solvents were then removed with a rotary evaporator. ^{1}H NMR spectroscopic analysis of the residue indicated a quantitative yield of endo ester sulfoxide **7b**. This crude product was purified by chromatography on a preparative-layer plate of silica gel, eluting with 10% methanol in ethyl acetate. Pure endo ester sulfoxide (16 mg, 84% yield) was obtained in this way, and its ^{1}H NMR and IR spectra were identical with that of the material prepared previously.

Oxidation of Endo Acid 5a with Peracetic Acid. A sample of peracetic acid in ethyl acetate, whose peracid concentration was determined by iodometry[19] (15.9 mL, 0.30 mmol), was added dropwise to a stirred solution of endo acid **5a** (56 mg, 0.30 mmol) dissolved in a 1:1 mixture of diethyl ether and acetone (5 mL) and cooled in an ice–water bath. After completion of the addition, the solution was stirred and allowed to warm to room temperature overnight. The solvents were then removed under reduced pressure with a rotary evaporator to give a viscous liquid (159 mg). ^{1}H NMR spectroscopic analysis of this material in deuteriochloroform with dichloromethane as an internal standard indicated an 84% yield of endo acid sulfoxide with a diastereomer ratio of 5:1 of **7a** and **8a**. Crystallization of this material by slow vapor diffusion of diethyl ether into a dichloromethane solution provided crystalline **7a** identical with material obtained previously.

Acknowledgment. We acknowledge support of this work by the U.S. Public Health Service, National Institutes of Health, Grant No. HL 15104. Crystal structure **7a** was done at the Molecular Structure Laboratory of the University of Arizona.

Registry No. **5a**, 64887-93-0; **5b**, 64887-94-1; **7a**, 108919-47-7; **7b**, 108919-48-8; **8a**, 109009-38-3; **8b**, 109009-39-4.

Supplementary Material Available: Stereoscopic view of the packing of the molecules in the unit cell of endo acid sulfoxide **7a** and tables of final atomic positional and thermal parameters, bond lengths, bond angles, and selected torsion angle data (4 pages) (a listing of structure factor amplitudes is available from the authors). Ordering information is given on any current masthead page.

The Isoxazoline Route to the Hypocholesterolemic Agent Compactin: Use of the Isoxazoline as a 1,3-Diene Equivalent

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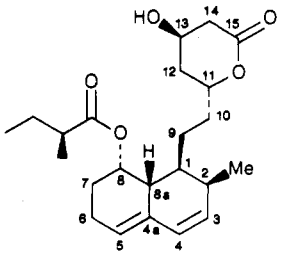
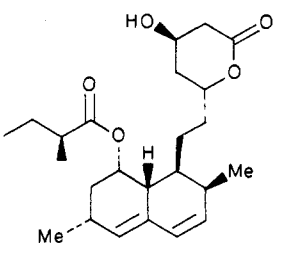
Received February 20, 1987

A total synthesis of the hypocholesterolemic agent compactin is described in which the hexahydronaphthalene portion of this molecule is constructed by an intramolecular nitrile oxide cycloaddition reaction. In the context of this synthesis, the isoxazoline ring system was found to serve as a useful 1,3-diene equivalent. The protocol developed for this conversion involves transformation of the isoxazoline to an allylic alcohol followed by regioselective dehydration using aluminum oxide. Molecular mechanics calculations on compactin-related octahydronaphthisoxazoles are also presented.

In 1976, an important new type of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor was isolated from the culture broth of the molds *Penicillium citrinum* and *Penicillium brevicompactum*. This compound compactin (1), also designated ML-236B,



compactin (1)



mevinolin (2)

is a competitive inhibitor of the rate-controlling enzyme in cholesterol biosynthesis.[1] The dihydroxy acid form of the structurally related product, mevinolin (2), has, moreover, been found to be one of the most potent HMG-CoA reductase inhibitors discovered.[2,3] Both compactin and mevinolin act as effective hypocholesterolemic agents in man and as such may find applications in treating atherosclerosis and coronary heart disease.[4]

Due to the significant biological activity of compactin, as well as our desire to investigate the use of the INOC (intramolecular nitrile oxide cycloaddition) reaction in the construction of decalins (a process in which for compactin the isoxazoline ring would serve as a 1,3-diene equivalent), we embarked on an effort to prepare this compound in the

(1) Compactin: Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31. Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.

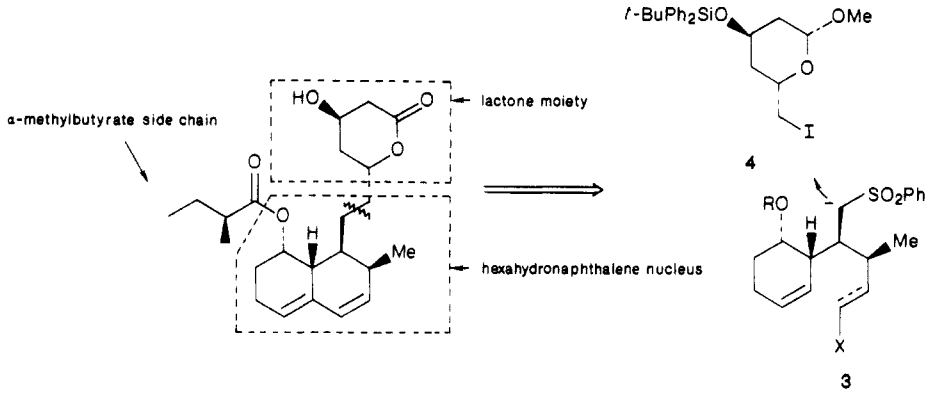
(2) Mevinolin: Endo, A. J. *J. Antibiot.* **1979**, *32*, 852. Endo, A. *Ibid.* **1980**, *33*, 334. Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

(3) A number of related structures have also been isolated. Dihydrocompactin: Lam, Y. K. T.; Gullo, V. P.; Goegelman, R. T.; Jorn, D.; Huang, L.; DeRiso, C.; Monaghan, R. L.; Putter, L. *J. Antibiot.* **1981**, *34*, 614. Dihydromevinolin: Albers-Schonberg, G.; Joshua, H.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Pachett, A. A. *J. Antibiot.* **1981**, *34*, 507. Monacolin J and L: (a) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic: New York, 1983; pp 138–139. (b) Endo, A.; Hasumi, K.; Negishi, S. *J. Antibiot.* **1985**, *38*, 420. Monoclin X: Endo, A.; Hasumi, K.; Nakamura, T.; Kunishima, M.; Masuda, M. *J. Antibiot.* **1985**, *38*, 321.

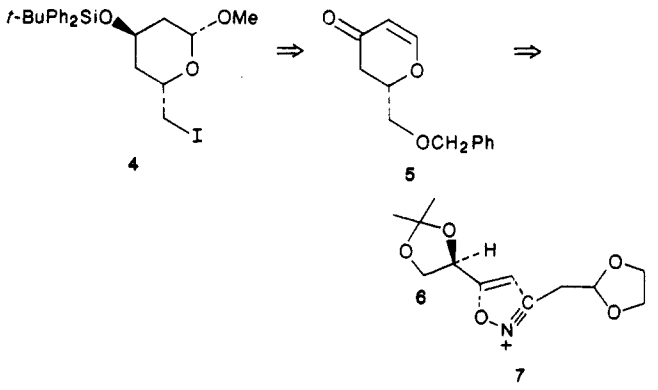
(4) For a detailed report on the hypocholesterolemic activity of compactin and related compounds, see: (a) Endo, A. *J. Med. Chem.* **1985**, *28*, 401. Also, see: (b) Endo, A. *Trends Biochem. Sci. (Pers. Ed.)* **1981**, *6*, 10. (c) Watanabe, Y.; Ito, T.; Saeki, M.; Kuroda, M.; Tanzawa, K.; Mochizuki, M.; Tsujita, Y.; Arai, M. *Atherosclerosis (Shannon, Irel.)* **1981**, *38*, 27. (d) Tsujita, Y.; Kuroda, M.; Tanzawa, K.; Kitano, N.; Endo, A. *Atherosclerosis (Shannon, Irel.)* **1979**, *32*, 307. (e) Kuroda, M.; Tsujita, Y.; Tanzawa, K.; Endo, A. *Lipids* **1979**, *14*, 585. (f) Yamamoto, A.; Sudo, H.; Endo, A. *Atherosclerosis (Shannon, Irel.)* **1980**, *35*, 259. (g) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478. (h) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 159.

0022-3263/87/1952-3541$01.50/0

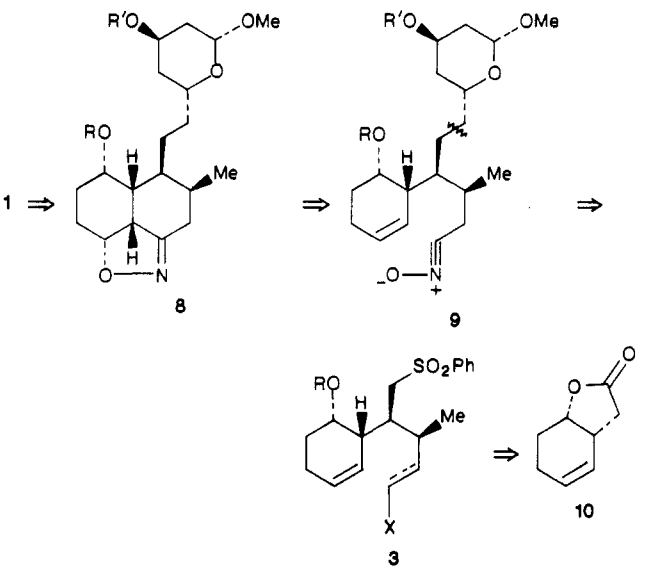
Scheme I



Scheme II



Scheme III

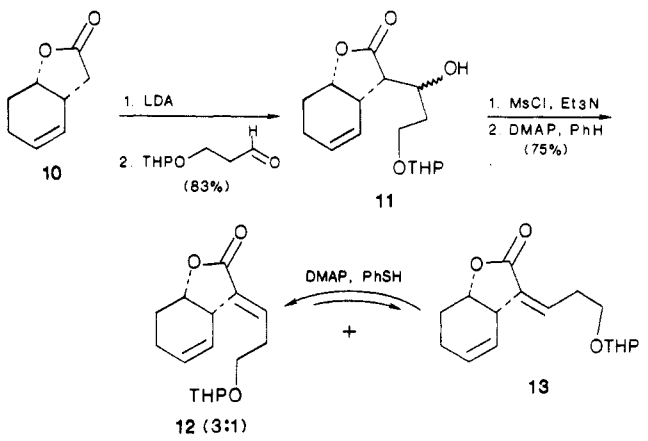


laboratory.[5-7] The results of these efforts are the subject of the present report.

An analysis of the structure of compactin reveals that it can be divided into two key fragments, a hexahydronaphthalene unit, the bottom portion, and the lactone unit, the upper portion (Scheme I). The hexahydronaphthalene unit is thus seen to possess five centers of chirality (four contiguous and one in the α-methylbutyrate side chain), while the lactone portion contains two centers of asymmetry. Our tactic for procuring optically pure (+)-compactin was to rely on coupling the racemic sulfone 3, the precursor to the bottom portion of compactin, with the optically active lactone 4 followed by chromatographic separation of the resulting diastereomeric products.

The construction of the lactone moiety of compactin in optically pure form has been described by us elsewhere.[7k] This synthesis was based on the ability of an allylic oxygen substitutent to control the π-facial course of a dipolar cycloaddition reaction employing a nitrile oxide (Scheme II).[8]

Scheme IV

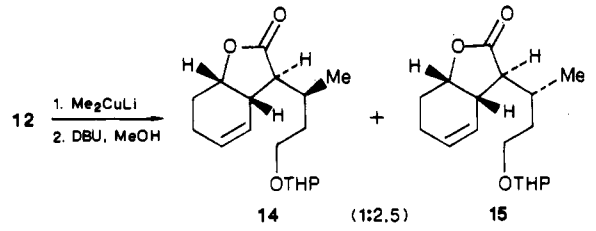


(5) For previous total syntheses of compactin, see: (a) Wang, N.-Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. Hsu, C. T.; Wang, N. Y.; Latimer, L. H.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 593. (b) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251. (c) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403. (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. (e) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731. Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. Mevinolin: (f) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811. Dihydrocompactin: (g) Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811. Dihydromevinolin: (h) Falck, J. R.; Yang, Y. L. *Tetrahedron Lett.* **1984**, *25*, 3563.

