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MACROCYCLES IN THE CONSTRUCTION OF ACYCLIC STEREOCHEMISTRY

W. CLARK STILL,[1] LAWRENCE J. MACPHERSON, TOSHIRO HARADA and JAMES F. CALLAHAN
Department of Chemistry, Columbia University, New York, NY 10027, U.S.A.

and

ARNOLD L. RHEINGOLD[2]
Department of Chemistry, University of Delaware, Newark, DE 19711, U.S.A.

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Abstract—The conformations of macrocyclic intermediates provide a useful medium through which distant chiral centers may control chemical reactions. In this paper, we show that macrocycles made by cyclization of simple acyclic starting materials with an auxiliary spacer may be used to prepare stereochemically complex acyclic products.

The development of highly efficient methods for the stereoselective construction of arrays of acyclic asymmetric centers is a significant goal for organic chemistry. Not only do such structures form major components of many important natural products but they can also provide a basis for the design of new compounds having desired arrangements of atoms in three dimensional space. The problem also provides an excellent context for detailed new investigations of reaction mechanisms, transition state structure and conformational analysis of flexible systems. Such studies are central to the synthetic problem of acyclic stereoselection and become particularly attractive when coupled with recently developed analytical and computational tools in that they suggest some most interesting tests of our current ideas about the factors which control chemical reactions and complex molecular structure.

In order to prepare stereochemically complex acyclic molecules, a variety of general methods and specific reactions have been devised for controlling diastereomeric relationships. Adjacent or 1,2-stereochemical relationships may be effectively established by reactions proceeding with high internal (e.g. olefin epoxidation or hydrogenation) or relative (e.g. hydroxyl-directed allylic alcohol epoxidation or hydrogenation) asymmetric induction. Remote stereochemical relationships present more of a challenge. While 1,3- and a few 1,4-relationships may be established using reactions based on well understood 5- and 6-membered ring intermediate structures, most compounds having remote sets of asymmetric centers are constructed by absolute stereocontrol methods. Thus each set of remote asymmetric centers is typically prepared from an enantiomerically pure starting material or by a reaction giving high enantioselection. Although such an approach cannot fail to produce desired stereoisomers, routes which are required to begin with a readily available chiral starting material or which use one of the few chirally efficient reactions can be quite lengthy and as a solution to the problem of acyclic diastereosynthesis the scheme is uninteresting.

During the past few years, we have been studying new methods for the construction of remote diastereorelationships using only distant chiral centers and the conformational properties of selected substrates as sources of stereocontrol for reactions which create new asymmetric centers. Such methods are inherently economical in that simple achiral reagents and starting materials are used. One of the schemes we have examined uses the conformational properties of macrocyclic intermediates as a medium for the long distance transmission of stereochemical information.[3] For the synthesis of acyclic molecules, the pathway entails tying the two ends of a molecular chain into an appropriate macrocycle, elaborating the desired stereochemistry and then cleaving the ring. As a strategy for acyclic stereoselection, the scheme has a minimum associated overhead of two steps, i.e. the formation and cleavage of the macrocycle. These steps as well as the remote diastereoselectivity obtained can be however quite efficient as illustrated by a recent application to the synthesis of the C30–C43 segment[4] of palytoxin. The key conversions are shown below.

In this paper, we discuss simple applications of the macrocyclic strategy to nonacetic acid (3) and the

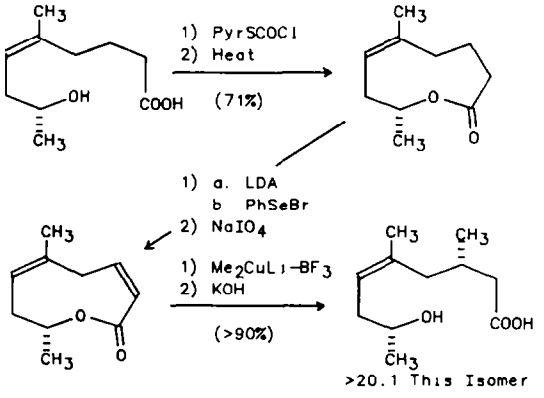


Fig. 1.

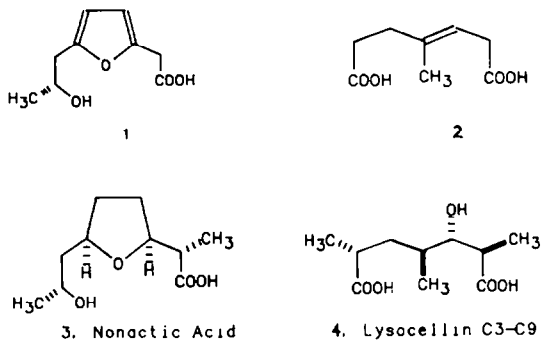


Fig. 2.

