(m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.57, 18.70, 32.60 (CSePh), 38.47 (CSPh), 126.50, 127.34, 128.78, 128.88, 129.61, 130.88, 134.36, 136.60; MS m/e = 348 (M^+, 1).

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No. 03215221) from the Ministry of Education, Science, and Culture, Japan.

Registry No. **1a**, 592-41-6; **1b**, 107-18-6; **1c**, 762-72-1; **1d**, 111-34-2; **1e**, 107-13-1; **1f**, 1629-58-9; **1g**, 140-88-5; **1h**, 142-29-0; **1i**, 110-83-8; **1j**, 498-66-8; **1k**, 592-42-7; **1l**, 513-81-5; **2**, 882-33-7; **3**, 1666-13-3; **4a**, 137258-85-6; **4b**, 137258-86-7; **4c**, 137258-87-8; **4d**, 137258-88-9; **4e**, 137258-89-0; **4f**, 137258-90-3; **4g**, 137258-91-4; **4h**, 137258-92-5; **4i**, 137258-93-6; **4j**, 137429-16-4; **4j'**, 137258-94-7; **4k**, 137258-95-8; **4k'**, 137258-96-9; (*E*)-**4l**, 137258-97-0; (*Z*)-**4l**, 137258-98-1.

S_N2' Addition of Cuprates to Acyclic Vinyloxiranes. Synthesis of Tylactone and Tylonolide Subunits

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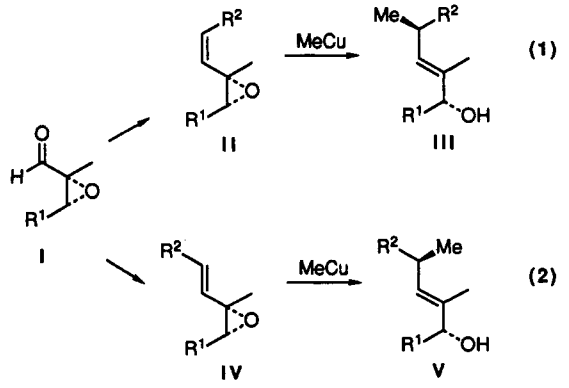
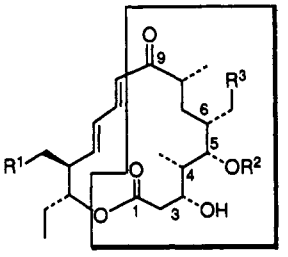
The chiral acyclic vinyloxiranes **8** and **18** undergo highly anti selective S_N2' additions upon treatment with Et_2CuLi and (*S*)-PMBOMOCH$_2$CH(CH$_3$)CH$_2$Cu(CN)Li, respectively. The product of the former addition, diol **9**, affords the α-epoxide **12** upon epoxidation with *m*-CPBA. Conversion to acetonide **15**, a possible C-1–C-7 segment of tylactone, was effected by hydrogenation of the methylene acetonide **14** obtained from epoxide **12** through $LiNEt_2$ elimination and ketalization with 2,2-dimethoxypropane (2,2-DMP). Allylic alcohol **24b**, a close analogue of diol **9**, gave only the β-epoxide **25b** upon treatment with *m*-CPBA. Epoxidation with magnesium monoperoxyphthalic acid (MMPP), however, yielded a separable 53:47 mixture of β- and α-epoxides **25b** and **26b**. The former was carried on to acetonide **29** by a sequence involving basic elimination ($LiNEt_2$), treatment with 2,2-DMP, and hydrogenation. Acetonide **30**, a diastereomer of **29**, was prepared from epoxide **26b** by a parallel sequence. Acetonide **30** was converted to the lactol methyl ether **48**, an intermediate in Nicolaou's synthesis of *O*-micinosyl tylonolide, through displacement of tosylate **43** with KCN and then reduction (DIBAH), methanolysis (HCl, MeOH), silylation (TBSOTf, 2,6-lutidine), and finally PMBOM cleavage (DDQ). An identical sequence was applied to acetonide **29** resulting in the isomeric lactol methyl ether **37**.

The macrolide antibiotics have been the focus of extensive synthetic investigation for over two decades.[1] The quest for synthetically viable routes to these medicinally important natural products has stimulated important methodological developments in acyclic and macrocyclic stereocontrol. In connection with a program on the synthesis of such compounds we undertook studies on the S_N2' addition of organocopper reagents to chiral acyclic vinyloxiranes.[2] Our initial investigations showed that, with certain structural constraints, additions of methylcuprates proceed with high anti diastereoselectivity to afford mainly *E* S_N2' substitution products (eqs 1 and 2). By varying the double-bond geometry or epoxide stereochemistry all diastereomers of a given product can be prepared.



The present study was initiated to examine these S_N2' additions with more complex cuprates as a possible route to subunits of tylactone (VI) or tylonolide (VII).[3] The former is the biosynthetic precursor and the latter the aglycon of tylosin (VIII), a commercially important antibiotic.[4]



VI Tylactone $R^1 = R^2 = H$, $R^3 = CH_3$
VII Tylonolide $R^1 = OH$, $R^2 = H$, $R^3 = CHO$
VIII Tylosin R^1 = Osugar, R^2 = sugar, $R^3 = CHO$

The goal of the tylactone investigation was to optimize ethylcuprate additions to a vinyloxirane such as IX, a modest extension of our previous work, and to develop methodology for further elaborating the S_N2' product X

(1) Cf.: Boeckman, R. K.; Goldstein, S. W. The Total Synthesis of Macrocyclic Lactones In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1988; Vol. 8, pp 1–140.

(2) Cf.: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1990**, *55*, 1540. Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225.

(3) Cf.: O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205. Omura, S.; Matsubara, H.; Nakagawa, A.; Furusaki, A.; Matsumoto, T. *J. Antibiot.* **1980**, *33*, 915. Hondo, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857.

(4) For previous synthetic work in this area, see: (a) Tatsuta, K.; Amemiya, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2030. (c) Grieco, P. A.; Inanaga, J.; Liss, N. H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. (d) Masamune, S.; Lu, L. D-L; Jackson, W. P.; Kaiko, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. (e) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonsmitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2219. (f) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

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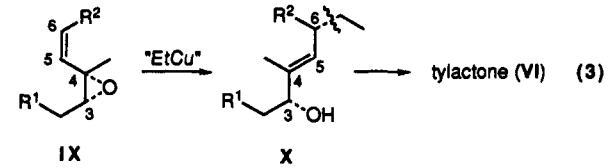
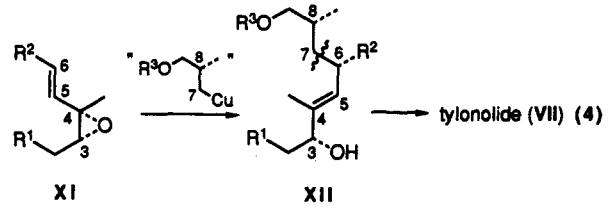
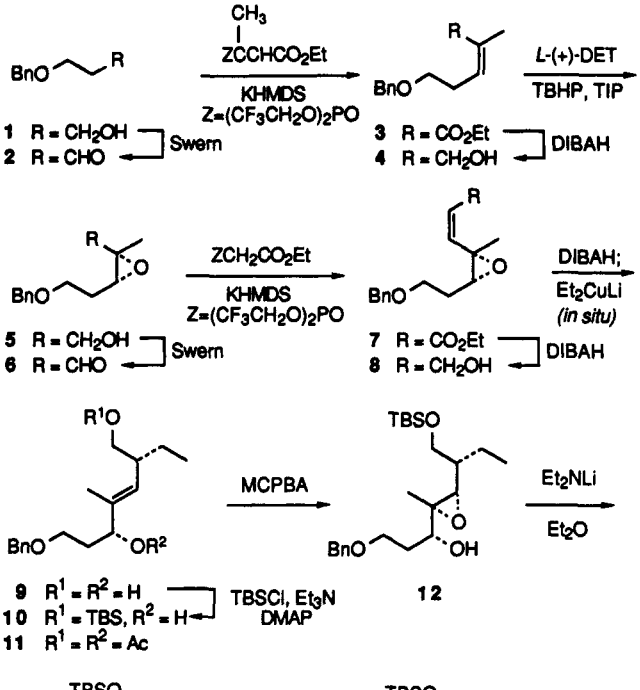


to introduce the C-5 OH with control of the C-4 stereocenter.[2] This methodology could then be applied to the potential tylonolide precursor XII whose synthesis would entail S_N2' addition of a more complex chiral cuprate to a vinyloxirane such as XI.

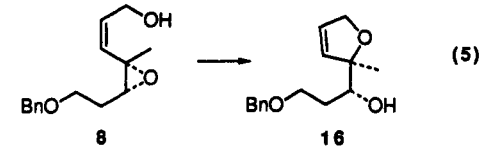


The starting material for these studies was the monobenzyl ether (1) of 1,3-propanediol. Swern oxidation[5] then Horner–Emmons condensation of the intermediate aldehyde 2 with the Still [(trifluoroethyl)phosphono]-propionate reagent[6] followed by reduction of the derived ester 3 afforded the *Z* allylic alcohol 4 in 75% overall yield. Sharpless epoxidation with the L-(+)-tartrate reagent gave epoxy alcohol 5 (80% ee) in 89% yield.[7] Sequential Swern oxidation and Still–Horner–Emmons homologation with [(trifluoroethyl)phosphono]acetate yielded a 96:4 inseparable mixture of *Z* and *E* isomers 7 and 17.

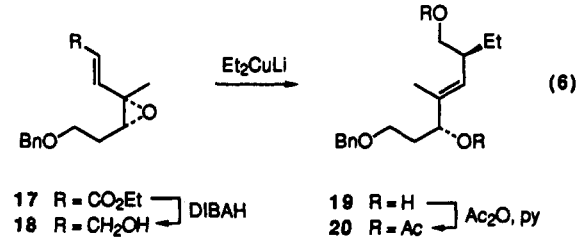


(5) Omuru, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(6) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(7) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Soo, Y. K.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

Reduction of this mixture was readily achieved with DIBAH. However, during isolation and attempted purification a considerable portion of the *Z* allylic alcohol 8 was converted to the dihydrofuran 16 (eq 5). This

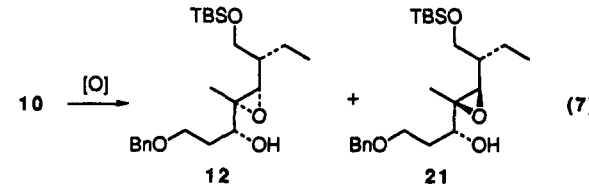


problem was overcome by carrying out the reduction of ester 7 and subsequent addition of Et_2CuLi in situ without isolation of the intermediate alcohol. The allylic alcohol 9 and its diastereomer 19 were thereby obtained in 63% yield. The stereochemical integrity of alcohol 9 was evaluated by GC analysis of the derived diacetate 11. An authentic sample of the diastereomeric diacetate 20 was prepared from ester 17 by a three-step sequence involving reduction, diethylcuprate addition, and acetylation (eq 6).