(6) For synthetic work on the hydronaphthalene portion of compactin, see: (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (b) Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. (c) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popjak, G. *Tetrahedron Lett.* **1982**, *23*, 4747. Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190. (d) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (e) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1983**, *24*, 3687. (f) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Tetrahedron Lett.* **1984**, *25*, 1655. (g) Girotra, N. N.; Reamer, R. A.; Wendler, N. L. *Tetrahedron Lett.* **1984**, *25*, 5371. Mevinolin: (h) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701. Hecker, S. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 5159. Dihydrocampactin: (i) Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. *Tetrahedron Lett.* **1985**, *26*, 1131.

(7) For synthetic work on the lactone portion, see: (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (c) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305. (d) Ho, P. T.; Chung, S. *Carbohydr. Res.* **1984**, *125*, 318. (e) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101. (f) Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 2435. (g) Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 3391. (h) Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 4889. (i) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994. (j) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185. (k) Kozikowski, A. P.; Li, C. S. *J. Org. Chem.* **1985**, *50*, 778.

Scheme V



For the synthesis of the "racemic" decalin nucleus, we were interested in pursuing an approach stemming from the nitrile oxide based dissection shown in Scheme III. The γ-lactone **10** was further selected to serve as the precursor to our nitrile oxide bearing intermediate **9**. This lactone possesses two of the four contiguous centers of a symmetry present in the hexahydronaphthalene unit. Thus, a method was required to elaborate **10** to **3** with introduction of the other two asymmetric centers. It is to these matters that we now turn in discussing our first effort to prepare **3**.

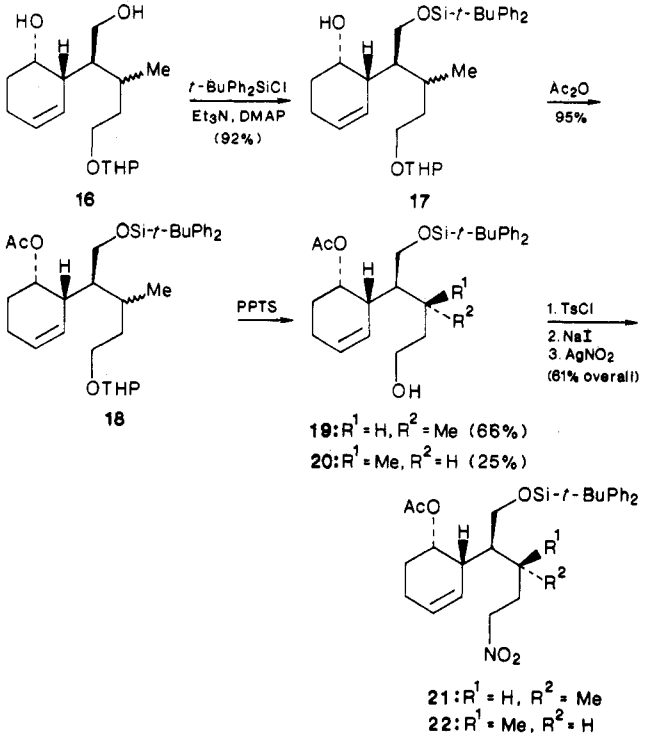
An Attempt To Prepare the Bottom Part of Compactin through a Copper Conjugate Addition Strategy

In the beginning of our efforts to assemble the hexahydronaphthalene unit of compactin from the γ-lactone **10**, we envisioned transforming it first to the alkylidene lactone **12** (Scheme IV). This intermediate would in turn be treated with lithium dimethylcuprate to transform the two sp^2 carbon centers to sp^3-hybridized atoms.[9] The cuprate addition process was anticipated to occur on the more accessible convex face of the bicyclic system (see **12**), thus correctly setting the C-2 center. A subsequent epimerization event α to the lactone carbonyl group would presumably properly set the stereochemistry of the C-1 center.

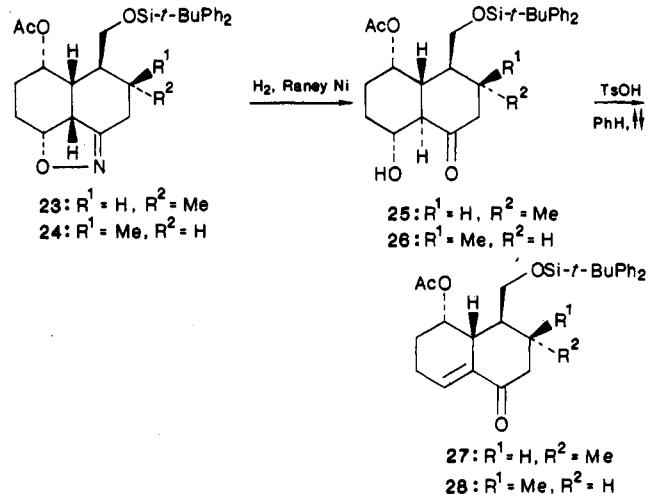
In pursuit of this strategy, the anion of **10**[10] was condensed with the tetrahydropyranyl ether of 3-hydroxypropionaldehyde[11] to afford the hydroxy lactone **11** as a diastereomeric mixture. Compound **11** could be converted in turn to a 3:1 mixture of the (*E*)- and (*Z*)-alkylidene lactones by mesylate elimination employing 4-(dimethylamino)pyridine.[12] The *Z* isomer could, moreover, be isomerized to a 2:1 mixture of **12** and **13** by heating with a catalytic amount of thiophenol and 1 equiv of 4-(dimethylamino)pyridine in benzene.[13] The assignment of structure to these isomeric compounds is based upon the downfield shift of the vinyl proton in the trans isomer **12** (δ 6.84) as compared with the higher field resonance of this proton in the cis isomer **13** (δ 6.36).[14]

With **12** in hand, the cuprate addition reaction was now studied. To our initial surprise, the stereochemical outcome of this reaction was opposite the expectations delineated above. Two major lactones **14** and **15** were isolated in a 1:2.5 ratio after equilibration of the products formed from the cuprate addition step (Scheme V). The stereochemistry of the products was confirmed by their conversion to decalins related structurally to the bottom

Scheme VI



Scheme VII



(8) For recent studies on the π-facial diastereoselectivity of nitrile oxide cycloaddition reactions with chiral allylic ethers, see: (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. (c) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(9) The conjugate addition of organocuprates to several types of α,β-unsaturated carboxylic acid functions has been reported. α,β-Unsaturated esters: (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (b) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1. α-Methylene lactones: (c) Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542. Enol lactones: (d) Boeckman, R. K.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3630. Cyclobutenyl esters: (e) Clark, R. D. *Synth. Commun.* **1979**, *9*, 325.

(10) Corey, E. J.; Ravindranathan, T. *Tetrahedron Lett.* **1971**, 4753. This γ-lactone has been resolved into both of its enantiomerically pure forms. Corey, E. J.; Snider, B. B. *J. Org. Chem.* **1974**, *39*, 256.

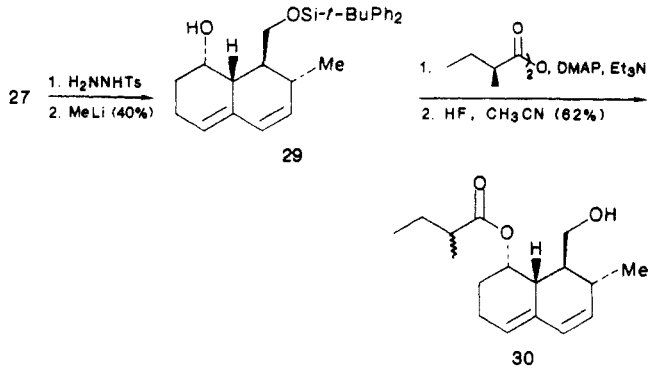
(11) The tetrahydropyranyl ether of 3-hydroxypropionaldehyde was prepared from 3-hydroxypropionitrile by THP ether formation and DIBAL reduction as described previously: Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301. For the preparation of aldehydes from nitriles, see: Winterfeldt, E. *Synthesis* **1975**, 617.

(12) For other approaches to α-alkylidene lactones, see: (a) Carlson, R. M.; DeLane, J. C.; Liu, T.-L. *Synth. Commun.* **1985**, *15*, 657. (b) Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065. (c) Yu, L.-C.; Helquist, P. M. *J. Org. Chem.* **1981**, *46*, 4536.

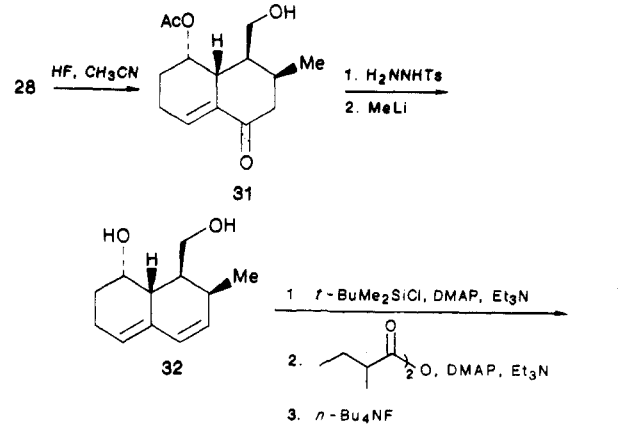
(13) The isomerization of (*Z*)-enoic acids to (*E*)-enoic acids by thiophenol has been reported: Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1.

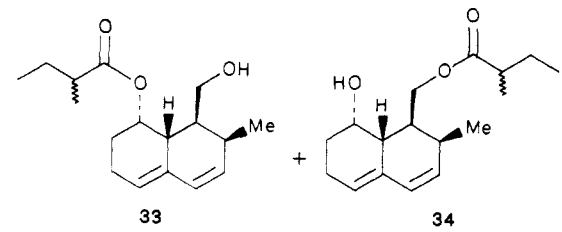
(14) This phenomenon originates from the anisotropic effect of the lactone carbonyl group: Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1972.

Scheme VIII

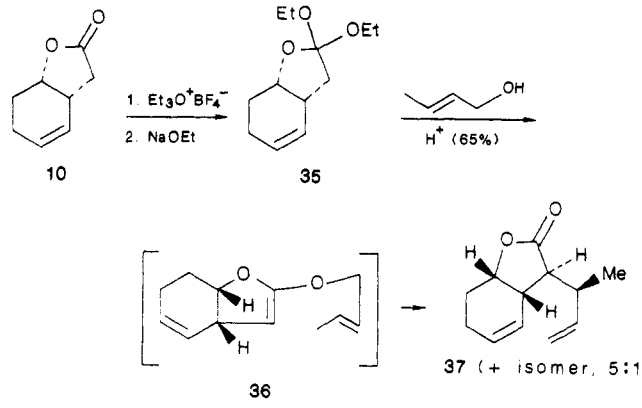


Scheme IX





Scheme X



portion of compactin (vide infra). Of equal surprise to us was the finding that the *Z* olefin **13** also gave rise to **15** as the major product of the cuprate addition/equilibration sequence (**14**:**15** = 1:3.5).

The stereochemical results clearly indicate that our original notions about the bicyclic lactone portion of **12** guiding the facial approach of the cuprate reagent were incorrect.[15,17] Consequently, one is led to the conclusion that the steric effects provided by the alkylidene side chain must also come into play.

In order to confirm the stereochemical assignments made for compounds **14** and **15**, a sequence of chemical transformations was carried out to provide the diene systems **30** and **33**. Compound **33** had previously been synthesized by Heathcock via a different route,[6c] and spectral data were available for comparison.[19] Accordingly, the diastereomeric mixture of **14** and **15** was reduced with lithium aluminum hydride to provide the diol **16** (Scheme VI). Selective protection of the primary (*t*-$BuPh_2Si$) and secondary (Ac) alcohols led after cleavage of the tetrahydropyranyl group to a separable mixture of the alcohols **19** and **20**.[20] These intermediates were transformed to their respective nitro compounds **21** and **22** via the corresponding tosylates and iodides.[21]

An INOC reaction[22] was now induced with phenyl isocyanate[23] as the dehydrating agent. A single isomer was formed in each case, and the products were assigned to be the cis-fused decalin systems (Scheme VII).[24] Upon hydrogenation[25] and dehydration, the enones **27** and **28** were obtained from the corresponding isoxazolines **23** and **24**, respectively.

