and starting material (4.7 min, 93 mg, 9.4%) as clear oils. The combined yield of **60** and **59** (15.7:1) based upon recovered starting material was 76%. **60**: oil; silica gel, 1:4 ether/hexane, R_f = 0.39; MS, exact mass calcd for $C_{23}H_{34}O_2S_1$ = 374.2271; found 374.2281, error = 2.6 ppm; IR (neat, cm^{-1}) C=O, 1719; 200 MHz NMR ($CDCl_3$) δ 7.38-7.20 (5 H, m), 5.79 (1 H, ddd, J = 15.4, 8.7, 5.3 Hz), 5.36 (1 H, dd, J = 15.4, 9.4 Hz), 4.52 (1 H, d, J = 11.7 Hz), 4.49 (1 H, d, J = 11.7 Hz), 3.31 (1 H, dd, J = 6.4, 3.9 Hz), 3.20 (1 H, dd, J = 8.0, 2.1 Hz), 2.85 (1 H, dq, J = 17.5, 7.3 Hz), 2.65-2.55 (1 H, m), 2.63 (1 H, dd, J = 13.2, 4.9 Hz), 2.50 (1 H, dq, J = 17.5, 7.3 Hz), 2.26 (1 H, ddd, J = 13.3, 8.7, 3.9 Hz), 2.12 (1 H, dd, J = 13.2, 4.2 Hz), 2.05-1.75 (3 H, m), 1.55 (1 H, ddd, J = 15.2, 8.0, 4.5 Hz), 1.20-0.95 (1 H, m), 1.08 (3 H, t, J = 7.3 Hz), 1.02 (3 H, d, J = 7.1 Hz), 1.00 (3 H, d, J = 6.2 Hz), 0.98 (3 H, d, J = 6.7 Hz). **59**: oil; silica gel, 1:4 ether/hexane, R_f = 0.28; MS, exact mass calcd for $C_{23}H_{34}O_2S_1$ = 374.2271; found 374.228, error = 2.4 ppm; IR (neat, cm^{-1}): C=O, 1716; 200 MHz NMR (C_6D_6) δ 7.39-7.21 (5 H, m), 5.21 (1 H, ddd, J = 15.0, 9.0, 0.9 Hz), 4.91 (1 H, ddd, J = 15.0, 10.1, 4.9 Hz), 4.46 (1 H, d, J = 11.5 Hz), 4.32 (1 H, d, J = 11.5 Hz), 2.97 (1 H, dd, J = 10.9, 2.3 Hz), 2.84-1.85 (7 H, m), 1.90-1.10 (2 H, m), 1.06 (3 H, d, J = 6.6 Hz), 1.05 (3 H, t, J = 7.3 Hz), 1.04 (3 H, d, J = 7.1 Hz), 1.03 (3 H, d, J = 7.3 Hz), 0.92 (3 H, d, J = 6.4 Hz).

Supplementary Material Available: Experimental details for the acyclic route to **11b**, dienes **32** and **33**, and ether **34** and spectral data (R_f, IR, MS, and ^{1}H NMR) for **13**, **15**, **16**, **27**, **28**, **30**, **11b**, **32**, **33**, and **34** (6 pages). Ordering information is given on any current masthead page.

Total Synthesis of *d,l*-Methynolide. Sulfur Removal and Remote Stereocontrol

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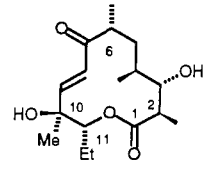
Abstract: The details for the conversion of **1** into *d,l*-methynolide are described. Key steps include the highly selective reduction to alcohol **3**, the oxidation α to sulfide sulfur from **3** to thiolactone **13**, and the acyl transfer from **14** to the lactone **16**. Photochemical oxidation converts phenacyl sulfide **17** into the ketone **21** via an intermediate thione and the derived 2 + 3 adduct **20**. Finally, selective Grignard addition to enone alcohol **24** introduces the last asymmetric center. Redox adjustments and deprotection completes the total synthesis. A similar route to C_{10}-*epi*-methynolide **37** is also reported. The synthetic sequence depends on relative stereocontrol. This is achieved by using the predictable conformational properties of medium-sized ring intermediates and by taking advantage of the stereoelectronic effect of sulfur α to ketone carbonyl.

We now describe the final stages in the sulfur-mediated total synthesis of *d,l*-methynolide. Two potential precursors of methynolide, the thiacycloundecenes **1** and **2** (Scheme I), are available by a sequence of sulfur ylide ring expansions.[1] Selectivity as high as 40:1 for the isomer-assigned structure **1** can be achieved by starting with purified precursors, but substantial amounts of **2** can also be obtained by base-induced equilibration or by performing the isolation procedure without suitable precautions. In principle, either **1** or **2** can be reduced to give the correct C_{11} hydroxyl stereochemistry of methynolide, depending on whether the reducing agent is chosen to maximize Felkin-Nguyen (Anh) or chelation control.[2-4] This key feature of the sulfur-based strategy for remote stereocontrol requires only that one of the two isomers can be obtained with high selectivity, as demonstrated in the preceding paper.



METHYNOLIDE

Initially, the stereochemical assignment at C_{10} (α to sulfur) was not known with certainty because neither ketone was crystalline. Accordingly, both **1** and **2** were treated with $LiEt_3BH$ to promote Felkin-Nguyen selectivity, and each gave a unique preponderant alcohol. The major byproduct in each case (ca. 5%) proved to be the alcohol derived from reduction of the epimerized starting material, suggesting that minor interconversion of the ketones **1** and **2** by enolization was competitive with reduction. In any event, the alcohol obtained from the minor ring expansion ketone **2** could be crystallized, and the structure **3*** was established by X-ray crystallography. This evidence proved that previous stereochemical assignments had been made correctly and that Felkin-Nguyen facial selectivity had in fact been followed in the reduction of **2**. Assuming that **1** likewise had been reduced under Felkin-Nguyen control by $LiEt_3BH$, the (noncrystalline) alcohol product must be **3** (94% yield). If so, then this isomer has the methynolide stereochemistry at all five relevant asymmetric centers. Alcohol **3** is of course also the most accessible isomer since it corresponds to the kinetic product (**1**) from ring expansion.

