Tetrahedron Letters,Vol.23,No.28,pp 2887-2890,1982 0040-4039/82/282887-04$03.00/0
Printed in Great Britain

TOTAL SYNTHESIS OF (±)-SPIROLAURENONE[1]

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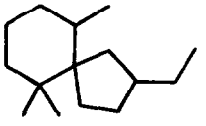
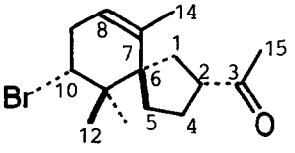
Summary: The total synthesis of (±)-spirolaurenone is described. The synthesis also confirms the assigned absolute configuration to C-2 of the sesquiterpene.

Spirolaurenone[2] (1), an antifungal[3] compound isolated from the red alga Laurencia glandulifera, is the sole naturally occurring sesquiterpene with a unique spirolaurane (2-ethyl-6,6,10-trimethylspiro[4.5]decane) skeleton. The structure and configurations of C-6 and C-10 were determined on the basis of the chemical and spectral data.[2] We report herein the first total synthesis of (±)-spirolaurenone, which is based on our efficient cyclization of geranonitrile and related compounds.[4]



spirolaurane



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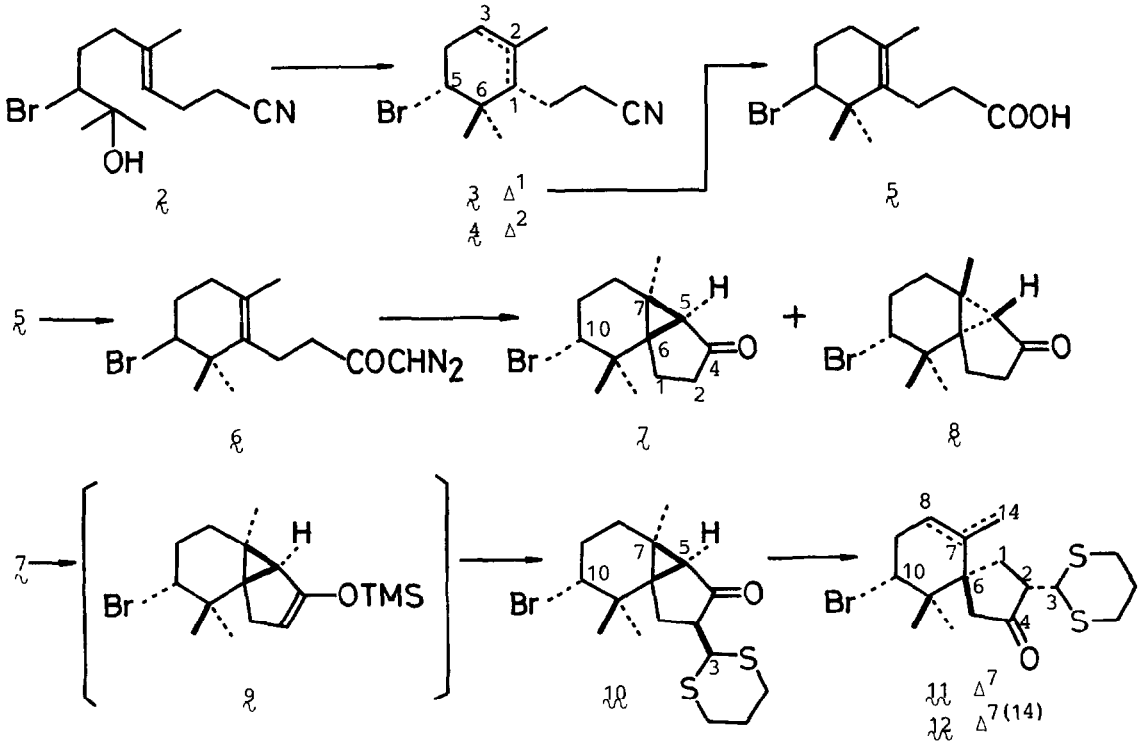
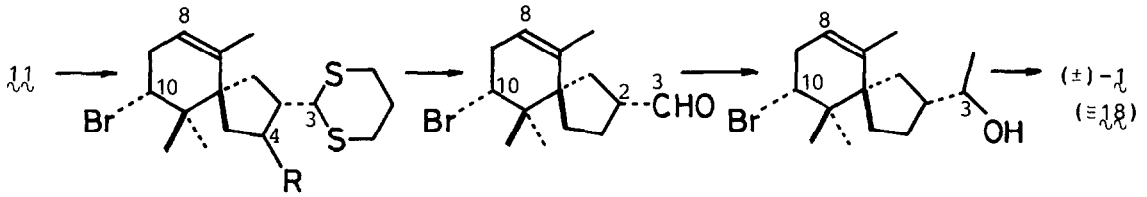
Treatment of bromohydrin[4] (2) of homogeranonitrile,[5] prepared easily from geraniol, with the boron trifluoride-acetic acid complex in acetonitrile under reflux afforded a 4:1 mixture of cyclized products, 2,6,6-trimethyl-5-bromocyclohex-1-enylpropiononitrile[6] (3), oil, and its Δ^2-isomer (4), oil, from which the former (3) was isolated by chromatography over silica gel in 51% yield: 3, MS, m/e 257, 255 (M^+), and 119 (base); IR,[7] 2225, 1390, and 1365 cm^{-1}; NMR (CCl_4),[7] δ 1.15, 1.17, and 1.66 (each 3H, s), and 4.10 (1H, m, 5-H). The nitrile (3) was converted by hydride reduction (DIBAH in toluene, -15 °C, 2.5 h) and subsequent oxidation (PDC in DMF, room temp, 20 h)[8] into the propionic acid (5), mp 132.5-134 °C, in 85% yield: MS, m/e 276, 274 (M^+), and 119 (base); IR, 3650-2300 cm^{-1}; NMR, δ 1.17, 1.19, and 1.63 (each 3H, s), and 4.23 (1H, dd, J = 9 and 4 Hz, 5-H). The acid (5) was further transformed by a reported procedure[9] [(i) $(COCl)_2$ in C_6H_6, room temp, 15 h, and (ii) CH_2N_2 in ether, room temp, 12 h] into the corresponding diazoketone (6), which on reflux with copper in cyclohexane[10] underwent cycloaddition with concurrent elimination of nitrogen. The resulting product was separated by recrystallization followed by preparative