C3–C9 segment (**4**) of the polyether antibiotic lysocellin. Stereochemical problems aside, simple 2-step pathways to these compounds may be imagined in which the furanoic hydroxyacid **1** is methylated and reduced to **3** and in which the olefinic diacid **2** is dimethylated and hydroborated to **4**.

Although one might consider directly cyclizing these materials as a means to stereocontrol, the medium rings which could result are quite strained and would be difficult to prepare and use. To avoid such problematic strain, an auxiliary segment or spacer could be spliced between the terminal –OH groups to give a larger ring. Such a spacer provides additional advantages in that it is a strategic element which may be varied to change the conformational properties of the substrate without changing the segment destined to become part of the final product. In our nonactic acid synthesis, we describe several different achiral spacers which can be used to vary the chemistry involved in converting **1** to **3**. The lysocellin segment offers an additional opportunity since the starting main chain is achiral. By incorporating an enantiomerically pure chiral spacer into the macrocycle, we use the spacer asymmetry to produce both the desired diastereomer and enantiomer of **4**.

Nonactic acid

As outlined above our pathway to nonactic acid[5] is a simple one in which an initial asymmetric center at C8 provides stereocontrol to an enolate alkylation which methylates C2 and a furan reduction which establishes C3 and C6 (Fig. 2). A variety of spacer groups can be envisaged which would link the C8 alcohol to the C1 carboxylic acid and two of those we have investigated are shown below.

Using our ring-generating computer program at 30 degree dihedral angle resolution and MM2 molecular mechanics calculations, the low energy conformations of **5** and **6** were constructed. The ethylene-spaced macrocycle **5** was found to exist in a

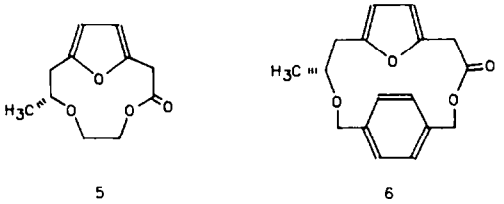


Fig. 3.

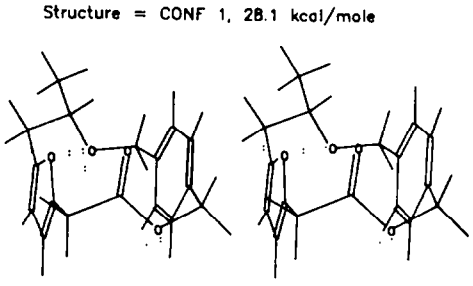


Fig. 4.

number of energetically similar pairs of conformers having the furan tilted slightly above or below the plane of the macrocycle. Since the conformational orientation of the furan with respect to the macrocycle would be expected to have major consequences on control of the adjacent C2 stereochemistry and since the energetic distinctions between the conformers of **5** were not great, it was not surprising to find that both kinetic and thermodynamic C2 methylation of **5** proceed without useful stereoselection. In contrast the xylene-spaced macrocycle **6** was found to consist of conformations in which the furan is oriented more nearly perpendicular to the plane of the macrocycle and thus the two faces of the macrocycle are effectively distinguished. The energy differences separating the conformers were also found to be somewhat larger than in **5** and the lowest energy conformer of **6** is shown below.

Synthesis of the macrocyclic nonactic acid precursors was straightforward[6] and is summarized in the scheme below. Cyclizations were effected using the standard Corey–Nicolaou thiopyridyl ester method[7] and afforded the desired monolactones in 20–40% yield.

When **6** was treated with strong base ($LiNiPr_2$ or $KN(TMS)_2$, THF, −78°) and methyl iodide, a single diastereomer (>70:1) was formed in high yield. The product was shown to be a kinetic one by its subsequent isomerization to a 1:1.1 mixture of diastereomers using lithium t-butoxide in t-butanol. The relationship of these results to molecular mechanics strain energies is interesting. By calculating the strain energies of all conformations up to approx. 3 kcal/mole excess strain for both *cis* and *trans* products, a Boltzmann distribution at 25° may be used to give an expected thermodynamic *cis*:*trans* ratio of 1:1.3. Calculated energies should however be regarded with some reservation since our compounds

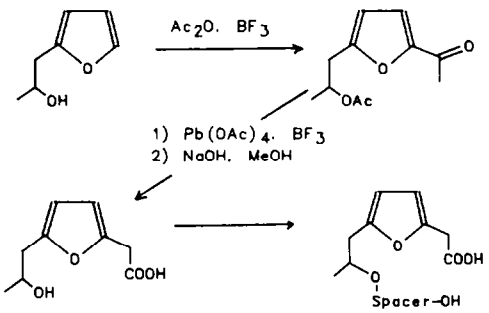
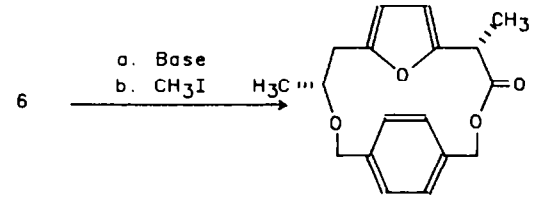


