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HYPOCHOLESTEROLEMIC AGENT COMPACTIN. AN ALTERNATIVE DIELS-ALDER STRATEGY FOR THE SYNTHESIS OF THE HEXAHYDRONAPHTHALENE PORTION

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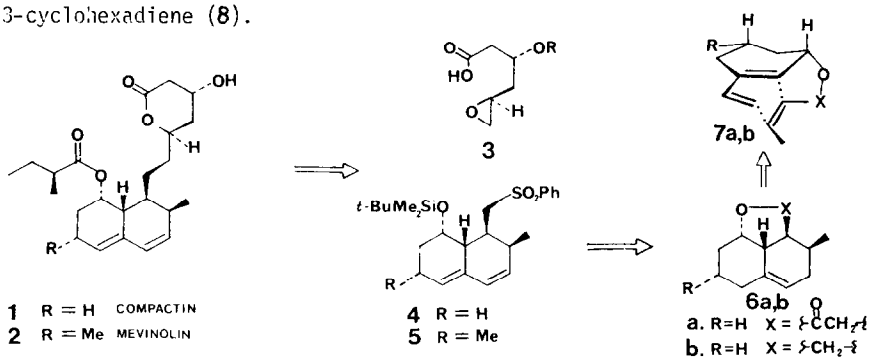
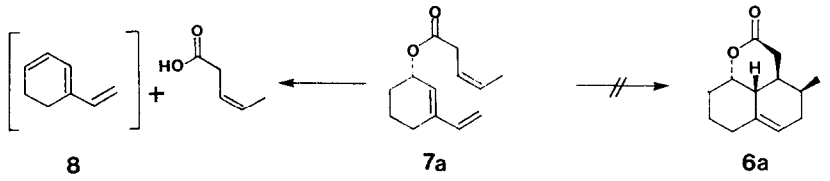
Summary: *The synthesis of the hexahydronaphthalene segment* (**4**) *of compactin* (**1**) *has been accomplished in a short sequence* (8 *steps from* **9**) *featuring the intramolecular Diels-Alder cycloaddition of* **7b**.

The fungal metabolites compactin **1**[1a,b] and mevinolin **2**[1c,d] are effective inhibitors of the enzymatic reduction of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid, the rate-limiting step in cholesterol biosynthesis.[2] Consequently, considerable attention has been devoted to the synthesis of these hypocholesterolemic agents.[3,4] An obvious strategy for the synthesis of the cyclohexenyl-bearing lower segment of compactin is application of the Diels-Alder reaction. Indeed, an interesting case study of this reaction is documented in all of the total[3] and partial[4d-h] syntheses reported to date. In this paper, we describe a concise Diels-Alder-based route to the hexahydronaphthalene synthon **4** for eventual deployment in the projected convergent total synthesis outlined below (Scheme I).[5]

The intramolecular cycloaddition of **7** was expected to proceed via sterically unencumbered exo delivery of the unactivated dienophilic side-chain from the same side as the oxygen atom[6]. Therefore, the resulting cycloadduct **6** would possess the correct stereorelationship of the four contiguous asymmetric centers analogous to those in compactin and, in addition, the requisite functionality for elaboration of the diene and phenylsulfonylmethyl moieties in **4**/**5**.

We first examined the intramolecular cycloaddition of ester **7a** which was easily prepared by acylation of 3-ethenyl-2-cyclohexen-1-ol (**9**) with cis-propenylketene.[8] Thermolysis of **7a** (170°, 12 h, dichlorobenzene) led not to the desired cycloadduct **6a**, but instead to the isolation of cis-3-pentenoic acid and uncharacterized nonpolar material presumably derived from 1-ethenyl-1,3-cyclohexadiene (**8**).

