

## 175. The Synthesis of $\beta$ , $\gamma$ - and $\alpha$ , $\beta$ -Unsaturated Aldehydes via Polyene Epoxides

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Dedicated to Dr. O. Isler on the occasion of his 70th birthday

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### Summary

A substitute for the *Darzens* glycidic ester synthesis for converting unsaturated ketones or aldehydes into the homologated  $\beta$ ,  $\gamma$ - or  $\alpha$ ,  $\beta$ -unsaturated aldehydes employing sulfur ylides is described. The carbonyl group is converted into the unsaturated oxirane which is then rearranged to the new aldehyde. High yields of isomerically pure aldehydes are available by this method and the process is of practical importance in the conversion of  $\beta$ -ionone into the  $\beta$ -C<sub>14</sub>-aldehyde, a key intermediate in the *Isler* synthesis of vitamin A. The efficient preparation of  $\alpha$ - and  $\beta$ -cyclocitral by the novel process is also described.

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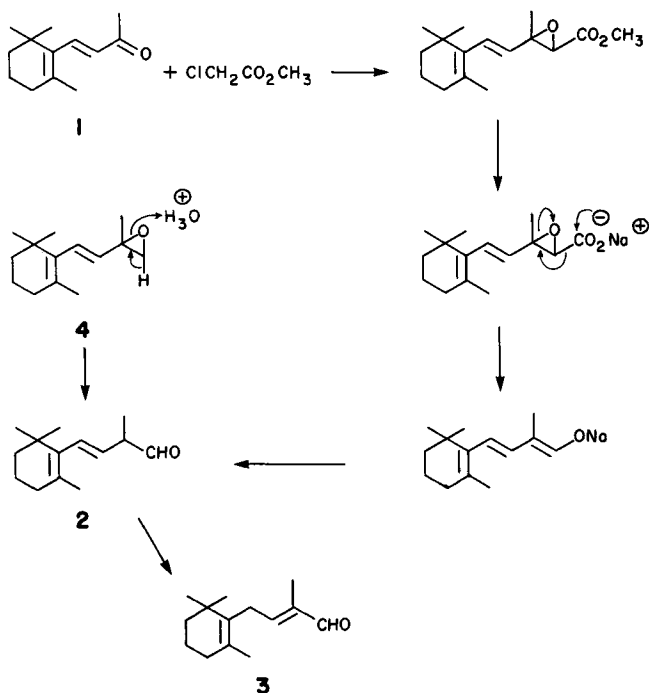
The development of a commercial synthesis of vitamin A by *Isler et al.* is one of the major industrial achievements of the fifties [1]. This complex process [2] is still the major source of this essential vitamin, and the overall synthetic scheme has changed very little in the past twenty-five years.

One key step of this process is the formal addition of one C-atom to  $\beta$ -ionone (1) (*Scheme 1*), using the *Darzens* glycidic ester [3] reaction and proceeding through the aldehyde 2 originally used by *Milas et al.* [4] in their vitamin-A work; the glycidic ester is hydrolyzed, decarboxylation then leads to the aldehyde enolate and kinetic protonation results in the aldehyde 2; further exposure to base then yields the thermodynamic product 3. While the overall yield for this transformation is good (84–86%), the economy of the process in today's market place leaves much to be desired. An excess of methyl chloroacetate and sodium methoxide has to be used to add the C-atom and it would be better to just add this C-atom without waste.

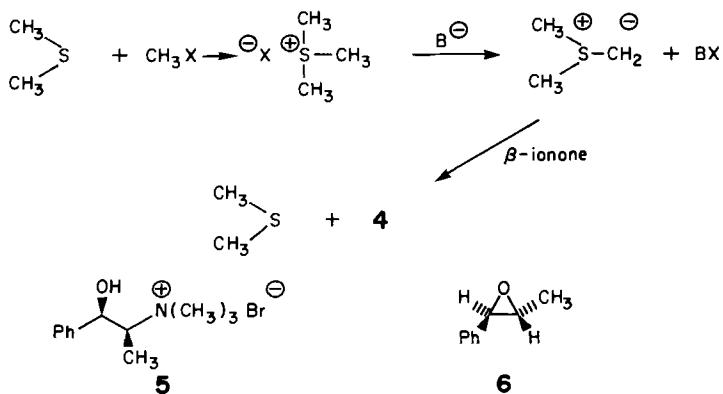
A similar process involving epoxide 4, can also be envisioned as a possible route to 2. Therefore, the epoxide 4 was prepared (94% yield) from  $\beta$ -ionone (1) by the action of (dimethylsulfonyl)methanide [5]. The conversion of this epoxide to the aldehyde 2 initially proved difficult but eventually yielded to the action of magnesium bromide [6].

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Scheme 1



Scheme 2. Dimethyl sulfide cycle



These conditions give *no* halohydrins with unsaturated epoxides of this type and yield  $\beta,\gamma$ -unsaturated aldehydes of high isomeric purity. The isomerization of the aldehyde **2** to **3** then follows the original route. The overall yield from **1** to **3** is 90%. The sequence fulfills our original requirements, one C-atom, supplied as the methyl halide, is consumed and the dimethyl sulfide is recycled and there is no waste of C-atoms (Scheme 2). As this sequence of reactions has had few applica-

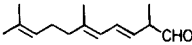
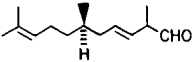
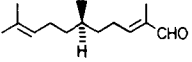
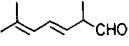
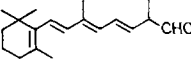
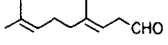


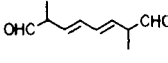
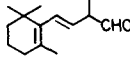
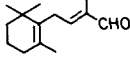
Table 1