To confirm the above assignment of stereochemistry, both **3** and **3*** were carried through several of the subsequent steps, up to the point of final sulfur removal. We will use the asterisk (*) designation to identify the unnatural stereochemistry at C_{11} in a series of intermediates derived from **2** (these isomers also differ at C_{10} compared to precursors of methynolide). Thus, **3** was protected as the silyl ether **4** (99%) and oxidized with MCPBA to give sulfoxide **5** (99%), and **3*** was similarly taken on to **5***. Earlier model studies had established a technique for conversion of sulfoxides into the thiolactones required for acyl transfer,[5] and the sequence of sulfoxide anion phosphenylation to **7** followed by

(1) Vedejs, E.; Buchanan, R. A.; Conrad, P. C.; Meier, G. P.; Mullins, M. J.; Schaffhausen, J. C.; Schwartz, C. E. *J. Am. Chem. Soc.* **1989**, preceding paper in this issue.

(2) For evidence of chelation by α-sulfur, see: (a) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, J.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775. (b) Shimagaki, M.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Ibid.* **1984**, *25*, 4779.

(3) Vedejs, E.; Stults, J. S.; Wilde, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5452. Vedejs, E.; Rodgers, J. D.; Wittenberger, S. *J. Am. Chem. Soc.* **1988**, *110*, 4822.

(4) Carreno, M. C.; Dominquez, E.; Garcia-Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619.

(5) (a) Vedejs, E.; Meier, G. P.; Powell, D. W.; Mastalerz, H. *J. Org. Chem.* **1981**, *46*, 5253. (b) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046. (c) Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840.

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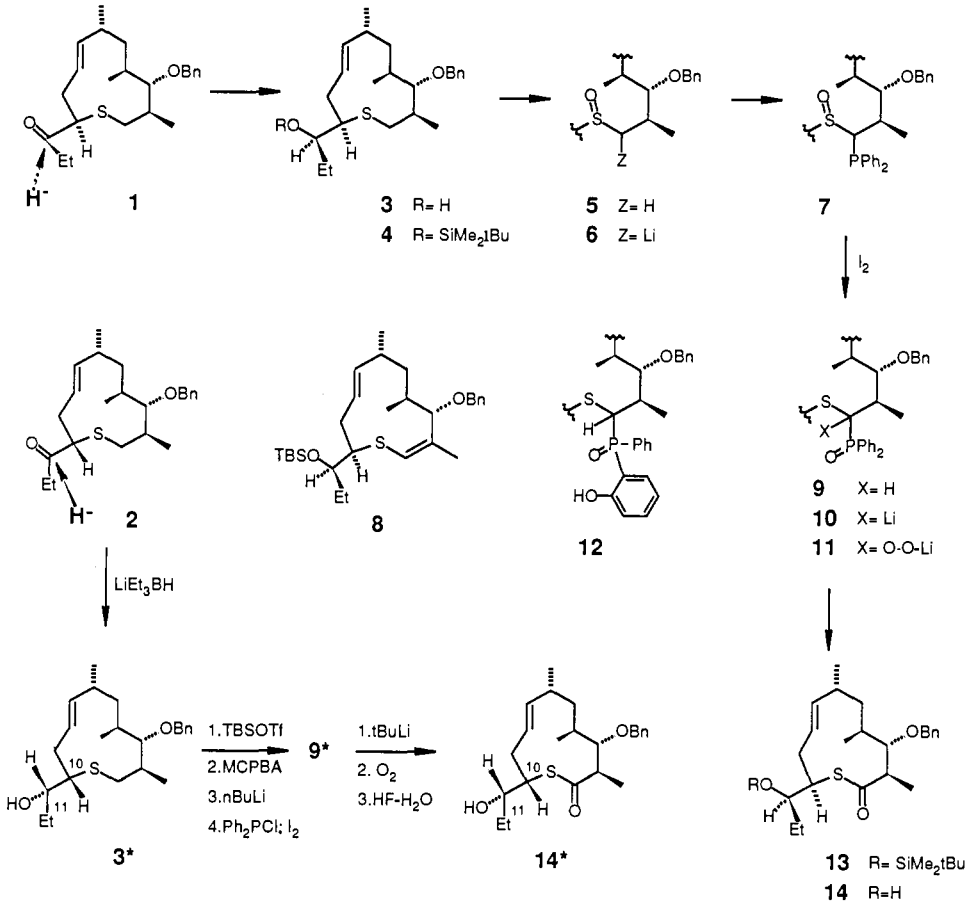
Scheme I



iodine-induced oxygen migration from sulfur to phosphorus[5a] provided **9** in 60% overall yield. A minor byproduct tentatively assigned the vinyl sulfide structure **8** was also obtained in 5–10% yield. The elimination product was easily removed and posed no significant problem for the synthetic sequence. However, our earlier approach based on intermediates which retained the C_4–C_5 double bond had encountered extensive elimination under the conditions of oxygen migration, and the added complication of a subsequent transannular cyclization reaction.[1] No sign of the latter complication was detected in the conversion from **7** to **9**.

Next, it was necessary to deprotonate **9** at C_1 to allow Horner–Bestmann oxygenation to give the thiolactone **13**. This procedure had been optimized in simple model compounds where good results were consistently obtained by using alkyllithium bases for the deprotonation step.[5] On the other hand, a more highly substituted analogue of **9** containing an additional methyl group at C_{10} had resisted all attempts at this deprotonation. As might be expected, **9** also proved resistant to proton removal α to phosphorus, probably due to a conformational preference that places the bulky $Ph_2P(O)$ substituent in a pseudoequatorial environment and therefore confines the C_1 hydrogen to the more demanding interior of the ring. However, the desired transformation was achieved after considerable optimization of solvent and base.

