resulted in, following standard workup and preparative TLC (3% ether–CH_2Cl_2), 0.58 g (45%) of **(4R*)-4-[(S*)-1-hydroxy-1-phenylmethyl]-5-(phenylsulfonyl)-2,3-dihydro-4H-pyran (63)** as a white solid: mp 150–152 °C; ^1H NMR (79.5 MHz, $CDCl_3$) δ 1.55 (m, 2 H), 2.52 (dt, 1 H, J = 6 and 1 Hz), 3.3 (dt, 1 H, J = 12 and 4 Hz), 3.9 (m, 3 H, 1 H exchanged D_2O), 4.94 (dd, 1 H, J = 7 and 2.5 Hz, collapsed to d, J = 7 Hz, on D_2O exchange), and 7.12–7.9 (M, 11 H); m/e 330, 225, 224 (base), 107, 99, 83, and 77. Anal. Calcd for $C_{18}H_{18}SO_4$: C, 65.44; H, 5.50; S, 9.69. Found: C, 65.30; H, 5.52; S, 9.79.

LDA-Induced Cyclization of (1R*,2R*,6R*)-2-[[2-(Phenylsulfonyl)ethenyl]oxy]-7-oxabicyclo[4.1.0]heptane (65). A solution containing 0.5 g of epoxy alcohol **64** and 1.0 g of 1-chloro-2-(phenylsulfonyl)ethylene in 20 mL of dry THF was cooled to −20 °C and was treated with NaH (5.2 mmol). Standard reaction conditions, workup, and preparative TLC of the residue afforded 0.48 g (40%) of **65**: mp 77–79 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.13–2.16 (m, 6 H), 3.13 (m, 2 H), 4.21 (t, 1 H, J = 6 Hz), 5.80 (d, 1 H, J = 12 Hz), 7.42–8.05 (m, 6 H); m/e 281, 185, 125, 97 (base), and 79. Anal. Calcd for $C_{14}H_{16}SO_4$: C, 59.98; H, 5.76; S, 11.42. Found: C, 59.98; H, 5.81; S, 11.43.

Treatment of a 0.48-g sample of **65** in 15 mL of THF with 2 mL of a 1.0 M LDA solution, under the reaction conditions outlined above, gave, after standard workup and preparative TLC, 0.2 g (44%) of **(3aR*,4R*,7aR*)-3a,4,5,6,7,7a-hexahydro-3-(phenylsulfonyl)-4-benzofuranol (66)**: mp 59–61 °C; ^1H NMR (79.5 MHz, $CDCl_3$) δ 1.10–2.13 (m, 6 H), 2.43 (t, 1 H, J = 5 Hz), 3.67 (m, 1 H), 4.22 (d, 1 H, J = 2.5 Hz), 4.60 (m, 1 H, exchanged D_2O), and 7.36–8.05 (m, 6 H); m/e 281, 280, 236, 143, 125, 95 (base), and 77. Anal. Calcd for $C_{14}H_{16}SO_4$: C, 59.98; H, 5.76; S, 11.42. Found: C, 60.39; H, 5.89; S, 11.60.

Acknowledgment. This work was supported by the National Cancer Institute (CA-26750). Use of the high-field NMR spectrometers used in these studies was made possible through equipment grants from the National Science Foundation and the National Institute of Health.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra (75 MHz) for all compounds with high-resolution mass spectra (7 pages). Ordering information is given on any current masthead.

Novel Synthesis of Mevinolin-Related Compounds. Large-Scale Preparation of HMG-CoA Reductase Inhibitor L-679,336

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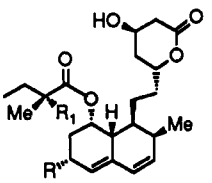
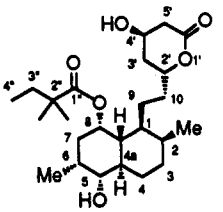
A novel synthetic route to a mevinolin-related HMG-CoA reductase inhibitor L-679,336 is described. The key features of the synthesis are a diastereoselective osmium tetraoxide catalyzed dihydroxylation reaction and a highly selective, phosphorus-mediated, pinacol-type rearrangement to give ketone **6**. In situ multinuclear NMR experiments were used to gain a detailed understanding of the pinacol step. The above route was used for multikilogram preparation of the title compound. Also described are Lewis acid catalyzed rearrangement reactions of epoxide intermediates **4** and **5**, as well as the intramolecular hydrosilylation reaction of deacylated olefinic substrates **17** and **18**.

Introduction

Recently, there has been strong interest in the chemistry and biology of the mevinic acid family of compounds.[1] Members of this class, which include Mevacor (**1a**), Zocor (**1b**), compactin (**1c**), and others, are useful in the treatment of elevated bloodserum cholesterol in humans. They function as potent inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme which governs the rate-determining step in cholesterol biosynthesis.[2] The parent natural products **1a** and **1c** are obtained as fermentation products of *Streptomyces* fungi.[3]



1a R = Me, R_1 = H
1b R = R_1 = Me
1c R = R_1 = H



2
L-679,336

In an effort to improve pharmacological properties, semisynthetic derivatives of Mevacor (**1a**), including Zocor (**1b**) and many others have been prepared.[4] We wish to describe some novel and very interesting chemistry that has been revealed in our synthetic studies of an important new analogue L-679,336 (**2**).

Discussion

The original synthesis of **2** from **1b** was reported by medicinal chemists at Merck.[5] In order to facilitate larger

(1) (a) Review: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909. (b) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197 and references therein. (c) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis*, **1989**, 539. (d) Clive, D. L. J.; Murthy, K. S. K.; Nee, A. G. H.; Prasad, J. S.; daSilva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914. (e) Burke, S. D.; Takeuchi, K.; Murtiashaw, C. W.; Liang, D. W. M. *Tetrahedron Lett.* **1989**, 6299.

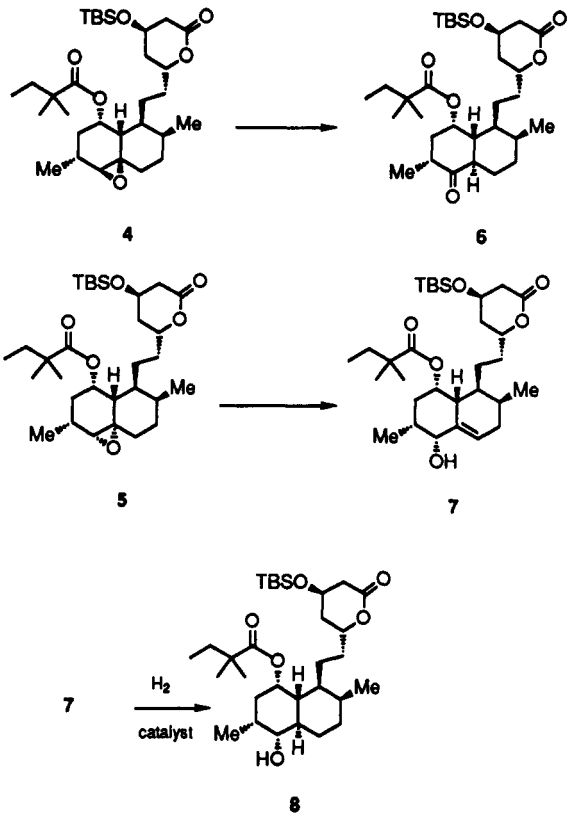
(2) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monoghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensen, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

(3) (a) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H.; *J. Chem. Soc., Perkin Trans.* **1**, **1976**, 1165. (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (c) Endo, A. *Ibid.* **1979**, *32*, 852.

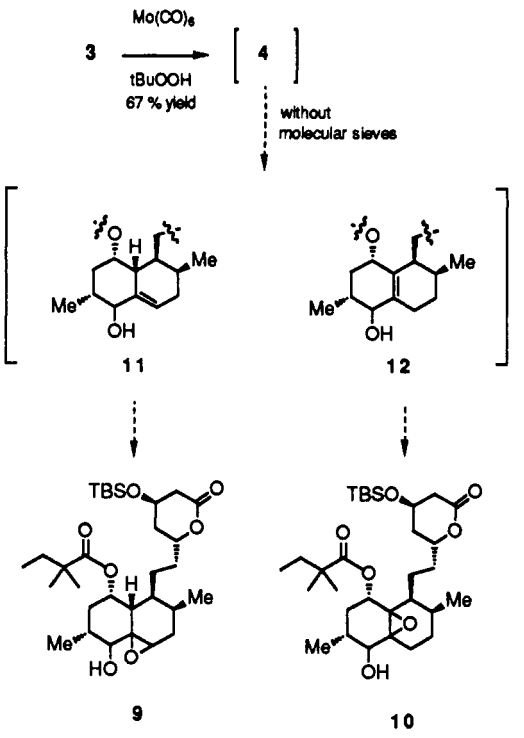
(4) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849 and references therein.