Substrate		Epoxide		% Yield
	<b>1</b>		<b>4</b>	94
	<b>7</b>		<b>16</b>	83
	<b>8</b>		<b>17</b>	80
	<b>9</b>		<b>18</b>	85
	<b>10</b>		<b>19</b>	—
	<b>11</b>		<b>20</b>	79
	<b>12</b>		<b>21</b>	87
	<b>13</b>		<b>22</b>	40-60
	<b>14</b>		<b>23</b>	—
	<b>15</b>	<b>4</b>		—

tions [7], a series of substrates were taken through the synthetic steps (Tables 1 and 2). The yields of epoxides are high and rearrangement to the aldehydes, some of which are very sensitive materials, is also a high yield process. This route is efficient to either pure  $\alpha$ -cyclocitral (**29**) [8] or  $\beta$ -cyclocitral (**32**)<sup>2</sup>.

<sup>2</sup>) The past methods available for the synthesis of both  $\alpha$ - and  $\beta$ -cyclocitrals have been cumbersome and technically difficult to perform on a large scale.

Table 2

Epoxide	$\beta,\gamma$ -Aldehyde	% Yield	$\alpha,\beta$ -Aldehyde	% Yield
16	 <b>24</b>	> 90 <sup>a)</sup>	—	—
17	 <b>25</b>	—	 <b>31</b>	72 17 → 31
18	 <b>26</b>	> 90 <sup>a)</sup>	—	—
19	 <b>27</b>	> 90 <sup>a)</sup>	—	—
20	 <b>28</b>	> 90 <sup>a)</sup>	—	—
21	 <b>29</b>	80	 <b>32</b>	89 12 → 32
22	 <b>30</b>	—	—	—
4	 <b>2</b>	85	 <b>3</b>	90 1 → 3

<sup>a)</sup> Estimated by <sup>1</sup>H-NMR. spectrometry.

The above results showed that (dimethylsulfonyl)methanide is an excellent reagent for extending  $\alpha,\beta$ -unsaturated ketones or aldehydes by one C-atom to give either a new  $\beta,\gamma$ - or  $\alpha,\beta$ -unsaturated aldehyde. However, while the concept is attractive, the experimental conditions do not make the process economical for the conversion of **1** into **3**.

A series of important papers [9] showed that dilute aqueous NaOH-solution converted trimethylsulfonium chloride and benzaldehyde into styrene oxide. It was also observed that concentrated (18M) aqueous NaOH-solutions in the presence of a phase transfer catalyst [10] could generate epoxides from the less reactive acetophenones and trimethylsulfonium iodide [11]. Neither of these reaction conditions *alone* were sufficient to effect the transformation of **1** into **3**, however, a combination of the two processes proved successful. Thus, aqueous NaOH 18M and trimethylsulfonium chloride will readily convert **1** into **4** (> 90%). The addition

of a phase transfer reagent [10] to this system, triethylbenzylammonium chloride [11], approximately doubled the rate of reaction. The use of trimethylsulfonium bromide results in a sluggish reaction, the corresponding iodide salt is unreactive while the fluoride salt is exothermic. Clearly the hard counter ion of the sulfonium salt plays an important role in the success of this process.

From *Table 1*, one sees that  $\alpha$ -ionone (**14**) reacts to give the corresponding epoxide while the ionone isomer **15** [12] yields the same epoxide as  $\beta$ -ionone. This is not unexpected because when one interrupts the reaction of  $\beta$ -ionone (**1**) and (dimethylsulfonio)methanide, the reaction mixture contains appreciable amounts of the 'deconjugated' ionone **15** but *no*  $\alpha$ -ionone. Clearly  $\beta$ -ionone is continuously enolizing and reprotonating during this process and fails to protonate at C(6) to give  $\alpha$ -ionone.

Recently [13] the use of trimethylsulfonium methyl sulfate and sodium ethoxide was described as a means for generating epoxides from unreactive acetophenones. While these conditions give excellent yields for the reported cases, they failed to give *any* epoxide **4** with  $\beta$ -ionone. However, dodecyldimethylsulfonium methyl sulfate and aqueous NaOH 18M gave high yields of the epoxide **4**, *albeit* slowly. The corresponding chloride proved to be an excellent methylene-transfer reagent [14]. In this case, a phase transfer catalyst is not required as the reagent acts as a *phase transfer reagent* and the reactions are rapid.

Interestingly, exposure of the dodecyldimethylsulfonium chloride to silver oxide in water yields a solution of the sulfonium hydroxide which is reasonably stable and can be used to generate epoxides from carbonyl compounds.

The use of a phase-transfer catalyst in these processes employing trimethylsulfonium chloride does not show as dramatic an effect as is seen in alkylations [10] and indicates that the catalyst is not strongly associated with the ylide as has been suggested [15]. It was claimed, for example, that employing a chiral phase-transfer catalyst, one can prepare nearly optically pure styrene oxide from benzaldehyde, trimethylsulfonium iodide and aqueous base, and that the optical yield improves with catalyst concentration. We found this work incorrect<sup>3)</sup> and observed that the 'optical purity' of the styrene oxide improved when going from trimethylsulfonium chloride to the iodide for generation of the ylide. This is not surprising as the optical activity is derived from the epoxide **6** formed from the catalyst **5**<sup>4)</sup> and as the reaction employing trimethylsulfonium iodide is so much slower than in the case of the chloride there is a greater opportunity for the catalyst to decompose into **6**. Compound **6** has a high specific rotation which is *not* highly solvent dependent and small amounts of this material in the styrene oxide readily explain the claimed 'chiral synthesis' [15].