Conditions optimized for the deprotonation of simple model compounds (*n*BuLi in ether solvents followed by oxygen) afforded the dephosphinoylated sulfide **4** as a major byproduct in addition to **13**. The undesired side reaction involves alkyllithium attack at phosphorus and could largely be suppressed by using *tert*-butyllithium in THF for the deprotonation step. Under optimum conditions, 49% of thiolactone **13** was obtained from anion oxygenation together with recovered **9**, and recycling gave an eventual 70% conversion to the desired thiolactone. In similar experiments using ether in place of THF, anion oxygenation produced the thiolactone in much lower yield. A new major product was obtained which had not lost phosphorus, and which had a molecular formula corresponding to that of **9** + one oxygen atom. The spectroscopic evidence[6] is most consistent with the formation of a phenol **12** resulting from the ortho-metalation of the $Ph_2P(O)$ moiety followed by anion oxygenation. It is surprising that such a process can compete with formation of **10** by removal of the C_1 proton α to phosphorus and sulfur, and the result gives some indication of the extent to which C_1–H is sterically protected from external reagents.

No further difficulties were encountered in the sulfur removal sequence. Treatment of **13** with aqueous HF in acetonitrile resulted in quantitative deprotection to give **14**, and acyl transfer via the intermediate **15** proceeded in the presence of camphorsulfonic acid at 70 °C to the lactone **16** in 66% yield. No indication of an equilibrium concentration of thiolactone **14** was detected, a result that is consistent with the model study.[5] The lactone products are consistently more stable than the starting thiolactones due to the improved delocalization involving $2p$–2π orbitals, and S to O acyl transfer is favored unless ring strain factors discriminate strongly in favor of the thiolactone. The same sequence of oxidative activation and acyl transfer was also applied to the diastereomeric series corresponding to the minor ring expansion-derived alcohol **3*** via **4***–**10***. Acyl transfer from **14*** to **16*** was somewhat more facile, and the other steps were unexceptional. This sequence was examined only briefly due to the limited quantities of **3*** available.

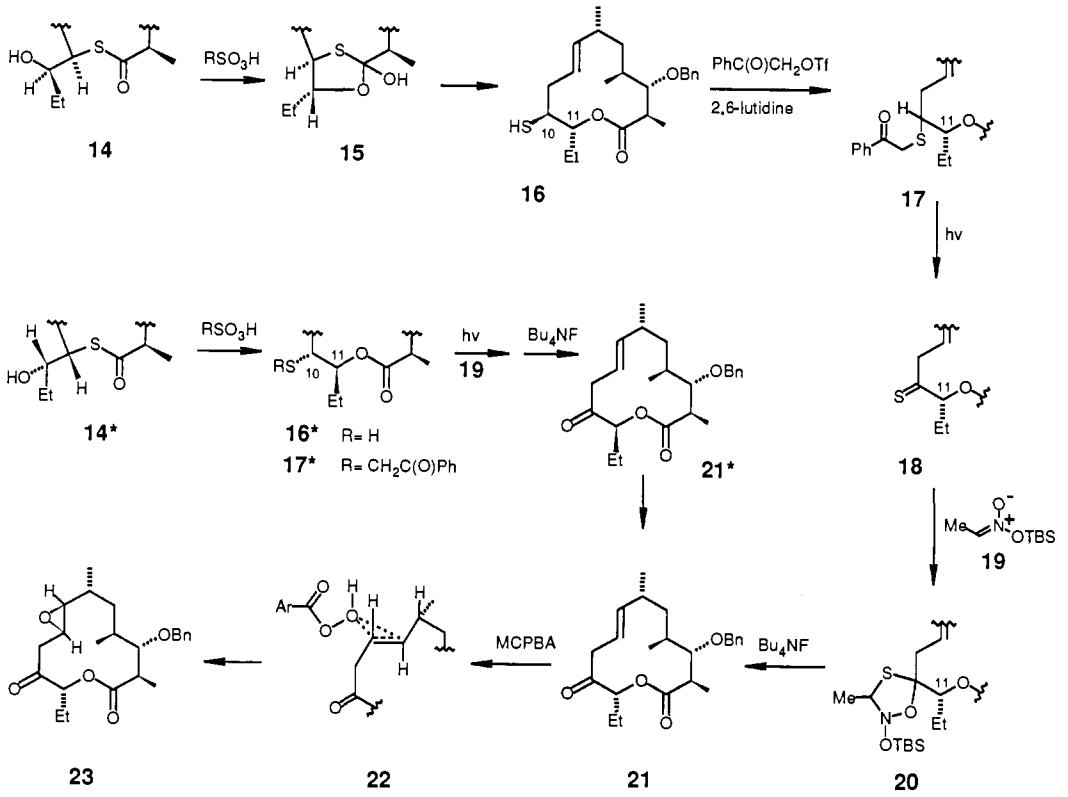
To effect final sulfur removal, the mercaptans **16** and **16*** were converted into the ketones **21** and **21*** by using a photochemical oxidation procedure that had been developed for this purpose.[7] Thus, alkylation of **16** or **16*** with phenacyl triflate[8] produced

(6) The principal difference in NMR spectra of **12** vs **9** was a characteristic phenolic OH signal at δ 11.39 ppm (singlet) in the former. Other evidence for the structure **12** includes an infrared absorption for internally coordinated OH at 3660 cm^{-1}.

(7) Vedejs, E.; Perry, D. *J. Org. Chem.* **1984**, *49*, 573.

(8) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

Scheme II



17 (87%) or **17***, respectively. Sunlamp irradiation then induced a six-center Norrish-type fragmentation and produced the corresponding thioketones **18** or **18*** which were trapped in situ with the reactive nitronate dipolarophile **19**.[9] The 2 + 3 cycloadducts **20** or **20*** were cleaved (Bu_4NF) without isolation to give the ketones **21** (73%) and **21*** (85%). A single isomer was obtained in each case, and no products of epimerization or double bond migration could be detected. More important, the fact that a different ketone **21*** was formed in the sequence starting from alcohol **3*** proved for the first time that **3** and **3*** differ in C_{11} stereochemistry. Earlier, this assignment had been made based on the assumption that both ketones **1** and **2** were reduced under Felkin–Nguyen control. There can be no further doubt regarding this assignment, and the stereochemistry of **21** must correspond to that of methynolide at the relevant carbons. Interestingly, treatment of **21*** with diazabicycloundecene catalyst resulted in efficient (>10:1) conversion into **21**. Simple thermodynamics would have solved the problem of C_{11} stereochemistry in the event that our plans for sulfur-mediated control of remote stereochemistry had not.

