A first synthesis of (±)-2,3-dihydroxytrinervitanes†

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The total synthesis of 2,3-dihydroxytrinervitanes, 1a and 1b, was performed from secotrinervitane-type allyl chloride 2

More than two decades ago, characterization of 2,3-dihydroxytrinervitanes **1a** and **1b** (Fig. 1) was reported as the typical defensive substances from several species of termite soldiers inhabiting the tropics.[1] In spite of their unique structure and interesting biological activity, the total synthesis of **1a** and **1b** remained unpublished.[2]

We have been greatly interested in the biogenetic-type synthesis of diterpenoids secreted by termites and have explored the synthetic route of trinervitane **3** and kempane **5** skeletons through the intermediate, allyl chloride **2**, as illustrated in Scheme 1.[3] Our further effort led to completion of the synthesis of trinervitanes **1a** and **1b** as a *dl*-form. This paper reports the result of our study.

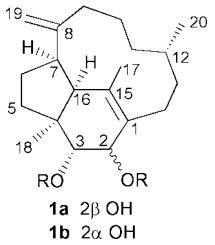
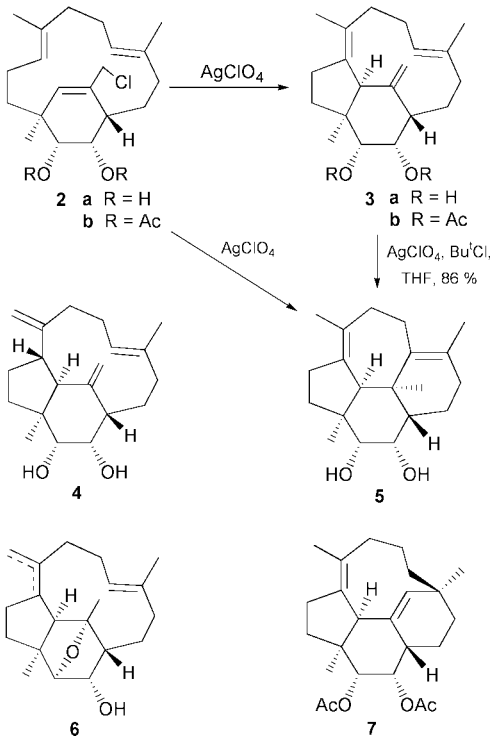


Fig. 1 Structure of 2β- and 2α-trinervitanes.



Scheme 1 Construction of trinervitane **3** and kempane **5** skeletons.

As reported previously,[4] the desired trinervitanes **3a** and **4** were provided in 68 and 5% yields, respectively, with accompanying formation of etheric compound **6** as unpurified minor product when **2a** was submitted to the reaction with $AgClO_4$ in THF at −20 °C. This ring-closure reaction depends largely on the reaction temperature, *i.e.* a completely different tetracyclic kempane diol **5** was formed in 50% yield when the reaction of **2a** with $AgClO_4$ was carried out at +20 °C. Treatment of **3a** at rt with $HClO_4$ in THF, prepared *in situ* by the reaction of *tert*-butyl chloride and $AgClO_4$, gave the kempane diol **5** in high yield. Based on this evidence, we first attempted to improve the yield of **3**.‡ We were surprised to find that completely different tetracyclic diacetate **7**[5] was isolated in high yield when diacetate **2b**, quantitatively prepared from **2a**, was treated with $AgClO_4$ in THF at rt. Eventually, **2b** was converted into **3b** in 91% yield by treatment with $AgClO_4$ (1.2 eq.) in the presence of pyridine (1.5 eq.) at rt.

