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THE TOTAL SYNTHESIS OF (±) COMPACTIN AND ITS NATURAL (+) ENANTIOMER

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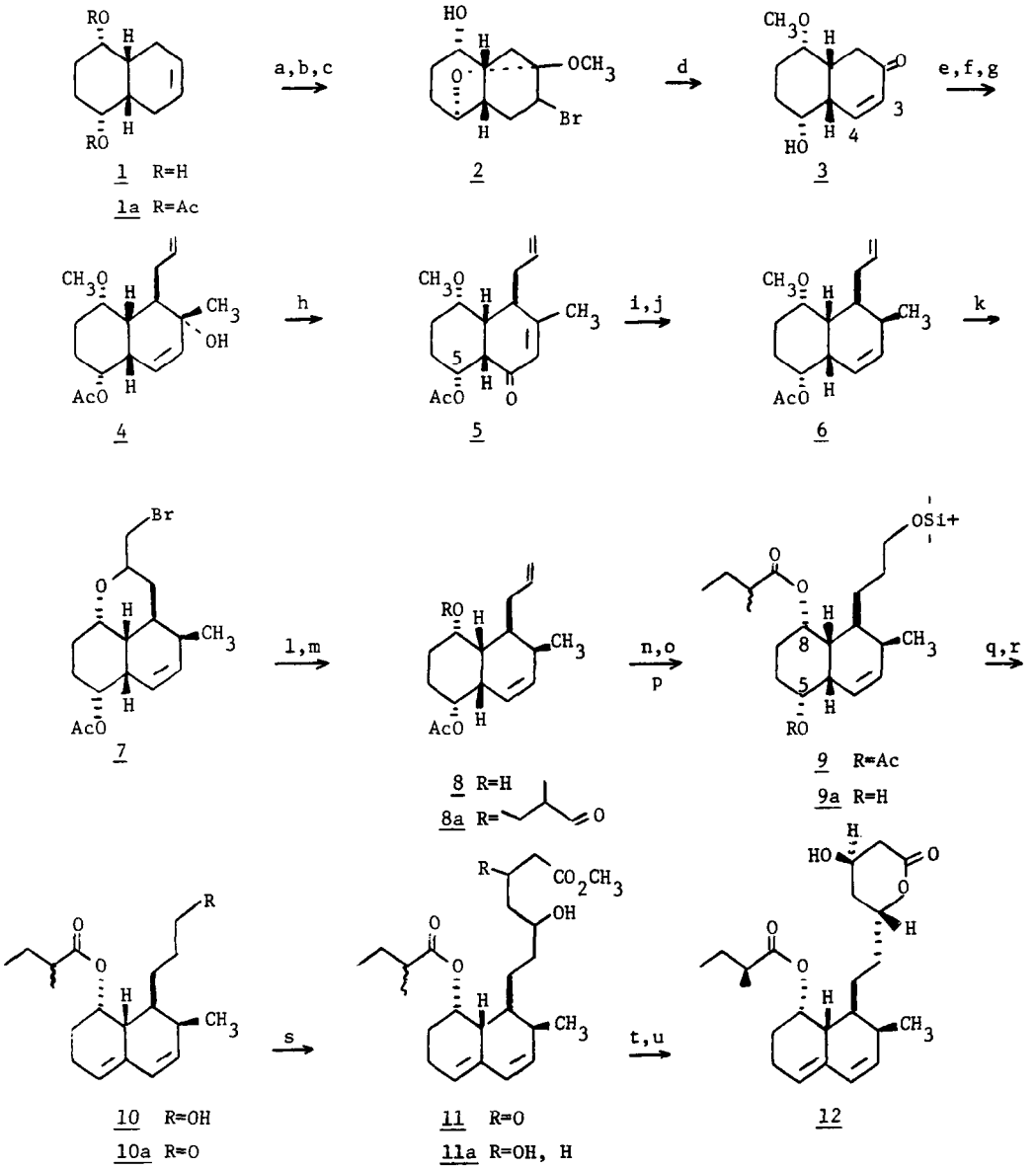
Summary: Total synthesis of (±) compactin 12 and its natural (+) enantiomer has been achieved via a multistep sequence originating from butadiene and p-benzoquinone.

Recently syntheses of the important hypocholesterolemic agent (+) compactin were reported[1] in which it was found possible via biological reduction pathways to obtain key optically active intermediates in the same chiral series as the natural product. Other synthetic activity concerned with the upper and lower segments of the compactin molecule has been reported.[2] We wish to present our work on the synthesis of this natural product.