Final transformation of **21** into methynolide began with the introduction of the C_7 oxygen. This was accomplished by treatment of **21** with MCPBA to form a single major epoxide **23** followed by DBU-induced elimination to give an (*E*)-enone alcohol **24** (60% overall). A small amount of an isomeric substance tentatively assigned as the hemiketal **25** was also obtained. This structure is supported by the presence of signals for a *Z*-disubstituted alkene in the NMR spectrum and the absence of a ketone carbonyl infrared absorption. The stereochemistry of **24** and **25** is defined at the stage of the epoxidation, and the expected olefin face selectivity of the MCPBA reaction (>10:1) is shown in the structure **23**. Support for this assignment was obtained adventitiously upon attempted debenzylation of the protected C_3 oxygen of **23** by using catalytic transfer hydrogenolysis.[10] Debenzylation did not occur at a reasonable rate until acidic conditions were used (Pd/C + 1,4-cyclohexadiene in toluene + 1 equiv of camphorsulfonic acid). This procedure afforded a bicyclic ether **27** rather than the expected diol. According to molecular models, backside displacement of epoxide C–O bonds by C_3–OH is feasible for **23**, but the corresponding reaction with the diastereomeric epoxide encounters severe nonbonded interactions because the product would be an anti-fused bridged bicycle. The stereochemistry of **23** is well precedented and corresponds to epoxidation via the local conformation **22** having a pseudoequatorial C_6 methyl group in a crownlike environment.[11] Similar relative stereochemistry has been established for the epoxidation of a number of analogous medium-ring alkenes.[11,12]

Since the C_7 hydroxyl must eventually be oxidized to the C_7 ketone of methynolide, we had not initially been concerned with the stereochemistry of epoxidation. However, this issue acquired some significance when it was found that the introduction of the C_{10} methyl group is influenced by subtle factors involving the nature of C_7 substituents. A model study had shown that the unsubstituted enone **26** is attacked by organometallic methyl donors CH_3–M (M = Li, $AlMe_2$, $TiCl_3$, MgX, etc.) predominantly or exclusively from the β-face, as in the geometry **32** for the addition step.[13] This result would produce the unnatural C_{10} epimer in the methynolide series.

In apparent agreement with this study, Grignard addition to the silyl-protected enone **28** produced a 7:1 ratio of tertiary alcohols that gave a 7:1 ratio of **29** and **30** after desilylation. The same major product **29** was also obtained directly from **24** with methyllithium (3:1 ratio), while trimethylaluminum addition was nonselective. However, the reaction of **24** with CH_3MgI proved to be strikingly different. The ratio of **29** and **30** was inverted

(9) Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697.

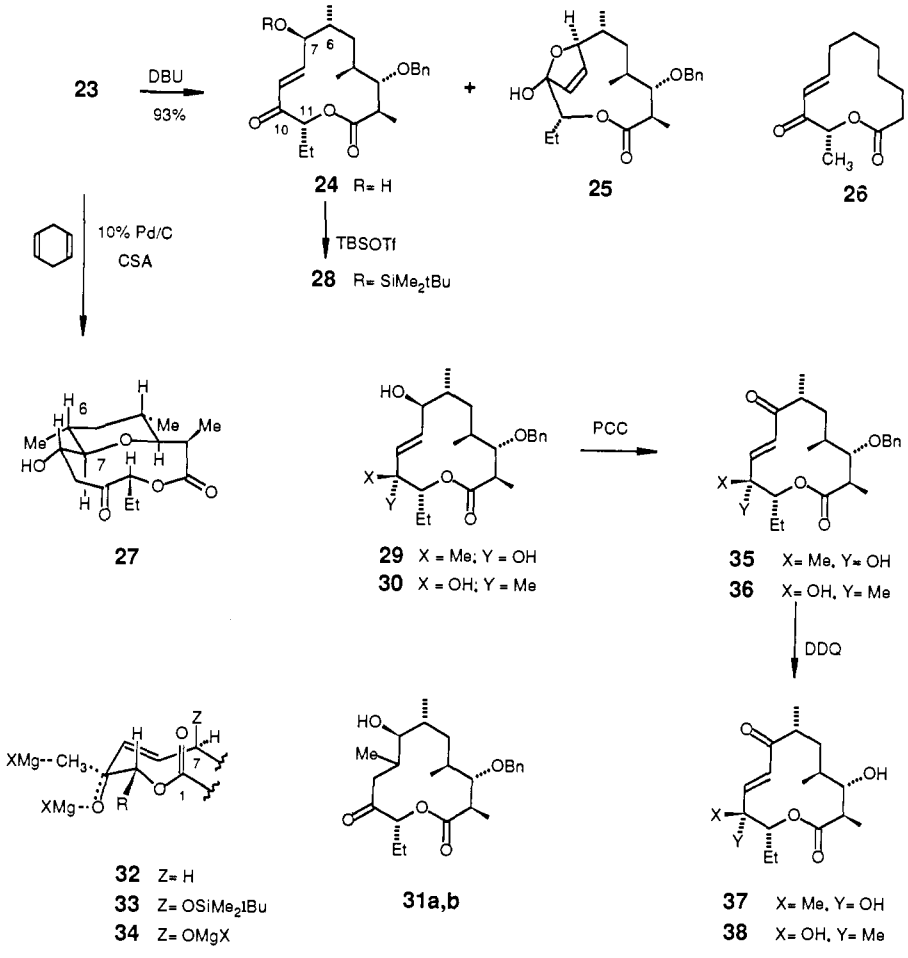
(10) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194. Anantharamaiah, G.; Sivanandaiah, K. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 490.

