been identified as being chiral, it can be used to seed a second crystallization of the racemic solution. This well-known procedure, termed resolution by entrainment, can lead to a complete or partial separation of enantiomers.[43,47]

Conclusion

A comparison of densities of 65 chiral/racemic pairs culled from the Cambridge Structural Database has shown that the racemic crystals are, on average, ca. 1% more tightly packed than their chiral counterparts (although for many individual pairs the racemic crystal has the lower density). A corresponding comparison of densities for 64 polymorphic pairs (i.e., pairs of structures containing molecules or ions that are achiral or enantiomers that interconvert rapidly in solution) shows no significant difference in packing density between the racemic and chiral members. Wallach's 1895 rule seems to be substantiated, but only for resolvable enantiomers.

The key to this difference is the recognition that any such comparison of chiral/racemic pairs will be affected by bias if the enantiomers are resolvable. Pairs for which the racemic crystal is more stable than its chiral counterpart will be included in the comparison, but pairs for which the racemic crystal is markedly less stable will be excluded, the racemic crystal being then unobtainable. Because of this bias, *any* comparison of corresponding chiral/racemic pairs will suggest that racemic crystals are the more stable. This is the case, for example, for the 36 pairs of racemic and chiral crystals for which thermodynamic data concerning melting behavior were collected by Jacques, Collet, and Wilen.[7] A theoretical argument has been advanced by these authors for the greater stability of racemic crystals in general.[28] This argument, however, is invalid since it rests on an erroneous assumption, namely that the entropy of a racemic crystal is systematically larger than that of a chiral crystal by $R \ln 2$ because of the mixing of the enantiomers. This assumption contradicts the third law of thermodynamics, which states that all ordered crystals have zero entropy at 0 K.

In estimating the relative thermodynamic stabilities, the direct comparison of the melting points of the chiral and racemic crystals can be misleading because the two solids are not in equilibrium with the same liquid phase. It is more informative to compare the melting point of the racemic crystal with the melting point of the 1:1 conglomerate, i.e., the eutectic temperature of the mixture of enantiomeric chiral crystals. If one of the enantiomers is not available, the eutectic temperature can be estimated from the melting point and heat of fusion of the other.

Although much of the evidence for the apparent greater density and thermodynamic stability of racemic crystals relative to their chiral counterparts is undermined by the presence of the aforementioned bias, there is probably also a genuine intrinsic difference in their relative stabilities. About 90% of the compounds that can crystallize in either racemic or chiral space groups prefer the former. This preference need not be a result of special kinds of interactions between opposite enantiomers; rather, it can be attributed to the additional possibilities for favorable packing arrangements available in racemic space groups.

The evidence collected here adds some support to the general correlation between the densities and packing energies of polymorphic crystals.

There is also a kinetic factor that could be important during crystallization from a racemic solution or melt. The presence of the "wrong" enantiomer is likely to inhibit the formation of viable nuclei of the chiral crystal but not of the racemic one and might also act as a "tailor-made" impurity in the subsequent growth phase of the chiral crystal.

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Supplementary Material Available: Line drawings and literature references for structures included in the final tabulation (37 pages). Ordering information is given on any current masthead page.

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Stealth Stereocontrol: Stereochemical Reversal of a Michael Addition Reaction

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Abstract: The nitroalkene, methyl 5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-6-(phenylthio)-β-D-ribo-hex-5(*Z*)-enofuranoside (**1**), was found to react with nucleophiles to give, on ozonolysis, the corresponding phenyl thiolesters **3**, **5**, **6a–c**, and **7** bearing the nucleophilic residue α to the carbonyl group. The nucleophiles Me_3SiOK, NaOMe, $NaOCH_2Ph$, and TsNHK all stereoselectively (7:1–50:1) reacted to give products with the *allo*-thiouronate configuration. In contrast, potassium succinimide and phthalimide, nucleophiles with aerofoil bulk, gave substituted *talo*-thiouronates (>15:1).

The addition reactions of nucleophiles to 1-nitro-1-(phenylthio)alkenes, followed by ozonolysis of the intermediate nitronates, represent a convenient method for the synthesis of α-substituted phenyl thiolesters.[1] This chemistry is useful for the preparation of acyclic systems,[2] bicyclic β-lactams,[3] and tetrahydrofuran and tetrahydropyran derivatives.[4] Recently we had occasion to employ this methodology in the total synthesis of polyoxin C and related