The next step was focused on the regio- and face-selective hydrogenation of triene **3a** possessing three different types of double bonds. The PtO_2-catalyzed hydrogenation in MeOH afforded a 7:3 mixture of 11,12-dihydro derivatives, revealing the two remaining double bonds at 7(8) and 15(17) positions are inert under the employed conditions. The separation of the reduction products was unsuccessful at this stage since it forms prism-shaped mixed crystals, mp 92–94 °C and HPLC of the mixture showed the single peak under several conditions. As regards the reasonable conformation of the macro ring of the triene **3**, two gross structures are possible as shown in Fig. 2. The plane of the 11(12) double bond is perpendicular to the cyclohexane ring in one conformation (*perpendicular* conformation: PC) and horizontal in the other conformation (*horizontal* conformation: HC). The hydrogenation may occur from the opposite faces depending on the conformation, that is, the perpendicular conformation gives the 12β-methyl product by selective H_2 addition from the α-side. The horizontal conformation leads to the 12α-Me isomer by the preferential β-face attack, the opposite α-face being partly masked by the 15(17) double bond. The existence of **3a** as the horizontal conformation was deduced by the fact that **3a** is easily convertible to the cyclized products **5** and **7** under protonic conditions as mentioned in Scheme 1. The detailed NOESY experiments in the NMR spectrum of **3a** supported this deduction. Expecting the conformational change of the methylenecyclohexane moiety of **3a**, the five-membered carbonate ring was introduced at the 2 and 3 positions with carbonyldiimidazole to give **3c**. The 0.2 ppm up-field shift of 11-H of **3c** was observed, indicating the change of the chair-type cyclohexane ring of **3a** to the twisted form, in which the 15(17)

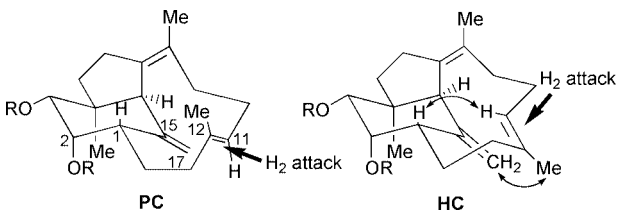


Fig. 2 Possible conformations of the triene **3**.

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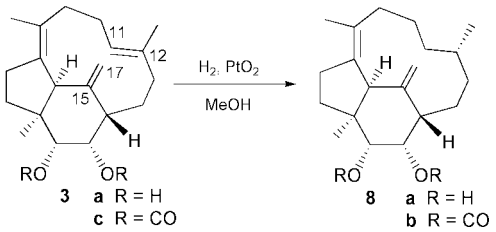


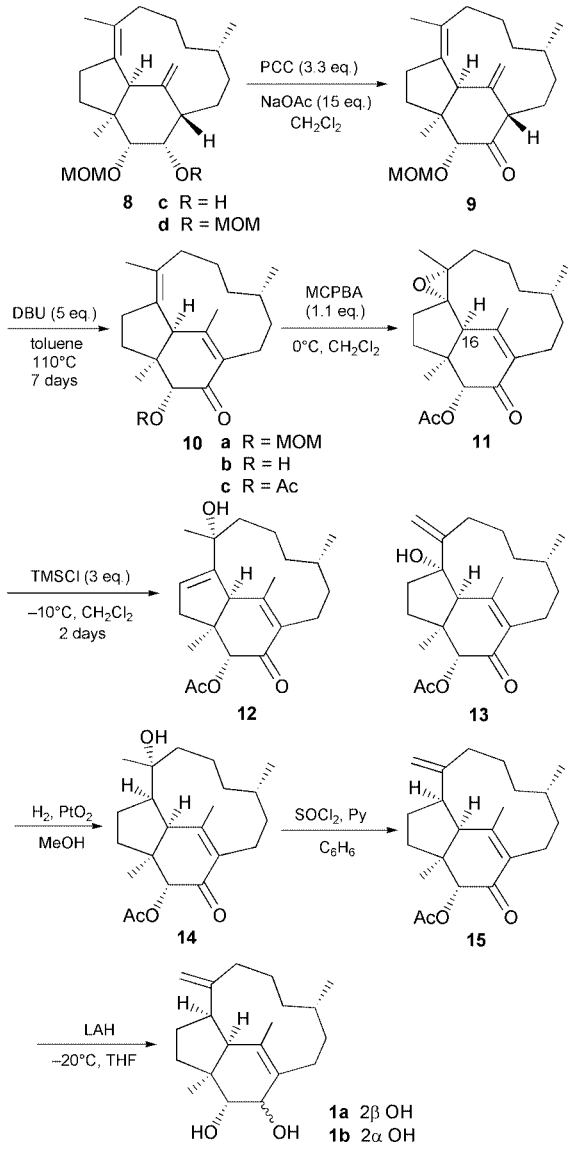
Scheme 2 Hydrogenation of triene **3**.

double bond locates more closely to the plane of the 11(12) double bond. The hydrogenation of **3c** in CH_2Cl_2 provided a 6:1 mixture of C_{12}-stereoisomers (Scheme 2). It was luckily found that both stereoisomers of the carbonate **8b** were easily separable by flash chromatography, affording the corresponding reduction products suitable for X-ray crystallographic analyses. The X-ray analyses demonstrated unequivocally the major product possessed 12α-Me configuration.