(11) (a) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. (b) Vedejs, E.; Dophin, J. M.; Gapinski, D. M.; Mastalerz, H. *Current Trends in Organic Synthesis*; Pergamon Press: New York, NY, 1983, p 221. (c) Vedejs, E.; Dent, W. H. III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(12) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106.

(13) Buchanan, R. A., unpublished findings.

Scheme III



in favor of the methynolide stereochemistry (1:7 **29**:**30**). In addition, this reaction produced significant amounts of diastereomeric saturated ketones having a new methyl doublet in the NMR spectrum. Spectral data support the 1,4-adduct structure **31a,b**. The conjugate addition pathway appears related to the recently described ligand-assisted nucleophilic addition process of hydroxy enones[14] and can be attributed to the presence of a magnesium alkoxide at C_7, next to the enone β-carbon. We do not know why the C_7 alkoxide also promotes the desired stereochemistry of methyl addition to the C_{10} ketone. Direct intramolecular involvement of C_7 alkoxide is difficult to accept since the intervening (*E*)-olefin would discourage cyclic transition states spanning the distance from C_7 to C_{10}. The most likely alternative explanation for the difference in stereochemistry in the Grignard addition between C_7–OMgX vs C_7–OSiMe$_2$*t*-Bu assumes a change in transition state conformation in the alkoxide relative to the silyl ether **28**. The neutral **28** probably reacts via the same local conformation **33** (R = ethyl) that was deduced for the simpler enone **26** (conformation **32**, R = Me). There are several alternative geometries to consider (not illustrated) for the surprising α-face addition to **24**, and the C_7 alkoxide apparently increases their relative stability compared to the undesired mode of addition as in **34**.

With the last stereocenter in place, the total synthesis of *d,l*-methynolide could be completed. Oxidation of the C_7 hydroxyl group of **30** using the PCC reagent occurred without interference from the C_{10} hydroxyl subunit of **36** (78%). The last step of benzyl ether cleavage was then performed by using the precedent developed by Yonemitsu et al.[15c] Thus, enone **36** was treated with DDQ at 20 °C to afford *d,l*-methynolide **38** (77%). Since the *d,l*-macrolide had not been previously synthesized, extensive comparison of NMR chemical shifts with spectra of the optically pure synthetic or natural enantiomer of methynolide[15] was performed to establish the identity of the synthetic *d,l*-material, and no differences in chemical shifts of >0.003 ppm were found (Table I). To provide further proof, the unnatural C_{10} epimer **29** was also taken through the oxidation–deprotection sequence via **35**, and the resulting *d,l*-C_{10}-*epi*-methynolide **37** was characterized. The NMR spectra of the two epimers were similar for the ring protons as might be expected, but there were significant differences in the signals of protons corresponding to the C_{11}-ethyl substituent (see Experimental Section).

Table I. ^{1}H NMR Chemical Shift Comparisons of Natural, Synthetic (*d,l*), and C_{11}-*epi*-Methynolide[a]

proton	methynolide	synthetic (*d,l*) (**38**)	C_{11}-*epi* (**37**)
H10	6.5886	6.5879	6.6730
H9	6.3451	6.3433	6.4639
H12	4.7781	4.7788	4.8601
H4	3.5829	3.5827	3.5806
H3	2.6119	2.6133	2.6687
C11-Me	1.3776	1.3793	1.3561
C7-Me	1.3356	1.3362	1.3395
C3-Me	1.2077	1.2090	1.2312
C5-Me	1.0154	1.0144	1.0128
C13-Me	0.9119	0.9092	0.9135

[a] 500 MHz, ppm, $CDCl_3$ solution.

(14) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.

(15) (a) Masamune, S.; Kim, C. V.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021. (c) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647.

In conclusion, the synthesis of a complex macrolide using concepts of relative stereocontrol has been demonstrated.[11] Powerful conformational factors are at work in medium-size rings, and their exploitation allows surprising degrees of stereocontrol.[11,12,16] More often than not, the selectivity is larger than in the analogous transformations of alkene or carbonyl groups in the extensively studied six-membered rings.

The use of sulfur-mediated ring expansion via ylide- or acyl-transfer chemistry can be a viable alternative to macrolactonization strategies.[15,17] The overall conversion from cyclic sulfide derivatives to lactones using the sequence of oxidative activation α-to-sulfur and S-to-O acyl transfer has proved to be efficient in a variety of ring sizes.[5] It does not always compare well in overall yield with approaches to macrolides that rely upon the Horner–Emmons cyclization,[18] but the sulfur-based approach encounters interesting stereochemical opportunities. These arise because medium-ring intermediates are encountered at an early stage. The combination of predictable ring conformations together with the stereoelectronic directing effects of sulfur substituents provides the basis for relaying stereochemical information and for controlling remote stereocenters.

Experimental Section

Preparation of Hydroxy Thiolactones 14 and 14*. A solution of $LiHBEt_3$ (1.0 M in THF, 2.8 mL) was added via cannula to ketone **1** (705.6 mg, 1.887 mmole) in THF (12 mL) at −78 °C. Forty minutes later, an additional portion of $LiHBEt_3$ (1.2 mL) was added. After 2 h at −78 °C, the cooling bath was removed, and the reaction was stirred at room temperature for 0.5 h. Excess reducing agent was quenched with saturated ammonium chloride (2 mL), and the two layers were partitioned between ether (150 mL) and water (5 mL). The ether layer was extracted with water (2 × 5 mL). The alcohol diastereomers were separated by flash chromatography (25 g, 10%:20% ether–hexane) to give **3** (668.5 mg, 94.2%), an unknown minor diastereomer (8.8 mg, 1.2%) and **3*** (24.5 mg, 3.5%). Alcohol **3*** was the main product resulting from reduction of ketone **2**. The same conditions are described above, but scaled down by a factor of 7, were performed with ketone **2** (102 mg, 0.0273 mmol) to give alcohol **3*** (91 mg, 89%) and alcohol **3** (4.7 mg, 4.6%) after separation by flash chromatography.

