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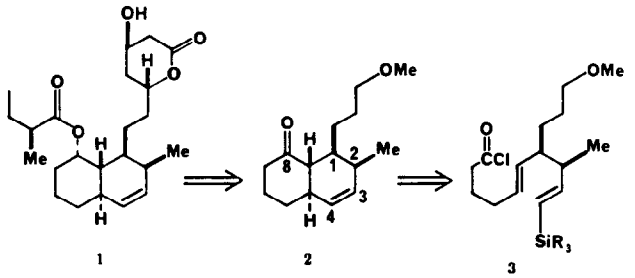
VINYLSILANE-MEDIATED POLYENE CYCLIZATION. SYNTHESIS OF THE OCTAHYDRONAPHTHALENOL PORTION OF DIHYDROCOMPACTIN.

Steven D. Burke,*‡ Jeffrey O. Saunders, Jeffrey A. Oplinger, and Charles W. Murtiashaw
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Abstract: A synthesis of the octahydronaphthalenol portion **12** of the HMG-CoA reductase inhibitor dihydrocompactin (**1**) is described, wherein a vinylsilane-terminated polyene cyclization and variants of the Claisen rearrangement provide key elements of regio- and stereocontrol.

An earlier report from these laboratories described a spiroannulation based upon an intramolecular vinylsilane acylation.[1] Our interest in developing a dihydrocompactin (**1**)[2] synthesis led us to investigate a related bicyclization by which the octalone **2** would be produced from the vinylsilane **3**. In addition to the well-precedented[3] conversion of internal *E*-olefin sp^2 geometry in **3** to trans ring-fusion sp^3 stereochemistry in **2**, such a process would exploit the "superproton" behavior of the silyl residue to regioselectively generate the C3-C4 unsaturation.[4] The implementation of this synthetic strategy for the octahydronaphthalenol portion of dihydrocompactin (**1**), with stereocontrolled generation of five contiguous asymmetric centers, is described herein.



1 2 3

The first of two routes to the precursor of dienic acid chloride **3** is outlined in Scheme I.[5] Addition of phenyldimethylsilyllithium[6] to *trans*-crotonaldehyde in tetrahydrofuran at -100°C gave the allylic alcohol **4** (55%). Acylation of **4** with 5-methoxypentanoyl chloride gave ester **5** (87%), which was subjected to an Ireland ester enolate Claisen rearrangement[7] to give the γ,δ-unsaturated acid **6a** (mp 50-51°C). Treatment of **6a** with ethereal CH_2N_2 afforded ester **6b** (64% from **5**), which was shown by glass capillary GC[8] to favor the indicated diastereomer by a 42:1 ratio.[9] The aldehyde **6c** was best produced (89%) by over-reduction ($LiAlH_4$, Et_2O, 0 → 25°C) and reoxidation with Collins reagent.[10] Addition of vinylmagnesium bromide (THF, -78°C) to **6c** gave the allylic alcohol diastereomers **7** (75%), which converged to a single dienic aldehyde **8** (81%). Straightforward Wittig homologation and hydrolysis gave the aldehyde **9a** (98%) which afforded the carboxylic acid **9b** (Jones reagent, 25°C, 30 min, 88%).

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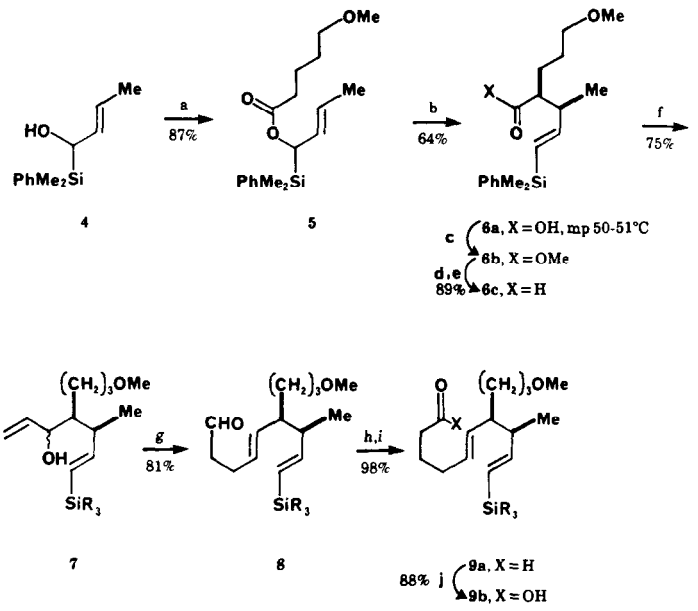
Scheme I[5]



