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SYNTHETIC STUDIES ON DITERPENES FROM A TERMITE SOLDIER: TOTAL SYNTHESIS OF (±)-BIFLORA-4,10(19),15-TRIENE

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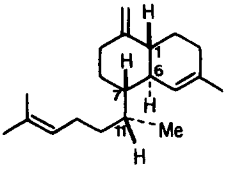
Summary: The total synthesis of (±)-biflora-4,10(19),15-triene is detailed which features a Diels-Alder strategy for elaboration of the four contiguous stereocenters at C(1), C(6), C(7), and C(11).

Biflora-4,10(19),15-triene(1),[1] a new example of the rare biflorane skeleton,[2] is a diterpene isolated from the oily defensive secretions released from the frontal glands of termite soldiers (Cubitermes umbratus Williams) found in Kwale, Kenya. In addition to 1, three additional diterpenes [cubitene(2),[3] cembrene A(3),[4] and (3Z)-cembrene A(4)[4]] have been found in the same secretions which raises several intriguing biogenetic questions. We detail below the first total synthesis of (±)-biflora-4,10(19),15-triene which features a Diels-Alder strategy for elaboration of the four contiguous stereocenters at C(1), C(6), C(7), and C(11).



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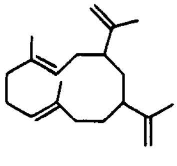

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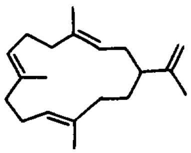

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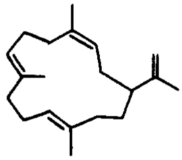

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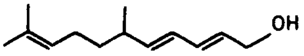
Diels-Alder reaction of trienol 5[5] and maleic anhydride in benzene (reflux, 10 h) gave a 1:1 mixture of endo adducts 6 (R=H) in 65% yield which were inseparable by chromatography on silica gel. Treatment of 6 (R=H) with an ethereal diazomethane solution and subsequent exposure of 6 (R=Me) to diazabicyclo[5.4.0]undecene in refluxing benzene gave rise selectively upon crystallization to



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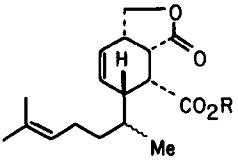
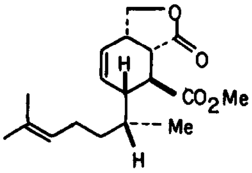
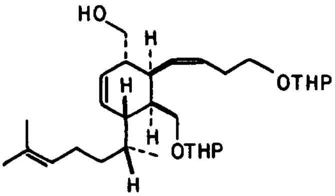




6 7

ester 7,[6] mp 70.5°-71.5°C, in 50% yield. The structure of 7 was unambiguously established by single-crystal x-ray analysis.[7] The carboxylic acid derived (KOH, ethanol, 91%) from ester 7 was transformed in 86% yield into the corresponding primary alcohol 8 by sequential treatment with (1) ethyl chloroformate (1 equiv)-triethylamine (1 equiv) in ether at 0°C to form the mixed anhydride and (2) ethanolic sodium borohydride at -23°C.

