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## Enantioselective terpene synthesis based on R-(+)-limonene

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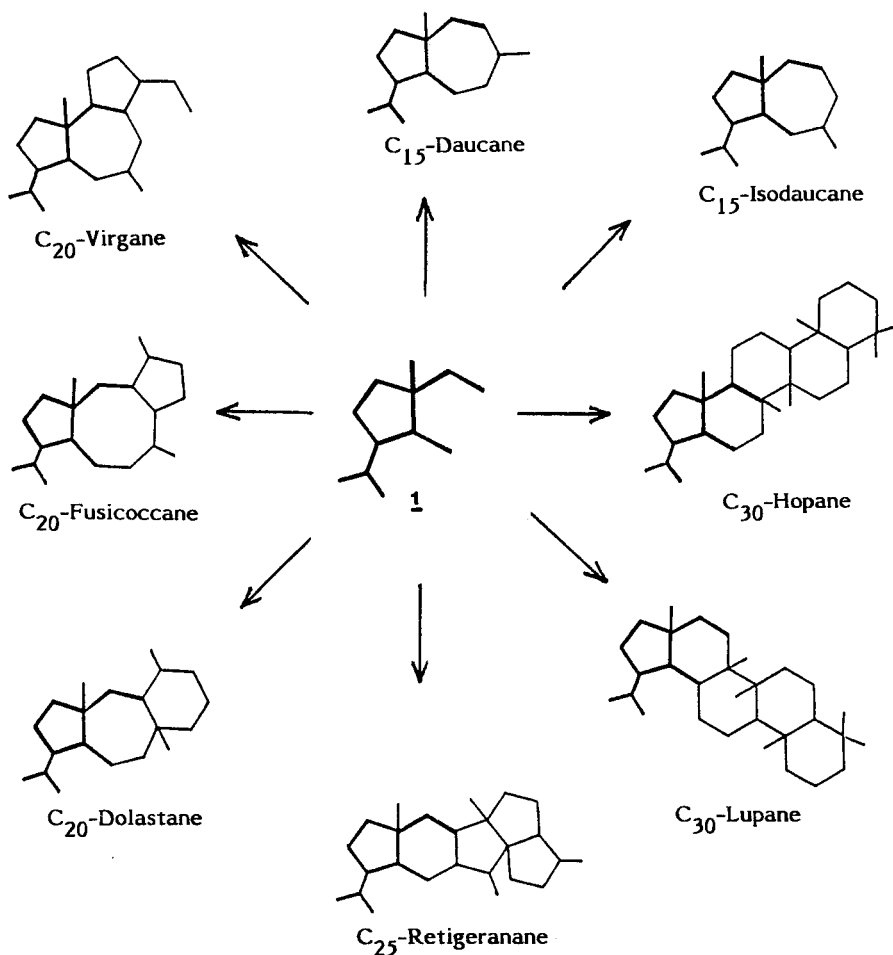
### ABSTRACT

The prevalence of a C<sub>12</sub>-common core in diverse C<sub>15</sub>-C<sub>30</sub> terpenes has been recognised. A bifunctional C<sub>12</sub>-cyclopentanoid derivative **2**, corresponding to this common-core has been prepared from R-(+)-limonene. The enantiomerically pure **2** has been elaborated to several sesqui- and diterpene skeleta. In particular, enantioselective syntheses of isodaucane sesquiterpene, (+)-aphanamol-I, **33** and a dolabellane diterpene,  $\delta$ -araneosene **26** have been accomplished for the first time. A general solution to the stereochemical problem associated with this class of compounds has been devised. Syntheses of (-)-daucene **8** and (+)-isoamijiol **17** are also described.