After **27** was subjected to the Shapiro reaction using Bond's trisylhydrazone modification,[28] the diene **29** was isolated (Scheme VIII). Acylation with 2-methylbutyric anhydride and desilylation yielded **30**. The ^1H NMR spectrum of this compound was quite different from that of the known compound **33**, especially in regard to the signals observed for their respective olefinic protons. Accordingly, **30** was assigned the relative stereochemistry displayed in the accompanying structure. Since diene **30** was derived from the major product formed in the cuprate addition step, the lack of correlation between **30** and **33** confirmed the ill-conceived nature of this conjugate ad-

(15) MM2 calculations made with the aid of the CHEMGRAF program reveal that the conformations of **12** involving placement of the (tetrahydropyranyloxy)methyl group above or below the plane defined by the exocyclic double bond are nearly equally populated:[16] Davies, E. K. *ChemGraf*; Chemical Crystallography Laboratory, Oxford University, developed and distributed by Chemical Design Ltd.; Oxford, 1983–1985. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(16) Perrin, C. L.; Seeman, J. I. *J. Org. Chem.* **1984**, *49*, 2887 and references therein.

(17) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *26*, 3063.

(18) Also, recent studies indicate that vinylcuprate additions to carbohydrate-derived enones and to α,β-unsaturated esters are anti to the polar substituents and independent of the geometry of the starting olefinic systems: Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231.

(19) We thank Professor Heathcock for providing us with the NMR spectral data for **33**.

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(21) Kornblum, N.; Ungnade, H. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 724.

(22) The synthetic versatility of isoxazolines has been reviewed: Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. Also, see: Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 277–406.

(23) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(24) For related observations regarding ring fusion stereochemistry, see: Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845.

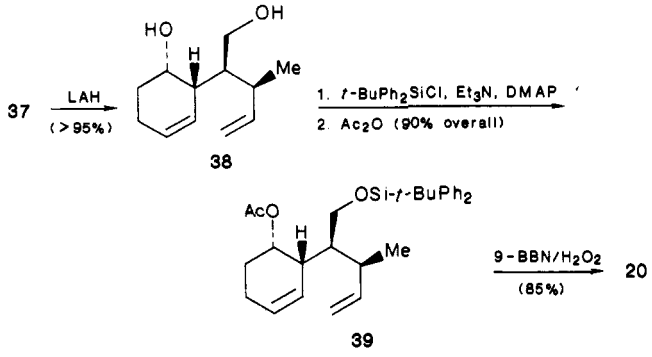
(25) Hydrogenation was effected by using a modification of the Wollenberg conditions: Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. Also, see: (a) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. (b) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (c) Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337. (d) Andersen, S. H.; Das, N. B.; Jorgenson, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta. Chem. Scand., Ser. B* **1982**, *B36*, 1.

(26) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023.

(27) For a discussion of stereoelectronic effects in trans elimination reactions, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 252–257.

(28) (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (b) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

Scheme XI



dition process for setting the stereochemistry at C-2.

The minor isomer **28** was converted to the stereochemically correct hexahydronaphthalene unit **33** by a low-yielding sequence of steps (Scheme IX). The enone **28** was first desilylated and then hydrazone formation brought about by using the sterically less hindered reagent, (*p*-tolylsulfonyl)hydrazine. Hydrazone formation employing the silyl derivative **28** was not successful. The Shapiro reaction led in turn to the diene **32**. Selective protection of the primary alcohol, acylation of the sedondary alcohol, and desilylation yielded the hexahydronaphthalene **33** and its acyl migration product **34** in a 1:2 ratio. The ^{1}H NMR spectrum of **33** was identical with that of the Heathcock compound, thus further verifying the stereochemical course of the conjugate addition reaction.

While the foregoing chemistry served to demonstrate that one could indeed employ the isoxazoline ring as a "masked 1,3-diene equivalent", several glaring issues needed to be addressed in order to improve the overall scheme. A better method was needed to correctly set the stereochemistry of the C-2 methyl bearing center; and additionally, a higher yielding strategy for converting the isoxazoline-derived enone to a 1,3-diene was required.

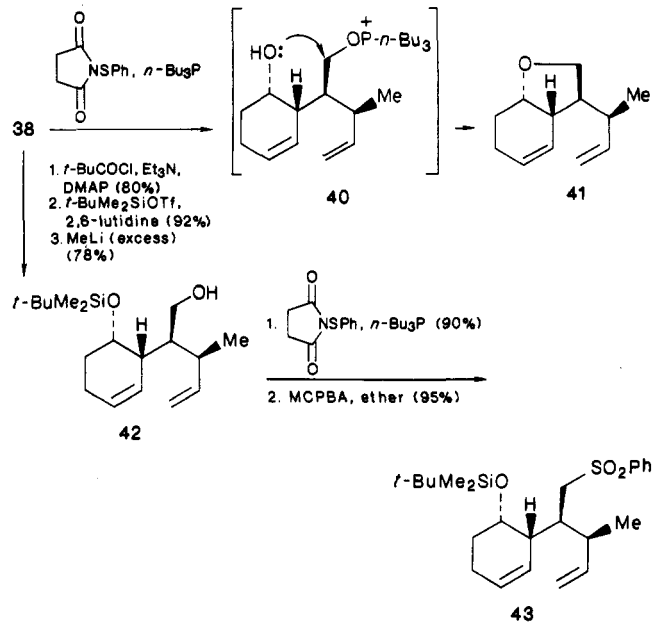
Claisen Approach to the Bottom Part of Compactin

Since the copper conjugate addition chemistry failed to properly fix the stereochemistry of the four contiguous centers of the decalin unit, we were prompted to explore a Claisen approach instead in which the same γ-lactone **10** would serve as the starting material. Strong precedent for the successful outcome of such a [3,3] sigmatropic rearrangement reaction could be found in the work of Ziegler et al.[29]

Hence, the γ-lactone **10** was transformed to its ortho lactone **35** by use of Meerwein's salt (Scheme X).[30] On heating this ortho lactone with crotyl alcohol in the presence of propionic acid as catalyst, a 5:1 diastereomeric mixture of products resulted. The stereochemistry of the major isomer, which presumably derives from the chair transition state **36**, was confirmed by its conversion to the previously known alcohol **20** (Scheme XI).

In order to allow for eventual appendage of the "upper lactone portion of compactin", we now wished to transform the primary hydroxyl group of **38** to a sulfone. After **38** was reacted with *N*-(phenylthio)succinimide and tri-*n*-butylphosphine,[31] the tetrahydrofuran **41** was formed

Scheme XII



(Scheme XII).[32] This result was not particularly surprising, for the proximity of the hydroxyl groups does greatly favor such an intramolecular process.

Consequently, the secondary hydroxyl function required protection prior to formation of the phenyl sulfide. A double-protection/deprotection sequence provided **42** in high yield. The sulfide was generated and a MCPBA oxidation[33] to the sulfone carried out in diethyl ether.

Instead of completing the hexahydronaphthalene unit at this point and then coupling the completed bottom with the "protected lactone", we felt that the coupling reaction might best be carried out with use of **43**. Compound **43** presents a more open, more flexible system for coupling with the iodide **4** than does the sulfone analogue having a bond between carbons 4 and 4a. The successful execution of the required S_N2 displacement reaction, a reaction that had eluded other workers in the past, thus appeared significantly higher.

Sulfone **43** was converted to its dianion by reaction with 2 equiv of *n*-butyllithium in the presence of HMPA,[34] and the dianion[35] reacted with the iodide **4**. Two separable diastereomeric dienes **45** (more polar) and **46** (less polar) were formed. Both of these compounds were converted by the same sequence of operations (Scheme XIII) to the compactin derivative **47** and its 1,2,8,8a-tetra-epi isomer **48**. Since we had also converted natural compactin into **47**, a stereochemical assignment of the products formed in the coupling step could be made. The more polar compound was accordingly found to possess the correct absolute stereochemistry required for completion of the synthesis.

From **45**, the synthesis was completed by first selectively hydrating the terminal double bond with 9-BBN/H_2O_2[36] and then reductively removing the sulfone group (Scheme

(29) (a) Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1982**, *23*, 3531. (b) Ziegler, F. E.; Kneisley, A. *Tetrahedron Lett.* **1985**, *26*, 263. Also, see: Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(30) (a) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, H. *Chem. Ber.* **1956**, *89*, 2060. (b) For a review on ortho ester synthesis, see: DeWolfe, R. H. *Synthesis* **1974**, 153.

(31) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.

(32) Castro, B. R. *Org. React.* (*N.Y.*) **1983**, *29*, 1.

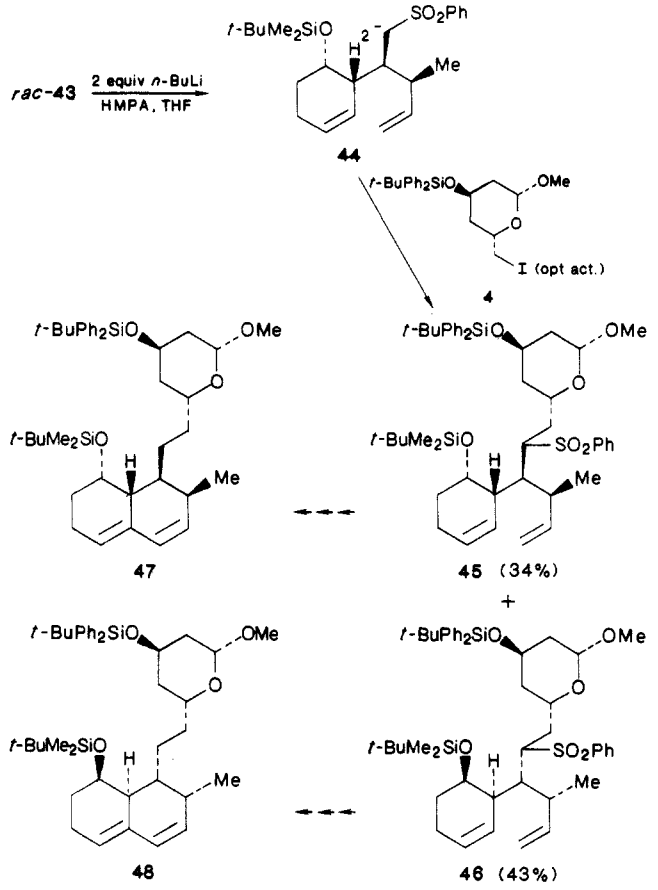
(33) For a recent study on the selective oxidation of sulfides to sulfones, see: Purrington, S. T.; Glenn, A. G. *Org. Prep. Proced. Int.* **1984**, *17*, 227.

(34) For a review of sulfone chemistry, see: Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) For the recent utilization of sulfone dianions to prepare hydroxy ketones from lactones, see: Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246.

(35) Related sulfone dianion chemistry has been employed by Falck in the synthesis of (+)-dihydrocompactin. See ref 5g.

(36) Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

Scheme XIII



XIV).[37] The free alcohol was converted via its aldehyde[38] to its oxime, and the oxime was reacted with aqueous sodium hypochlorite in the presence of triethylamine to furnish the desired isoxazoline **50**.[39] Use of this oxidative method for nitrile oxide generation proved more efficient than the dehydrative method requiring a nitroalkane, a method that had been used previously in the conversion of **21**/**22** to **23**/**24**.