Fig. 5.

are rather complex and contain a variety of substructures for which force field parameters are at best crudely approximated. Although methods for the prediction of kinetic product distributions are not yet straightforward, we recently reported a semi-quantitative relation between macrolide enolate ground state energies and kinetic methylation results assuming peripheral approach of reagents to a *Z*-enolate. When this simple model was applied to the reaction at hand, the five lowest energy enolate conformations were found to be closely related and all led to the *cis* dimethyl product. The lowest energy enolate conformation leading to the *trans* product was found to be 1.2 kcal/mole above the ground state enolate conformation. Although *trans* product could arise alternatively from the *E*-enolate, its most stable conformer lies almost 4 kcal/mole above the most stable *Z*-enolate and *E*-enolates are furthermore known to be minor products of the related kinetic deprotonation of acyclic esters with lithium diisopropylamide.[8] By considering all reasonably populated enolate conformations, the enolate ground state = transition state model predicted a product ratio of 12:1 in favor of *cis*. The product of peripheral alkylation was readily assigned by inspection of the three-dimensional geometry of the enolate as may be seen with the most stable conformation of the enolate **6** (below) which leads to the *cis* dimethyl lactone **7**.

To confirm the *cis* stereochemical assignment, **7** was reduced first with lithium aluminum hydride (LAH) and then with hydrogen and catalyst to yield a 1:1 mixture of tetrahydrofuranoid diastereomers. One of the two diastereomers was found to be indistinguishable from the LAH reduction product of natural nonactic acid by 270 MHz ^{1}H NMR. The *cis* assignment for **7** was further confirmed by X-ray crystallographic analysis which showed not only that the two methyls were indeed *cis* but also that the macrocycle conformation in the crystal was very similar to that predicted for the lowest energy macrolide conformation by our ringmaking/molecular mechanics programs. Interestingly, the crystal underwent a nondestructive phase transition from orthorhombic to monoclinic symmetry on prolonged X-ray irradiation and a structure determination on the new monoclinic form yielded the same basic conformation of the macrocycle. Least squares superimpositions of the molecular mechanics and the two X-ray structures gave r.m.s. deviatins of 0.27 and 0.28 ang/atom (see superimposition below). The discrepancy between the X-ray and molecular mechanics results probably reflects the crude force field parameterization employed since the gross conformations are essentially the same. By comparison, the macrocycle conformations found in the two different crystal forms show an r.m.s. deviation of 0.16 ang/atom with most of the difference arising from minor rotations of the aromatic rings with respect to the plane of the macrocycle.



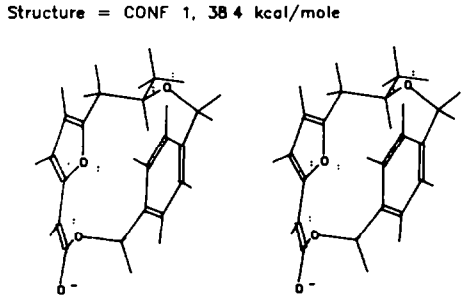


Fig. 6.

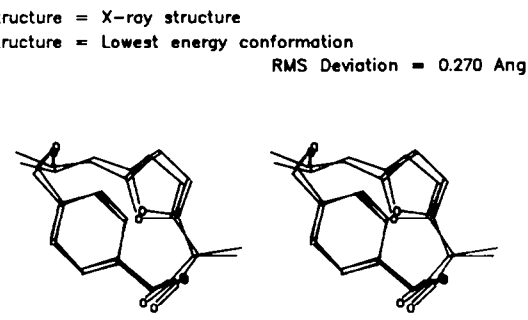


Fig. 7.

Although **7** incorporates the natural *cis* arrangement of the C2 and C8 methyls, further conversion was problematic due to the extreme lability of the benzylic ester linkage. To circumvent this problem, we prepared the homolog **8**.

The 16-membered macrolide **8** shares many properties with the 15-membered **6** but the additional methylene increases the ring's flexibility and allows its *E*-enolate to become more stable than the *Z*-isomer by approximately 1 kcal/mole. Interestingly, the *Z*- and *E*-enolates appear by inspection of the molecular mechanics structures to lead to *cis*- and *trans*-dimethyl products respectively. Our study of the alkylation of **8** is still under way; however, the picture which is emerging is indeed one in which the control

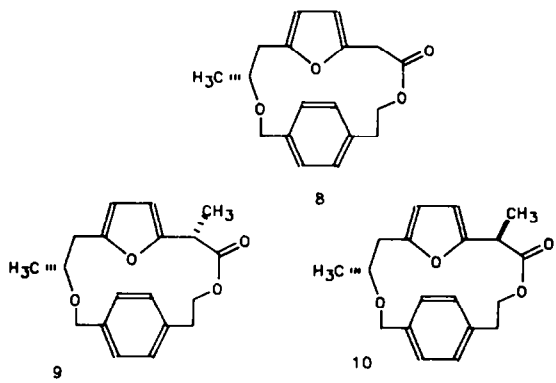


Fig. 8.