HPLC on μ-Porasil to give two stereoisomeric tricyclic ketones[11] (7), mp 92-94 °C, and (8), mp 76-76.5 °C, in 47 and 11% yields, respectively. The major and minor ketones were assigned the configurations indicated by formulas 7 and 8 on the basis of the NMR spectra: 7, MS, m/e 272, 270 (M^+), and 191 (base); IR, 1710 cm^{-1}; NMR, δ 1.18 (6H, s), 1.20 (3H, s), 1.65 (1H, s, 5-H), and 3.74 (1H, m, 10-H): 8, MS, m/e 272, 270 (M^+), and 191 (base); IR, 1715 cm^{-1}; NMR, δ 1.12, 1.22, and 1.28 (each 3H, s), 1.79 (1H, s, 5-H), and 3.98 (1H, m, 10-H). α-Alkylation of the ketone (7), leading to formation of the acetyl group of 1, was performed *via* its O-silylated enolate by a modification of the Paterson and Price procedure;[12] treatment of 7 with lithium bis(trimethylsilyl)amide [$LiN(SiMe_3)_2$] in tetrahydrofuran (0 °C, 1 h)[13] and then with trimethylsilyl chloride yielded its trimethylsilyl ether (9), which was immediately treated with 1,3-dithienium fluoroborate in dichloromethane (-78 °c, 30 min).[12] Addition of the 1,3-dithienium cation to the double bond of 9 took place with high stereoselectivity from the less-hindered β-side, giving a single 1,3-dithian-2-yl derivative (10), amorphous, of 7 in 94% (99%)[14] yield: MS, m/e 390, 388 (M^+), and 119 (base); IR, 1710 cm^{-1}; NMR, δ 1.19, 1.27, and 1.29 (each 3H, s), 1.75 (1H, s, 5-H), 2.80-3.10 (4H, m), 3.80 (1H, m, 10-H), and 4.61 (1H, d, J = 3 Hz, 3-H). The tricyclic ketone (10), when treated with acid (60% $HClO_4$ in DME, 60 °C, 24 h), underwent cleavage of the cyclopropane ring at the C-5-C-7 bond as expected, yielding an



