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Synthesis of (+)-Dihydrocompactin and (+)-Compactin via Vinylsilane Terminated Cationic Cyclization

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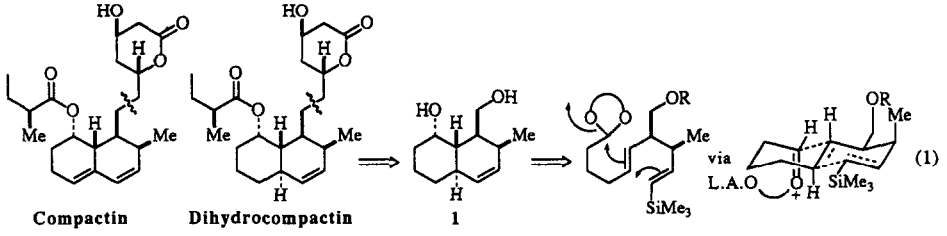
Abstract: *Two enantioselective routes to the octalin diol 1 are described, featuring cationic polyene cyclization mediated by a vinylsilane terminating group and a benzenedimethanol acetal initiator. Further transformations resulting in formal and total syntheses of (+)-compactin and (+)-dihydrocompactin, respectively, are also reported.*

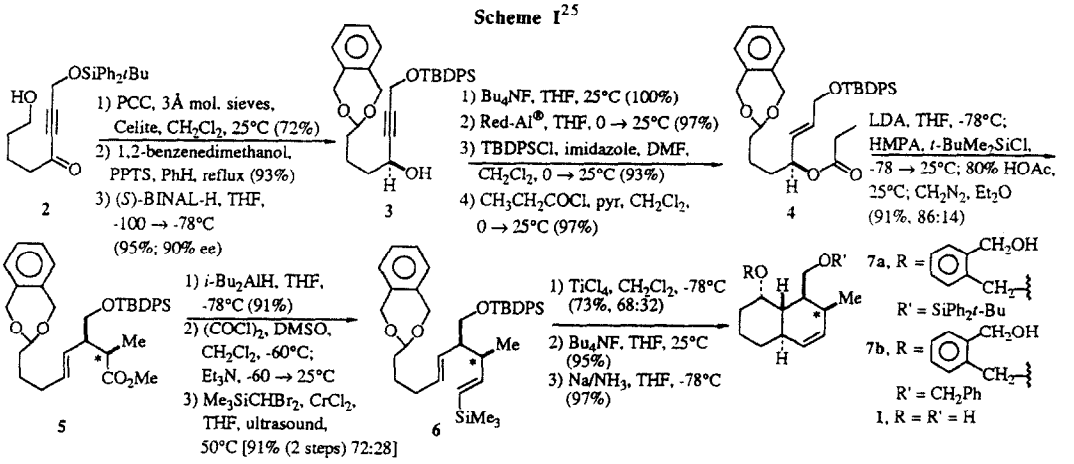
Numerous synthetic approaches to the hypocholesterolemic mevinic acids have been reported,[2] often featuring Diels-Alder or aldol constructions of the hydronaphthalene subunit.[3] We have explored an alternative strategy toward these medicinally-significant substances that employs an acetal initiated cationic polyene cyclization[4] terminated by a vinylsilane. This route directly emplaces the alkene and secondary alkoxyl groups with the required contrathermodynamic regio-[5] and stereochemistry, respectively, in the bicyclic product. Reported here are enantioselective syntheses of dihydrocompactin[6] and compactin[7] by the approach outlined antithetically in eq 1, with bicyclic diol **1**[3m] as an intermediate in common.



