A Formal Synthesis of (±)-Compactin

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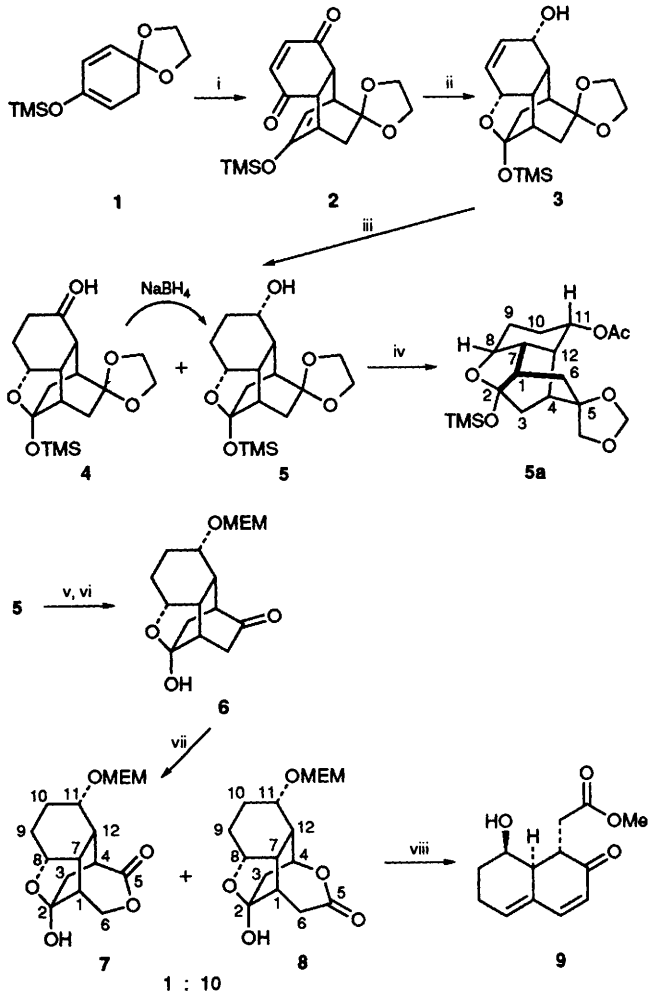
Compound **9**, a key intermediate in the synthesis of (±)-compactin, has been prepared from the Diels–Alder adduct of **1** and *p*-benzoquinone in seven steps.

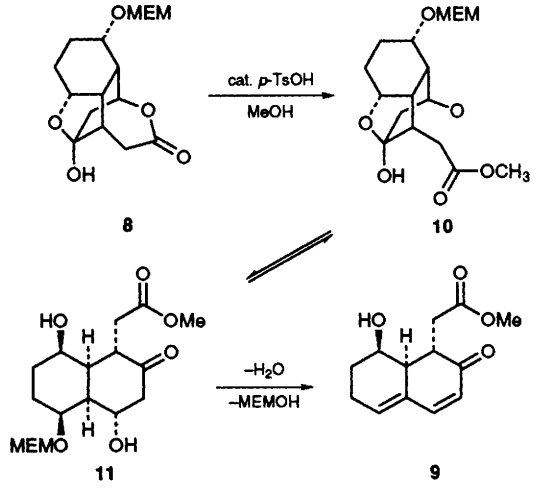
The compactin-mevinolin family,[1] owing to their potent hypocholesterolaemic activity,[2] have attracted much attention; many strategies of synthesis have been developed.[3] Numerous approaches were based on the construction of the hydronaphthalene and lactone portions that were coupled at a late stage. We report here the synthesis of **9**, which has been reported to be transformed into (±)-compactin.[4]

The synthetic sequence is shown in Scheme 1. Compound **2**, prepared from the Diels–Alder reaction of **1**[5] and *p*-benzoquinone, was transformed into **3** by Luche's reduction.