In summary, there are many conditions which can be employed to convert unsaturated ketones to epoxides. For molecules containing other base-sensitive groups, the original conditions developed by *Corey et al.* [5], being essentially neutral and very fast, are preferred but if the substrates and products are base stable, then the other methods are more convenient, especially on a large scale.

<sup>3)</sup> The authors were informed of our results in 1975, but have failed to issue a correction.

<sup>4)</sup> The use of amino acids as routes to chiral epoxides through the agency of a hydroxy-substituted quaternary ammonium salt of type **5** has been used previously [16].

## Experimental Part

*General remarks.* Melting points (m.p.) were determined with a *Thomas-Hoover* capillary apparatus and are uncorrected. All reactions were carried out under  $N_2$ , and the organic extracts were concentrated in a *Büchi* Rotavapor (RV.) at water aspirator pressure (i.v.) and 40–50°, then at 0.5 Torr and 45°. Column chromatography was performed using *Merck* (Darmstadt) silica gel (0.2–0.5 mm), and thin-layer chromatograms (TLC.) were run on *Brinkmann* silica gel G plates with a UV.-indicator. Spots were made visible by UV.-light,  $I_2$  vapor, or spraying with 50% aqueous solution of *p*-toluene-sulfonic acid and heating at 120°. UV.-visible spectra ( $\lambda_{max}$  nm ( $\epsilon$ )) were measured in EtOH using a *Cary* Model 14 M spectrophotometer. IR.-spectra ( $cm^{-1}$ ) were recorded on a *Beckman* IR-9 spectrometer. *Varian* HA-100 and A-60 spectrometers were employed to record  $^1H$ -NMR. spectra in  $CCl_4$  unless otherwise stated. Chemical shifts ( $\delta$ ) are given in ppm downfield from tetramethylsilane as an internal standard and coupling constants *J* in Hz.

(RS)-(E)-2-Methyl-4-(2',6',6'-trimethyl-1'-cyclohexenyl)-1,2-epoxy-3-butene (**4**). Dry trimethylsulfonium iodide (61.2 g) was added to dry dimethyl sulfoxide (DMSO, 120 ml), stirred for 30 min and then treated with dry tetrahydrofuran (THF, 100 ml) to yield a finely divided suspension of the sulfonium salt. This mixture was then cooled to 0° and treated rapidly (2–3 min) with a solution of dimethyl sodium (from NaH, 12.6 g, 57% oil dispersion, and DMSO 70 ml). The resulting grey colored suspension was stirred for a further 4 min at 0° and then treated with a solution of  $\beta$ -ionone (**1**, 38.4 g) in THF (50 ml) over ~3 min. After stirring for a further 1 h at 0°, the mixture was warmed to RT., treated with water and extracted with hexane. The combined extracts were washed with water, dried ( $Na_2SO_4$ ) and concentrated to dryness to yield the epoxide **4** (39.8 g). Distillation yielded the pure material (37.4 g); b.p. 75–80°/0.2 Torr. - UV.: 240 (6220). -  $^1H$ -NMR. ( $CDCl_3$ ): 6.08 (*d*, *J* = 16, 1H, H-C(4)); 5.16 (*d*, *J* = 16, 1H, H-C(3)); centered at 2.55 (2 *d*, *J* = 6, 2H, H-C(1)); 1.6 (*s*, 3 H,  $H_3C-C(2)$ ); 1.4 (*s*, 3 H,  $H_3C-C(2)$ ); 0.96 (*s*, 6 H,  $H_3C-C(6')$ ).

$C_{14}H_{22}O$  (206.3) Calc. C 81.50 H 10.75% Found C 81.11 H 10.51%

(RS)-(E,EZ)-2,6,10-trimethyl-1,2-epoxy-3,5,9-undecatriene (**16**). Employing the same conditions as above but using  $\psi$ -ionone (**7**) yielded the crude epoxide (40.7 g). Distillation gave pure material (33.2 g; (Z)-(E) about the 5,6-double bond); b.p. 85–90°/0.5 Torr (this material was unstable and slow distillation led to extensive polymer formation). - UV.: 240 (20,800). - IR. (film): 1660–1680 (olefin); 960 (terminal oxirane). -  $^1H$ -NMR. ( $CDCl_3$ ): 6.5 (2 *d*, *J* = 16 and 11, 1H, H-C(4)); 5.8 (br. *d*, *J* = 11, 1H, H-C(5)); 5.25 (*d*, *J* = 16, 1H, H-C(3)); centered at 2.6 (2 *d*, *J* = 6, 2H, H-C(1)); 1.6–1.8 (3 *s*, 9 H,  $CH_3$ -vinyl); 1.4 (*s*, 3 H,  $H_3C-C(2)$ ).

$C_{14}H_{22}O$  (206.3) Calc. C 81.50 H 10.75% Found C 80.91 H 10.54%

(2R,6R)-(E)-2,6,10-Trimethyl-1,2-epoxy-3,9-undecadiene (**17**). When (6R)-(E)-6,10-dimethyl-3,9-undecadien-2-one (**8**, 19.4 g, ~85% ee) was employed as above, the epoxide **17** (15.7 g), b.p. 92–97°/0.1 Torr was isolated,  $[a]_D^{25} = -2.8^\circ$  ( $c = 1.7132$ , hexane). -  $^1H$ -NMR. ( $CDCl_3$ ): 5.7 (*d*  $\times$  *t*, *J* = 16 and 6, 1H, H-C(4)); 5.2 (*d*, *J* = 16, 1H, H-C(3)); 5.0 (br. *t*, *J* = 7, 1H, H-C(9)); centered at 2.6 (2 *d*, *J* = 5, 2H, H-C(1)); 1.6 (2 *s*, 6 H,  $H_3C-C(10)$ ); 1.35 (*s*, 3 H,  $H_3C-C(2)$ ); 0.9 (*d*, *J* = 6, 3 H,  $H_3C-C(6)$ ).