### INTRODUCTION

Nature's expertise and virtuosity in creating a phenomenal array of carbocyclic frameworks finds its full expression in the terpenoid group of natural products. Indeed, Nature assembles its vast repertoire of terpenic skeleta from very few biogenetic precursors like FPP, GGPP, squalene oxide

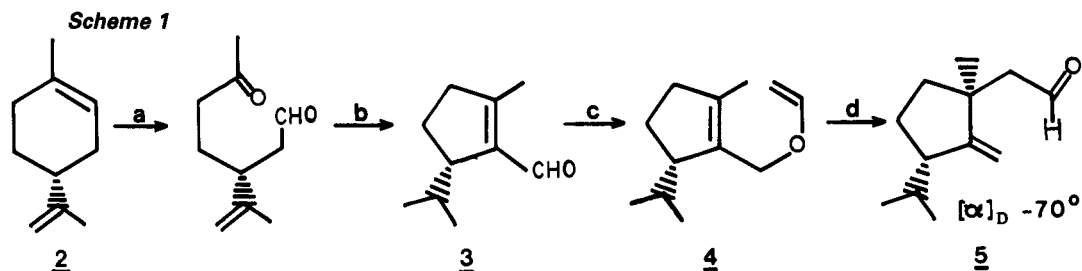
Chart 1



etc. There are several closely related modes of cyclisations available to these acyclic terpene precursors and as a result one finds many common structural moieties present in  $C_{10}$ -mono,  $C_{15}$ -sesqui-,  $C_{20}$ -di-,  $C_{25}$ -sester- and  $C_{30}$ -triterpenes. One such structural fragment that attracted our attention on account of its extensive presence among diverse terpenes (Chart 1, heavilylined portion) was 1. The prevalence of this  $C_{12}$ -core among so many terpenoid natural products suggested to us the possibility of utilising an appropriately functionalised derivative of 1 as a versatile building-block in terpene synthesis. It became apparent at the outset that the monoterpene-like cyclopentanoid 1 with a quaternary carbon centre and potential for three stereogenic centres should be accessible in an enantiomerically pure form by reforming an abundantly available mono-terpene like limonene. Convenient synthesis of the  $C_{12}$ -chiron 5 from R-(+)-limonene 2 and its subsequent elaboration to a diverse range of terpene skeletons has been explored. In particular, application of 5 in the synthesis of sesquiterpenes (-)-daucene 8, (+)-aphanamol-I 31 and diterpenes (+)-isoamijiol 17 and  $\delta$ -araneosene 26 is summarised in this lecture.

### CONSTRUCTION OF THE $C_{12}$ -CHIRON 5

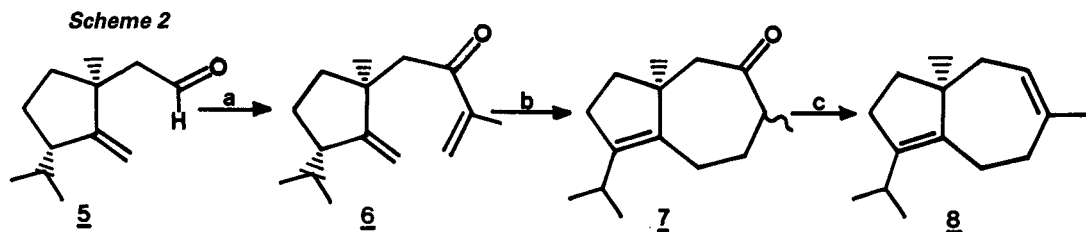
R-(+)-limonene 2 was selectively elaborated into the enantiomerically pure  $C_{12}$ -synthon 5 as shown in Scheme 1. The essential features of this transformation being the restructuring of the cyclohexene ring in 2 to a methylcyclopentene derivative 3 with retention of chirality (ref. 1) and the stereoselective quaternisation-2C annulation leading to 5. The latter operation was effected through an efficient distereofacial selective [3.3] shift (Claisen rearrangement 4  $\rightarrow$  5). With secured relative stereochemistry and well differentiated functionalities, (-)-5 was ready for exploitation in pursuing the objectives indicated in Chart 1, (ref. 2).



**Reagents, Conditions & Yields:** a) (i) m-CPBA,  $CHCl_3$ ,  $0^\circ C$ , 10h, 80%; (ii) 1%  $H_2SO_4$ , THF, RT, 1h; (iii)  $NaIO_4$ , THF,  $H_2O$ ,  $25^\circ C$ , 75% after two steps. b) (i)  $H_2$ -PtO<sub>2</sub>, EtOAc, 20psi, 1h, 90%; (ii) piperidine, AcOH, benzene,  $\Delta$ , 1h, 70%. c) (i)  $NaBH_4$ ,  $CeCl_3 \cdot 6H_2O$ , MeOH,  $0^\circ C$ , 0.5 h, 100%; (ii) ethyl vinyl ether,  $Hg(OAc)_2$ , RT, 20h, 80%. d) sealed tube,  $200^\circ C$ , 1h, 80%.