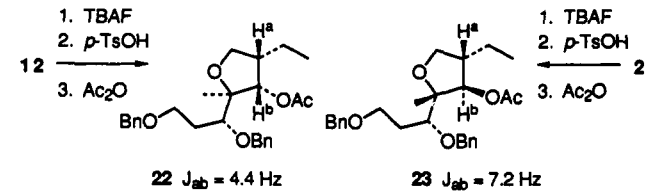
The ratio of diacetates derived from cuprate addition to the ca. 96:4 mixture of (*Z*)- and (*E*)-vinyloxiranes 8 and 18 was found to be 92:8. Thus, the S_N2' addition to 8 is surmised to be more than 95% anti selective. Addition to the (*E*)-vinyloxirane 18 was 98% anti selective but an 86:14 mixture of (*E*) and (*Z*) products was produced.

Sharpless epoxidation of the mono-TBS-protected allylic alcohol 10 with the L-(+)-tartrate reagent afforded a 30:70 mixture of α- and β-epoxides 12 and 21.[7] The D-(−)-tartrate reagent yielded only the β-epoxide 21, resulting from cooperative substrate and reagent controlled epoxidation. Fortunately, the desired α-epoxide 12 could be obtained in 93% yield through treatment of allylic alcohol 10 with *m*-CPBA.



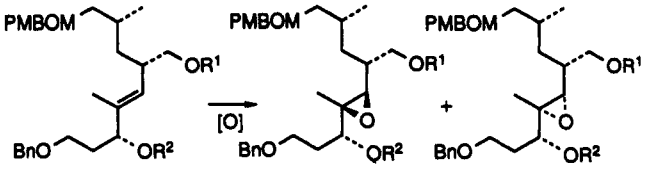
[O]	12 : 21
L-(+)-DET, TIP, TBHP	30 : 70
D-(−)-DET, TIP, TBHP	0 : 100
MCPBA	95 : 5

The relative stereochemistry of epoxides 12 and 21 was assigned from the ^1H NMR coupling constants of the derived five-membered acetoxy ethers 22 and 23.



Attempts at OH-directed selective reduction of epoxide 12 with inversion at the tertiary center were not successful.

Table I. Epoxidation of Allylic Alcohol Derivatives 24a–h



entry	series	R^1	R^2	[O][a]	β:α
1	a	H	H	A	100:0
2	b	TBS	H	A	100:0
3	b	TBS	H	B	100:0
4	b	TBS	H	C	100:0
5	c	TBS	TBS	A	60:40
6	d	TIPS	TIPS	A	45:55
7	e	H	CONHPh	A	85:15
8	f	CONHPh	H	A	85:15
9	g	CONHPh	CONHPh	A	76:24
10	a	H	H	D	87:13
11	b	TBS	H	D	53:47
12	h	TIPS	H	D	51:49
13	c	TBS	TBS	D	–[b]

[a] A = MCPBA, Na_2HPO_4, CH_2Cl_2; B = L-(+)-DET, TIP, TBHP, CH_2Cl_2, –23 °C; C = D-(–)-DET, TBHP, CH_2Cl_2, –23 °C; D = magnesium monoperoxyphthalic acid, *i*-PrOH–H_2O. [b] No reaction after 2.5 d at rt.

Epoxide **12** did not react with Red-Al (Aldrich) under a variety of conditions.[8] It also proved inert to $NaBH_3CN$ in the presence of Lewis acids.[9] We therefore explored a less direct approach to the reduction.

Elimination of epoxide **12** was effected with excellent regioselectivity by $LiNEt_2$ in Et_2O affording allylic alcohol **13** in 73% yield.[10] The acetonide derivative **14** provides a rigid framework with a strong facial bias for β attack on the exocyclic double bond. In accord with this expectation, catalytic hydrogenation over PtO_2 led to the α-methyl isomer as the sole product. The stereochemistry of **15** was confirmed by ^{13}C and ^1H NMR analyses.[11]

Our plan for tylonolide called for the use of a chiral cuprate to introduce the C-7–C-9 segment of the target subunit XII. Accordingly, the C-6 side chain would be present in the vinyloxirane as a double bond substituent (R^2 in XI). Since the S_N2' addition is expected to proceed by an anti pathway, an (*E*)-vinyloxirane (XI) would be required.[2]

Lithiation of the [(*p*-methoxybenzyl)oxy]methyl ether (PMBOM)[12] of (*S*)-(+)-3-bromo-2-methyl-1-propanol by the method of Bailey[13] and then addition of CuCN led to the cyanocuprate reagent.[14] Reaction of this cuprate with vinyloxirane **18** at –78 °C to room temperature afforded diol **24a** as the only S_N2' product in 55–60% yield.

Epoxidation of the TBS-protected unsaturated alcohol **24b**, as with **10**, gave a single epoxide, **25b**, in 89% yield. Basic elimination with $LiNEt_2$ in Et_2O[10] then led to the allylic diol **27** in 84% yield. The acetonide derivative **28** underwent catalytic hydrogenation over PtO_2 to afford the

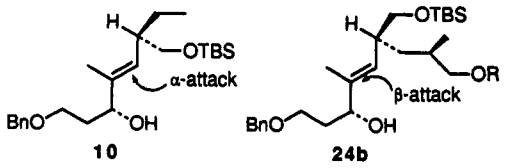
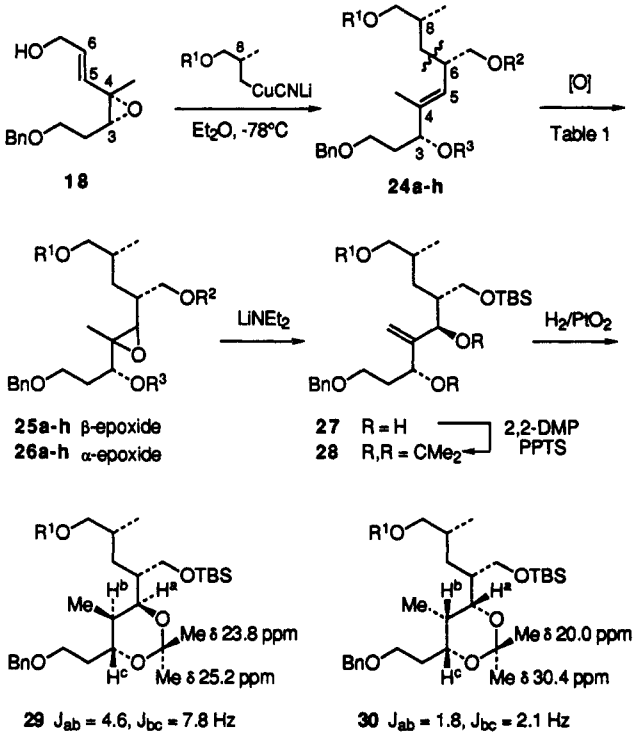


Figure 1. Conformational preferences for allylic alcohols **10** and **24b**.

dihydro compound **29** as the sole product. Initially we assumed that the conversion of allylic alcohol **10** to acetonide **15** provided adequate stereochemical precedent for the parallel sequence on allylic alcohol **25**. However, we later realized that this was not the case. One important finding that led to the eventual assignment of **29** to the acetonide was the ^{13}C NMR spectrum which showed the two quaternary methyls at similar chemical shifts as expected for a twist-boat conformation.[11] This conclusion was supported by the observed coupling constants for H^a–H^c obtained through homodecoupled 2D *J*-resolved NMR analysis.[15] When in fact we finally synthesized acetonide **30**, as detailed below, the chemical shift and coupling data were in complete accord with the assigned stereochemistry.



Thus, the seemingly structurally similar allylic alcohols **10** and **24b** exhibit opposite stereochemical preferences upon epoxidation with *m*-CPBA. It could be argued that these two allylic alcohols are configurationally opposite at the remote allylic position and attack on the double bond is sensitive to the steric environment at this center (CH_2OTBS < $PMBOMOCH_2CH(CH_3)CH_2$) as depicted in Figure 1. Whatever its origins, the effect is significant as attempted formation of the α-epoxide **26b** through Sharpless epoxidation of **24b** with the L-(+)-tartrate reagent also met with failure.[7] Only the β-epoxide **25b** was obtained (Table I, entry 3). In view of these unpromising results, we decided to abandon OH-directed epoxidations and examine various derivatives of diol **24a** in the hopes of inducing a conformational change favorable to α-ep-

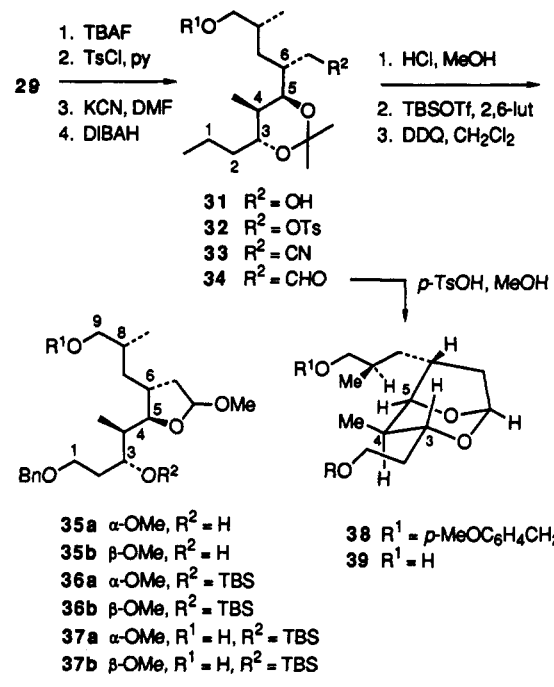
(8) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. Finan, J. M.; Rishi, R. *Tetrahedron Lett.* **1982**, *23*, 2719.
(9) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569.
(10) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526, 4527. Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060.
(11) Rychnovsky, S. D.; Shalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
(12) Cf.: Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651. Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.
(13) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901.
(14) Lipschutz, B. H. *Synthesis* **1987**, 325.
(15) This analysis was performed by Dr. A. R. Garber and H. Cohen of our department.

oxidation. This approach was moderately successful. The bis-TBS ether **24c** was converted to a 60:40 mixture of β- and α-epoxides **25c** and **26c** upon treatment with MCPBA (Table I, entry 5). With the bis-TIPS ether **24d**, MCPBA slightly favored the α-epoxide **26d** (Table I, entry 6). Various phenylcarbamate derivatives (**24e–g**) led to mixtures of epoxides but in all cases the β-isomer predominated (Table I, entries 7–9). Magnesium monoperoxyphthalic acid (MMPP) proved more intrinsically α-selective than *m*-CPBA with allylic diol **24a** and the monosilylated derivatives (Table I, entries 10–12). Both the TBS ether **24b** and the TIPS ether **24h** gave a nearly 1:1 separable mixture of epoxides. The bis-TBS ether failed to react (Table I, entry 13). These findings show that double-bond substituents can exert considerable influence on directed epoxidations of allylic alcohols (compare **10** with **24**).[16] In view of the small energy differences separating acyclic conformers it is not surprising that seemingly modest changes in substituents lead to measurable variations in selectivity.[17] The origin of these variations is presently obscure.