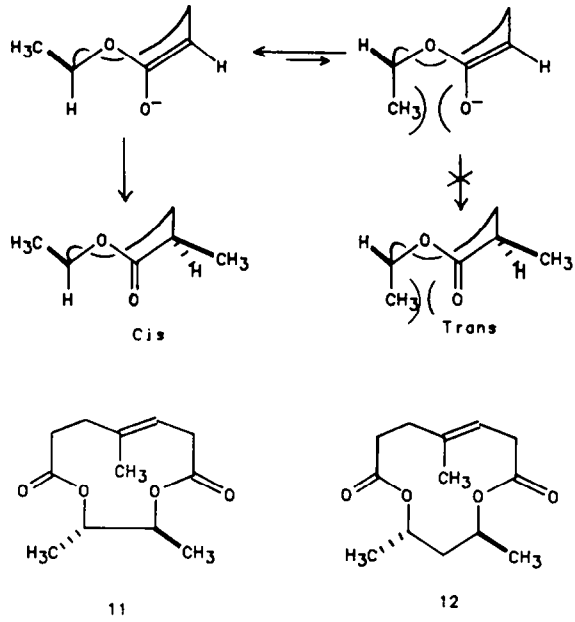


Fig. 9.

of enolate geometry plays a major role in alkylation stereoselectivity. The experimental facts are as follows. Using $KN(TMS)_2$ in toluene or toluene/18-crown-6 at low temperature, the *cis* dimethyl lactone (**9**) was cleanly formed in high yield (ratio 15–25:1). When the enolate prepared under these conditions was allowed to warm and stand prior to alkylation, the preference for the *cis* product fell substantially. The *trans* dimethyl product (**10**) could furthermore be produced as the major product (3–4:1) using $LiN(TMS)_2$ in THF-HMPA. The foregoing diastereomeric product distributions appear kinetic at the level of the alkylation and equilibration (KOtBu, tBuOH–THF) gave rise to a 40:60 *cis*:*trans* mixture (MM2 predicts 60:40).

Although our synthesis of nonactic acid is not yet complete, it is clear that spaced macrocycles can provide excellent control to reactions establishing remote stereochemical relationships and that molecular mechanics can provide a useful tool for understanding and predicting experimental results in conformationally flexible systems such as ours.

Lysocellin C3–C9

Our synthesis of the C3–C9 segment (**4**) of lysocellin[9] was based in large part on previous observations that the macrolactones of secondary alcohols undergo highly stereoselective enolate alkylation to yield *cis* products.[3] This selectivity was rationalized on the basis of conformations of the macrolide *Z*-enolate in which the sterically demanding alkoxide selects the less hindered environment as diagrammed below.

If the same *cis* selectivity were found in dilactones such as **11** or **12**, then both the C4 and the C8 methyl could be established with the correct stereochemistry both relative to each other and to chiral centers on the spacer. Peripheral hydroboration to the desired isomer would then follow from the usual interaction of the vinyl methyl adjacent C4 asymmetric center.

Preparation of dilactone **11** began with methacrolein and readily available (*S*,*S*)-2,3-butanediol[10] via an ester enolate aldol reaction (90% yield) and a subsequent Claisen rearrangement (85% yield) as outlined in the scheme below. Cyclization was effected as before using the thiopyridyl ester method and yielded **11** in 40–45% yield.

Alkylation of the allylic C8 methylene was effected using potassium hexamethyldisilazide and methyl iodide in tetrahydrofuran (−78°, 10 min) to produce an 81% yield of methylated lactone as the expected beta (*cis*) diastereomer (**13**, >20:1). The C4 methyl was then appended by a second ester enolate methylation using lithium tetramethylpiperidide in tetrahydrofuran. Under these conditions a single diastereomer (>15:1) was again produced but turned out to possess the unanticipated beta (*trans*) stereochemistry (**14**). The same major product (60% yield, 5–6:1 diastereoselection) was formed directly by dienolatedouble alkylation of **11**. The stereochemical assignments for **14** followed from its hydroboration with borane (75% yield, *ca* 17:1 diastereoselection) and conversion to the known 2-epi Prelog–Djerassi lactonic acid (**15**).

The *trans* selectivity of the second alkylation was

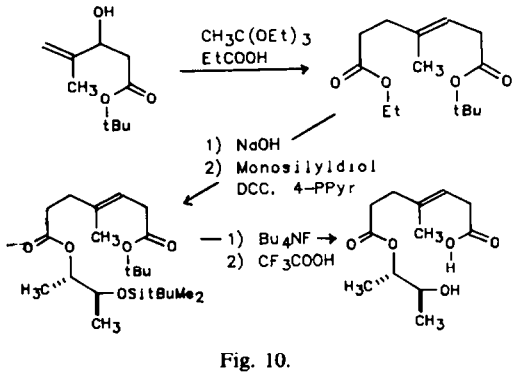


Fig. 10.