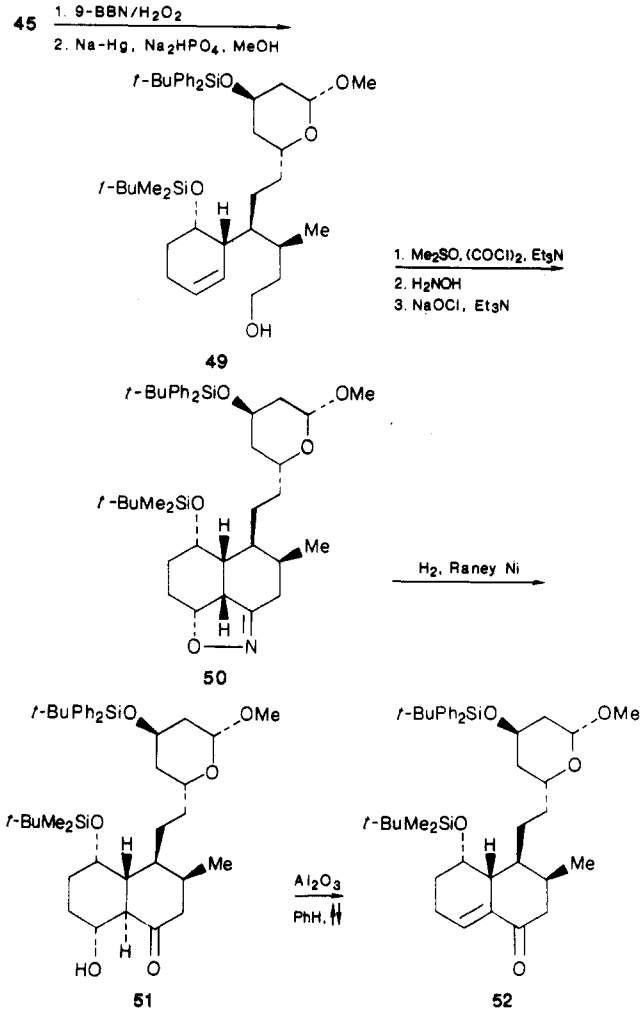
While hydrogenation of the isoxazoline **50** proceeded readily, the resulting β-ketol **51** was converted to an unidentifiable mixture upon attempted dehydration with *p*-toluenesulfonic acid (a reagent successfully used in the conversion of **25**/**26** to **27**/**28**).

The precedented dehydration of a steroidal β-ketol to an enone with basic aluminum oxide, however, provided us with a hint for solving this minor problem.[40] Indeed, exposure of **51** to basic aluminum oxide proceeded smoothly to afford **52** in high yield.

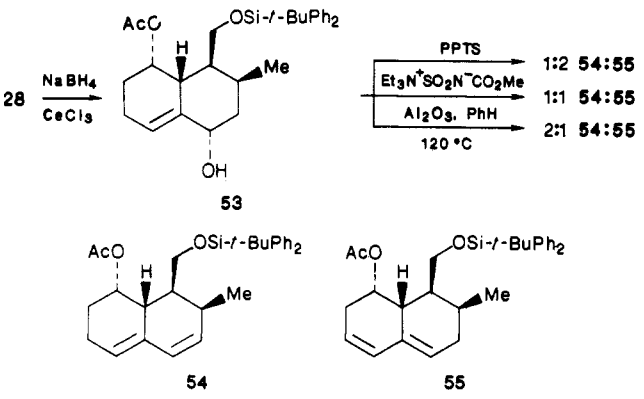
While we could conceivably use the Shapiro reaction to transform enone **50** to 1,3-diene, the yields obtained for this conversion in the model systems (i.e., **27** → **28** and **31** → **32**) were disappointing. Alternatives were therefore sought.

With enone **28** as a model, this compound was reduced to the corresponding allylic alcohol,[41] and dehydration was attempted by using pyridinium *p*-toluenesulfonate[42] and

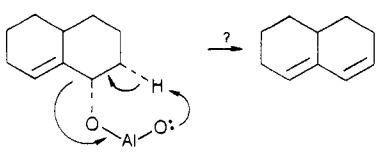
Scheme XIV



Scheme XV



Scheme XVI



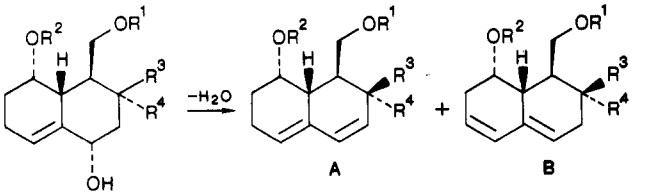
the Burgess salt (Scheme XV).[43] The former reagent gave a 1:2 mixture of the isomeric dienes **54** and **55**, respectively, while the latter gave a 1:1 mixture of dienes.

Stimulated by our earlier success with aluminum oxide as a dehydrating agent, we considered the possibility that

(37) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(38) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(39) Lee, G. A. *Synthesis* **1982**, 508.
(40) Bible, R. H.; Atwater, N. W. *J. Org. Chem.* **1961**, *26*, 1336.
(41) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(42) The use of PPTS to promote the dehydration of a structurally related allylic alcohol was found to afford mainly the rearranged 1,3-diene. See ref 6c.

(43) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.

Table I. Dehydration of the Compactin-Related Allylic Alcohols



entry	R^1	R^2	R^3	R^4	dehydr agent	A:B
1	*t*-$BuPh_2Si$	Ac	Me	H	PPTS[a]	1:2
2	*t*-$BuPh_2Si$	Ac	Me	H	Al_2O_3[b]	2:1
3	*t*-$BuPh_2Si$	Ac	H	Me	PPTS[a]	1:1
4	*t*-$BuPh_2Si$	Ac	H	Me	Al_2O_3[b]	2:1
5	*t*-$BuPh_2Si$	MOM	Me	H	Al_2O_3[b]	2:1
6	*t*-$BuPh_2Si$	Me_3CCO	Me	H	Al_2O_3[b]	3:1
7	*t*-$BuPh_2Si$	*t*-$BuMe_2Si$	Me	H	Al_2O_3[b]	4:1
8	*t*-$BuMe_2Si$	Me_3CCO	Me	H	PPTS[a]	1:2
9	*t*-$BuMe_2Si$	Me_3CCO	Me	H	Al_2O_3[b]	7:1

[a] A mixture of 10 mg of substrate and PPTS (catalyst) in 2 mL of dichloroethane was refluxed for 12 h. [b] A mixture of 10 mg of substrate and 200 mg of basic aluminum oxide (Woelm B, grade I) in 2 mL of benzene was heated at 120 °C for 2–3 h in a sealed tube.

complexation of the hydroxyl oxygen of **53** with the Lewis acidic aluminum center might allow for a regioselective dehydration reaction through a cyclic, six-membered transition state (Scheme XVI).[44] Indeed, when **53** was heated with basic aluminum oxide in benzene at 120 °C, the isomer ratio was reversed to 2:1 in favor of the desired product. Additional examples of this dehydration reaction employing other derivatives of **53** and its C-2 epimer can be found in Table I. PPTS-promoted dehydration of some of these compounds was carried out as well in order that comparisons with the aluminum oxide dehydration could be made.

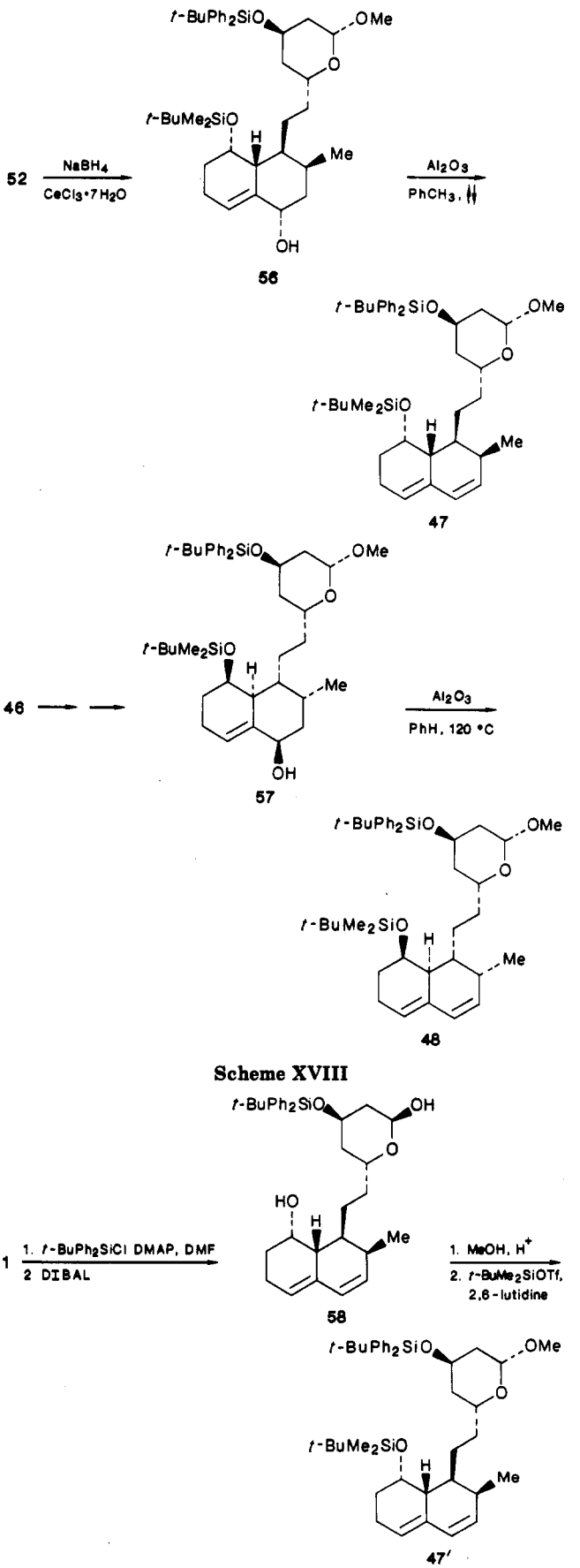
The aluminum oxide promoted dehydration reaction always produced the unrearranged diene A (i.e., the 1,2-elimination product) as the major product, whereas the PPTS led to more of the rearranged diene B or to an equivalent amount of each. An interesting trend was also observed with regard to the bulkiness of the hydroxyl protecting groups. A larger protecting group on the secondary alcohol and a smaller protecting group on the primary alcohol appeared to favor production of the unrearranged diene (cf. entries 2 and 9 as well as 5–7).

With this information in hand, enone **52** was reduced with sodium borohydride and cerium trichloride[41] to the allylic alcohol **56** (Scheme XVII). Dehydration with aluminum oxide did, in fact, now lead to nearly exclusively the desired 1,3-diene **47**, with but a trace of the regioisomeric compound being detectable by high-field NMR. The other diastereomer **46** produced in the coupling reaction was also carried through the same sequence of reactions to produce the diene **48**.

To confirm the stereochemistry of the dienes **47** and **48**, natural compactin was derivatized as shown in Scheme XVIII. The β-hydroxy group of the lactone moiety was silylated, and the lactone carbonyl was reduced with DIBAL. This reduction was also accompanied by cleavage of the 2-methylbutyryl group. The lactol was converted to its α-methoxypyran derivative by methanol/acid treatment, and the free hydroxyl group was silylated.

Although the ^1H NMR spectra of the 1,3-dienes **47** and **48** are very similar, they do exhibit some small differences. The C-2 methyl group of **47** appears at δ 0.88 as a doublet,

Scheme XVII

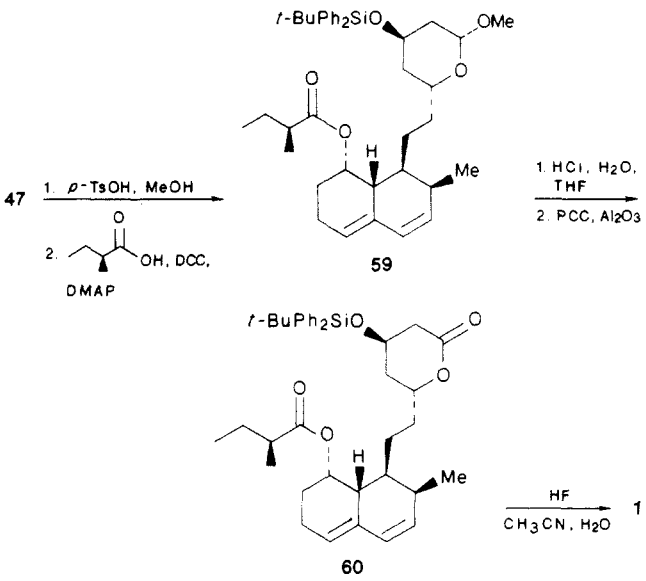


Scheme XVIII

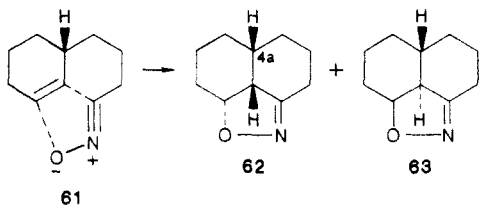
while the two methyl groups of its *tert*-butyldimethylsilyl group are located at δ 0.10 and 0.08 as singlets. The C-2 methyl group of **48** is at δ 0.83, and the two methyl groups of its *tert*-butyldimethylsilyl group are almost overlapping

(44) For an excellent review on the use of alumina in organic synthesis, see: Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487.

