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# Progress towards the total synthesis of 2,3-dihydroxytrinervitanes

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ABSTRACT

Intramolecular Diels–Alder approach to construct the fused AB ring of trinervitane has been demonstrated efficiently. The key intermediate for the Diels–Alder cyclization has been achieved following highly stereoselective Julia–Kocienski olefination, Sharpless epoxidation and Evan's asymmetric alkylation as the key reactions.



Diterpenoid compounds play a key role in chemical communications and defense of nasute termite soldiers by squirting at potential predators. 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] Recently, trinervitanes **1a** and **1b** have entered into phase I clinical trials though they are ten times less potent than any clinically practiced antibiotic and the potency can be improved by structural optimization.[2] To the best of our knowledge there are only a few reports of its biogenetic-type synthesis but no chemical synthesis has been known so far.[3] Because of its unique structural features and interesting biological activity, an effort towards the total synthesis of 2,3-dihydroxytrinervitanes (**1a**) was considered attractive.

The key compound **3** was prepared following standard protocol starting from geraniol **2** (Scheme 1).[4] Chlorination of hydroxyl group of **3** with triphenylphosphine (TPP) and catalytic amount of $NaHCO_3$ in $CCl_4$ at reflux temperature afforded the epoxychloro compound **4** in 90% yield.

Double elimination reaction of epoxy-chloride **4** to secondary propargylic alcohol **5** was achieved with Li/liq.$NH_3$ and catalytic amount of ferric nitrate at −78 °C.[5] The hydroxyl group was protected as its *tert*-butyl diphenylsilyl (TBDPS) ether, and formylation with formaldehyde in the presence of *n*-butyllithium (*n*-BuLi) followed by its methoxyethoxymethyl (MEM) ether formation with MEM-Cl and *N,N*-diisopropylethylamine (DIPEA) in dichloromethane afforded **6** in 72% yield over three steps.[6] Selective deprotection of the TBDPS group on primary hydroxyl functionality was achieved with (±)-10-camphorsulfonic acid (CSA) (0.1 equiv) in MeOH and $CH_2Cl_2$ (1:1).[7] The free hydroxyl group was then

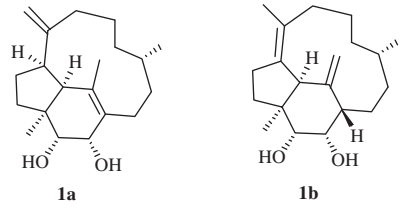
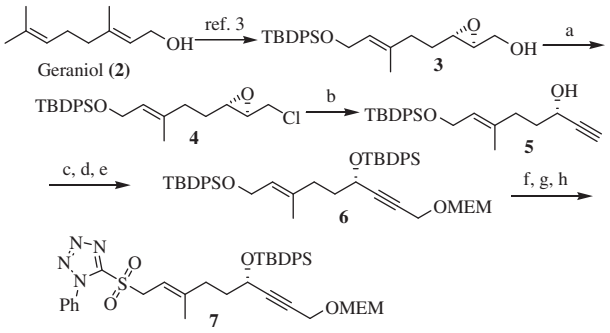



**Figure 1.** Typical trinervitanes from termites.




**Scheme 1.** Reagents and conditions: (a) TPP, $NaHCO_3$, $CCl_4$, 90%; (b) $LiNH_2$, cat. $Fe(NO_3)_3$ −78 °C, 95%; (c) TBDPS-Cl, imidazole, $CH_2Cl_2$, 90%; (d) *n*-BuLi, THF, −78 °C to rt, $CH_2O$, 0 °C to rt, 89%; (e) MEM-Cl, DIPEA, $CH_2Cl_2$, 0 °C to rt, 90%; (f) CSA, MeOH/$CH_2Cl_2$ (1:1), 12 h, 90%; (g) DEAD, TPP, tetrazole, THF, 80%; (h) $(NH_4)_2MoO_4$, $H_2O_2$, EtOH, 0 °C to rt 70%.

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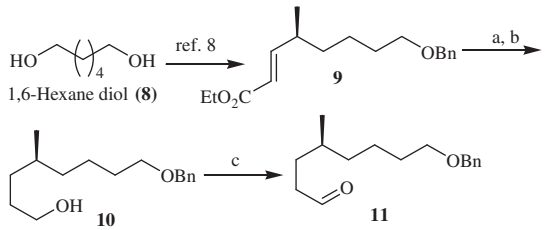
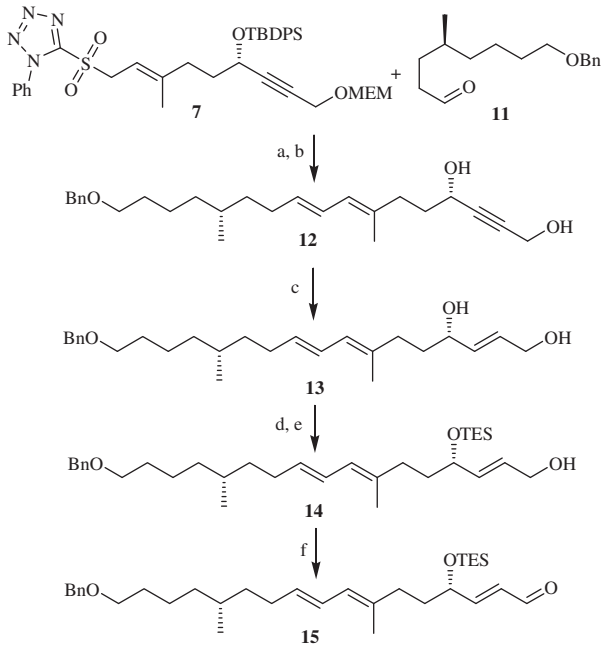