For the sake of convenience, we prepared the α-epoxide **26** by epoxidation of the TBS ether **24b** with MMPP and subsequent chromatographic separation from the β-isomer **25b**. A reaction sequence for the elaboration of a possible tylonolide subunit (see VII) was initially developed with the more accessible β-epoxide **25b** whose conversion to acetonide **29** is described above. Of several sequences examined for homologation of the C-6 side chain, cyanide displacement of the tosylate **32** followed by reduction with DIBAH gave the best results. Aldehyde **34** was thereby secured in nearly 70% overall yield. Cleavage of the acetonide with *p*-TsOH in MeOH was expected to afford the methyl acetal **35** but gave instead a mixture of the bicyclic acetal **38** and alcohol **39**. However, the use of 0.5% anhydrous HCl in MeOH at 0 °C for 5 min led to the desired acetal **35** as a 35:65 mixture of α- and β-epimers in 91% yield with no apparent cleavage of the *p*-methoxybenzyl ether. Conversion to the TBS ether **36a/b** then oxidative cleavage of the PMBOM grouping with DDQ[12] yielded the anomeric lactols **37a** and **37b**. This mixture is epimeric at C-4 and C-5 with an intermediate employed by Nicolaou in his synthesis of *O*-micinosyl tylonolide.[4]

Our synthesis of the actual Nicolaou intermediate commenced with the α-epoxide **26b**, obtained by oxidation of allylic alcohol **24b** with MMPP and then separation from the slightly favored β-epoxide **25b**. Elimination, as before, with $LiNEt_2$ and then acetonide formation yielded **41** which gave the dihydro compound **30** upon hydrogenation over PtO_2. The ^1H and ^{13}C NMR[11] spectra of **30** were in complete accord with the assigned structure.

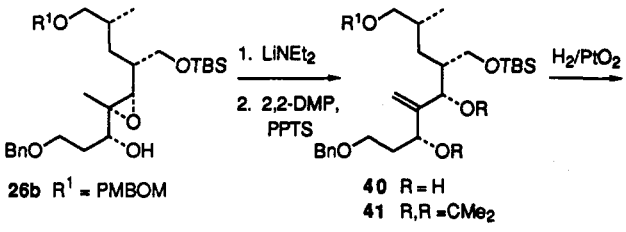
Side-chain homologation was effected as detailed for the diastereomeric acetonide **29**. Treatment of the resulting aldehyde with HCl in methanol led to an epimeric mixture of γ-lactol ethers **46**. None of the bicyclic acetal **49** corresponding to **38** or **39** was formed in this reaction, even after prolonged time. This is understandable in view of the substantial nonbonded interactions present in **49** vs **38**. Silylation of the alcohol **46** with TBSOTf and 2,6-lutidine afforded the TBS ether **47**. The PMBOM group was removed with DDQ[12] whereupon the Nicolaou intermediate **48** was obtained. The ^1H NMR and infrared spectra of **48** were identical to those of an authentic sample.



31 R^2 = OH
32 R^2 = OTs
33 R^2 = CN
34 R^2 = CHO

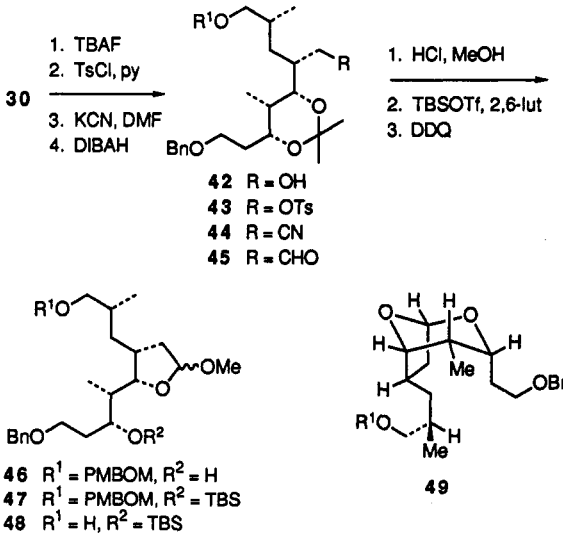
35a α-OMe, R^2 = H
35b β-OMe, R^2 = H
36a α-OMe, R^2 = TBS
36b β-OMe, R^2 = TBS
37a α-OMe, R^1 = H, R^2 = TBS
37b β-OMe, R^1 = H, R^2 = TBS

38 R^1 = *p*-$MeOC_6H_4CH_2OCH_2$
39 R^1 = H



26b R^1 = PMBOM

40 R = H
41 R,R = CMe_2



42 R = OH
43 R = OTs
44 R = CN
45 R = CHO

46 R^1 = PMBOM, R^2 = H
47 R^1 = PMBOM, R^2 = TBS
48 R^1 = H, R^2 = TBS

49

Experimental Section[18]

(*Z*)-5-(Benzyloxy)-2-methyl-2-penten-1-ol (4). To a solution of oxalyl chloride (11.0 mL, 126 mmol) in 400 mL of CH_2Cl_2 in a 1-L round-bottomed flask at −60 °C was added DMSO (12.0 mL, 169 mmol). The solution was cooled to −78 °C over 20 min whereupon alcohol **1** (14.007 g, 84.3 mmol) in 15 mL of CH_2Cl_2 was added. The solution was stirred 30 min at −78 °C, and then Et_3N (47.0 mL, 337 mmol) was added.[5] The mixture was stirred

(16) For some previous studies in this area, see: Isobe, M.; Kitamura, M.; Shigeru, M.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221. Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347. Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229.

(17) Cf.: McCormick, M.; Monahan, R.; Sorea, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 4485. Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647. Smith, Z.; Carballo, N.; Wilson, E. B.; Marstokk, K.-M.; Mollendal, H. *J. Am. Chem. Soc.* **1985**, *107*, 1951.

(18) For a general description of experimental parameters, see: Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225.

30 min at room temperature, diluted with Et_2O and hexanes (1:1), and filtered through $MgSO_4$. The filtrate was concentrated, taken up in CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated to give the crude aldehyde as a yellow liquid.

To a solution of ethyl 2-[bis(trifluoroethyl)phosphono]-propionate (33.860 g, 97.8 mmol) and 18-C-6 (68.965 g, 261 mmol) in 800 mL of THF in a 2-L round-bottomed flask at −78 °C was added a 0.5 M solution of KHMDS in toluene (186 mL, 93.0 mmol) over 15 min.[6] The solution was stirred for 15 more min, and then the crude aldehyde **2** in 20 mL of THF was added at −78 °C over 20 min. The mixture was stirred for 45 min at −78 °C and then warmed to 0 °C over 19 h. The mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated. Purification by filtration through a pad of silica gel (hexanes–Et_2O, 8:2) gave the desired ester **3** as a yellow liquid.

To a solution of DIBAH (200.0 mL) in 1100 mL of CH_2Cl_2 in a 2-L round-bottomed flask at −78 °C was added the ester over 20 min. The solution was stirred for 1 h at −78 °C, 5 mL of MeOH was added, and the mixture was stirred 0.5 h at room temperature. The mixture was diluted with saturated potassium sodium tartrate (Rochelle's salt) solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a yellow liquid. Purification by Kugelrohr distillation gave allylic alcohol **4** (14.883 g, 86% overall) as a pale yellow liquid: bp 160–165 °C (2.0 Torr); IR (film) ν 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (d, J = 1.3 Hz, 3 H, vinyl CH_3), 2.33 (q, J = 6.0 Hz, 2 H, H4), 3.44 (t, J = 6.0 Hz, 2 H, H5), 4.01 (s, 2 H, H1), 4.50 (s, 2 H, $PhCH_2O$), 5.31 (t, J = 7.9 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl); HMRS m/z calcd for $C_{13}H_{18}O_2$ 206.1307, m/z observed 206.1307.

(2*S*,3*R*)-5-(Benzyloxy)-2,3-epoxy-2-methyl-1-pentanol (5). To a stirred, cooled (−15 °C) slurry of 0.21 g of 3-Å molecular sieves in 10 mL of dry CH_2Cl_2 was added 0.082 mL (0.48 mmol) of L-(+)-diethyl tartrate and 0.119 mL (0.040 mmol) of titanium isopropoxide. The mixture was cooled to −23 °C, and 0.92 mL (6.0 mmol) of 6.52 M *tert*-butyl hydroperoxide in isooctane was added.[8] The mixture was stirred for 10 min, and 0.825 g (4.0 mmol) of *Z* allylic alcohol **4** was added dropwise as a solution in 1 mL of CH_2Cl_2. The mixture was stirred overnight at −15 °C, and 2.3 mL of water was added. The mixture was stirred at room temperature for 1 h, and 1.0 mL of 30% NaOH in brine was added with stirring for an additional hour. The mixture was filtered through Celite and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography on silica gel (elution with 25% EtOAc–hexanes) afforded 0.790 g (89%) of the *cis*-epoxy alcohol **5** as an oil: $[\alpha]^{24}_D$ +15.3° ($CHCl_3$, *c* 1.90); IR (film) ν 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3 H, C2-CH_3), 1.75 (m, 1 H, H4), 2.1 (m, 1 H, H4), 2.78 (dd, J = 4.1, 9.6 Hz, 1 H, H3), 3.2–3.7 (m, 4 H, H1, H5), 4.52 (AB, J = 11.8 Hz, $\Delta\nu$ = 10.6 Hz, 2 H, $PhCH_2O$), 7.3 (m, 5 H, phenyl); ^{13}C NMR (80 MHz, $CDCl_3$) δ 20.12, 28.85, 60.33, 62.11, 63.90, 66.59, 73.35, 127.80, 127.92, 128.39, 137.14 ppm. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.04; H, 8.22.