Scheme XIX



Scheme XX



at δ 0.09 and 0.08. The ^{1}H NMR spectrum of the synthetic diene **47** is identical with that of the diene **47′** prepared from natural compactin. The optical rotations ($[\alpha]_D$) of the dienes **47** (synthetic), **47′** (natural), and **48** are +102.4° (*c* 0.335, $CHCl_3$), +102.2° (*c* 0.220, $CHCl_3$), and −144.3° (*c* 0.345, $CHCl_3$), respectively. The synthetic diene **47** thus possesses the "natural compactin" configuration.

At this point, only the stereochemically correct isomer was carried on further. The *tert*-butyldimethylsilyl group of **47** was selectively cleaved by mild acid treatment, and the free alcohol was acylated with (*S*)-(+)-2-methylbutyric acid with DCC/DMAP (Scheme XIX). The α-methoxypyran was then converted to lactone **60** by hydrochloric acid treatment followed by PCC oxidation in the presence of aluminum oxide. Hydrofluoric acid in an acetonitrile–water mixture effected cleavage of the last remaining silyl protecting group in poor yield to afford compactin.

A Discussion of the INOC Transition State

We have carried out molecular mechanics calculations on the two compactin-related decalin structures that can result from the INOC reaction of the cyclohexene **61** (Scheme XX). These calculations reveal that a minimum energy difference of at least 3 kcal/mol exists between the lower energy cis product **62** and the trans product **63**. To the extent that the higher energy of the trans product **63** is reflected in the transition state for cycloaddition, one would expect to observe exclusive production of the cis-fused product. Indeed, experimentally one does observe the transformation of **21**/**22** and **49** to exclusively the cis-fused products **23**/**24** and **50**. From an examination of the transition states available to **61** through the use of Dreiding models, it is easy to see that the dipole can be more easily aligned with the dipolarophile if the nitrile oxide adds to that face of the olefin on which the tethering chain resides. Considerable strain must be introduced into the system at carbon 4a in order to achieve a good parallel plane alignment of dipole and dipolarophile in the transition state that leads to the trans-fused decalin. In a more appropriate quantitative sense, computation-based modeling methods developed by Houk and Brown for the INOC reaction reveal a 2.8 kcal/mol energy difference between the *transition states* leading to **62** and **63**.[45] Such a large energy difference would again lead to a prediction that only a single isomer should result from the cycloaddition reaction of **61**. Since kinetic factors must control the product outcome in these INOC reactions, it is probably only a fortuitous circumstance that the difference in the calculated transition state energies and the product energies are so similar.

Summary

The work reported herein establishes the ultility of the INOC reaction for the construction of highly substituted decalin systems. It also further illustrates the versatility of the isoxazoline ring in synthesis, for here this heterocycle serves as a masked 1,3-diene.[46] Additionally, valuable lessons were learned regarding the various elements that can control the stereochemical course of copper conjugate addition reactions. Our synthesis will not, however, supplant the fermentation processes presently used to produce compactin and its relative mevinolin.

Experimental Section

Infared spectra (IR) were obtained on a Perkin-Elmer Model 247 spectrometer or a Beckman Model Acculab 4 spectrometer and are calibrated to the polystyrene absorption at 1602 cm^{-1}. Spectra were obtained as dilute solutions in chloroform or as neat films. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (Varian EM-360 or T-60A) or at 300 MHz (Bruker WH-300) in the solvents noted. Chemical shifts (δ) are reported downfield from internal Me_4Si (δ 0.00). Low-resolution mass spectra were obtained on a LKB-9000 instrument operating at 15- or 70-eV ionization potential. High-resolution mass spectra were determined on a Varian MAT CH-5DF instrument by peak matching. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at the sodium D line. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected.

Silica gel 60 (Merck, 70–230 or 230–400 mesh for flash chromatography) and Mallinckrodt SilicAR CC-7 were used for column chromatography. Thin-layer chromatography (TLC) was performed on Merck 60 F-254 silica gel coated on aluminum. Visualization of compounds on TLC plates was accomplished by UV illumination, iodine vapor, or staining with a solution comprised of 25 g of ammonium molybdate and 1 g of ceric sulfate in 500 mL of 10% sulfuric acid, followed by heating. Distilled reagent-grade solvents were used for all chromatographic separations.

Benzene and toluene were distilled from calcium hydride; tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride or calcium oxide under reduced pressure and stored over 4-Å molecular sieves. Dimethyl sulfoxide (Me_2SO) was distilled from calcium hydride under reduced pressure and stored over 4-Å molecular sieves. Pyridine was distilled from sodium hydroxide and stored over sodium hydroxide. Other solvents were purified by distillation prior to use. Solid reagents were used as supplied, while liquid

(45) Brown, F. K. Ph.D. Thesis, University of Pittsburgh, 1985.

(46) For other applications of isoxazolines, see: (a) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365. (b) Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147. (c) Kozikowski, A. P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, pp 413–491. (d) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199.

reagents were distilled prior to use. *n*-Butyllithium in hexanes (Aldrich) was titrated with diphenylacetic acid in tetrahydrofuran (0.1–0.2 M) under argon.

All reactions were carried out under a nitrogen or argon atmosphere with magnetic stirring. Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing addition funnels where appropriate.

***cis*-(±)-2,2-Diethoxy-2,3,3a,6,7,7a-hexahydrobenzofuran (35).** A mixture of lactone **10** (8.0 g, 58 mmol) and triethyloxonium tetrafluoroborate (13.0 g, 68 mmol) was kept at 0 °C under nitrogen with occasional stirring (one or two times each day) for 5 days. Anhydrous diethyl ether (ca. 20 mL) was then added, and the mixture was stirred for 2 min. After the mixture was cooled to −78 °C, the upper liquid was removed by syringe. The solid residue was washed with anhydrous ether (2×) by successively warming to 0 °C, stirring for 2 min, cooling to −78 °C again, and removing the ethereal washings.

The dark brown solid obtained was dissolved in 15 mL of dry CH_2Cl_2, and the resultant mixture was added dropwise via syringe to a solution of 2.0 g (87 mmol) of sodium in 40 mL of absolute ethanol at 0 °C over a period of 1 h. The resulting mixture was stirred at room temperature for 12 h, treated with 100 mL of 2 N aqueous sodium carbonate, and extracted with ether three times. The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give a brown liquid. Bulb-to-bulb distillation provided 7.0 g (57%) of the ortho lactone **35** as a colorless liquid: bp 70–80 °C (0.7 mm); ^1H NMR ($CDCl_3$) δ 5.80–5.50 (m, 2 H), 4.30 (m, 1 H), 3.70–3.45 (m, 4 H), 2.84 (m, 1 H), 2.38–1.66 (m, 6 H), 1.20 (t, 3 H, J = 7.5 Hz), 1.18 (t, 3 H, J = 7.5 Hz).

[3α(*R),3aα,7aα]-(±)-3a,6,7,7a-Tetrahydro-3-(1-methyl-2-propenyl)-2(3*H*)-benzofuranone (37).** A mixture of ortho lactone **35** (7.0 g, 33 mmol), *trans*-2-buten-1-ol (3.40 mL, 40 mmol), and propionic acid (300 μL) in 160 mL of xylene was refluxed for 18 h. After cooling, the solvent was evaporated in vacuo to yield a yellow liquid. Chromatography over silica gel with hexanes–ethyl acetate (6:1) as eluent afforded 4.2 g (65%) of a less polar fraction as a colorless liquid, which by ^1H NMR analysis was a 5:1 diastereomeric mixture of **37** (major) and its methyl epimer: IR (thin film) 2940, 1755, 1640, 1450, 1330, 1175, 1030, 915, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85 (m, 2 H), 5.54 (m, 1 H), 5.12 (m, 2 H), 4.67 (m, 1 H), 2.80 (m, 2 H), 2.45 (dd, 1 H, J = 6.3, 4.2 Hz, major), 2.30 (dd, 1 H, J = 6.4, 5.1 Hz, minor), 2.22–1.76 (m, 4 H), 1.21 (d, 3 H, J = 6.9 Hz, minor), 1.18 (d, 3 H, J = 7.1 Hz, major); mass spectrum (70 eV), m/z 192 (M^+); exact mass calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1155.

Preparation of Diol 38. To a suspension of 1.0 g (26 mmol) of lithium aluminum hydride in 40 mL of tetrahydrofuran was added dropwise a solution of 4.0 g (21 mmol) of lactone **37** in 10 mL of tetrahydrofuran at 0 °C. After being stirred at room temperature for 1 h, the mixture was quenched by the slow addition of ethyl acetate. Water (ca. 2 mL) was then added dropwise until a white precipitate was formed from the gray slushy mass. The mixture was filtered, and the precipitate was washed with ethyl acetate. The combined filtrates were dried over anhydrous $MgSO_4$ and evaporated in vacuo to give diol **38** in quantitative yield as a colorless oil, which solidified on refrigeration. The product was used for further reaction without purification: IR (thin film) 3225, 2900, 1625, 1440, 1360, 1315, 1275, 1190, 1160, 1110, 1070, 1030, 995, 970, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90–5.65 (m, 2 H), 5.48 (td, 1 H, J = 10.5, 2.1 Hz), 3.66 (dd, 1 H, J = 11.5, 6.8 Hz), 3.12 (br, 2 H), 2.68–1.40 (m, 7 H), 1.14 (d, 3 H, J = 7.0 Hz, major), 1.06 (d, 3 H, J = 7.0 Hz, minor); mass spectrum (70 eV), m/z 196 (M^+), 178 ($M^+ - H_2O$); exact mass calcd for $C_{12}H_{20}O_2$ 178.1358, found 178.1360.

Formation of the Pivaloate Ester of Diol 38. A mixture of 2.20 g (11.2 mmol) of diol **38**, 1.5 g (12.4 mmol) of trimethylacetyl chloride, 3.5 mL (24.5 mmol) of triethylamine, and 20 mg (catalytic amount) of 4-(dimethylamino)pyridine in 20 mL of methylene chloride was stirred at room temperature for 20 min. A saturated aqueous sodium bicarbonate solution (20 mL) was added, and the mixture was stirred for 5 min. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield a yellow oil. Chromatography over silica gel with hexanes–ethyl acetate (5:1) as eluent afforded 2.51 g (80%) of the pivaloate ester as a colorless oil: IR (thin film) 3510, 2985, 1740, 1665, 1490, 1470, 1405, 1370, 1280, 1160, 1075, 1030, 995, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88–5.60 (m, 3 H), 5.02 (m, 2 H), 4.27 (dd, 1 H, J = 12.0, 3.8 Hz), 4.22 (dd, 1 H, J = 12.0, 4.5 Hz), 4.12 (br, 1 H), 2.65 (m, 1 H), 2.40–1.65 (m, 6 H), 1.20 (s, 9 H), 1.04 (d, 3 H, J = 7.0 Hz); mass spectrum (70 eV), m/z 280 (M^+), 225, 206.

Silylation of the Pivaloate Ester. To a solution of 2.40 g (8.6 mmol) of the above pivaloate ester and 2.0 mL (17.2 mmol) of 2,6-lutidine in 20 mL of methylene chloride was added 3.40 g (13 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After being stirred at room temperature for 15 min, the mixture was quenched with saturated aqueous sodium bicarbonate and extracted with methylene chloride (2×). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to give a yellow oil. Chromatography over silica gel with hexanes–ethyl acetate (50:1) as eluent yielded 3.10 g (92%) of the silyl ether as a colorless liquid: IR (thin film) 2940, 1725, 1625, 1470, 1445, 1390, 1350, 1265, 1240, 1150, 1080, 1025, 990, 960, 935, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90–5.50 (m, 3 H), 5.05–4.86 (m, 2 H), 4.22–4.04 (m, 3 H), 2.68–1.60 (m, 7 H), 1.18 (s, 9 H), 1.10 (d, 3 H, J = 7.0 Hz), 0.88 (s, 9 H), 0.08 (s, 6 H); mass spectrum (70 eV), m/z 394 (M^+), 337 ($M^+ - C_4H_9$).