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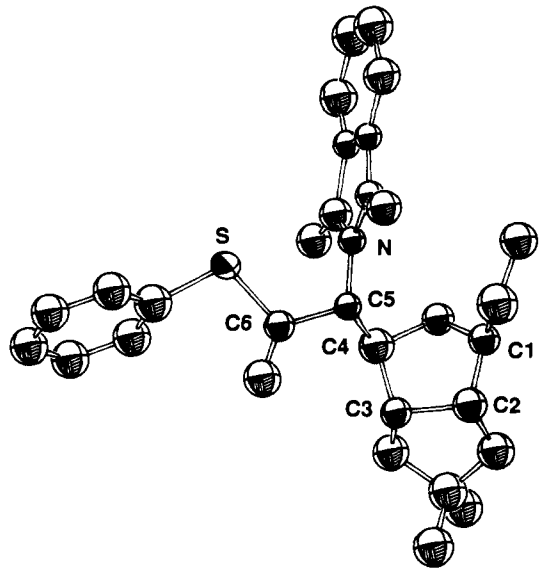
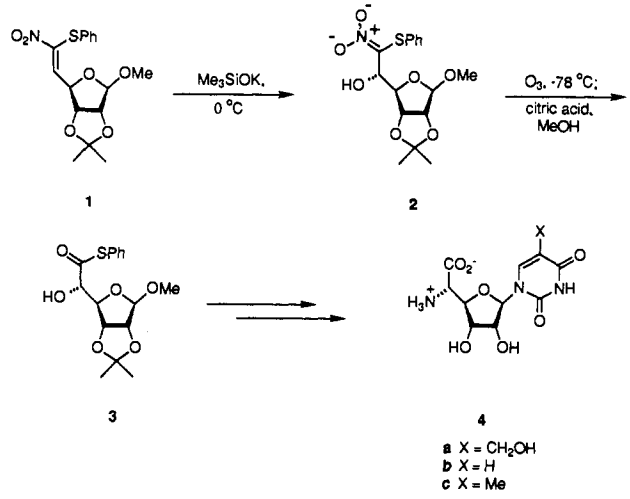


Figure 1. ORTEP of phenyl (methyl 2,3-*O*-isopropylidene-5-phthalimido-5-deoxy-β-D-allofuranoside)thiouronate (**5**) drawn at the 50% probability level.

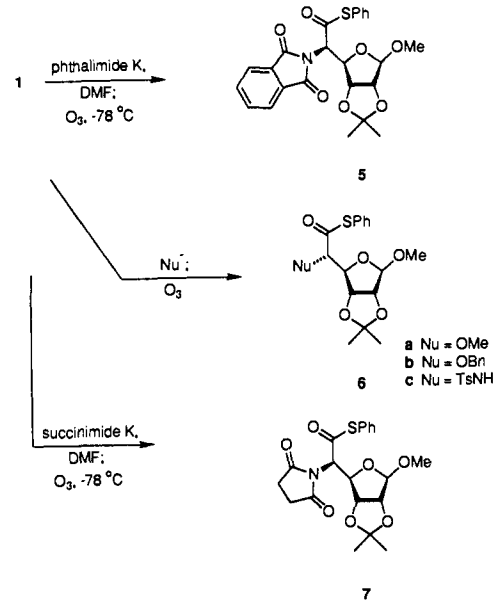
Scheme I



nucleosides.[5] A key step in the synthesis was the highly stereoselective (>50:1) Michael addition of potassium trimethylsilanolate to the nitroalkene **1**. Ozonolysis of the intermediate nitronate **2**, without isolation, and workup with desilylation gave only the *allo* adduct **3**. This in turn was converted into polyoxin C (**4a**), uracil polyoxin C (**4b**), and thymine polyoxin C (**4c**) (Scheme I). Herein we report further observations on the additions of nucleophiles to the nitroalkene **1**. These results clearly demonstrate a most unusual reversal of stereochemistry with nucleophiles that are aerofoil in shape. These results are presented in a chronological order since this will underscore the dangers and treachery of stereochemical assignments by analogy.

The nitroalkene **1** was readily prepared from D-ribose using the methods recently described.[5] Potassium phthalimide in DMF solution was found to smoothly add to **1** to provide, on ozonolysis,

Scheme II



Scheme III

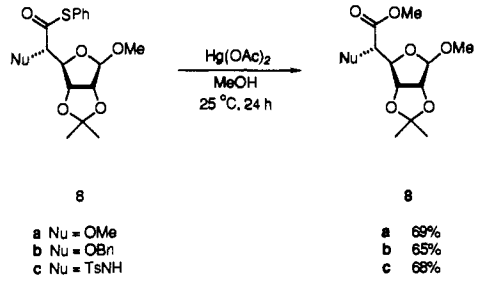


Table I. Michael Addition Reactions of Nitroalkene **1**[a]

nucleophile	temp (°C)	time (min)	yield (%)	isomeric ratio[b]	C-5 config[c]	product
Me_3SiOK	10	30	94	>50:1	*S*	**3**
K phthalimide	25	240	83	15:1	*R*	**5**
NaOMe	25	30	39	7:1	*S*	**6a**
NaOBn	25	90	62	10:1	*S*	**6b**
p-TsNHK	25	25	41	>15:1	*S*	**6c**
K succinimide	25	25	75	>15:1	*R*	**7**

[a] Addition reactions were performed with the conditions shown in the table, using DMF as the solvent. The crude reaction mixtures were diluted with either MeOH or CH_2Cl_2, cooled to −78 °C, and ozonolyzed. [b] Determined by ^1H NMR. [c] C-5 configuration of the major isomer.