0022-3263/91/1956-3564$02.50/0

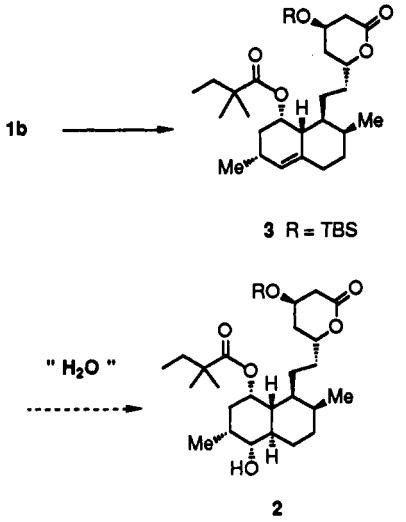
Scheme I



Scheme II



scale synthesis, we have explored alternative routes to **2**, primarily via the previously described olefin intermediate **3**.[6] Theoretically, **2** could be prepared by the syn addition of water to the very hindered α-face of the C_{4a-5} double bond of **3** in an anti-Markovnikov orientation. Unfortunately, this straightforward approach was not feasible via simple intermolecular hydroboration or hydrosilylation protocols,[7] due to preferential β-face attack and/or competitive lactone reactivity. We therefore investigated several alternative routes to **2**.



Synthesis of 2 via Epoxides. The synthesis of **2** via epoxide intermediates **4** and **5** was explored as shown in Scheme I. Lewis acid catalyzed rearrangement[8] of β-epoxide **4** could lead to known ketone intermediate **6**.[5] Alternatively, ring opening of α-epoxide **5** could lead to allylic alcohol **7**,[9] which would be subjected to hydroxyl-directed reduction[10] to give the previously described[5] alcohol **8**.

Epoxide **4** was prepared from **3** (R = TBS) by molybdenum hexacarbonyl catalyzed epoxidation[11] (Scheme II). No epoxide **5** was formed under these conditions. Interestingly, byproducts **9** and **10**[12] were formed (in 17% yield), probably via **11** and **12**, respectively, *unless* molecular sieves (4A) were present in the reaction medium. Conversely, epoxide **5** was selectively prepared from **3** by the procedure of Ganem (hexafluoroacetone hydrate, H_2O_2).[13] Peracid epoxidation reagents (including MCPBA, perphthalic acid, magnesium perphthalate) gave unusable mixtures of **4** and **5**.

With epoxides **4** and **5** in hand, their chemistry was explored as shown in Schemes III and IV, respectively. Certain Lewis acids (for example, boron trifluoride eth-

(5) Duggan, M.; Hartman, G. *European Patent Publication* Ser. No. 0349063, published Jan. 3, 1990; U.S. Patent 4,921,974. Duggan, M. E.; Alberts, A. W.; Bostedor, R.; Chao, Y.; Germershausen, J. I.; Gillfillan, J. L.; Halczenko, W.; Hartman, G. D.; Hunt, V.; Imagire, J. S.; Schwartz, M. S.; Smith, R. L.; Stubbs, R. J. *J. Med. Chem.*, submitted for publication.

(6) (a) DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. U.S. Patent No. 4,831,165. (b) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991.

(7) Tamaro, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983.

(8) (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Maruoka, K.; Nagahara, S.; Takashi, O.; Yamamoto, H. *Tetrahedron Lett.* **1989**, 5607 and references therein. (c) Smith, J. G. *Synthesis* **1984**, 629.

(9) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596.

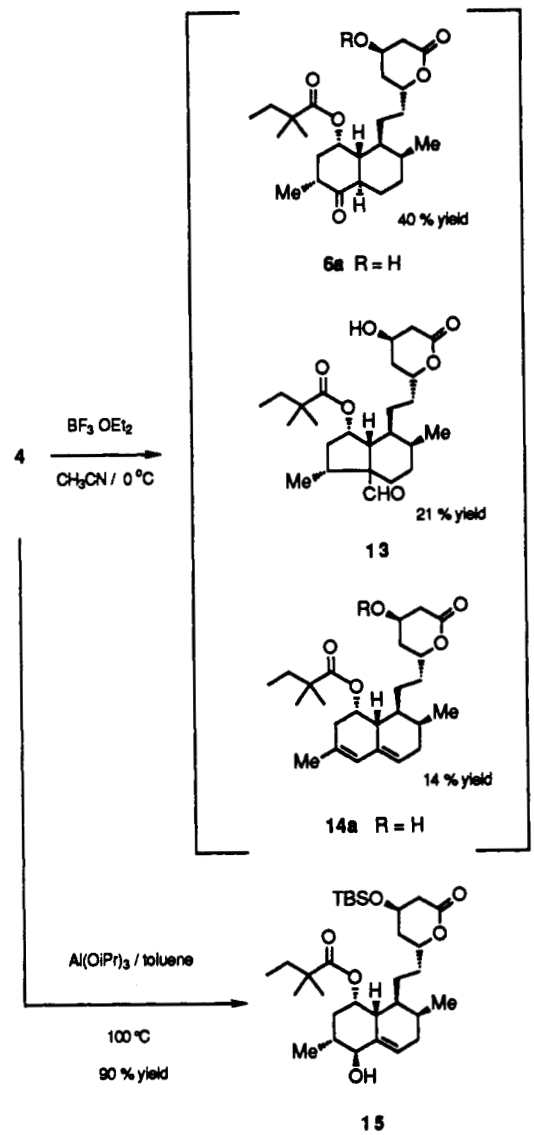
(10) (a) Crabtree, R. H.; Davis, M. H. *J. Org. Chem.* **1986**, *51*, 2655. (b) DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. *Ibid.* **1989**, *54*, 3207. (c) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (d) Evans, D. A.; Morrissey, M. M. *Ibid.* **1984**, *106*, 3866.

(11) (a) Groen, M. B.; Zeelen, F. J. *Tetrahedron Lett.* **1982**, 3611. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(12) **9** and **10** were characterized as a 50/50 mixture. **9**: ^{1}H NMR ($CDCl_3$, 400.1 MHz) 5.27 (br ddd, J = 5.6, 2.8, 1.2 Hz, H_8), 3.63 (dd, J = 10.3, 9.5 Hz, H_5), 3.30 (br t, J = 2.0 Hz, H_4), 2.01 (d, J = 9.5 Hz, C_5-OH), 1.04 (d, J = 6.7 Hz, C_6-Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 70.5 (C_5), 69.2 (C_8), 60.9 (C_{4a}), 56.9 (C_4, $^1J_{CH}$ = 173.5 Hz), 35.3 (C_7), 31.4 (C_6), 19.3 (C_6-Me). **10**: ^{1}H NMR ($CDCl_3$, 400.1 MHz) 4.98 (dd, J = 7.1, 5.6 Hz, H_8), 3.42 (dd, J = 9.4, 8.1 Hz, H_5), 1.80 (d, J = 9.4 Hz, C_5-OH), 1.00 (d, J = 6.7 Hz, C_6-Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 77.0 (C_5), 70.4 (C_8), 68.6 and 66.2 (C_{4a}, C_{8a}), 33.1 (C_7), 30.9 (C_6), 18.8 (C_6-Me).

(13) Heggs, R. P.; Ganem, B. *J. Am. Chem. Soc.* **1979**, *101*, 2484.

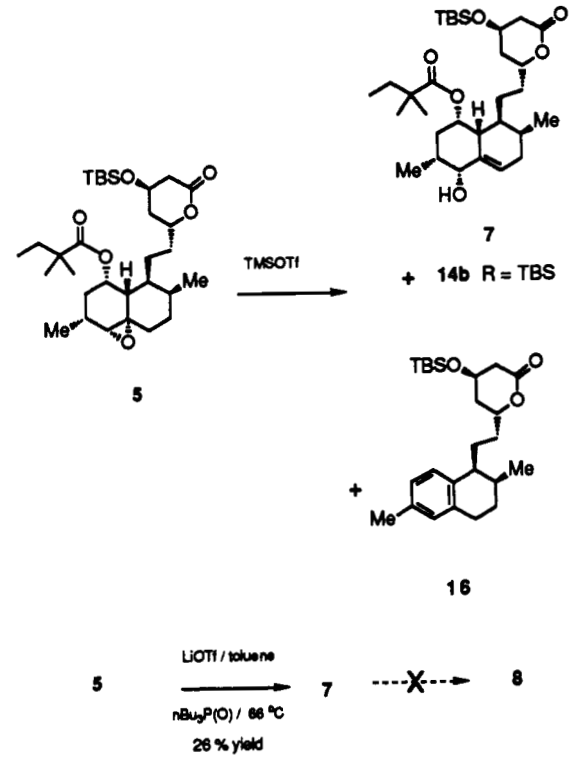
Scheme III



erate, CH_3CN, 0 °C) caused rearrangement of **4** to desilylated carbonyl compounds **6a** (40%) and **13** (21%) as well as elimination to diene **14a** (17%).[14] Evidently, 1,2-alkyl shift to give **13** is competitive with the desired 1,2-hydride shift to give **6a**. Similar rearrangements have been observed in steroid systems.[15]

Aluminum isopropoxide[16a,b] (toluene, reflux) reacted cleanly with **4** to give allylic alcohol **15**[16c] in 90% yield.

