Enantioselective Approach to Isodaucane Sesquiterpenes. Total Synthesis of (+)-Aphanamol-I and (+)-2-Oxo-isodauc-5-en-12-al

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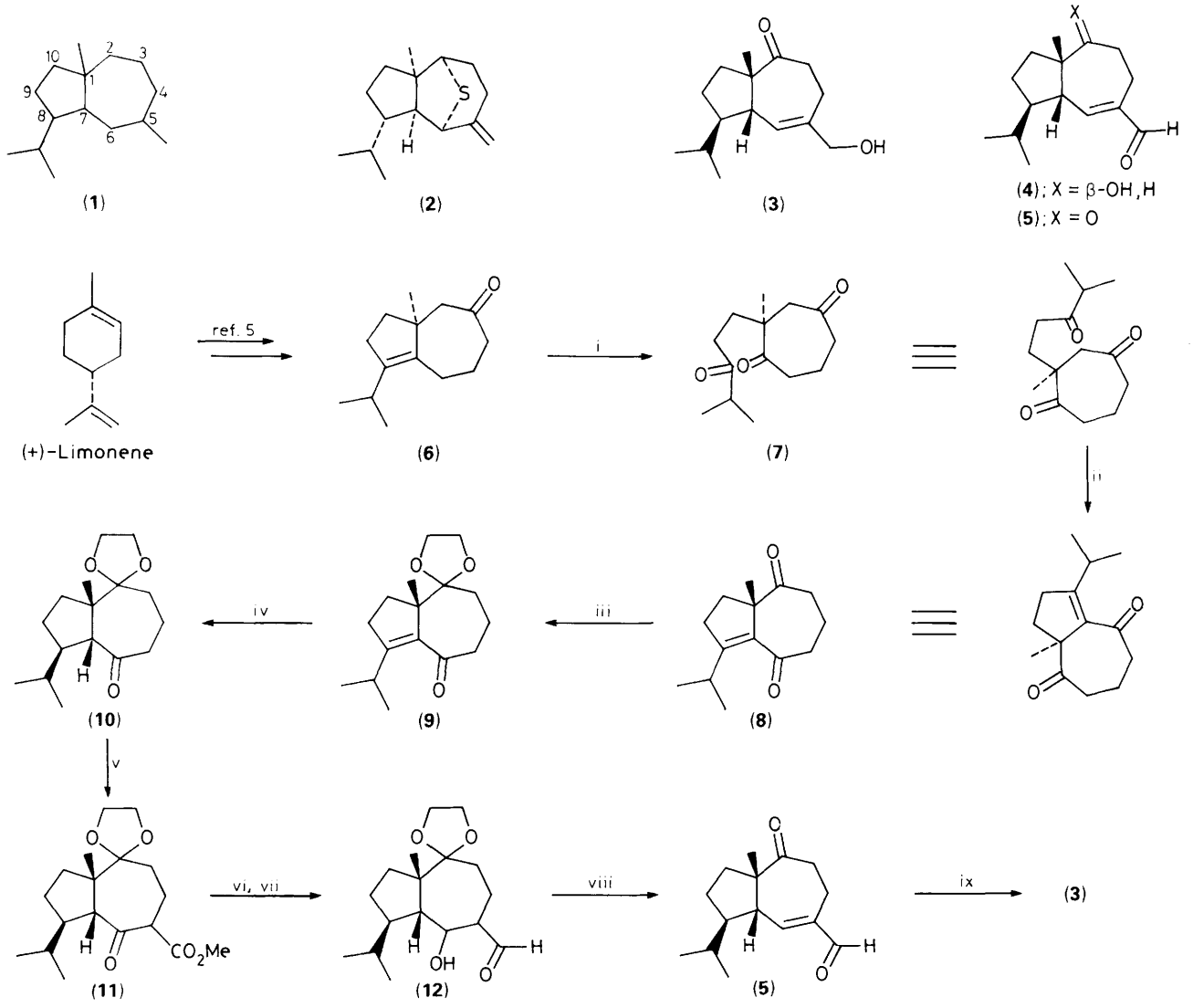
A general approach to isodaucane sesquiterpenes from (*R*)-(+)-limonene, resulting in the total synthesis of (+)-aphanamol-I (**3**) and (+)-2-oxo-isodauc-5-en-12-al (**5**), is described.

The hydroazulene-type isodaucane skeleton (**1**) is rare among sesquiterpenoids and has been found in nature only very recently.[1,2] Natural products based on framework (**1**) include (−)-mintsulphide (**2**) from peppermint oil,[1a] (+)-aphanamol-I (**3**) and -II (**4**) from the Meliaceous plant *Aphanamixis grandifolia*,[1b] and (+)-2-oxo-isodauc-5-en-12-al (**5**) from *Chromo-laen laevigata* (Lam).[1c] While structures of (**3**)—(**5**) have been assigned mainly on the basis of incisive n.m.r. spectroscopic studies,[1b,c] the absolute configuration of these natural products has not been determined so far. In this Communication, we report the first enantioselective synthesis of isodaucane sesquiterpenes (+)-(**3**) and (+)-(**5**),[3] which confirms their stereostructures and establishes the absolute configuration of aphanamol-I (**3**) and -II (**4**).[4]

The main synthetic challenge of isodaucane natural products (**3**)—(**5**) resides in the creation of the thermodynamically less favourable stereochemistry at the three contiguous stereogenic centres (C-1, C-7, and C-8) and the generation of



