([$^3$H] **216**)



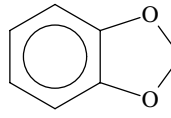

([$^{125}$I] **217**)

### *3. Synthesis of iodine-125-labelled ω-iodoundecenyl cholesteryl ether*

Radioiodinated vinyl iodides[185] possessing superior *in vivo* stability relative to the alkyl iodides[186] have been used for myocardial imaging[185]. The title vinyl iodide **218** has been synthesized[187,188] therefore for use as a liposomar marker via the hydroboration–iodination sequence shown in equation 78.



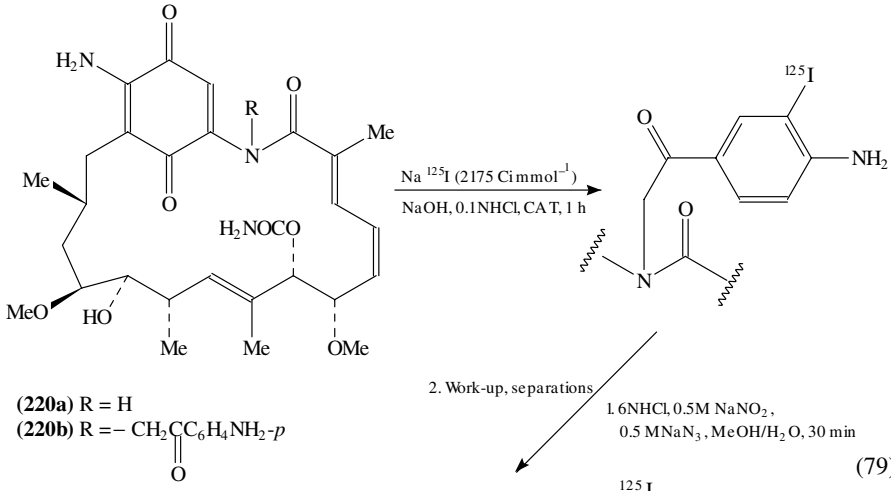

**(218)** 17% radiochemical yield




= catecholborane

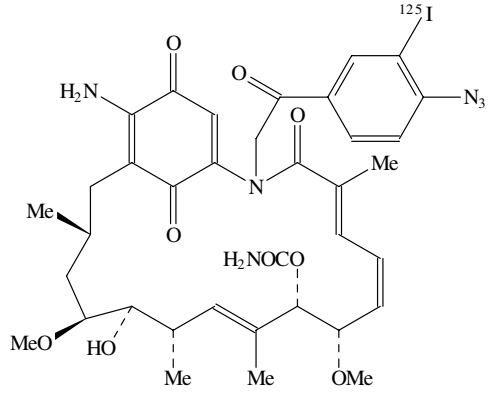
### *4. Synthesis of 17-amino-22-(4′-azido-3′-$^{125}$I-iodophenacyl)-17-demethoxygeldanamycin,* ***219***

The title compound, **219**, suitable for mechanistic studies with oncogen transformed tumor cells has been synthesized[189] in a one-pot two-step process from 17-amino-22-(4′-aminophenacyl)-17-demethoxygeldanamycin, **220b** (equation 79). (**220a**, 17-amino-17-demethoxygeldanamycin as such, inhibits cell growth of SV40 transformed cells[190]). **220b** has been prepared[189] by treating **220a** with *t*-BuOK in DMSO, then with 4′-aminophenacyl chloride at RT for 3 hours. The use of the 4-azido-3-[$^{125}$I]iodophenyl moiety as a photolabile radiolabelling tool had been reported by Patel and coworkers[191].




**(220a)** R = H
**(220b)** R = $-CH_2C(=O)C_6H_4NH_2$-*p*

(79)



([$^{125}$I] **219**)

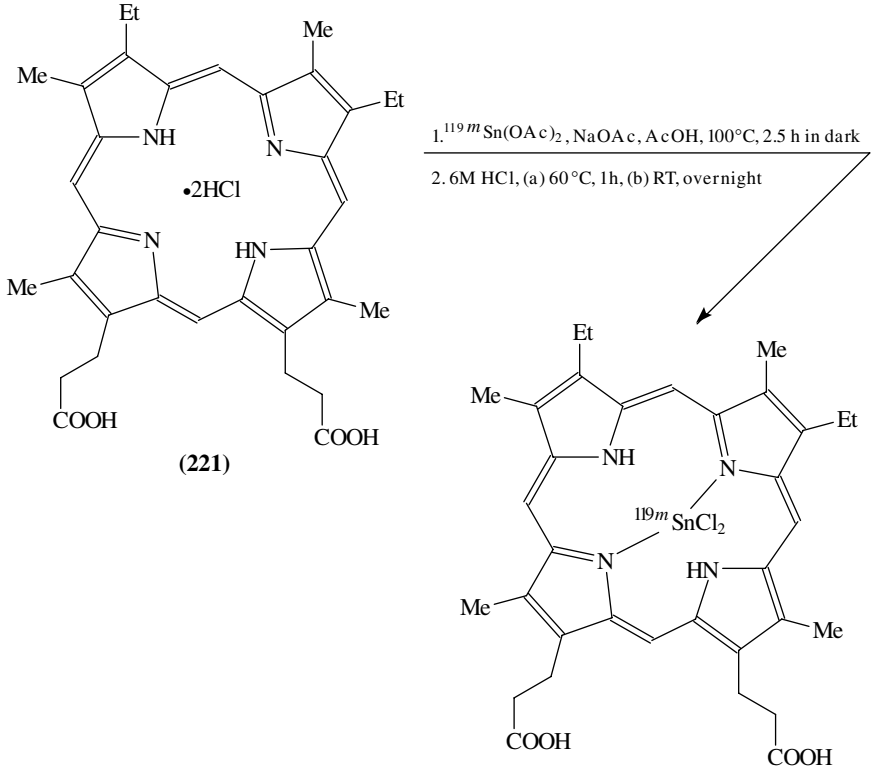
1-2% overall radiochemical yield

## B. Synthesis of Compounds Labelled with Tin

### *1. Synthesis of [$^{119m}$Sn]-mesoporphyrin IX dichloride*

This compound, Sn-MP$Cl_2$, decreases effectively plasma billirubin levels in both adult and neonatal animals[192] and is under current evaluation as an alternative to phototherapy

in the treatment of neonatal hyperbilirubinemia[193]. [$^{19m}$Sn]-$MPCl_2$, **222**, has been prepared[194] in 60% radiochemical yield by metalation of the porphyrin nucleus of **221** with tin(II)-119*m* acetate (equation 80). A 1% radiochemical impurity presumably arose from traces of unreacted tin-119*m* reagent. The amount of unmetalated mesoporphyrin starting material found in labelled product **222** was <3% by HPLC analysis.




**(221)**

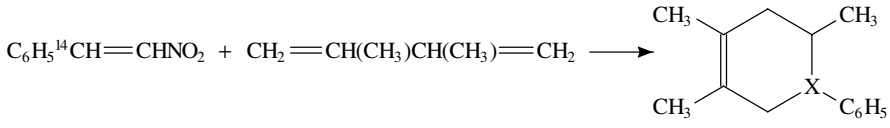
**(222)** 633 μCi, specific activity 43.4 mCi mmol$^{-1}$ (58 μCi mg$^{-1}$), 99% radiochemical purity (80)

## VI. ISOTOPE EFFECT STUDIES WITH DIENES AND POLYENES

### A. Carbon-14 and Deuterium Isotope Effect Studies of the Diels-Alder Reaction

#### *1. Experimental $^{14}C$ KIE study of the Diels-Alder addition of β-nitrostyrene to 2,3-dimethylbutadiene*

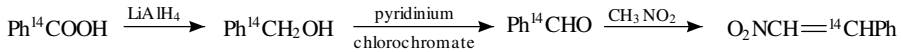
The title Diels-Alder (DA) addition reaction shown in equation 81[195] has been reinvestigated recently[196] by labelling **223** with $^{14}C$ successively at $C_{(1)}$ and at $C_{(2)}$. The [2-$^{14}$C]-1-nitro-2-phenylethene has been obtained in the reaction of [7-$^{14}$C]benzaldehyde with nitromethane (equation 82).




**(223)** **(224)** **(225)**

X = $^{14}$C

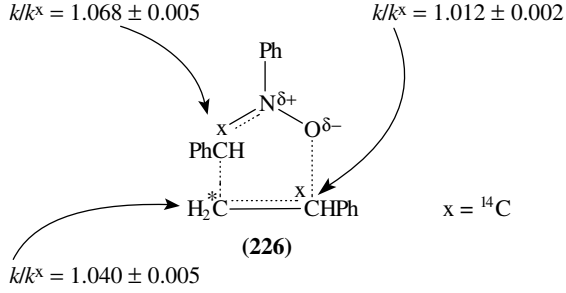
(81)



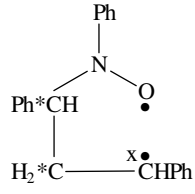

(82)

The [$^{14}$C]nitromethane needed for preparation of [1-$^{14}$C]**223** has been made by reaction of [$^{14}$C]MeI with silver nitrite[197]. The low-conversion and high-conversion isotopic experiments have been carried out using 1.20 mmol of **224** and 5.00 mmol of [2-$^{14}$C]**223** in dry toluene or 3.35 mmol of **224** and 1.68 mmol of [2-$^{14}$C]**223** in 3 ml of toluene, respectively. The reactants, sealed in a snap-neck ampoule, were placed in an oven at 115 °C for 3 days to achieve the 100% conversion. The [1-$^{14}$C]**223** KIE and [2-$^{14}$C]**223** KIE were found to be 1.0438 ± 0.0012 and 1.0474 ± 0.0015, respectively. The earlier workers[195], counting data on KIE at $^{14}C_{(1)}$, erred probably because they achieved 60% rather than 100% conversion in their experimental work. No exchange at 130 °C during 24 h between **223** and unlabelled adduct **225** at melt has been found. Thus the possibility that the KIE in the DA reaction studied is masked by the exchange between the adduct and unreacted dienophile has been eliminated. The DA reaction (equation 81) is suggested to be concerted[196].

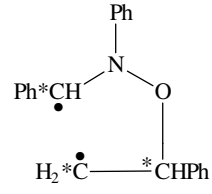
The primary $^{14}$C KIEs in the 1,3-dipolar addition of *N*-α-diphenylnitrone, PhCH=N(O)Ph, and styrene to yield 2,3,5-triphenylisoxazoline **226**[198] are also consistent with Huisgen's[199] concerted, cyclic mechanism and inconsistent with the diradical mechanism[200] (structures **227** and **228**).