$C_{14}H_{24}O$  (208.3) Calc. C 80.71 H 11.61% Found C 80.25 H 11.81%

(RS)-(E)-2,6-Dimethyl-1,2-epoxy-3,5-heptadiene (**18**). (E)-6-Methyl-3,5-heptadien-2-one **9** [17] gave the pure epoxide, b.p. 33–35°/0.3 Torr (85% yield). This material was unstable and failed to give satisfactory combustion analyses. -  $^1H$ -NMR. ( $CCl_4$ ): 6.4 (2 *d*, *J* = 15 and 10, 1H, H-C(4)); 5.73 (*d*, *J* = 10, 1H, H-C(5)); 5.23 (*d*, *J* = 15, 1H, H-C(3)); centered at 2.6 (2 *d*, *J* = 5, 2H, H-C(1)); 1.77 (*s*, 6 H,  $H_3C-C(6)$ ); 1.4 (*s*, 3 H,  $H_3C-C(2)$ ).

(RS)-(E,EZ,E)-2,6-Dimethyl-8-(2',6',6'-trimethyl-1'-cyclohexenyl)-1,2-epoxy-3,5,7-octatriene (**19**). The ketone **10** [2] (2.5 g, 2:1 E/Z mixture about the C(3),C(4)-double bond) on exposure to (dimethylsulfonio)methanide, yielded the epoxide **19** (2.7 g). This material was unstable to chromatography on silica gel or alumina (neutral) and decomposed on distillation. -  $^1H$ -NMR.: 6.6 (2 *d*, *J* = 16 and 11, 1H, H-C(4)); 6.4 (br. *d*, *J* = 11, 1H, H-C(5)); 6.0 (*m*, 2H, H-C(7) and H-C(8)); 5.4 (2 *d*, *J* = 16, 1H, H-C(3), 2:1 E/Z at C(5),C(6)); centered at 2.4 (2 *d*, *J* = 5, 2H, H-C(1)); 1.9 (*s*, 3 H,  $H_3C-C(2)$ ); 1.65 (2 *s*, ~2:1, 3 H,  $H_3C-C(6)$ ); 1.4 (*s*, 3 H,  $H_3C-C(2)$ ); 1.0 (*s*, 6 H, 2  $H_3C-C(6')$ ).

(RS)-(EZ)-4,8-Dimethyl-1,2-epoxy-3,7-nonadiene (**20**). A mixture of neral and geranial **11** (34.4 g) yielded the crude epoxide (35.8 g). Distillation of a portion (34.7 g) gave the epoxide **20** (28.9 g): b.p. 60–65°/0.5 Torr. - <sup>1</sup>H-NMR.: 5.05 (*m*, 1H, H-C(7)); 4.75 (*d*, *J*=8, 1H, H-C(3)); 3.4 (3 *d*, *J*=8, 4 (*cis*) and 2 (*trans*), 1H, H-C(2)); 2.75 (*m*, *J*=4, 1H, H-C(1) *cis*); 2.4 (*m*, *J*=2, 1H, H-C(1) *trans*); 1.8 (2 *d*, *J*=1-2, 3H, H<sub>3</sub>C-C(4), *E/Z* ~2:1); 1.6 (2 *s*, 6H, H<sub>3</sub>C-C(8)).

C<sub>11</sub>H<sub>18</sub>O (166.3) Calc. C 79.46 H 10.92% Found C 79.31 H 10.71%

(RS)-4,8,8-Trimethyl-1-oxaspiro[2,5]oct-4-ene (**21**). 2,6,6-Trimethyl-2-cyclohexenone (**12**, 38.4 g) yielded the pure oxirane **21** (37 g), b.p. 67–68°/8 Torr. - <sup>1</sup>H-NMR. (CDCl<sub>3</sub>): 5.76 (*m*, 1H, H-C(5)); centered at 2.85 (2 *d*, *J*=4.5, 2H, H-C(2)); 2.1 (*m*, 2H, H-C(6)); 1.55 (*m*, 2H, H-C(7)); 1.52 (br. *s*, 3H, H<sub>3</sub>C-C(4)); 0.9 (2 *s*, 6H, 2 H<sub>3</sub>C-C(8)).

C<sub>10</sub>H<sub>16</sub>O (152.2) Calc. C 78.90 H 10.59% Found C 78.97 H 10.63%

(RS)-(E,E)-2,7-Dimethyl-1,2-7,8-bisepoxy-3,5-octadiene (**22**). The diketone **13** [2] and the corresponding epoxide **22** were very labile compounds and the yield of 40–60% is mainly a reflection of the instability of **13** towards base. The epoxide (crude) showed only minor impurities in the <sup>1</sup>H-NMR. spectrum and showed the expected peaks for the bis-epoxide. - <sup>1</sup>H-NMR. (Alox III treated CDCl<sub>3</sub>): 5.85 (symm. *m*, 4H, H-vinyl); centered at 2.75 (2 *d*, *J*=5, 4H, 2 H-C(1) and 2 H-C(8)); 1.63 (*s*, 6H, H<sub>3</sub>C-C(2) and H<sub>3</sub>C-C(7)).