Catalytic hydrogenation of **3** afforded a mixture of **5** and **4** in 60 and 31% yields respectively; the latter was effectively transformed into **5** by reduction with $NaBH_4$. The *endo* stereochemistry in **2**, which was expected to be the major isomer from theoretical point of view, was mainly deduced from the formation of ketal in **3** after Luche's reduction; this result would not be possible for the *exo* adduct. This result also determined the stereochemistry of C-8 (as indicated in **5a**) in **3–8**. The assignments of the stereochemistry of the hydroxy group in **5** and the corresponding functional groups in **5a–8** were based on the ^1H NMR spectral pattern of the hydrogen atom on C-11 in **5a**, a pattern of ddd (J 12.1, 7.0, 4.7 Hz); the large coupling constant 12.1 Hz is due to the coupling between two vicinal diaxial proton indicating that the hydrogen on C-11 is in the axial position. The stereochemistry of the hydroxy group in **3** is expected to be the same as that in **5**. Treatment of **5** with methoxyethoxymethyl chloride (MEMCl) in the presence of ethyldiisopropylamine followed by acidic hydrolysis of the ketal moiety yielded **6**. Baeyer–Villiger oxidation of **6** produced a mixture of **7** and **8** in the ratio 1 : 10 determined from the integration of the ^1H NMR spectrum [δ 4.39 (J 12.2, 3.3 Hz) and δ 4.53 (J 12.2, 3.3 Hz) for the two protons on C-6 in **7**; δ 4.12 (J 3.1 Hz) for the proton on C-4 in **8**]. Treatment of the mixture of **7** and **8** with toluene-*p*-sulfonic acid (*p*-TsOH) and trimethyl orthoformate in methanol generated **9** in 57% yield after column chromatography. The formation of **9** from **8** is presumably *via* the reaction pathway depicted in Scheme 2. Opening of the lactone ring by transesterication furnished **10** which equilibrated with its keto form **11**. Consecutive elimination of H_2O and MEMOH from **11** yielded the desired product **9**† that was converted to (±)-compactin by Girotra and Wendler.[4]



Scheme 1 *Reagents and conditions*: i, *p*-benzoquinone, PhH, 90 °C, (95%); ii, $CeCl_3 \cdot 7H_2O$, $NaBH_4$, 0 °C, (68%); iii, Ru/C H_2 (92%); iv, AcCl, pyridine; v, MEMCl, Pr^i_2NEt, (85%); vi, 1 mol dm^{-3} HCl, (98%); vii, *m*-chloroperbenzoic acid, (82%); viii, *p*-TsOH (cat.), MeOH, $CH(OMe)_3$, 90 °C, (57%) (TMS = trimethylsilyl)



Scheme 2

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† Pertinent spectral data of **9**: IR ν/cm^{-1} ($CHCl_3$) 3447, 2927, 1728, 1663, 1437, 1209, 1092, 859; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J 9.7 Hz, 1 H), 6.22 (t, J 2.4 Hz, 1 H), 5.88 (d, J 9.7 Hz, 1 H), 4.03 (t, J 2.2 Hz, 1 H), 3.70 (s, 3 H), 3.01 (ddd, J 13.5, 6.4, 3.9 Hz, 1 H), 2.60 (dd, J 13.5, 2.2 Hz, 1 H), 2.46–2.56 (m, 1 H), 2.43 (dd, J 17.8, 6.4 Hz, 1 H), 2.25 (m, 1 H), 2.06 (m, 1 H), 1.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.45 (C), 175.11 (C), 147.62 (CH), 136.15 (CH), 131.67 (C), 124.46 (CH), 64.28 (CH), 52.22 (CH_3), 44.16 (CH), 43.06 (CH), 31.06 (CH_2), 27.41 (CH_2), 21.33 (CH_2); MS (75 eV) *m/z* 236 (M^+, 2%), 218 (100%), 186 (76%), 160 (98%), 158 (76%), 145 (76%), 132 (68%); HRMS (EI) Calc. for $C_{13}H_{16}O_4$ 236.1049, found 236.1054.