Scheme 1. *Reagents and conditions:* i, RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, quantitative; ii, 5% KOH–MeOH, 60 °C, 66%; iii, $HOCH_2$-CH_2OH, *p*-$MeC_6H_4SO_3H$, C_6H_6, 92%; iv, Li, liq. NH_3, tetrahydrofuran (THF)–MeOH, pyridinium chlorochromate-molecular sieves 4 Å, CH_2Cl_2, 70% from (**9**): v, Bu^nLi, hexamethyldisilazane (HMDS), THF, $ClCO_2Me$, −78 °C, 86%; vi, $NaBH_4$, MeOH, 0 °C, 62%; vii, $(COCl)_2$–DMSO (DMSO = dimethyl sulphoxide), CH_2Cl_2, Et_3N, −60 °C, 70%; viii, *p*-$MeC_6H_4SO_3H$, C_6H_6, 80 °C, 37%; ix, $NaBH_4$–$CeCl_3 \cdot 6H_2O$, MeOH, −5 °C, quantitative.

the sensitive oxygen functionalisation across the seven-membered ring. A solution has been devised employing enantiomerically pure bicyclic enone (**6**), whose synthesis from (*R*)-(+)-limonene we have recently reported.[5]

Oxidative cleavage of the tetra-substituted double bond in (**6**) with catalytic RuO_2–$NaIO_4$[6] furnished the triketone (**7**)† in quantitative yield. Base promoted cyclisation of (**7**) proceeded smoothly and regioselectively to give bicyclic enedione (**8**)† as the sole product, Scheme 1. Thus, in a two-step synthetic strategy, (**6**) was not only converted to (**8**) with an increase in the number of functional groups, but also (**8**) is enantiomeric with respect to (**6**) and has requisite enone functionalisation for the generation and control of the C-7 and C-8 stereogenic centres.

Li–NH_3 (liq.) reduction of the enone-acetal (**9**), derived from (**8**), proceeded stereoselectively and a 7.5 : 1 mixture of (**10**)† and its *trans*-ring junction isomer was obtained in 70% yield.[7] Having secured (**10**) with the required stereochemistry at C-1, C-7, and C-8, the seemingly straightforward functional group manipulation *en route* to (**3**) proved quite cumbersome. Success was eventually obtained through the following sequence. Kinetically controlled deprotonation of (**10**) with LiHMDS and quenching with methyl chloroformate furnished α-keto ester (**11**) as a mixture of C-5-isomers. Sodium borohydride reduction of (**11**) furnished a single diol, probably *via* reduction of the enol ester, which on chemoselective Swern oxidation[8] gave the hydroxy aldehyde (**12**).† Brief exposure of (**12**) to catalytic toluene-*p*-sulphonic acid resulted in dehydration as well as deacetalisation to give (**5**), $[\alpha]_D^{22}$ +33° (*c* 0.2, $CHCl_3$), having spectral properties identical to those of the natural product.[1c,3]‡ Chemoselective reduction of (**5**) with $NaBH_4$–$CeCl_3$[9] led to aphanamol-I (**3**), $[\alpha]_D^{22}$ +10° (*c* 0.4, $CHCl_3$; lit. +13.8°),[1b] whose identity was established by direct spectral (i.r., ^1H n.m.r.) comparison with the natural product. Since aphanamol-I (**3**) has already been correlated[1b] with aphanamol-II (**4**), our synthesis of (+)-(**3**) outlined here establishes the absolute configuration of both the aphanamols.

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† All new compounds were characterised on the basis of their spectroscopic and analytical data. Selected spectroscopic values for some key compounds are as follows. (**7**): $[\alpha]_D^{22}$ +84.2 ° (*c* 3.0, $CHCl_3$); i.r. (neat) 1700, 920 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz) δ 3.1—2.2 (8H, m), 2.1—1.5 (5H, m), 1.12 (3H, s), 1.05 (6H, d, *J* 6 Hz); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz) δ 213.4, 213.2, 209.6, 50.0, 47.3, 43.5, 40.4, 39.6, 34.2, 32.5, 21.4, 20.6, 17.7(2C). (**8**): $[\alpha]_D^{22}$ +177.1 ° (*c* 2.0, $CHCl_3$); i.r. (neat) 1700, 1670, 1590 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz) δ 3.62 (3H, m), 3.1—1.45 (10H, m), 1.35 (3H, s), 1.06 (3H, d, *J* 7 Hz), 1.04 (3H, d, *J* 7 Hz); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz) δ 213.7, 199.8, 167.3, 136.8, 61.3, 41.4, 37.2, 35.0, 29.7, 27.7, 20.9, 20.7, 20.5 (2C). (**10**): $[\alpha]_D^{22}$ +17.5 ° (*c* 1.6, $CHCl_3$); i.r. (neat) 1700, 1380, 1120 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz) δ 4.0 (4H, m), 3.72 (1H, br. d, *J* 9 Hz), 2.6—1.2 (12H, m), 0.9 (3H, s), 0.84 (3H, d, *J* 7 Hz), 0.72 (3H, d, *J* 7 Hz); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz) δ 218.8, 113.1, 65.4(2C), 52.7, 52.0, 50.8, 44.0, 34.4, 33.5, 30.0, 28.0, 23.5, 22.1, 21.8, 19.4. (**12**): i.r. (neat) 2720, 1720 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz) δ 9.72 (1H, s), 4.72—4.48 (1H, m), 4.08—3.84 (4H, m), 2.68—1.12 (13H, m), 1.28 (3H, s), 1.02 (3H, d, *J* 7 Hz), 0.92 (3H, d, *J* 7 Hz).

‡ Copies of the spectra of the natural product for direct comparison could not be obtained.[1c]