the protected amino acid **5**. Much to our delight this substance was formed both in good yield (83%) and with excellent diastereoselectivity (15:1). The structure of the major diastereoisomer was determined by X-ray crystallography, and the stereochemistry of the C-5 center was shown unequivocally to be *R*. The ORTEP plot of this substance is shown in Figure 1.[6] We considered, on the basis of this result, that the addition of an oxygen-centered nucleophile to the nitroalkene **1** should provide an intermediate useful for the synthesis of the polyoxins **4a–c**. Thus, potassium trimethylsilanolate was allowed to add to the nitroalkene **1** in DMF solution. Ozonolysis and workup with methanolic citric acid gave a single α-hydroxy thiolester (94%). By analogy with the phthalimide derivative **5**, this substance was assumed to have the C-5(*R*) configuration. Unfortunately this assumption proved to be incorrect, becoming apparent when the α-hydroxy thiolester was converted into the C-5 epimers of both polyoxin C (**4a**) and uracil polyoxin C (**4b**).[7] At this point the α-hydroxy thiolester

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(6) Details of the crystal structure for **5** will be published elsewhere; Sabat, M. Unpublished observations.

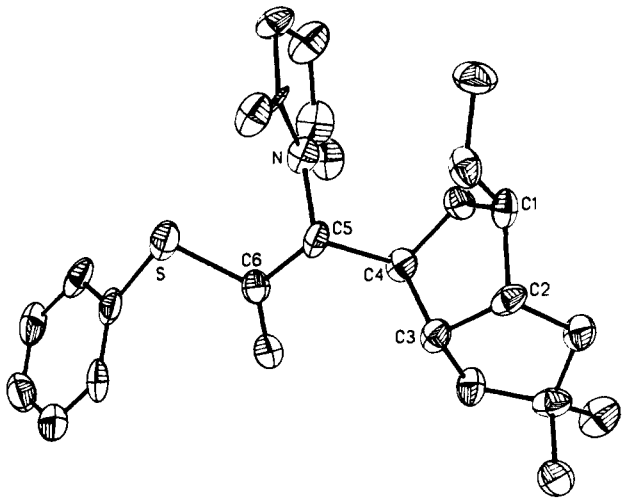
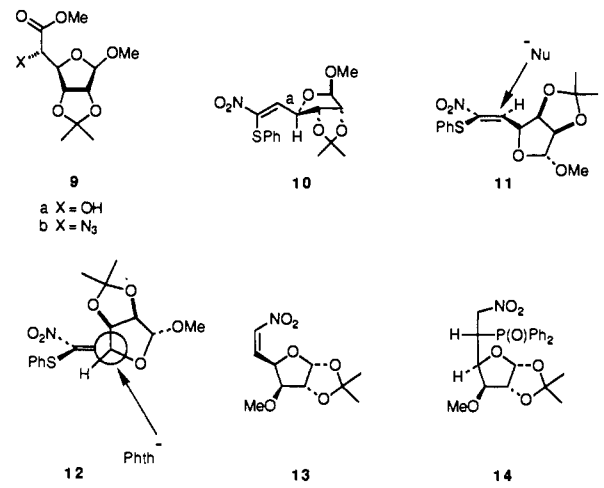


Figure 2. Thermal ellipsoid plot of phenyl (methyl 2,3-*O*-isopropylidene-5-succinimido-5-deoxy-β-D-allofuranoside)thiouronate (7). The thermal ellipsoids are drawn at the 50% probability level.

was shown to indeed have the C-5(*S*) stereochemistry (**6**) by correlation with D-allose.[5] Curiously, the nitroalkene **1** showed completely opposite stereochemical bias on the addition of two different nucleophiles. To be absolutely positive that indeed the structural assignments for **3** and **5** were secure, the very crystal used for the X-ray structural determination of **5** was rechecked by ^{1}H NMR spectroscopy. The material was indeed the major isomer.

The addition of a series of nucleophiles to the nitroalkene **1** were examined, and the results are summarized in Scheme II and Table I. All of the nucleophiles examined provided substituted phenyl thiolesters with good to excellent diastereoselectivities. The determination of the configuration of the major diastereoisomer was accomplished either by conversion to known compounds or by solution of single-crystal X-ray data. Products **6a–c** were cleanly converted into the methyl esters **8a–c** using methanolic mercuric acetate (Scheme III).[8] The configuration of ether **8a** was determined to be C-5(*S*) by comparison with authentic material prepared via the methylation of the known α-hydroxy methyl ester **9a**[5] using a vast excess of diazomethane solution in the presence of silica gel as catalyst.[9] Compound **8b** was debenzylated by catalytic hydrogenolysis over palladium black to afford **9a** (89%). Determination of the configuration of **8c** was accomplished by reduction of the known azide **9b**[5] by hydrogenation over palladium and subsequent toluene-4-sulfonylation to give an authentic sample of **8c** (71%). Finally an X-ray crystallographic structural study of the major succinimide adduct established its structure as the C-5(*R*) isomer (Figure 2).[10] It is clear from these results that both succinimide and phthalimide showed opposite stereochemical bias to alkoxide nucleophiles and toluene-4-sulfonamide.