3. Oil; silica gel, 1:4 ether–hexane, R_f = 0.21; MS, exact mass calcd for $C_{23}H_{36}O_2S_1$ = 376.2427; found = 376.2438, error = 2.9 ppm; IR (neat, cm^{-1}) OH, 3475; 270 MHz NMR ($CDCl_3$) δ 7.40–7.19 (5 H, m), 5.54 (1 H, ddd, J = 15.5, 6.9, 6.4 Hz), 5.40 (1 H, dd, J = 15.5, 8.7 Hz), 4.56 (1 H, d, J = 11.5 Hz), 4.46 (1 H, d, J = 11.5 Hz), 3.73 (1 H, dd, J = 4.8, 3.7 Hz), 3.52–3.40 (1 H, m), 2.79 (1 H, d, J = 3.7 Hz), 2.76 (1 H, dd, J = 14.0, 7.8 Hz), 2.51 (1 H, ddd, J = 9.8, 7.3, 3.4 Hz), 2.37 (1 H, ddd, J = 13.7, 7.1, 3.6 Hz), 2.18 (1 H, ddd, J = 13.8, 11.6, 6.3 Hz), 2.06–1.80 (3 H, m), 1.75 (1 H, ddq, 13.7, 3.6, 7.4), 1.58–1.29 (3 H, m), 1.27 (1 H, ddd, J = 14.3, 3.9, 1.6 Hz), 1.02 (3 H, d, J = 7.4 Hz), 1.01 (3 H, t, J = 7.4 Hz), 0.99 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 6.9 Hz). Unknown minor diastereomer: oil; silica gel, 20% ether–hexane, R_f = 0.18; MS, exact mass calcd for $C_{23}H_{36}O_2S_1$ = 376.2427; found 376.244, error = 3.4 ppm; IR (neat, cm^{-1}) OH, 3600; 200 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 5.61 (1 H, ddd, J = 15.8, 7.3, 5.7 Hz), 5.49 (1 H, dd, J = 15.8, 8.0 Hz), 4.57 (1 H, d, J = 11.4 Hz), 4.43 (1 H, d, J = 11.4 Hz), 4.01 (1 H, dd, J = 4.4, 4.4 Hz), 3.64–3.52 (1 H, m), 2.82–2.55 (2 H, m), 2.45–1.80 (6 H, m), 1.70–1.10 (5 H, m), 1.04 (6 H, d, J = 7.4 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 7.4 Hz).

3*. Solid, mp 79–80 °C (cryst from ether–hexane); MS, exact mass calcd for $C_{23}H_{36}O_2S_1$ = 376.2427; found 376.2438, error = 2.9 ppm; IR (neat, cm^{-1}) OH, 3425; 270 MHz NMR ($CDCl_3$) δ 7.35–7.15 (5 H, m), 5.45–5.20 (2 H, m), 4.57 (1 H, d, J = 11.3 Hz), 4.51 (1 H, d, J = 11.3 Hz), 3.43 (1 H, dddd, J = 9.8, 8.0, 6.0, 3.9 Hz), 2.78 (1 H, d, J = 10.1 Hz), 2.70–2.45 (2 H, m), 2.45–2.30 (3 H, m), 2.18–1.95 (1 M, m), 2.01–1.85 (2 H, m), 1.80–1.65 (3 H, m), 1.70–1.35 (1 H, m), 1.22 (1 H, s), 1.07 (3 H, d, J = 7.4 Hz), 1.04 (3 H, d, J = 6.9 Hz), 1.00 (3 H, d, J = 6.6 Hz), 0.97 (3 H, t, J = 7.3 Hz).

***tert*-Butyldimethylsilyl Ether 4.** *tert*-Butyldimethylsilyl triflate[20] (0.625 mL, 1.05 equiv) and 2,6-lutidine (0.52 mL, 2.0 equiv) were added to alcohol **3** (850 mg, 2.26 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring for 2 h, the reaction mixture was diluted with 20% ether–hexane (100 mL) and extracted with 10% H_2SO_4 (1 × 5 mL) and saturated $NaHCO_3$ (1 × 5 mL). The resulting oil was purified by flash chromatography (10 g, 10% ether–hexane) to give **4** (1.095 g, 99%).

4. Oil; silica gel, 5% ether–hexane, R_f = 0.49; MS, exact mass calcd for $C_{29}H_{50}O_2S_1Si_1$ = 490.3289; found 490.3301, error = 2.6 ppm; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 5.62 (1 H, ddd, J = 16.1, 8.0, 5.3 Hz), 5.42 (1 H, dd, J = 16.1, 8.6 Hz), 4.56 (1 H, d, J = 11.5 Hz), 4.46 (1 H, d, J = 11.5 Hz), 3.87 (1 H, dd, J = 4.5, 4.3 Hz), 3.67 (1 H, ddd, J = 8.3, 3.6, 3.6 Hz), 2.75 (1 H, dd, J = 14.1, 8.6 Hz), 2.62–2.46 (2 H, m), 2.16 (1 H, dd, J = 14.1, 5.7 Hz), 2.14–1.98 (2 H, m), 1.86 (1 H, ddd, J = 13.8, 8.0, 2.1 Hz), 1.64 (1 H, ddq, 13.7, 3.6, 7.4), 1.60–1.23 (4 H, m), 1.01 (3 H, d, J = 7.2 Hz), 0.99 (3 H, d, J = 6.9 Hz), 0.99 (3 H, d, J = 6.9 Hz), 0.89 (3 H, t, J = 7.4 Hz), 0.87 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s).

Sulfoxide 5. *m*-Chloroperbenzoic acid (362 mg, 1.07 equiv) in CH_2Cl_2 (15 mL) was added via cannula to sulfide **4** (812 mg, 1.66 mmol) in CH_2Cl_2 (25 mL) at −78 °C. After 3 h the reaction was warmed to, and maintained at, −40 °C for 1 h. Excess peracid was quenched with dimethyl sulfide (3 drops). The solvent was diluted with 80% ether–hexane (200 mL) and extracted with 10% NaOH (5 × 5 mL) to give an oil after solvent removal. Purification by flash chromatography (5 g, 50% ether–hexane) gave a mixture of sulfoxide diastereomers **5** (835 mg, 99%) in a 4:1 ratio by NMR. For characterization purposes, the sulfoxide diastereomers were separated on silica gel (50% ether–hexane).