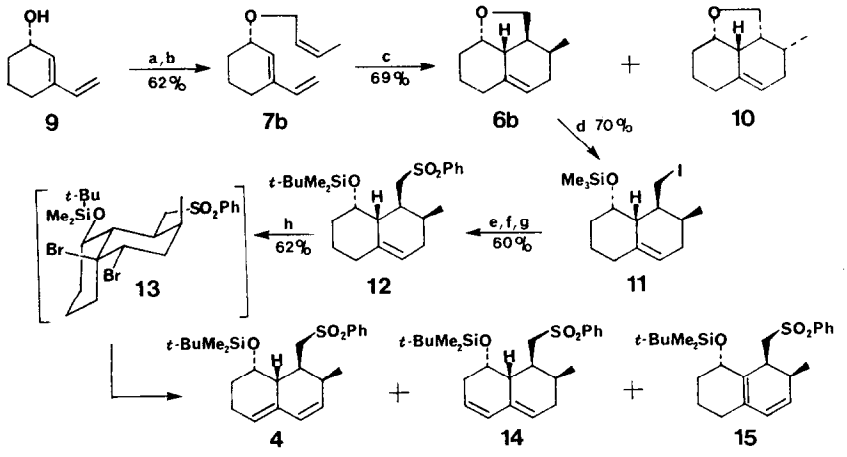




8 7a 6a

In order to deter this elimination pathway, the troublesome ester linkage[9] was replaced with the less labile ether functionality, e.g. **7b**.[10] Thus, alkylation of alcohol **9**[7] with 1-bromo-2-butyne followed by hydroboration with dicyclohexylborane and protonolysis of the resulting alkenylborane with acetic acid produced the desired ether **7b**. Thermolysis of **7b** at 165°C in toluene (sealed tube) gave a mixture of two isomers (4:1) which were separable by column chromatography (rf .33, .38; 1:4 EtOAc/hexanes). The major, more polar isomer was assigned structure **6b** based upon detailed analysis of the ^{1}H NMR spectrum[11] and comparison with the spectrum of the minor, endo cycloadduct **10**.[11] The eventual conversion of **6b** to **4** confirms this assignment. Toward this end, the tetrahydrofuran moiety of **6b** was regiospecifically cleaved with trimethylsilyl iodide in the presence of quinoline (other bases were unsatisfactory) to afford iodide **11**. A subsequent three-step sequence involving hydrolysis of the trimethylsilyl ether, displacement of the primary iodide with sodium phenylsulfinate and reprotection of the hydroxyl (Me_2t-BuSiOTF) served to convert **11** to sulfone **12** (mp 91-92°C).

One-pot oxidation of monoene **12** to diene **4** was effected by the low-temperature addition of Br_2 (1 equiv, -60°C → -15°C, 1h) to an ether solution of **12** followed by DBU (10 equiv, -15° → 35°, 12h) to promote bisdehydrobromination of the resulting dibromide **13**.[12] A mixture of three isomeric dienes were produced (22.8:2.2:1, **4:14:15**)[11] and readily separated by HPLC.[13] The predominate isomer **4** (mp 105-106°C) was identical in all respects with a sample prepared by our alternate route.[4d]



a) 1.5 equiv. $CH_3{\equiv}CCH_2Br$, 1.1 equiv. NaH, 45°C, 4 days; 79%. b) Cy_2BH, 25°C, 12h; 10 equiv. AcOH, 25°C, 2h; 78%. c) 165°C, toluene, sealed tube, .1% BHT, 2 days; 69%. d) 1 equiv. Me_3SiI, 5 equiv. quinoline, CH_2Cl_2, 0° → 25°C, 15 min.; 70%. e) 1 equiv. HF, CH_3CN, 25°C, 10 min.; 100%. f) 1.1 equiv. $NaSO_2Ph$, DMF, 70°C, 3 days; 84%. g) 1.5 equiv. Me_2t-BuSiOTf, 2.5 equiv. lutidine, CH_2Cl_2, 0°C, 30 min.; 72%. h) 1 equiv. Br_2 (3M in CCl_4), Et_2O, -60°C → -15°C, 1h; 10 equiv. DBU, -15°C → 35°C, 12h, 62%.