Scheme IV



Compound **15** was also obtained, although in lower yield, by treatment of **4** with lithium triflate[17] (n-Bu_3PO, toluene, reflux) or 9-BBN-triflate (CH_2Cl_2, −78 °C). Since compound **15** possesses the undesired stereochemistry at C_5, similar reactions were attempted on the α-epoxide **5** in order to prepare **7**. Application of the Noyori[18] conditions (TMSOTf, lutidine, −78 °C) on **5** resulted in a low yield of **7** accompanied by elimination and aromatization products **14b** and **16**, respectively[14b,19a] (Scheme IV). Epoxide **5** was inert to 9-BBN-triflate (CH_2Cl_2, −78 °C to rt), probably due to steric hindrance. Treatment with n-Bu_2B-triflate (CH_2Cl_2, −78 °C) gave a myriad of elimination products. However, lithium triflate (n-Bu_3PO, toluene, 66 °C, 2 h) gave a 26% yield of the desired allylic alcohol **7**.[19b] Unfortunately we have thus far been unable to achieve the hydroxyl-directed reduction of **7** to give **8** either with homogeneous hydrogenation catalysts or under haptophilic heterogeneous hydrogenation conditions.[10]

Intramolecular Hydrosilylation. Due to the lack of β-face selectivity in the intermolecular hydrosilylation of **3**, the analogous intramolecular reactions[20] were explored on deacylated substrates **17**[21a] and **18**[22a] as depicted in

(14) (a) **13** was characterized in a crude reaction mixture. **13**: ^1H NMR ($CDCl_3$, 400.1 MHz) δ 9.29 (d, J = 1.2 Hz, CHO), 5.25 (ddd, J = 9.1, 7.9, 5.9 Hz, H_8, 1 H); selected ^{13}C NMR ($CDCl_3$, 100.6 MHz) 205.0 (C_8), 76.1 (C_8), 56.8 (C_{4a}), 19.4 (C_6-Me), 12.7 (C_2-Me). (b) **14b** (R = TBS): ^1H NMR ($CDCl_3$, 400.1 MHz) δ 5.86 (m, H_5), 5.46 (m, H_4), 5.32 (m, H_8), 2.59 (m, $H_{8'}$, 2 H), 1.70 (br s, C_6-Me), 0.89 (s, Me_3C-Si), 0.08 (s, Me_2-Si); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 177.7 ($C_{1''}$), 170.4 ($C_{8'}$), 132.6 and 129.4 (C_{4a}, C_8), 124.9 and 122.2 (C_4, C_5), 76.5 ($C_{2'}$), 67.9 (C_8), 63.5 ($C_{4'}$), 42.9 ($C_{2''}$), 39.5, 39.3, 37.3, 36.8, 36.3, 33.7, 33.2, 33.1, 27.5, 25.7 (Me_3C-Si), 25.3 (C_9), 24.8 ($C_{2''}$-Me), 24.4 ($C_{2''}$-Me), 23.1 (C_6-Me), 17.9 (Me_3C-Si), 12.8 (C_2-Me), 9.23 ($C_{4''}$), −4.9 (Me_2-SiCMe$_3$).

(15) Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* **1969**, *25*, 4999.

(16) (a) Terao, S.; Shiraishi, M.; Kato, K. *Synthesis* **1979**, 467. (b) Scheidl, F. *Synthesis* **1982**, 728. (c) **15**: ^1H NMR ($CDCl_2$, 300.1 MHz) δ 5.72 (m, H_4), 5.21 (m, H_8), 4.58 (m, $H_{2'}$), 4.27 (m, $H_{4'}$), 3.98 (m, H_5), 2.57 (dd, J = 15.8, 6.0 Hz, $H_{8'}$), 2.47 (dm, J = 15.8 Hz, $H_{8'}$), 2.39 (br s, OH), 1.10 (s, $C_{2''}$-Me), 1.09 (s, $C_{2''}$-Me), 0.97 (d, Me), 0.07 (s, Me_2Si); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 177.5 ($C_{1''}$), 170.6 ($C_{8'}$), 135.6 (C_{4a}), 126.3 (C_4), 78.4 ($C_{2'}$), 76.8 (C_8), 74.8 (v br, C_5), 64.2 ($C_{4'}$), 43.2 ($C_{2''}$), 39.8, 38.8 (br), 38.5, 36.9, 34.8, 34.2, 33.7, 32.2 (br), 31.4, 28.2 (br), 26.0 (Me_3C-Si), 25.2 ($C_{2''}$-Me), 25.0 ($C_{2''}$-Me), 24.6 (br, C_9), 19.7 (C_6-Me), 18.4 (Me_3C-Si), 14.3 (v br, C_2-Me), 9.8 ($C_{4''}$), −4.6 (Me-SiCMe$_3$), −4.7 (Me-SiCMe$_3$).

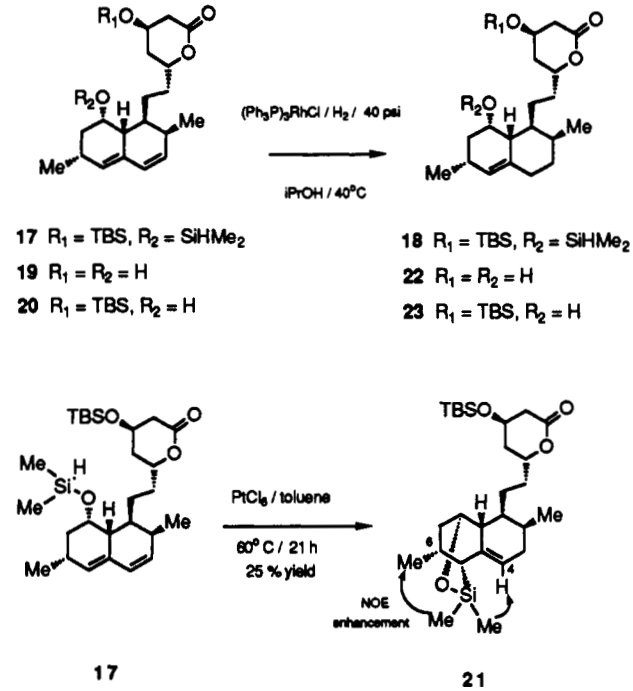
(17) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 4193.

(18) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2739.

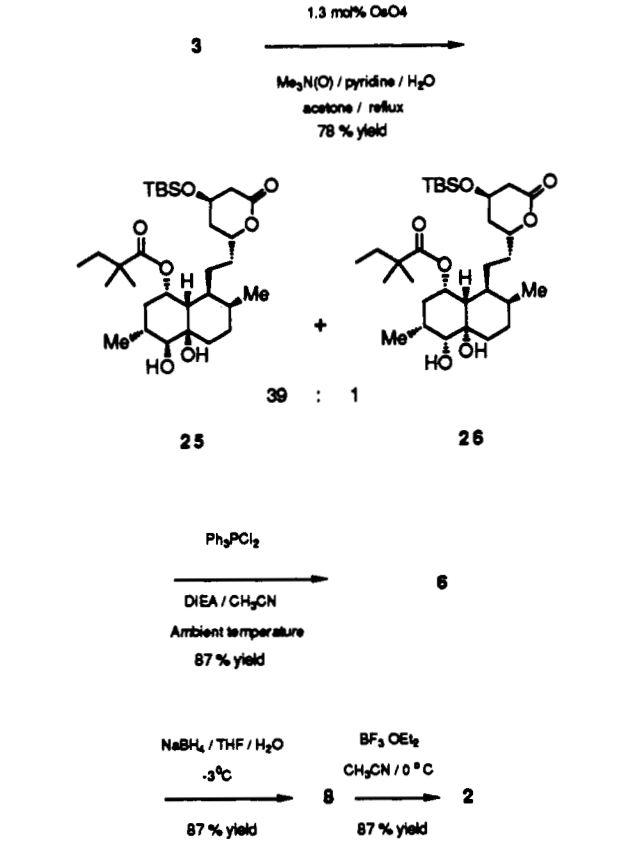
(19) (a) **16**: ^1H NMR ($CDCl_3$, 300.1 MHz) δ 6.88–7.0 (m, H_5, H_7, H_8), 4.62 (m, $H_{8'}$, 1 H), 4.27 (m, $H_{4'}$), 2.81 (m, H_4, 2 H), 2.47–2.66 (m, $H_{8'}$ and H_1, 3 H), 2.29 (s, C_6-Me), 1.02 (d, J = 7.8 Hz, C_2-Me), 0.07 (s, Me-SiCMe$_3$), 0.09 (s, Me-SiCMe$_3$). (b) **7**: ^1H NMR (CD_3CN, 300.1 HMz) δ 5.74 (m, H_4), 5.14 (m, H_8), 4.54 (m, $H_{2'}$), 4.32 (m, $H_{4'}$), 4.10 (m, H_5), 2.78 (d, J = 6.0 Hz, OH), 2.56 (dd, J = 17.7, 4.8 Hz, $H_{8'}$), 2.47 (dm, J = 17.7 Hz, $H_{8'}$), 1.10 (s, $C_{2''}$-Me), 1.09 (s, $C_{2''}$-Me), 0.09 (s, Me_2Si); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) 177.8 ($C_{1''}$), 170.6 ($C_{8'}$), 135.7 (C_{4a}), 119.5 (C_4), 76.8 (C_2), 74.5 (C_8), 72.2 (v br, C_5), 64.2 ($C_{4'}$), 43.6 (C_1), 43.2 ($C_{2''}$), 39.9 ($C_{8'}$), 39.2 (br), 37.0, 35.4, 35.0, 34.3, 33.7, 31.9 (br), 28.2 (br), 26.0 (Me_3C-Si), 25.2 ($C_{2''}$-Me), 25.1 (br, obsc, C_9), 25.0 ($C_{2''}$-Me), 18.4 (Me_3C-Si), 14.4 (br, obsc, C_2-Me), 14.2 (C_6-Me), 9.8 ($C_{4''}$), −4.6 (Me_2-SiCMe$_3$).