The origin of stereocontrol in these curious reactions requires further comment. In the *Z*-nitroalkene **1**, the eclipsed conformation **10** is strongly favored due to the avoidance of 1,3-allylic strain.[11] However, partial rotation (~30°) about bond a allows the system to adopt conformation **11** in which the electronegative oxygen atom is coplanar with the π-system. This conformation meets the stereoelectronic requirements for antiperiplanar addition of the nucleophile, with the result of a high (7:1 to >50:1) 5(*S*) stereochemical bias in the reactions. However, such an analysis is not appropriate for the phthalimide nor for the succinimide nucleophiles. Examination of molecular models of **11** showed that the addition of phthalimide or succinimide anion would be disfavored due to steric congestion between one of the carbonyl groups and the C-3 oxygen substituent. In contrast, addition to the higher energy conformation **12**, which is derived from **10** by partial rotation (~30°) in the opposite direction, should not suffer from such congestion. It is nonetheless remarkable that the nitroalkene **1** underwent highly stereoselective nucleophilic addition reactions with complete reversal of relative asymmetric induction. We term the effect of the wingtip carbonyls on the reaction as stealth stereocontrol. The nucleophilic addition of potassium phthalimide to **1** closely follows the stereocontrol outcome of the addition of several nucleophiles to the simple *Z*-nitroalkene **13**. For example, Yamashita et al.[12] have shown that Ph_2POH reacted with **13** to give predominantly the 5(*S*) isomer **14** (ds 11:1).



It is clear from these results that the stereochemistry of the Michael addition of simple nucleophiles with the nitroalkene **1** can vary greatly. Undoubtedly the addition of all nucleophiles is controlled by the minimization of 1,3-allylic strain. Most nucleophiles undergo Felkin–Anh addition via a transition state with the allylic carbon–oxygen bond coplanar with the π-system. However, minimization of long-range steric congestion in the addition of aerofoil bulky nucleophiles can overwhelm such a stereoelectronic preference. Recently Reetz has observed a similar reversal of diastereoselectivity,[13] and the phenomenon is probably common.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry N_2 at room temperature in oven-dried glassware unless otherwise noted. Reaction temperatures were recorded as bath temperatures. The preparations of compounds **1**, **3**, **9a**, and **9b** have been previously published.[5] Transesterification of phenyl thiolesters **6a–c** was accomplished using the published procedure[5,8] with a reaction time of 24 h to provide the corresponding methyl esters **8a–c**. DMF was dried by distillation at reduced pressure from BaO or P_2O_5. Anhydrous CH_2Cl_2, *iso*-Pr_2NEt, and pyridine were dried by distillation from CaH_2. All other chemicals were used without further purification unless otherwise noted. All organic extracts were dried with either $MgSO_4$ or Na_2SO_4 and evaporated in vacuo on a rotary evaporator at or below 40 °C. Column chromatography was performed on E. Merck silica gel 60, 230–400 mesh, using distilled solvents.

Mass spectra were recorded on either a VG70-250SE mass spectrometer by the Analytical Services Laboratory, Northwestern University, or on a Hewlett-Packard 5890GC-5970MS. Elemental analyses were determined by G. D. Searle and Company, Skokie, IL.

Phenyl (Methyl 2,3-*O*-isopropylidene-5-phthalimido-5-deoxy-β-D-allofuranoside)thiouronate (5). To the nitroalkene **1** (0.50 g, 1.4 mmol) in DMF (10 mL) was added potassium phthalimide (0.311 g, 1.7 mmol). After 20 min, the solution was cooled to −78 °C and diluted with MeOH (50 mL). Ozone was bubbled through the solution until a colorless end point was reached. The solution was allowed to warm to room temper-

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ature, poured into H_2O (100 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (eluant, 4:1 hexanes/EtOAc) to give **5** (0.55 g, 83%) as a 15:1 (5(*R*):5(*S*)) mixture of isomers as a white solid. Recrystallization (Et_2O/hexanes) gave diastereomerically pure **5** as white crystals: mp 82–83 °C; $[\alpha]_D$ −12.5° (*c* 0.16 in $CHCl_3$); IR (KBr) 1783, 1725, 1384, 1112, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.0–7.8 (m, 4 H), 7.38 (m, 5 H), 5.29 (d, 1 H, *J* = 10.8 Hz), 5.08 (d, 1 H, *J* = 6 Hz), 5.07 (d, 1 H, *J* = 10.4 Hz), 4.89 (s, 1 H), 4.65 (d, 1 H, *J* = 6.4 Hz), 3.09 (s, 3 H), 1.50 (s, 3 H), 1.32 (s, 3 H) (the minor isomer in the crude product showed, inter alia, a signal at δ 4.54 (d, *J* = 6.4 Hz) and this peak was used in the estimation of diastereoselectivity); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 167.6, 134.6, 134.4, 131.6, 129.6, 129.1, 125.7, 123.7, 112.6, 110.1, 84.8, 83.9, 82.2, 60.9, 56.1, 26.4, 25.7; MS (EI) *m/e* 454 (M − Me^+), 438, 394, 360, 274, 242, 214, 186. Anal. Calcd for $C_{24}H_{23}NO_7S$: C, 61.40; H, 4.94; N, 2.98. Found: C, 61.75; H, 5.04; N, 2.81.