Cleavage of the Pivaloate Ester. To a solution of 3.0 g (7.6 mmol) of the above silyl ether in 100 mL of ether at 0 °C was added dropwise 25 mL of methyllithium (1.5 M) in ether. The mixture was stirred at 0 °C for 30 min, and water was then added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residual oil was chromatographed over silica gel with hexanes–ethyl acetate (20:1) as the eluent to give a small amount of the minor isomer (less polar) as a colorless liquid and 1.85 g (78%) of **42** (more polar) as a colorless liquid.

Minor isomer: IR (thin film) 3390, 2940, 1625, 1460, 1450, 1245, 1060, 1000, 970, 935, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90–5.40 (m, 3 H), 5.10–4.85 (m, 2 H), 4.14 (br s, 1 H), 3.76 (dd, 1 H, J = 10.4, 1.6 Hz), 3.57 (dd, 1 H, J = 10.4, 7.4 Hz), 2.70–1.40 (m, 7 H), 1.12 (d, 3 H, J = 6.8 Hz), 0.90 (s, 9 H), 0.09 (s, 6 H).

Major isomer **42**: IR (thin film) 3450, 2940, 1635, 1460, 1450, 1220, 1080, 1000, 930, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90–5.50 (m, 3 H), 5.10–4.90 (m, 2 H), 4.14 (m, 1 H), 3.67 (dd, 1 H, J = 11.8, 2.4 Hz), 3.54 (dd, 1 H, J = 11.8, 6.6 Hz), 2.65–1.55 (m, 7 H), 1.12 (d, 3 H, J = 6.8 Hz), 0.90 (s, 9 H), 0.12 (s, 6 H); mass spectrum (70 eV), m/z 253 ($M^+ - C_4H_9$).

[1α,2α[(1*R,2*R**)]-(±)-(1,1-Dimethylethyl)dimethyl[[2-[2-methyl-1-[(phenylthio)methyl]-3-butenyl]-3-cyclohexen-1-yl]oxy]silane.** To a solution of 1.4 mL (5.6 mmol) of tri-*n*-butylphosphine in 50 mL of benzene was added 1.20 g (5.6 mmol) of *N*-(phenylthio)succinimide in one portion. The mixture was stirred for 5 min. A solution of 1.70 g (5.5 mmol) of **42** in 15 mL of benzene was added. After the mixture was stirred at room temperature for 2 h, the solvent was evaporated in vacuo. The residual dark brown oil was chromatographed over silica gel with hexanes/ethyl acetate (50:1) as eluent to yield 2.0 g (90%) of the title complound as a colorless oil: IR (thin film) 2940, 1665, 1610, 1490, 1450, 1265, 1100, 1050, 1035, 1010, 945, 915, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.06 (m, 5 H), 5.96 (m, 1 H), 5.80–5.48 (m, 2 H), 5.06–4.90 (m, 2 H), 4.13 (m, 1 H), 3.07 (dd, 1 H, J = 12.5, 6.3 Hz), 2.99 (dd, 1 H, J = 12.5, 5.4 Hz), 2.72 (m, 1 H), 2.60 (m, 1 H), 2.30–1.50 (m, 5 H), 1.08 (d, 3 H, J = 6.9 Hz), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.01 (s, 3 H); mass spectrum (70 eV), m/z 402 (M^+), 345 ($M^+ - C_4H_9$); exact mass calcd for $C_{24}H_{38}OSSi - C_4H_9$ 345.1684, found 345.1709.

[1α,2α(1*R,2*R**)]-(±)-(1,1-Dimethylethyl)dimethyl[[2-[2-methyl-1-[(phenylsulfonyl)methyl]-3-butenyl]-3-cyclohexen-1-yl]oxy]silane (43).** To a solution of 1.70 g (4.2 mmol) of the above sulfide in 30 mL of ether at 0 °C was added dropwise a solution of 2.6 g (12.8 mmol) of *m*-chloroperoxybenzoic acid (Aldrich, technical grade, 80–85%) in 15 mL of ether over a period of 5 min. The mixture was further stirred at 0 °C for 5 min and then quenched with 30 mL of 1 M aqueous sodium sulfite at 0 °C. The ethereal layer was separated, and the aqueous layer was extracted with ether (2×). The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residual oil was chromatographed over silica gel

with hexanes–ethyl acetate (6:1) as eluent to give 1.74 g (95%) of sulfone **43** as a colorless oil, which solidified on refrigeration: IR (thin film) 2940, 1640, 1585, 1465, 1455, 1440, 1300, 1250, 1135, 1080, 1035, 1000, 935, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.45 (m, 5 H), 5.85–5.45 (m, 3 H), 5.05–4.86 (m, 2 H), 4.18 (m, 1 H), 3.54 (dd, 1 H, J = 15.0, 4.2 Hz), 3.04 (dd, 1 H, J = 15.0, 4.6 Hz), 2.72–1.50 (m, 7 H), 1.03 (d, 3 H, J = 6.7 Hz), 0.73 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); mass spectrum (70 eV), m/z 434 (M^+), 377 ($M^+ - C_4H_9$); exact mass calcd for $C_{24}H_{38}O_3SSi - C_4H_9$ 377.1607, found 377.1605.

Coupling Reaction of Sulfone 43 with Iodide 4. To a solution of 1.20 g (2.8 mmol) of sulfone **43** in 40 mL of tetrahydrofuran and 8 mL of hexamethylphosphoramide at −78 °C was added 4.5 mL (5.9 mmol) of *n*-butyllithium (1.3 M) in hexanes. The mixture was stirred for 30 min, and then a solution of 1.7 g (3.3 mmol) of iodide **4** in 5 mL of tetrahydrofuran was added dropwise over a period of 10 min. The cooling bath was removed, and the mixture was stirred at room temperature for 6 h. After being cooled to 0 °C, the mixture was quenched by the addition of 10 mL of saturated aqueous ammonium chloride. Tetrahydrofuran was removed by rotary evaporation. The residue was diluted with 50 mL of water and extracted with ether (3×). The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo.

The resulting oily residue was stirred with 30 mL of methanol at room temperature for 30 min, at which time a white precipitate formed. The whole mixture was filtered. The white precipitate was washed with a small amount of methanol and dried in the air to give 603 mg (43% based on recovered sulfone) of a white powder (the less polar product on TLC), which was identified as diasteromer **46**: IR ($CHCl_3$) 2940, 1635, 1590, 1465, 1435, 1415, 1380, 1350, 1300, 1250, 1175, 1140, 1090, 1030, 980, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00–7.30 (m, 15 H), 5.90–5.50 (m, 3 H), 5.05–4.90 (m, 2 H), 4.40 (dd, 1 H, J = 9.7, 2.0 Hz), 4.30–4.00 (m, 4 H), 3.36 (s, 3 H), 2.80 (br s, 1 H), 2.60–1.20 (m, 12 H), 1.09 (s, 9 H), 0.89 (s, 9 H), 0.86 (d, 3 H, J = 7.0 Hz), 0.13 (s, 3 H), 0.09 (s, 3 H); mass spectrum (70 eV), m/z 784 ($M^+ - CH_3OH$), 759 ($M^+ - C_4H_9$).

The combined filtrates were evaporated in vacuo and chromatographed over silica gel with hexanes–ethyl acetate (8:1) as eluent to yield 470 mg of the starting sulfone **43** and 471 mg (34% based on recovered sulfone) of the desired diastereomer **45** (more polar isomer on TLC): IR (thin film) 2940, 1640, 1590, 1465, 1435, 1415, 1380, 1350, 1300, 1250, 1205, 1175, 1140, 1110, 1080, 1030, 1000, 940, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.30 (m, 15 H), 5.72–5.50 (m, 3 H), 5.02–4.90 (m, 2 H), 4.65 (dd, 1 H, J = 9.7, 2.0 Hz), 4.30–4.00 (m, 3 H), 3.52 (m, 1 H), 3.42 (s, 3 H), 2.90 (br s, 1 H), 2.60–1.15 (m, 12 H), 1.10 (s, 9 H), 0.95 (d, 3 H), J = 7.0 Hz), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.10 (s, 3 H); mass spectrum (70 eV), m/z 784 ($M^+ - CH_3OH$), 759 ($M^+ - C_4H_9$); exact mass calcd for $C_{47}H_{68}O_6SSi_2 \cdot C_4H_9$ 759.3571, found 759.3571.

Hydroboration of 45. A mixture of 1.3 g (1.6 mmol) of **45** and 20 mL (10 mmol) of 9-borabicyclo[3.3.1]nonane (0.5 M) in tetrahydrofuran was stirred at room temperature for 2 h. Excess reagent was destroyed by the addition of 1.5 mL of ethanol. After the addition of 3.6 mL (10.8 mmol) of 3 N aqueous sodium hydroxide, 3.8 mL (33.5 mmol) of 30% hydrogen peroxide was added dropwise at ice-bath temperature. The mixture was then heated at 50 °C for 30 min. The tetrahydrofuran was removed by rotary evaporation, and the residue was diluted with 50 mL of water and extracted with ethyl acetate (3×). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oil. Chromatography over silica gel with hexanes–ethyl acetate (2.5:1) as eluent afforded 1.14 g (86%) of the desired alcohol as a colorless oil: IR (thin film) 3570, 2940, 1590, 1470, 1445, 1425, 1385, 1350, 1300, 1250, 1205, 1175, 1140, 1110, 1080, 1030, 1000, 940, 920, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.30 (m, 15 H), 5.72–5.50 (m, 2 H), 4.72 (dd, 1 H, J = 9.7, 2.0 Hz), 4.30–4.05 (m, 3 H), 3.75–3.55 (m, 3 H), 3.42 (s, 3 H), 2.88 (br s, 1 H), 2.60–1.15 (m, 14 H), 1.08 (s, 9 H), 0.92 (s, 9 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.15 (s, 3 H), 0.14 (s, 3 H); mass spectrum (70 eV), m/z 802 ($M^+ - CH_3OH$), 777 ($M^+ - C_4H_9$); exact mass calcd for $C_{47}H_{70}O_7SSi_2 - C_4H_9$ 777.3677, found 777.3674.

[2*R*-[2α[γ*S,δ*S**(1*S**,6*S**)],4β,6α]]-δ-[6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclohexen-1-yl]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]tetrahydro-6-methoxy-γ-(*S*)-methyl-2*H*-pyran-2-hexanol (49).** To an efficiently stirred mixture of 1.14 g (1.4 mmol) of the above alcohol and 5 g of disodium hydrogen phosphate in 120 mL of methanol at room temperature was added 10 g (excess) of pulverized 6% sodium amalgam. The mixture was stirred for 1 h and then filtered through Celite. The filtrate was evaporated in vacuo to yield an oil. Chromatography over silica gel with hexanes–ethyl acetate (3:1) as eluent gave 580 mg (61%) of **49** as a colorless oil: IR (thin film) 3510, 2985, 1575, 1460, 1420, 1380, 1350, 1240, 1200, 1140, 1090, 1035, 1005, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.68 (m, 2 H), 4.81 (dd, 1 H, J = 9.7, 2.0 Hz), 4.26 (br s, 1 H), 4.06 (m, 1 H), 3.90 (m, 1 H), 3.75–3.50 (m, 2 H), 3.52 (s, 3 H), 2.30–1.10 (m, 17 H), 1.09 (s, 9 H), 0.95 (d, 3 H, J = 7.0 Hz), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); mass spectrum (70 eV), m/z 662 ($M^+ - CH_3OH$), 605 ($M^+ - CH_3OH - C_4H_9$); $[\alpha]^{24}_D$ −45.4° (*c* 0.335, $CHCl_3$); exact mass calcd for $C_{41}H_{60}O_5Si_2 - CH_4O$ 662.4187, found 662.4188. Anal. Calcd for $C_{41}H_{66}O_5Si_2$: C, 70.84; H, 9.57. Found: C, 70.70; H, 9.80.

