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, owing to their potent hypocholesterolaemic activity, have attracted much attention; many strategies of synthesis have been developed. 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. The synthetic sequence is shown in Scheme 1. Compound 2, prepared from the Diels–Alder reaction of 1 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 NaBH₄. 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 dddd (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 methoxymethyl chloride (MEMCl) in the presence of ethylidiosopropylamine 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 [6] 4.39 (J 12.2, 3.3 Hz) and 6.45 (J 12.2, 3.3 Hz) for the two protons on C-6 in 7; δ 4.12 (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 transesterification furnished 10 which equilibrated with its keto form 9t determined as the major isomer from theoretical point of view, was mainly deduced from the conversion of 8 to 9. Pertinent spectral data of 9: IR ν/cm⁻¹ (CHCl₃) 3447, 2927, 1728, 1663, 1437, 1209, 1092, 859; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 138.45 (C), 137.11 (C), 147.62 (CH), 136.15 (CH), 131.67 (CH), 124.46 (CH), 64.28 (CH), 52.22 (CH₃), 44.16 (CH), 43.06 (CH), 31.06 (CH), 27.41 (CH), 21.33 (CH₂); MS (75 eV) m/z 236 (M⁺, 2%), 218 (100%), 186 (76%), 169 (98%), 158 (76%), 145 (76%), 132 (88%); HRMS (EI) Calc. for C₁₃H₂₀O₄ 236.1049, found 236.1054.

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References


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