After removal of the carbonyl group of **8b**, the diol **8a** was treated with MOMCl (2 eq.) and diisopropylethylamine (4 eq.) in CH_2Cl_2 for 3 h at rt to furnish the 3-MOM ether **8c** in 74% yield accompanied with the 2-MOM ether (13%) and 2,3-diMOM ether **8d** (7%). The unnecessary minor products were converted to **8c** by hydrolysis (2 M HCl in MeOH), followed by etherification with MOMCl under the same conditions. The PCC oxidation of **8c** proceeded smoothly to give the corresponding ketone **9** in 91% yield (Scheme 3). For the isomerization of **9** to the conjugated enone **10**, we had to attempt several basic conditions[6] before finding the successful conditions of DBU in refluxing toluene for a week (89% yield). The convex face selective oxidation of **10c**, obtained from **10a** by the usual procedures, took place exclusively with MCPBA, affording the epoxide **11** in quantified yield.

The ring-opening conditions of the epoxide **11** were quite restricted since the 16-proton is labile under acidic and basic conditions. Of the reagents we examined TMSCl at −10 °C was the only choice and it gave a 1:1 mixture of **12** and its isomer **13** in 30% respective yields.[7] The hydrogenation of **12** afforded, as expected, a single product **14** (85%), the stereochemistry of the 7-position being assigned based on the convex selectivity as in the case of epoxidation of **10c**. The dehydration of the *tert*-alcohol **14** furnished a *ca.* 5:3:1 mixture of **10c**, **15** and trisubstituted isomer in total 83% yield. After separation with $AgNO_3$–SiO_2 column chromatography, **15** was reduced with LAH, giving an easily separable 1:1 mixture of 2,3-dihydroxytrinervitanes, **1a** and **1b**. The chemical shifts and coupling constants in the proton NMR of the synthetic materials were in complete accord with the reported values[1b] within experimental deviation due to the applied instruments.

Thus, we have accomplished the total synthesis of 2,3-dihydroxytrinervitanes in *dl*-form. Our recent study[8] on the enantiometrically pure synthetic intermediate may enable us to perform the enantiospecific synthesis of **1a** and **1b**.



Scheme 3 Synthesis of (±)-trinervitanes **1a** and **1b**.

Notes and references

† This is Part 61 of Cyclization of Polyenes; for part 60, see ref. 3.
‡ The IR, ^1H and ^{13}C NMR and mass spectra were in agreement with all the new compounds.

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5 Diol prepared from deprotection of **7**; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, Me(20)), 1.18 (s, Me(18)), 1.57 (s, Me(19)), 3.19 (s, H-C(16)), 3.49 (br s, H-C(3)), 3.84 (br s, H-C(2)), 5.56 (s, H-C(17)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6 (q, C(18)), 22.7 (q, C(19)), 23.4 (t, C(14)), 24.2 (t, C(10)), 28.7 (q, C(20)), 30.0 (t, C(6)), 32.0 (t, C(13)), 34.0 (t, C(9)), 37.8 (t, C(5)), 39.3 (s, C(12)), 39.3 (d, C(1)), 45.6 (t, C(11), 46.5 (s, C(4)), 59.2 (d, C(16)), 72.7 (d, C(3)), 74.7 (d, C(2)), 132.2 (s, C(8)), 136.2 (s, C(7)), 137.1 (s, C(15)) and 139.6 (d, C(17)).

6 Isomerization was unsuccessful under the following conditions; i) Bu^{t}OK, THF, reflux, ii) NaH, THF, iii) NaH, DMSO, reflux, iv) LDA.

7 Hydroboration–oxidation of **10** took place at the undesired position, affording the 8(19)-dihydro-7-hydroxy derivative of **13**. All the trials of dehydration of the 7,8-diol of **10**, obtained by OsO_4 oxidation, gave only hopeless results.

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