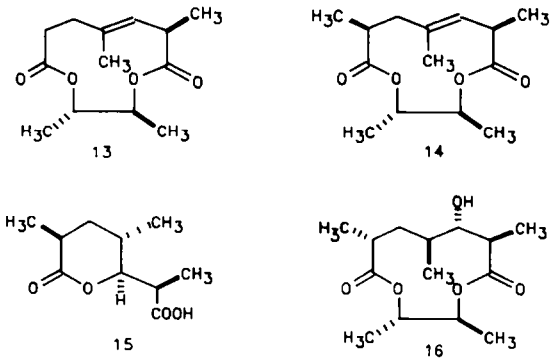


Fig. 11.

surprising since it runs contrary to more than a dozen previous examples of secondary alcohol macrolide alkylations and may reflect some unusual properties of our particular macrocyclic substrate. Indeed, while a molecular mechanics ring generation for the C8 *Z*-enolate gave structures resembling the generalized enolate picture shown at the beginning of this section, an analogous ring generation for the C4 *Z*-enolate produced the conformer below as the lowest energy form. The conformation of this enolate is substantially distorted by the strain of the ring from the geometry shown in the generalized picture above and orients the enolate in approximately the same plane as the ring. Thus a prediction of alkylation stereochemistry cannot be made on simple steric grounds although the second lowest energy conformation (+0.4 kcal/mole) does show a steric preference for the *trans* mode of alkylation.

An alternative rationale for the *trans* selectivity is based on a C4 *E*-enolate. Although such an enolate would be rather strained (MM2 *Z,E* energy difference *ca* 7 kcal/mole), it could be expected to yield *trans* alkylation products by the generalized enolate alkylation picture above.

In an attempt to increase the flexibility of the ring, we hydroborated (stereoselectivity >10:1) the first alkylation product **13** prior to the second alkylation. When the dianion of the resulting hydroxydilactone was then generated using lithium tetramethylpiperidide in tetrahydrofuran and treated with excess methyl iodide, a single diastereomer (**16**, >20:1) was formed in 78% yield. Interestingly that material was identical to the minor isomer of the preceding olefinic dilactone alkylations and had the desired relative and absolute stereochemistry as shown by its conversion to the natural enantiomer of the Prelog–Djerassi lactonic acid.

Although the experiments described above lead to

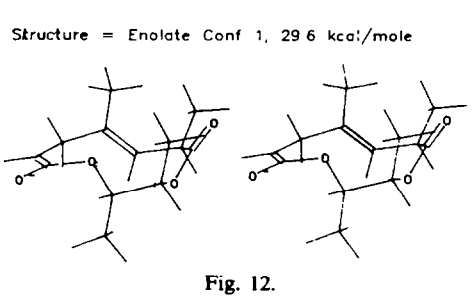


Fig. 12.

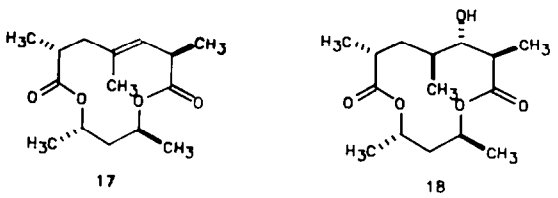


Fig. 13.

the correct stereoisomer of **4**, the desire for a single-step, double alkylation route to **4** prompted us to investigate the homologated and more flexible 12-membered macrodilactone **12**. Compound **12** was prepared by analogy with the preparation of **11** from (*S,S*)-2,5-pentanediol[11] and was cyclized via the thiopyridyl ester in 65–75% yield. When **12** was treated with 2.5 equivalents of lithium tetramethylpiperidide in THF–HMPA and then with 20 equivalents of methyl iodide, a 90% yield of C4, C8 dialkylated material was obtained. Careful analysis of the product showed it to consist of a 12:1 mixture of diastereomers in which the major isomer had the desired stereochemistry (**17**). The minor isomer was found to be epimeric at the previously problematic center C8. Hydroboration as before proceeded with >9:1 stereoselectvity for the desired hydroxydilactone **18** (65%) and the structural assignment was confirmed (a) 10% KOH, (b) 1 M HCl, (c) CH_2N_2; 80% overall) to the methyl ester of the Prelog–Djerassi lactone ($[\alpha]_D(CH_3OH) = +26°$ ($c = 0.15$)). Although the general rationale presented above is consistent with the experiments described, related alkylations of a further homologated dilactone gave significantly poorer diastereoselection and remind us that the particular properties of employed macrocycles can have significant effects on the outcome of their chemical reactions.

