Stereocontrolled Synthesis of (-)-Zonarene[1]

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The first synthesis of the sesquiterpene (-)-zonarene (**1b**) is reported featuring a stereocontrolled synthesis of *trans*-decalin derivatives based on the thermolysis of photoadducts derived from substituted cyclobutenes and (-)-piperitone.

(-)-Zonarene (**1b**), the major hydrocarbon component of the brown seaweed *Dictyopteris zonarioides*,[3] has also been identified as a constituent in nine essential oils.[4] It has been biomimetically prepared, along with a mixture of isomers, by the acid-catalyzed cyclization of farnesol.[5]

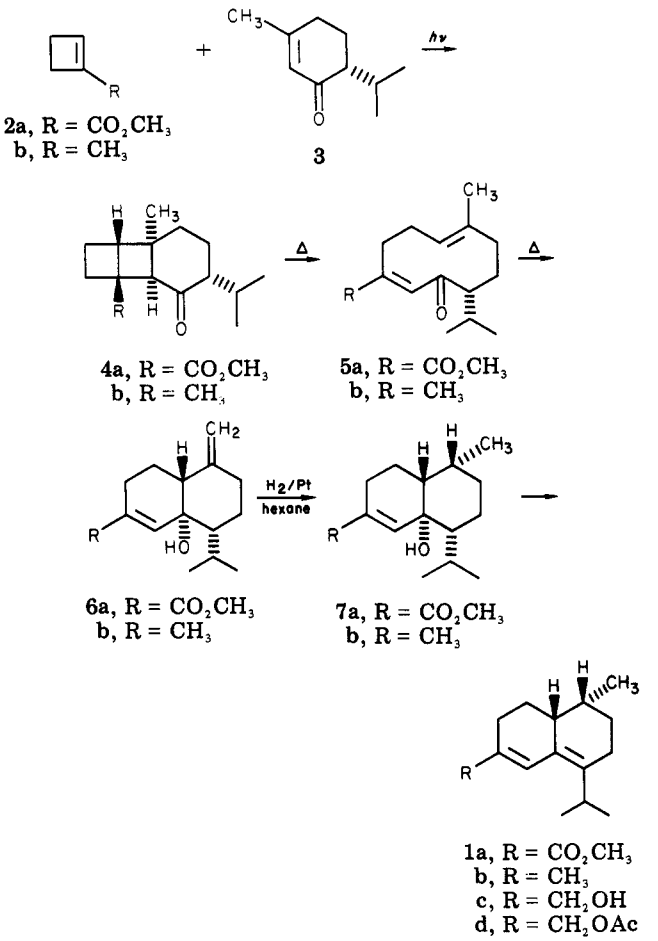
Previous work in our laboratory showed a method for the conversion of readily available cycloalkenones to *trans*-decalin derivatives (**3** → **4** → **5** → **6**) with a hydroxyl group at the ring junction.[6] Since the hydroxyl group is tertiary and should readily dehydrate, the synthesis of zonarene (**1b**) afforded a suitable target molecule to test this methodology. Furthermore, this sequence proceeds with asymmetric induction,[1] so that starting with (-)-piperitone (**3**) should afford (-)-zonarene (**1b**) enantioselectively as outlined in Scheme I.

The reaction sequence was first tried with the ester **2a** due to its ready availability and higher yielding olefin metathesis transannular ene cyclization sequence to yield **6a**.[1] Selective catalytic hydrogenation of **6a** in hexane over Pt gave the unsaturated ester **7a**. The stereochemistry of the C-14 methyl group, predicted by assuming attack at the less hindered β face, was confirmed by the completion of the synthesis. Dehydration of **7a** with $POCl_3$ in pyridine[3b] followed by aluminum hydride reduction[7] gave the primary alcohol **1c**. Acetylation of **1c** followed by lithium in ammonia reduction[8] gave (-)-zonarene **1b** in seven steps with a 17% overall yield.

This synthesis may be shortened to four steps by using the isoprene synthon, 1-methylcyclobutene (**2b**, Scheme I). Unfortunately, thermolysis of the methyl photoadduct **4b** afforded the *trans*-decalin **6b** in 50% yield in contrast to the almost quantitative yield obtained in the case of **6a**.