(RS)-(E)-2-Methyl-4-(2',6',6'-trimethyl-1'-cyclohexenyl)-3-butenal (**2**). Magnesium (150 mg) was treated with a solution of 1,2-dibromoethane (0.54 ml) in ether (10 ml) at RT. to yield a mixture of MgBr<sub>2</sub> and ether (two-phase system). To this mixture, cooled to -10°, was added a solution of the epoxide **4** (5 g) dissolved in ether (10 ml). The resulting clear solution, after a further 5 min at -10°, was washed with water, dried (NaSO<sub>4</sub>), filtered and distilled to yield the pure aldehyde **2** (3.9 g), b.p. 77–80°/0.2 Torr. - <sup>1</sup>H-NMR.: 9.5 (*d*, *J*=1, 1H, H-C(1)); 6.0 (*d*, *J*=16, 1H, H-C(4)); 5.23 (2 *d*, *J*=16 and 8, 1H, H-C(3)); 3.07 (*d* × *qa*, *J*=8 and 7, 1H, H-C(2)); 1.63 (br. *s*, 3H, H<sub>3</sub>C-C(2')); 1.2 (*d*, *J*=7, 3H, H<sub>3</sub>C-C(2)); 1.0 (*s*, 6H, 2 H<sub>3</sub>C-C(6')).

(E)-2-Methyl-4-(2',6',6'-trimethyl-1'-cyclohexenyl)-2-butenal (**3**). The aldehyde **2** (6.18 g) was dissolved in methanol (15 ml) and treated with a solution of KOH (250 mg) in water/methanol (0.3 ml and 5 ml) and left at RT. for 35 min. Work-up with hexane and water followed by distillation gave the pure aldehyde **3** (4.75 g), b.p. 85–88°/0.5 Torr. - <sup>1</sup>H-NMR.: 9.23 (*s*, 1H, H-C(1)); 6.27 (*t*, *J*=6, 1H, H-C(3)); 3.0 (*d*, *J*=6, 2H, 2 H-C(4)); 1.75 and 1.53 (2 *s*, 6H, H<sub>3</sub>C-vinyl); 1.02 (*s*, 6H, 2 H<sub>3</sub>C-C(6')).

The aldehyde **3** can be prepared in a 'through' process as follows: β-Ionone **1** (19.2 g) was converted to the crude epoxide (20.6 g) as before. This material was dissolved in ether (40 ml) and added to MgBr<sub>2</sub> (from Mg, 600 mg) as before. After the isomerization, the ether solution was washed with water and treated with a solution of NaOH (2 g) dissolved in aqueous methanol (100 ml, 1:1). After stirring rapidly for 15 min at RT., the ether layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Distillation of the residue (20.8 g) gave the aldehyde **3** (18.9 g, 91% yield), b.p. 95–98°/0.2 Torr.

Dodecyldimethylsulfonium chloride. The described procedure [14] was followed and the total reaction mixture was taken to dryness to yield a syrup containing ~70% sulfonium salt (S and Cl analysis). This material was dissolved in acetone (181 g in 500 ml), stirred with anhydrous K<sub>2</sub>CO<sub>3</sub> (1/2 mol-equiv.) for 30 min, filtered and concentrated to yield the crude salt as a syrup (139 g) (84% sulfonium salt by S and Cl analysis). The salt can be crystallized from acetone but this does not improve his quality very much (85–89% purity).

Dodecyldimethylsulfonium methyl sulfate. Dodecylmethylsulfide (21.6 g) was added to dimethyl sulfate (12.6 g) and heated at 100° for 2 h. On cooling, the mixture solidified, m.p. 75–82°. Crystallization from acetone yielded the pure salt (32.5 g), m.p. 75–82°.

C<sub>15</sub>H<sub>34</sub>O<sub>4</sub>S<sub>2</sub> (342.6) Calc. C 52.59 H 10.00 S 18.72% Found C 52.37 H 10.10 S 18.57%

Preparation of **3** employing dodecyldimethylsulfonium salts. The mixture of crude dodecyldimethylsulfonium chloride (66 g, 89% purity), toluene (200 ml), aqueous NaOH (100 ml, 17M) and β-ionone (**1**, 38.4 g) was stirred rapidly for 2.5 h at RT. The solids were then filtered off, washed with more toluene and the combined extracts were added to MgBr<sub>2</sub> (from 1.6 g Mg) in ether (50 ml) at -70°. The mixture was then stirred for a further 10 min at -10° and quenched with aqueous NH<sub>4</sub>Cl-solution (10%, 20 ml). The aqueous phase was removed and replaced with aqueous methanolic (1:2) NaOH-

solution (90 ml, 4 g) and the two-phase system was stirred for 1 h at RT. The organic phase was then washed with water and concentrated to yield a mixture of virtually pure aldehyde and dodecylmethyl sulfide (91 g). Counter current separation employing a hexane/acetonitrile system and a  $10' \times 1''$  Karr column [18] yielded pure dodecyl methyl sulfide (44.2 g) in the hexane extract and pure 3 (35.4 g after distillation) in the acetonitrile fraction.

When dodecyldimethylsulfonium methyl sulfate (56.4 g) and  $\beta$ -ionone (**1**, 28.8 g) reacted with aqueous NaOH 17M (72 ml) in toluene (144 ml) at RT. for  $2\frac{1}{2}$  days and then worked up as above, the pure aldehyde **3** (27.7 g) was obtained.

(RS)-(E)-2-Methyl-4-(2',6',6'-trimethyl-2'-cyclohexenyl)-1,2-epoxy-3-butene (**23**). When  $\alpha$ -ionone (**14**) was subjected to dodecyldimethylsulfonium chloride and aqueous base, the epoxide **23** was formed after 2 h (highly colored reaction mixture). -  $^1\text{H-NMR.}$ : 5.45 (2d,  $J=16$  and 8, 1 H, H-C(4)); 5.4 (m, 1 H, H-C(3')); 5.2 (d,  $J=16$ , 1 H, H-C(3)); centered at 2.6 (2d,  $J=5$ , 2 H, 2 H-C(1)); 2.4 (m, 2 H, 2 H-C(4')); 2.0 (s, 9 H,  $\text{H}_3\text{C-C}(2')$  and 2  $\text{H}_3\text{C-C}(6')$ ); 1.3 (s, 3 H,  $\text{H}_3\text{C-C}(2)$ ).