**(226)**




**(227)**

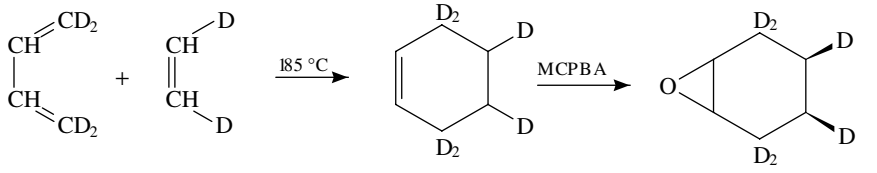



**(228)**

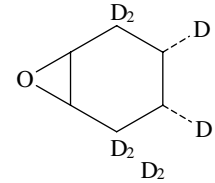
The prototype concerted addition of ethene to butadiene is discussed in the next section.

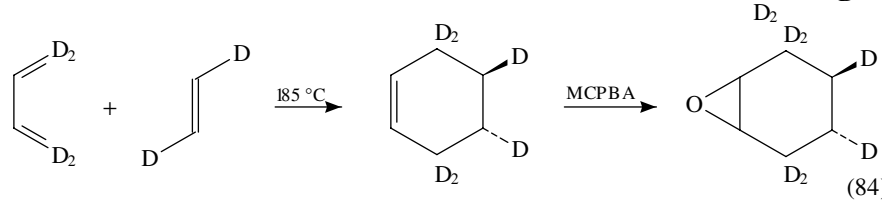
### *2. Experimental studies of the DA reaction with the use of deuterium*

*a*. Evidence for the concerted mechanism of the DA reaction of butadiene with ethylene has been provided by Houk and coworkers[201], who established the stereospecificity of this addition by carrying out the reaction of 1,1,4,4-tetradeuterio-1,3-butadiene with *cis*- or *trans*-1,2-dideuterioethylene at 185 °C for 36 h at a pressure of 1800 psi in a stainless steel bomb (equations 83 and 84). The dideuterioethylenes do not isomerize under these conditions. The cyclohexene products, separated from butadiene dimers by GLC, were then epoxidized with *m*-chloroperbenzoic acid (MCPBA) and their NMR spectra determined.



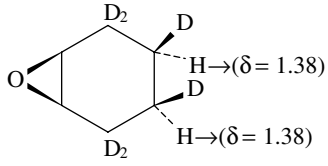

(83)



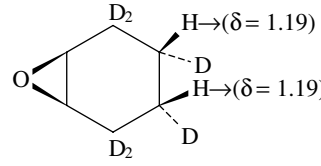




(84)

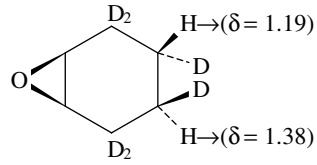
The proton NMR spectra corresponding to the cyclohexene oxides **229** and **230**, obtained in the reaction with *cis*-dideuterioethylene, and to cyclohexene **231**, obtained in the




**(229)**



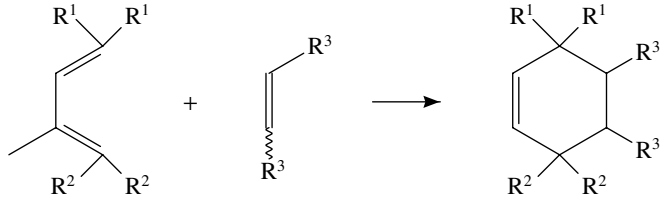

**(230)**




**(231)**

reaction with *trans*-dideuterioethylene, have been recorded and analysed[201]. Calculations of the transition state frequencies[201] are consistent with a synchronous concerted mechanism for the reaction of butadiene with ethylene.

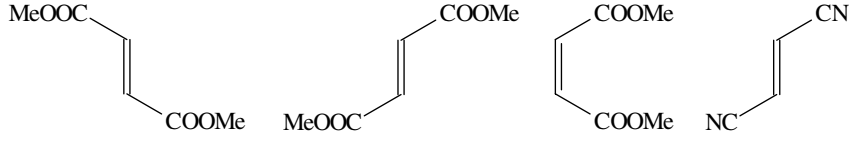
*b*. Secondary kinetic deuterium isotope effects have been determined[202–206] in the various Diels-Alder additions of symmetrical addends[202–204] expressed by equation 85, in Diels-Alder reactions of unsymmetrical addends[205] (equation 86) and in the Diels-Alder reaction of anthracene, butadiene and cyclopentadiene with maleic anhydride[206].



$R^1 = R^2 = D$
$R^1 = D, R^2 = H$
$R^3 = CN, COOMe$

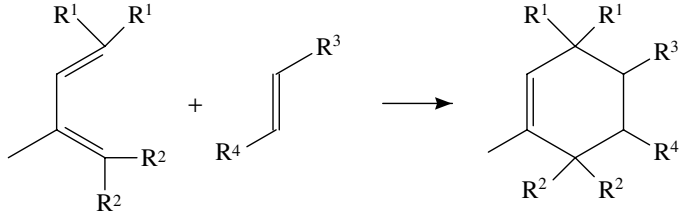
| | Expt. KIE at 373 K |
|---|---|
| $R^1 = D, R^2 = H, R^3 = CN$[d] | 0.95 |
| $R^1 = H, R^2 = D, R^3 = CN$ | 0.95 |
| $R^1 = D, R^2 = D, R^3 = CN$ | 0.90 |
| $R^1 = H, R^2 = D, R^3 = COOMe$[a] | 0.92 |
| $R^1 = D, R^2 = D, R^3 = COOMe$[b] | 0.85 |
| $R^1 = H, R^2 = D, R^3 = COOMe$[c] | 0.92 |
| $R^1 = D, R^2 = H, R^3 = COOMe$[b] | 0.93 |
| $R^1 = D, R^2 = D, R^3 = COOMe$[c] | 0.87 |

(85)



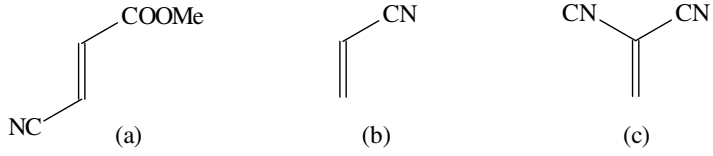
(a) (b) (c) (d)

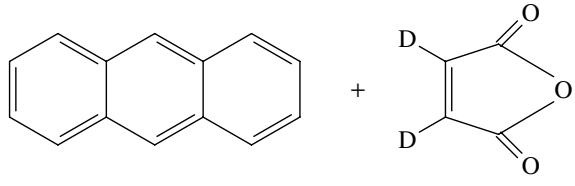
In the reaction of cyclopentadiene with maleic-$D_2$ anhydride[206] an inverse experimental KIE of 8% (KIE = 0.92) was found at 298 K. The reaction between butadiene-$D_4$, $D_2C{=}CHCH{=}CD_2$ and maleic anhydride gave a large inverse $D_4$-KIE of 0.76. The two reactions between anthracene and maleic anhydride presented below also favour the concerted rather than the stepwise mechanism which requires 3–6% KIE in the normal direction (i.e. $>1$).



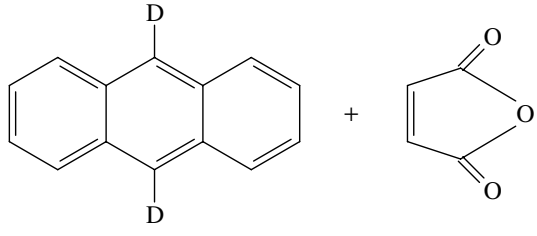

| | | Expt. KIE | | |
|---|---|---|---|---|
| $R^1$ = D, $R^2$ = H, $R^3$ = COOMe, | $R^4$ = CN[a] | 0.88 | at | 298 K |
| $R^1$ = H, $R^2$ = D, $R^3$ = COOMe, | $R^4$ = CN | 0.92 | | 298 |
| $R^1$ = D, $R^2$ = D, $R^3$ = COOMe, | $R^4$ = CN | 0.81 | | 298 |
| $R^1$ = D, $R^2$ = H, $R^3$ = CN, | $R^4$ = H[b] | 0.91 | | 373 |
| $R^1$ = H, $R^2$ = D, $R^3$ = CN, | $R^4$ = H | 0.98 | | 373 |
| $R^1$ = D, $R^2$ = D, $R^3$ = CN, | $R^4$ = H | 0.89 | | 373 |
| $R^1$ = D, $R^2$ = H, $R^3$ = $(CN)_2$, | $R^4$ = H[c] | 0.79 | | 298 |
| $R^1$ = H, $R^2$ = D, $R^3$ = $(CN)_2$, | $R^4$ = H | 0.98 | | 298 |
| $R^1$ = D, $R^2$ = D, $R^3$ = $(CN)_2$, | $R^4$ = H | 0.78 | | 298 |

(86)



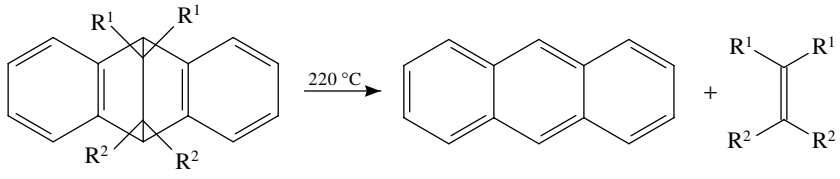




KIE = 0.93 at 373 K



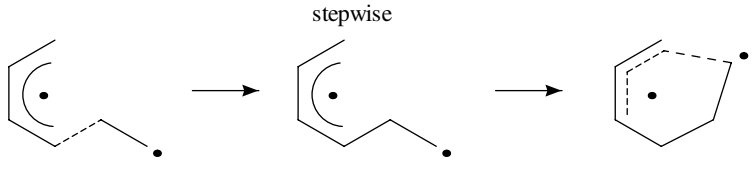

KIE = 0.91 at 373 K

The secondary deuterium KIEs for the retro-Diels-Alder reaction of ethanoanthracene has been investigated also[207] (equation 87)[206].

