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Total Synthesis of (±)-Tricyclohexaprenol, A Possible Forerunner of Sterols in the Evolution of Biomembranes

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Summary: (±)-Tricyclohexaprenol (**1**) has been synthesized by a route involving concurrent generation of the three rings by Hg(II)-promoted conversion of **3** to **4**, and subsequent attachment of a C_{10}, *E,E*-diene unit using the allylic silane **10**, prepared from geraniol.

Tricyclohexaprenol (**1**) has been postulated by G. Ourisson to be a possible component of biomembranes in early evolution.[1,2] This interesting triterpenoid, having the unusual regular arrangement of prenyl units, has never been synthesized or isolated from present day microbial sources, although it is thought that very primitive microorganisms which depend on this evolutionary forerunner of sterols may still exist on earth. The availability of synthetic reference samples would greatly facilitate the search for such microorganisms and the testing of this interesting speculation. This note reports the first total synthesis of (±)-**1** by a simple, stereocontrolled route.

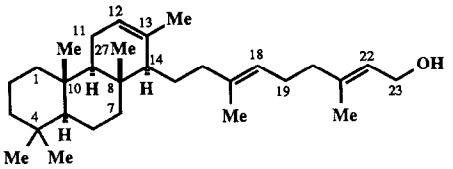
The tricyclic nucleus of **1** was established by a cationic cyclization process which generated all three rings in a single step. A similar construction has previously been employed in this laboratory for the synthesis of limonoids.[3,4] Methyl 4-(*E,E*-farnesyl)-3-oxobutyrate (**2**)[3] was transformed into the enol silyl ether **3** in 99% yield by reaction with *t*-butyldimethylsilyl chloride (TBMSCl) (1.4 equiv) and imidazole (2.8 equiv) in dimethylformamide solution (1.5 M in **2**) at 25°C for 12 h.[5] Treatment of **3** with 1.15 equiv of mercuric trifluoroacetate in dry nitromethane (0.23 M) at 0°C for 1 h, subsequent stirring with saturated aqueous sodium chloride, and column chromatography on silica gel gave a mixture of tricyclic (**4**) and bicyclic (**5**) chloromercurials which were more easily separated at the next stage of the synthesis.[6] The mixture was subjected to ketalization using excess ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux for 12 h and subsequent demercuration using 1 mol equiv of sodium borohydride in 3 N sodium hydroxide-tetrahydrofuran at 0°C for 1 h. Chromatography of the resulting mixture on silica gel, using 9 : 1 hexane/ethyl acetate for elution, afforded tricyclic ketal ester **6** (33% overall yield from **3**) and bicyclic ketal ester **7** (30% overall yield from **3**).[7] Reduction of tricyclic ketal ester **6** with 3 equiv of diisobutylaluminum hydride in toluene

at 0°C for 5 min and 23°C for 4 h gave the ketal alcohol **8** in 97% yield. This alcohol was transformed into α,β-enone **9** (89% overall) by a three-step sequence, (1) deketalization by exposure to 0.015 M oxalic acid in 100 : 1 acetone-water at 23°C for 12 h (99%); (2) mesylate formation using excess methanesulfonyl chloride and triethylamine in methylene chloride at 0°C for 0.5 h and 23°C for 10 h; and (3) elimination by reaction with 3 equiv of 1,8-diazabicyclo [5.4.0]undec-7-ene in benzene at 23°C for 2 h (90%).

Attachment of the diprenyl unit to α,β-enone **9** was accomplished successfully using the allylic silane derivative **10** (TBPS = *t*-butyldiphenylsilyl) and titanium tetrachloride as Lewis acid promoter. Enone **9** was treated with 1.1 equiv of titanium tetrachloride in methylene chloride (0.1 M) at -78°C for 5 min, the resulting solution was brought to 8°C, and then a solution of **10** (1.2 equiv) in methylene chloride was added and the coupling was allowed to proceed at 8°C for 0.5 h to afford the desired product **11**[8] in 54% yield (79% yield based on recovered enone **9**). Reaction of **11** with 3 equiv of methyllithium in ether (0°C for 0.5 h and 23°C for 2 h) furnished a tertiary alcohol (93% yield) which upon dehydration with 4 equiv of thionyl chloride and 16 equiv of pyridine in methylene chloride (0.1 M in tertiary alcohol) at -20°C for 1 h produced the *t*-butyldiphenylsilyl ether of (±)-tricyclohexaprenol in 82% yield. Desilylation of this compound with tetrabutylammonium fluoride hydrate in tetrahydrofuran (Aldrich Chem. Co., 4 equiv) at 23°C for 4 h proceeded smoothly to form (±)-tricyclohexaprenol (**1**)[9] in 92% yield.