### SYNTHESIS OF (-)-DAUCENE 8

The hydroazulenenic sesquiterpene daucene 8 (from *Daucus carota* L) is the parent hydrocarbon of the growing family of carotane sesquiterpenoids. It is one of the simpler terpenes incorporating the structural fragment 1 and therefore, was chosen as our first synthetic objective. The main synthetic task here was the construction of a seven membered ring utilising the two functionalities present in 5. This was accomplished as indicated in Scheme 2 and an intramolecular cationic enone-olefin cyclisation was employed as the pivotal step (6  $\rightarrow$  7). This short synthesis of (-)-8 is flexible enough to be readily adaptable for the synthesis of other members of the carotane family (ref. 3,4).

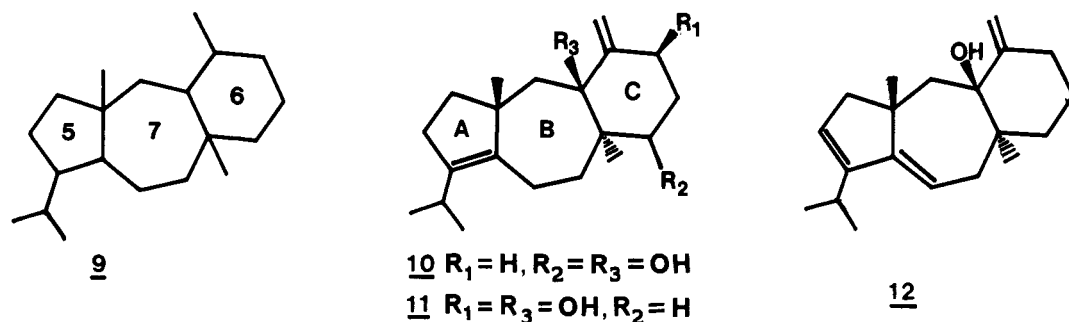


**Reagents, Conditions & Yields:** a) (i) isopropenyl magnesium bromide, THF, RT, 1h, 83%; (ii) PCC, DCM, 4A molecular sieves, RT, 1h, 65%. b) cat.  $HClO_4$ , EtOAc-Ac<sub>2</sub>O, RT, 0.5h, 70%. c) (i) LAH, Et<sub>2</sub>O, RT, 0.5h, 70%; (ii)  $POCl_3$ -Py, RT, 12h, 50%.

