Tetrahedron Letters,Vol.25,No.47,pp 5371-5372,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

AN ALTERNATIVE SYNTHETIC ROUTE TO COMPACTIN VIA A MICHAEL-ALKYLATION SEQUENCE

N. N. Girotra, R. A. Reamer and N. L. Wendler
Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc.
P. O. Box 2000, Rahway, NJ 07065 USA

Summary: The cis-octalinone **1**, derived from p-benzoquinone and butadiene, was transformed via a Michael-alkylation sequence to the key triene precursor **5b** in a total synthesis of the HMG-CoA reductase inhibitor compactin.

The cis-octalinone **1** is a key intermediate in a total synthesis of compactin.[1] Originally the side chains were introduced into **1** by allylation of its kinetic enolate followed by replacement-methylation of the carbonyl function. In the present instance an alternative pathway employs this same intermediate as acceptor for a tandem Michael-alkylation sequence. This strategy provides a facile pathway to **6** and incorporates as well a new access route to the diene chromophore of compactin.[2]

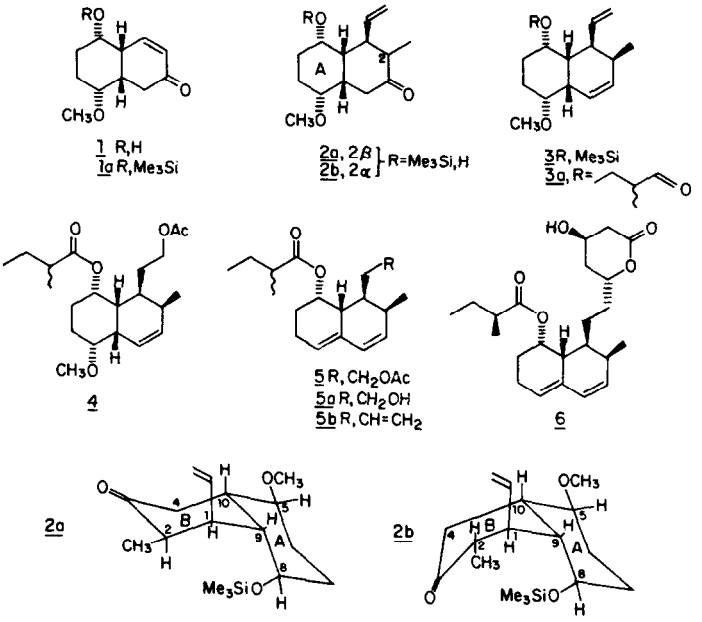
Reaction of **1a** with lithium divinylcuprate[3] followed by quenching of the intermediate enolate with methyl iodide provided a 60:40 mixture (85%) of **2a** (M^+=310) and **2b**, respectively, separable on silica gel (EtOAc-hexane 20:80).[4]

Low temperature ^{13}C and ^1H NMR as well as ambient temperature two-dimensional (2-D) spectra were employed to characterize **2a** and **2b**.[5] In the ^1H NMR spectrum of **2a**, $^3J_{1,2}$=6.1 Hz is in conformity with an axial-equatorial relationship of hydrogens, whereas in **2b**, $^3J_{1,2}$=11.3 Hz indicates these hydrogens to be diaxial. Further, geminal coupling between the 4-methylene protons differs sharply in a manner interpretable in terms of C-H bond orientation relative to the carbonyl π lobes;[6] thus, in **2a**, -12.4 Hz coupling suggests that the carbonyl eclipses one proton whereas in **2b** bisection of the H-C-H angle explains its -18.8 Hz coupling. Finally, in both **2a** and **2b** the C_8-H is equatorial (three small couplings) and the C_5-H is axial (one large and two small couplings). These data require for **2a** a 2β-methyl function in a chair-chair ring system, and for **2b** a 2α-methyl function in a chair (A)-boat (B) ring conformation.

Desilylation (2% aq. HCl, THF, 0°, 15 min) of **2a** and **2b**, R=Me_3Si yielded, respectively, **2a** (R=H), mp 83-85°, M^+=238 and **2b** (R=H), mp 143-144°; M^+238. Equilibration of **2a** and **2b** separately ($NaOCH_3$-CH_3OH) yielded the same 1:4 mixture with **2b** predominating.

