A Stereoselective Total Synthesis of (±)-$\Delta^{9(12)}$-Capnellene *via* the Intramolecular Diels–Alder Approach

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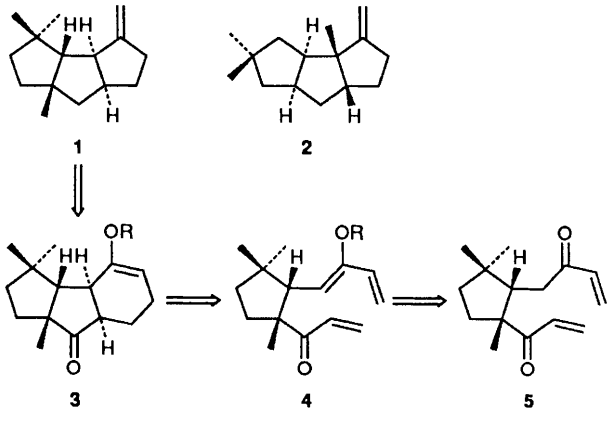
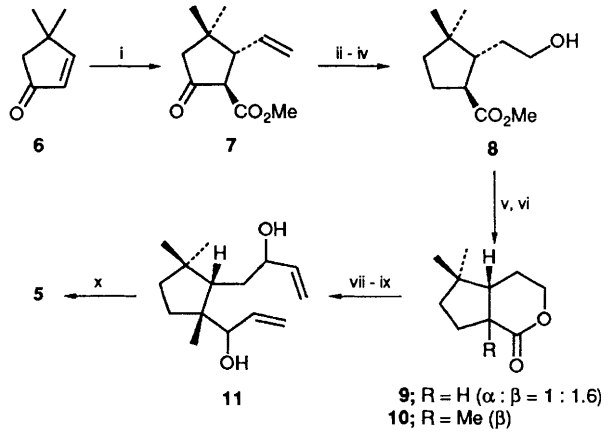
A formal total synthesis of (±)-$\Delta^{9(12)}$-capnellene **1** was achieved by the intramolecular Diels–Alder reaction of the triene **4**.

$\Delta^{9(12)}$-Capnellene **1** and hirsutene **2** are putative precursors of linear triquinane type sesquiterpenes, capnellane and hirsutane families, which are known to have important biological activities. Thus construction of their *cis-transoid-cis*-tricyclo[6.3.0.$0^{2,6}$]undecane skeleton has been the focus of current synthetic attention due to their biological properties as well as their unique structural features. We have designed a novel synthetic approach to $\Delta^{9(12)}$-capnellene **1**[1–3] *via* the *cis-transoid-cis*-tricyclo[7.3.0.$0^{2,7}$]dodecane derivative **3**, which would be produced by the intramolecular Diels–Alder reaction of the triene **4** as shown in Scheme 1.

The synthetic precursor **5** of the triene **4** was stereoselectively synthesised starting from 4,4-dimethylcyclopent-2-enone **6**[4] (Scheme 2). Conjugate addition of vinylmagnesium bromide in the presence of CuI and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), followed by trapping the enolate with methyl cyanoformate[5] in the presence of hexamethylphosphoric triamide (HMPA), gave the alkene **7** in 89% yield as a single stereoisomer. The alkene **7** was transformed into the alcohol **8** in three steps, thioketalisation (93% yield), hydroboration–oxidation (88% yield) and dethioketalisation (100% yield). Heating **8** with (+)-camphor-10-sulphonic acid (CSA) in hot benzene formed the lactones **9** in 97% yield as a mixture (1 : 1.6) of *trans* and *cis* fused compounds, which were methylated in the presence of lithium diisopropylamide (LDA) to afford the *cis*-lactone **10** in 74% yield as the sole product. Reduction (100% yield) of **10** with diisobutylaluminium hydride (DIBAL), followed by Swern oxidation and Grignard reaction gave a diastereoisomeric mixture of the bis-allyl alcohol **11** in 96% yield. Oxidation of **11** was effectively carried out using Dess-Martin periodinane[6] to provide the bis-enone **5** in 75% yield.



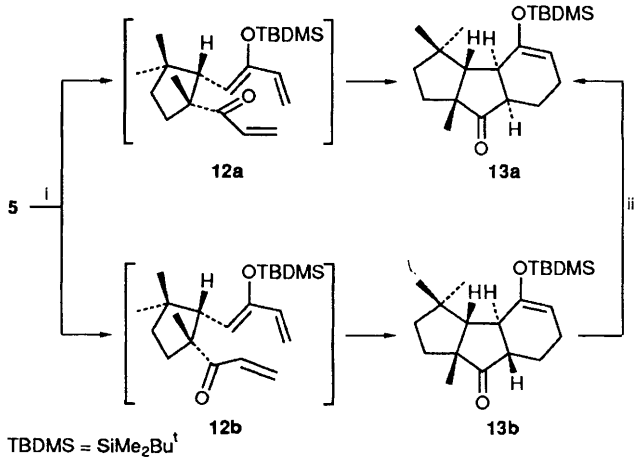
Scheme 1



Scheme 2 *Reagents*: i, CH_2=CHMgBr, CuI, TMEDA then $NCCO_2Me$, HMPA; ii, $HSCH_2CH_2SH$, BF_3·OEt_2; iii, dicyclohexylborane then H_2O_2, NaOH; iv, Raney-Ni; v, CSA; vi, LDA then MeI; vii, DIBAL; viii, $(COCl)_2$, dimethyl sulphoxide then Et_3N; ix, CH_2=CHMgBr; x, periodinane[6]