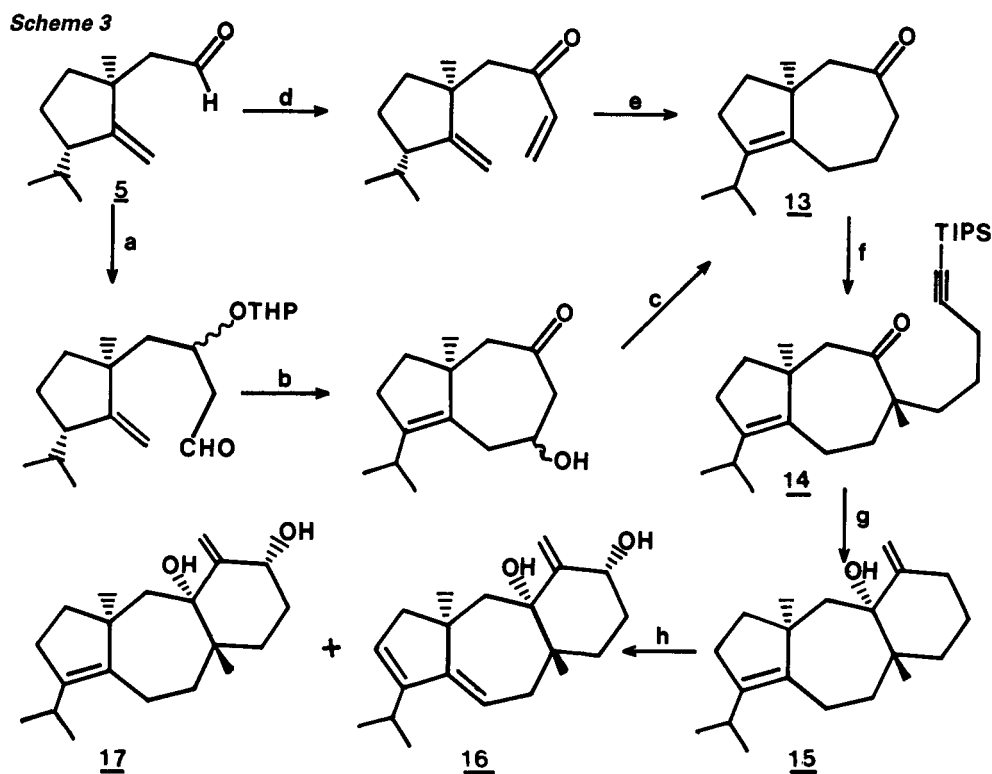
### SYNTHESIS OF (+)-ISOSAMIJIOL 17 AND (-)-DOLASTA-(15), 7,9-TRIEN-14-OL 16

The tricyclic dolastane diterpenes, embodying a unique 5-7-6 fused carbocyclic system 9, are widely occurring marine natural products and over 30 of them are presently known (ref. 5). Typical examples are the doubly unsaturated alcohols (-)-amijiol 10, (-)-isoamijiol 11 and the triply unsaturated com-

pound 12. Retrosynthetic analysis on dolastanes led to the identification of hydroazulenone 13, incorporating the AB rings and accessible from the chiron 5, as an advanced intermediate suitable for the stereoselective appendage of six-membered (C) ring.



The bicyclic hydroazulenone 13 was readily assembled from 5 as shown in Scheme 3, employing the cationic enone-olefin cyclisation and intramolecular Prins reaction stratagems. The annulation of ring C with attendant functionality was achieved via an alkyne-carbonyl radical cyclisation (14 → 15). Prior to this step, the second angular methyl group was stereoselectively installed taking advantage of the topological bias in 13 for reaction from the face opposite to the preexisting methyl group. The dolastane derivative 15 was further transformed to the natural products (+)-isoamijiol 17 and (+)-dolasta-1(15),7,9-trien-14-ol 16 through catalytic selenium dioxide oxidation, Scheme 3, (ref. 6,7).