Conversion of **2a** by Shapiro reaction ($TosNHNH_2$; LDA, THF, -65 to 0°)[7] to **3**, followed by desilylation (2% aq HCl, THF, 25°) and acylation (± $(C_4H_9CO)_2O$, Py, DMAP, 25°) yielded the diene **3a** (66%), M^+=306. Hydroboration-oxidation (9 BBN, H_2O_2; 75% complete in 5 hrs, conversion yield 92%) with ensuing acetylation (Ac_2O, Py, 25°) afforded the diester olefin **4**, M^+=376. Treatment of **4** with boron tribromide in CH_2Cl_2 at -25°for 5 hrs[8] followed after work-up by mesylation (CH_3SO_2Cl, Py, 0°) and heating the resultant product in pyridine for 2.5 hrs at 105°, produced the

diene **5** (45%), mp 73-75°. The latter was selectively saponified (aq K_2CO_3, CH_3OH, 25°) to **5a** M^+=292, in turn oxidized (CrO_3, Py, CH_2Cl_2) and the intermediate aldehyde converted directly by Wittig olefination ($Ph_3P{=}CH_2$, THF, 0°) to the target triene **5b** (88%). The 250 MHz ^{1}NMR spectrum of **5b** was identical with that of authentic material which had previously been transformed to compactin **6**[1a].



References and Notes

1. N. N. Girotra and N. L. Wendler, Tetrahedron Letters **23**, 5501 (1982); (a) **ibid., 24**, 3687 (1983).
2. For other syntheses of compactin see: R. L. Funk, C. J. Mossman and W. E. Zeller, **ibid. 25**, 1655 (1984).
3. R. M. Coates and L. O. Sandefur, J. Org. Chem. **39**, 275 (1974); H. O. House, C. Y. Chu, J. M. Wilkins and M. J. Umen, **ibid. 40**, 1460 (1975).
4. Michael-alkylation in the trans-octalinone series has been observed to give exclusively the α-methyl isomer (N.Y. Wang, C. T. Hsu and C. J. Sih, J. Am. Chem. Soc. **103**, 6538 (1981)).
5. ^{1}H spectra were obtained on a Bruker WM-250 NMR spectrometer with .391 Hz/point digital resolution. Tetramethylsilane was the internal reference. Assignments were unequivocally made via 2-D "COSY-45" NMR and selected double-resonance experiments.
   2a ^{1}NMR (CD_2Cl_2) δ 0.84, 2-CH_3 (d, 6.9); 2.17, 4-CH_e (d of d of d, 12.4, 4.2, 1.0); 2.61 10-CH (d of m, 13.8); 2.73, 1-CH (d of d of d, 9.9, 6.1, 1.3); 2.86, 4-CH_a (d of d of d, 13.8, 12.4, 1.0); 3.22, 5-CH (d of d of d, 11.4, 5.1, 4.1); 3.28, OCH_3 (s); 3.53, 2-CH (q of d of d, 6.9, 6.1, 1.0); 4.15, 8-CH (q, 2.5).
   2b ^{1}H NMR (CD_2Cl_2), T-60° δ 0.93, 2-CH_3 (d, 6.3); 1.94, 1-CH (d of d of d, 11.3, 10.1, 3.0); 2.12, 4-CH_e (d of d 18.8, 6.8); 2.41, 2-CH (d of q, 11.3, 6.3); 2.53, 4-CH_a (d of d, 18.8, 12.9); 2.94, 10-CH, (d of m, 12.9); 3.32, OCH_3 (s); 5-CH is partially obscured by OCH_3 resonance; 3.76, 8-CH (q, 2.5).
6. M. Barfield and D. M. Grant, J. Am. Chem. Soc. **85**, 1899 (1963).
7. See for example: R. M. Adlington and A. G. M. Barrett, Acc. Chem. Res. **16**, 55 (1983).
8. The BBr_3 product consisted primarily of bromide together with lesser amounts of carbinol and triene.

(Received in USA 9 July 1984)