Phenyl (Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-allofuranoside)thiouronate (6a). To a solution of NaOMe (0.91 M in MeOH; 0.39 mL, 0.35 mmol) in DMF (2 mL) was added a solution of the nitroalkene **1** (0.101 g, 0.29 mmol) in DMF (1.5 mL). After 30 min, the solution was cooled to −78 °C and diluted with MeOH (2 mL). Ozone was bubbled through the solution until no further color change was observable. The mixture was allowed to warm to room temperature, poured into H_2O (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (eluant, 3:1 hexanes/EtOAc) to give **6a** (41 mg, 39%) as a 7:1 (5(*S*):5(*R*)) mixture of isomers as a colorless oil. Recrystallization from CH_2Cl_2 gave diastereoisomerically pure **6a**: mp 46–51 °C; $[\alpha]_D$ −133.1° (*c* 0.152 in $CHCl_3$); IR (KBr) 3620–3120, 2992, 2915, 1705, 1110, 1090, 1056, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5 H), 5.00 (s, 1 H), 4.85 (dd, 1 H, *J* = 6.0, 1.0 Hz), 4.61 (d, 1 H, *J* = 6.0 Hz), 4.39 (dd, 1 H, *J* = 8.5, 1.0 Hz), 3.78 (d, 1 H, *J* = 8.5 Hz), 3.56 (s, 3 H), 3.38 (s, 3 H), 1.50 (s, 3 H), 1.34 (s, 3 H) (the minor isomer in the crude product showed, inter alia, a signal at δ 3.86 (d, *J* = 8.5 Hz), and this peak was used in the estimation of diastereoselectivity); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 134.8, 129.6, 129.4, 129.2, 127.0, 112.7, 110.2, 87.0, 86.8, 85.0, 81.9, 59.4, 55.9, 26.6, 25.1; MS (EI) *m/e* 354 (M^+) 339, 326, 295, 245, 217, 185, 173, 153, 113. Anal. Calcd for $C_{17}H_{22}O_6S$: C, 57.61; H, 6.26; S, 9.05. Found: C, 57.29; H, 6.42; S, 8.86.

Phenyl (Methyl 2,3-*O*-isopropylidene-5-*O*-(phenylmethyl)-β-D-allofuranoside)thiouronate (6b). To a solution of $NaOCH_2Ph$ (1.0 M in $PhCH_2OH$; 0.34 mL) in DMF (2 mL) was added a solution of the nitroalkene **1** (0.10 g, 0.28 mmol) in DMF (1.5 mL). After 90 min, the solution was cooled to −78 °C and diluted with MeOH (2 mL). Ozone was bubbled through the solution until the solution became pale yellow in color. The mixture was allowed to warm to room temperature, poured into H_2O (10 mL), and extracted with Et_2O (1 × 10 mL, 2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (eluant, 4:1 hexanes/EtOAc) to give **6b** (66mg, 62%) as a 10:1 (5(*S*):5(*R*)) mixture of isomers as a colorless oil. Recrystallization from hexane afforded diastereoisomerically pure **6b** as a white solid: mp 72–73 °C; $[\alpha]_D$ −98.3° (*c* 0.36 in $CHCl_3$); IR (neat) 3063, 2989, 2937, 1704, 1455, 1210, 1107, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.31 (m, 10 H), 4.98 (s, 1 H), 4.85 (d, 1 H, *J* = 11 Hz), 4.80 (d, 1 H, *J* = 6 Hz), 4.56 (d, 1 H, *J* = 11 Hz), 4.54 (d, 1 H, *J* = 6 Hz), 4.48 (d, 1 H, *J* = 8 Hz), 4.01 (d, 1 H, *J* = 8 Hz), 3.38 (s, 3 H), 1.48 (s, 3 H), 1.31 (s, 3 H) (the minor isomer in the crude product showed, inter alia, a signal at δ 4.11 (d, *J* = 8.0 Hz) and this peak was used in the estimation of diastereoselectivity); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 136.6, 134.8, 129.4, 129.2, 128.5, 128.3, 128.2, 127.0, 112.6, 110.4, 86.7, 85.5, 85.1, 81.9, 73.6, 55.9, 26.6, 25.2; MS (EI) *m/e* 321 (M − SPh^+), 293, 200, 109, 91, 43. Anal. Calcd for $C_{23}H_{26}O_6S$: C, 64.17; H, 6.09; S, 7.45. Found: C, 63.98; H, 6.20; S, 7.53.