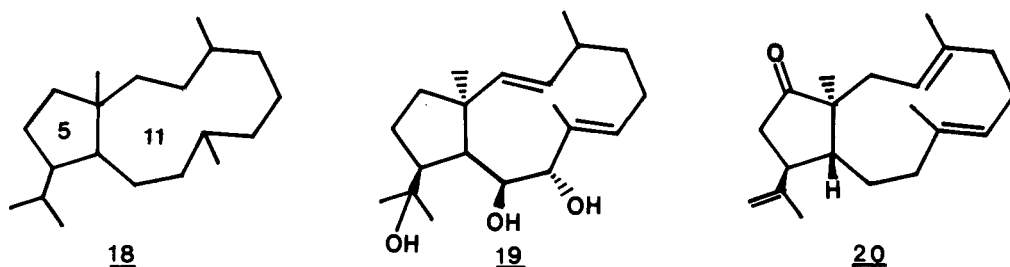


**Reagents, Conditions & Yields:** a) (i) Zn-BrCH<sub>2</sub>COOEt, dioxane, RT, 1h, 72%; (ii) DHP, PPTS, DCM, RT, 6h, 100%; (iii) DIBAL-H, DCM, -78°C, 0.5h, 65%. b) (i) SnCl<sub>4</sub>, DCM, RT, 1h, 20%; (ii) PCC, DCM, 0°C, 0.5h, 50%. c) (i) MsCl, pyridine, 0°C, 4h, 70%; (ii) LAH, ether, RT, 0.5h; (iii) PCC, DCM, RT, 4A molecular sieves, 50% in two steps. d) (i) vinyl bromide (THF), Mg, THF, RT, 0.5h, 75%; (ii) PCC, DCM, 4A molecular sieves, RT, 1h, 65%. e) Cat.HClO<sub>4</sub>, Ac<sub>2</sub>O-EtOAc, RT, 25 min., 65%. f) (i) LHMS, THF-HMPA, I-(CH<sub>2</sub>)<sub>3</sub>C≡C-Si(CH<sub>3</sub>)<sub>2</sub>, -10°C, 1h, 80%; (ii) NaH, DME, MeI, RT, 24h, 65%. g) (i) n-Bu<sub>4</sub>N<sup>+</sup>F<sup>-</sup>, THF, RT, 5 min., 100%; (ii) sodium naphthalene, THF, RT, 40%. h) SeO<sub>2</sub>, t-BuOOH, DCM, 0°C, 60%.

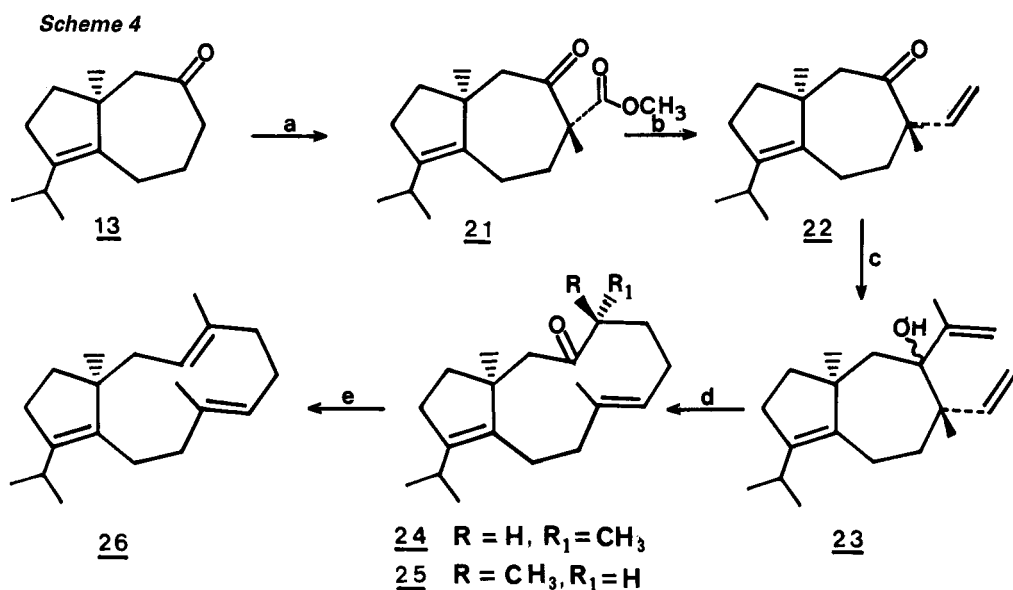
### SYNTHESIS OF DOLABELLANE-TYPE DITERPENE δ-ARANEOSENE 26

The novel 5-11 fused bicyclic dolabellane framework 18 occurs widely among marine sources and currently about seventy diterpenes of this family with varying degrees of functionalisation are known.

Diterpenes 19 and 20 represent typical functionalisation patterns present among dolabellanes (ref. 8). Besides the wide occurrence and novel 5,11-fused system, dolabellanes are important as they are considered to be the biogenetic precursors of several novel diterpenes like dolastanes, crinipellins and fusicoccanes. No synthesis of dolabellanes has been achieved so far.