**Scheme 2.** Reagents and conditions: (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH; (b) $LiAlH_4$, THF, 0 °C, 80% (two steps); (c) IBX, DMSO, THF, 91%.

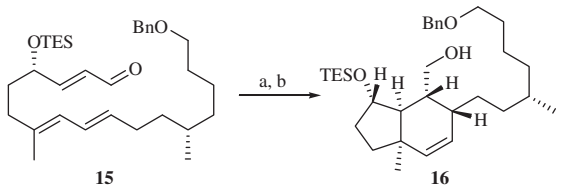



**Scheme 3.** Reagents and conditions: (a) KHMDS, THF, −78 °C; (b) 2 N HCl, MeOH, 55% (two steps); (c) Red-Al, ether, 89%; (d) TES-Cl, $Et_3N$; (e) TBAF, 0 °C, 5 min, 68% (two steps); (f) IBX, DMSO, THF, 1 equiv $NaHCO_3$, 82%.

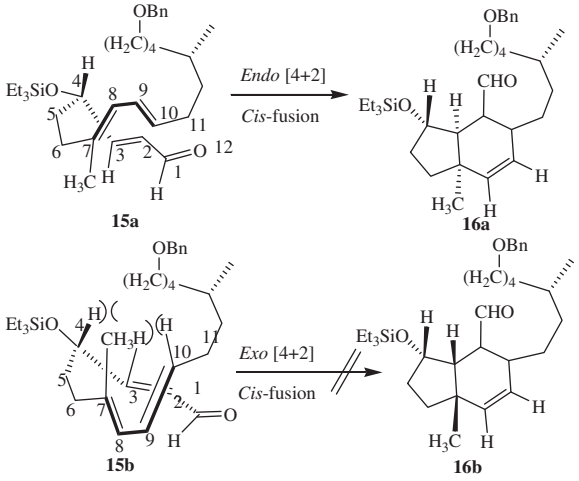
converted to sulfide following Mitsunobu protocol with 1-phenyl-1*H*-tetrazole-5-thiol, TPP and diethyl azodicarboxylate (DEAD) in THF at room temperature followed by oxidation with ammonium molybdate and $H_2O_2$ in ethanol to provide sulfone **7** in 53% yield over three steps.[8,9]

Compound **9** was obtained from 1,6-hexane diol **8** following a reported protocol (Scheme 2).[10] Compound **10** was obtained in a two-step sequence from **9** by treatment with $NaBH_4$ and $NiCl_2{\cdot}6H_2O$ in methanol for 10 min. at 0 °C followed by work-up[11] and reduction of saturated ester with lithium aluminium hydride ($LiAlH_4$) in THF. The alcohol **10** was oxidized with 2-iodoxybenzoic acid (IBX) in DMSO and THF at ambient temperature to afford the aldehyde **11**.[12]

Having fragments **7** and **11** in hand, Julia–Kocienski olefination was next performed to obtain compound **12** as the only product. As retention time for both the coupled product and aldehyde was same, both MEM and TBDPS groups were deprotected to obtain the pure product **12** in 55% yield over two steps (Scheme 3).[13] The allyl alcohol **13** was obtained by treatment of **12** with Red-Al in diethyl ether.[14,15] Both the hydroxyl groups were protected as triethylsilyl (TES) ether with TES-Cl and $Et_3N$ in $CH_2Cl_2$ followed by selective deprotection to afford **14**. The primary hydroxyl group of **14** was oxidized with IBX to obtain the aldehyde **15**,[16,17] which is the key intermediate for the intramolecular Diels–Alder cyclization.




**Scheme 4.** Reagents and conditions: (a) 0.1 equiv BHT, toluene, 180 °C, sealed tube, 20 h; (b) $NaBH_4$, MeOH, 0 °C, 70% (two steps).