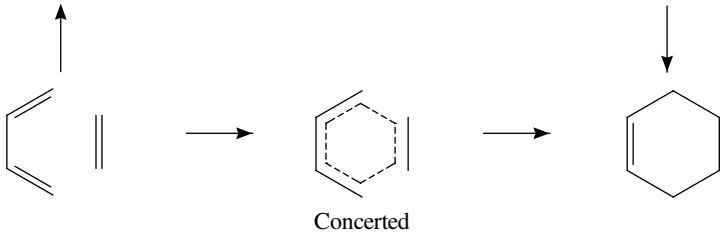



$R^1 = D, R^2 = H; R^1 = R^2 = D, k_H/k_{D_2} = 1.08$ and $k_H/k_{D_4} = 1.17$ at 220 °C (87)

These experimental secondary deuterium KIEs observed in Diels-Alder reactions have been compared with the respective theoretical KIEs for the stepwise mechanism involving a diradical intermediate (equation 88a) and for concerted synchronous and asynchronous mechanisms (equation 88b) for the Diels-Alder reaction of butadiene with ethylene[207].




(88a)




(88b)

Vibrational analysis has been carried out for each isotopomer transition state and the $k_H/k_D$ values were calculated[207] with the transition state theory approximation (equation 89)[208,209]:

$$k_H/k_D = (\nu_H^{\neq}/\nu_D^{\neq}) \frac{\prod^{3N-6}\left(\frac{u_H}{u_D}\right)\prod^{3N-6}\frac{[1-\exp(-u_H)]}{[1-\exp(-u_D)]}\exp\left(\sum^{3N-6}\frac{(u_H-u_D)}{2}\right)}{\prod^{3N^{\neq}-7}\left(\frac{u_H^{\neq}}{u_D^{\neq}}\right)\prod^{3N^{\neq}-7}\frac{[1-\exp(-u_H^{\neq})]}{[1-\exp(-u_D^{\neq})]}\exp\left(\sum^{3n^{\neq}-7}\frac{(u_H^{\neq}-u_D^{\neq})}{2}\right)} \quad (89)$$

where $u = h\nu/kT$.

The activation energy of the concerted mechanism is only 3–7 kcal mol$^{-1}$ lower than that for the first step of the stepwise mechanism. However, the geometries of the two transition states are dissimilar, one bond being formed in the stepwise structure while two bonds are formed in the concerted case, and this leads to different KIEs. The secondary KIEs calculated for concerted TS (terminal hydrogens) are always inverse (and vary from 0.93 to 0.99, depending on the position and the level of theory), in agreement with expectations for $sp^2$ to $sp^3$ hybridization changes. The most reliable values are 3% and

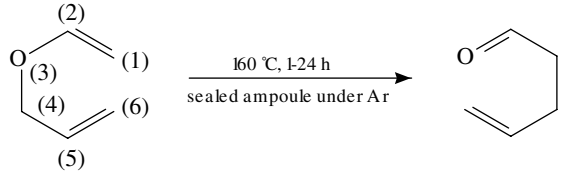
6% for $D_2$ and $D_4$ substrates, respectively. The $D_2$- and $D_4$-KIEs for TS-1 are normal with values of 1% and 4% for $D_2$ and $D_4$, respectively. The KIEs in TS-2 are also normal and opposite in direction to those of the concerted mechanism. The detailed comparison of the theoretical and experimental secondary KIEs for Diels-Alder reactions showed that the concerted mechanism gives a good account of the experimental isotope effects[207,210].

$^{14}C$ Primary kinetic isotope effects for the concerted reaction of butadiene with ethylene, for the stepwise reaction of butadiene with ethylene and for the concerted reaction of butadiene with acrolein, have also been calculated[207]. The experimental values of 1.0438 and 1.0474 found recently[196] in the reaction of 2,3-dimethylbutadiene with [1-$^{14}C$]- and [2-$^{14}C$]-1-nitro-2-phenylethylene, respectively, similar at both reacting termini, are in accord with the calculated value of 1.046 for $k_{12_C}/k_{14_C}$ (373.15 K) in a synchronous concerted reaction of butadiene with ethylene. The $^{14}C$ KIE values predicted for the asynchronous acrolein reaction are 1.015 and 1.045 for the '1' and '2' isotopomer, respectively[207].

## B. Kinetic Isotope Effects in the Thermal Rearrangement of 3-Oxa-1,5-hexadienes

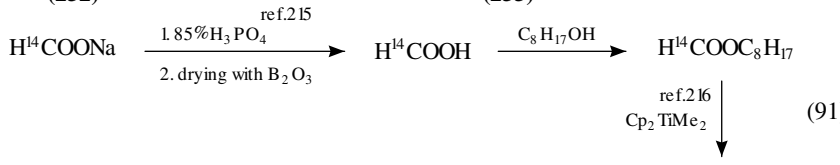
### *1. Heavy atom KIE studies with allyl vinyl ethers*

*a*. The mechanism of the thermal aliphatic Claisen rearrangement[211] has been studied recently by heavy-atom KIE methodology[212]. Carbon-14 KIE in the rearrangement of allyl vinyl ethers, **232**, labelled with $^{14}C$ at the 2-, 4- and 6-positions, and with $^{18}O$ at the 3-position, to the corresponding 4-pentenals, **233** (equation 90), have been determined at 160 °C. The isotopomers [4-$^{14}C$]-**232**, [6-$^{14}C$]-**232** and [$^{18}O$]-**232** have been prepared by the reactions of *n*-octyl vinyl ether[213] with [1-$^{14}C$]-, [3-$^{14}C$]- and [1-$^{18}O$] allyl alcohol in the presence of mercuric acetate[214]. [2-$^{14}C$]-**232** has been prepared from allyl alcohol and *n*-octyl [2-$^{14}C$] vinyl ether which was synthesized as shown in equation 91.




(90)

**(232)** **(233)**




(91)

The $^{14}C$ labelled 4-pentenals, **233**, have been converted to their dimedone derivatives for radio assay. The $^{18}O$-**233** has been reduced to 4-pentenol for MS isotopic assay. The average $^{18}O$ and $^{14}C$ KIEs in the rearrangement of **232** were found to be:

$$1.0506 \pm 0.0007/\text{for}^{18}\text{O isotope},$$

$$1.0271 \pm 0.0006/\text{for } 2 -^{14} \text{C},$$

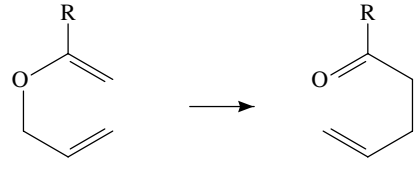
$$1.0720 \pm 0.0008/\text{for } 4-{}^{14}\text{C},$$

$$1.0178 \pm 0.0005/\text{for } 6-{}^{14}\text{C}.$$

The large 3-$^{18}$O and 4-$^{14}$C KIEs indicate that the cleavage of the carbon–oxygen bond contributes strongly to the reaction coordinate motion. All the above data collectively show that the six skeletal atoms of **232** are coupled in motion in the transition state. The $^{14}$C KIE for $C_{(1)}$ has not been determined. The degrees of bonding changes at $C_{(1)}$ and at $C_{(6)}$ in the transition state of reaction 90 cannot be intercompared. The hybridization at $C_{(1)}$ and at $C_{(6)}$ changes from $sp^2$ to $sp^3$. The model calculations with the use of the BEBOVIB IV program[217–219] led the authors[212] to the conclusion that the $C_{(4)}$–O bond is 50–70% broken ('central to product-like') and the $C_{(1)}$–$C_{(6)}$ bond is 10–30% formed ('reactant-like') in the transition state.

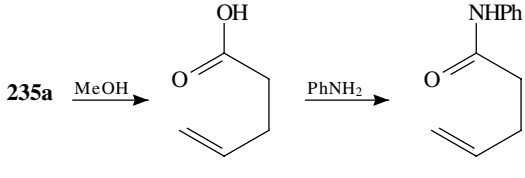
The density functional theory calculations of primary $^{14}$C KIE and secondary deuterium kinetic isotope effects (SKIE)[220] did not reproduce satisfactorily all the experimentally determined $^{14}$C KIE and deuterium (4,4-$^2H_2$)- and 6,6-$^2H_2$-SKIE, though the non-local DFT methods provide transition state energies on a par with correlated molecular orbital theory[221].

*b*. Carbon-14 KIE in the rearrangement of 2-(trimethylsiloxy)[222,223] and 2-(methoxycarbonyl)-3-oxa-1,5-hexadiene[203], both labelled with $^{14}$C at $C_{(1)}$, $C_{(2)}$, $C_{(4)}$ and $C_{(6)}$ positions, have been measured at 22 °C and 80 °C, respectively[224] (equation 92), and the $^{14}$C KIE have been compared with deuterium SKIE in the rearrangement of [4,4-$^2H_2$]**234a** and [6,6-$^2H_2$]**234a**[225,226]. The products **235a** and **235b** have been converted into the solid colourless anilide **236** (equation 93) and semicarbazone **237** (equation 94) for purifications required by precise $^{14}$C scintillation counting with $2\sigma$ at the 0.5% level.




(92)

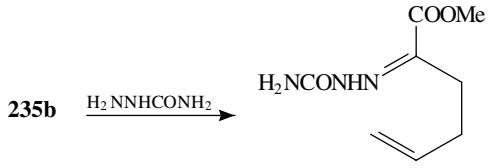
**(234a)** R = $OSiMe_3$ **(235a)**
**(234b)** R = COOMe **(235b)**




(93)

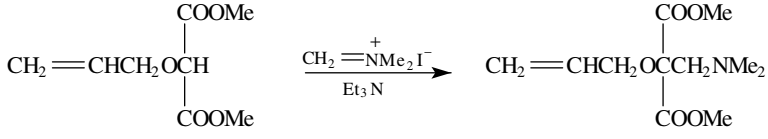
**(236)**

The [1-$^{14}$C] **234b**, [2-$^{14}$C] **234b**, [4-$^{14}$C] **234b** and [6-$^{14}$C] **234b** (with specific activities in the range 4–8 mCi mmol$^{-1}$) have been prepared[224] in the reaction sequence shown in equation 95 using [$^{14}$C] Eschenmoser's salt labelled in the methylene group[227], dimethyl [2-$^{14}$C]diazomalonate (equation 96), [1-$^{14}$C] allyl alcohol[213] and [3-$^{14}$C] allyl alcohol[213].