Major Isomer of 5. Oil; silica gel, 1:2 ethyl acetate–hexane, R_f = 0.12; MS, exact mass calcd for $C_{29}H_{50}O_3S_1Si_1$ = 506.3238; found = 506.325, error = 2.5 ppm; IR (neat, cm^{-1}) S=O, 1025; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 5.70 (1 H, ddd, J = 16.0, 7.5, 3.4 Hz), 5.37 (1 H, ddd, J = 16.0, 9.4, 2.1 Hz), 4.57 (2 H, s), 3.93 (1 H, ddd, J = 7.1, 5.3, 3.5 Hz), 3.24 (1 H, dd, J = 12.2, 0.9 Hz), 2.87–2.55 (2 H, m), 2.41 (1 H, dd, J = 12.2, 12.2 Hz), 2.12 (1 H, ddd, J = 16.5, 2.8, 2.8 Hz), 2.10–1.85 (1 H, m), 1.85–1.40 (7 H, m), 1.16 (3 H, d, J = 6.2 Hz), 1.07 (3 H, d, J = 7.1 Hz), 0.97 (3 H, d, J = 6.4 Hz), 0.92 (3 H, t, J = 6.7 Hz), 0.89 (9 H, s), 0.10 (3 H, s), 0.07 (3 H, s).

Minor Isomer of 5. Oil; silica gel, 1:2 ethyl acetate–hexane, R_f = 0.25; MS, exact mass calcd for $C_{29}H_{50}O_3S_1Si_1$ = 506.3238; found 506.325, error = 2.5 ppm; IR (neat, cm^{-1}) S=O, 1020; 270 MHz NMR ($CDCl_3$) δ 7.45–7.20 (5 H, m), 5.46 (1 H, dd, J = 15.8, 7.9 Hz), 5.36 (1 H, dd, J = 15.8, 6.3 Hz), 4.59 (1 H, d, J = 11.4 Hz), 4.56 (1 H, d, J = 11.4 Hz), 4.16 (1 H, ddd, J = 8.0, 5.3, 2.5 Hz), 3.24 (1 H, ddd, J = 9.0, 5.3, 2.8 Hz), 3.10–2.70 (2 H, m), 2.87 (1 H, dd, J = 13.5, 3.9 Hz), 2.66 (1 H, dd, J = 13.5, 9.6 Hz), 2.38–2.15 (1 H, m), 2.10–0.90 (7 H, m), 1.29 (3 H, d, J = 6.7 Hz), 1.05 (3 H, d, J = 7.1 Hz), 0.97 (3 H, d, J = 6.4 Hz), 0.94 (3 H, t, J = 7.8 Hz), 0.89 (9 H, s), 0.10 (3 H, s), 0.09 (3 H, s).

Phosphine Oxide 9. The sulfoxides **5** (70.2 mg, 0.139 mmol) and 1,10-phenanthroline (0.2 mg) were dissolved in THF (2.5 mL) and cooled to −78 °C. Enough *n*-BuLi (1.0 M, 0.025 mL) was added to obtain a persistent red-brown color, and then 1.3 more equiv of *n*-BuLi were added. One hour later, addition of chlorodiphenylphosphine (0.037 mL, 1.3 equiv) significantly lightened the color to yellow-orange almost immediately. CH_2Cl_2 (3 mL) was added 15 min later, and, after warming to 0 °C, iodine (35 mg in 2 mL of CH_2Cl_2, 1.0 equiv) was added. Stirring at 0 °C was continued for 3 h, and then the reaction mixture was diluted with 50% ether–hexane (20 mL) and extracted with saturated $Na_2S_2O_3$ (3 × 3 mL) and water (1 × 3 mL). The solvent was removed to give an oil which was purified by flash chromatography (5 g, 10%:20% ethyl acetate–hexane). Two phosphine oxide diastereomers of **9** (58 mg, 60%) were obtained in a ratio of 2:1, by NMR. The vinyl sulfide **8** was also formed in 9% yield.

9, Major Diastereomer. Oil; silica gel, 1:4 ethyl acetate–hexane, R_f = 0.42; MS, exact mass calcd for $C_{41}H_{59}O_3P_1S_1Si_1$ = 690.3678; found 690.3692, error = 2.1 ppm; IR (neat, cm^{-1}) P=O, 1105; 200 MHz NMR ($CDCl_3$) δ 7.95–7.75 (3 H, m), 7.50–7.19 (7 H, m), 5.58 (1 H, ddd, J = 16.0, 7.6, 4.1 Hz), 5.42 (1 H, ddd, J = 16.0, 8.7, 1.4 Hz), 4.61 (1 H, d, J = 11.3 Hz), 4.53 (1 H, d, J = 11.3 Hz), 4.27 (1 H, dd, J = 9.9, 5.3 Hz), 4.24 (1 H, dd, J = 10.7, 3.0 Hz), 3.53 (1 H, ddd, J = 8.6, 3.3, 3.3 Hz), 3.23 (1 H, dd, J = 10.2, 3.3 Hz), 2.61 (1 H, ddd, J = 15.6, 3.3, 1.4 Hz), 2.31 (1 H, dddq, 14.8, 5.3, 3.0, 7.1), 2.15–1.80 (2 H, m), 1.70–1.45 (4 H, m), 1.40–0.90 (6 H, m), 1.14 (3 H, d, J = 7.1 Hz), 1.04 (3 H, d, J = 7.3 Hz), 0.97 (3 H, d, J = 6.6 Hz), 0.85 (9 H, s), 0.71 (3 H, t, J = 7.4 Hz), 0.11 (3 H, s), 0.07 (3 H, s).