Achiral ynone **2** (Scheme I) was formed in 99% yield by acylation of the lithium acetylide from (*t*-butyldiphenyl)siloxypropyne with δ-valerolactone. Oxidation to the aldehyde[8] and conversion to the benzenedimethanol acetal[9] were followed by a Noyori asymmetric reduction[10] to provide propargylic alcohol **3** in 90% enantiomeric excess.[11] Temporary desilylation,[12] stereoselective alkyne reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®),[13] resilylation[14] of the primary hydroxyl, and acylation with propionyl chloride gave the *trans*-allylic propionate **4** (88% overall from **3**). Ireland-Claisen rearrangement[15] of **4** via the (*E*)-silylketene acetal gave, after conversion to the methyl ester, the (*E*)-alkene **5** in diastereomeric ratios of 6 → 8:1, differing at the center marked (*). The four contiguous sp^2 and sp^3 stereogenic centers in **5** were thus established via the well-known features of the Claisen rearrangement transition state.[16]

Installation of the vinylsilane residue required homologation of the aldehyde derived from **5**. A modification of Takai's procedure[17] was employed that resulted in a dramatic increase in the rate of formation of *trans*-vinylsilane **6**. Sonication[18] of the heterogeneous mixture at 50°C increased the reaction rate by

Scheme I[25]



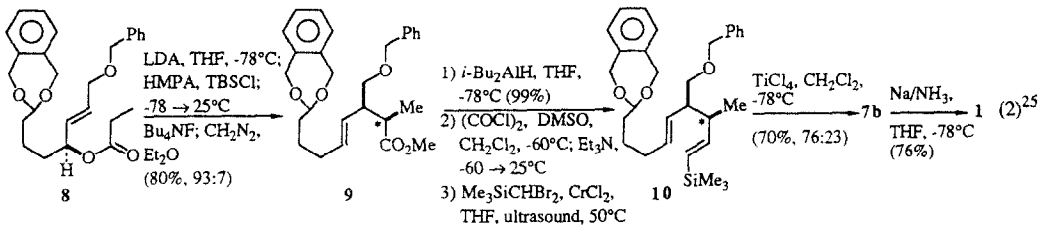
approximately twenty-fold, minimizing the extent of randomization of the α-chiral center in the aldehyde substrate. Cyclization substrate **6** was thus produced as a 2 → 4:1 mixture of diastereomers, with the indicated configuration (*) predominating.

Treatment of acetal **6** with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at -78°C triggered polyene cyclization to give octalins **7a** (as a mixture carried over from **6**) which were separated by flash chromatography.[19] Cleavage of the silyl ether with fluoride[14] and reductive removal of the acetal remnant gave diol **1** (92%), which was spectroscopically identical to an authentic sample.[3m]

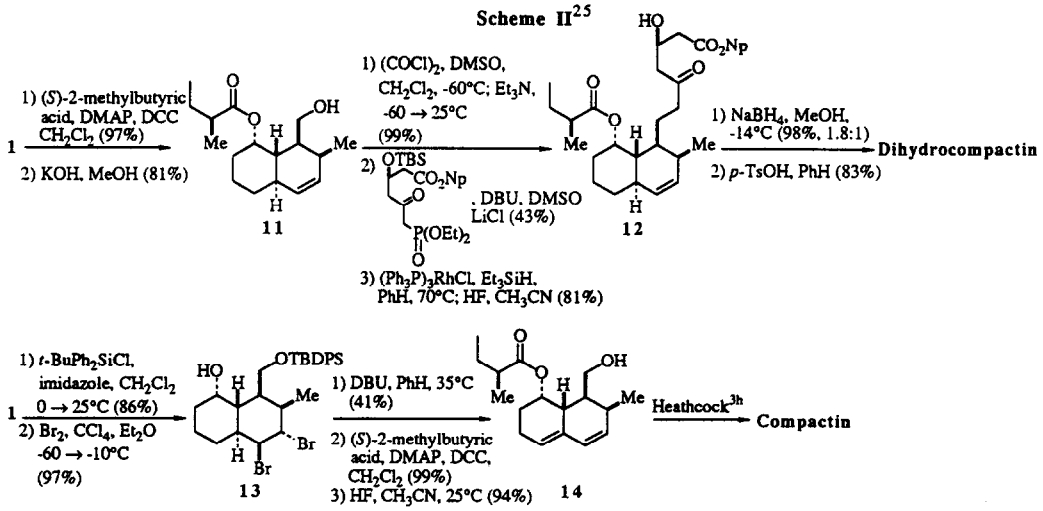
Noteworthy features of the bicyclization step are: (1) the selective displacement of the "equatorial" acetal oxygen,[20] (2) the emergence of five contiguous asymmetric centers controlled by the equatorial deployment (see eq 1) of the siloxymethyl substituent, and (3) the successful involvement of the (*E*)-vinylsilane,[21] which cannot provide optimal stabilization via the β-effect.[22]