(94)

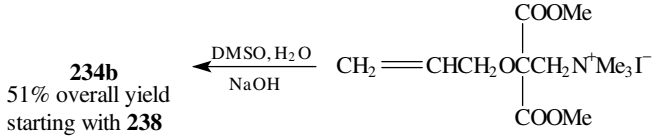
**(237)**



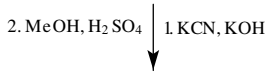


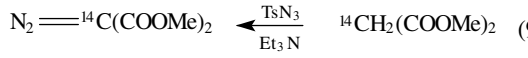


(95)




**234b**
51% overall yield
starting with **238**

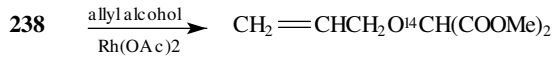




(96)

**(238)**

3.3% overall yield,
specific activity 4.1 mCi mol$^{-1}$




The average $^{14}C$ KIEs for the rearrangement of **234a** to 1-(trimethylsiloxy)-4-pentenal **235a** in THF at 22 °C are:

$1.0164 \pm 0.0013$ for [1 – $^{14}$C]**234a**,

$1.0240 \pm 0.0021$ for [2 – $^{14}$C]**234a**,

$1.1048 \pm 0.0022$ for [4 – $^{14}$C]**234a**,

$1.0174 \pm 0.0010$ for [6 – $^{14}$C]**234a**.

(The values $1.1122 \pm 0.0045$ and $1.0919 \pm 0.0031$ are the maximum and minimum values of $^{14}C$ KIE in the series of independent runs aimed at the determination of [4-$^{14}$C] KIE.)

The deuterium SKIE in the rearrangement of [4,4-$D_2$]- and [6,6-$D_2$] **234a**, determined previously[225,226], are 1.48 and 0.917, respectively.

The $^{14}C$ KIE for the rearrangement of **234b** to methyl 2-oxo-5-hexenoate, **235b**, in $CCl_4$ at 80 °C, deduced from the scintillation counting data on the semicarbazone **237**, are:

$$\text{Av. } 1.0280 \pm 0.0011 \text{ for } [1-{}^{14}\text{C}]\mathbf{234b},$$

$$1.0087 \pm 0.0009 \text{ for } [2-{}^{14}\text{C}]\mathbf{234b},$$

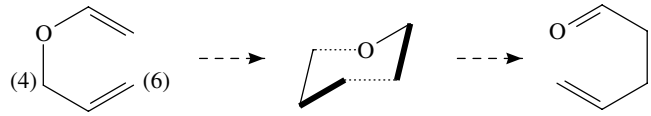
$$1.0330 \pm 0.0015 \text{ for } [4-{}^{14}\text{C}]\mathbf{234b},$$

$$1.0118 \pm 0.0008 \text{ for } [6-{}^{14}\text{C}]\mathbf{234b}.$$

The degrees of partial conversions of **234b** to **235b** were in the range 0.23–0.29. The secondary deuterium KIE in the rearrangement of [4,4-$D_2$]**234b** and [6,6-$D_2$]**234b** are 1.12 and 0.91, respectively.

All the $^{14}C$ primary KIE data above and the $C_{(4)}$ and $C_{(6)}$ secondary deuterium KIEs have been fitted to BEBOVIB modeling calculations and it has been deduced that, in the transition state of the reaction of **234a**, 70–80% bond breaking and 20% bond making occurs, while for **234b** both bond breaking and bond formation amount to 30–40%.

*c*. Secondary deuterium KIEs at the $C_{(4)}$ and $C_{(6)}$ of the allyl vinyl ether Claisen rearrangement, proceeding via a chair-like transition state[228] (equation 97), have been determined recently[229] in the relatively non-polar *m*-xylene, and in 75% and 25% $CD_3OD$ in $D_2O$ at 100 °C. The $k_{(H)}/k_{(D_2)}$ values were found to be:




(97)

**(239)**

1.119(0.019 S.D.) for (4 − $D_2$)**239** in *m*-xylene
0.953(0.015) for (6 − $D_2$)**239**

1.059(0.007) for (4 − $D_2$)**239** in 75% $CD_3OD$:25%$D_2O$
0.981(0.018) for (6 − $D_2$)**239**

1.145(0.04) for (4 − $D_2$)**239** in 25% $CD_3OD$:75%$D_2O$
0.958(0.04) for (6 − $D_2$)**239**

In the gas phase[230] the $(k_H/k_{D_2})$ SKIE are 1.092(0.005) for (4-$D_2$) **239** and 0.98(0.005) for (6-$D_2$) **239** at 160.3 °C.

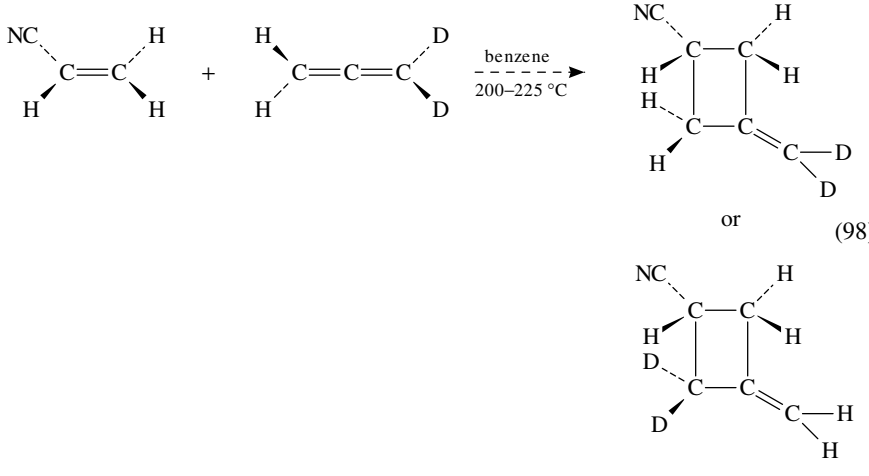
The above SKIE data were taken as evidence against an ionic transition state. Allylic cation-like species would result in much larger normal SKIE at $C_{(4)}$ in a polar medium than in non-polar media by approaching the maximum possible value for conversion of an $sp^3$ $C_{(4)}$ of the ether to an $sp^2$ carbon of an allyl cation.

*Final remarks*. The $^{14}C$-KIE and $^{2}H$-SKIE data presented in this Section (VI.B) clearly indicate the usefulness of isotope effect methodology in studies of mechanistic details of thermally induced Claisen rearrangement, which provides a synthetic route to $\gamma,\delta$-unsaturated carbonyl compounds. The primary and secondary $^{14}C$ KIE supplement strongly the deuterium SKIE. Especially easy for interpretation are $^{14}C$ and $^{2}H$ isotope

effects at $C_{(4)}$ and at $C_{(6)}$ (as well as at $C_{(1)}$). They show directly the degrees of $C_{(4)}-O$ bond clearge and $C_{(6)}-C_{(1)}$ bond formation in the 'TS'. Unfortunately, the investigation of the effect of substituents at $C_{(2)}$ is obscured by the lack of the temperature dependencies of the determined $^{14}C$ and $^{2}H$ isotope effects. The different isotopic studies are carried out at different single temperatures (at 22 °C, at 80 °C and at 160 °C, respectively) depending on the nature of the substituent at $C_{(2)}$. The value of 1.0720 obtained at 160 °C in the rearrangement of unsubstituted [4-$^{14}$C]**232** is smaller than the primary $^{14}C$ KIE of 1.1048 at 22 °C in the rearrangement of [4-$^{14}$C]-2-(trimethylsiloxy)-3-oxa-1,5-hexadiene, **234a**, chiefly because of the higher reaction temperature in the former case. The $^{14}C$ KIE in the last case is very close to the $^{14}C$ KIE expected for the complete rupture of the $^{12}C-^{16}O/^{14}C-^{16}O$ bond pair. The values of the $^{14}C_{(6)}$ KIE equal $1.0178 \pm 0.0005$ and $1.0174 \pm 0.0010$ in the rearrangements of **232** and **234a**, both labelled at $C_{(6)}$, respectively. Substituent and 'temperature independent' effects within the experimental error, indicate that the $C_{(6)}-C_{(1)}$ bond is not completely formed in the 'TS' corresponding to the transformation of $sp^2$ hybridization to $sp^3$ hybridization at $C_{(6)}$ and at $C_{(1)}$. A negligible $^{14}C_{(6)}$ KIE is expected in the complete transformation of one C=C bond into two C−C single bonds (neglecting the effects of $^{14}C-^{1}H$ changes during the hybridization changes). The $^{14}C$ KIEs in the Claisen rearrangement were investigated much more computationally than experimentally. Particularly, the dependence of the $^{14}C_{(4)}$ KIE values on the degrees of conversion of **234b** at different reaction temperatures has not been studied.

### C. Brief Outline of Isotopic Studies with Unsaturated Compounds

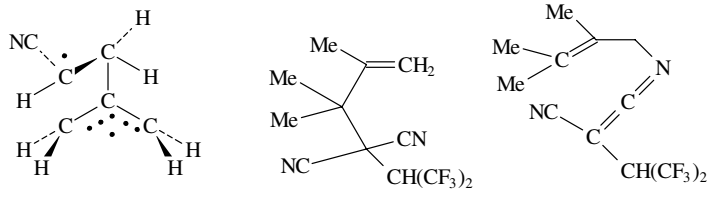
The intramolecular and intermolecular deuterium isotope effects in the cycloaddition of acrylonitrile to allene (equation 98) have been studied by Dolbier and Dai[231,232]. The intramolecular KIEs in the allene–acrylonitrile system were found to be $1.21 \pm 0.02$ at 206 °C and $1.14 \pm 0.02$ at 225 °C. A negligible intermolecular SKIE was found in the reaction of the mixture of tetradeuteriated and undeuteriated allene using a limited amount of acrylonitrile; $(k_H/k_D) = 1.04 \pm 0.05$ at 190–210 °C for $D_0/D_4$ allene. An 'equilibrium deuterium IE' of $0.92 \pm 0.01$ was found at 280–287± 5 °C (15–45 h reaction time).