The allylic silane **10** was synthesized starting from geraniol which was converted to the TBPS ether **12** (99% yield) by reaction with 1.1 equiv of TBPS chloride and 2 equiv of imidazole in dimethylformamide (0.5 M in geraniol) at 23°C for 12 h. Oxidation of **12** with 1 equiv of selenium dioxide and 2 equiv of pyridine in 95% ethanol (1 M in **12**) at reflux for 1 h followed by reduction of the resulting product with sodium borohydride (0.5 mol. equiv) in ethanol at 0°C for 1 h afforded, after chromatography on silica gel, the *E*-allylic alcohol **13** in 47% yield. Reaction of **13** with 1.4 equiv of triphenylphosphine in carbon tetrachloride (1 M in **13**) at reflux for 2 h produced the *E*-allylic chloride **14** in 68% yield. Conversion of **14** to the allylic transposition product **10** was effected by the excellent method of J. G. Smith *et al.*[10] Reaction of **14** with trimethylsilyl copper in excess (from 5 equiv of hexamethyldisilane and 5 equiv of ethereal methyllithium in hexamethylphosphoramide at 0°C for 5 min followed by 5 equiv of cuprous iodide dissolved in dimethyl sulfide) at -60°C for 1 h afforded a single allylic silane, **10**, in 81% yield.[11]

With the completion of an effective synthesis of (±)-tricyclohexaprenol the search for this substance in nature can proceed. Efficient screening of microbial samples using GC or GC-MS techniques with appropriate derivatives of **1** as a reference should now be possible.[12]



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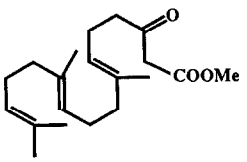

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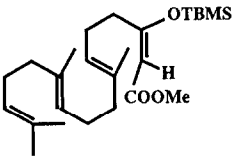

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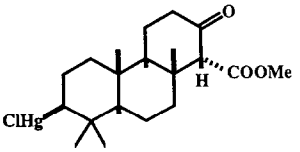

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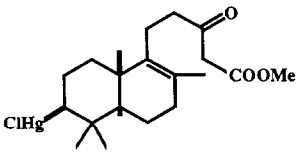

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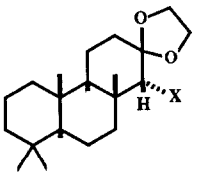
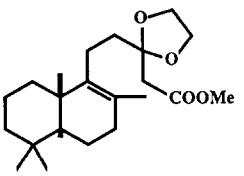


6 X=COOMe
8 X=CH_2OH



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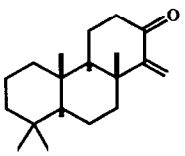

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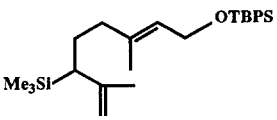
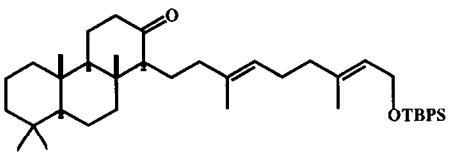


10



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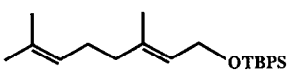
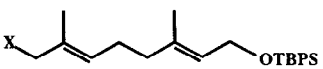


12



13 X=OH
14 X=Cl

References and Notes

1. (a) G. Ourisson, *Nachr. Chem. Tech. Lab.*, **34**, 8 (1986); (b) D. Heissler, R. Ocampo, P. Albrecht, J. Riehl, and G. Ourisson, *J. Chem. Soc. Chem. Comm.*, 496 (1984).
2. See also (a) G. Ourisson, P. Albrecht, and M. Rohmer, *Trends Biochem. Sci.*, **7**, 236 (1982); (b) K. Bloch, *Crit. Rev. Biochem.*, **14**, 47 (1982).
3. E. J. Corey, J. G. Reid, A. G. Myers, and R. W. Hahl, *J. Am. Chem. Soc.*, **109**, 918 (1987).
4. For related syntheses of polycyclic systems depending on cationic bicyclization reactions see (a) E. J. Corey, M. A. Tius and J. Das, *J. Am. Chem. Soc.*, **102**, 1742 (1980) (aphidicolin); (b) E. J. Corey, M. A. Tius and J. Das, *J. Am. Chem. Soc.*, **102**, 7612 (1980) (stemodin); and (c) E. J. Corey and J. Das, *J. Am. Chem. Soc.*, **104**, 5551 (1982) (Otsuka K-76).
5. This and other reactions involving possibly air-sensitive reactants or products were conducted in an atmosphere of dry Ar. Satisfactory PMR, infrared and mass spectral data were obtained for each purified product using chromatographically homogeneous samples.
6. Purified samples of **4** and **5** could be obtained for characterization on a small scale by recrystallization from methylene chloride-ether and careful chromatography.
7. Spectral data for **6** and **7** are as follows (numbering as in **1**). For **6**: ^{1}H NMR (500MHz, $CDCl_3$): δ 3.98 - 3.63 (4H, m OCH_2CH_2O), 3.67 (3H, s, OCH_3), 2.43 (H_{14eq}, d, $J_{12eq,14eq}$ = 1.9Hz), 2.23 (H_{12ax}, dt, $J_{12ax,12eq}$ = 13.6Hz, $J_{11,12}$ = 4.6Hz), 1.77 (H_{9ax}, dd, $J_{9ax,11ax}$ = 12.5Hz, $J_{9ax,11q}$ = 2.3Hz), 1.70 - 0.72 (14H, m), 1.14 (3H, s), 0.823 (3H, s), 0.820 (3H, s), 0.79 (3H, s); ^{13}C NMR (75MHz, $CDCl_3$): 172.6, 109.1, 64.6, 64.0, 63.1, 56.5, 51.1, 50.2, 42.3, 40.2, 38.9, 38.3, 37.6, 33.6, 33.4, 23.1, 21.8, 18.9, 18.8, 18.5, 16.7 ppm; IR ($CHCl_3$): 1735 cm^{-1}; EIMS: 364 (M^+); mp 205-6°C.