The ee of this material was calculated to be 80% through ^1H NMR analysis of the derived *O*-methyl mandelic esters.[19]

Ethyl (*Z*)-(4*S*,5*R*)-7-(Benzyloxy)-4,5-epoxy-4-methyl-2-heptenoate (7). To a stirred, cooled (−78 °C) solution of 6.66 mL (76.3 mmol) of oxalyl chloride in 320 mL of dry CH_2Cl_2 was added 6.14 mL (86.5 mmol) of DMSO. The mixture was stirred for 10 min, and 11.31 g (50.88 mmol) of alcohol **5** was added as a solution in 15 mL of CH_2Cl_2. The mixture was stirred for 40 min, and 35.5 mL (254 mmol) of Et_3N was added.[5] The mixture was diluted with 250 mL of Et_2O and 250 mL of hexanes and filtered through $MgSO_4$. The solution was concentrated under reduced pressure, and the residue, aldehyde **6**, was used in the next step without further purification. To a stirred solution of 14.0 g (66.1 mmol) of ethyl 2-[bis(trifluoroethyl)phosphono]acetate in 600 mL of THF at room temperature was added 40 g (150 mmol) of 18-crown-6. The mixture was cooled to −78 °C, and 112 mL (56.0 mmol) of 0.5 M KHMDS in toluene was added dropwise. The solution was stirred for 10 min, and a solution of aldehyde **6** in 20 mL of THF was added dropwise.[6] The mixture was stirred for 45 min, allowed to warm to room temperature, and diluted with an equal volume of saturated NH_4Cl. The aqueous phase was extracted three times with EtOAc, and the combined organic phases were concentrated and filtered through a pad of silica gel (elution with 25% EtOAc–hexanes) to remove the 18-crown-6. Chromatography on silica gel (elution with 15% EtOAc–hexanes) afforded 10.66 g (72%) of an inseparable 22:1 mixture of the *Z* unsaturated ester **7** and the isomeric *E* unsaturated ester **17**: $[\alpha]^{25}_D$ +109° ($CHCl_3$, *c* 1.34); IR (film) ν 1710, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.51 (s, 3 H, epoxy CH_3), 1.8–2.0 (m, $BnOCH_2CH_2$), 3.14 (m, 1 H, epoxy H), 3.6 (m, 2 H, $BnOCH_2$), 4.15 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.50 (s, 2 H, $PhCH_2O$), 5.87 (d, J = 11.8 Hz, 1 H, vinyl H), 6.23 (d, J = 11.8 Hz, 1 H, vinyl H), 7.3 (m, 5 H, phenyl). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.20; H, 7.68.

(*E*)-(2*R*,5*R*)-7-(Benzyloxy)-2-ethyl-4-methyl-3-heptene-1,5-diol (9). To a stirred, cooled (−10 °C) slurry of 0.394 g (2.07 mmol) of azeotropically dried CuI in 10 mL of dry THF was added 4.6 mL (4.14 mmol) of 0.9 M EtLi in ether. The resulting dark blue solution was stirred for 20 min. To a stirred, cooled (−78 °C) solution of 0.150 g (0.517 mmol) of ester **7** (22:1 *Z*/*E* olefin) in 6 mL of dry ether was added 1.09 mL (1.09 mmol) of 1.0 M diisobutylaluminum hydride in hexanes over 2 min. The clear solution was stirred for 20 min, one drop of water was added, and the mixture was stirred an additional 5 min at −78 °C. The mixture was transferred by cannula to the cuprate solution, and the whole was allowed to warm from −10 °C to 4 °C overnight whereupon an equal volume of 1:1 NH_4Cl–3% NH_4OH was carefully added. The aqueous phase was extracted three times with ether, and the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (elution with 50% EtOAc–hexanes) to yield 0.0905 g (63%) of the diol **9** as an oil. Analysis of the diacetate derivatives **11**/**20** by gas chromatography and ^1H NMR showed (*E*)-olefin products exclusively and a 92:8 ratio of syn to anti products: $[\alpha]^{22}_D$ −7.8° ($CHCl_3$, *c* 0.95); IR (film) ν 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.0–1.5 (m, 2 H, CH_2CH_3), 1.62 (s, 3 H, vinyl CH_3), 1.7–2.0 (m, 2 H, CH_2CHOH), 2.4 (m, 1 H, $CHCH_2CH_3$), 3.30 (m, 2 H, CH_2OH), 3.4–3.7 (m, 2 H, $BnOCH_2$), 4.0 (m, 1 H, CHOH), 4.49 (s, 2 H, $PhCH_2$), 5.19 (d, J = 9.9 Hz, 1 H, vinyl H), 7.3 (m, 5 H, phenyl). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.38; H, 9.35. Found: C, 73.31; H, 9.41.

(*E*)-(3*R*,6*R*)-1-(Benzyloxy)-6-ethyl-4-methyl-7-[(*tert*-butyldimethylsilyl)oxy]-4-hepten-3-ol (10). To a stirred solution of 1.138 g (4.09 mmol) of diol **9** in 40 mL of CH_2Cl_2 at room temperature was added 0.822 mL (5.89 mmol) of triethylamine, 10 mg of 4-(dimethylamino)pyridine, and 0.74 g (4.9 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature overnight and poured into water. The organic phase was washed three times with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 10% EtOAc–hexanes) to yield 1.474 g (92%) of the mono-TBS ether **10** as an oil: $[\alpha]^{23}_D$ −12.6° ($CHCl_3$, *c* 2.2); IR (film) ν 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6 H, $SiCH_3$), 0.79 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $(CH_3)_3C$), 1.0–1.2 (m, 2 H, CH_2CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.7–2.0 (m, 2 H, $BnOCH_2CH_2$), 2.2–2.4 (m, 1 H, $CHCH_2OTBS$), 2.55 (br s, 1 H, OH), 3.4 (m, 2 H, CH_2OTBS), 3.6 (m, 2 H, $BnOCH_2$), 4.2 (m, 1 H, CHOH), 4.49 (s, 2 H, $PhCH_2O$), 5.14 (d, J = 9.8 Hz, 1 H, vinyl H), 7.3 (m, 5 H, phenyl). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.35; H, 10.27. Found: C, 70.51; H, 10.30.

(3*R*,4*S*,5*S*,6*R*)-1-(Benzyloxy)-4,5-epoxy-6-ethyl-4-methyl-7-[(*tert*-butyldimethylsilyl)oxy]-3-heptanol (12). To a stirred solution of 0.063 g (0.37 mmol) of *m*-CPBA and 0.063 g of Na_2HPO_4 in 1.5 mL of CH_2Cl_2 at 0 °C was added 0.048 g (0.122 mmol) of alkene **10**. The mixture was stirred at 0 °C overnight and poured into water. The organic phase was washed three times with saturated sodium bisulfite, twice with sodium bicarbonate, and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 15%

(19) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

EtOAc–hexanes) to yield 0.046 g (93%) of epoxide **12** as an oil: $[\alpha]^{25}_D$ −15.2° ($CHCl_3$, *c* 2.2); IR (film) ν 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6 H, $SiCH_3$), 0.87 (m, 12 H, CH_2CH_3, $SiC(CH_3)_3$), 1.26 (s, 3 H, epoxy CH_3), 1.2–1.4 (m, 2 H, CH_2CH_3), 1.6 (m, 2 H, $CHCH_2OTBS$, H_2O), 1.77, 1.81 (AB q, J = 6.1 Hz, 2 H, $BnOCH_2CH_2$), 2.5 (s, 1 H, OH), 2.78 (d, J = 9.3 Hz, 1 H, epoxy-H), 3.5 (m, 1 H, CHOH), 3.6–3.8 (m, 4 H, CH_2OTBS, $BnOCH_2$), 4.50 (s, 2 H, $PhCH_2O$), 7.3 (m, 5 H, C_6H_5); ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.45, 11.53, 12.42, 18.37, 21.24, 25.95, 32.75, 41.38, 62.36, 63.26, 63.68, 67.95, 73.30, 74.88, 127.72, 128.45, 138.04. Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.65; H, 9.80. Found: C, 67.54; H, 9.87.

(2*S*,3*S*,5*R*)-7-(Benzyloxy)-2-ethyl-4-methylene-1-[(*tert*-butyldimethylsilyl)oxy]heptane-3,5-diol (13). To a stirred, cooled (0 °C) solution of 2.78 mL (26.9 mmol) of diethylamine in 30 mL of dry ether was added 10.76 mL (26.9 mmol) of 2.5 M *n*-BuLi in hexanes. The mixture was stirred for 10 min at 0 °C, 5 min at room temperature, and 5 min at 0 °C, and 1.100 g (2.69 mmol) of epoxy alcohol **12** was added.[10] The mixture was stirred at 0 °C for 72 h and poured into an equal volume of saturated aqueous NH_4Cl. The aqueous phase was extracted three times with ether, and the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (elution with 15% EtOAc–hexanes) to yield 0.798 g (73%) of diol **13** as a light yellow oil: $[\alpha]^{24}_D$ +7.1° ($CHCl_3$, *c* 1.9); IR (film) ν 3410 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H, CH_3Si), 0.88 (m, 9 H, $SiC(CH_3)_3$), 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.2–1.6 (m, 2 H, CH_2CH_3), 1.7 (m, 1 H, $CHCH_2CH_3$), 2.0 (m, 2 H, $BnOCH_2CH_2$), 3.28 (d, J = 3.5 Hz, 1 H, OH), 3.5–4.0 (m, 4 H, $ROCH_2$), 4.16 (d, J = 5.3 Hz, 1 H, CHOH), 4.30 (t, J = 5.5 Hz, 1 H, CHOH), 4.40 (s, 1 H, OH), 4.50 (s, 2 H, $PhCH_2O$), 5.14 (s, 1 H, vinyl H), 5.24 (s, 1 H, vinyl H), 7.3 (m, 5 H, C_6H_5). Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.61; H, 9.90.