(20) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090.

Scheme V



Scheme VI



Scheme V. Olefin **17** was prepared by selective *tert*-butyldimethylsilyl protection of the known diol **19**[23] to give **20**.[23] Silylation of **20** ($(Me_2SiH)_2NH$, CH_2Cl_2) to give **17** was followed by treatment with chloroplatinic acid (toluene, 60 °C, 21 h). A 25% yield was obtained of the interesting product **21**,[21b] in which hydrosilylation formally occurred in a 1,4-sense. The corresponding intramolecular hydrosilylation reaction was attempted on monoolefin **18**. Selective reduction of diol **19** (40 psi of H_2, Wilkinson's catalyst, 40 °C, 2-propanol) afforded **22**[22b] which was selectively protected (TBS-Cl, DMF, imidazole) to give **23**.[22c] Silylation ($(Me_2SiH)_2NH$, CH_2Cl_2) of **23** to give **18**, followed by treatment with chloroplatinic acid (toluene, 60 °C, 4 h) provided the very unusual product **24**[22d] in low yield (derived from metal-catalyzed isomerization and concurrent silicon oxidation).

Synthesis of 2 via Diol Rearrangement. The most successful and practical approach to the synthesis of L-679,336 (**2**) is outlined in Scheme VI. Stereoselective cis dihydroxylation of **3** afforded β-diol **25** (78% yield). Pinacol-type rearrangement of the β-diol **25** led to known trans-fused ketone intermediate **6**[5] (87% yield) and stereoselective ketone reduction gave TBS-protected L-679,336 **8**[5] (87% yield). Deprotection of the sensitive β-

(21) (a) **17**: ^1H NMR (CD_2Cl_2, 300.1 MHz) 5.92 (d, J = 9.3 Hz, C_4), 5.73 (dd, J = 9.3, 6.3 Hz, C_3), 5.45 (m, C_5), 4.68 (m, Si-H), 4.62 (m, $C_{2'}$), 4.28 (m, $C_{4'}$ and C_8), 2.52 (m, $H_{5'}$, 2 H), 1.12 (d, J = 7.5 Hz, C_6-Me), 0.86 (m, *Me*$_3$C-Si and C_2-Me, 12 H), 0.20 (d, J = 3.0 Hz, *Me*-SiH), 0.17 (d, J = 3.0 Hz, *Me*-SiH), 0.06 (s, *Me*-SiCMe$_3$), 0.05 (s, *Me*-SiCMe$_3$); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) 170.3 ($C_{6'}$), 133.4 (C_3), 132.2 (C_{4a}), 130.2 (C_5), 129.2 (C_4), 77.0 ($C_{2'}$), 68.2 (C_8), 64.2 ($C_{4'}$), 39.8, 39.4, 37.2, 36.9, 35.9, 33.6, 31.0, 28.6, 26.0 (*Me*$_3$C-Si), 24.6 (C_9), 23.4 (C_6-Me), 18.3 (Me$_3$*C*-Si), 14.4 (C_2-Me), −0.13 (*Me*-SiH, 3 H), −0.75 (*Me*-SiH, 3 H), −4.6 (*Me*-SiCMe$_3$, 3 H), −4.7 (*Me*-SiCMe$_3$, 3 H). (b) **21**: ^1H NMR (CD_2Cl_2, 250.1 MHz) δ 5.21 (m, H_4), 4.64 (m, $H_{2'}$), 4.28 (m, $H_{4'}$), 4.21 (m, H_8), 2.53 (m, $H_{5'}$), 2.25 (m, H_6), 1.61 (d, J = 2.4 Hz, H_5), 1.07 (d, J = 7.0 Hz, C_6-Me), 0.88 (s, *Me*$_3$C-Si), 0.85 (C_2-Me, 3 H, overlaps with *Me*$_3$C-Si), 0.29 (s, Me$_b$-Si), 0.07 (s, *Me*-SiCMe$_3$), 0.06 (s, *Me*-SiCMe$_3$), 0.04 (s, Me$_a$-Si); ^{13}C NMR (CD_2Cl_2, 62.9 MHz) δ 170.5 ($C_{6'}$), 138.7 (C_{4a}), 118.8 (C_4), 77.0 ($C_{2'}$), 70.2 (C_8), 64.4 ($C_{4'}$), 54.4, 54.0, 53.6, 42.9, 41.5, 40.0, 37.9, 37.8, 37.3, 34.3, 34.1, 28.7, 28.6, 26.1 (*Me*$_3$C-Si), 21.4 (C_6-Me), 18.4 (Me$_3$*C*-Si), 14.0 (C_2-Me), 4.5 (*Me*-Si-C_4), 0.40 (*Me*Si-C_4), −4.6 (*Me*$_2$-SiCMe$_3$). The NOEDS (NOE difference spectroscopy) experiments were crucial in establishing the bridge between C_5 and C_8. Irradiation of each methyl group (a and b) on the C_5 silicon yielded NOE enhancements (as indicated by the arrows) to the C_6-methyl and H_4, respectively, indicating their rigid orientation in the tricyclic system.

(22) (a) **18**: ^1H NMR (CD_2Cl_2, 300.1 MHz) δ 5.31 (m, H_5), 4.66 (m, Si-H), 4.62 (m, $H_{2'}$), 4.28 (m, $H_{4'}$), 4.19 (m, H_8), 2.57 (dd, J = 15.8, 4.5 Hz, $H_{5'}$, 1 H), 2.48 (m, $H_{5'}$, 1 H), 1.10 (d, J = 7.5 Hz, Me); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) 170.5 ($C_{6'}$), 135.5 (C_{4a}), 125.8 (C_5), 77.2 ($C_{2'}$), 69.8 (C_8), 64.3 ($C_{4'}$), 42.0, 40.4, 39.9, 37.3, 36.0, 33.8, 33.3, 30.1, 29.1, 29.0, 26.0, (*Me*$_3$C-Si), 25.9 (C_9), 22.9 (C_6-Me), 18.4 (Me$_3$*C*-Si), 12.1 (C_2-Me), −0.13 (*Me*-SiH), −0.72 (*Me*-SiH), −4.6 (*Me*-SiCMe$_3$), −4.7 (*Me*-SiCMe$_3$). (b) **22**: ^1H NMR ($CDCl_3$, 250.1 MHz) δ 5.42 (m, H_5), 4.70 (m, $H_{2'}$), 4.38 (m, $H_{4'}$), 4.17 (m, H_8), 2.74 (dd, J = 20.4, 4.5 Hz, $H_{5'}$, 1 H), 2.62 (dm, J = 20.4 Hz, $H_{5'}$ 1 H), 2.30 (m, H_6, H_{8a}), 1.17 (d, J = 7.4 Hz, C_6-Me), 1.07 (d, J = 6.9 Hz, C_2-Me). Irradiation of the C_6-Me in an NOEDS experiment yielded a 0.7% enhancement to the olefinic C_5 proton. (c) **23**: ^1H NMR (mp 138.5–140.5 °C) ($CDCl_3$, 300.1 MHz) δ 5.42 (m, H_5), 4.68 (m, $H_{2'}$), 4.30 (m, $H_{4'}$), 4.18 (m, H_8), 2.58 (m, $H_{5'}$, 2 H); IR ($CHCl_3$) 3615, 2965, 2940, 1730, 1265, 1090 cm^{-1}. Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.15. Found: C, 68.78; 10.45. (d) **24**: ^1H NMR (CD_2Cl_2, 400.1 MHz, ambient temperature) δ 5.41 (m, H_4), 4.74 (m, $H_{2'}$), 4.35 (m, H_8), 4.30 (m, $H_{4'}$) 3.49 (br s, Si-O*H*, 1 H, shifts downfield to ca. 5.0 ppm when the ^1H NMR is run at −60 °C), 2.55 (m, $H_{5'}$), 2.23 (m, H_{5ax}), 2.12 (m, H_{3ax}), 1.83 (m, H_6), 1.05 (d, J = 7.1 Hz, C_6-Me), 0.88 (s, *Me*$_3$C-Si), 0.80 (d, J = 6.7 Hz, C_2-Me), 0.11 (s, *Me*-SiOH), 0.081 (s, *Me*-SiCMe$_3$), 0.076 (s, *Me*-SiCMe$_3$), 0.04 (s, *Me*-SiOH). NOE studies revealed that irradiation of the hydroxyl signal at 3.49 ppm resulted in enhancement to a single methyl on silicon, and vice versa, which suggests a preferred orientation of the hydroxyl group, possibly due to intermolecular hydrogen bonding. ^{13}C NMR (CD_2Cl_2, 100.6 MHz, −80 °C) δ 172.6 ($C_{6'}$), 134.5 (C_{4a}), 120.3 (C_4), 73.8 ($C_{2'}$), 67.4 (C_8), 63.1 ($C_{4'}$), 44.5 (C_1), 40.9 (C_5), 38.8 ($C_{5'}$), 37.8 (C_7), 35.8 (C_3), 32.5 (C_{8a}), 32.2 (C_3), 30.6 (C_{10}), 28.3 (C_6), 25.9 (C_2), 25.2 (*Me*$_3$C-Si), 22.4 (C_9), 20.9 (C_6-Me), 17.6 (Me$_3$*C*-Si), 11.9 (C_2-Me), −0.18 (*Me*-SiOH), −0.82 (*Me*-SiOH), −5.4 (*Me*-SiCMe$_3$), −5.5 (*Me*-SiCMe$_3$); ^{29}Si NMR (CD_2Cl_2, 79.5 MHz) δ +19.7 (Me$_3$*C*-*Si*Me$_2$), −6.3 (Me$_2$*Si*OH). Silicon-29 NMR chemical shifts are consistent with the literature (e.g. Schram L. J.; Bellama, J. M. In *Determ. Org. Struct. Phys. Methods* **1976**, *6*, 203–269.