Preparation of ionone **15**. A solution of  $\beta$ -ionone (**1**, 38.4 g) in dimethyl sulfoxide (150 ml) cooled to  $-10^\circ$  was treated with powdered sodium methoxide (12 g). The temperature rose to  $12^\circ$  and after stirring for a further 1 h at RT., the mixture was poured onto ice and extracted with hexane. Removal of the solvents, after drying ( $\text{Na}_2\text{SO}_4$ ), and distillation gave pure **15** (26.6 g), b.p.  $75-81^\circ/0.3$  Torr. -  $^1\text{H-NMR.}$ : 5.6 (m, 2 H, 2 H-vinyl); 3.4 (2d,  $J=7$ , 2 H, 2 H-C(3),  $\sim 3:1$  isomers about the exocyclic double bond); 2.1 (s, 3 H, 3 H-C(1)); 1.8 (br. s, 3 H,  $\text{H}_3\text{C-vinyl}$ ); 1.15 and 1.05 (2 s, 6 H, 2  $\text{H}_3\text{C-C}(6')$ ,  $\sim 3:1$ ).

Trimethylsulfonium chloride [9] [19]. Dimethyl sulfide (146 ml), methyl chloride (150 ml) and methanol (100 ml) were heated for 20 h at  $85^\circ$ . The solids were washed with ether and dried to give the pure salt (207 g).

Preparation of **4** and **3** employing trimethylsulfonium chloride. A mixture of trimethylsulfonium chloride (24 g),  $\beta$ -ionone (**1**, 38.4 g),  $\text{CH}_2\text{Cl}_2$  (100 ml), and benzyltriethylammonium chloride (1 g) was treated with aqueous NaOH 18M (125 ml), stirred rapidly at RT. for 9.5 h and then filtered. Removal of the solvents yielded the crude epoxide **4** (41.5 g) which was virtually identical ( $^1\text{H-NMR.}$ ) with distilled material. Conversion of this crude epoxide as before yielded pure aldehyde **3** (36.6 g, 100% pure).

When the above conditions were applied to 2,6,6-trimethyl-2-cyclohexenone (**12**), 84% of epoxide **21** resulted after 10 days.

(RS)-(E,EZ)-2,6,10-Trimethyl-3,5,9-undecatrienal (**24**). The epoxide **16** (1 g) in ether (2 ml) was added to  $\text{MgBr}_2$  (from Mg, 30 mg) in ether (5 ml) at  $-20^\circ$ . After 60 s, aqueous  $\text{NH}_4\text{Cl}$ -solution (10%, 5 ml) and more ether were added and the ether extract was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to yield the aldehyde **24** (1 g) as a colourless liquid. -  $^1\text{H-NMR.}$ : 9.4 (d,  $J \sim 2$ , 1 H, H-C(1)); 6.3 (2d,  $J=16$  and 10, 1 H, H-C(4)); 5.75 (br. d,  $J=10$ , 1 H, H-C(5)); 5.4 (2d,  $J=16$  and 8, 1 H, H-C(3)); 5.0 (m, 1 H, H-C(9)); 3.2 (br. d  $\times$  qa,  $J=7$ , 1 H, H-C(2)); 2.1 (m, 4 H, 2 H-C(7) and 2 H-C(8)); 1.7 (3 s, 9 H, 3  $\text{H}_3\text{C-vinyl}$ ); 1.2 (d,  $J=7$ , 3 H,  $\text{H}_3\text{C-C}(2)$ ).

This unstable material gave mixtures of products on exposure to  $\text{MgBr}_2$  at RT., aqueous base or distillation. This material was characterized further by conversion into (RS)-2,6,10-trimethylundecanol as follows: The crude epoxide (5 g) was rearranged as before to the crude aldehyde and the ether extract was added directly to a mixture of sodium borohydride (3 g) in ethanol (20 ml), water (10 ml) and stirred for 30 min at RT. More water was then added and the ether extract was concentrated. The residue was dissolved in ethanol (30 ml) containing Pd/C (10%, 0.5 g) and hydrogenated at RT. and atmospheric pressure. After the hydrogen uptake had stopped, the solids were filtered off, the solvents were removed and the residue was distilled to yield the pure alcohol (3.2 g), b.p.  $87-90^\circ/0.2$  Torr. This material was identical to an authentic sample (GC., UV. and  $^1\text{H-NMR.}$ ).

(2RS,6R)-(E)-2,6,10-Trimethyl-3,9-undecadienal (**25**) and (2RS,6R)-(E)-2,6,10-trimethyl-2,9-undecadienal (**31**). The crude epoxide **17** (110 g) was dissolved in ether (200 ml) and added to  $\text{MgBr}_2$  (from Mg, 2 g) in ether (100 ml) at  $-20^\circ$ . After stirring for a further 5 min at this temperature, the aldehyde **25** was isolated as before (98 g crude). -  $^1\text{H-NMR.}$ : 9.4 (d,  $J=2$ , 1 H, H-C(1)); 5.4 (m, 2 H, H-C(3) and H-C(4)); 5.0 (br. t,  $J \sim 6$ , 1 H, H-C(9)); 3.0 (m, 1 H, H-C(2)); 1.7 (2 s, 6 H, 2  $\text{H}_3\text{C-vinyl}$ ); 1.1 (d,  $J \sim 6$ , 3 H,  $\text{H}_3\text{C-C}(6)$ ); 0.8 (d,  $J=6$ , 3 H,  $\text{H}_3\text{C-C}(2)$ ).