(98)

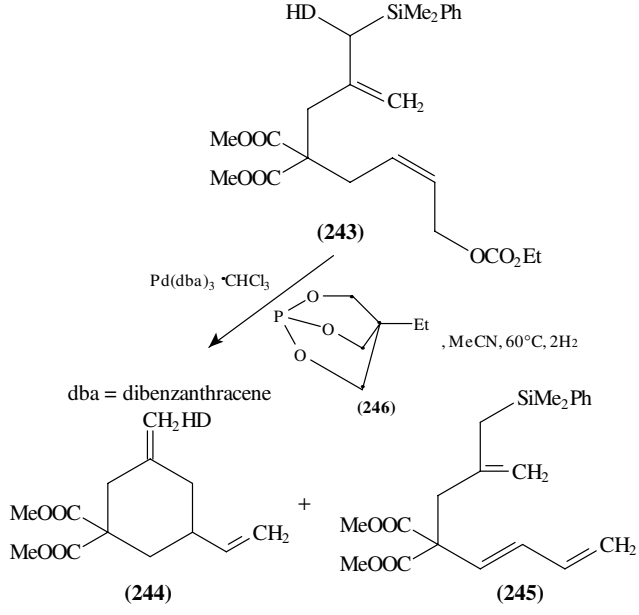
It has been suggested that the reaction in equation 98 proceeds through the biradical intermediate **240**. The 15–20% preference for incorporation of deuterium in the exocyclic

methylene group of vinylcyclobutane has been reproduced theoretically by Halevi and Wolfsberg[233]. The value $k_{exo}/k_{endo} = 1.166$ has been computed using the AM1 Hamiltonian with limited CI. The normal SKIE, $(k_H/k_D) > 1$, was ascribed[232] to slower rotation of the deuteriated methylene group before ring closure from the planar configuration toward the orthogonal geometry which is necessary for $\sigma$ bond formation. No $^{14}C$ KIEs have been studied in reaction 98. In the reaction of 1,1-dideuterioallene with hexachlorocyclopentadiene, the intramolecular $k_H/k_D$ values are $0.89 \pm 0.01$ at 150 °C and $0.92 \pm 0.01$ at $135 \pm 1$ °C. The intermolecular KIE is 0.88–0.93±0.04 at 135 °C[231].



'TS' (**240**) (**241**) (**242**)

The deuterium labelling established[234] that the $\gamma,\delta$-unsaturated, nitrile **241** equilibrates at room temperature with the *N*-allylketene imine **242** through an intramolecular rearrangement mechanism. Deuterium has been applied in the study of the novel palladium(0)-catalysed cyclization of 2,7-octadienyl carbonate containing an allylsilane moiety, **243**, to product **244** (in 89%) and some **245** in the presence of phosphite **246** (equation 99)[235]. Intramolecular KIEs ($k_H/k_D = 3.0$ and 3.5) have been observed in a bicyclic olefin formation (monoterpinene biosynthesis from [1-$^3$H,4-$^2$H$_2$]- and [10-$^2$H$_2$]-geranyl pyrophosphates) catalysed by pinene synthases from sage (*Salvia officinalis*)[236].



(**243**)

$Pd(dba)_3 \cdot CHCl_3$

(**246**)

, MeCN, 60°C, $2H_2$

(99)

dba = dibenzanthracene

(**244**) (**245**)

70% combined (10:1) yield of **(244)**-D, 28% recovery of **243-D**, D atom resided completely on methylene carbon of **(244)-D**.

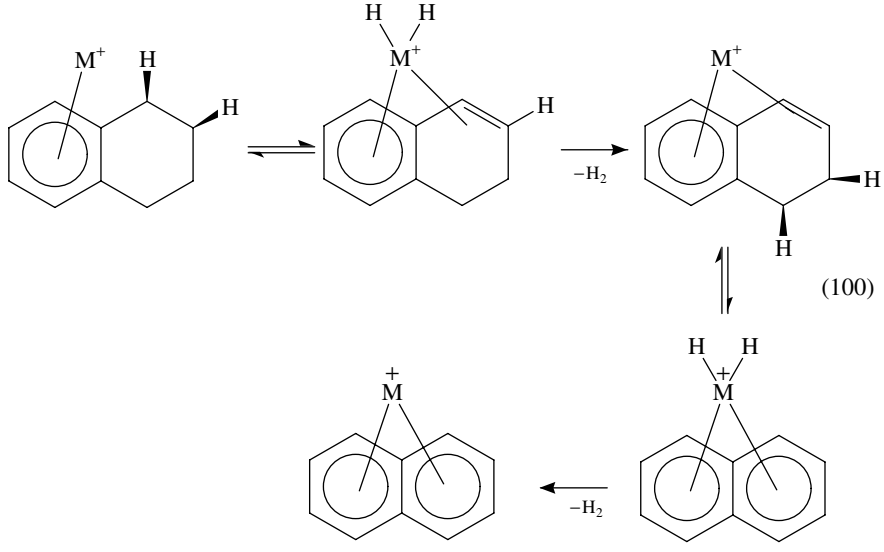
$\beta$-Deuterium secondary isotope effects in an olefinic cationic polycyclization have been reviewed by Borcic and coworkers[237].

A tritium isotope effect in high-performance liquid chromatography of 11 eicosanoids has been observed. Multi-tritium-labelled eicosanoids were eluted earlier than the corresponding unlabelled eicosanoid. Variations in retention time are 3–7%, depending on the separation conditions as well as on the number and position of the tritium substituents[238].

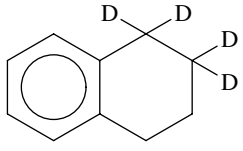
A deuterium kinetic isotope effect of 2 has been found in the hydrogenation of 1,3-pentadiene[239] using a Ziegler–Natta catalyst, cobalt(II,III) $\mu^3$-oxostearate-$AlEt_3$, $Co_2^{III} \cdot Co^{II}O(C_{17}H_{35}CO_2)_6(H_2O)_3 \cdot 5H_2O$–$AlCl_3$. The reaction was found to be of a kinetic order of 0.3 in the diene, and first order in the hydrogen and the catalyst. The kinetics and the selectivity of the reaction has been studied at 253–293 K.

A very large deuterium isotope effect has been observed[240] by ESR at 77 K on hydrogen–deuterium elimination reaction from 2,3-dimethylbutane (H-DMB)-$SF_6$ and 2,3-dimethylbutane-2,3-$D_2$ (D-DMB)-$SF_6$ (0.6 mol% mixtures), $\gamma$-irradiated at 70 K and then stored at 77 K. The significant isotope effect, $k_{H_2}/k_{D_2} = 1.69 \times 10^4$ at 77 K, has been explained by tunnelling elimination of hydrogen ($H_2$) molecules from a $DMB^+$ ion[240].

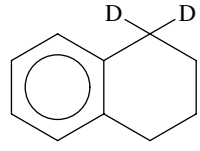
Labelling experiments provided the evidence that the $Fe^I$- and $Co^I$-mediated losses of $H_2$ and $2H_2$ from tetralin are extremely specific. Both reactions follow a clear *syn*-1,2-elimination involving $C_{(1)}/C_{(2)}$ and $C_{(3)}/C_{(4)}$, respectively. In the course of the multistep reaction the metal ions do not move from one side of the $\pi$-surface to the other. The kinetic isotope effect associated with the loss of the first $H_2$ molecule, $k(H_2)/k(D_2) = 3.4 \pm 0.2$, is larger than the KIE, $k(H_2)/k(HD) = 1.5 \pm 0.2$, for the elimination of the second $H_2$ molecule. A mechanism of interaction of the metal ion with the hydrocarbon $\pi$-surface, ending with arene-$M^+$ complex **246** formation in the final step of the reaction, outlined in equation 100, has been proposed[241] to rationalize the tandem MS studies of the unimolecular single and double dehydrogenation by $Fe^+$ and $Co^+$ complexes of tetraline and its isotopomers **247–251**.



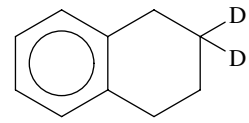

**(246)**



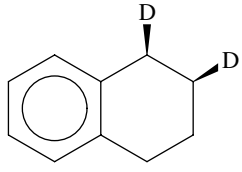

**(247)**



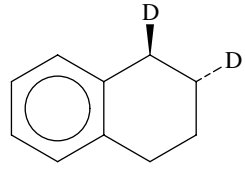

**(248)**




**(249)**




**(250)**




**(251)**

## VII. ACKNOWLEDGEMENTS

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## VIII. REFERENCES

1. F. Turecek, *J. Labelled Compd. Radiopharm.*, **24**, 73 (1987).
2. K. R. Maples, J. L. Lane and A. R. Dalh, *J. Labelled Compd. Radiopharm.*, **31**, 469 (1992).
3. M. Heylin, *Chem. Eng. News*, **69**, 28 (1991).
4. A. R. Dahl, J. D. Sun, L. S. Birnbaum, J. A. Bond, W. C. Griffith, J. L. Mauderly, B. A. Muggenburg, P. J. Sabourin and R. F. Henderson, *Toxicol. Appl. Pharmacol.*, **110**, 9 (1991).
5. K. R. Maples, and A. R. Dahl, *Drug Metab. Dispos.*, **19**, 835 (1991).
6. R. O. Adlof and E. A. Emken, *J. Labelled Compd. Radiopharm.*, **24**, 699 (1987).
7. J. T. Bernett and H. Sprecher, *Biochim. Biophys. Acta*, **398**, 354 (1975).
8. R. T. Holman and S. B. Johnson, in *Dietary Fats and Health*. (Eds. E. G. Perkins and W. J. Visek) Am. Oil Chem. Soc., Champaign, IL, 1983, pp. 247–266.
9. R. O. Adlof and E. A. Emken, *J. Labelled Compd. Radiopharm.*, **23**, 149 (1986).
10. D. F. Taber, M. A. Phillips and W. C. Hubbard, *Prostaglandins*, **22**, 349 (1981).
11. A. Vos, M. Reinhart, S. Sankarappa and H. Sprecher, *J. Biol. Chem.*, **266**, 19995 (1991).
12. D. F. Taber and K. You, *J. Labelled Compd. Radiopharm.*, **34**, 747 (1994).
13. C. A. Brown and V. K. Ahuja, *J. Org. Chem.*, **38**, 2226 (1973).
14. H. J. Bestmann, C. O. Meese and T. Röder, *J. Labelled Compd. Radiopharm.*, **27**, 1325 (1989).
15. C. O. Meese, *J. Labelled Compd. Radiopharm.*, **23**, 295 (1986).
16. D. Keppler, M. Huber, W. Hagmann, H. A. Ball, A. Guhlmann and S. Kaestner, *Ann. N. Y. Acad. Sci.*, **524**, 68 (1988).
17. D. S. Newcombe, *J. Clin. Pharmacol.*, **28**, 530 (1988).
18. J. P. Lellouche, F. Aubert and J. P. Beaucourt, *Tetrahedron Lett.*, **29**, 3069 (1988).
19. H. Hughes, J. R. Mitchell and S. J. Gaskell, *Anal. Biochem.*, **179**, 304 (1989).
20. D. Tsikas, J. Fauler and J. C. Frölich, *J. Labelled Compd. Radiopharm.*, **31**, 341 (1992).
21. M. Balazy and R. C. Murphy, *Anal. Chem.*, **58**, 1098 (1986).
22. B. Samuelson, *Science*, **200**, 568 (1973).
23. R. Pontikis, Y. Le Merrer and J. C. Depezay, *J. Labelled Compd. Radiopharm.*, **28**, 1127 (1990).