Thermolysis of **4** would be expected to yield the cyclodecadienone **5a**, via a concerted cycloreversion process or an orbital-overlap-controlled fragmentation of a diradical intermediate. This diradical species is stabilized much better by an adjacent electronegative ester group rather than an neighboring methyl group, thereby facilitating the rearrangement of **4a** over **4b**. Catalytic hydrogenation of **6b** also proceeded selectively to yield **7b** which upon dehydration afforded (-)-zonarene. The overall yield for the four-step sequence was 23%.

Scheme I



Experimental Section

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 137 Infracord spectrophotometer. ^1H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer. Chemical shifts are reported in δ units from the internal standard Me_4Si in chloroform-*d*. Optical rotations were measured at the sodium D line on a Perkin-Elmer 241 polarimeter by using a 1-dm cell with cyclohexane as the solvent unless otherwise specified. Low-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMU-6H. High-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMH-2. TLC was carried out on silica gel GF plates, and column chromatography was performed by using Woelm silica gel. Flash column chromatography was performed by using Merck silica gel 60.

1-Methyl-4-(1-methylethyl)-6-carbomethoxy-1,2,3,4,4a,7,8,8a-octahydro-4a-naphthalenol (7a). The diene **6a** (0.440 g, 1.66 mmol)[1b] was added to hexane (22 mL) and PtO_2 (0.044 g), and the solution was treated with H_2 at room temperature and 1 atm. pressure for 30 min. The Pt was filtered off and the solvent removed at reduced pressure. Purification by flash chromatography (10% ethyl acetate–hexane) gave 0.340 g (77%) of **7a**: IR (neat) 3507, 1713, 1643 cm^{-1}; NMR δ 7.17 (s, 1

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(6) Initial reports of this reaction [Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749] were corrected by: Williams, J. R.; Callahan, J. F. ref. 1. Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. This reaction sequence has been elaborated to yield *trans*-decalin derivatives with an alkyl substituent at the ring junction: Wender, P. A.; Letendre, L. J. *J. Org. Chem.* **1980**, *45*, 367.
(7) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.
(8) Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435.

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H), 3.74 (s, 3 H), 1.06 (d, 3 H, J = 8 Hz), 1.00 (d, 3 H, J = 8 Hz), 0.97 (d, 3 H, J = 8 Hz); MS, m/e (relative intensity) 266 (M^+, 27), 181 (100), 135 (69), 110 (33), 95 (30), 83 (44); calcd for $C_{16}H_{26}O_3$ m/e 266.1882, found m/e 266.1893.

1-Methyl-4-(1-methylethyl)-6-carbomethoxy-1,2,3,7,8,8a-hexahydronaphthalene (1a). To a solution of **7a** (0.310 g, 1.16 mmol) in pyridine (35 mL) was added $POCl_3$ (15 mL, 161 mmol) at −20 °C, and the subsequent mixture was stirred at room temperature for 24 h and then at reflux for 2 h. The reaction mixture was cooled, poured onto ice, and extracted with ether. The combined organic extracts were washed with 5% HCl, dried over anhydrous $MgSO_4$, and evaporated. Purification by flash chromatography (5% ethyl acetate–hexane) gave 0.229 g (80%) of **1a**: IR (neat) 1709, 1609, 1580 cm^{-1}; NMR δ 7.63 (s, 1 H), 3.67 (s, 3 H), 3.30–2.96 (m, 1 H), 0.95 (d, 6 H, J = 7.0 Hz), 0.72 (d, 3 H, J = 7.0 Hz); MS, m/e 248 (M^+, 55), 206 (19), 205 (100), 189 (17), 173 (17), 145 (46), 105 (22), 91 (21); calcd for $C_{16}H_{24}O_2$ m/e 248.1776, found m/e 248.1785.

1-Methyl-4-(1-methylethyl)-6-(hydroxymethyl)-1,2,3,7,8,8a-hexahydronaphthalene (1c). Aluminum chloride (0.600 g, 4.50 mmol) was added to a solution of $LiAlH_4$ (0.500 g, 13.2 mmol) in ether (70 mL) at 0 °C under N_2, and the resulting solution was stirred for 2 h. After this time, **1a** (1.24 g, 5.00 mmol) was added in ether (5 mL), and the solution was stirred at 0 °C for 30 min. The excess hydride was destroyed with cold water and extracted with ether. The combined ether extracts were dried over anhydrous $MgSO_4$ and evaporated. Purification by flash chromatography (5% ethyl acetate–hexane) gave 0.745 g (68%) of **1c**: IR (neat) 3324, 1638, 1609 cm^{-1}; NMR δ 6.53 (br s, 1 H), 4.08 (s, 2 H), 3.27–2.89 (m, 1 H), 1.00 (d, 6 H, J = 8 Hz), 0.82 (d, 3 H, J = 7.6 Hz); MS, calcd for $C_{15}H_{24}O$ m/e 220.1827, found m/e 220.1813.