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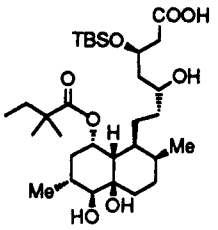
hydroxy lactone group was achieved (in 87% yield), without competitive elimination, by the action of boron trifluoride etherate (CH_3CN, 0 °C).[24] The preceeding route was used to produce multikilogram quantities of L-679,336.

Osmylation Reaction. The osmium tetraoxide catalyzed cis dihydroxylation reaction of **3** to give **25** and **26** was studied in depth, and an optimized procedure evolved from the generalized literature method of Matteson and Ray[25] (t-BuOH, H_2O, OsO_4, Me_3NO, pyridine, reflux) with incorporation of mechanistic insights published by Sharpless and others.[26] Relatively stringent conditions were required to catalytically dihydroxylate this very hindered, trisubstituted olefin. Stereoselective formation of diol **25** was maximized in order to cleanly establish the trans ring junction in the subsequent rearrangement reaction to give **6**. Dihydroxylation of **3** under Narasaka's conditions,[27] in the presence of dihydroxyphenylborane, was sluggish. Polymer-bound osmium tetraoxide[28] was similarly unsuccessful. Although the diastereoselectivity of the reaction was acceptable under Matteson's conditions (**25**:**26** = 26:1), high levels (up to 20%) of hydroxy acid **27** were produced. In addition, reaction times were inconsistent as the reaction was scaled up. Our goals were to minimize lactone hydrolysis, maintain or improve the diastereoselectivity, and insure consistent, reasonable reaction times.

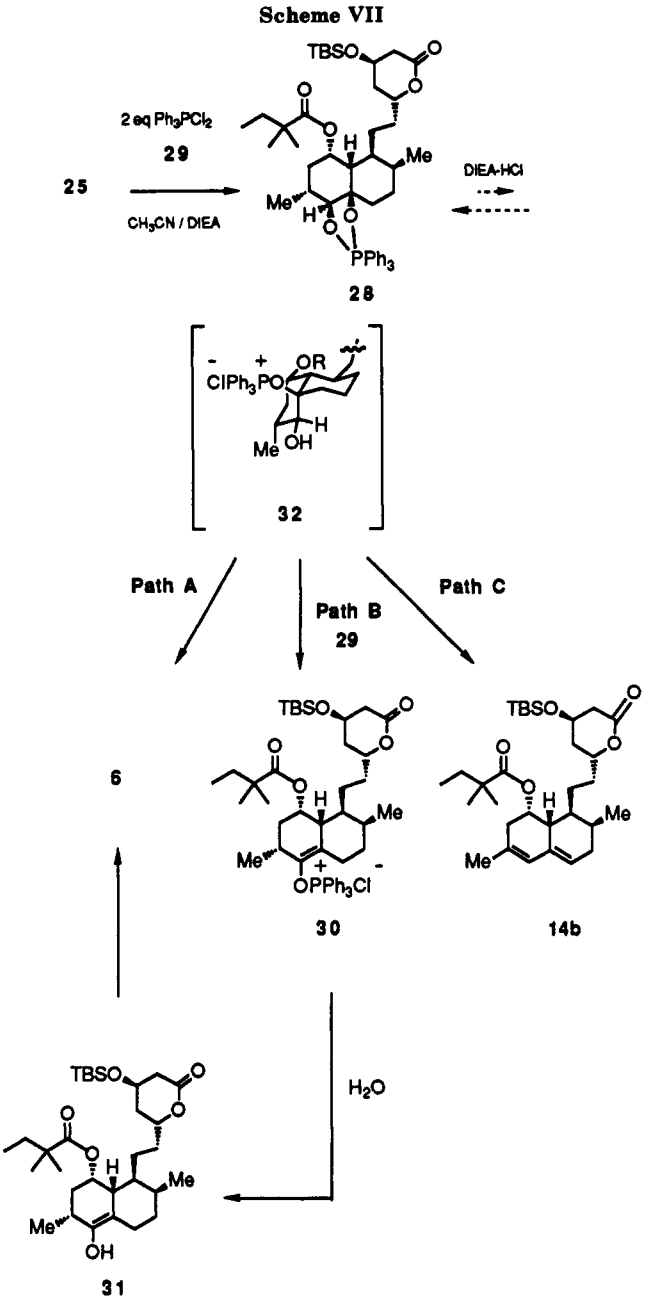


27

Empirically, we found that lactone hydrolysis could be avoided by changing the reaction solvent to acetone/water (at reflux), initially in the presence of tetraethylammonium acetate. Acetate ion is thought to increase the rate of catalytic osmylation reactions by facilitating the hydrolysis of osmate ester intermediates.[29] Further studies showed that decreasing the percentage of water in the reaction medium from 25% to 7.5% v/v in the presence of acetate ion reduced the reaction time by half.

Unfortunately, the conditions which allowed the fastest reaction rates also exhibited the poorest diastereoselectivity (**25**:**26** decreased from 40:1 to 12:1). We found that a slight decrease in the water percentage (to 20% v/v) and elimination of the acetate ion optimized both the reaction times (20 h on a 20-kg scale) and the diastereoselectivity (**25**:**26** = 39:1).

Scheme VII



Further studies of this reaction have incorporated the recently reported work of Sharpless et al. (0.2–0.4% OsO_4, acetone, water, NMO, dihydroquinine *p*-chlorobenzoate) on the enantioselective dihydroxylation of relatively unhindered olefinic substrates.[26] Under equivalent conditions the dihydroquinine *p*-chlorobenzoate ligand (acetone/water, Et_4NOAc reflux) was compared to pyridine ligand. The former increased the diastereoselectivity (**25**:**26** = 20:1 vs 12:1), although no marked rate enhancement was noted. No optimization of the diastereoselectivity, using Sharpless ligands, was attempted. For steric reasons, both the complementary[26c] dihydroquinine and dihydroquinidine-derived ligands vastly favor the formation of the β-diol (**25**:**26** = 20:1 vs 11:1). The slow addition method[26d] was unsuccessful for olefin substrate **3** under the Sharpless conditions or those of Matteson and Ray; very low conversions were observed despite protracted addition times. We believe

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(26) (a) Lohray, B. B.; Kalanter, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, 2041. (b) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (c) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *Ibid.* **1988**, *110*, 1968. (d) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *Ibid.* **1989**, *111*, 737. (e) Erdik, E.; Matteson, D. S. *J. Org. Chem.* **1989**, *54*, 2742.
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(28) (a) Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* **1989**, 45. (b) The recently reported polymer bound alkaloid was not tried: Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, 3003. (c) The alternative reoxidant potassium hexacyanoferrate III [potassium ferricyanide] was not tried: Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Ibid.* **1990**, 2999.
(29) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

that the differences noted between our results and those of Sharpless are due mainly to the highly hindered nature of trisubstituted olefin substrate **3** and the resultant difficulty in turnover of the putative osmate ester intermediates.[26]

Phosphorus Pinacol Reaction. Our initial efforts to perform a pinacol-type rearrangement on β-diol **25** were discouraging. Probe experiments under various protic or Lewis acid conditions indicated that the sensitive β-silyloxy lactone group decomposed before rearrangement took place. An alternative method was suggested by Applequist's report of a pinacol reaction being effected by triphenylphosphine in carbon tetrachloride.[30] No speculation about the mechanism was given, but, based on the work of Evans,[31] it seemed that a hydride migration via cyclic phosphorane **28** (Scheme VII) was likely. Since triphenylphosphine dichloride **29** was probably the active reagent in the literature reaction,[32] we explored the chemistry of this reagent on diol **25**. Generation of a phosphorane would produce 2 equiv of HCl, so 2 equiv of an amine base per **29** were used to prevent loss of the silyl group. The moisture-sensitive triphenylphosphine dichloride was generated in situ by the quantitative reaction of triphenylphosphine with hexachloroethane.[32] In situ generated reagent was superior to commercial **29**, probably due to higher purity.