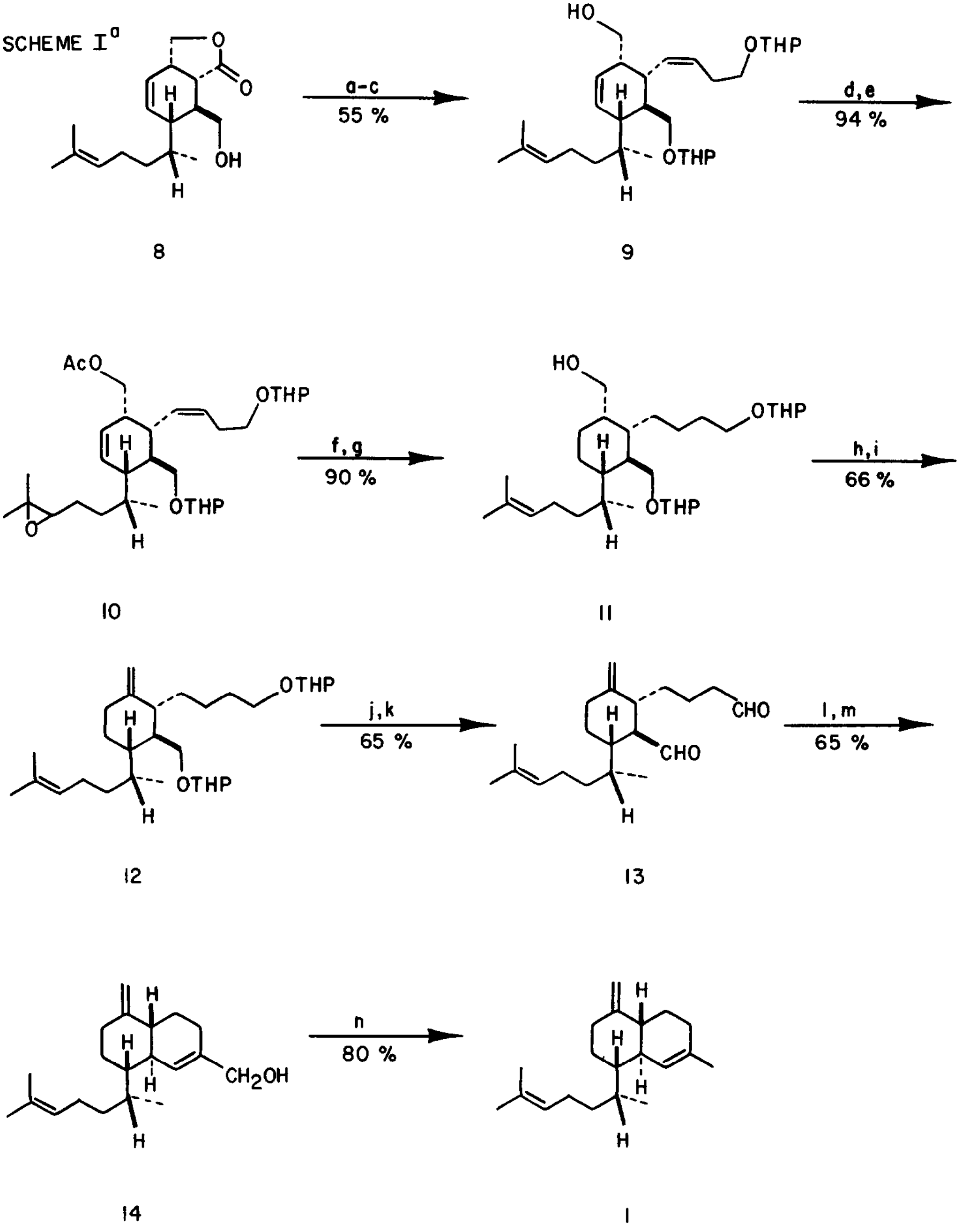
Having assembled the four contiguous stereocenters located at C(1), C(6), C(7), and C(11) attention was focussed on construction of the bicyclic nucleus. Toward this end, hydroxy lactone 8 was protected (Scheme 1) as its tetrahydropyranyl ether and the lactone was reduced with diisobutylaluminium hydride. Condensation at ambient temperature of the resultant lactol with the ylid derived from 3-(tetrahydropyranyloxy)propyltriphenylphosphonium iodide[8] (10 equiv) in DME-HMPA (2:1) gave rise to 9 as the sole product in 55% overall yield. Efforts to improve upon the yield of 9 led to somewhat surprising results. For example use of 2.5 equiv of phosphonium salt in DME-HMPA (95:5) [-23°C(30 min)$\longrightarrow$R.T.(20 h)] gave rise exclusively to the isomerized olefin 15 in 53% yield.