CONCLUSIONS

In the preceding paragraphs we have described experiments which demonstrate that spaced macrocycles have useful properties for the construction of stereochemically complex acyclic molecules having widely separated asymmetric centers. The examples described are simple ones but are suggestive of the potential of the approach as a strategy for the synthesis of more complex compounds. The reactions are also intriguing from a stereomechanistic standpoint and we believe that a thorough analysis of these and related results will provide useful new insights into reaction pathways and asymmetric induction in general.[13]

EXPERIMENTAL

Thiopyridyl ester macrolactonization to **6**

To a dry argon-filled flask was added the carefully dried (azeotropic distillation of toluene) hydroxyacid (254 mg, 0.834 mM) and 8 ml ether. The soln was chilled to 0° and 0.128 ml Et_2N and 4.2 ml of a 0.2 M CH_2Cl_2 soln of thiopyridyl chloroformate was added. After stirring 30 min at 0°, the resulting white ppt was removed by filtration through a short column of Florisil and the solvent was removed at reduced pressure.

The resulting crude thiopyridyl ester was added to 200 ml of degassed xylene and the soln was heated at reflux under argon for 18 hr. Removal of the solvent at reduced pressure and flash chromatography (silica gel, 12% EtOAc in petro-

leum ether) gave **6** as an off-white solid (60 mg, 25% yield (up to 40% yield on smaller scale cyclizations): ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17 (d, 3H, j = 6 Hz), 2.40 (m, 2H), 3.20 (d, 1H, j = 13 Hz), 3.25 (m, 1H), 3.40 (d, 1H, j = 13 Hz), 4.10 (d, 1H, j = 12 Hz), 4.65 (d, 1H, j = 12 Hz), 4.80 (d, 1H, j = 11 Hz), 5.30 (d, 1H, j = 11 Hz), 5.85 (d, 1H, j = 3 Hz), 5.95 (d, 1H, j = 3 Hz), 7.1 (m, 4H); IR (neat): 2900, 1740, 1520, 1220, 1120 cm^{-1}; MS (CI, isobutane): m + 1 = 287 *m/e*; TLC (silica gel, 25% ethyl acetate in petroleum ether): R_f = 0.46.

Alkylation of **6** *to the* cis *dimethyl lactone* **7**

A 0.5 M soln of lithium diisopropylamide in THF was prepared as usual from iPr_2NH and nBuLi and 0.195 ml was transferred via a teflon-tipped syringe to a N_2-filled 10 ml serum vial. The LDA soln was chilled to −78° and 22 mg (0.078 mM) of **6** in 1.4 ml anhyd THF was added. After stirring the bright yellow soln at −78° for 45 min, 0.15 ml MeI in 0.2 ml anhyd HMPA and 0.2 ml anhyd THF was added. The mixture was allowed to warm to −45° over a 45 min period and several ml of sat NH_4Cl aq was added in a single portion. The mixture was then partitioned between water and CH_2Cl_2, the water layer was extracted with fresh CH_2Cl_2 and the organic layers were combined and dried ($MgSO_4$). Solvent evaporation and flash chromatography (silica gel, 5% EtOAc/petroleum ether) gave **7** as a white solid (20 mg, 87% yield): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (d, 3H, j = 6 Hz), 1.40 (d, 3H, j = 7 Hz), 2.4 (m, 2H), 3.25 (m, 1H), 3.50 (q, 1H, j = 7 Hz), 4.10 (d, 1H, j = 12 Hz), 4.65 (d, 1H, j = 12 Hz), 4.90 (d, 1H, j = 11 Hz), 5.20 (d, 1H, j = 11 Hz), 5.88 (d, 1H, j = 3 Hz), 5.95 (d, 1H, j = 3 Hz), 7.0 (m, 4H); IR (neat): 2900, 1740, 1560, 1460, 1360, 1240 cm^{-1}; MS (CI, ammonia): m + 18 = 318 *m/e*; TLC (silica gel, 15% ethyl acetate in petroleum ether) R_f = 0.43.

Mitsunobu macrolactonization[12] *to* **8**

After azeotropically drying (toluene) 216 mg (0.68 mM) of hydroxyacid, it was dissolved in 120 ml of anhyd THF and 588 mg triphenylphosphine and 0.35 ml diethyl diazodicarboxylate were added. The soln was stirred at room temp for 26 hr. The solvent was then removed at reduced pressure and the residue was purified by flash chromatography (silica gel, 10% EtOAc/petroleum ether) to yield **8** (70 mg, 35%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (d, 3H, j = 6 Hz), 2.50 (m, 2H), 2.85 (m, 2H), 3.30 (d, 1H, j = 14 Hz), 3.35 (m, 1H), 3.40 (d, 1H, j = 14 Hz), 4.00 (m, 1H), 4.10 (d, 1H, j = 11 Hz), 4.65 (d, 1H, j = 11 Hz), 4.70 (m, 1H), 5.95 (s, 2H), 6.90 (m, 4H); IR (neat): 2900, 1740, 1570, 1280, 1130, 1070 cm^{-1}; MS (CI, ammonia): m − 18 = 318 *m/e*; TLC (silica gel, 15% EtOAc in petroleum ether) R_f = 0.44.