Phenyl [Methyl 2,3-*O*-isopropylidene-5-(toluene-4-sulfonamido)-5-deoxy-β-D-allofuranoside]thiouronate (6c). To a mixture of *p*-$TsNH_2$ (0.155 g, 0.91 mmol) and *t*-BuOK (0.120 g, 1.1 mmol) in DMF (5 mL) stirred for 25 min was added a solution of the nitroalkene **1** (0.250 g, 0.71 mmol) in DMF (2.5 mL). After 25 min, the solution was cooled to −78 °C and diluted with CH_2Cl_2 (25 mL). Ozone was bubbled through the solution until a colorless end point was reached (Sudan Red 7B used as an internal indicator[14]), and the reaction mixture was purged of excess ozone with a stream of N_2, poured into 4:1 H_2O/brine (25 mL), and extracted with CH_2Cl_2 (3 × 25 mL) and EtOAc (25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (eluant, 2:2:1 hexanes/CH_2Cl_2/Et_2O) to give diastereoisomerically pure **6c** (0.143 g, 41%) as a white solid: mp 189–190 °C (EtOAc/hexanes); $[\alpha]_D$ −43.0° (*c* 0.068 in $CHCl_3$); IR (KBr) 3410, 3278, 2980, 2914, 1685, 1334, 1161, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 2 H, *J* = 8.2 Hz), 7.33–7.40 (m, 5 H), 7.08 (m, 2 H), 5.44 (d, 1 H, *J* = 8.8 Hz), 5.05 (dd, 1 H, *J* = 5.9, 1.0 Hz), 5.01 (s, 1 H), 4.62 (d, 1 H, *J* = 5.9 Hz), 4.18 (m, 2 H), 3.49 (s, 3 H), 2.45 (s, 3 H), 1.45 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 144.1, 136.8, 134.1, 129.9, 129.8, 129.2, 127.6, 126.3, 112.7, 111.1, 87.2, 84.7, 81.4, 63.4, 57.1, 26.5, 25.0, 21.6; MS (CI, NH_3) *m/e* 511 (M + NH_4^+), 479, 462, 356, 326, 189, 126. Anal. Calcd for $C_{23}H_{27}NO_7S_2$: C, 55.97; H, 5.51; N, 2.84; S, 12.99. Found: C, 55.63; H, 5.56; N, 2.83; S, 12.85.

Phenyl (Methyl 2,3-*O*-isopropylidene-5-succinimido-5-deoxy-β-D-allofuranoside)thiouronate (7). A mixture of succinimide (73 mg, 0.74 mmol) and *t*-BuOK (95 mg, 0.85 mmol) in DMF (2.5 mL) was stirred for 20 min and added to a solution of the nitroalkene **1** (0.20 g, 0.57 mmol) in DMF (2.5 mL). After 25 min, the mixture was cooled to −78 °C and diluted with CH_2Cl_2 (20 mL). Ozone was bubbled through the mixture until a colorless end point was reached (Sudan Red 7B used as indicator[14]). The reaction mixture was purged of excess ozone with a stream of N_2, poured into 4:1 H_2O/brine (30 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica (eluant, 5:3:2 CH_2Cl_2/hexanes/Et_2O) to give **7** (0.179 g, 75%) as a white solid. Recrystallization (EtOAc/hexane) gave diastereoisomerically pure **7** (0.116 g) as white crystals: mp 154–155 °C; $[\alpha]_D$ −15.4° (*c* 0.078 in $CHCl_3$); IR (KBr) 2993, 2916, 1710, 1386, 1172, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.34 (m, 5 H), 5.18 (dd, 1 H, *J* = 10.6, 1.2 Hz), 4.97 (dd, 1 H, *J* = 6.0, 1.2 Hz), 4.93 (d, 1 H, *J* = 10.6 Hz), 4.91 (s, 1 H), 4.61 (d, 1 H, *J* = 6.0 Hz), 3.21 (s, 3 H), 2.83–2.95 (m, 4 H), 1.47 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 175.9, 134.9, 129.8, 129.3, 125.4, 112.7, 110.1, 84.7, 83.5, 81.9, 61.3, 56.1, 28.3, 26.4, 25.0; MS (CI, NH_3) *m/e* 439 (M + NH_4^+), 407, 390, 362, 312, 293, 271, 254, 215, 187, 126, 94. Anal. Calcd for $C_{20}H_{23}NO_7S$: C, 57.00; H, 5.50; N, 3.32; S, 7.61. Found: C, 56.77; H, 5.61; N, 3.27; S, 7.76.