   For **7**: ^{1}H NMR (500MHz, $CDCl_3$): δ 4.02 - 3.95 (4H, m, OCH_2CH_2O), 3.69 (3H, s, OCH_3), 2.67 (2H, s, $CH_2CO_2CH_3$), 2.16 - 1.82 (4H, m), 1.56 (3H, s), 1.70 - 0.82 (11H, m), 0.93 (3H, s), 0.87 (3H, s), 0.82 (3H, s); ^{13}C NMR (75MHz, $CDCl_3$): 170.0, 139.8, 126.3, 109.5, 65.3, 52.1, 51.8, 42.5, 42.4, 42.0, 39.3, 38.1, 37.1, 36.4, 33.8, 33.5, 33.3, 21.9, 21.8, 20.2, 19.4, 19.2 ppm; IR (neat): 1742 cm^{-1}; EIMS: 364 (M^+).
8. For **11**: ^{1}H NMR (500MHz, $CDCl_3$): δ 7.69 - 7.68 (4H, m, ArH), 7.46 - 7.35 (6H, m, ArH), 5.38 (H_{22}, t, $J_{22,23}$ = 6.4Hz), 5.03 (H_{18}, t, $J_{18,19}$ = 6.7Hz), 4.22 (2H, d, J = 6.3Hz, CH_2OSiR_3), 2.35 (H_{12eq}, ddd, $J_{12ax,12eq}$ = 12.1Hz, $J_{11eq,12ax}$ = 4.9Hz, $J_{11ax,12eq}$ = 2.3Hz), 2.26 - 2.20 (H_{12ax}, m), 2.10 - 1.95 (7H, m), 1.75 - 0.79 (16H, m), 1.57 (3H, s), 1.43 (3H, s), 1.04 (9H, s), 0.87 (3H, s), 0.83 (3H, s), 0.81 (3H, s), 0.71 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$): 186.6, 137.1, 135.6, 135.3, 134.0, 129.4, 127.5, 124.4, 123.9, 63.3, 61.1, 59.0, 56.4, 43.0, 42.3, 41.9, 40.6, 40.2, 39.5, 38.9, 37.9, 33.3, 33.2, 26.8, 26.3, 23.0, 21.4, 19.5, 19.1, 18.8, 18.5, 16.3, 16.1, 15.8, 15.6 ppm; IR ($CHCl_3$): 1710, 1115, 740, 705 cm^{-1}; CIMS: 667 $(M + H)^+$, 609 (M^+ - TBPS).
9. Spectral data for **1**: ^{1}H NMR (500MHz, $CDCl_3$): δ 5.42 (H_{22}, t, $J_{22,23}$ = 6.5Hz), 5.35 (H_{12}, m), 5.10 (H_{18}, t, $J_{18,19}$ = 6.9Hz), 4.15 (2H, d, J = 6.5Hz, CH_2OH), 2.18 - 1.84 (9H, m), 1.68 (3H, s), 1.61 (3H, s), 1.25 (3H, s), 1.61 - 0.70 (15H, m), 0.86 (3H, s), 0.85 (3H, s), 0.81 (3H, s), 0.72 (3H, s); IR (neat): 3340, 1650 cm^{-1}; EIMS: 426 (M^+), 408 ($M^+ - H_2O$), 393, 272.
10. J. G. Smith, S. E. Drozda, S. P. Petraglia, N. R. Quinn, E. M. Rice, B. S. Taylor, and M. Viswanathan, *J. Org. Chem.*, **49**, 4112 (1984).
11. Found for **10**: ^{1}H NMR (500MHz, $CDCl_3$): δ 7.70 - 7.68 (4H, m, ArH), 7.43 - 7.35 (6H, m, ArH), 5.36 (H_2, t, $J_{1,2}$ = 6.2Hz), 4.71 (H_{8a}, br s), 4.50 (H_{8b}, br s), 4.22 (d, J = 6.2Hz, CH_2OSiR_3), 2.15 - 2.01 (2H, m), 1.88 - 1.82 (2H, m), 1.66 (3H, s), 1.46 - 1.41 (H_6, m), 1.41 (3H, s), 1.04 (9H, s), 0.00 (9H, s); ^{13}C NMR (75MHz, $CDCl_3$): 146.7, 137.4, 135.8, 134.4, 129.7, 127.7, 124.6, 108.7, 61.4, 39.0, 37.5, 27.1, 26.7, 23.8, 19.4, 16.3, -1.7 ppm; IR (neat): 1630, 1115, 740, 705 cm^{-1}.

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