Exposure of this material to aqueous base as before yielded the conjugated aldehyde **31** (33.1 g), b.p.  $84-88^\circ/0.5$  Torr. -  $^1\text{H-NMR.}$ : 9.25 (s, 1 H, H-C(1)); 6.3 (t  $\times$  qa,  $J=8$  and 1, 1 H, H-C(3)); 5.0 (t with multiple fine structure,  $J=6$ , 1 H, H-C(9)); 0.9 (d,  $J=6$ , 3 H,  $\text{H}_3\text{C-C}(6)$ ).



Both the aldehydes **25** and **31** were unstable to distillation. On a smaller scale run, ketone **8** (12.8 g) yielded the aldehyde **31** (9.9 g), b.p. 84–86°/0.5 Torr;  $[\alpha]_D^{25} = -1.58^\circ$  ( $c = 2.214$ , hexane). - UV.: 230 (13,600). - IR. (film): 1700 and 1655 (conjugated aldehyde). -  $^1\text{H-NMR}$ . as above.

$\text{C}_{14}\text{H}_{24}\text{O}$  (208.3) Calc. C 80.71 H 11.61% Found C 80.10 H 11.65%

(RS)-(E)-2,6-Dimethyl-3,5-heptadienal (**26**). Magnesium (60 mg) was converted to the bromide as before (in ether 4 ml) and then treated with the epoxide **18** (1.38 g) in ether (4 ml) at  $-20^\circ$ . The temperature rose to  $-6^\circ$  and after 3 min more at this temperature, the mixture was quenched as before to yield the highly labile aldehyde **26** (1.27 g). -  $^1\text{H-NMR}$ .: 9.4 (*d*,  $J = 2$ , 1H, H-C(1)); 6.28 (2 *d*,  $J = 15$  and 10, 1H, H-C(4)); 5.7 (br. *d*,  $J = 10$ , 1H, H-C(5)); 5.33 (2 *d*,  $J = 15$  and 8, 1H, H-C(3)); 1.73 (*s*, 6 H, 2  $\text{H}_3\text{C-vinyl}$ ); 1.13 (*d*,  $J = 7$ , 3 H,  $\text{H}_3\text{C-C}(2)$ ).

(RS)-(E,EZ,E)-2,6-Dimethyl-8-(2',6',6'-trimethyl-1'-cyclohexenyl)-3,5,7-octatrienal (**27**). The crude epoxide **19** (2.6 g) was exposed to  $\text{MgBr}_2$  (from Mg, 60 mg) in ether (20 ml) at  $-20^\circ$  for 10 min and then worked up as before to yield the aldehyde as a pale yellow oil. -  $^1\text{H-NMR}$ .: 9.43 (*d*,  $J = 2$ , 1H, H-C(1)); 6.0 (*m*, 5 H, H-olefins); 3.07 (*d*  $\times$  *qa*,  $J = 6$  and 7, 1H, H-C(2)); 1.92 and 1.67 (2 *s*, 6 H,  $\text{H}_3\text{C-vinyl}$ ); 1.23 (*d*,  $J = 7$ , 3 H,  $\text{H}_3\text{C-C}(2)$ ); 1.0 (*s*, 6 H, 2  $\text{H}_3\text{C-C}(6')$ ).

(EZ)-4,8-Dimethyl-3,7-nonadienal (**28**). Exposure of the epoxide **20** to  $\text{MgBr}_2$  in ether at  $-20^\circ$  as before resulted in furan products and *no* aldehydes. At  $-70^\circ$  for 5 min and careful work-up ( $-70^\circ$  quench) yielded the labile aldehyde **28**. -  $^1\text{H-NMR}$ .: 9.55 (*t*,  $J = 2$ , 1H, H-C(1)); 5.03 (*m*, 2 H, H-C(3) and H-C(7)); 3.02 (*d*,  $J = 7$ , 2 H, 2 H-C(2)); 1.63 (2 *s*, 9 H, 3  $\text{H}_3\text{C-vinyl}$ ). The more stable dimethyl acetal was readily prepared with methanolic hydrogen chloride. Purification by preparative TLC. yielded the acetal. -  $^1\text{H-NMR}$ .: 5.07 (br. *t*,  $J = 6$ , 2 H, H-C(3) and H-C(7)); 4.23 (*t*,  $J = 6$ , 1H, H-C(1)); 3.3 (*s*, 6 H, 2  $\text{H}_3\text{CO}$ ); 2.23 (*t*,  $J = 6$ , 2 H, 2 H-C(2)); 2.07 (*m*, 4 H, 2 H-C(5) and 2 H-C(6)); 1.63 (*m*, 9 H, 3  $\text{H}_3\text{C-vinyl}$ ).

$\alpha$ - and  $\beta$ -Cyclocitral (**29** and **32**). A solution of the epoxide **21** (5 g) in ether (20 ml) was added to  $\text{MgBr}_2$  (from Mg, 0.25 g) in ether (25 ml) and the mixture was stirred for 45 min at RT. Work-up with aqueous  $\text{NH}_4\text{Cl}$ -solution and more ether as before yielded pure  $\alpha$ -cyclocitral (**29**, 4 g) after distillation, b.p. 70–72°/8 Torr. -  $^1\text{H-NMR}$ .: 9.4 (*d*,  $J = 5$ , 1H, CHO); 5.67 (*m*, 1H, H-C(3)); 1.6 (*s*, 3 H,  $\text{H}_3\text{C-C}(2)$ ); 1.33 (2 *s*, 6 H, 2  $\text{H}_3\text{C-C}(6)$ ). No  $\beta$ -cyclocitral (**32**) was detected in the  $^1\text{H-NMR}$ . spectrum.