**Scheme 5.** Transition states of cyloaddition reaction.

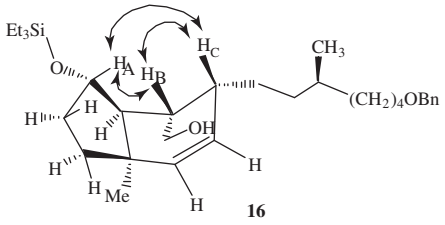



**Figure 2.** NOESY interaction between the protons $H_A$, $H_B$ and $H_C$.

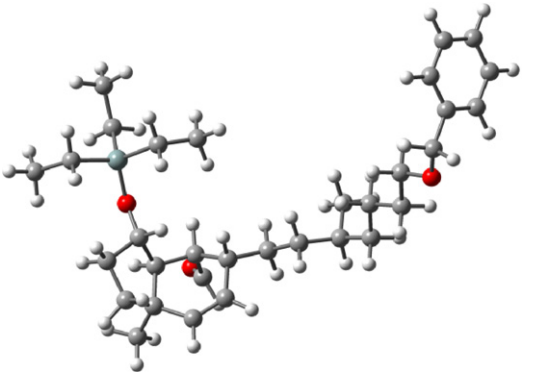
**Table 1**
Relative energies (kJ/mol) at AM1, PM3, MNDO and B3LYP/6-31G(d) levels of theory

| Structure | AM1 | PM3 | MNDO | B3LY/6-31G(d) |
|---|---|---|---|---|
| **16a**(α,α) | 0.0 | 0.0 | 0.0 | 0.0 |
| **16b**(β,β) | 18.3 | 22.8 | 15.0 | 5.14 |

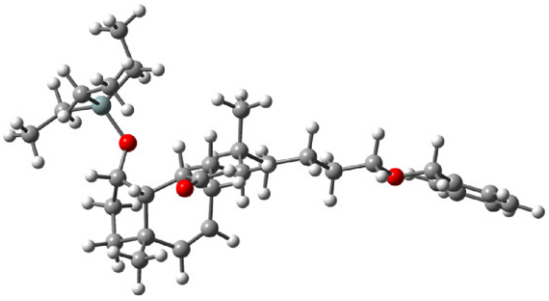
Compound **15** underwent intramolecular Diels–Alder cyclization upon heating with 10 mol % of butylated hydroxytoluene (BHT) at 180 °C with toluene in a sealed tube. Reduction of the crude bicyclic aldehyde with $NaBH_4$ in MeOH afforded the fused ring system **16** of trinervitanes as the sole product (Scheme 4).[18,19] The proposed transition states indicated that half chair conformation **15a** is more favourable than **15b** as the latter intermediate exerts more steric hindrance between H3, H4, $CH_3$ and H10 (Scheme 5).

The stereochemistry of the fused ring system **16** was supported by NOESY experiment which showed strong interaction between $H_A$, $H_B$ and $H_C$ protons (Fig. 2).

Quantum mechanical energy minimized studies suggest that molecule **16b** with *exo*-fusion shows a substantial preference for



**16a** (α,α)-OSiEt$_3$ down 0.0 kJ/mol



**16b** (β,β)-OSiEt$_3$ down 5.14 kJ/mol

**Figure 3.**

*endo*-cyclization compared to *exo*-cyclization (Table 1). The optimized minimum structure obtained at B3LYP/6-31G(d) level of theory is depicted in Figure 3.

In conclusion, we have demonstrated a stereoselective synthesis of the fused bicyclic ring framework of the diterpene, 2,3-dihydroxytrinervitanes, following intramolecular Diels–Alder approach. The key intermediate for Diels–Alder cyclization has been executed in a highly stereoselective manner utilizing Julia–Kocienski olefination for the construction of the conjugated *E*-alkene, Sharpless asymmetric epoxidation and Evan's asymmetric alkylation. This simple and practical approach can be applied for the total synthesis of trinervitanes and other related bioactive natural products.

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19. *Spectral and analytical data of* **16**. IR (Neat): $\nu_{max}$ 3448, 2924, 2855, 1633, 1459, 1376, 1106 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.30–7.22 (m, 5H), 5.50 (d, 1H, *J* = 2.2 Hz), 5.47 (dd, 1H, *J* = 2.2, 3.0 Hz), 4.49 (s, 2H), 3.98–3.88 (m, 1H), 3.70–3.55 (m, 2H), 3.49 (t, 2H, *J* = 6.7 Hz), 2.33–2.02 (m, 1H), 2.00–1.91 (m, 1H), 1.92–1.80 (m, 2H), 1.1.76–1.52 (m, 7H), 1.50–1.22 (m, 8H), 1.05 (s, 3H), 1.02–0.82 (m, 12H), 0.67–0.55 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 138.9, 135.8, 135.7, 129.7, 128.0, 127.5, 127.4, 71.8, 67.4, 63.8, 59.5, 54.2, 43.2, 40.9, 36.5, 34.8, 30.9, 30.8, 29.85, 29.75, 27.1, 24.7, 23.0, 19.5, 16.3, 7.8, 4.7; ESIMS: *m*/*z* 515 $[M+1]^+$, 514 $[M]^+$, 513 $[M-1]^+$; HRMS calcd for $C_{32}H_{54}NaO_3Si$: 537.8542; found: 537.8546.