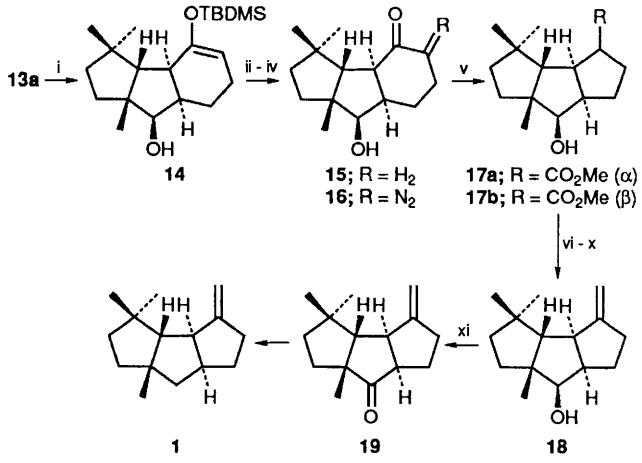
Conversion of **5** into the triene **4** was tried under various conditions, and this was done by the modification of the Lévy's procedure.[7] Addition of a tetrahydrofuran (THF) solution of KOBu^t to a solution of bis-enone **5** and *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF at −78 °C produced the siloxy diene **12**, which was subjected to an intramolecular Diels–Alder reaction. Two stereoisomers **13a** and **13b** were obtained in a ratio of 1 : 2 (55% yield) on heating **12** in refluxing benzene for 2 h. When the cycloaddition was performed in the presence of neutral alumina[8] as Lewis acid at room temperature for 20 h, two cyclised products **13a** and **13b** were obtained in a ratio of 10 : 1 (26% yield). It was found that **13b** completely epimerised upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hot benzene to **13a**. Thus, **13a** was prepared in 55% yield from **5** as a single isomer after treatment of the mixture of products **13a** and **13b** with DBU. It was considered from the above results that the former would be the desired *cis-transoid-cis*-isomer **13a**, formed through the *endo* transition state **12a** of the (*Z*)-siloxy diene, while the latter would be the *cis-transoid-trans*-isomer **13b**, derived from the *exo* transition state **12b** as shown in Scheme 3. The tentative structural assignment was confirmed by the following transformation.

Reduction of **13a** with sodium borohydride produced an alcohol **14** in 92% yield as the sole product. The β-hydroxy structure was supported by the exclusive formation of the other isomer in 90% yield by Birch type reduction of **13a** using Li in lioquid NH_3 in the presence of MeOH. After deprotection (100% yield) of the silyl enol ether **14**, formylation of the resulting ketone, **15**, m.p. 84–85 °C, followed by diazo-exchange reaction gave **16**, which was subjected to the Wolff rearrangement.[9] Two separable isomers **17a**, (m.p. 101–102



TBDMS = $SiMe_2Bu^t$

Scheme 3 *Reagents*: i, TBDMSCl, KOBu^t; ii, DBU



Scheme 4 *Reagents*: i, $NaBH_4$; ii, Bu^n_4NF; iii, NaOMe, HCO_2Et; iv, toluene-*p*-sulphonyl azide, Et_3N; v, hv, MeOH; vi, TBDMSOTf, 2,6-lutidine, DMAP; vii, DIBAL; viii, methanesulphonyl chloride, Et_3N; ix, *o*-$NO_2PhSeCN$, $NaBH_4$ then H_2O_2; x, Bu^n_4NF; xi, periodinane[6]

°C) and **17b** (m.p. 90–93 °C) were obtained in 48% yield for three steps in a 3:1 ratio. The hydroxy group of the major product **17a** possessing the α-oriented methoxycarbonyl group was protected in 98% yield using *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf), 2,6-lutidine and 4-*N*,*N*-dimethylaminopyridine (DMAP). The conversion of the methoxycarbonyl group into the methylene group was accomplished in 70% overall yield by the application of the Sharpless method,[10] reduction with DIBAL, mesylation, substitution with *o*-nitrophenyl selenide anion and oxidative elimination. After deprotection, the resulting alcohol **18** was oxidised with the periodinane[6] to give the ketone **19** (91% yield), whose spectral data were identical with those of the authentic compound.[2o] Since **19** had been converted into (±)-$\Delta^{9(12)}$-capnellene **1**,[2h,o] the formal total synthesis was achieved (Scheme 4).

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