Reaction of 2 equiv of **29** with diol **25**, in the presence of diisopropylethylamine (DIEA), proceeded smoothly at room temperature over 24 h, giving isolated yields of 80–87%. Somewhat surprisingly, little solvent effect was observed: ethylene dichloride, toluene, and acetonitrile gave similar reaction times and yields. Acetonitrile was the preferred solvent due to uniformly homogeneous conditions and slightly higher yields.

In order to gain a more detailed picture of this unusually selective reaction, extensive in situ, multinuclear NMR studies were carried out. When diol **25** was combined with 2 equiv of triphenylphosphine dichloride and 4 equiv of DIEA in CD_3CN at room temperature, a new species gradually grew to a maximum after 3.5 h. The ^{31}P (162.0 MHz) spectrum showed the appearance of a new signal at −38.0 ppm while ^{13}C revealed an ipso aromatic signal at 148.1 ppm (d, $^1J_{CP}$ = 118.8 Hz), consistent with the cyclic phosphorane **28**[31d] (Scheme VII). Additional support came from ^1H–^{13}C and ^1H–^{31}P heteronuclear correlation experiments which were used to correlate H_5 (3.28, dd, J = 17.4, 8.7 Hz) with both C_5 at 81.6 ppm and the phosphorus signal at −38.0 ppm. As phosphorane **28** disappeared, three species grew in: the product ketone **6**, the byproduct diene **14**, and a new species characterized by a signal at +62.7 ppm in the ^{31}P spectrum, consistent with the enol phosphonium species **30**.[33] In the proton spectrum of **30**, H_8 came at 5.1 ppm (a tenth of a ppm upfield from the corresponding signal of ketone) while the methyl group at C_6 was shielded to 0.53 ppm. Carbon-13 NMR of **30** had several characteristic signals and ^{13}C–^{31}P spin–spin coupling constants: C_5 (145.9 ppm, $^2J_{CP}$ = 12.7 Hz), C_{4a} (126.6, $^3J_{CP}$ = 6.3 Hz) and the ipso aromatic (120.2, $^1J_{CP}$ = 106.7 Hz).[33]

After 16 h, the mixture consisted of about 65% ketone **6**, 27% of the enol phosphonium species **30**, and 9% of byproduct diene **14**. This mixture was stable for extended periods of time. However, when 2–4 equiv of water were added, the enol phosphonium salt **30** immediately disappeared, and a new species appeared, as evidenced by the disappearance of the signal at +62.7 ppm in the ^{31}P spectrum and the formation of additional triphenylphosphine oxide. The C_6-methyl signal in the ^1H spectrum at 0.53 ppm was shifted downfield, while H_8 remained at 5.1 ppm consistent with the enol **31**. Over the next 12–24 h, the enol tautomerized, with high selectivity at C_{4a}, to the product ketone **6**, a total yield of 86–88%. It was crucial that the pH of the reaction mixture be between 8 and 8.5 prior to the addition of water. Abnormally high or low pH's led to nonselective enol tautomerization and/or epimerization of the C_6 methyl group of **6** to its more stable equatorial orientation.

In order to study the reactivity of phosphorane **28**, we attempted to prepare it by treating diol **25** with triphenylphosphine and diisopropyl azodicarboxylate (Mitsunobu conditions) in various solvents.[33] The phosphorane formed very poorly in CD_3CN or 1,2-dichloroethane-d_4, but a 25% conversion could be obtained in warm dioxane-d_8. The phosphorane so formed was stable for several hours, at temperatures up to 60 °C. No decomposition or conversion to ketone was observed.

One possible explanation for our observations is shown in Scheme VII. We propose that the key intermediate for the formation of products is the hydroxy oxyphosphonium salt **32**, which is transiently formed by amine hydrochloride catalyzed opening of the phosphorane **28**. This intermediate **32** was not observed spectroscopically.[31b] The primary reaction of **32** is the stereoelectronically allowed hydride migration shown in path A, which provides ketone directly. Pathway B leads to enol phosphonium salt **30** by elimination to form an enol **31** followed by rapid reaction with excess triphenylphosphine dichloride. Addition of water causes hydrolysis of **30** to give enol **31**, which tautomerizes over time to ketone **6**. Byproduct path C results from competitive elimination reactions via **32** or perhaps through a C_{4a} tertiary carbocation intermediate.[31b] The fate of α-diol impurity **26** (~2.5%) was not rigorously determined by these studies. A hydride migration mechanism (as in path A, Scheme VII) would result in ketone with the undesired cis ring fusion. We believe that elimination byproducts, such as **14b**, predominate. However it should be noted that formation of trans-fused ketone **6** is mechanistically possible via enol phosphonium salt **30**.

Ketone Reduction and Deprotection. Ketone **6** was reduced with excellent stereoselectivity by sodium borohydride in tetrahydrofuran–water (3–5 °C)[5] to give alcohol **8** in 80% yield after chromatography. Desilylation of **8** to give L-679,336 was achieved with boron trifluoride etherate in acetonitrile.

This method was cleaner and much faster (30 min at 0 °C vs 24 h at room temperature) than the normally used tetrabutylammonium fluoride method.[23] In addition, the reaction was not plagued by competitive elimination reactions to form the α,β-unsaturated lactone byproduct, as is sometimes the case in fluoride induced desilylation of mevinic acid derivatives.[34]

Experimental Section

General Procedure. Melting points were determined in capillary tubes and are uncorrected. Selected ^1H NMR data are reported. NMR assignments were derived from both 1D (^1H, ^{13}C,

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(34) Unpublished results of DeCamp, A. E., and Verhoeven, T. R.

^{31}P, ^{29}Si, APT, NOEDS) and 2D (COSY-45, 1-bond and long-range HETCOR) experiments. Flash chromatography refers to the procedure of Still[35] and was done on E. Merck silica gel of particle size 40–63 μm. HPLC analyses were done using a refractive index detector or UV detector at 220 nm. A Zorbax C-8 reverse-phase analytical column (4.6 × 250 mm) was used, flow rate = 2.0 mL/min, mobile phase was acetonitrile/water. TLC was performed on Analtech 250 μm silica gel GF plates, developed with ethyl acetate/hexanes (as detailed below for individual compounds) and visualized with ethanolic phosphomolybdic acid solution followed by heating. Reaction solvents were dried with 3- or 4A molecular sieves, and the residual water content determined by Karl Fischer titration on a Brinkmann 652 KF-Coulometer. Reactions were performed under N_2 in oven-dried (140 °C) glassware.

6(*R*)-[2-[[1a(*S*),8a(*R*)]-4(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*R*),6(*S*)-dimethyl-1a,2,4,4a,5,6,7,8-octahydro-3*H*-napth[1,8a-*b*]oxiren-5-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (4). A suspension of molybdenum hexacarbonyl (0.528 g, 2.0 mmol, 10 mol %), anhydrous toluene (15.0 mL), anhydrous, powdered Na_2HPO_4 (0.10 g, 0.70 mmol), molecular sieves (4A beads, 5 g) was stirred at 60 °C as a solution of anhydrous tBuOOH (3.0 M, in 2,2,4-trimethylpentane, 13.3 mL, 40.0 mmol) was added over 5 min. The mixture stirred at 60–65 °C for 5 min. A solution of the olefin **3** (10.7 g, 20.0 mmol) in anhydrous toluene (35 mL) was added over 15 min at 65–71 °C. The reaction progress was followed by TLC (30% ethyl acetate in hexanes, R_f **3** = 0.61, R_f **4** = 0.50). After 2.75 h, the mixture was cooled to 0 °C, filtered, and quenched by dropwise addition to aqueous Na_2SO_3 (10% w/v, 70 mL), maintaining the temperature at ≤7 °C. The mixture was allowed to warm to ambient temperature. The phases were separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were washed with deionized water (60 mL) and saturated NaCl solution (60 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give cream-colored waxy crystals (11.6 g). The crude product was recrystallized from hexanes (75 mL) to give **4** as a cream-colored solid (7.40 g, 67% yield, mp 103.0–105.0 °C): ^1H NMR ($CDCl_3$, 300.1 MHz) δ 5.31 (dt, J = 12.2, 3.2 Hz, H_8), 4.68 (m, $H_{2'}$), 4.29 (m, $H_{4'}$), 2.57 (m, H_5, 2 $H_{5'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.0 ($C_{1''}$), 170.0 ($C_{6'}$), 76.1 ($C_{2'}$), 69.6 (C_8), 65.7 (C_{4a}), 63.5 and 63.4 ($C_{4''}$ and C_5), 42.5 ($C_{2''}$), 40.8, 39.3, 39.1, 36.5, 33.3, 33.2, 31.0, 30.3, 29.6, 28.5, 28.4, 25.6 (Me_3CSi), 25.5 (C_9), 24.8 and 24.5 (2 $C_{2''}$-Me), 19.7 (C_6-Me), 17.9 (Me_3C-Si), 12.2 (C_2-Me), 9.2 ($C_{4''}$), −4.9 (*Me*-SiCMe$_3$), −5.0 (*Me*-SiCMe$_3$); IR ($CHCl_3$) 2960, 1720, 1465, 1260, 1159 cm^{-1}. Anal. Calcd for $C_{31}H_{54}O_6Si$: C, 67.59; H, 9.88. Found: C, 67.76; H, 9.67.