24. B. Samuelsson, S. E. Dahlen, J. A. Lindgren, C. A. Rouzer and C. N. Serhan, *Science*, **237**, 1171 (1987).
25. J. Y. Wescott, K. R. Stenmark and R. C. Murpy, *Prostaglandins*, **31**, 227 (1986).
26. W. R. Mathews, G. L. Budny, M. A. Wynalda, D. M. Guido, W. P. Schneider and F. A. Fitzpatrick, *Anal. Chem.*, **60**, 349 (1988).
27. A. A. Liebman, W. Burger, D. H. Malarek, L. Serico, R. R. Muccino, C. W. Perry and S. C. Choudhry, *J. Labelled Compd. Radiopharm.*, **28**, 525 (1990).
28. R. R. Muccino and C. A. Wasiowich, *J. Labelled Compd. Radiopharm.*, **17**, 463 (1980).
29. H. R. Bergen, H. C. Furr and J. A. Olson, *J. Labelled Compd. Radiopharm.*, **25**, 11 (1988).
30. D. R. Hughes, P. Rietz, W. Vetter and G. A. J. Pitt, *Int. J. Vit. Nutr. Res.*, **46**, 231 (1976).
31. M. M. Mathews- Roth, *Pure Appl, Chem.*, **57**, 717 (1985).
32. G. W. Burton and K. U. Ingold, *Science*, **224**, 569 (1984).
33. H. R. Bergen III and J. A. Olson, *J. Labelled Compd. Radiopharm.*, **27**, 783 (1989).
34. C. O. Meese and S. Holzer, *J. Labelled Compd. Radiopharm.*, **27**, 319 (1989).
35. S. Izumi, M. Aihara, Y. Hiraga, T. Hirata and T. Suga, *J. Labelled Compd. Radiopharm.*, **29**, 591 (1991).
36. T. Suga, T. Hirata, T. Aoki and T. Shishibori, *Phytochemistry*, **25**, 2769 (1986).
37. C. Salles, J. C. Jallageas, Y. Beziat and H. J. Cristeau, *J. Labelled Compd. Radiopharm.*, **31**, 11 (1992).
38. K. E. A. Ishag, H. Jork and M. Zeppezauer, *Fresenius Z. Anal. Chem.*, **321**, 331 (1985).
39. F. E. Huelin and I. M. Coggiola, *J. Sci. Food Agric.*, **19**, 297 (1968).
40. W. G. Jennings and R. Tressl, *Chem. Microbiol. Technol. Lebensm.*, **3**, 52 (1974).
41. E. F. L. J. Anet. *J. Sci. Food Agric.*, **25**, 299 (1974).
42. P. M. Chen, D. M. Varga, E. A. Mielke, T. J. Facteau and S. R. Drake, *J. Food Sci. Food Agric.*, **55**, 171 (1990).
43. S. Fielder, D. D. Rowan and P. F. Reay, *J. Labelled Compd. Radiopharm.*, **33**, 965 (1993).
44. S. Fielder and D. D. Rowan, *J. Labelled Compd. Radiopharm.*, **34**, 1075 (1994).
45. M. Shibasaki, Y. Torisawa and S. Ikegami, *Tetrahedron Lett.*, **24**, 3493 (1983).
46. R. J. Gryglewski, A. Szczeklik and J. C. McGift *Prostaglandin: Clinical Trials*, (Eds.) Raven Press, New York, 1985.
47. K. Hoshi and Y. Mizushima, *Prostaglandins*, **40**, 155 (1990).
48. T. Tanaka, K. Bannai, A. Hazato, K. Manabe and S. Kurozumi, *J. Labelled Compd. Radiopharm.*, **29**, 667 (1991).
49. S. Kurozumi, in *Kohza Prostaglandin Z. Iyakuhin* (Eds. S. Yamamoto and S. Murota), Chap. 3, Tokyo Kagaku Dohjin, Tokyo, 1988, pp. 96–98.
50. A. Hazato, T. Tanaka, K. Watanabe, K. Bannai, T. Tora, N. Okomura, K. Manabe, A. Ohtsu, F. Kamimoto and K. Kurozumi, *Chem. Pharm. Bull.*, **33**, 1815 (1985).
51. S. Sugiura, T. Tanaka, K. Bannai and S. Kurozumi, *J. Labelled Compd. Radiopharm.*, **29**, 1041 (1991).
52. H. Shibasaki, T. Furuta and Y. Kasuya, *J Labelled Compd. Radiopharm.*, **29**, 1033 (1991).
53. N. Hirota, T. Furuta and Y. Kasuya, *J. Chromatogr.*, **425**, 237 (1988).
54. H. Shibasaki, T. Furuta, Y. Kasuya, T. Okabe, T. Katoh, T. Kogo and T. Hirayama, *Biomed. Environ. Mass Spectrom.*, **19**, 225 (1990).
55. T. Furata, K. Kusano and Y. Kasuya, *J. Chromatogr.*, **525**, 15 (1990).
56. R. Nyfeler and W. Keller-Schierlein, *Helv. Chim. Acta*, **57**, 2459 (1974).
57. A. N. Jones, R. E. Simpson and H. J. Jenkins, *J. Labelled Compd. Radiopharm.*, **31**, 297 (1992).
58. P. G. Williams, H. Morimoto and D. E. Wemmer, *J. Am. Chem. Soc.*, **110**, 8038 (1988).
59. E. A. Halevi, M. Nussin and A. Ron, *J. Chem. Soc.*, 866 (1963).
60. H. C. Brown and G. J. McDonald, *J. Am. Chem. Soc.*, **88**, 2514 (1966).
61. J. R. Heys, *J. Chromatogr.*, **407**, 34 (1987).
62. N. Tanaka and E. R. Thornton, *J. Am. Chem. Soc.*, **98**, 1617 (1976).
63. R. Baweja, *Anal. Chem. Acta*, **192**, 345 (1987).
64. N. El Tayar, H. van de Waterbeemd, M. Gryllaki, B. Testa and W. F. Trager, *Int. J. Pharm.*, **19**, 271 (1984).
65. J. Bigeleisen, *J. Chim. Phys.*, **60**, 37 (1963).
66. W. A. van Hook, *Isotopenpraxis*, **4**, 161 (1968).
67. G. G. Devyatykh, *J. Chemistry and Chem. Technol.*, **2**, 239 (1958) (in Russian); *Chem. Abstr.*, **52**, 5903a (1958); **52**, 12607e (1958).

68. G. Janco and W. A. van Hook, *Chem. Rev.*, **74**, 689 (1974).
69. W. A. van Hook, in *Isotope Effects in Chemical Reactions* (Eds. C. J. Collins and N. S. Bowman), Chap. 1, Van Nostrand Reinhold, New York, 1970.
70. M. Zielinski, in *Isotope Effects in Chemistry* (Ed. A. Wawrzenczak), Chap. 6, Polish Sci. Publ., Warsaw, 1979; pp. 131–143.
71. T. Hoshino, H. J. Williams, K. Shishido and A. I. Scott, *J. Labelled Compd. Radiopharm.*, **28**, 1285 (1990).
72. *Biochemicals, Organic Compounds*, SIGMA, 1992, p. 598.
73. E. Granstrom and M. Kumlin, in *Prostaglandins and Related Substances. A Practical Approach* (Ed. C. Benedetto), IRL Press, Oxford, 1987; p. 5.
74. M. J. Raftery and S. J. Gaskell, *J. Labelled Compd. Radiopharm.*, **29**, 313 (1991).
75. D. F. Nogales and D. A. Lightner, *J. Labelled Compd. Radiopharm.*, **34**, 453 (1994).
76. S. Boiadjiev, R. V. Person, G. Puzicha, C. Knobler, E. Maverick, K. N. Trueblood and D. A. Lightner, *J. Am. Chem. Soc.*, **114**, 10123 (1992).
77. M. Kogan and A. Valasinas, *J. Labelled Compd. Radiopharm.*, **34**, 943 (1994).
78. A. Valasinas and B. Frydman, *J. Org. Chem.*, **41**, 2991 (1976).
79. A. W. Johnson, E. Markham, R. Price and K. B. Shaw, *J. Chem. Soc.*, 4254 (1958).
80. U. Sonnewald and S. Seltzer, *J. Labelled Compd. Radiopharm.*, **24**, 787 (1987).
81. D. Oesterhelt and W. Stoeckenius, *Nature New Biology*, **233**, 149 (1971).
82. W. Stoeckenius and R. A. Bogomolni, *Annu. Rev. Biochem.*, **52**, 587 (1982).
83. A. A. Levin, L. J. Sturzenbecker, S. Kazmer, T. Bosakowski, C. Huselton, G. Allenby, J. Speck, C. L. Kratzeisen, M. Rosenberg, A. Lovey and J. F. Grippo, *Nature*, **355**, 359 (1992).
84. M. I. Dawson, P. D. Hobbs, J. F. Cameron and S. W. Rhee, *J. Labelled Compd. Radiopharm.*, **33**, 245 (1993).
85. H. Kaegi, in *Synthesis of Retinoids Labeled with Radioisotopes. The Retinoids* I (Eds. M. B. Sporn, A. B. Roberts and D. S. Goodman), Academic Press, New York, 1984.
86. M. I. Sherman, M. L. Paternoster and M. Taketo, *Cancer Res.*, **43**, 4283 (1983).
87. (a) I. Ujvary, W. Eng and G. D. Prestwich, *J. Labelled Compd. Radiopharm.*, **28**, 65 (1990).
    (b) W. Eng and G. D. Prestwich, *J. Labelled Compd. Radiopharm.*, **25**, 627 (1988).
88. H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 53 (1968).
89. E. J. Corey and A. G. Myers, *Tetrahedron Lett.*, **25**, 3559 (1984).
90. I. Ujvary and G. D. Prestwich, *J. Labelled Compd. Radiopharm.*, **28**, 167 (1990).
91. D. W. Borst, H. Laufer, M. Landau, E. S. Chang, W. A. Hertz, F. C. Baker and D. A. Schooley, *Insect Biochem.*, **17**, 1123 (1987).
92. H. Parnes, *J. Labelled Compd Radiopharm.*, **28**, 29 (1990).
93. K. L. Goa and J. P. Monk, *Drugs*, **34**, 539 (1987).
94. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
95. K. Manabe, T. Tanaka, S. Kurozumi and Y. Kato, *J. Labelled Compd. Radiopharm.*, **29**, 1107 (1991).
96. K. Hoshi and Y. Mizushima, *Prostaglandins*, **40**, 155 (1990).
97. S. I. Shram, T. Y. Lazurkina, V. P. Shevchenko, I. Y. Nagaev and N. F. Myasoedov, *J. Labelled Compd. Radiopharm.*, **34**, 359 (1994).
98. V. P. Shevchenko, G. I. Myagkova, T. Y. Lazurkina, P. M. Dyomin, S. I. Shram, D. A. Zabolotsky, I. Y. Nagaev, Y. Y. Belosludtsev, R. P. Evstigneeva and N. F. Myasoyedov, *J. Labelled Compd. Radiopharm.*, **27**, 1177 (1989).
99. Z. Joffe, *Fusarium Species—Their Biology and Toxicology*, Wiley, New York, 1986.
100. B. B. Jarvis and C. S. Yatawara, *J. Org. Chem.*, **51**, 2906 (1986).
101. B. Yagen and B. B. Jarvis, *J. Labelled Compd. Radiopharm.*, **27**, 675 (1989).
102. L. G. Dring, P. E. Gunraj, A. H. Parton and J. R. Jones, *Int. J. Appl. Radiat. Isotop.*, **39**, 578 (1988).
103. V. P. Shevchenko, V. V. Bezuglov, N. M. Gretskaya, G. S. Kogteva, E. M. Manevich and N. F. Myasoedov, *Int. J. Appl. Radiat. Isotop.*, **39**, 610 (1988).
104. Y. H. Li, L. M. Chan, L. Tyer, R. T. Moody, C. M. Himel and D. M. Hercules, *J. Am. Chem. Soc.*, **97**, 3118 (1975).
105. V. Fussgänger, *Chem. Ber.*, **35**, 976 (1902).
106. *Aldrich Catalogue of Fine Chemicals*, 1992–1993, p. 507.
107. Y. Hiraga, H. Danjo, T. Ito and T. Suga, *J. Labelled Compd. Radiopharm.*, **33**, 733 (1993).
108. R. Kjonaas and R. Croteau *Arch. Biochem. Biophys.*, **220**, 79 (1983).