(2*S*,3*S*,5*R*)-7-(Benzyloxy)-2-ethyl-4-methylene-1-[(*tert*-butyldimethylsilyl)oxy]-3,5-(isopropylidenedioxy)heptane (14). To a stirred solution of 0.149 g (0.364 mmol) of diol **13** in 25 mL of dry 2,2-dimethoxypropane was added 0.030 g of pyridinium *p*-toluenesulfonate. The mixture was stirred for 36 h at 35 °C. It was then poured into water and extracted three times with ether. The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (elution with 10% EtOAc–hexanes) to yield 0.155 g (95%) of acetonide **14** as an oil: $[\alpha]^{24}_D$ −6.3° ($CHCl_3$, *c* 0.56). ^1H NMR (300 MHz, $CDCl_3$) δ 0.014 (s, 6 H, CH_3Si), 0.87 (m, 9 H, $SiC(CH_3)_3$), 0.9 (m, 3 H, CH_2CH_3), 1.2–1.6 (m, 2 H, CH_2CH_3), 1.32 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.7 (m, 1 H, $CHCH_2CH_3$), 2.0 (m, 2 H, $BnOCH_2CH_2$), 3.5–3.8 (m, 4 H, $ROCH_2$), 4.27 (d, J = 6.5 Hz, 1 H, CHOR), 4.46 (m, 1 H, CHOR), 4.50 (AB q, J = 12.0 Hz, $\Delta\nu$ = 8.7, 2 H, $PhCH_2O$), 4.91 (s, 1 H, vinyl H), 4.96 (s, 1 H, vinyl H), 7.3 (m, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.60; H, 9.88. Found: C, 69.84; H, 9.91.

(2*S*,3*S*,4*S*,5*R*)-7-(Benzyloxy)-2-ethyl-4-methyl-1-[(*tert*-butyldimethylsilyl)oxy]-3,5-(isopropylidenedioxy)heptane (15). A 25-mL flask was charged with 0.100 g of PtO_2 in 6 mL of EtOH and blanketed under argon. The argon atmosphere was replaced by H_2, and the mixture was stirred for 15 min. The brown suspension turned black, and 0.191 g (0.426 mmol) of alkene **14** was added. Stirring was continued until GC analysis showed that all of the starting material had been consumed (15 min). The mixture was filtered through Celite, concentrated under reduced pressure, and chromatographed on silica gel (elution with 5% EtOAc–hexanes) to yield 0.189 g (98%) of **15** as an oil: $[\alpha]^{26}_D$ +4.1° ($CHCl_3$, *c* 0.4). ^1H NMR (300 MHz, C_6D_6) δ 0.079 (s, 6 H, CH_3Si), 0.9 (m, 6 H, CH_2CH_3, C4-CH_3), 1.00 (s, 9 H, $SiC(CH_3)_3$), 1.3 (m, 1 H, C4-H), 1.3–1.6 (m, 3 H, CH_2CH_3, C2-H), 1.43 (s, 3 H, CH_3), 1.51 (s, 1 H, CH_3), 1.65 (m, 1 H, $BnOCH_2CH_2$), 1.9 (m, 1 H, $BnOCH_2CH_2$), 3.4–3.6 (m, 2 H, $BnOCH_2$), 3.67 (B of ABX, 1 H, $TBSOCH_2$), 3.91 (dd, J = 2.3, 9.8 Hz, 1 H, C3-H), 3.96 (A of ABX, 1 H, $TBSOCH_2$), 4.05 (m, 1 H, C5-H), 4.37 (AB q, J = 12.3 Hz, $\Delta\nu$ = 9.6, 2 H, $PhCH_2O$), 7.3 (m, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29. Found: C, 69.43; H, 10.34.

Methyl (*E*)-(4*S*,5*R*)-7-(Benzyloxy)-4,5-epoxy-4-methyl-2-heptenoate (17). To a stirred solution of 2.14 mL (24.5 mmol) of oxalyl chloride in 200 mL of dry CH_2Cl_2 at −78 °C was added 1.97 mL (27.8 mmol) of DMSO. The mixture was stirred at −78 °C for 15 min, and 3.63 g (16.3 mmol) of alcohol **5** was added. The mixture was stirred for 20 min, and 11.4 mL (82 mmol) of triethylamine was added dropwise.[5] The mixture was diluted with an equal volume of ether and filtered through $MgSO_4$. The solvent was removed under reduced pressure, and the residue, aldehyde **6**, was dissolved in 100 mL of CH_2Cl_2. The solution was cooled to 0 °C, and 7.11 g (21.2 mmol) of (carbomethoxymethylene)-triphenylphosphorane was added. The mixture was stirred at 0 °C overnight and poured into water. The aqueous phase was extracted three times with ether, and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel (elution with 10% EtOAc–hexanes) afforded 4.153 g (92%) of ester **17** as an oil: $[\alpha]^{27}_D$ +32° ($CHCl_3$, *c* 2.6); IR (film) ν 1720, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3 H, epoxy-CH_3), 1.7–1.9 (m, 2 H, $BnOCH_2CH_2$), 3.14 (dd, J = 5.6, 6.7 Hz, 1 H, epoxy-H), 3.5–3.7 (m, 2 H, $BnOCH_2$), 3.71 (s, 3 H, CO_2CH_3), 4.47, 4.49 (AB, J = 12.0 Hz, 2 H, $PhCH_2O$), 5.98 (d, J = 15.7 Hz, 1 H, vinyl-H), 6.86 (d, J = 15.7 Hz, 1 H, vinyl-H), 7.3 (m, 5 H, phenyl); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 21.67, 29.33, 52.05, 59.96, 64.48, 67.55, 73.45, 123.47, 127.96, 128.02, 128.78, 138.62, 146.12, 166.68. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.66; H, 7.32.

(*E*)-(4*S*,5*R*)-7-(Benzyloxy)-4,5-epoxy-4-methyl-2-hepten-1-ol (18). To a solution of ester **17** (1.488 g, 5.38 mmol) in 100 mL of Et_2O in a 250-mL round-bottomed flask at −78 °C was added a 1.0 M solution of DIBAH in hexanes (11.0 mL, 11.0 mmol) over 70 min. The mixture was stirred 15 min at −78 °C, quenched with 1 mL of MeOH, and stirred for 10 min at room temperature. The mixture was quenched with saturated Rochelle's salt solution and extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated. Purification by chromatography on silica gel deactivated by prior elution with 1% Et_3N in hexane (hexanes–EtOAc, 1:1) gave alcohol **18** (1.053 g, 79%) as a pale yellow liquid: $[\alpha]^{26}_D$ +13.1° ($CHCl_3$, *c* 0.84); IR (film) ν 3432 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3 H, CH_3), 1.6–1.9 (m, 2 H, $BnOCH_2CH_2$), 3.04, 3.06 (AB, J = 5.5 Hz, 1 H, epoxy-H), 3.58 (m, 2 H, $BnOCH_2$), 4.1 (m, 2 H, CH_2OH), 4.50 (s, 2 H, $PhCH_2O$), 5.64 (d, J = 15.8 Hz, 1 H, vinyl-H), 5.86 (dt, J = 15.8 Hz, 5.2 Hz, 1 H, vinyl-H), 7.3 (m, 5 H, aryl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.80, 21.97, 29.04, 40.89, 59.78, 62.80, 63.56, 67.44, 73.07, 127.64, 127.67, 128.42, 128.79, 132.81, 138.25.

(*E*)-(2*R*,4*S*,7*R*)-9-(Benzyloxy)-4-(hydroxymethyl)-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethyl-5-nonen-7-ol (24a). To a stirred solution of 3.0 g (9.9 mmol) of (2*S*)-1-bromo-3-[[(*p*-methoxybenzyl)oxy]methoxy]-2-methylpropane in 90 mL of ether at −78 °C was added 11.5 mL (17.2 mmol) of 1.5 M t-BuLi in pentane.[13] The mixture was stirred for 2 h at −78 °C and 3 min at −23 °C. It was recooled to −78 °C, and 0.884 g (9.87 mmol) of azeotropically dried CuCN was added. The solution was stirred for 2 h at −78 °C, and 0.837 g (3.37 mmol) of vinyloxirane **18** was added over 15 min as a solution in 2 mL of ether. The solution was stirred at −78 °C for 0.5 h, warmed to −40 °C, and allowed to slowly warm to 0 °C overnight. An equal volume of 1:1 NH_4Cl–3% NH_4OH was carefully added, the aqueous phase was extracted three times with ether, and the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (elution with 50% EtOAc–hexanes) to yield 0.961 g (60%) of the diol **24a** as an oil: $[\alpha]^{23}_D$ +1.6° ($CHCl_3$, *c* 1.4); IR (film) ν 3421 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.9 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.2 (m, 2 H, H8), 1.66 (s, 3 H, vinyl CH_3), 1.6–2.0 (m, 3 H, H3,H2), 2.03 (br, 1 H, OH), 2.66 (m, 1 H, H4), 3.3–3.6 (m, 4 H, CH_2OBn, CH_2OH), 3.58, 3.62 (m, 2 H, $PMBOCH_2OCH_2$), 3.77 (s, 3 H, $CH_3OC_6H_4$), 4.18 (dd, J = 6.9, 4.7 Hz, 1 H, CH_2OH), 4.5 (m, 4 H, $PhCH_2O$, $CH_3OC_6H_4CH_2O$), 4.68 (s, 2 H, $PMBOCH_2O$), 5.15 (d, J = 10.0 Hz, 1 H, vinyl-H), 6.85 (d, J = 8.6 Hz, 2 H, aryl), 7.3 (m, 7 H, aryl); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 13.54, 16.90, 31.09, 34.92, 35.40, 38.29, 55.28, 66.91, 68.55, 68.93, 73.27, 74.00, 75.59, 94.41, 113.84, 126.56, 127.74, 127.77, 128.47, 129.55, 129.96, 137.96, 140.25, 159.24. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.58.

(*E*)-(3*R*,6*S*,8*R*)-1-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9-[[(*p*-methoxybenzyl)oxy]methoxy]-4,8-dimethyl-4-nonen-3-ol (24b). To a stirred solution of 1.60 g (3.39 mmol) of diol **24a** in 45 mL of CH_2Cl_2 at room temperature were added 0.68 mL (4.9 mmol) of triethylamine, 2 mg of 4-(di-

methylamino)pyridine, and 0.612 g (4.1 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature overnight and poured into water. The organic phase was washed three times with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 10% EtOAc–hexanes) to yield 1.848 g (93%) of the mono-TBS ether **24b** as an oil: $[\alpha]^{22}_D$ +10.2° ($CHCl_3$, *c* 1.85) IR (film) ν 3500 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6 H, CH_3Si), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.89 (d, J = 6.7 Hz, 3 H, C2-CH_3), 1.2–1.4 (m, CH_2), 1.63 (s, 3 H, vinyl-CH_3), 1.6–2.0 (m, CH_2), 2.6 (m, 1 H, H4), 2.70 (d, J = 3.1 Hz, 1 H, OH), 3.3–3.5 (m, 4 H, CH_2OR), 3.6, 3.7 (m, 2 H, CH_2OR), 3.77 (s, 3 H, $CH_3OC_6H_4$), 4.18 (dd, J = 4.2, 3.7 Hz, 1 H, CHOH), 4.5 (m, 4 H, PhCH_2O, $MeOC_6H_4CH_2O$), 4.67 (s, 2 H, OCH_2O), 5.12 (d, J = 10.0 Hz, 1 H, vinyl-H), 6.8, 7.3 (m, 9 H, aryl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.30, -5.24, 12.63, 16.92, 18.34, 25.96, 31.12, 34.95, 35.70, 38.23, 55.28, 67.11, 68.75, 68.81, 73.29, 74.18, 76.09, 94.35, 113.83, 127.31, 127.68, 127.71, 128.46, 129.58, 130.01, 138.09, 138.63, 159.24. Anal. Calcd for $C_{34}H_{54}O_6Si$: C, 69.58; H, 9.74. Found: C, 69.79; H, 9.46.