olefin mixture, from which endo- (11), mp 150-152 °C, and exo-isomers (12), mp 168-169 °C, were isolated by preparative HPLC in 53% (59%) and 12% (13%) yields, respectively: 11, MS, 390, 388 (M^+), and 119 (base); IR, 1735 and 1670 cm^{-1}; NMR, δ 1.05 and 1.20 (each 3H, s), 1.60 (3H, br s), 2.80-3.04 (4H, m), 4.19 (1H, t, J = 9 Hz, 10-H), 4.61 (1H, d, J = 4 Hz, 3-H), and 5.16 (1H, br t, J = 4 Hz, 8-H): 12, MS, m/e 390, 388 (M^+), and 119 (base); IR, 3100, 1745, and 1650 cm^{-1}; NMR, δ 1.08 and 1.19 (each 3H, s), 2.80-3.06 (4H, m), 4.19 (1H, dd, J = 10 and 5 Hz, 10-H), 4.60 (1H, d, J = 3 Hz, 3-H), 4.76 and 5.00 (each 1H, br s, 14-H).

Conversion of the bromo tricyclic ketone (11) into 1 commenced with removal of the carbonyl oxygen atom. Hydride reduction of 11 ($LiAlH_4$ in ether, 0 °C, 40 min) gave the corresponding alcohol (13), mp 171-172.5 °C, probably with the α-configuration as the sole isolable product in 78% yield, which was converted by a standard procedure[15] ($MeSO_2Cl$ and Et_3N in CH_2Cl_2, -15 °C, 20 min) into the mesylate (14) quantitatively. However, hydrogenolysis of the mesyloxyl group in 14, leaving the bromine atom and 1,3-dithianyl group unchanged, proceeded with difficulty. After many attempts, the mesylate was treated with lithium aluminiumhydride in ether under reflux for 16 h to give the hydrogenolysis product (15), oil, in 38% yield: MS, m/e 376, 374 (M^+), and 119 (base); IR, 3050 and 1670 cm^{-1}; NMR, δ 0.94 and 1.12 (each 3H, s), 1.69 (3H, br s), 2.80-3.00 (4H, m), 4.04 (1H, d, J = 8 Hz, 3-H), 4.43 (1H, t, J = 9 Hz, 10-H), and 5.04 (1H, br t, J = 4 Hz, 8-H). The thioacetal (15) was then submitted to hydrolysis by treatment with methyl iodide in refluxing aqueous acetone,[16] giving aldehyde (16), oil, in 67% (95%) yield: MS, m/e 286, 284 (M^+), and 205 (base); IR, 3030, 2710, 1730, and 1670 cm^{-1}; NMR, δ 0.96 and 1.11 (each 3H, s), 1.68 (3H, br s), 2.80 (1H, m, 2-H), 4.39 (1H, t, J = 8 Hz, 10-H), 5.08 (1H, br t, J = 4 Hz, 8-H), and 9.56 (1H, d, J = 4 Hz, 3-H). The aldehyde, when treated with methyllithum in ether (-15 °C, 10 min) followed by oxidation of the resulting alcohol (17) with Jones reagent in acetone (0 °C, 10 min), produced methyl ketone (18), oil, in a quantitative yield: 17, MS, m/e 302, 300 (M^+), and 203 (base); IR, 3450, 1670, 1395, and 1370 cm^{-1}; NMR, δ 0.94 and 1.07 (each 3H, s), 1.21 (3H, d, J = 6 Hz, 15-H), 1.68 (3H, br s), 3.59 (1H, quintet, J = 6 Hz, 3-H), 4.42 (1H, t, J = 8 Hz, 10-H), and 5.02 (1H, br t, J = 4 Hz, 8-H): 18, MS, m/e 300, 298 (M^+), 285, 283, 257, 255, 219, 164, and 43 (base); IR, 3025, 1715, 1668, 1392, 1372, 1353, 1180, 1160, 840, 790, 760, and 740 cm^{-1}; NMR, δ 0.95 and 1.11 (each 3H, s), 1.70 (3H, br s), 2.11 (3H, s, 15-H), 2.85 (1H, m, 2-H), 4.33 (1H, t, J = 8 Hz, 10-H), and 5.08 (1H, br t, J = 4 Hz, 8-H). The methyl ketone (18) was identified as (±)-spirolaurenone (±)-(1) (MS, IR, NMR, and TLC). The present synthesis involves 13 steps and the overall yield is 2.4% (3.9%) from 2. The synthesis also confirms the R-configuration of C-2, which had been assigned only on the basis of the reaction mechanism in the chemical correlation with glanduliferol with the established configurations.[2]



References and Footnotes

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(Received in Japan 8 April 1982)