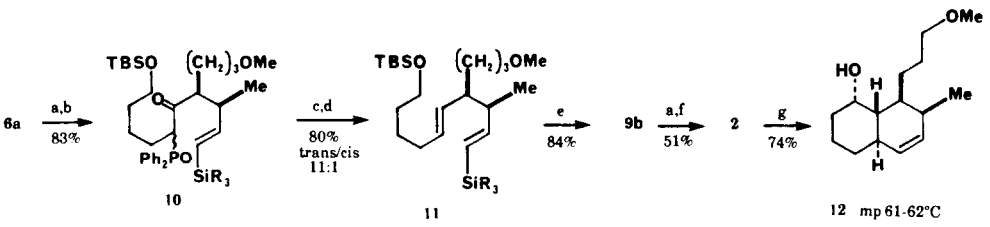
(a) $ClCO(CH_2)_4OMe$, PhH, pyridine, 0 → 25°C, 6 h. (b) LDA, THF, -78°C, 45 min; *t*-$BuMe_2SiCl$, TMEDA, -78 → 25°C, 3 h; 5% aq HCl, 12 h. (c) CH_2N_2, Et_2O, 0 → 25°C. (d) $LiAlH_4$, Et_2O, 0 → 25°C. (e) CrO3·2 pyr, CH_2Cl_2. (f) $H_2C=CHMgBr$, THF, -78°, 20 min. (g) $H_2C=CHOEt$, $Hg(OCOCF_3)_2$; PhH, sealed tube, 200°C, 2 h. (h) $Ph_3P=CHOMe$, THF, -78°C, 1 h. (i) 5% aq HCl, THF, 25°C, 2 h. (j) $H_2Cr_2O_7$, aq acetone, 25°C, 30 min.

The use of two variants of the Claisen rearrangement[11] in this sequence accomplished three requirements: (1) generation of the vinylsilane moiety; (2) control of the relationship between the C1 and C2 stereocenters; and (3) the establishment of the *E*-disubstituted central olefin. Each of these consequences follow directly from the inherent stereocontrol elements of the Claisen rearrangement.

A second route to **9b** is detailed in Scheme II.[5] Coupling of the acid chloride from **6a** with [1-lithio-5-(*t*-butyldimethylsiloxy)pentyl]diphenylphosphine oxide (THF, -78°C) gave a mixture of diastereomeric phosphine oxides **10** in 83% yield.[12] Carbonyl reduction with DIBAL (*i*-Bu_2AlH) in Et_2O at -12°C followed by treatment of the resulting alcohols with NaH (THF, 25°C, 18 h) gave the diene **11** (80%, trans/cis = 11).[13] Exposure of **11** to Jones reagent at 0°C resulted in cleavage of the silyl ether and oxidation to the carboxylic acid **9b** (85%).

Reaction of **9b** with 10 eq of oxalyl chloride (C_6H_6, 25°C, 8 h) followed by removal of the volatile components *in vacuo* gave the crude acid chloride **3**, which was used without purification. A solution of **3** in CH_2Cl_2 (0.18 M, -78°C) was treated with 3 eq of $SbCl_5$ (1 M in CH_2Cl_2). After 10 min the reaction was quenched with aq $NaHCO_3$ to afford, after standard work-up and silica gel chromatography, the desired octalone **2** in 51% yield. Other combinations of Lewis acids ($TiCl_4$, $SnCl_4$, $ZnCl_2$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $BF_3·Et_2O$, $AgBF_4$, $SbCl_3$, SbF_3) and solvents (CH_2Cl_2, $CHCl_3$, C_6H_6, CH_3NO_2) at various temperatures were less effective.

Scheme II[a]



(a) $(ClCO)_2$, PhH, 25°C, 8 h. (b) $Ph_2P(O)CHLi(CH_2)_4OSiMe_2t$-Bu, THF, -78°C, 30 min. (c) i-Bu_2AlH, Et_2O, -12°C, 2 h. (d) NaH, THF, 25°C, 18 h. (e) $H_2Cr_2O_7$, aq acetone, 0°C, 30 min. (f) 3 equiv $SbCl_5$, CH_2Cl_2, -78°C, 10 min. (g) KBH (sec-Bu)$_3$, THF, 0 → 25°C, 1 h.