In summation, we have disclosed an efficient, stereoselective synthesis of a racemic hexahydronaphthalene synthon (**4**) for compactin total synthesis. In principle, our route is amenable to enantioselective synthesis which, of course, is mandated by this convergent approach. Furthermore, the extension of this strategy to the preparation of the mevinolin synthon **5** from commercially available chiral starting material appears to be straightforward and, moreover, may benefit from an increased exo-endo ratio in the analogous intramolecular Diels-Alder cycloaddition. Accordingly, this study and completion of the total syntheses are under active investigation in our laboratory.

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11. All new compounds reported herein exhibit satisfactory spectral (IR, NMR), analytical, and/or high resolution mass spectral characteristics. Pertinent resonances in the corresponding ^{1}H NMR spectra (360 MHz, $CDCl_3$) for: **6b**, δ 5.24 (br s, 1H), 4.07 (ddd, J=11.9, 9.3, 4.1 Hz, 1H), 3.82 (dd, J=7.5, 6.2 Hz, 1H), 3.48 (dd, J=11.7, 7.5 Hz, 1H), .94 (d, J=7.0 Hz, 3H). **10**, δ 5.35 (br s, 1H), 3.93 (m, $w_{1/2}$=7 Hz, 1H), 3.69 (dd, J=8.7, 8.2 Hz, 1H), 3.57 (dd, J=8.7, 8.7 Hz, 1H), .82 (d, J=6.6 Hz, 3H). **12**, δ 5.45 (br, s, 1H), 3.98 (br s, $w_{1/2}$= 7 Hz, 1H), 3.04 (dd, J=14.3,2.65 Hz, 1H), 2.86 (dd, J=14.3, 8.9 Hz, 1H), .68 (d, J=6.8 Hz, 3H). **4**, δ 5.95 (d, J=9.45 Hz, 1H), 5.71 (dd, J=9.45, 6.2 Hz, 1H), 5.53 (br s, 1H), 3.98 (br s, $w_{1/2}$= 7 Hz, 1H), 3.28 (dd, J=13.4, 3.3 Hz, 1H), 3.13 (dd, J=13.4, 12.5 Hz, 1H), 1.03 (d, J=6.9 Hz, 3H). **14**, δ 6.05 (dd, J=9.1, 2.1 Hz, 1H), 5.59 (br s, $w_{1/2}$=10.5 Hz, 1H), 5.38 (m, 1H), 4.05 (br s, 1H), 3.07 (m, 2H), .86 (d, J=6.9 Hz, 3H). **15**, δ 5.72 (dd, J=9.3, 2.9 Hz, 1H), 5.38 (d, J=9.3 Hz, 1H), 4.52 (m, 1H), 3.24 (dd, J=14.1, 3.6 Hz, 1H), 3.07 (dd, J=14.1, 7.8 Hz, 1H), 1.03 (d, J=7.4 Hz, 3H).

12. The dibromide **13** could be isolated by omitting DBU. A single isomer was produced and is assigned the cis-ring fusion. The ^{1}H NMR spectrum (360 MHz, $CDCl_3$) was consistent with the preferred conformer **13**: δ 4.84 (dd, J=13.1, 4.8 Hz, 1H), 4.76 (ddd, J=12.4, 9.1, 3.5 Hz, 1H), 4.54 (m, 1H), 2.82 (m, 2H), 1.15 (d, J=7.0 Hz, 3H). The diagnostic resonances are those α to the bromine atom (δ 4.84) and the oxygen atom (δ 4.76). The resonance at δ 4.54 was assigned to one of the protons α to the phenylsulfonyl group and was confirmed by preparing the analogous dideutero compound (**12** + NaOMe, DOMe, 50°, 12 h; Br_2). An intramolecular hydrogen bond with the proximate ether oxygen atom may be the factor responsible for this significant downfield shift.

13. The separation was accomplished on a Waters 6000A pump using a Beckman 5μ silica ultrasphere column (10 mm x 25 cm, 1:20 ethyl acetate/hexane, 3mL/min). The retention times were 13.12, 15.75, and 17.8 minutes for **15**, **4**, and **14**, respectively.

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