Methyl (Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-allofuranosid)uronate (8a). Mercuric acetate mediated transesterification of **6a** in MeOH solution[5] and chromatography on silica (eluant, 4:1 hexanes/EtOAc) gave **8a** (18mg, 68%) as a colorless oil: $[\alpha]_D$ −75.1° (*c* 0.43 in $CHCl_3$); IR (neat) 2973, 1740, 1460, 1376, 1228, 1128, 1039, 986, 965, 902, 833 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.96 (s, 1 H), 4.81 (dd, 1 H, *J* = 6, 1 Hz), 4.58 (d, 1 H, *J* = 6 Hz), 4.34 (dd, 1 H, *J* = 9, 1 Hz), 3.81 (s, 3 H), 3.73 (d, 1 H, *J* = 9 Hz), 3.40 (s, 3 H), 3.34 (s, 3 H), 1.47 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.8, 112.7, 110.2, 86.5, 85.3, 82.1, 82.0, 58.3, 55.5, 51.9, 26.6, 25.3; MS (EI) *m/e* 276 (M^+) 261, 245, 217, 173, 113, 99, 59, 45, 43. Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found: C, 51.82; H, 7.32.

Methyl (Methyl 2,3-*O*-isopropylidene-5-*O*-(phenylmethyl)-β-D-allofuranosid)uronate (8b). Mercuric acetate mediated transesterification of **6b** in MeOH solution[5] and chromatography on silica (eluant, 3:1 hexanes/EtOAc) gave **8b** (58 mg, 61%) as a white solid: 66–67 °C (Et_2O/hexane); $[\alpha]_D$ −68.8° (*c* 0.46 in $CHCl_3$); IR (neat) 2937, 1747, 1455, 1373, 1272, 1238, 1200, 1161, 1095, 1016, 870, 741 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.43–7.25 (m, 5 H), 4.94 (s, 1 H), 4.77 (d, 1 H, *J* = 6.0 Hz), 4.62, 4.48 (AB q, 2 H, *J* = 11.6 Hz), 4.52 (d, 1 H, *J* = 6.0 Hz), 4.42 (d, 1 H, *J* = 8.9 Hz), 3.92 (d, 1 H, *J* = 8.9 Hz), 3.75 (s, 3 H), 3.32 (s, 3 H), 1.46 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.9, 137.1, 128.4, 128.1, 128.0, 112.6, 110.3, 86.5, 85.3, 81.9, 79.8, 72.9, 55.5, 51.8, 26.6, 25.3; MS (EI) *m/e* 352 (M^+), 337, 305, 261, 246, 214, 173, 113, 91, 43. Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.26; H, 7.00.

Methyl (Methyl 2,3-*O*-isopropylidene-5-(toluene-4-sulfonamido)-5-deoxy-β-D-allofuranosid)uronate (8c). Mercuric acetate mediated transesterification of **6c** in MeOH solution[5] and chromatography on silica (eluant, 3:1 hexanes/EtOAc) gave **8c** (10 mg, 68%) as a white solid: mp 119–120 °C; $[\alpha]_D$ +16.0° (*c* 0.60 in $CHCl_3$); IR (neat) 3259, 2937, 1745, 1598, 1567, 1446, 1374, 1345, 1202, 1164, 1092, 981, 868, 816, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.72 (d, 2 H, *J* = 8.2 Hz), 7.31 (d, 2 H, *J* = 8.2 Hz), 5.25 (dd, 1 H, *J* = 9.9, 4.0 Hz), 4.94 (s, 1 H), 4.93 (d, 1 H, *J* = 4.5 Hz), 4.56 (d, 1 H, *J* = 6.0 Hz), 4.17 (d, 1 H, *J* = 9.1 Hz), 3.97 (t, 1 H, *J* = 9.5 Hz), 3.44 (s, 3 H), 3.30 (s, 3 H), 2.42 (s, 3 H), 1.45 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.1, 143.8, 129.6, 127.5, 117.9, 112.8, 110.8, 87.6, 85.0, 81.6, 58.3, 55.9, 52.2, 26.5, 25.1, 21.4; MS (EI) *m/e* 400 (M − Me^+), 384, 356, 260, 173, 155, 91. Anal. Calcd for $C_{18}H_{25}NO_8S$: C, 52.04; H, 6.07; N, 3.37. Found: C, 51.99; H, 6.04; N, 3.25.

Preparation of Methyl (Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-allofuranosid)uronate (8a) from Alcohol 9a. To a solution of the alcohol **9a** (28 mg, 0.11 mmol) in Et_2O (1 mL) at 0 °C was added silica

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gel (0.1 g) followed by diazomethane in Et_2O[15] (2.6 M, 1 mL). After the solution was stirred for 1 h, silica gel (0.1 g) followed by diazomethane in Et_2O (2.6 M, 1 mL) was added. The mixture was maintained at 0 °C for 1 h and allowed to warm up to room temperature overnight. The silica gel was removed by filtration and washed with Et_2O (5 × 1 mL). The combined eluants were evaporated, and the residue was chromatographed on silica gel (eluant, 3:1 hexanes/EtOAc) to give **8a** (24 mg, 82%) as a colorless oil, which was identical by ^1H NMR and TLC with the major isomer reported above.

