First Synthesis of the Trinervitane System from Secotrinervitane by Transannular Ring Construction†

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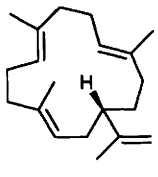
The unique skeleton of the tricyclic diterpene, trinervitane, was synthesized for the first time in racemic form by a transannular cyclization of a secontrinervitane derivative.

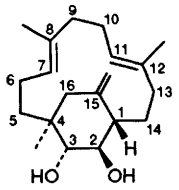
Since termites have no ability to synthesize steroids *de novo* because of the lack of an enzyme to couple two farnesyl pyrophosphate units, they develop *de novo* biosynthesis of unique cyclic diterpene derivatives such as cembrene **1**, secotrinervitane **2**, trinervitane **3** and other polycyclic diterpenes instead of steroids.[1] The unusual diterpenes **2** and **3** were isolated from defence chemicals of termite soldiers while **1** is a trail pheromone of termite workers. The tricyclic trinervitane **3** was proposed to be biosynthesized from the monocylic **1** *via* the bicyclic **2**.[2] A plausible biogenesis of **3** from **2** may involve the transannular cyclization of the hypothetical secotrinervitane **4** with concomitant 1-H hydride transfer to C-12 position as shown.‡

Because of their unique structural features, the synthesis of these compounds has attracted much interest.[3] We have planned the syntheses of polycyclic terpenoids from cembrene derivatives by application of biomimetic transannular cyclization and have already synthesised the naturally occurring secotrinervitane **2** in racemic form.[4] Extension of our strategy forms the subject of the present communication concerning first synthesis of the trinervitane skeleton.

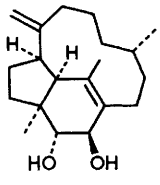
According to our published results, (±)-2β-acetoxy-3α-hydroxysecotrinervitene **5** was prepared from commercially available geranylgeranic acid over 7 steps in 27% overall yield.[4,5] After protection of the hydroxy group of **5** as the methoxymethyl ether (MOM), the acetyl group was removed by hydrolysis with potassium hydroxide. Since regioselective oxidation of the exocyclic methylene group of the resulting ether **6** would not be expected to be aided by the C-2 hydroxy group because it is equatorial, the stereochemistry at C-2 was inverted to give the axial alcohol **7** by converting **6** to the corresponding ketone followed by reduction with $NaBH_4$. The reduction of the carbonyl group proceeded stereoselectively by virtue of the C-4 axial methyl group. The exocyclic methylene group was then epoxidised by the Sharpless procedure, in which the C-2 axial hydroxy group assisted the regioselective oxidation to yield the epoxide **8** as a single product.[6] The epoxide ring was opened selectively under basic conditions to give the allyl alcohol **9** after removal of the MOM group by the action of aqueous HCl and then protection of the resulting vicinal diol as a carbonate ring.