109. P. Maetz, F. Sobrio, C. Mioskowski and B. Rousseau, *J. Labelled Compd. Radiopharm.*, **34**, 807 (1994).
110. J. J. Rooney and G. Webb, *J. Catal.*, **3**, 488 (1964).
111. J. Hiltunen, C. T. Peng and Z. C. Yang, *J. Labelled Compd. Radiopharm.*, **28**, 543 (1990).
112. B. E. Gordon, C. T. Peng, W. R. Erwin and R. M. Lemmon, *Appl. Radiat. Isot.*, **33**, 715 (1982).
113. C. T. Peng, in *Isotopes in the Physical and Biomedical Sciences*, Vol. 1, *Labelled Compounds. Part A* (Eds. E. Buncel and J. R. Jones), Elsevier, Amsterdam, 1987, pp. 6–51.
114. A. A. Liebman, in *Isotopes in Physical and Biomedical Sciences*, Vol. 1, *Labelled Compounds. Part A* (Eds. E. Buncel and J. R. Jones), Elsevier, Amsterdam, 1987, pp. 193–210.
115. E. A. Evans, D. C. Warrell, J. A. Elvidge and J. R. Jones, *Handbook of Tritium NMR Spectroscopy and Applications*, Wiley, Chichester, 1985, 249 pp.
116. C. T. Peng, S. F. Ding, R. L. Hua and Z. C. Yang, *J. Chromatogr.*, **436**, 137 (1988).
117. N. Hirai, D. G. I. Kingston, R. I. van Tassell and T. D. Wilkins, *J. Am. Chem. Soc.*, **104**, 6149 (1982).
118. N. Hirai, D. G. I. Kingston, R. L. van Tassell and T. G. Wilkins, *J. Nat. Prod.*, **48**, 622 (1985).
119. M. Z. Kassaee and D. G. I. Kingston, *J. Labelled Compd. Radiopharm.*, **24**, 1071 (1987).
120. E. Browne and R. B. Firestone, in *Table of Radioactive Isotopes* (Ed. V. S. Shirley), Wiley, Chichester, 1986, p. A-1.
121. L. Cattel, M. Ceruti, G. Balliano. F. Viola, G. Grosa and F. Schuber, *Steroids*, **53**, 363 (1989).
122. M. Ceruti, G. Grosa, F. Rocco, F. Dosio and L. Cattel, *J. Labelled Compd. Radiopharm.*, **34**, 577 (1994).
123. M. A. Channing and N. Simpson, *J. Labelled Compd. Radiopharm.*, **33**, 541 (1993).
124. D. Barton, D. Crich and W. B. Motherwell, *Tetrahedron Lett.*, **24**, 4979 (1983).
125. J. J. DeGeorge, T. Nariai, S. Yamazaki, W. M. Williams and S. I. Rapoport, *J. Neurochemistry*, **56**, 352 (1991).
126. M. A. Channing *J. Nucl. Med.*, **32**, 1093 (1991).
127. A. Foster, B. Fitzsimmons, J. R. Rokach and L. G. Letts, *Biochem. Biophys. Acta*, **921**, 486 (1987).
128. M. Huber, A. Guhlmann, P. L. M. Jansen and D. Keppler, *Hepatology*, **7**, 224 (1987).
129. F. Oberdorfer, T. Siegel, A. Guhlmann, D. Keppler and W. Maier-Borst, *J. Labelled Compd. Radiopharm.*, **31**, 903 (1992).
130. S. K. Luthra, V. W. Pike and F. Brady, *Appl. Radiat. Isot. Part A*, **41**, 471 (1990).
131. D. LeBars, S. K. Luthra, V. W. Pike and D. C. Luu Duc, *Appl. Radiat. Isot.*, **38**, 1073 (1987).
132. D. Keppler, A. Guhlmann, F. Oberdorfer, K. Krauss, J. Müller, H. Ostertag and M. Huber, *Ann. N.Y. Acad. Sci.*, **629**, 100 (1991).
133. T. Kihlberg and B. Långström, *J. Labelled Compd. Radiopharm.*, **34**, 617 (1994).
134. T. Kihlberg and B. Langstrom, *Acta Chem. Scand.*, **48**, 570 (1994).
135. M. Zielinski, *Nukleonika*, **31**, 81 (1986).
136. M. Zielinski, *Nukleonika*, **32**, 3 (1987).
137. M. Zielinski, *Nukleonika*, **34**, 3 (1989).
138. M. Zielinski, *Nukleonika*, **34**, 287 (1989).
139. M. Zielinski and M. Kanska, in *The Chemistry of Acid Derivatives, Vol. 2, Supplement B* (Ed. S. Patai), Chap. 9, Wiley, Chichester, 1992.
140. P. Gullberg, Y. Watanabe, H. Svärd, O. Hayaishi and B. Langström, *Appl. Radiat. Isot.*, **38**, 647 (1987).
141. H. Tokumoto, Y. Watanabe, A. Yamashita, Y. Arai and O. Hayashi, *Brain Res.*, **362**, 114 (1986).
142. N. Balasubramanian, P. J. Brown, J. D. Catt, W. T. Han, R. A. Parker, S. Y. Sit and J. J. Wright, *J, Med. Chem.*, **32**, 2038 (1989).
143. G. M. Luke and J. E. Swigor, *J. Labelled Compd. Radiopharm.*, **29**, 193 (1991).
144. G. E. Stokker, W. F. Hoffman, A. W. Alberts, E. J. Cragoe Jr., A. A. Deana, J. L. Gilfillan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith and A. K. Willard *J. Med. Chem.*, **28**, 347 (1985).
145. T. Y. Shen and T. B. Windholz, *J. Am. Chem. Soc.*, **85**, 488 (1963).
146. S. Abe, I. Yamatsu, C. Yamato, S. Kobayashi and M. Mishima, *J. Labelled Compd. Radiopharm.*, **29**, 619 (1991).
147. P. Parent, F. Leborgne, J. P. Lellouche, J. P. Beaucourt and A. Vanhove, *J. Labelled Compd. Radiopharm.*, **28**, 633 (1990).
148. F. Michelassi, L. Landa, F. D. Hill, E. Lowenstein, W. D. Watkins, A. J. Petkav and W. M. Papol, *Science*, **217**, 841 (1982).