6(*R*)-[2-[[1a(*R*),8a(*S*)]-4(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*R*),6(*S*)-dimethyl-1a,2,4,4a,5,6,7,8-octahydro-3*H*-naphth[1,8a-*b*]oxiran-5-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5). A mixture of olefin **3** (5.35 g, 10 mmol), hexafluoroacetone trihydrate (0.33 g, 1.5 mmol, 15 mol %), H_2O_2 (10 mL, 30% solution, 98 mmol), and CH_2Cl_2 (50 mL) was heated at reflux for 4 h. TLC (30% ethyl acetate in hexanes, R_f **3** = 0.61, R_f **5** = 0.48) indicated incomplete reaction. Additional hexafluoroacetone trihydrate (0.66 g, 3.0 mmol) and H_2O_2 (10 mL, 98 mmol) were added and the mixture heated at reflux an additional 18 h. The mixture was cooled to ambient temperature, diluted with deionized water (150 mL) and extracted with ethyl acetate (2 × 300 mL). The combined organic phases were washed with aqueous $NaHSO_3$ (10% w/v, 2 × 200 mL), dried ($MgSO_4$), filtered, and evaporated to a foam (5.73 g). Purification by flash chromatography (30% ethyl acetate in hexanes) gave 1.5 g (30% yield) of an oil which crystallized as white needles (mp 94–95 °C) upon trituration with petroleum ether (bp 35–60 °C): ^1H NMR (CD_2Cl_2, 300.1 MHz) δ 4.95 (m, H_8), 4.31 (m, $H_{2'}$), 4.25 (m, $H_{4'}$), 2.88 (dd, J = 4.5, 0.75 Hz, H_5), 2.56 (dd, J = 17.7, 4.5 Hz, $H_{5'}$), 2.47 (m, $H_{5'}$), 1.12 (s, $C_{2''}$-Me), 1.11 (s, $C_{2''}$-Me) 1.05 (d, J = 7.5 Hz, Me), 0.89 (d, J = 7.4 Hz, Me), 0.85 (s, Me_3C-Si), 0.80 (t, J = 7.5 Hz, $H_{4''}$), 0.06 (s, *Me*-SiCMe$_3$), 0.05 (s, *Me*-SiCMe$_3$); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 177.9 ($C_{1''}$) 170.3 ($C_{6'}$), 76.8 ($C_{2'}$), 68.3 (C_8), 64.2 and 62.4 ($C_{4'}$ and C_5), 61.3 (C_{4a}), 43.1 ($C_{2''}$), 39.7, 39.3, 38.7, 37.3, 33.4, 33.3, 32.4, 30.4, 29.8, 29.0, 26.0 (Me_3C-Si), 25.7, 25.1 (C_9), 24.9 (2 $C_{2''}$-Me), 19.1 (C_6-Me), 18.3 (Me_3C-Si), 11.4 (C_2-Me), 9.6 ($C_{4''}$), −4.7 (Me_2-SiCMe$_3$); IR (solid state) 2929, 1723, 1262, 1239, 1084, 1047 cm^{-1}. Anal. Calcd for $C_{31}H_{54}O_6Si$: C, 67.59; H, 9.88. Found: C, 67.76; H, 10.17.

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-4a(*R*),5(*S*)-dihydroxy-2(*S*),6(*R*)-dimethyl-1,2,3,4,4a,5,6,7,8,8a(*R*)-decahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (25). A 12-L, three-necked flask, fitted with a mechanical stirrer, a temperature probe, and a N_2 inlet was charged sequentially with acetone (1.8 L), deionized water (0.6 L), olefin **3** (500.0 g, 0.935 mol), trimethylamine *N*-oxide dihydrate (207.8 g, 1.87 mole), pyridine (75.3 mL, 0.935 mol), and OsO_4 solution (prepared by dissolving the solid OsO_4 [3.1 g, 0.012 mol, 1.3 mol %] in 100 mL of acetone). The brown solution was heated at reflux (60–62 °C) until the reaction was complete (18 h, TLC: 50% ethyl acetate/hexane, R_f **3** = 0.77, R_f **25** = 0.32, R_f **26** = 0.40). The mixture was cooled to room temperature, diluted with ethyl acetate (5.0 L), and cooled in an ice bath to 18 °C. Aqueous $NaHSO_3$ (1.5 L, 20% w/v) was added at such a rate to maintain the temperature <25 °C (exothermic), and the mixture was vigorously stirred for 30 min. The phases were separated, and the aqueous phase was extracted with ethyl acetate (5.0 L). The combined organic phases were washed with aqueous saturated NaCl (1.5 L), and agitated with Florisil (magnesium silicate, 1.0 kg) for 30 min. The Florisil was removed by filtration, and the cake washed with ethyl acetate (2.0 L). The filtrate was azeotropically dried (<40 °C) by vacuum distillation of ethyl acetate (to a water content of ≤0.20 mg/mL) and concentrated to a final volume of 1.9 L containing 416 g (78% yield) of the title compound **25** as determined by quantitative HPLC analysis (ratio of diols **25**:**26** was 39:1; 95% de).

An analytically pure sample of **25**, free of **26**, was prepared by flash chromatography (ethyl acetate/hexanes). **25**: ^1H NMR ($CDCl_3$, 300.1 MHz) 5.61 (dt, J = 12.3, 3.0 Hz, H_8), 4.65 (m, $H_{2'}$), 4.30 (m, $H_{4'}$), 3.44 (d, J = 9.9 Hz, H_5), 2.56 (d, J = 3.8 Hz, $H_{5'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.4 ($C_{1''}$), 170.1 ($C_{6'}$), 76.3 ($C_{2'}$), 75.8 (C_{4a}), 72.4 and 71.1 (C_5 and C_8), 63.5 ($C_{4'}$), 45.5, 42.5 ($C_{2''}$), 39.3, 37.8, 36.5, 34.7, 33.3, 33.2, 33.1, 30.7, 29.2, 28.5, 26.0, 25.6 (Me_3C-Si), 24.8 ($C_{2''}$-Me), 24.5 ($C_{2''}$-Me), 19.0, 17.9 (Me_3C-Si), 11.5, 9.2 ($C_{4''}$), −4.9 (*Me*-SiCMe$_3$), −5.0 (*Me*-SiCMe$_3$); IR ($CHCl_3$) 3560 (br), 2965, 2940, 1723, 1260, 1162 cm^{-1}. Anal. Calcd for $C_{31}H_{56}O_7Si$: C, 65.45; H, 9.92. Found: C, 65.64; H, 10.21. **26**: ^1H NMR ($CDCl_3$, 300.1 MHz) δ 5.23 (m, H_8), 4.57 (m, $H_{2'}$), 4.28 (m, $H_{4'}$), 3.39 (m, H_5), 2.58 (m, $H_{5'}$), 0.87 (s, Me_3C-Si), 0.08 (s, *Me*-SiCMe$_3$), 0.07 (s, *Me*-SiCMe$_3$); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 176.6 ($C_{1''}$), 170.3 ($C_{6'}$), 76.6 and 76.3 ($C_{2'}$ and C_5), 75.1 (C_{4a}), 70.4 (C_8), 64.2 ($C_{4'}$), 43.6, 43.3 ($C_{2''}$), 39.7, 37.1, 35.3, 34.3, 33.6, 33.4, 32.3, 30.3, 28.5, 27.7 25.9 (Me_3C-Si), 25.1 and 25.0 ($C_{2''}$-Me_2 and C_9), 18.3 (Me_3C-Si), 16.1, 11.2, 9.6 ($C_{4''}$), −4.7 (*Me*-SiCMe$_3$), −4.8 (*Me*-SiCMe$_3$); IR ($CHCl_3$) 3580 (br), 2970, 2940, 1730, 1260, 1058 cm^{-1}.