(2*R*,4*R*,5*R*,6*R*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,6-epoxy-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethyl-7-nonanol (25b). To a stirred solution of 1.45 g (8.43 mmol) of *m*-CPBA and 1.45 g of Na_2HPO_4 in 65 mL of CH_2Cl_2 at 0 °C was added 1.65 g (2.81 mmol) of allylic alcohol **24b**. The mixture was stirred at 0 °C overnight and poured into water. The organic phase was washed three times with saturated sodium bisulfite, twice with sodium bicarbonate, and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 20% EtOAc–hexanes) to yield 1.51 g (89%) of the epoxide **25b** as an oil: $[\alpha]^{20}_D$ +16.9° ($CHCl_3$, *c* 1.6); IR (film) ν 3477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6 H, $SiCH_3$), 0.87 (m, 9 H, $SiC(CH_3)_3$), 0.92 (d, J = 6.6 Hz, 3 H, CH_2CH_3), 1.26 (s, 3 H, epoxy-methyl), 1.4–2.0 (m, 6 H, CH_2), 2.74 (s, 1 H, OH), 2.85 (d, J = 9.2 Hz, 1 H, epoxy-H), 3.37 (m, 2 H, CH_2OR), 3.5–3.8 (m, 5 H, CHOH, CH_2OTBS, CH_2OR), 3.78 (s, 3 H, $CH_3OC_6H_4$), 4.50 (s, 2 H, $PhCH_2O$), 4.68 (s, 2 H, OCH_2O), 6.8–7.4 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.41, 13.94, 18.06, 18.35, 25.96, 30.51, 32.66, 32.89, 37.43, 55.28, 62.30, 62.89, 63.72, 68.25, 68.98, 72.65, 73.29, 73.60, 94.46, 113.86, 127.69, 127.72, 128.44, 129.60, 129.87, 138.15, 159.29. Anal. Calcd for $C_{34}H_{54}O_7Si$: C, 67.74; H, 9.03. Found: C, 67.71; H, 9.06.

(2*R*,4*R*,5*S*,6*S*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,6-epoxy-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethyl-7-nonanol (26b) and (2*R*,4*R*,5*R*,6*R*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,6-epoxy-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethyl-7-nonanol (25b). To a solution of olefin **24b** (0.935 g, 1.59 mmol) in 12.0 mL of 2-propanol–water (1:1) in a 100-mL round-bottomed flask at room temperature was added 80% technical grade MMPP (0.687 g, 1.11 mmol).[20] The reaction mixture was stirred for 20 h at room temperature. The 2-propanol was removed under reduced pressure, and the resulting aqueous residue was extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a clear, colorless liquid. Flash column chromatography of this material on deactivated (1% Et_3N–hexanes) silica gel (hexanes–Et_2O, 6:4) gave α-epoxide **26b** (0.354 g, 37%) as a colorless liquid and β-epoxide **25b** (0.407 g, 43%) as a colorless liquid.

Epoxide **26b**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H, CH_3Si), 0.87 (s, 9 H, $(CH_3)_3C$), 0.94 (d, 3 H, J = 6.6 Hz, C2-CH_3), 1.28 (s, 3 H, C6-CH_3), 1.65 (m, 3 H, CH_2 and CH), 1.80 (m, 2 H, CH_2), 2.03 (m, 1 H, CH), 2.47 (d, 1 H, J = 3.7 Hz, OH), 2.70 (d, 1 H, J = 9.0 Hz, epoxy-CH), 3.39 (m, 2 H, OCH_2), 3.49 (m, 2 H, OCH_2), 3.64 (m, 2 H, OCH_2), 3.78 (s, 3 H, CH_3O), 4.49 (s, 2 H, $PhCH_2O$), 4.50 (s, 2 H, $PhCH_2O$), 4.70 (s, 2 H, OCH_2O), 6.86 (d, 2 H, J = 8.7 Hz, *p*-MeO-aryl), 7.30 (m, 7 H, *p*-MeO-aryl and phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.1, -5.0, 13.2, 17.9, 18.8, 26.4, 31.3, 33.3, 35.2, 38.0, 55.7, 63.3, 64.9, 65.2, 68.3, 69.2, 73.5, 74.2, 75.2, 94.8, 114.2, 127.9, 128.0, 128.8, 129.9, 130.5, 138.6, 159.6; IR (neat) ν 3456 cm^{-1}; $[\alpha]_D$ -2.4° (*c* 1.10, $CHCl_3$); HRMS calcd for $C_{34}H_{55}O_7Si$ (M + H) m/z 603.3717, found m/z 603.3703. Anal. Calcd for $C_{34}H_{54}O_7Si$: C, 67.74; H, 9.03. Found: C, 67.82; H, 9.03.

(20) MMPP was purchased from Aldrich Chemical Co., Milwaukee, WI.

Epoxide **25b** was spectroscopically identical to the material obtained by epoxidation of olefin **24b** with *m*-CPBA.

(2*R*,4*R*,5*S*,6*S*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,7-(isopropylidenedioxy)-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethylnonane (30). To a 2-neck 25-mL round-bottomed flask at room temperature was introduced platinum oxide (0.076 g, 0.33 mmol). The flask was evacuated and flushed with nitrogen three times and then evacuated and flushed three times with hydrogen. Olefin **41** (0.137 g, 0.21 mmol) in 3.0 mL of dry ethanol was then added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was decanted, and the black solids were washed with Et_2O. The combined washes were concentrated. Flash column chromatography of this material on silica gel (hexanes–EtOAc, 95:5) gave acetonide **30** (0.108 g, 80%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$): δ 0.00 (s, 3 H, CH_3Si), 0.05 (s, 3 H, CH_3Si), 0.86 (d, 3 H, J = 11.2 Hz, C6-CH_3), 0.87 (s, 9 H, $(CH_3)_3C$), 0.98 (d, 3 H, J = 6.7 Hz, C2-CH_3), 1.18–1.85 (m, 6 H, CH_2 and CH), 1.32 (s, 3 H, acetonide-CH_3), 1.35 (s, 3 H, acetonide-CH_3), 3.30 (dd, 1 H, J = 9.4, 7.2 Hz, TBSOC*H*), 3.53 (m, 5 H, TBSOC*H* and OCH_2), 3.69 (dd, 1 H, J = 9.4, 1.8 Hz, C5-C*H*), 3.79 (s, 3 H, OCH_3), 3.99 (ddd, 1 H, J = 9.3, 4.3, 2.1 Hz, C7-C*H*), 4.45 and 4.52 (AB q, 2 H, J_{AB} = 12.0 Hz, OCH_2Ar), 4.50 and 4.55 (AB q, 2 H, J_{AB} = 11.4 Hz, OCH_2Ar), 4.71 (s, 2 H, OCH_2O), 6.87 (d, 2 H, J = 8.7 Hz, *p*-MeO-aryl, 7.27 (d, 2 H, J = 8.7 Hz, *p*-MeO-aryl), 7.32 (m, 5 H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.2, 5.9, 18.6, 19.3, 20.0, 26.2, 30.4, 31.9, 33.0, 33.8, 33.9, 39.7, 55.7, 61.8, 67.4, 69.1, 70.8, 73.4, 73.7, 75.7, 94.7, 99.3, 114.2, 127.9, 128.0, 128.7, 130.0, 130.5, 139.0, 159.6; $[\alpha]_D$ -3.9° (*c* 1.26, $CHCl_3$); HRMS calcd for $C_{36}H_{57}O_7Si$ (M - CH_3) m/z 629.3874, found m/z 629.3858. Anal. Calcd for $C_{37}H_{60}O_7Si$: C, 68.90; H, 9.38. Found: C, 68.99; H, 9.41.

(2*R*,4*R*,5*S*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-methyl-6-methylene-1-[[(*p*-methoxybenzyl)oxy]methoxy]-5,7-nonanediol (40). To a solution of freshly distilled (from KOH) diethylamine (0.70 mL, 6.8 mmol) in 15.0 mL of diethyl ether in a 100-mL round-bottomed flask at 0 °C was added a 2.5 M solution of *n*-BuLi in hexanes (2.6 mL, 6.5 mmol). The reaction mixture was stirred for 10 min at 0 °C, 5 min at room temperature, then 5 more min at 0 °C. Oxirane **26b** (0.289 g, 0.48 mmol) in 2.0 mL of diethyl ether was then added at 0 °C.[10] The mixture was stirred 52 h at 0 °C. The reaction was quenched with saturated NH_4Cl solution and then extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a clear, colorless liquid. Flash column chromatography of this material on silica gel (hexanes–Et_2O, 8:2) gave diol **40** (0.248 g, 89%) as a colorless liquid and recovered oxirane **26b** (0.009 g, 3%) as a colorless liquid.

Diol **40**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H, CH_3Si), 0.89 (s, 9 H, $(CH_3)_3C$), 0.97 (d, 3 H, J = 6.7 Hz, C2-CH_3), 1.26 (m, 2 H, CH_2), 1.48 (m, 1 H, CH), 1.75 (m, 1 H, CH), 1.95 (m, 2 H, CH_2), 3.18 (d, 1 H, J = 3.5 Hz, OH), 3.30 and 3.42 (AB q, 1 H, J_{AB} = 9.5 Hz, $SiOCH_2$), 3.33 and 3.44 (AB q, 1 H, J_{AB} = 9.5 Hz, $SiOCH_2$), 3.49 (d, 1 H, J = 2.5 Hz, OH), 3.65 (m, 2 H, OCH_2), 3.78 (s, 3 H, OCH_3), 4.37 (m, 1 H, CHOH), 4.48 (s, 2 H, $PhCH_2O$), 4.49 (s, 2 H, $PhCH_2O$), 4.54 (bs, 1 H, CHOR), 4.66 (s, 2 H, OCH_2O), 5.16 (bs, 2 H, vinyl-H), 6.85 (d, 2 H, J = 8.7 Hz, *p*-MeO-aryl), 7.24 (d, 2 H, J = 8.7 Hz, *p*-MeO-aryl), 7.30 (m, 5 H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.2, 18.6, 19.4, 26.3, 26.4, 28.6, 31.8, 36.4, 41.7, 55.7, 66.3, 69.1, 69.3, 72.7, 73.4, 74.7, 75.5, 94.9, 112.3, 114.2, 128.1, 128.8, 129.9, 130.4, 138.4, 151.8, 159.6; IR (neat) ν 3475 cm^{-1}; $[\alpha]_D$ -4.4° (*c* 1.40, $CHCl_3$); HRMS calcd for $C_{34}H_{55}O_7Si$ (M + H) m/z 603.3717, found m/z 603.3724. Anal. Calcd for $C_{34}H_{54}O_7Si$: C, 67.74; H, 9.03. Found: C, 67.78; H, 9.05.