When the ethereal extract, from another experiment as above, was exposed to methanolic KOH-solution (30%, 3 ml) for 40 min at RT. and then worked up as usual, pure  $\beta$ -cyclocitral (4 g), b.p. 81–88°/8 Torr, identical with an authentic sample was obtained.

In a through process as practiced in the preparation of **3**, 2,6,6-trimethyl-2-cyclohexenone (**12**, 38.4 g) yielded pure  $\beta$ -cyclocitral (37.7 g), b.p. 83–89°/8–9 Torr.

(RS)-(E,E)-2,7-Dimethyl-3,5-octadien-1,8-dial (**30**). Exposure of the epoxide **22** to  $\text{MgBr}_2$  in ether at  $0^\circ$  for 1 h resulted in the formation of the dialdehyde **30** contaminated by some conjugated aldehyde. -  $^1\text{H-NMR}$ .: 9.67 (*d*,  $J = 2$ , 2 H, H-C(1) and H-C(8)); 6.0 (*m*, 4 H, 4 H-vinyl); 3.07 (*d*  $\times$  *qa*,  $J \sim 6$ , H-C(2) and H-C(7)); 1.23 (*d*,  $J = 6$ , 6 H,  $\text{H}_3\text{C-C}(2)$  and  $\text{H}_3\text{C-C}(7)$ ).

Trimethylsulfonium fluoride. A solution of trimethylsulfonium chloride (8.8 g) in water (25 ml) was treated with an aqueous solution of silver fluoride (10 g, 50 ml). The solids were filtered off and the aqueous solution was concentrated. The solution of the residual syrup in methanol was then filtered and concentrated again to yield an aqueous solution of the salt (8 g, 70% salt content by  $^1\text{H-NMR}$ ).

When  $\beta$ -ionone (1, 3.9 g), benzyltriethylammonium chloride (0.1 g), and the fluoride salt (2.7 g) in toluene were exposed to solid NaOH at RT., a rapid exothermic reaction followed to yield the epoxide **4** in 70–77% yield after  $\sim 0.5$  h. No further conversion was observed after this time, possibly because of the destruction of the sulfonium salt.

Styrene oxide. Benzaldehyde (10.6 g) and trimethylsulfonium bromide (17 g) in  $\text{CH}_2\text{Cl}_2$  (100 ml) were treated with the catalyst **5** (1 g, prepared from  $\psi$ -ephedrin) and aqueous NaOH 18M (50 ml) and stirred rapidly for 7 h at  $50^\circ$ . The organic layer was washed with brine, concentrated and distilled to yield the styrene oxide (8.9 g), b.p. 81–82°/12 Torr;  $[\alpha]_D^{25} = +3.7^\circ$  (neat),  $+3.98^\circ$  ( $c = 9.27$ , benzene) ([20];  $[\alpha]_D^{20} = +32.9^\circ$  (neat),  $[\alpha]_D^{25} = +44.5^\circ$  ( $c = 1.05$ , benzene),  $[\alpha]_D^{25} = -24.6^\circ$  ( $c = 1.34$ ,  $\text{CHCl}_3$ )). -  $^1\text{H-NMR}$ .: 7.1 (*s*, 5 H, arom. H); 3.6 (*d*  $\times$  *d*,  $J = 4$  and 2, 1H, H-C( $\alpha$ )); 2.9 (*d*  $\times$  *d*,  $J = 6$  and 4, 1H, H-C( $\beta$ ) *cis*); 2.3 (*d*  $\times$  *d*,  $J = 6$  and 2, 1H, H-C( $\beta$ ) *trans*). A doublet at  $\sim 1.3$  ( $J = 6$ ) is due to the impurity **6**.

A GC/MS. analysis of such a mixture yielded only 2 components, each of which gave a parent mass ion at  $m/z$  120 and 134 (styrene oxide and **6** respectively).

Employing trimethylsulfonium iodide in the above sequence, a 20% yield of epoxide resulted containing 3% of **6**.  $[\alpha]_D^{25} = +4.3^\circ$  (neat).  $[\alpha]_D^{25} = +3.0^\circ$  ( $c=1.0$ , acetone),  $+2.72^\circ$  ( $c=5.44$ , acetone),  $+2.8^\circ$  ( $c=9.91$ , acetone).

(2R,3R)-3-Methyl-2-phenyloxirane (**6**). The salt **5** (10 g) was heated at reflux for 18 h in a mixture of  $\text{CH}_2\text{Cl}_2$  (50 ml) and aqueous NaOH 18M (40 ml). Separation of the organic phase and distillation gave the epoxide **6** (75% yield); b.p. 85–87°/10 Torr.  $[\alpha]_D^{25} = +125^\circ$  (neat),  $+131^\circ$  ( $c=20$ , benzene),  $+71.8^\circ$  ( $c=1.546$ , acetone),  $+74.6^\circ$  ( $c=5.913$ , acetone),  $+75.4^\circ$  ( $c=8.367$ , acetone). -  $^1\text{H-NMR}$ .: 7.2 (s, 5 H, arom. H); 3.4 (d,  $J=2$ , 1H, H-C(2)); 2.8 (d  $\times$  qa,  $J=6$  and 2, 1H, H-C(3)); 1.4 (d,  $J=6$ , 3 H,  $\text{H}_3\text{C-C}(3)$ ).

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