The gross structure of **2** was apparent from the IR ($\nu_{C=O}$ = 1718 cm^{-1}) and mass (parent at m/e 236) spectra. Evidence for the relative stereochemistries at C1, C4a, and C8a was available from a J-resolved 2D ^{1}H NMR experiment,[14] wherein the angular proton at C8a was found to be strongly coupled to two others with J = 11.3 and 11.4 Hz.

Conclusive proof of structure was obtained by x-ray diffraction analysis of the axial alcohol **12** (mp 61-62°C), derived from **2** by reduction with KBH(s-Bu)$_3$[15] (THF, 0 → 25°C, 74%). An ORTEP drawing of **12** is shown in Figure 1.[16]

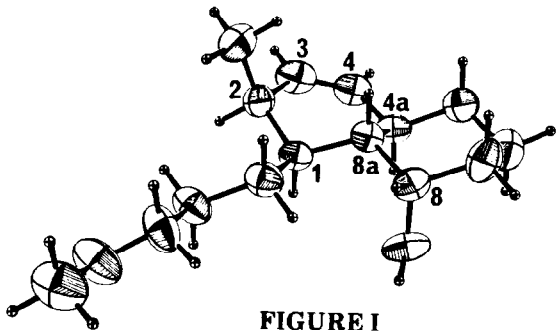


FIGURE I

In summary, a novel and convergent route to the octahydronaphthalenol portion of dihydrocompactin has been developed. The refinement and application of this sequence to the synthesis of the mevinic acids is underway.

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3. For a review detailing biomimetic polyene-to-polycycle conversions, see: Johnson, W. S. *Bioorganic Chemistry* **1976**, *5*, 51.

4. For examples of reactions between carbon electrophiles and vinylsilanes, see: (a) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. I* **1984**, 1815. (b) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (c) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297. (d) Tius, M. A. *Tetrahedron Lett.* **1981**, *22*, 3335. (e) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642 and references therein.

5. In the Schemes, all chiral substances were produced as racemates; a single enantiomer is shown for simplicity. All structural assignments are supported by IR, 400 MHz ^{1}H NMR, ^{13}C NMR, and mass spectrometric and elemental analyses. Yields cited are for chromatographically and spectroscopically pure substances.

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7. (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479. (b) Ireland, R. E.; Vevert, J.-P. *Ibid.* **1980**, *45*, 4259. (c) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *Ibid.* **1980**, *45*, 48. (d) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (e) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *Ibid.* **1976**, *98*, 2868. (f) Ireland, R. E.; Mueller, R. H. *Ibid.* **1972**, *94*, 5897. Concurrent with our studies, a related vinylsilane generation was forthcoming from the Ireland laboratories. See (g) Ireland, R. E.; Varney, M. D. *Ibid.* **1984**, *106*, 3668.

8. Glass capillary GC analyses were performed on a 25 m x 0.2 mm i.d. column coated with SE-54 (Alltech Assoc., Inc., Deerfield, IL).

9. In our hands the typical conditions as described by Ireland[7] for such rearrangements lead to diastereoselectivities ranging from 7.5:1 to 13:1. The use of TMEDA as an additive decreases enolate *C*-silylation dramatically, with the observed enhanced diastereoselection as the benefit. The 42:1 ratio reflects the *trans/cis* isomeric purity of the crotonaldehyde used.

10. Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**. *35*, 4000.

11. For general reviews of the Claisen rearrangement, see: (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

12. (a) Buss, A. D.; Cruse, W. B.; Kennard, O.; Warren, S. *J. Chem. Soc., Perkin Trans. I* 1984, 243. (b) Buss, A. D.; Mason, R.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 5293.

13. The conditions usually cited by Warren[12] for elimination of the β-hydroxy phosphine oxides involve NaH/*DMF* at 50°C. The somewhat milder conditions used here gave, on two occasions, *t/c* ratios exceeding 40:1, presumably reflecting selective elimination of the threo isomer.

14. For a general discussion of J-resolved 2D and related NMR methods, see: Benn, R.; Günther, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 350. We are grateful to Ms. Helga Cohen of the South Carolina Magnetic Resonance Laboratory in our Department for assistance in acquiring these data.

15. KBH (*s*-Bu)$_3$ is available as a 1 M solution in THF from the Aldrich Chemical Company, Milwaukee, WI. For a related use of this reagent, see: Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.

16. The structure determination was done on an Enraf-Nonius CAD-4 diffractometer. The structure was solved by multisolution tangent refinement using MULTAN80. The calculations were done with the Enraf-Nonius structure determination package (Frenz, 1982). We thank Dr. Lukasz Lebioda of this Department for x-ray structural services.

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