149. D. A. Holt, M. A. Levy, H. J. Oh, J. M. Erb, J. I. Heaslip, M. Brandt, H. Y. Lan-Hargest and B. W. Metcalf, *J. Med. Chem.*, **33**, 943 (1990).
150. A. Y. L. Shu and J. R. Heys, *J. Labelled Compd, Radiopharm.*, **34**, 587 (1994).
151. L. M. Thompson, C. H. Yates and A. D. Odell, *J. Am. Chem. Soc.*, **76**, 1194 (1954).
152. J. R. Heys, *J. Chem. Soc. Chem. Commun.*, 681 (1992).
153. J. R. Heys, A. Y. L. Shu, S. G. Senderoff and N. M. Philips, *J. Labelled Compd. Radiopharm.*, **33**, 431 (1993).
154. M. LeRocque, A. Broen and S. Szabo, *Pharmacologist*, **27**, 116 (1985).
155. T. Shimada, T. Yanagisawa, T. Tomiyama, and M. Okazaki, *J. Labelled Compd. Radiopharm.*, **34**, 79 (1994).
156. H. Suzuka, T. Tomiyama and S. Ikegami, *J. Labelled Compd. Radiopharm.*, **28**, 901 (1990).
157. T. Tomiyama, M. Yokota, S. Wakabayashi, K. Kosakai and T. Yanagisawa, *J. Med. Chem.*, **36**, 791 (1993).
158. S. S. Bhagwat, P. R. Hammam, W. C. Still, S. Bunting and F. A. Fitzpatrick, *Nature*, **315**, 511 (1985).
159. T. Yanagisawa, M. Yokota, T. Tomiyama and S. Ikegami, *J. Labelled Compd. Radiopharm.*, **34**, 205 (1994).
160. G. Pattendon and B. C. L. Weedon, *J. Chem. Soc. (C)*, 1984 (1968).
161. U. J. Haynes and J. E. Swigor, *J. Labelled Compd. Radiopharm.*, **33**, 991 (1993).
162. K. Shimada, K. Tadano, T. Satoh, K. Hashimoto, S. Tanaka and T. Yuzuriha, *J. Labelled Compd. Radiopharm.*, **27**, 1293 (1989).
163. X. Xiao and G. D. Prestwich, *J. Labelled Compd. Radiopharm.*, **29**, 883 (1991).
164. L. J. Mulheirn and P. J. Ramm, *Chem. Soc. Rev.*, 259 (1972).
165. L. J. Floyd, L. D. Barnes and R. F. Williams, *Biochemistry*, **28**, 8515 (1989).
166. O. Boyé and A. Brossi, in *The Alkaloids*, Vol. 41, Academic Press, New York 1992, p. 125.
167. O. Boyé, Z. Getahun, S. Grover, E. Hamel and A. Brossi, *J. Labelled Compd. Radiopharm.*, **33**, 293 (1993).
168. G. J. Kang, Z. Getahun, A. Muzzafar, A. Brossi and E. Hamel, *J. Biol. Chem.*, **265**, 10255 (1990).
169. S. Grover, O. Boyé, Z. Getahun, A. Brossi and E. Hamel, *Biochem. Biophys. Res., Commun.*, *187*, 1350 (1992).
170. H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, *J. Am. Chem. Soc.*, **109**, 5031 (1987).
171. S. Sawada G. Suzuki, Y. Kawase and T. Takaku, *J. Immunol.*, **139**, 1797 (1987).
172. S. P. O'Connor, R. L. Ellsworth, M. N. Omstead, R. G. Jenkins and L. Kaplan, *J. Labelled Compd. Radiopharm.*, **31**, 103 (1992).
173. G. D. Crouse and N. H. Terando, *J. Labelled Compd. Radiopharm.*, **27**, 465 (1989).
174. E. E. Ose. *J. Antibiotics*, **40**, 190 (1987).
175. W. T. Stolle and R. S. P. Hsi, *Appl. Radiat. Isot.*, **39**, 552 (1988).
176. S. R. Prakash and R. L. Ellsworth. *Appl. Radiat. Isot.*, **39**, 606 (1988).
177. K. M. Damodaran, M. W. Epperly, K. M. R. Pillai and W. D. Bloomer, *J. Labelled Compd. Radiopharm.*, **34**, 17 (1994).
178. R. M. Hoyte, W. Rosner, I. S. Johnson, J. Zielinski and R. B. Hochberg. *J. Med. Chem.*, **28**, 1695 (1985).
179. Y. B. Fang, J. Mukherjee, Z. Y. Yang, and M. Cooper, *J. Nucl. Med.*, **33**, 982 (1992).
180. P. J. D. Cruz, H. E. Smith, B. J. Danzo, J. A. Clanton and N. S. Mason, *J. Labelled Compd. Radiopharm.*, **33**, 853 (1993).
181. R. N. Hanson and L. A. Franke, *J. Nucl. Med.*, **25**, 998 (1984).
182. B. J. Danzo, C. A. Taylor Jr and B. C. Eller, *Endocrinology*, **111**, 1270 (1982).
183. N. S. Mason, H. E. Smith, B. J. Danzo and J. A. Clanton, *J. Labelled Compd. Radiopharm.*, **31**, 729 (1992).
184. N. J. Turro, *Modern Molecular Photochemistry*, Benjamin Cummings, Menlo Park, CA, 1978.
185. F. F. Knapp, M. M. Goodman, G. W. Kabalka and K. A. R. Sastry, *J. Med. Chem.*, **27**, 94 (1984).
186. G. W. Kabalka, R. S. Varma, V. K. Jinaraj, L. Huang and S. K. Painter, *J. Labelled Compd. Radiopharm.*, **21**, 333 (1985).
187. G. W. Kabalka, S. J. Lambert and V. K. Jinaraj, *Appl. Radiat. Isot.*, **39**, 1113 (1988).
188. G. W. Kabalka, M. Varma, R. S. Varma, P. C. Srivastava and F. F. Knapp Jr., *J. Org. Chem.*, **51**, 2386 (1986).

189. R. C. Schnur and M. L. Corman, *J. Labelled Compd. Radiopharm.*, **34**, 329 (1994).
190. K. Sasaki, H. Yasuda and K. Onodera, *J. Antibiotics*, **32**, 849 (1993).
191. A. Patel, R. H. Craig, S. M. Daluge and J. Linden, *Molecular Pharmacology* **33**, 585 (1988).
192. G. S. Drammond, R. Galbraith, M. K. Sardana and A. Kappas, *Arch. Biochem. Biophys.*, **255**, 64 (1987).
193. R. A. Galbraith and A. Kappas, *Hepatology*, **9**, 882 (1989).
194. J. F. Denissen, *J. Labelled Compd. Radiopharm.*, **28**, 1421 (1990).
195. G. A. Ropp, V. F. Raaen and A. Weinberger, *J. Am. Chem. Soc.*, **75**, 3694 (1953).
196. L. Kupczyk-Subotkowska, and H. J. Shine, *J. Am. Chem. Soc.*, **115**, 5296 (1993).
197. J. E. Baldwin, R. M. Adlington, R. A. Russell, C. J. Schofield and M. E. Wood, *J. Labelled Compd. Radiopharm.*, **27**, 1091 (1989).
198. B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **95**, 6145 (1973).
199. R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).
200. R. A. Firestone, *J. Org. Chem.*, **37**, 2181 (1982).
201. K. N. Houk, Y. T. Lin and F. K. Brown, *J. Am. Chem. Soc.*, **108**, 554 (1986).
202. J. J. Gajewski, K. B. Peterson and J. R. Kagel, *J. Am. Chem. Soc.*, **109**, 5545 (1987).
203. J. J. Gajewski, in *Isotopes in Organic Chemistry* (Eds. E. E. Buncel and C. C. Lee) Vol. 7, Chap. 3, Elsevier, New York, 1987.
204. J. J. Gajewski, K. B. Peterson, J. R. Kagel and Y. C. Huang, *J. Am. Chem. Soc.*, **111**, 9087 (1989).
205. M. Taagepera and E. R. Thornton, *J. Am. Chem. Soc.*, **94**, 1168 (1972).
206. D. E. van Sickle and O. J. Rodin, *J. Am. Chem. Soc.*, **86**, 3091 (1964).
207. J. W. Storer, L. Raimondi and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 9675 (1994).
208. J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, **15**, 261 (1947).
209. M. Zieliński, in *The Chemistry of Quinonoid Compounds* (Ed.S. Patai) Chap. 12, Wiley, London, 1974, p. 619.
210. K. N. Houk, Y. Li, J. Storer, L. Raimondi and B. Beno, *J. Chem. Soc., Faraday Trans.*, **90**, 1599 (1994).
211. F. E. Ziegler, *Chem. Rev.*, **88**, 1423 (1988).
212. L. Kupczyk-Subotkowska, W. H. Saunders, Jr., H. J. Shine and W. Subotkowski, *J. Am. Chem. Soc.*, **115**, 5957 (1993).
213. W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).
214. L. Kupczyk-Subotkowska and H. Shine, *J. Labelled Compd. Radiopharm.*, **31**, 381 (1992).
215. M. Zieliński, A. Zielińska and H. Papiernik-Zielińska, *J. Radioanal. Nucl. Chem., Articles*, **183**, 301 (1994).
216. K. Claus and H. Bestian, *Justus Liebigs Ann. Chem.*, **654**, 8 (1962).
217. L. B. Sims, G. W. Burton and D. E. Lewis, BEBOVIB-IV, QCPE No. 337, Dept. of Chem., Indiana University. Bloomington, IN 47405.
218. M. Wolfsberg and M. Stern, *J. Pure Appl. Chem.*, **225**, 8 (1964); J. H. Keller and P. Yankwich, *J. Am. Chem. Soc.*, **96**, 2303 (1974).
219. L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley-Interscience, New York, 1980, pp. 64–66.
220. O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 10336 (1994).
221. R. V. Stanton and K. J. Merz, *J. Chem. Phys.*, **100**, 434 (1994).
222. R. E. Ireland, and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5897 (1972).
223. R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
224. L. Kupczyk-Subotkowska, W. H. Saunders, Jr., H. J. Shine and W. Subotkowski, *J. Am. Chem. Soc.*, **116**, 7088 (1994).
225. J. J. Gajewski and J. Emram, *J. Am. Chem. Soc.*, **106**, 5733 (1984).
226. J. J. Gajewski, L. P. Olson and K. J. Tupper, *J. Am. Chem. Soc.*, **115**, 4548 (1993).
227. L. Kupczyk-Subotkowska and H. J. Shine, *J. Labelled Compd. Radiopharm.*, **33**, 301 (1993).
228. P. Wipf, in *Comprehensive Organic Synthesis* (Eds. B. M. Trost and I. Fleming), Vol. 5, Chap. 72, Pergamon Press, Oxford, 1991.
229. J. J. Gajewski and N. L. Brichford, *J. Am. Chem. Soc.*, **116**, 3165 (1994).
230. J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **101**, 6693 (1979).
231. W. R. Dolbier, Jr., and S. H. Dai, *J. Am. Chem. Soc.*, **90**, 5028 (1968).
232. S. H. Dai and W. R. Dolbier, Jr., *J. Am. Chem. Soc.*, **94**, 3946 (1972).
233. E. A. Halevi and M. Wolfsberg, *J. Chem. Soc., Perkin Trans. 2*, 1493 (1993).

234. R. Brueckner and R. Huisgen, *Tetrahedron Lett.*, **35**, 3281 (1994).
235. M. Terakado, M. Miyazawa and K. Yamamoto, *Synlett.*, 134 (1994).
236. K. C. Wagschal, H. J. Pyun, R. M. Coates and R. Croteau, *Arch. Biochem. Biophys.*, 308, 477 (1994).
237. S. Borcic, O. Kronja and K. Humski, *Croat. Chem. Acta*, **67**, 171 (1994); *Chem. Abstr.*, **121**, 254950g (1994).
238. U. H. Do, S. L. Lo, J. Iles, T. Rosenberger, P. Tam, Y. Hong and D. Ahern, *Prostaglandins, Leukotrienes Essent., Fatty Acids*, **50**, 355 (1994).
239. N. B. Fazlitdinova, N. F. Noskova, M. M. Mansurov and S. R. Savel'ev, *Neftekhimiya*, **34**, 249 (1994); *Chem. Abstr.*, **121**, 178951r (1994).
240. T. Miyazaki, S. Kitamura, Y. Kozono and H. Matsunaga, *J. Phys. Chem.*, **98**, 10767 (1994).
241. K. Seemeyer, T. Pruesse and H. Schwarz, *Helv. Chim. Acta*, **76**, 113 (1993).