[4*S*-[4α,5α(2*S,4*S**,6*S**),5aα,6β,8aα,8bα]]-6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[2-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]tetrahydro-6-methoxy-2*H*-pyran-2-yl]ethyl]-4,5,5a,6,7,8,8a,8b-octahydro-4-methyl-3*H*-naphth[1,8-*cd*]isoxazole (50).** To a solution of 238 μL (1.58 mmol) of oxalyl chloride in 5 mL of methylene chloride at −78 °C was added a solution of 223 μL (3.16 mmol) of dimethyl sulfoxide in 1 mL of methylene chloride. After the mixture was stirred for 5 min, a solution of 550 mg (0.79 mmol) of alcohol **49** in 1 mL of methylene chloride was added dropwise. The mixture was stirred for an additional 30 min, and 1.1 mL (8 mmol) of triethylamine was added. After being stirred for 5 min, the mixture was slowly warmed to room temperature. Water was added, the organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude aldehyde as a yellow oil: IR (thin film) 1725 cm^{-1}.

The crude aldehyde was dissolved in 10 mL of ether, and a solution of 550 mg (8 mmol) of hydroxylamine hydrochloride in 2 mL of water was added. The mixture was vigorously stirred at room temperature, and a solution of 850 mg (8 mmol) of sodium carbonate in 2 mL of water was added dropwise. After the mixture was stirred for 8 h, the two layers were separated. The aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the oxime as a yellow oil.

To a solution of the above yellow oil and 20 μL (catalytic amount) of triethylamine in 10 mL of methylene chloride at 0 °C was added dropwise 4.5 mL (~2.4 mmol) of 5% aqueous sodium hypochlorite over a period of 15 min. After the mixture was stirred for 2 h, the organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to yield a yellow oil. Chromatography over silica gel with hexanes–ethyl acetate (5:1) as eluent gave 260 mg (46.5%) of **50** as a white foam: IR (thin film) 2960, 1465, 1390, 1385, 1335, 1250, 1205, 1175, 1145, 1090, 1060, 1030, 1010, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 4.83 (dd, 1 H, J = 9.7, 2.0 Hz), 4.65 (ddd, 1 H, J = 10.0, 10.0, 7.5 Hz), 4.28 (br s, 1 H), 4.04–3.85 (m, 2 H), 3.53 (s, 3 H), 3.15 (t, 1 H, J = 10.0 Hz), 2.80 (m, 1 H), 2.54 (dd, 1 H, J = 15.3, 4.4 Hz), 2.04–1.15 (m, 15 H), 1.09 (s, 9 H), 1.00 (d, 3 H, J = 15.3, 4.4 Hz), 1.04–1.15 (m, 15 H), 1.09 (s, 9 H), 1.00 (d, 3 H, J = 7.0 Hz), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); mass spectrum (70 eV), m/z 705 (M^+); $[\alpha]^{24}_D$ −18.5° (*c* 0.755, $CHCl_3$); exact mass calcd for $C_{41}H_{63}NO_5Si_2$ 705.4245, found 705.4237. Anal. Calcd for $C_{41}H_{63}NO_5Si_2$: C, 69.74; H, 8.99; N, 1.98. Found: C, 69.94; H, 9.00; N, 1.93.

Hydrogenation of Isoxazoline 50. A mixture of 260 mg (0.37 mmol) of **50**, 200 μL (~3.5 mmol) of acetic acid, and a small spatula amount of Raney nickel in 30 mL of methanol–water (10:1) was hydrogenated under a hydrogen atmosphere (balloon) for 2 h. The catalyst was removed by filtration through Celite. The filtrate was neutralized by the addition of saturated aqueous sodium bicarbonate (ca. 2 mL) and concentrated in vacuo. The residue was diluted with 10 mL of water and extracted with ethyl acetate (3×). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to leave an oil. Chromatography over silica

gel with hexanes–ethyl acetate (4:1) as eluent afforded 200 mg (76.5%) of **51** as a white foam: IR (thin film) 3570, 2960, 1710, 1475, 1430, 1390, 1360, 1255, 1140, 1105, 1040, 1025, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 4.83 (dd, 1 H, J = 9.7, 2.0 Hz), 4.27 (br s, 1 H), 4.07 (br s, 1 H), 4.00–3.80 (m, 2 H), 3.52 (s, 3 H), 2.63 (dd, 1 H, J = 11.0, 10.5 Hz), 2.53 (dd, 2 H, J = 13.0, 5.7 Hz), 2.40 (m, 1 H), 2.21 (dd, 1 H, J = 13.0, 3.0 Hz), 2.05–1.15 (m, 14 H), 1.09 (s, 9 H), 0.93 (s, 9 H), 0.79 (d, 3 H, J = 7.0 Hz), 0.11 (s, 3 H), 0.07 (s, 3 H); mass spectrum (70 eV), m/z 658 ($M^+ - CH_3OH - H_2O$), 651 ($M^+ - C_4H_9$), 633 ($M^+ - C_4H_9 - H_2O$); $[\alpha]^{24}_D$ −24.2° (c 0.450, $CHCl_3$); exact mass calcd for $C_{41}H_{64}O_6Si_2 - C_4H_9$ 651.3537, found 651.3540. Anal. Calcd for $C_{41}H_{64}O_6Si_2$: C, 69.44; H, 9.10. Found: C, 69.31; H, 9.11.

[3*S*-[3α,4α(2*S,4*S**,6*S**),4aα,5β]]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-[2-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]tetrahydro-6-methoxy-2*H*-pyran-2-yl]ethyl]-3,4,4a,5,6,7-hexahydro-3-methyl-1(2*H*)-naphthalenone (52).** A mixture of 115 mg (0.16 mmol) of β-hydroxy ketone **51** and 1.5 g of basic aluminum oxide (Woelm B, grade I) in 10 mL of benzene was refluxed for 15 min. After cooling, the mixture was filtered, and the solvent was removed by rotary evaporation. Chromatography over silica gel with hexanes–ethyl acetate (5:1) yielded 100 mg (89%) of enone **52** as a colorless oil: IR (thin film) 2940, 1680, 1615, 1460, 1415, 1380, 1350, 1240, 1185, 1135, 1100, 1055, 1030, 1000, 950, 990, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 6.75 (br s, 1 H), 4.85 (dd, 1 H, J = 9.7, 2.0 Hz), 4.30–4.20 (m, 2 H), 3.96 (m, 1 H), 3.53 (s, 3 H), 2.45–1.20 (m, 17 H), 1.09 (s, 9 H), 0.87 (overlapping s and d: s, 9 H; d, 3 H, J = 7.0 Hz), 0.10 (s, 3 H), 0.07 (s, 3 H); mass spectrum (70 eV), m/z 658 ($M^+ - CH_3OH$), 633 ($M^+ - C_4H_9$); $[\alpha]^{24}_D$ −2.4° (c 0.290, $CHCl_3$); exact mass calcd for $C_{41}H_{62}O_5Si_2 - C_4H_9$ 633.3432, found 633.3427.

Preparation of Alcohol 56. To a stirred solution of 100 mg (0.14 mmol) of enone **52** and 81 mg (0.22 mmol) of cerium(III) chloride heptahydrate in 10 mL of methanol was added 5.5 mg (0.14 mmol) of solid sodium borohydride. Vigorous gas evolution took place. After the mixture was stirred at room temperature for 10 min, 200 μL of acetic acid was added, and the methanol was removed by rotary evaporation. The residue was diluted with 10 mL of water and extracted with ethyl acetate (3×). The combined extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Chromatography over silica gel with hexanes–ethyl acetate (2:1) as eluent yielded 94 mg (94%) of **56** as a white foam: IR (thin film) 3635, 2985, 1590, 1470, 1425, 1385, 1350, 1250, 1210, 1185, 1135, 1095, 1050, 1030, 955, 940, 910, 890, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.77 (br s, 1 H), 4.82 (dd, 1 H, J = 9.7, 2.0 Hz), 4.30–4.08 (m, 3 H), 3.92 (m, 1 H), 3.52 (s, 3 H), 2.35–1.15 (m, 17 H), 1.09 (s, 9 H), 0.93 (d, 3 H, J = 7.0 Hz), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); mass spectrum (70 eV), m/z 674 ($M^+ - H_2O$), 617 ($M^+ - C_4H_9 - H_2O$); exact mass calcd for $C_{41}H_{64}O_5Si_2 - C_4H_9 - H_2O$ 617.3482, found 617.3469.

[1*S*-[1α(2*S,4*S**,6*S**),2α,8β,8aα]]-(1,1-Dimethylethyl)-[[2-[2-[8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2,6,7,8,8a-hexahydro-2-methyl-1-naphthalenyl]ethyl]-tetrahydro-6-methoxy-2*H*-pyran-4-yl]oxy]diphenylsilane (47).** A mixture of 89 mg (0.129 mmol) of allylic alcohol **56** and 1 g of basic aluminum oxide (Woelm B, grade I) in 5 mL of toluene was refluxed for 30 min. After cooling, the mixture was filtered. The aluminum oxide residue was washed with chloroform. The combined organic filtrates were evaporated in vacuo. Chromatography over silica gel with hexanes–ethyl acetate (20:1) as eluent gave 36.5 mg (42%) of diene **47** as a white foam: IR (thin film) 2940, 1590, 1465, 1455, 1440, 1425, 1385, 1350, 1245, 1190, 1140, 1100, 1030, 955, 935, 910, 890, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.94 (d, 1 H, J = 9.6 Hz), 5.67 (dd, 1 H, J = 9.6, 6.0 Hz), 5.49 (br s, 1 H), 4.83 (dd, 1 H, J = 9.7, 2.0 Hz), 4.26 (m, 2 H), 3.95 (m, 1 H), 3.53 (s, 3 H), 2.40–1.15 (m, 15 H), 1.09 (s, 9 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); mass spectrum (70 eV), m/z 647 (M^+); $[\alpha]^{24}_D$ +102.4° (c 0.335, $CHCl_3$); exact mass calcd for $C_{41}H_{62}O_4Si_2$ 674.4187, found 674.4190.

Monodesilylation of 47. A mixture of 18 mg (0.027 mmol) of **47** and 5 mg (0.027 mmol) of p-toluenesulfonic acid monohydrate in 6 mL of methanol was stirred at room temperature for 12 h. The mixture was neutralized with saturated aqueous sodium bicarbonate, and the methanol was removed by rotary evaporation. The residue was diluted with 5 mL of water and extracted with ethyl acetate (3×). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chromatography of the residue over silica gel with hexanes–ethyl acetate (4:1) as eluent afforded 11.5 mg (77%) of the monodesiylated alcohol (containing a small amount of the α-glycoside isomer) as a white foam: IR (thin film) 3510, 2940, 1590, 1465, 1455, 1440, 1425, 1385, 1350, 1250, 1205, 1180, 1140, 1110, 1050, 1025, 925, 905, 845, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.97 (d, 1 H, J = 9.6 Hz), 5.77 (dd, 1 H, J = 9.6, 6.0 Hz), 5.57 (br s, 1 H), 4.82 (d, 1 H, J = 8.0 Hz), 4.25 (m, 2 H), 3.96 (m, 1 H), 3.53 (s, 3 H), 2.45–1.20 (m, 15 H), 1.09 (s, 9 H), 0.91 (d, 3 H, J = 7.0 Hz); mass spectrum (70 eV), m/z 528 ($M^+ - CH_3OH$), 510 ($M^+ - CH_3OH - H_2O$); $[\alpha]^{24}_D$ +94.4° (c 0.305, $CHCl_3$).