$\delta$ -Araneosene 26, a dolabellane diene from *Sordaria araneosa* (ref. 9) was chosen as our initial synthetic objective which could be approached from the bicyclic hydroazulenone 13 (Scheme 3). The key operation in this context was identified as a four carbon annulative ring-expansion (7  $\rightarrow$  11-membered) with installation of two methyl groups and *trans*-double bonds at appropriate locations. An oxy-Cope protocol was considered to be ideally suited for this purpose and 13 was duly prepared for this operation, Scheme 4. Regioselective carbomethoxylation and methylation furnished 21 as

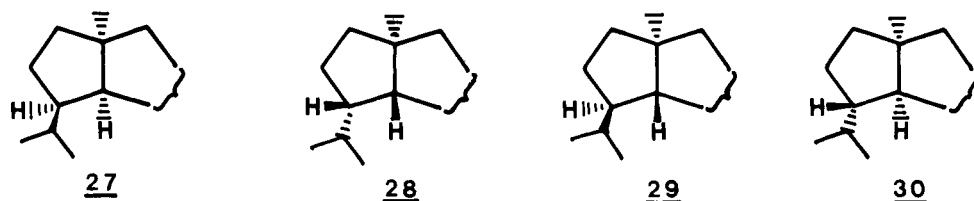


**Reagents, Conditions & Yields:** a) (i) NaH, (CH<sub>3</sub>O)<sub>2</sub>CO,  $\Delta$ , 6h, 78%; (ii) K<sub>2</sub>CO<sub>3</sub>, acetone, MeI,  $\Delta$ , 24h, 85%. b) (i) LAH, Et<sub>2</sub>O, RT, 1h, 65%; (ii) (COCl)<sub>2</sub>, DMSO, DCM, NEt<sub>3</sub>, -60°C; (iii) Ph<sub>2</sub>P<sup>+</sup>-CH<sub>2</sub>Br, Na-t-amylxide, RT, 10 min., 72% in two steps. c) isopropenyl magnesium bromide, THF,  $\Delta$ , 0.5h, 64%. d) sealed tube, 170°C, 1h, 70%. e) (i) LAH, Et<sub>2</sub>O, RT, 1h, 100%; (ii) MsCl, pyridine, DCM, 20h, 15%.

the major diastereomer but a separation at this stage was not considered necessary. The carbomethoxy group in 21 was routinely transformed into a vinyl group as in 22. An appropriate Grignard addition to give 23 set the stage for the oxy-Cope process. Thermal activation of 23 gave a mixture of C<sub>20</sub> dolabellane ketones 24 and 25. Reduction and elimination furnished  $\delta$ -araneosene 26 in small yield along with some interesting transannularly cyclised products. The methodology delineated here for the construction of 5,11-system can be readily adapted for gaining access to the other members of the dolabellane family.

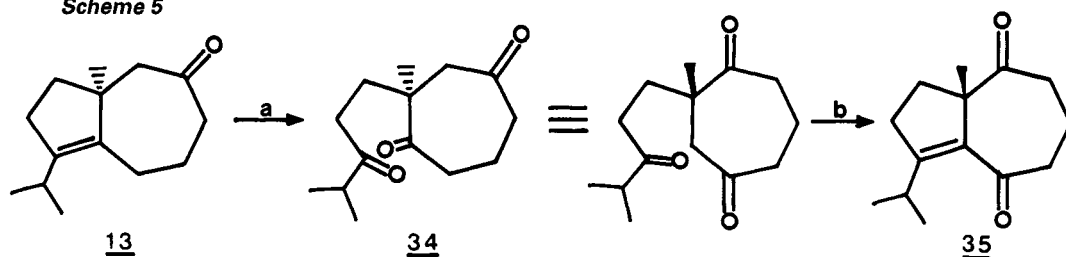
#### SYNTHESIS OF ISODAUCA NE SESQUITERPENOIDS (+)-APHANAMOL-I 31 AND (+)-2-OXISODAUCA-5-EN-2-AL 33

To further enhance the synthetic utility of the bicyclic hydroazulenone 13, it was considered necessary to generate stereogenic centres at C<sub>7</sub> and C<sub>8</sub> in a controlled manner. Four diastereomeric forms 27-30 are possible for the system at hand and three of these 28-30 have been frequently encountered among natural products. These stereochemical patterns are not accessible from 13, particularly because the considerably hindered tetrasubstituted double bond in it is resistant to catalytic hydrogenation. A new tactic, therefore, had to be devised for generating stereochemical patterns 27-30 from 13.