Preparation of Methyl (Methyl 2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (9a) from Benzyl Ether 8b. To a solution of the benzyl ether **8b** (22 mg, 0.062 mmol) in MeOH (4 mL) was added palladium black (5 mg), and H_2 (ca. 1 L) was bubbled through the rapidly stirred mixture over 5 min. A static source of H_2 was attached and the mixture was allowed to stir for 48 h. The catalyst was removed by filtration through Celite, washed with MeOH (2 × 1 mL), and the solution evaporated. The residue was chromatographed on silica (eluant, 3:1 hexanes/EtOAc) to give **9a** (16 mg, 89%) as a colorless oil, which was identical by ^1H NMR and TLC with an authentic sample of **9a**.[5]

Preparation of Methyl (Methyl 2,3-*O*-isopropylidene-5-(toluene-4-sulfonamido)-5-deoxy-β-D-allofuranosid)uronate (8c) from Azide 9b. To a solution of the azide **9b**[5] (17 mg, 0.059 mmol) in MeOH (2 mL) was added palladium black (4 mg), and H_2 (ca. 1 L) was passed through the rapidly stirred mixture over 5 min. A static source of H_2 was attached and the mixture was stirred for 30 min. The catalyst was removed by filtration through Celite, washed with MeOH (5 × 1 mL), and the solution evaporated. To the residue (16 mg) in CH_2Cl_2 (2 mL) at 0 °C was added *p*-TsCl (69 mg, 0.36 mmol), *iso*-Pr_2NEt (24 μL, 0.14 mmol), and DMAP (2 mg, 0.02 mmol). The reaction mixture was maintained at 0 °C for 4 h, poured into H_2O (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (eluant, 3:1 hexanes/EtOAc) to give **8c** (17 mg, 71%) as a white solid, which was identical by ^1H NMR and TLC with the major isomer reported above.

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Registry No. 1, 127646-30-4; (*R*)-**5**, 137232-68-9; (*S*)-**5**, 137232-69-0; (*R*)-**6a**, 137232-70-3; (*S*)-**6a**, 137232-71-4; (*R*)-**6b**, 137232-72-5; (*S*)-**6b**, 137232-73-6; (*R*)-**6c**, 137232-74-7; (*S*)-**6c**, 137232-75-8; **7**, 137232-76-9; **8a**, 137232-77-0; **8b**, 137232-78-1; **8c**, 137232-79-2; **9a**, 64697-70-7; **9b**, 127646-34-8.

Core Size and Flexibility of Metallohydroporphyrin Macrocycles. Implications for F_{430} Coordination Chemistry

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Abstract: We have used molecular mechanics calculations to investigate the effect of macrocycle reduction on core-hole size and flexibility of a series of metallo(hydro)porphyrin molecules. Macrocycle reduction at β-pyrrole positions results in an increase in core size, whereas reduction at methine positions results in a decrease in core size. The tetrapyrroles are found to become significantly more flexible (susceptibile to S_4 ruffling) only when reduction occurs at methine positions. These results are used to explain the unique ligand-binding ability of the nickel-tetrapyrrole F_{430} cofactor of the *S*-methyl coenzyme M reductase enzyme of methanogenic bacteria. Molecular mechanics also predicts the increased axial-ligand affinity of the native F_{430} isomer compared to the 12,13-diepimer, as a result of the increase in macrocycle torsional strain in the 4-coordinate native isomer.

The final step of archaebacterial methanogenesis (eq 1) involves F_{430}, the nickel-containing cofactor of *S*-methyl coenzyme M

$$CH_3SCoM + HSHTP \rightarrow CH_4 + CoMSSHTP \quad (1)$$

reductase.[2,3] F_{430} possesses the most highly reduced 16-membered tetrapyrrolic macrocycle yet encountered in nature (Figure 1). The precise role of F_{430} in methane production remains unknown, but could involve redox, substrate binding (i.e., coenzyme M or *N*-7-mercaptoheptanoyl-*O*-phospho-L-threonine, HSHTP), or methyl transfer. Investigation of the chemical reactivity of F_{430} will help evaluate this role.

The Ni(II) ion of F_{430} is the most electrophilic metal center of a series of nickel-containing hydroporphyrin complexes.[4] Three factors have been proposed to contribute to the unique ligand-binding ability of F_{430}.

(a) Steric Inhibition of S_4 Ruffling. This ruffling is known to occur in nickel-containing hydroporphyrins[5-9] and reduces the

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(2) Abbreviations used: CH_3SCoM, *S*-methyl coenzyme M (2-(methylthio)ethanesulfonic acid); HSHTP, *N*-7-mercaptoheptanoyl-*O*-phospho-L-threonine; hexahydroporphyrin, 1,2,3,7,8,20-hexahydroporphyrin; pyrrocorphin, 2,3,7,8,12,13-hexahydroporphyrin, isobacteriochlorin, 2,3,7,8-tetrahydroporphyrin; chlorin, 2,3-dihydroporphyrin; metallo(hydro)porphyrin refers generally to metal complexes of porphyrins or hydroporphyrins.

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