Preparation of 59. A mixture of 11 mg (0.02 mmol) of the alcohol from above, 22 μL (0.02 mmol) of (*S*)-(+)-2-methylbutyric acid, 40 mg (0.2 mmol) of 1,3-dicyclohexylcarbodiimide, and 24 mg (0.20 mmol) of 4-(dimethylamino)pyridine in 1 mL of methylene chloride was stirred at room temperature for 3 days. The precipitate formed was filtered off, and the filtrate was concentrated in vacuo. Chromatography over silica gel with hexanes–ethyl acetate (12:1) as eluent yielded 9.5 mg (75%) of **59** as a white foam: IR (thin film) 2940, 1725, 1460, 1455, 1435, 1415, 1380, 1350, 1255, 1235, 1175, 1140, 1110, 1100, 1050, 1035, 935, 920, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.98 (d, 1 H, J = 9.6 Hz), 5.75 (dd, 1 H, J = 9.6, 6.0 Hz), 5.56 (br s, 1 H), 5.30 (br s, 1 H), 4.80 (dd, 1 H, J = 9.7, 2.0 Hz), 4.23 (m, 1 H), 3.87 (m, 1 H), 3.52 (s, 3 H), 2.45–1.16 (m, 15 H), 1.12 (d, 3 H, J = 7.0 Hz), 1.08 (s, 9 H), 0.91 (d, 3 H, J = 7.3 Hz), 0.87 (t, 3 H, J = 7.3 Hz); exact mass calcd for $C_{40}H_{56}O_5Si_2 - C_5H_{13}O$ 555.2931, found 555.2933.

Preparation of Lactone 60. To a solution of 9 mg (0.014 mmol) of **59** in 2 mL of THF was added 0.5 mL of 10% aqueous hydrochloric acid. The mixture was stirred at 50 °C for 4 h. After cooling, the mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ether (3×). The combined ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed over silica gel and eluted with hexanes–ethyl acetate (2:1) to furnish the lactol as a colorless oil.

A solution of above lactol in 100 μL of methylene chloride was added to a mixture of 10 mg of pyridinium chlorochromate and 20 mg of neutral aluminum oxide (Woelm N, activity I) in 500 μL of methylene chloride. The mixture was stirred at room temperature for 8 h. After dilution with 2 mL of ether, the whole mixture was filtered through a short column of Florisil. The solvent was removed by rotary evaporation to give a yellow oil. Chromatography over silica gel with hexanes–ethyl acetate (6:1) as eluent yielded 4.4 mg (51%) of **60** as a white foam: IR (thin film) 2940, 1725, 1450, 1420, 1370, 1340, 1250, 1235, 1175, 1150, 1110, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.30 (m, 10 H), 5.99 (d, 1 H, J = 9.5 Hz), 5.74 (dd, 1 H, J = 9.5, 6.0 Hz), 5.57 (br s, 1 H), 5.31 (br s, 1 H), 4.72 (m, 1 H), 4.27 (m, 1 H), 2.65–1.20 (m, 18 H), 1.12 (d, 3 H, J = 7.0 Hz), 1.07 (s, 9 H), 0.89 (d, 3 H, J = 7.0 Hz), 0.87 (t, 3 H, J = 7.3 Hz); mass spectrum (70 eV), m/z 628 (M^+); $[\alpha]^{24}_D$ +124° (c 0.261, $CHCl_3$); exact mass calcd for $C_{39}H_{52}O_5Si$ 628.3584, found 628.3585.

Compactin (1). To a solution of 12 mg (0.02 mmol) of **60** in 3 mL of acetonitrile was added 0.3 mL of 50% hydrofluoric acid. The mixture was stirred at 45 °C for 8 h. After cooling the mixture was quenched with saturated aqueous sodium bicarbonate. The whole mixture was diluted with 5 mL of water and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Chromatography over silica gel with hexanes–ethyl acetate (1:3) as eluent gave 2.2 mg (30%) of **1** as a white powder: mp 151–152 °C; IR ($CHCl_3$) 3400, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.99 (d, 1 H, J = 9.7 Hz), 5.75 (dd, 1 H, J = 9.7, 5.9 Hz), 5.57 (br s, 1 H), 5.35 (br s, 1 H), 4.63 (m, 1 H), 4.38 (m, 1 H), 2.75 (dd, 1 H, J = 17.6, 5.1 Hz), 2.62 (dd, 1 H, J = 17.6, 3.8 Hz), 2.45–1.25 (m, 16 H), 1.13 (d, 2 H, J = 7.0 Hz), 0.89 (d, 3 H, J = 7.0 Hz), 0.89 (t, 3 H, J = 7.3 Hz); $[\alpha]^{24}_D$ +281° (c 0.11, Me_2CO) [lit.[1] $[\alpha]^{22}_D$ +283° (c 0.84, Me_2CO)].

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Registry No. 1, 73573-88-3; 4, 86031-03-0; (±)-10, 43119-22-8; 11, 108712-85-2; (±)-12, 108712-86-3; (±)-13, 108712-87-4; (±)-14, 108712-88-5; (±)-15, 108813-29-2; (±)-16 (isomer 1), 108712-89-6; (±)-16 (isomer 2), 108813-30-5; (±)-17 (isomer 1), 108712-90-9; (±)-17 (isomer 2), 108813-31-6; (±)-18 (isomer 1), 108712-91-0; (±)-18 (isomer 2), 108813-32-7; (±)-19, 108712-92-1; (±)-20, 108813-33-8; (±)-21, 108814-46-6; (±)-22, 108712-93-2; (±)-23, 108712-94-3; (±)-24, 108813-34-9; (±)-25, 108712-95-4; (±)-26, 108712-96-5; (±)-27, 108712-97-6; (±)-28, 108712-98-7; (±)-29, 108712-99-8; 30, 108713-00-4; (±)-31, 108713-01-5; (±)-32, 95218-60-3; 34, 108713-02-6; (±)-35, 108712-46-5; (±)-37, 108712-47-6; (±)-37 (methyl epimer), 108712-48-7; (±)-38, 108712-49-8; (±)-38 (pivalate), 108712-50-1; (±)-42, 108712-52-3; (±)-42 (pivalate), 108712-51-2; (±)-42 (methyl epimer), 108813-28-1; (±)-43, 108712-54-5; (±)-43 (sulfate), 108712-53-4; 45, 108712-55-6; 47, 108712-64-7; 49, 108712-57-8; 49 ($PhSO_2$ deriv), 108712-56-7; 49 (aldehyde), 108712-58-9; 49 (aldoxime), 108712-59-0; 50, 108712-60-3; 51, 108712-61-4; 52, 108712-62-5; (±)-53, 108712-67-0; (±)-2-*epi*-53, 108712-68-1; (±)-53 (8-MOM ether), 108712-69-2; (±)-53 (8-$OCMe_3$ ether), 108712-70-5; (±)-53 (8-*t*-$BuMe_2Si$ ether), 108712-71-6; (±)-53 (1-*t*-$BuMe_2Si$, 8-$OCMe_3$ ether), 108712-72-7; (±)-54, 108712-73-8; (±)-2-*epi*-54, 108712-74-9; (±)-55, 108712-75-0; (±)-2-*epi*-55, 108712-76-1; 56, 108712-63-6; 59, 108712-66-9; 59 (8-alcohol), 108712-65-8; 60, 108713-03-7; 60 (lactol), 108743-01-7; (±)-A (R^1 = *t*-$BuPh_2Si$, R^2 = MOM), 108712-77-2; (±)-A (R^1 = *t*-$BuPh_2Si$, R^2 = Me_3CO), 108712-79-4; (±)-A (R^1 = *t*-$BuPh_2Si$, R^2 = *t*-$BuMe_2Si$), 108712-81-8; (±)-A (R^1 = *t*-$BuMe_2Si$, R^2 = Me_3CO), 108712-83-0; (±)-B (R^1 = *t*-$BuPh_2Si$, R^2 = MOM), 108712-78-3; (±)-R (R^1 = *t*-$BuPh_2Si$, R^2 = Me_3CO), 108712-80-7; (±)-B (R^1 = *t*-$BuPh_2Si$, R^2 = *t*-$BuMe_2Si$), 108712-82-9; (±)-B (R^1 = *t*-$BuPh_2Si$, R^2 = Me_3CO), 108712-84-1; (±)-THPO$(CH_2)_2$CHO, 89922-81-6; $(CH_3CH_2CH(CH_3)CO)_2O$, 1519-23-9; *trans*-$CH_3CH{=}CHCH_2OH$, 504-61-0; (*S*)-$CH_3CH_2CH(CH_3)CO_2H$, 1730-91-2.

Nickel-, Palladium-, and Platinum-Catalyzed Reactions of Perfluoro- and Polyfluoroalkyl Iodides with Tertiary Amines

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The relative catalytic activities of Ni group metals in the reactions of perfluoroalkyl and polyfluoroalkyl iodides with tertiary amines to give enamines were compared, giving a reactivity order Ni > Pd > Pt, which parallels the order of the first ionization potential of the three metals. In comparing the Ni-catalyzed reaction of iodide **1** with tertiary amines containing zero to three methyl groups, it was found that in the case of trimethylamine only the reduced product **4** was formed, while the other three types of tertiary amines produced enamines (**19**, **21**, **23**) as well as **4**. The chemoselectivity of this reaction was studied. A mechanism is proposed for the reaction. Acid hydrolysis of (fluoroalkyl)enamines afforded enaminones or aldehydes depending upon the presence or absence of an alkyl group at the β-carbon.

It is well-known that fluoroalkyl halides (R_FX: R_F = perfluoro- or polyfluoroalkyl; X = Cl, Br, I), unlike the alkyl halides, are not able to form quarternary ammonium salts. Pullin et al.[1] reported that perfluoroalkyl halides react with tertiary amines to form 1:1 acceptor/donor adducts:

$$R_F{\cdots}I{\cdots}NR_3$$

Since then, few reports have appeared in the literature concerning this reaction.

Our discovery of the formation of enamines in the Pd-catalyzed reactions of perfluoro- and polyfluoroalkyl iodides with tertiary amines[2] led us to study this novel reaction in detail. The following is the general equation of this reaction

$$2R_FCF_2I + 3RCH_2CH_2NR^1R^2 \xrightarrow[n\text{-}C_6H_{14}]{ML_4} R_FCF_2C(R){=}CHNR^1R^2 + R_FCF_2H + 2(RCH_2CH_2)NR^1R^2{\cdot}HI$$

where R_F = $CF_3(CF_2)_n$, $ClCF_2(CF_2)_n$; R = H, alkyl; R^1, R^2 = alkyl; M = Ni, Pd, Pt; and L = PPh_3.

Results and Discussion

Relative Reactivities of the Catalysts. In a comparison of the relative activity of Ni group metals (Scheme I), it was found that in the reaction of iodide **1** with tri-

Scheme I

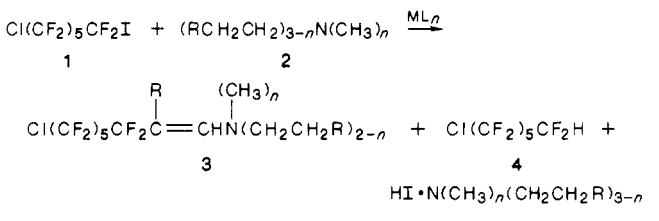

Table I. Relative Reactivities of the Catalysts in the Reactions of 1 with Various Amines

amine	catalyst	temp, °C/time,[a] h	yield,[b] % 3	4
$(CH_3CH_2)_3N$	$Ni(PPh_3)_4$	room temp/0.5	50	50
$(CH_3CH_2)_3N$	$Pd(PPh_3)_4$	60/0.5	50	50
$(CH_3CH_2)_3N$	$Pt(PPh_3)_4$	60/0.5	48	52
$(n\text{-}Pr)_3N$	$Ni(PPh_3)_4$	room temp/0.5	50	50
$(n\text{-}Pr)_3N$	$Pd(PPh_3)_4$	60/0.5	45	55
$(n\text{-}Pr)_3N$	$Pt(PPh_3)_4$	60/0.5	50	50
$(CH_3CH_2)_2NCH_3$	$Ni(PPh_3)_4$	room temp/0.5	35	65
$(CH_3CH_2)_2NCH_3$	$Pd(PPh_3)_4$	60/0.5	36	65
$(CH_3CH_2)_2NCH_3$	$Pt(PPh_3)_4$	70/2	tr	89
$(n\text{-}Pr)N(CH_3)_2$	$Ni(PPh_3)_4$	room temp/2	15	85
$(n\text{-}Pr)N(CH_3)_2$	$Pd(PPh_3)_4$	70/1	7	83
$(n\text{-}Pr)N(CH_3)_2$	$Pt(PPh_3)_4$	70/2	tr	90

[a] Conditions for complete reaction of 1. [b] Determined by ^{19}F NMR.

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