We observed that cis-Δ^6-octal-1,4-dione[3] was reduced preponderantly from the exo face (85%, $LiB(C_4H_9)_3H$; 75%, $LiAlH_4$) to give the endo-cis diol 1[4] mp 63-65°; Diacetate 1a mp 56-57°.[5] Conversion of 1a to its bromohydrin (NBS, aq DMSO, 0°) followed by oxidation (CrO_3-H_2SO_4, Acetone) to bromoketone[6] and ensuing treatment with 3% methanol-HCl yielded predominantly (85%) the 6-ring cyclic methyl ketal 2.[7] Crude 2 was successively methylated and dehydrobrominated in one reaction ($KOBu^t$, DMSO, CH_3I, 25°) to give on acidification the crystalline ketone 3 mp 79-80°,[5] IR ($CHCl_3$) 6.0 μ, NMR ($CDCl_3$, 60 MHz) δ3.27 (OCH_3, s), 6.08 (H_3, broad d) and 6.87 (H_4, dd, J_1 = 10, J_2 = 4); 3 was obtained directly by crystallization or more efficiently by silica gel chromatography (30% acetone-CH_2Cl_2) in an overall yield of 65% from 1. The trimethyl silyl ether of 3 [$(CH_3)_3SiCl$, Py, 0°] mp 46-49° underwent exclusive exo-face allylation (LDA, THF, C_3H_5Br, -78° to 25°) followed by methylation (CH_3Li, THF, -78°) to yield after desilylation (CH_3OH, K_2CO_3) and acetylation (Ac_2O, Py, 0°) crystalline carbinol 4[8] mp 61-62°,[5] NMR ($CDCl_3$, 60 MHz) δ1.22 (CH_3, s), 2.07 (OAc, s) and 3.27 (OCH_3, s); the latter was directly oxidized (PCC, CH_2Cl_2) to the unsaturated ketone 5[8] mp 44-46°[5] in 50% overall yield from 3, NMR ($CDCl_3$, 60 MHz) δ1.92 (CH_3, d, J = ca 1.5), 2.03 (OAc, s), 3.17 (OCH_3, s) and 4.73 (H_5, td, J_1 = 11, J_2 = 4.5).

The tosylhydrazone of 5 ($C_7H_7SO_2NHNH_2$, THF, 25°) was reduced via the Kabalka Reaction[9] by catecholborane with essentially complete stereoselectivity from the exo-face producing a presumed



(a) NBS, aq DMSO, 0°; (b) CrO_3, H_2SO_4, Me_2CO, 5°; (c) 3% HCl-CH_3OH, 0°; (d) $KOBu^t$, CH_3I, 25° then 1% H_2SO_4-aq Me_2CO; (e) $(CH_3)_3SiCl$, Py then LDA, THF, C_3H_5Br, -78°to 25°; (f) CH_3Li, THF, -78° then aq CH_3OH; (g) Ac_2O, Py; (h) PCC, CH_2Cl_2; (i) $C_7H_7SO_2NHNH_2$, THF, 25°; (j) Catechol-borane, Chf, then NaOAc·$3H_2O$; (k) 2,4,4,6-tetrabromocyclohexadienone, CH_2Cl_2; (l) Zn, $(CH_3)_2CHOH$, HOAc, 85°; (m) $(C_4H_9CO)_2O$, Py, DMAP; (n) 9BBN, H_2O_2; (o) Imid., DMF, $Bu^t(CH_3)_2SiCl$; (p) K_2CO_3, aq CH_3OH, 25°; (q) CH_3SO_2Cl, Py, 0°; Py,110°; aq HCl-THF; (r) CrO_3, Py, CH_2Cl_2; (s) Diketene, $TiCl_4$, CH_2Cl_2, -78°, CH_3OH; (t) $NaBH_4$; K_2CO_3, aq CH_3OH; HCl-CH_2Cl_2.

transitional endo diazine in turn delivering hydrogen via sigmatropic rearrangement to the methyl-bearing carbon to yield 6 in overall yield of 65% from 5,[10a] NMR ($CDCl_3$, 60 MHz) 0.92 (CH_3, d, J = 7), 2.00 (OAc, s) and 3.30 (OCH_3, s). Compound 6 possesses all four chiral centers in the correct steric orientation as they occur in compactin itself.[11]

Cleavage of the methyl ether could not be effected directly in the desired sense. However, demethylation occurred with formation (95%) of the cyclic bromoether 7 mp 82-84°[05] on treatment of 6 with 2,4,4,6-tetrabromocyclohexadienone[12] in CH_2Cl_2 solution. Subsequent reduction of 7 (Zn, 2-propanol, HOAc, 85°) afforded the desired hydroxydiene 8 (94%). Acylation of 8 ($\pm C_4H_9CO)_2O$, Py, DMAP, 25°) quantitatively produced 8a, which in turn was hydroborated (9BBN, H_2O_2, 84% yield, purified on silica gel/30% ethyl acetate-hexane) and silylated (Bu^tSiMe_2Cl, imid, DMF) to give 9, NMR ($CDCl_3$, 60 MHz) δ 2.02 (OAc, s), 3.62 ($-CH_2-O$, m) and 5.00 (H_5 and H_8, m). Selective hydrolysis of 9 (K_2CO_3, aq CH_3OH, 25°) proceeded in 95% yield to 9a.[10b] Conversion of 9a to its mesylate (CH_3SO_2Cl, py, 0°) and subsequent dehydromesylation (Py. 110°) followed by treatment with aq HCl-THF afforded the dienol 10 (85% from 9a) mp. 59-61°, M^+ Calcd for $C_{19}H_{30}O_3$: 306.2193. Fd 306.2191. NMR ($CDCl_3$, 60 MHz) δ3.56 ($-CH_2-O$, m), 5.77 (H_3, broad d) and 5.97 (H_4, d, J = 10).