A streamlined synthesis of the Funk-Zeller diol **1** is presented in eq 2. Ireland-Claisen rearrangement substrate **8** was synthesized in 47% overall yield from δ-valerolactone by a sequence analogous to that used to produce **4** (Scheme I). Stereogenicity transfer from the allylic propionate **8** to the γ,δ-unsaturated ester **9** proceeded with >13:1 diastereoselectivity. Homologation of the derived aldehyde via the modified Takai procedure[17] (*vide supra*) gave the (*E*)-vinylsilane **10** in ratios of 3 → 5:1, differing in configuration at the indicated carbon. $TiCl_4$-induced bicyclization afforded octalins **7b** (76:23), which were separated at this stage by flash chromatography.[19] Reductive cleavage of both benzylic ether linkages with sodium in ammonia gave the scalemic[23] diol **1** in twelve steps from δ-valerolactone.

Production of (+)-dihydrocompactin from **1** involved an adaptation of Heathcock's protocol,[3h] except that we did not require a resolution. Bis(acylation)[24] of diol **1** with (*S*)-2-methylbutyric acid followed by



Scheme II[25]



selective saponification of the less hindered ester gave primary alcohol **11** (Scheme II). Heathcock's ketophosphonate route for the introduction of the hydroxylactone moiety provided (+)-dihydrocompactin, which was identical to an authentic sample.[3a]

The Funk sequence[3m] for effecting net dehydrogenation via bromination/double dehydrobromination was applied to the mono TBDPS ether[14] of **1**. Vicinal dibromide **13** was formed (97%) and subjected to dehydrohalogenation with DBU, affording the product of successive 1,2- and 1,4-eliminations in modest yield. Acylation of the axial secondary hydroxyl group with (*S*)-2-methylbutyric acid via the Steglich procedure (99%) and silyl ether cleavage (94%) gave hexalin **14**, an intermediate in Heathcock's synthesis of (+)-compactin.[3h]

In summary, a nineteen step total synthesis of (+)-dihydrocompactin and a formal synthesis of (+)-compactin have been completed. The vinylsilane terminated/acetal initiated cationic cyclization route is well-suited to the production of bicyclic intermediate **1** and is unlike any of the other reported strategies.[2,3]

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REFERENCES AND NOTES

1. Recipient of a National Science Foundation Presidential Young Investigator Award (1984-89); Research Fellow of the Alfred P.Sloan Foundation (1984-88).
2. For a review of synthetic efforts in this area, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.
3. Synthesis of (+)-dihydrocompactin: (a) Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811. Synthesis of (+)-compactin: (b) Daniewski, A. R.; Uskokovic, M. R. *Tetrahedron Lett.* **1990**, *31*, 5599. (c) Clive, D. L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Siva Prasad, J.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (d) Danishefsky, S. J.; Simoneau, B. *Ibid.* **1989**, *111*, 2599. (e) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1987**, *52*, 3541. (f) Keck, G. E.; Kachensky, D. F. *Ibid.* **1986**, *51*, 2487. (g) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908. (h) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. (i) Girotra, N. N.; Reamer, R. A.; Wendler, N. L. *Tetrahedron Lett.* **1984**, *25*, 5371. (j) Girotra, N. N.; Wendler, N. L. *Ibid.* **1983**, *24*, 3687 and **1982**, *23*, 5501. (k) Hsu, C.-T.; Wang, N.-Y.; Latimer, L. H.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 593. (l) Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251.

