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A Stereocontrolled Total Synthesis of (±)-Δ^2-Cedrene

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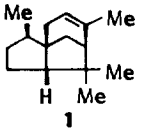
Abstract: An efficient stereocontrolled synthesis of (±)-Δ^2-cedrene **2** has been accomplished using intramolecular anionic cyclisation of the bromophenol **13** as a key step.

The isomeric sesquiterpenes α-cedrene **1**[1] and Δ^2-cedrene **2**[2] incorporate tricyclo[5.3.1.$0^{1,5}$]undecane framework but differ in the position of a double bond and in relative stereochemistry of the respective secondary methyl group. The total synthesis of these tricyclic sesquiterpenes presents an interesting problem in view of the presence of four asymmetric centres and an isolated double bond in one of the rings. Although α-cedrene **1** has been synthesised[3] a number of times, the synthesis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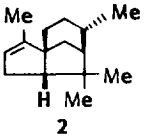
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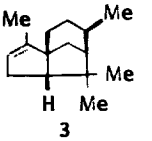
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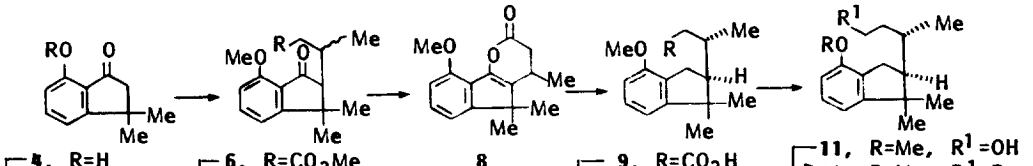
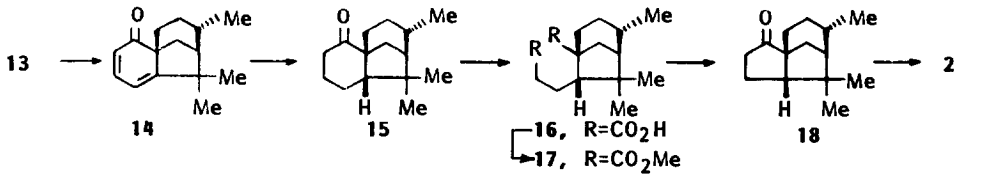
of Δ^2-cedrene **2** has not been reported yet. We report here an efficient stereocontrolled synthesis of (±)-Δ^2-cedrene **2** starting from the easily accessible indanone derivative **4**. The salient features of our synthesis are (i) facile conversion of **4** into the bromophenol **13**, (ii) Ar_1-6 cyclisation[4] of **13** to provide the tricyclic dienone **14** in high yield, and (iii) efficient transformation of **14** into Δ^2-cedrene **2** using the functional groups in the ring A of **14**. A synthesis of (±)-Δ^2-8-epicedrene **3** has been reported[5] recently by Chen and Lin.

The hydroxyindanone **4**, prepared[6] from phenol, was purified by steam distillation. Michael reaction of the corresponding methyl ether **5**, m.p. 111-112°C with methyl crotonate in the presence of NaOMe furnished the ketoester **6**[7] as a diastereoisomeric mixture in 60% yield. Saponification of **6** yielded the corresponding ketoacid **7** which on refluxing with Ac_2O and NaOAc afforded the enol lactone **8** (85%),





m.p. 112-113°C. Catalytic hydrogenation of **8** furnished a single acid **9**, m.p. 160-161°C in 92% yield which was converted into the methyl ester **10**, m.p. 72-73°C. The stereochemical assignments of the compounds **9** and **10** followed from subsequent transformations leading to the tricyclic ketone **15**, the stereostructure of which was established by single crystal X-ray crystallography. Reduction of **10** with $LiAlH_4$ yielded the primary alcohol **11**, m.p. 108-109°C which was converted into the bromo-ether **12**, m.p. 71-72°C with PBr_3. Demethylation of **12** with BBr_3 in CH_2Cl_2 afforded the bromophenol **13**, m.p. 54-55°C in 90% yield. Aryl participated intramolecular cyclisation[4] of **13** using *t*-BuOK as the base furnished the tricyclic dienone **14**, m.p. 85-86°C in 74% yield.

Catalytic hydrogenation of **14** proceeded stereoselectively with rapid uptake of two moles of hydrogen to provide the A/B *cis*-fused ketone **15** (96%), m.p. 90-91°C. As mentioned earlier, the relative stereochemistries of the four asymmetric centres present in **15** were determined by X-ray crystallography. The ketone **15** was condensed wih ethyl formate in the presence of NaH and the resulting hydroxymethylene derivative was treated with alkaline H_2O_2 to afford the diacid **16**, m.p. 172-173°C in 84% yield. Dieckmann cyclisation of the corresponding dimethyl ester **17** with *t*-BuOK in benzene followed by decarbomethoxylation of the crude β-ketoester furnished the tricyclic ketone **18**, m.p. 105-106°C in 73% overall yield. Treatment of **18** with MeMgI followed by dehydration of the resulting tertiary alcohol with dimethyl sulphoxide at 155°C afforded a mixture of hydrocarbons in 87% yield. From the integration of the ^1H NMR signals in the olefinic region, the mixture was estimated to contain ca. 80% of the desired hydrocarbon **2** and 20% of an isomeric hydrocarbon in which the double bond was exocyclic. The mixture was directly treated with a catalytic amount of *p*-toluenesulfonic acid (0.1 equiv.) in CH_2Cl_2 at 25°C for 3 h. Isomerisation of the exocyclic double bond was complete by this treatment. Chromatography of the crude product over silica gel and elution with pentane afforded pure (±)-Δ^2-cedrene **2** in 82% yield from **18**. The identity of synthetic **2** was secured through ^1H NMR, ^{13}C NMR, IR, and microanalytical data. The structure of **2** was further confirmed from DEPT experiments.

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