Oxidation of 10 (CrO_3, py, CH_2Cl_2) provided aldehyde 10a (75%) which on treatment with diketene-$TiCl_4$,[13a] (-78°) followed by methanol or preferably with the dianion of methylacetoacetate,[13b] furnished the corresponding diastereoisomeric δ-hydroxy-β-ketomethylesters 11. Since the latter were not easily separable they were reduced directly ($NaBH_4$, CH_3OH, 0°) to a mixture of dihydroxy esters 11a (72% from 10) which were separated on silica gel into two sets of diols.[14] The more mobile set of diols was saponified (K_2CO_3, aq CH_3OH, 25°) and cyclized (10% HCl-CH_2Cl_2) to give a mixture of lactones (cf. 12) consisting of four stereoisomers (80%). The latter was cleanly and efficiently separated into two lactone pairs by HPLC after the manner of Sih and coworkers[1a] in the optically active series, employing a Waters radial compression module.[15] Ultimate separation of the more mobile lactone pair was effected on a reverse phase column[16] to give (±) compactin 12 mp 146-148°;[17] the latter was identical in its HPLC, IR, 250 MHz H^1NMR, C^{13}NMR and MS with natural (+) compactin.

Finally, transformation of intermediate 8, in which the optically active (+) α-methylbutyryl function has replaced the corresponding racemic grouping, leads to compound 10 as a mixture of optically active diastereoisomers separable on the reverse phase column (vide supra)[16b] to give (+) 10 mp 63-65° $[\alpha]_D^{25}$ + 322° (C 0.28, $CHCl_3$).[18] Since the latter has already been converted to (+) compactin (ref. 1a), the present synthesis of (+) 10 constitutes accordingly a total synthesis of the optically active natural product.

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3. cis-Δ^6-Octal-1,4-dione (cis-2,3,4a,5,8,8a-hexahydronaphthalene-1,4-dione was prepared by Zn-HOAc reduction of the Diels-Alder adduct from butadiene and p-benzoquinone. Cf. K. Alder and G. Stein, Annalen 501, 247 (1933); W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger and W. N. Hubbard, J. Am. Chem. Soc. 83, 606 (1961).

4. Purified by chromatography on silica gel (30% acetone-CH_2Cl_2); trans-diol had mp 139-140° and its diacetate mp 87-86°.

5. Satisfactory elemental analyses obtained.

6. Isolable on silica gel (5% acetone-CH_2Cl_2) as two bromo stereoisomers mp 116-117° (major) and 119-120°.

7. Separable on silica gel (5% acetone-CH_2Cl_2) into two bromo stereoisomers mp 86-87° and 100-102°. Both isomers independently produced 3 on methylation-dehydrobromination.

8. Purified on silica gel with 40% ethyl acetate-hexane.

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10. Purified on silica gel: (a) 10% ethyl acetate-hexane; (b) 20% ethyl acetate-hexane.

11. Configurational confirmation was obtained by a detailed 300 MHz NMR determination on the corresponding triene derived from 6 (conversion route via carbinol and mesylate, cf. 9 → 10).

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14. Solvent system 50% ethyl acetate-hexane. The more mobile set of diols corresponded in tlc mobility with the dihydroxy ester obtained from (+) compactin by methanolysis; cf. ref. 1a.

15. Waters radial compression module (RCM-100) with radial-pak 10 μ silica gel cartridge (0.5 x 10 cm.) (mobile phase chloroform, flow rate 2 ml/min). The retention times of the desired lactone pair and the isomeric lactone pair were 15.6 and 22.6 min. respectively.

16. Altex ultrasphere-octyl 5 μ column (1 x 25 cm); mobile phase acetonitrile-water (40:60) (flow rate 5 ml/min). The retention times of (±)-compactin and its isomer were 71.5 and 73.5 min. respectively. (b) ibid. the retention times of (+) 10 and its diastereomer were 78.5 and 81 min. respectively. Similar separations in the mevinolin series using this column have been effected by T. J. Lee, A. K. Willard, W. J. Holtz, W. F. Hoffman and R. L. Smith, J. Org. Chem. 1982 in press.

17. Crystallized from CH_2Cl_2-ether (plates), mp (uncorr.) determined on a microscope hot-stage apparatus. (±) 12 exhibited polymorphism melting at 123-125° on crystallization from aq. acetone.

18. Reported[1a] mp 66-67°; $[\alpha]_D^{25°}$ + 347° (C 1.06 $CHCl_3$). Deutsch and Snider[2e] did not report the isolation of this compound. 10 is unstable and deteriorates substantially in a very short time to more polar entities, even when stored in the cold under nitrogen. This instability is inherent to all compounds in this series bearing the dienic system and was observed to be most pronounced in the case of compound 10.

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