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5-oxo-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6). A dry, 5-L, three-necked flask, fitted with a mechanical stirrer, a N_2 inlet, a temperature probe and a septum was charged with triphenylphosphine (422 g, 1.608 mol) and acetonitrile (1.5 L). To this stirred heterogeneous mixture was added hexachloroethane (381 g, 1.608 mol) in portions over 25 min while maintaining the temperature between 30 and 36 °C (exothermic). When the addition was complete, diisopropylethylamine (560 mL, 416 g, 3.22 mol) was added. The triphenylphosphine dichloride solution was added to an ethyl acetate solution of diol **25** (416 g in 1.9 L total volume, at 15 °C) by cannula, keeping the temperature below 22 °C. The black reaction solution was allowed to warm to rt and was stirred under N_2 until the starting material was >99% consumed (24–30 h, TLC: 50% ethyl acetate/hexanes, R_f **25** = 0.32, R_f **6** = 0.63). The mixture was cooled to 15 °C and deionized water (27.7 mL) added (exothermic); keeping the temperature <22 °C. When the addition was complete, the mixture was stirred at room temperature until the reaction was complete (24–30 h, TLC: 30% EtOAc in hexanes, R_f **6** = 0.34). The solution was evaporated in vacuo (internal temperature <33 °C) and diluted with ethyl acetate to a total volume of 2.6–2.8 L. The resulting slurry was transferred with a rinse of 500 mL of ethyl acetate, to a 12-L, three-necked flask

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

fitted with a mechanical stirrer and a N_2 inlet. To the resulting vigorously stirred slurry was slowly added 4.5 L of hexanes over 2 h at rt. When the addition was complete, the mixture was filtered and the solids (mainly diisopropylamine hydrochloride) were washed with 4.5 L of hexanes. The cloudy filtrate was concentrated in vacuo (internal temperature ≤33 °C) to a volume of 2.8 L. The resulting slurry was transferred with a rinse of a 500 mL of hexanes to a 12-L, three-necked flask fitted with a mechanical stirrer and a N_2 inlet. The rapidly stirred mixture was treated with 4 L of hexanes over 1.2 h. The resulting mixture was filtered, and the solids (mainly triphenylphosphine oxide) were washed with 1 L of hexanes. Quantitative HPLC analysis of the filtrate showed that 382 g (87% yield) of product ketone **6** were contained in the filtrate. The crude ketone could be used in the next reaction following evaporation of the solvent. Alternatively, the ketone could be crystallized from hexane solution (4 mL/g product). The suspension was stirred at 0 °C for 1 h, and the solids were collected by filtration (washed with 2 mL of 0 °C hexanes/g product). The light tan solid was dried to give an 82.5% yield of product ketone **6**. Analytically pure samples (mp 114.0–116.5 °C) of **6** were obtained by flash chromatography (ethyl acetate/hexanes), followed by recrystallization from hexanes: ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 5.30 (m, H_8), 4.57 (m, $H_{2'}$), 4.28 (m, $H_{4'}$), 2.57 (m, $H_{5'}$), 2.18 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 215.4 (C_5), 177.0 ($C_{1''}$), 170.2 ($C_{6'}$), 76.2 ($C_{2'}$), 67.7 (C_8), 63.5 ($C_{4'}$), 45.0 (C_{4a}), 43.4 (C_{8a}), 42.9 ($C_{2''}$), 41.5 (C_6), 40.6 (C_1), 39.2 ($C_{5'}$), 36.8 ($C_{3'}$), 36.0, 33.1 and 33.0 (C_{10} and $C_{3''}$), 31.7, 27.9 (C_2), 25.6 (Me_3C-Si), 24.8 ($C_{2''}$-Me and C_9), 24.7 ($C_{2''}$-Me), 19.8, 19.0 (C_6-Me), 17.9 (Me_3C-Si), 11.4 (C_2-Me), 9.3 ($C_{4''}$), −4.9 (*Me*-SiCHMe$_3$), −5.0 (*Me*-SiCMe$_3$); *IR* ($CHCl_3$) 2963, 2938, 1720, 1260 cm^{-1}.

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-hydroxy-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (8). A 5-L, three-necked flask, equipped with a mechanical stirrer, a temperature probe, and a N_2 inlet was charged with crude ketone **6** (241 g, 0.44 mol) as a solution in THF (2.2 L total volume) and water (110 mL). The solution was cooled to −3 °C, and $NaBH_4$ (11.6 g, 0.31 mol) was added portionwise as a solid (exothermic), maintaining the temperature at ≤5 °C. When the reaction was complete (1 h, TLC: 33% ethyl acetate in hexanes, R_f **6** = 0.50, R_f **8** = 0.30), it was quenched (exothermic) with saturated aqueous NH_4Cl (1.6 L) added over 20 min via an addition funnel (maintaining the temperature ≤9 °C). The two-phase mixture was stirred for 30 min (internal temperature 5–10 °C), and the layers were separated. The upper layer was evaporated in vacuo and diluted to 1.0 L with 75% ethyl acetate in hexanes. The solution was chromatographed (675 g silica gel (60–250 mesh) packed in 25% ethyl acetate in hexanes). The product was eluted with 3:1 hexanes/EtOAc (approximately 14 L). The appropriate fractions were combined, evaporated, and crystallized from hexanes (approximately 6.0 L) to give the title compound **8** (134 g, 62% yield). Additional product (60 g, 25% yield) was contained in the mother liquors and could be isolated by silica gel chromatography followed by crystallization from hexanes: ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 5.03 (m, H_8), 4.52 (m, $H_{2'}$), 4.26 (m, $H_{4'}$), 3.42 (m, H_5), 2.55 (m, $H_{5'}$), 1.14 (s, $C_{2''}$-Me), 1.13 (s, $C_{2''}$-Me), 1.04 (d, J = 8.3 Hz, C_6-Me), 0.05 (s, *Me*-SiCMe$_3$), 0.04 (s, *Me*-SiCMe$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.0 ($C_{1''}$), 170.3 ($C_{6'}$), 76.6 and 76.4 ($C_{2'}$ and C_5), 68.6 (C_8), 63.4 ($C_{4'}$), 42.8 ($C_{2''}$), 42.4, 39.5, 39.2, 37.4, 36.7, 34.4, 33.1, 33.0, 32.7, 32.0, 28.0, 25.6 (*Me*$_3$C-Si), 24.7 and 24.6 ($C_{2''}$-*Me*$_2$), 24.5, 22.9 (C_9), 17.8 (Me$_3$*C*-Si), 14.4 (C_6-Me), 11.6 (C_2-Me), 9.3 ($C_{4''}$), −4.9 (*Me*-SiCMe$_3$), −5.0 (*Me*-SiCMe$_3$); IR ($CHCl_3$) 3615, 2970, 2940, 1717, 1260, 1090 cm^{-1}. Anal. Calcd for $C_{31}H_{56}O_5Si$: C, 67.34; H, 10.21. Found: C, 67.58; H, 10.37.

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-hydroxy-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (L-679,336, 2). A dry, 2-L, three-necked flask equipped with a mechanical stirrer, a N_2 inlet, a temperature probe, and a septum was charged with silylated alcohol **8** (50.0 g, 0.0904 mol) and acetonitrile (500 mL). The clear colorless solution was cooled to 0–3 °C. Boron trifluoride etherate (12.5 mL, 0.102 mol) was added over 2.0 min, and the resulting pale yellow solution was stirred at 0–3 °C until the reaction was complete (30 min, TLC: 60% ethyl acetate in hexanes, R_f **8** = 0.74, R_f **2** = 0.42). The reaction was quenched by the addition of aqueous $NaHCO_3$ solution (41.4 mg/mL, 300 mL) over 5–7 min (temperature ≤10 °C). The mixture was vigorously stirred for 1.0 h while being allowed to warm to 20 °C. The phases were separated, and the pale yellow organic phase was washed with saturated aqueous NaCl (300 mL). The organic layer was evaporated in vacuo (internal temperature ≤30 °C) and diluted with isopropyl acetate to a volume of 1250 mL. The solution was washed with deionized water (750 mL), and the organic phase was dried by azeotropic distillation of isopropyl acetate. The solution was evaporated in vacuo to 280 mL and allowed to crystallize with mechanical stirring at rt for 30 min. Hexanes (840 mL) was added over 1.0 h, and the slurry was stirred at −5 °C for 17 h. L-679,336 (**2**) was isolated by filtration as a white crystalline solid (34.5 g, 87% yield). Analytically pure **2** was prepared by recrystallization from isopropyl acetate (6 mL/g **2**, 68 °C, cooled with stirring to rt, stirred at −10 °C for 5 h, crystals collected by filtration, 87% yield): ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 5.05 (br s, H_8), 5.55 (m, $H_{2'}$), 4.29 (m, $H_{4'}$), 3.42 (dd, J = 9.6, 5.7 Hz, H_5), 2.67 (dd, J = 18.0, 5.4 Hz, $H_{5'}$, 1 H), 2.56 (dd, J = 18.0, 3.4 Hz, $H_{5'}$, 1 H), 1.13 (s, $C_{2''}$-Me), 1.12 (s, $C_{2''}$-Me), 1.03 (d, J = 6.6 Hz, Me), 0.82 (t, J = 6.6 Hz, Me), 0.78 (d, J = 6.6 Hz, Me); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.5 ($C_{1''}$), 170.9 ($C_{6'}$), 76.6 (C_5), 76.5 ($C_{2'}$), 68.7 (C_8), 62.2 ($C_{4'}$), 42.9 ($C_{2''}$), 42.4 (C_{8a}), 39.3 (C_1), 38.4 ($C_{5'}$), 37.2 (C_{4a}), 35.9 ($C_{3'}$), 34.5 (C_7), 32.9 (C_{10}), 32.8, 32.6 (C_6), 31.9 ($C_{3''}$), 27.9 (C_2), 24.7 ($C_{2''}$-Me), 24.6 ($C_{2''}$-Me), 24.5 (C_9), 22.8, 14.5 (C_6-Me), 11.6 (C_2-Me), 9.3 ($C_{4''}$); IR ($CHCl_3$) 3620, 3500 (br), 1720, 1262, 1162, 1050 cm^{-1}. Anal. Calcd for $C_{25}H_{42}O_6$: C, 68.46; H, 9.65. Found: C, 68.67; H, 9.84.

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