(m) Funk, R. L; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180 and Zeller, W. E. Ph.D. thesis, University of Nebraska, **1985**.

4. (a) Burke, S. D.; Takeuchi, K.; Murtiashaw, C. W.; Liang, D. W. M. *Tetrahedron Lett.* **1989**, *30*, 6299. For a detailed review of polyene cyclizations with acetal and non-acetal initiators, see: (b) Bartlett, P. A. In "Asymmetric Synthesis," Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 341.
5. The exceptional electrofugality of the silyl group directs elimination away from the more substituted position. See ref. 21.
6. Lam, Y. K. T.; Gullo, V. P.; Goegelman, R. T.; Jorn, D.; Huang, L.; DeRiso, C.; Monaghan, R. L.; Putter, I. *J. Antibiot.* **1981**, *34*, 614.
7. (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. I* **1976**, 1165.
8. For pyridinium chlorochromate (PCC) oxidations utilizing molecular sieves and/or Celite, see: (a) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561. (b) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699. (c) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744.
9. Acetals of 1,2-benzenedimethanol have been previously prepared and used for carbonyl protection. See: (a) Smith, J. G.; Kruger, G. *J. Org. Chem.* **1985**, *50*, 5759. (b) Yamaguchi, M.; Okuma, T.; Nakamura, S.; Minami, T. *J. Chem. Soc., Perkin Trans. I* **1990**, 183. (c) Watanabe, H.; Mori, K. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1988**, *30*, 447. (d) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1989**, *30*, 4165.
10. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
11. The enantiomeric excess was determined by peak integration of the ^{19}F NMR spectrum of the derived Mosher's ester. See: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
12. Poor yields of the desired *trans*-allylic alcohol were obtained without first removing the silyl protecting group. This deprotection/reprotection was avoided by the alternative route (eq 2) using a benzyl ether.
13. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
14. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
15. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
16. For recent reviews of the Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Blechert, S. *Synthesis* **1989**, 71. (c) Hill, R. K. In "Asymmetric Synthesis," Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 503.
17. Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 1443.
18. For an excellent review of the use of ultrasound in chemistry, see: Suslick, K. S. In "Modern Synthetic Methods 1986," Scheffold, R., Ed.; Springer-Verlag: Berlin 1986, p 1.
19. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
20. We attribute the emergence of the axial C-O bond in **7a** and **7b** to cyclization via the axially-oriented oxocarbenium ion depicted in eq 1. The alternative orientation of the oxocarbenium residue suffers from a *syn* pentyl-type interaction with the equatorial alkoxymethyl substituent in the bicyclization transition state. Additional supporting data and discussion related to this observation will be presented elsewhere. For recent detailed discussions of mechanistic features of Lewis acid induced acetal substitution, see: (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (b) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258 and references cited therein.
21. For reviews of electrophilic substitution reactions of vinylsilanes, see: (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
22. Of the 38 kcal/mol of β-cation stabilization due to silicon, approximately one-fourth is due to inductive donation. Most of the effect is attributed to hyperconjugation, which requires a (*Z*)-vinylsilane in a chair-like cyclization transition state. (a) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496. (b) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. Use of a (*Z*)-vinylsilane in a related cyclization leads predominantly to cyclization via the alternative chair-chair conformer, in order to avoid a 1,3-diaxial interaction between the methyl and silyl substituents in the transition state. The stereochemistry at the three new sp^3 centers is then reversed relative to **7a** and **7b**.
23. For the first use of the term *scalemic*, see footnote 8 in: Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.
24. (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *46*, 4475.
25. Yields cited in the Schemes and eq 2 are for chromatographically pure substances. All structural assignments are in accord with spectroscopic and analytical data.

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