Alkylation of **8** *to the* cis *lactone* **9**

To a dry serum vial was added 0.018 ml of 0.655 M potassium hexamethyldisilazide in toluene (Callery Chemical Company) under N_2. The soln was cooled to −78° and **8** (3.4 mg, 0.011 mM) in 0.20 ml toluene was added. The resulting bright yellow soln was stirred for 45 min and a soln of 0.02 ml MeI, 10 mg 18-crown-**6** and 0.08 ml toluene was added. The mixture was allowed to warm to −55° and was then quenched with sat NH_4Cl aq. The resulting mixture was then partitioned between CH_2Cl_2 and water, and the aqueous phase was reextracted with fresh CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to yield the crude alkylated lactone. Flash chromatography (silica gel, 5% EtOAc/petroleum ether) gave **9** as a colorless oil weighing 2.5 mg (75%). 200 MHz proton NMR showed a 15:1 ratio of products on the crude material. ^{1}H NMR (200 MHz, $CDCl_3$) (major diastereomer—**9**): δ 1.17 (d, 3H, j = 6 Hz), 1.40 (d, 3H, j = 7 Hz), 2.5 (m, 2H), 2.90 (m, 2H), 3.55 (q, 1H, j = 7 Hz), 4.15 (d, 1H, j = 12 Hz), 4.25 (m, 1H), 4.50 (dt, 1H, j = 4, 10 Hz), 4.70 (d, 1H, j = 12 Hz), 6.00 (s, 2H), 6.95 (m, 4H), (minor diastereomer **10**—well-resolved signals) δ 1.27 (d, j = 7 Hz), 5.96 (s); IR (neat): 2900, 1740, 1550, 1450 cm^{-1}; MS (CI, ammonia): m + 18 = 332 *m/e*; TLC (silica gel, 15% EtOAc in petroleum ether): R_f = 0.35.

Alkylation of **8** *to the* trans *lactone* **10**

The alkylation described above was repeated with the exceptions that 0.5 M lithium hexamethyldisilazide (from nBuLi and $(TMS)_2NH$) in THF was used as the base and that soln of 0.02 ml MeI, 0.02 ml HMPA and 0.05 ml THF was used as the methylating reagent. Workup and chromatography as above gave 3.4 mg (>90%) of 4:1 mixture of methylated lactones containing **10** as the major product. ^{1}H NMR (200 MHz, $CDCl_3$) (major diastereomer—**10**): δ 1.17 (d, 3H, j = 6 Hz), 1.27 (d, 3H, j = 7 Hz), 2.5 (m, 2H), 2.90 (m, 2H), 3.35 (m, 1H), 3.55 (q, 1H, j = 7 Hz), 4.00 (m, 1H), 4.15 (d, 1H, j = 13 Hz), 4.70 (d, 1H, j = 13 Hz), 4.85 (m, 1H), 5.96 (s, 2H), δ 7.00 (m, 2H) (minor diastereomer **9**—well-resolved signals) δ 1.40 (d, 3H, j = 7 Hz), 6.00 (s, 2H); IR (neat): 2900, 1740, 1550, 1540 cm^{-1}; MS (CI, ammonia) m + 18 = 332 *m/e*; TLC (silica gel, 15% EtOAc in petroleum ether): R_f = 0.35.

Thiopyridyl ester macrolactonization to **12**

Dry hydroxyacid (205 mg) and Et_3N (0.13 ml) were dissolved in anhyd Et_2O and cooled to 0°. To this soln was added 1.9 mM of 0.2 M thiopyridyl chloroformate in CH_2Cl_2. After stirring for 30 min at 0°, the crude thiopyridyl ester was isolated as described in the preparation of **6** and flash chromatographed (silica gel, 50% EtOAc in petroleum ether) to yield the thiopyridyl ester (247 mg, 89%).

The thiopyridyl ester above was dissolved in 150 ml degassed xylene and heated at reflux under argon for 40 hr. Solvent removal and flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) gave **12** as an oil (138 mg, 82% (73% overall)): ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 (d, 3H, j = 7 Hz), 1.24 (d, 3H, j = 7 Hz), 1.67 (s, 3H), 2.05 (m, 2H), 2.2 (m, 2H), 2.4 (m, 3H), 2.90 (dd, 1H, j = 7.8, 15.8 Hz), 2.98 (dd, 1H, j = 8.3, 15.8 Hz), 5.04 (m, 1H), 5.28 (m, 2H); IR (CCl_4): 1735, 1450, 1355, 1255, 1150, 1100, 980 cm^{-1}; MS (CI, methane): m + 1 = 241 *m/e*; TLC (silica gel, 20% EtOAc in petroleum ether): R_f = 0.50.