(2*R*,4*R*,5*S*,7*R*)-9-(Benzyloxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,7-(isopropylidenedioxy)-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2-methyl-6-methylenenonane (41). To a solution of diol **40** (0.487 g, 0.81 mmol) in 5.0 mL of 2,2-dimethoxypropane in a 25-mL round-bottomed flask at room temperature was added pyridinium *p*-toluenesulfonate (0.083 g, 0.33 mmol). The reaction mixture was heated at 35 °C for 62 h. The reaction mixture was quenched with water and then extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated to give a yellow liquid. Flash column chromatography of this material on silica gel (hexanes–Et_2O, 9:1) gave acetonide **41** (0.462 g, 89%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6 H, CH_3Si), 0.87 (s, 9 H, $(CH_3)_3CSi$), 0.96

(d, 3 H, J = 6.7 Hz, C2-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 1.43 (s, 3 H, acetonide-CH_3), 1.55–2.03 (m, 6 H, CH_2 and CH), 3.29 (dd, 1 H, J = 9.3, 7.0 Hz, OCH) and 3.57 (m, 5 H, OCH and OCH_2), 3.78 (s, 3 H, OCH_3), 4.50 (s and m, 5 H, $PhCH_2O$ and p-$MeC_6H_4CH_2O$ and CHOR), 4.60 (d, 1 H, J = 3.8 Hz, C5-CH), 4.69 (s, 2 H, OCH_2O), 4.89 (s, 1 H, vinyl-H), 4.92 (s, 1 H, vinyl-H), 6.86 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.25 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.31 (m, 5 H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.4, –5.3, 18.3, 19.2, 21.7, 26.0, 30.0, 30.4, 31.7, 34.5, 41.0, 55.3, 62.3, 66.7, 68.9, 69.3, 71.2, 73.0, 73.1, 94.5, 98.6, 107.6, 113.9, 127.5, 127.7, 128.4, 129.6, 130.1, 138.6, 145.6, 159.3; $[\alpha]_D$ –22.5° (c 1.10, $CHCl_3$). Anal. Calcd for $C_{37}H_{58}O_7Si$: C, 69.12; H, 9.09. Found: C, 69.06; H, 9.11.

(2*R*,4*R*,5*S*,6*S*,7*R*)-9-(Benzyloxy)-4-(hydroxymethyl)-5,7-(isopropylidenedioxy)-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethylnonane (42). To a solution of silyl ether **30** (0.108 g, 0.17 mmol) in 1.0 mL of THF in a 25-mL round-bottomed flask at room temperature was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.85 mL, 0.85 mmol). The solution was stirred 5.5 h at room temperature, quenched with water, and extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated to give a pale yellow liquid. Purification by silica gel flash column chromatography (hexanes–EtOAc, 7:3) gave alcohol **42** (0.082 g, 91%) as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 3 H, J = 6.8 Hz, C6-CH_3), 0.97 (d, 3 H, J = 6.7 Hz, C2-CH_3) 1.20–2.00 (m, 8 H, CH_2 and CH and OH), 1.33 (s, 3 H, acetonide-CH_3), 1.37 (s, 3 H, acetonide-CH_3), 3.35 and 3.45 (AB q, 1 H, J_{AB} = 9.4 Hz, OCH_2), 3.37 and 3.43 (AB q, 1 H, J_{AB} = 9.4 Hz, OCH_2), 3.52 (m, 3 H, OCH_2), 3.63 (m, 1 H, OCH_2), 3.75 (m, 3 H, OCH), 3.78 (s, 3 H, OCH_3), 4.05 (m, 1 H, OCH), 4.45 and 4.50 (AB q, 2 H, J_{AB} = 12.0 Hz, OCH_2Ar), 4.52 (s, 2 H, OCH_2Ar), 4.71 (s, 2 H, OCH_2O), 6.86 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.26 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.31 (m, 5 H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.8, 19.2, 20.1, 30.4, 31.3, 32.7, 33.8, 33.9, 39.9, 55.7, 62.1, 67.2, 69.3, 70.6, 73.5, 73.9, 75.1, 94.7, 99.4, 114.2, 128.0, 128.1, 128.8, 130.0, 130.3, 138.9, 159.7; $[\alpha]_D$ +6.0° (c 0.72, $CHCl_3$); HRMS calcd for $C_{31}H_{47}O_7Si$ (M^+) m/z 530.3244, found m/z 530.3253. Anal. Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 70.05; H, 8.77.

(2*R*,4*R*,5*S*,6*S*,7*R*)-9-(Benzyloxy)-5,7-(isopropylidenedioxy)-4-[[(*p*-toluenesulfonyl)oxy]methyl]-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethylnonane (43). To a solution of alcohol **42** (0.082 g, 0.15 mmol) and Et_3N (0.09 mL, 0.65 mmol) in 0.4 mL of CH_2Cl_2 in a 25-mL round-bottomed flask at 0 °C was added p-toluenesulfonic anhydride (0.145 g, 0.07 mmol). The solution was stirred 5 h at 0 °C and 2 h at room temperature, quenched with water, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated to give a pink liquid. Purification by Et_3N deactivated silica gel flash column chromatography (hexanes–EtOAc, 8:2) gave tosylate **43** (0.101 g, 98%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 3 H, J = 6.8 Hz, C6-CH_3), 0.84 (d, 3 H, J = 6.4 Hz, C2-CH_3), 1.15–2.81 (m, 7 H, CH_2 and CH), 1.27 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3), 2.41 (s, 3 H, $CH_3C_6H_4SO_2$), 3.24 and 3.33 (AB of ABX, 2 H, J_{AB} = 9.5, J_{AX} = 6.0, J_{BX} = 5.3 Hz, $TsOCH_2$), 3.48 and 3.50 (AB, 2 H, J = 5.3 Hz, OCH_2), 3.63 (dd, 1 H, J = 9.6, 1.8 Hz, C5-OCH), 3.78 (s, 3 H, OCH_3), 3.93 (m, 1 H, C7-OCH), 3.93 and 4.01 (AB of ABX, 2 H, J_{AB} = 9.8, J_{AX} = 2.8, J_{BX} = 3.1 Hz, OCH_2), 4.46 and 4.51 (AB q, 2 H, J_{AB} = 12.0 Hz, OCH_2Ar), 4.46 (s, 2 H, OCH_2Ar), 4.63 (s, 2 H, OCH_2O), 6.85 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.29–7.34 (m, 9 H, aryl), 7.75 (d, 2 H, J = 8.3 Hz, p-toluenesulfonyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.6, 18.9, 20.0, 22.0, 30.3, 31.4, 32.8, 33.4, 33.8, 37.5, 55.7, 67.2, 69.2, 69.3, 70.2, 73.3, 73.5, 74.4, 94.7, 99.4, 114.2, 128.0, 128.1, 128.4, 128.8, 130.0, 130.3, 130.4, 133.0, 138.9, 145.3, 159.6; IR (neat) ν 2937 (s), 1613 (s), 1599 (m), 1514 (s), 1455 (m), 1362 (s), 1303 (m), 1248 (s), 1177 (s), 1099 (s), 1042 (s), 924 (m), 817 (s), 669 (s) cm^{-1}; $[\alpha]_D$ –1.3° (c 1.20, $CHCl_3$); HRMS calcd for $C_{38}H_{52}O_9S$ (M^+) m/z 530.3244, found m/z 530.3253. Anal. Calcd for $C_{38}H_{52}O_9S$: C, 66.64; H, 7.65. Found: C, 66.54; H, 7.66.

(2*R*,4*R*,5*S*,6*S*,7*R*)-9-(Benzyloxy)-4-(cyanomethyl)-5,7-(isopropylidenedioxy)-1-[[(*p*-methoxybenzyl)oxy]methoxy]-2,6-dimethylnonane (44). To a solution of tosylate **43** (0.054 g, 0.08 mmol) in 6.0 mL of DMF in a 25-mL round-bottomed flask at room temperature was added potassium cyanide (0.066 g, 1.01 mmol). After stirring for 42.5 h at room temperature the reaction mixture was poured into water and extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated. Purification by silica gel flash column (hexanes–EtOAc, 8:2) gave nitrile **44** (0.036 g, 83%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, 3 H, J = 6.8 Hz, C6-CH_3), 0.99 (d, 3 H, J = 6.4 Hz, C2-CH_3), 1.2–2.0 (m, 7 H, CH_2 and CH), 1.32 (s, 3 H, acetonide-CH_3), 1.37 (s, 3 H, acetonide-CH_3), 2.23 and 2.47 (AB of ABX, 2 H, J_{AB} = 17.2, J_{AX} = 4.9, J_{BX} = 4.3 Hz, CH_2CN), 3.35 and 3.40 (AB of ABX, 2 H, J_{AB} = 9.6, J_{AX} = 5.7, J_{BX} = 5.6 Hz, OCH_2CH), 3.52 (m, 2 H, OCH_2), 3.68 (dd, 1 H, J = 9.7, 1.9 Hz, C5-OCH), 3.78 (s, 3 H, OCH_3), 4.06 (ddd, 1 H, J = 9.0, 3.8, 2.2 Hz, C7-OCH), 4.47 and 4.50 (AB q, 2 H, J_{AB} = 11.9 Hz, OCH_2Ar), 4.51 (s, 2 H, OCH_2Ar), 4.67 and 4.69 (AB q, 2 H, J_{AB} = 6.7 Hz, OCH_2O), 6.87 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.26 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.32 (m, 5 H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.5, 17.9, 19.1, 20.0, 30.3, 31.4, 33.5, 33.8, 34.3, 35.9, 55.7, 67.0, 69.4, 70.3, 73.5, 73.6, 75.9, 94.8, 99.6, 114.2, 118.4, 128.0, 128.1, 128.8, 130.0, 130.3, 138.8, 159.7; IR (neat) ν 2253 cm^{-1}; $[\alpha]_D$ +2.3° (c 1.80, $CHCl_3$); HRMS calcd for $C_{32}H_{45}NO_6$ (M^+) m/z 539.3247, found m/z 539.3242. Anal. Calcd for $C_{32}H_{45}NO_6$: C, 71.21; H, 8.40. Found: C, 71.05; H, 8.42.