The need to resolve the stereochemical problem primarily arose in view of our synthetic interest in novel isodaucane sesquiterpenes aphanamol-I 31, -II 32 and 2-oxo-isodauc-5-en-12-al 33 isolated recently from the Meliaceae plant *Aphanamixis grandifolia* and *Chromolaena laevigata* (Lam), respectively (ref. 10). Besides the creation of the thermodynamically less stable stereochemistry at the three contiguous centres (cf. 27), the generation of the sensitive oxygen functionalisation across the seven membered ring was the chief concern in planning the synthesis of these isodaucane natural products. A solution was devised in which the bicyclic enone 13 was restructured to a new hydroazulenic ene-dione 35 in two steps involving oxidative scission of the double bond to a trione 36 and regioselective aldolisation dehydration (34 → 35), Scheme 5. The restructured 35 is not only enantiomeric with respect to 13 but also has amplified and relocated oxygen functionalities, specifi-

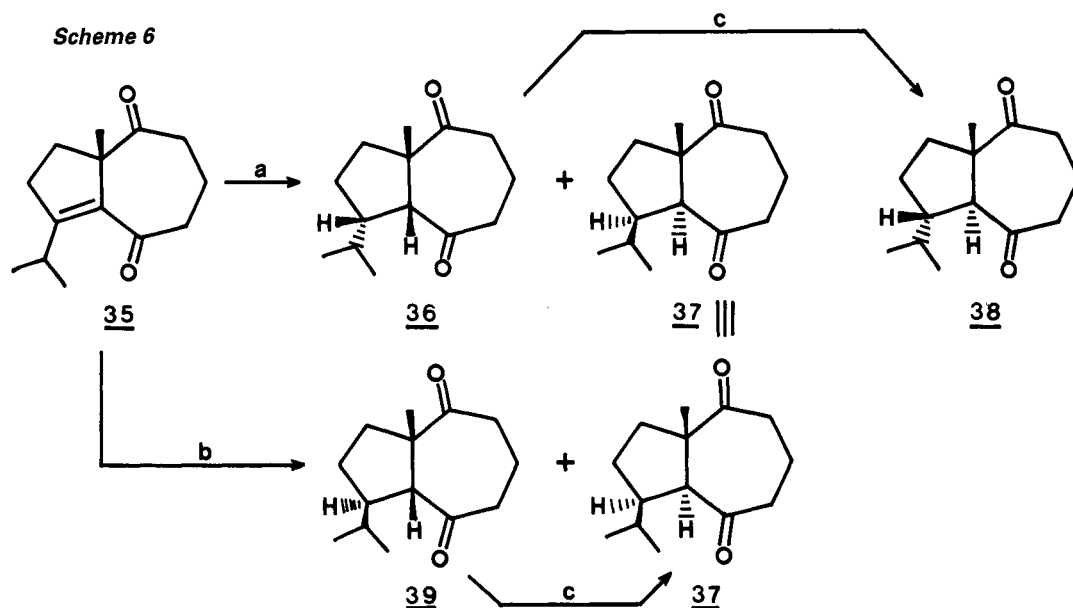
Scheme 5



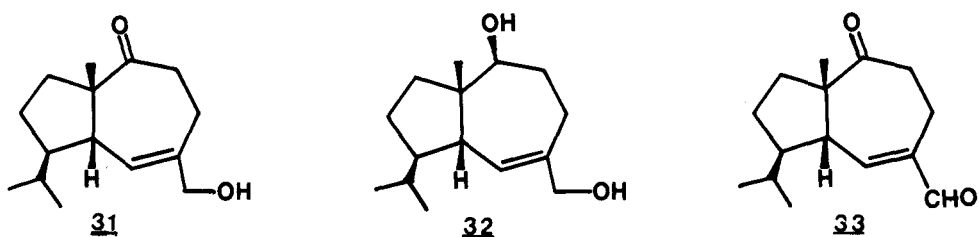
Reagents, Conditions & Yields: a)  $\text{RuO}_2$ ,  $\text{NaIO}_4$ ,  $\text{H}_2\text{O}-\text{CH}_3\text{CN}-\text{CCl}_4$ , RT, 1h, 100%. b) 5%  $\text{KOH}-\text{MeOH}$ ,  $\Delta$ , 0.5h, 60%.

cally an enone moiety for the generation and control of  $\text{C}_7-\text{C}_8$ -stereochemistry. The conjugated  $\text{C}_7-\text{C}_8$  double bond in 35 was now amenable to catalytic hydrogenation as well as metal-ammonia reduction and all the four diastereomers 36-39 corresponding (enantiomeric) to 27-30 could be attained, Scheme 6.