15

Attempts to selectively reduce the two disubstituted double bonds in compound 9 in the presence of the trisubstituted olefin proved unsuccessful. The more reactive nature of the isopropylidene double bond suggested that protection, prior to catalytic hydrogenation, might prove viable. Efforts to epoxidize the trisubstituted olefin proved nonselective. However, prior conversion of the hydroxymethyl group in 9 into its corresponding acetate followed by epoxidation

SCHEME I[a]



[a] a, DHP (1.2 equiv), PPTS, CH_2Cl_2, 12 h; b, i-Bu_2AlH (1.0 equiv), $PhCH_3$, −78 °C, 1 h; c, $Ph_3\overset{\oplus}{P}CH_2CH_2CH_2OTHP\ Cl^{\ominus}$ (10 equiv), KHMDS, (10 equiv, 1 M in $PhCH_3$), DME–HMPA (2:1), 3 h; d, Ac_2O, Et_3N, DMAP, CH_2Cl_2, 1 h; e, MCPBA (1.0 equiv), CH_2Cl_2, 0 °C; f, 5% Rh/Al_2O_3, MeOH, H_2 (50 psi), 30 min; g, KSeCN (25 equiv), MeOH–H_2O (9:1), 65 °C, 4 d; h, $\underline{o}$-$O_2NC_6H_4SeCN$ (2.0 eqiuv), Bu_3P (2.0 equiv), THF, 2 h; i, 30% H_2O_2, THF, 1 h; j, EtOH, PPTS, 55 °C, 10 h; k, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h; i-Pr_2NEt, −78 °C (30 min) ⟶ R.T. (30 min); l, $PhCH_2\overset{\oplus}{N}Et_3\ Cl^{\ominus}$ (1.0 equiv), 10% KOH, CH_2Cl_2; m, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h; n, Py·SO_3 (1.5 equiv), THF, 0 °C, 3.5 h; $LiAlH_4$, THF, 0 °C (30 min) ⟶ R.T. (5 h).

afforded 10 in 94% overall yield. Reduction of the disubstituted double bonds and subsequent deoxygenation of the epoxide unit employing potassium selenocyanate[9] in aqueous methanol gave rise to 11 in excellent yield. During the course of the epoxide to olefin conversion the primary acetate was cleaved. Introduction of the C(10) exocyclic olefin was achieved employing o-nitrophenylselenocyanate-tributylphosphine,[10] followed by oxidation. The transformation of 12 into dialdehyde 13 proceeded smoothly with PPTS[11] as the catalyst for the cleavage of the tetrahydropyranyl ethers and Swern's[12] procedure for the oxidation of alcohols to aldehydes. Dialdehyde 13, dissolved in methylene chloride (0.17 M), was treated with 10% potassium hydroxide solution (11.7 equiv) and benzyltriethyl ammonium chloride (1.0 equiv) at 40°C for 15 h. Work up provided an α,β-unsaturated aldehyde which was immediately reduced[13] to allylic alcohol 14. Deoxygenation[14] of 14 provided in 80% yield (±)-biflora-4,10(19),15-triene (1) whose ^1H NMR and MS spectra were identical with spectra provided by Professor Meinwald.

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5. Available in two steps [1. $(EtO)_2P(O)\overset{\ominus}{C}HCH=CHCO_2Et$, THF:HMPA(2:1), −65°C(2h) → R.T.(8h); 2. $LiAlH_4$, Et_2O, R.T., 3h] in 80% overall yield from 2,6-dimethyl-5-heptenal.
6. All new compounds have been fully characterized spectrally and have elemental composition determined by high-resolution mass spectroscopy and/or combustion analysis.
7. Compound 7 crystallizes in space group $P2_1/c$ with cell dimensions (−160°C) of a=16.147(7)Å, b=6.218(2)Å, and c=16.630(8)Å; beta=93.62(3)Å; V=1666.46$Å^3$, ρ calcd=1.221 g cm^{-3}(Z=4). A total of 3678 reflections were measured of which 1747 were determined to be observable, $F_o > 3.00\ \sigma\ (F_o)$. All atoms, including hydrogens, were located and refined to final residuals of R(F)=0.0393 and R_w(F)=0.0411.
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