Dialkylation of **12** *to the* trans *lactone* **17**

To a soln of 37 μl 2,2,6,6-tetramethylpiperidine in 220 μl anhyd THF at −20° was added 48 μl of 2.25 M n-BuLi in hexane. The soln was stirred chilled to −78° and 10.4 mg (0.043 mmol) **12** in 60 μl THF and 60 μl HMPA was added. After stirring for 45 min, 55 μl (20 equivs) MeI was added and the mixture was allowed to stir an additional 45 min. Water was then added and the product was extracted into 1:1 ether–petroleum ether. Drying (Na_2SO_4), solvent removal and flash chromatography (silica gel, 10% EtOAc in petroleum ether) gave 10.8 gm (93%) of the alkylated lactone. Calibrated capillary VPC analysis (carbowax) showed the presence of 7.7% of the 8-epi dialkylated material and 2% of an unidentified contaminant. The major component (90%) was the desired lactone **17**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 (d, 3H, j = 7 Hz), 1.20 (d, 3H, j = 7 Hz), 1.24 (d, 3H, j = 7 Hz), 1.25 (d, 3H, j = 6 Hz), 2.69 (s, 3H), 2.25 (m, 2H), 2.52 (dd, 1H, j = 4, 15 Hz), 2.80 (m, 1H), 3.25 (m, 1H), 5.02 (m, 2H), 5.15 (m, 1H); MS (CI, methane): m + 1 = 269 *m/e*; TLC (silica gel, 10% EtOAc in petroleum ether): R_f = 0.17.

Hydroboration of **17** to *hydroxydilactone* **18**

Lactone **17** (14.0 mg, 0.052 mM) was dissolved in 100 μl 1 M borane in THF under argon at −20°. After stirring for 2 hr, 35 μl of 3 N NaOH and 35 μl of 30% H_2O_2 were added. The mixture was maintained at −20° during the additions and the mixture was allowed to warm to 20°. After stirring for an additional 15 min, the mixture was repeatedly extracted with ether and the extracts were concentrated and flash chromatographed (silica gel, 35% EtOAc in petroleum

ether). The product (**18**, 8.2 mg, 55%) was crystalline and could be recrystallized from ether–hexane (m.p. = 104–105°). A more polar byproduct (1.5 mg) was also isolated and was found by NMR to be a mixture of compounds. The minimum stereoselectivity of the hydroboration could be set at 9:1. **18**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.04 (d, 3H, j = 7 Hz), 1.17 (d, 3H, j = 6 Hz), 1.19 (d, 3H, j = 7 Hz), 1.25 (d, 3H, j = 6 Hz), 1.31 (d, 3H, j = 6 Hz), 1.60–2.05 (m), 2.52 (m, 1H), 2.72 (m, 1H), 3.42 (br d, 1H, j = 11 Hz); IR (CCl_4): 3640 (sh), 3520, 1735, 1460, 1380, 1330, 1265, 1180, 1140, 1085, 1035, 1010 cm^{-1}; MS (CI, methane): m + 1 = 287 *m/e*; TLC (silica gel, 30% EtOAc in petroleum ether): $R_f = 0.45$.

X-Ray structural determinations

After collecting about 90% of the data in the structural study of **7**, check reflection intensities abruptly and randomly declined, the entire transition occurring within 3 min. The cause was determined to be a sudden, nondestructive transformation from an orthorhombic to a monoclinic symmetry, hereafter referred to as **7(o)** and **7(m)**. As the remaining crystals in the bulk sample were orthorhombic, the transition in the symmetry of the data crystal may have been radiation induced. Ninety per cent of the data for **7(o)** and all the data for **7(m)** were collected with the same crystal. Crystal data: **7(o)**, orthorhombic, *Pccn*, $a = 14.674(4)$, $b = 23.875(5)$, $c = 9.037(2)$ A, $Z = 8$, $V = 3166.2(9)$ A^3, d (calc) = 1.259 gm/cm^3, $R = 0.0435$, GOF = 1.431; **7(m)**, monoclinic, $P2_1/c$, $a = 5.941(1)$, $b = 14.528(3)$, $c = 18.623(4)$ A, *beta* = 98.26(2) deg, $Z = 4$, $V = 1590.7(6)$ A^3, d (calc) = 1.253 gm/cm^3, $R = 0.0536$, R_w, 0.0435, GOF = 1.324. For both structures one form of the data was collected ($4° < 2\theta < 45°$) on a Nicolet R3 diffractometer (Mo K_α) at 23°. The structures were solved by a combination of direct methods routines and Fourier syntheses. All non-H atoms were refined with anisotropic thermal parameters and H atoms were included as fixed idealized contributions. In both cases, large corrections for the effects of secondary extinction were required.

A full disclosure of the crystallographic data and structural information will appear elsewhere.

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