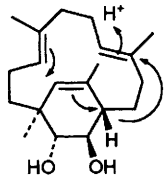
1: Cembrene-A



2: Secotrinerviten-2 β, 3α-diol

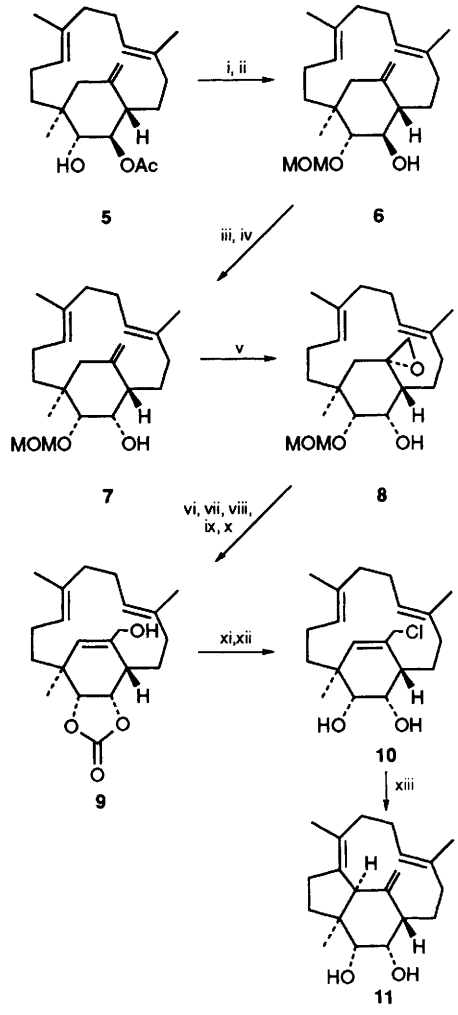


3: Trinerviten-2β,3α-diol



4

In order to make a new bond between C-7 and C-16, several reactions were tried with the allyl alcohol **9** and its derivatives. The unsuccessful results suggested that the additional ring strain due to the five-membered carbonate ring made the trinervitane skeleton unstable. A successful result was finally obtained from the allyl chloride **10**, which was derived from **9** by chlorination with methanesulfonyl chloride and LiCl followed by hydrolysis of the carbonate group. The reaction of the allyl chloride **10** with silver perchlorate afforded the cyclized product **11** almost exclusively. The structure of **11** was



Scheme 1 *Reagents and conditions*: i, MOMCl, Pr^i_2NEt (100%); ii, KOH, MeOH (100%); iii, pyridinium chlorochromate, NaOAc, 4 Å molecular sieve, CH_2Cl_2, room temp., 2 h (90%); iv, $NaBH_4$, MeOH, −15 °C (100%); v, *tert*-butyl hydroperoxide, $Ti(OPr^i)_4$, CH_2Cl_2, 0 °C (62%); vi, lithium cyclohexylisopropylamide, tetramethylethylenediamine, THF, reflux (54%); vii, aqueous HCl, MeOH, 0 °C (69%); viii, Bu^tMe_2SiCl, imidazole, dimethylformamide (83%); ix, $(imidazol\text{-}2\text{-}yl)_2CO$, CH_2Cl_2 (85%); x, tetrabutylammonium fluoride, THF (100%); xi, $MeSO_2Cl$, LiCl, 12-crown-4, CH_2Cl_2 (87%); xii, KOH, MeOH (92%); xiii, $AgClO_4$, THF–benzene, −30 °C to 0 °C, 8 h (80%)

confirmed by its electron-impact mass, IR, ^{13}C NMR and ^{1}H NMR spectra, including H–H COSY experiments.§

The striking feature of the cyclization of **10** to give **11** is the predominant formation of the tetra-substituted double bond between C-7 and C-8. This double bond arises from formation of the trinervitane skeleton including a C-8 cation, from which 7-H is selectively removed. This selective deprotonation may be controlled by the thermodynamic stability of the product. Molecular mechanics calculations using MM2 showed that the tetra-substituted isomer **11** is the most stable among the double bond isomers around C-8.[7] The remaining isomers were shown to be 25–40 kJ mol^{-1} less stable than **11** and therefore might not be formed in the cyclization. It seems probable that change of hybridisation of C-12 from sp^2 to sp^3 by the 1-H hydride transfer is important for the *de novo* construction of natural trinervitane **3** from the hypothetical progenitor **4**.

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Footnotes

† For Part 50 of the series Cyclization of polyenes, see *Chem. Lett.*, 1992, 2343.

‡ Numbering is based on that of the secotrinervitane skeleton.

§ *Selected spectroscopic data* for **11**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.07 (1 H, s), 4.99 (1 H, dd, *J* 10.7, 5.5 Hz), 4.94 (1 H, s), 3.74 (1 H, br s), 3.40 (1 H, d, *J* 3.8 Hz), 2.94 (1 H, br s), 2.53 (1H, dt, *J* 4.3, 12.6 Hz), 1.63 (3 H, s), 1.54 (3 H, s) and 0.99 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 148.4 (s), 136.0 (s), 132.7 (s), 129.4 (s), 125.7 (d), 112.5 (t), 78.3 (d), 72.7 (d), 61.0 (d), 50.6 (s), 44.0 (d), 40.1 (t), 37.3 (t), 32.9 (t), 30.6 (t), 25.9 (t), 24.2 (t), 21.6 (q), 18.7 (q) and 15.6 (q); MS *m/z* 302 (M^+), 297, 294, 269, 256, 246, 213, 173, 169, 145, 121, 105, 91, 81, and 41 (100%); HRMS found 302.2238, $C_{20}H_{30}O_2$ requires 302.2247.

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