Scheme 6

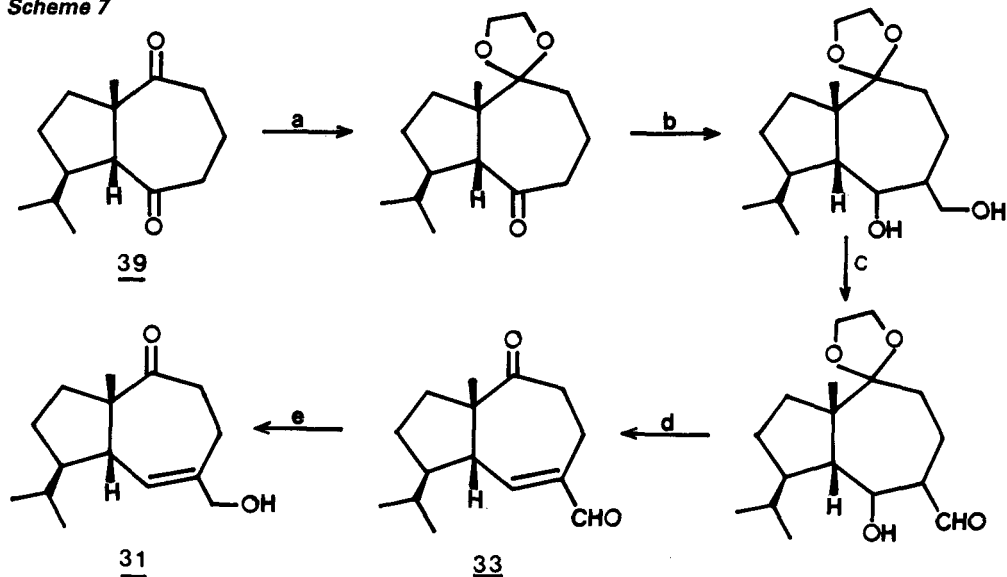


Reagents, Conditions & Yields: a)  $\text{H}_2$ , 10%  $\text{Pd/C}$ , 20 psi, 1h, 90%. b) (i)  $\text{Li}$ ,  $\text{liq.NH}_3$ ,  $\text{THF}$ ,  $\text{MeOH}$ ,  $-40^\circ\text{C}$ ; (ii)  $\text{PCC}$ ,  $\text{DCM}$ , 4 Å molecular sieves, RT, 1h, 70%. c) 5%  $\text{KOH}-\text{MeOH}$ , 24h, RT, 100%.



The dione 39 of required stereochemistry was now elaborated to the natural products 31 and 33 as detailed in Scheme 7. Our enantioselective synthesis of (+)-aphanamol-I 31 also establishes the absolute configuration of natural products 31 and 32 (ref. 11).

Scheme 7



**Reagents, Conditions & Yields:** a)  $(\text{CH}_2\text{OH})_2$ , PPTS,  $\text{C}_6\text{H}_6$ ,  $\Delta$ , 92%. b) LHMDS, ClCOOMe, THF,  $-78^\circ\text{C}$ , 0.5h, 86%; (ii) LAH, ether, RT, 1h, 40%. c)  $(\text{COCl})_2$ -DMSO,  $\text{Et}_3\text{N}$ , DCM,  $-60^\circ\text{C}$ , 1h, 70%. d) PTS,  $\text{C}_6\text{H}_6$ ,  $\Delta$ , 1h, 37%. e)  $\text{NaBH}_4$ ,  $\text{CeCl}_3 \cdot 6\text{H}_2\text{O}$ , MeOH,  $-5^\circ\text{C}$ , 10 min., 100%.

### Acknowledgements

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