(−)-Zonarene (1b). A solution of **1c** (0.923 g, 4.19 mmol) and acetic anhydride (1.0 mL, 10.60 mmol) in pyridine (3.0 mL) was stirred at room temperature for 24 h. The solution was diluted with water and extracted with ether. The combined ether extracts were washed with 5% HCl, dried over anhydrous $MgSO_4$, and evaporated. Flash chromatography (5% ethyl acetate–pentane) gave 0.921 g (83.7%) of **1d**: IR (neat) 1747, 1643, 1614 cm^{-1}; NMR δ 6.56 (s, 1 H), 4.55 (s, 2 H), 3.23–2.71 (m, 1 H), 2.04 (s, 3 H), 0.99 (d, 6 H, J = 8 Hz), 0.81 (d, 3 H, J = 7 Hz).

The acetate **1d** (0.665 g, 2.53 mmol) in ether (25 mL) was added to a solution of lithium (0.2 g, 28.8 mmol) in liquid ammonia (60 mL) at −78 °C and stirred for 0.5 h. Ammonium chloride (2 g, 37.4 mmol) was carefully added and the ammonia allowed to evaporate. The residue was diluted with water and extracted with ether. The combined ether extracts were dried over anhydrous $MgSO_4$ and evaporated. Purification by flash chromatography (pentane) gave 0.325 g (62.9%) of (−)-zonarene (**1b**): IR (neat) 1643, 1609 cm^{-1}; UV (EtOH) λ_{max} 247 nm (ϵ 18 500); NMR δ 6.29 (s, 1 H), 3.13–2.86 (m, 1 H), 1.78 (s, 3 H), 0.99 (d, 6 H, J = 8 Hz), 0.81 (d, 3 H, J = 7 Hz); MS, m/e 204 (M^+, 44), 189 (26), 161 (100), 133 (30), 119 (59), 105 (74), 91 (52), 81 (78).

Synthetic (−)-zonarene (**1b**) was identical in all respects, IR, UV, NMR, and sign of rotation with naturally occurring (−)-zonarene, $[\alpha]^{30}_D$ −217.8° (c 0.46, cyclohexane).[3,4]

Alternatively, the *trans*-decalin **7b** (110 mg, 0.50 mmol) was dehydrated with $POCl_3$ as described above to yield, following flash chromatography on a silica gel column (hexane), 91 mg (90%) of **1b**, $[\alpha]^{20}_D$ −100.8° (c 0.0125, cyclohexane). This was identical (IR, NMR, MS) with (−)-zonarene prepared previously except that in starting with (−)-piperitone with an enantiomeric excess (ee) of 79%, (−)-zonarene (46% ee) was obtained.

1-Methylene-4-(1-methylethyl)-6-methyl-1,2,3,4,4a,7,8,8a-octahydro-4a-naphthalenol (6b). The yield of **6b** (50%) was improved over that reported earlier[1a] by thermolyzing **4a** as a more dilute solution (0.03 M) in dry benzene at 250 °C for exactly 0.5 h.

1,6-Dimethyl-4-(1-methylethyl)-1,2,3,4,4a,7,8,8a-octahydro-4a-naphthalenol (7b). The diene **6b** (180 mg, 0.82 mmol) was hydrogenated in hexane over platinum at room temperature for 0.5 h as described above. Purification by flash chromatography (1% ethyl acetate–hexane) gave 133 mg (73%) of **7b**: IR (neat) 3500, 1600 cm^{-1}; NMR δ 5.86 (s, 1 H), 1.77 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 0.97 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz); MS, calcd for $C_{15}H_{26}O$ m/e 222.1984, found m/e 222.1983.

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Registry No. **1a**, 86669-13-8; **1b**, 41929-05-9; **1c**, 86669-14-9; **1d**, 86669-15-0; **6a**, 74923-23-2; **6b**, 72247-86-0; **7a**, 86669-16-1; **7b**, 86669-17-2.