(2*S*,3*R*)-2-[(1*R*,2*R*)-4-(Benzyloxy)-2-hydroxy-1-methylbutyl]-3-[(2*R*)-3-[[(*p*-methoxybenzyl)oxy]methoxy]-2-methylpropyl]-5-methoxy-1,2,3,4-tetrahydrofuran (46). To a solution of nitrile **44** (0.132 g, 0.24 mmol) in 1.2 mL of Et_2O in a 25-mL round-bottomed flask at –78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexanes (0.31 mL, 0.31 mmol). The solution was stirred for 30 min at 0 °C and then for 3 h at room temperature. The mixture was quenched with 1 mL of 1 N HCl solution and stirred for 15 min at room temperature. Saturated Rochelle's salt solution was added, and the mixture was extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated to give the desired aldehyde as a colorless liquid which was carried on directly. To a solution of the crude aldehyde **45** in 5.0 mL of dry MeOH in a 5-mL round-bottomed flask at 0 °C was added a 1.0 M solution of anhydrous HCl in Et_2O (0.12 mL, 0.12 mmol). The solution was stirred for 12 h at 0 °C, quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated to give a colorless liquid. Purification by silica gel flash column chromatography (hexanes–EtOAc, 8:2) gave tetrahydrofuran **46** (0.061 g, 49% overall) as a colorless liquid): ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3 H, J = 6.8 Hz, CH_3), 0.98 (d, 3 H, J = 6.7 Hz, CH_3), 1.0–2.0 (m, 8 H, CH_2 and CH), 2.53 (m, 1 H, CH), 3.12 (d, 1 H, J = 1.5 Hz, OH), 3.32 (s, 3 H, OCH_3), 3.36 (m, 2 H, OCH_2), 3.63 (m, 2 H, OCH_2), 3.78 (s, 3 H, $C_6H_4OCH_3$), 3.92 (d, 1 H, J = 8.1 Hz, OCH), 4.26 (dd, 1 H, J = 7.4, 4.2 Hz, OCH), 4.49 (s, 4 H, OCH_2Ar), 4.67 (s, 2 H, OCH_2O), 5.01 (dd, 1 H, J = 5.2, 1.5 Hz, OCHO), 6.86 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.25 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.30 (m, 5 H, phenyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.3, 19.0, 32.7, 33.2, 34.9, 37.6, 38.8, 39.5, 55.1, 55.7, 69.2, 69.3, 72.8, 73.6, 74.1, 84.4, 94.9, 104.6, 114.2, 128.0, 128.1, 128.8, 129.9, 130.3, 138.6, 159.7; $[\alpha]_D$ +34.8° (c 1.10, $CHCl_3$). Anal. Calcd for $C_{30}H_{44}O_7$: C, 69.74; H, 8.58. Found: C, 69.82; H, 8.58.

(2*S*,3*R*)-2-[(1*R*,2*R*)-4-(Benzyloxy)-2-[(*tert*-butyldimethylsilyl)oxy]-1-methylbutyl]-3-[(2*R*)-3-[[(*p*-methoxybenzyl)oxy]methoxy]-2-methylpropyl]-5-methoxy-1,2,3,4-tetrahydrofuran (47). To a solution of alcohol **46** (0.010 g, 0.02 mmol) and 2,6-lutidine (0.04 mL, 0.34 mmol) in 1.0 mL of CH_2Cl_2 in a 10-mL round-bottomed flask at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.05 mL, 0.22 mmol). The mixture was stirred for 30 min at 0 °C and then quenched with water and extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated to give a colorless liquid. Purification by silica gel flash column chromatography (hexanes–EtOAc, 9:1) gave tetrahydrofuran **47** (0.013 g, 100%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ –0.02 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.85 (s, 9 H, $C(CH_3)_3$), 0.91 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 0.93 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 1.0–2.0 (m, 9 H, CH_2 and CH), 2.35 (m, 1 H, CH), 3.28 (m, 2 H, OCH_2), 3.32 (s, 3 H, OCH_3), 3.46 (m, 2 H, OCH_2), 3.78 (s, 3 H, OCH_3), 4.12 (t, 1 H, J = 6.2 Hz, OCH), 4.45 (s, 2 H, OCH_2Ar), 4.47 (s, 2 H, OCH_2Ar), 4.65 (s, 2 H, OCH_2O), 4.96 (dd, 1 H, J = 4.8, 3.2 Hz, OCHMe), 6.85 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.24 (d, 2 H, J = 8.7 Hz, p-MeO-aryl), 7.30 (m, 5 H, phenyl); ^{13}C NMR (125

MHz, $CDCl_3$) δ -4.1, -3.8, 11.2, 18.5, 19.4, 26.3, 32.2, 33.3, 34.9, 37.5, 38.3, 39.4, 55.1, 55.7, 67.7, 69.3, 71.3, 72.7, 73.3, 80.5, 94.9, 104.2, 114.2, 127.9, 128.7, 130.0, 130.4, 138.9, 159.6; $[\alpha]_D$ +25.2° (c 1.10, $CHCl_3$); HRMS calcd for $C_{32}H_{49}O_7Si$ (M - t-Bu) m/z 573.3248, found m/z 573.3232.

(2*S*,3*R*)-2-[(1*R*,2*R*)-4-(Benzyloxy)-2-[(*tert*-butyldimethylsilyl)oxy]-1-methylbutyl]-3-[(2*R*)-3-hydroxy-2-methylpropyl]-5-methoxy-1,2,3,4-tetrahydrofuran (48). To a solution of ether **47** (0.005 g, 0.01 mmol) in 0.5 mL of CH_2Cl_2 in a 2-mL round-bottomed flask at 0 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.003 g, 0.01 mmol).[12] The resulting yellow-green solution was stirred 20 h at 0 °C and then was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated to give a yellow oil. Purification by silica gel flash column chromatography (hexanes–EtOAc, 8:2) gave recovered ether **47** (0.001 g, 20%) and tetrahydrofuran **48** (0.002 g, 42%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.85 (s, 9 H, $C(CH_3)_3$), 0.88 (d, 3 H, J = 6.8 Hz, $CHCH_3$), 0.94 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 1.23 (s, 1 H, OH), 1.4–2.0 (m, 8 H, CH_2 and CH), 2.25 (m, 1 H, CH), 3.32 (s, 3 H, OCH_3), 3.35 (m, 2 H, $BnOCH_2$), 3.47 (dd, 2 H, J = 6.2, 6.1 Hz, $HOCH_2$), 3.83 (ddd, 1 H, J = 6.6, 6.4, 2.0 Hz, OCH), 4.00 (dd, 1 H, J = 7.8, 5.4 Hz, OCH), 4.47 (s, 2 H, OCH_2Ar), 4.97 (dd, 1 H, J = 5.3, 3.5 Hz, $CHOCH_3$), 7.31 (m, 5 H, phenyl); IR (neat) ν 3479 (m), 2930 (s), 2857 (s), 1462 (m), 1361 (m), 1252 (m), 1098 (s), 1040 (s), 985 (m), 869 (w), 836 (m), 774 (m), 698 (w) cm^{-1}; $[\alpha]_D$ +38.0° (c 0.20, $CHCl_3$); HRMS calcd for $C_{26}H_{45}O_4Si$ (M - OCH_3) m/z 449.3087, found m/z 449.3072. The infrared spectrum, rotation, and ^1H NMR spectrum were virtually identical to those of material prepared by K. C. Nicolaou.

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Supplementary Material Available: Experimental procedures for **27–37** and selected ^1H NMR spectra (49 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Kinetics and Equilibria of Thiol/Disulfide Interchange Reactions of Selected Biological Thiols and Related Molecules with Oxidized Glutathione

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Rate constants for reaction of coenzyme A and cysteine with oxidized glutathione (GSSG) and equilibrium constants for the reaction of coenzyme A; cysteine, homocysteine, cysteamine, and related thiols with GSSG by thiol/disulfide interchange were determined over a range of pD values by NMR spectroscopy. The rate constants for reaction of the thiolate anion forms of coenzyme A and cysteine with GSSG suggest that reduction of GSSG by coenzyme A and cysteine is a mechanistically uncomplicated S_N2 reaction. Equilibrium constants for the thiol/disulfide interchange reactions show a strong dependence on the Bronsted basicity of the thiolate anion. In a similar way, $\Delta E^{\circ\prime}$, the difference between the half-cell potentials for the RSSR/RSH and GSSG/GSH redox couples, is linearly dependent on the difference between the pK_A values of RSH and glutathione: $\Delta E^{\circ\prime} = 64\Delta pK_A - 7.7$ where $\Delta E^{\circ\prime}$ is in units of mV. The reducing strength at a given pH is also determined by the fraction of the thiol present in the reactive thiolate form. At pD 7, the half-cell potentials for coenzyme A, cysteine, homocysteine, and cysteamine are close to that of glutathione, the major intracellular thiol redox system, which suggests that small changes in the intracellular redox potential can cause significant changes in the intracellular distribution of these biological thiols between their reduced and oxidized forms.

Introduction

Thiol/disulfide interchange reactions are important in maintaining the intracellular distribution of glutathione, coenzyme A, cysteine, and other thiols among their reduced and oxidized forms.[1] Glutathione is the most abundant nonprotein thiol in most cells, and the glutathione/oxidized glutathione (GSH/GSSG) pair forms the major intracellular thiol redox system.[2] The concentration of GSH in cells ranges between 0.5 and 10 mM,[3] and in most cells it is maintained largely in the form of free GSH by the activity of GSSG reductase (E.C. 1.6.4.2).[2,4] Glutathione participates in maintenance of the thiol/disulfide distribution of other thiol-containing molecules by reduction of symmetrical and mixed disulfides by GSH and oxidation of thiols by GSSG via thiol/disulfide interchange.

Thiol/disulfide interchange (eqs 1 and 2) takes place spontaneously and may also be catalyzed by thiol transferase (E.C. 2.5.1.18).[2] The distribution of intracellular

$$RSH + R'SSR' \rightleftharpoons RSSR' + R'SH \quad (1)$$

$$RSH + RSSR' \rightleftharpoons RSSR + R'SH \quad (2)$$

thiols among their thiol, disulfide, and mixed disulfide forms will depend on their half-cell potentials at the intracellular pH, the dynamics of their thiol/disulfide interchange reactions with GSH and GSSG, and the intra-

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