9, Minor Diastereomer. Oil; silica gel, 1:2 ethyl acetate–hexane, R_f = 0.21; MS, no peak match, parent; M − C_4H_9, calcd = 633.2974; found 633.3067, error = 14.7 ppm, formula = $C_{41}H_{59}O_3P_1Si_1S_1$; IR (neat, cm^{-1}) P=O, 1095; 270 MHz NMR ($CDCl_3$) δ 8.10–7.80 (3 H, m), 7.65–7.19 (7 H, m), 6.55–6.35 (2 H, m), 4.61 (1 H, d, J = 11.9 Hz), 4.43 (1 H, d, J = 11.9 Hz), 3.95 (1 H, d, J = 6.3 Hz), 3.69 (1 H, dd, J = 14.1, 1.0 Hz), 3.54 (1 H, ddd, J = 8.9, 2.8, 2.6 Hz), 2.60–2.20 (4 H, m), 2.20–2.00

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(1 H, m), 1.90–1.65 (2 H, m), 1.50–0.70 (8 H, m), 1.15 (3 H, d, J = 8.0 Hz), 1.04 (3 H, d, J = 6.9 Hz), 0.85 (9 H, s), 0.76 (3 H, d, J = 7.1 Hz), 0.70 (3 H, t, J = 6.8 Hz), 0.01 (3 H, s), –0.03 (3 H, s).

8. Oil; silica gel, 1:4 ethyl acetate–hexane, R_f = 0.76; MS, exact mass calcd for $C_{29}H_{48}O_2Si_1S_1$ = 488.3132; found 488.3137, error = 1 ppm; IR (neat, cm^{-1}) C=C, 1642; 270 MHz NMR ($CDCl_3$) δ 7.45–7.20 (5 H, m), 6.00 (1 H, s), 5.58 (1 H, dd, J = 15.5, 6.4 Hz), 5.29 (1 H, ddd, J = 15.5, 9.5, 5.1 Hz), 4.62 (1 H, d, J = 12.0 Hz), 4.22 (1 H, d, J = 12.0 Hz), 3.74 (1 H, ddd, J = 8.0, 3.9, 3.6 Hz), 3.49 (1 H, s), 2.85 (1 H, ddd, J = 10.1, 3.0, 1.7 Hz), 2.80–2.65 (1 H, m), 2.29–2.16 (1 H, m), 1.93–1.10 (6 H, m), 1.72 (3 H, s), 1.04 (3 H, d, J = 7.1 Hz), 0.98 (3 H, d, J = 6.3 Hz), 0.89 (9 H, s), 0.89 (3 H, t, J = 7.3 Hz), 0.08 (3 H, s), 0.06 (3 H, s).

Thiolactone Silyl Ether 13. The major phosphine oxide diastereomer **9** (342 mg, 0.496 mmol) and 1,10-phenanthroline (0.2 mg) in THF (8 mL) were cooled to –78 °C. Enough *t*-BuLi (1.3 mL, 0.54 M in hexane, 1.12 equiv) was added to obtain a persistent red color, and then 1.0 additional equiv of *t*-BuLi was added. The reaction was stirred at –78 °C for 2.5 h and then quenched by bubbling dry oxygen (dried by passing through the following: H_2SO_4, two traps cooled to –78 °C, and finally through a 2-foot U-tube (3-cm diameter) which was filled with Drierite) directly into the reaction via a 20 gauge stainless steel needle (CAUTION: dilute exit gas with nitrogen and perform the reaction behind a safety shield). Oxygenation was continued for 0.5 h, and then the reaction was quenched with a phosphate buffer (0.5 mL, 0.0125 M Na_2HPO_4 solution) and diluted with 80% ether–hexane (50 mL). The organic layer was extracted with 10% $NaHCO_3$ (1 × 5 mL) and brine (1 × 5 mL). The oil resulting from solvent removal was purified by flash chromatography (8 g, 10%:20% ethyl acetate–hexane) to give thiolactone **13** (125.7 mg, 50%), sulfide **4** (13.6 mg, 5%), *tert*-butyldiphenylphosphine oxide (6.9 mg, 5%), and recovered starting material (84.4 mg, 25%). The minor diastereomer **9** (100.1 mg, 0.0145 mmol) was submitted to the same reaction conditions as above, but on one-third the scale just described. The same products were obtained: thiolactone **13** (34.7 mg, 47%), sulfide **4** (3.7 mg, 5%), *tert*-butyldiphenylphosphine (1.9 mg, 5%) and recovered starting material (15.8 mg, 16%). Based on recycling the recovered starting material, the yield of thiolactone was 75%. When the solvent THF was replaced with diethyl ether, phenol **12** was formed as the major product.

13. Oil; silica gel, 25% ether–hexane, R_f = 0.62; MS, exact mass calcd for $C_{29}H_{48}O_3Si_1S_1$ = 504.3081; found 504.3094, error = 2.5 ppm; IR (neat, cm^{-1}) O=C—S, 1700; O=C—S, 1690; 270 MHz NMR ($CDCl_3$) δ 7.50–7.20 (5 H, m), 5.64 (1 H, dd, J = 15.5, 7.6 Hz), 5.41 (1 H, ddd, J = 15.5, 9.6, 4.2 Hz), 4.64 (1 H, d, J = 11.9 Hz), 4.51 (1 H, d, J = 11.9 Hz), 3.72 (1 H, ddd, J = 6.6, 6.6, 2.4 Hz), 3.70–3.60 (1 H, m), 3.50–3.40 (1 H, m), 3.10–2.90 (1 H, m), 2.47 (1 H, ddd, J = 13.3, 4.2, 3.4 Hz), 2.25–1.79 (3 H, m), 1.65–1.37 (3 H, m), 1.25 (3 H, d, J = 7.1 Hz), 1.15–1.01 (1 H, m), 0.99 (3 H, d, J = 6.8 Hz), 0.89 (9 H, s), 0.84 (3 H, t, J = 7.5 Hz), 0.06 (3 H, s), 0.04 (3 H, s), –0.95 (3 H, d, J = 6.8 Hz).

12. Oil; silica gel, 20% ether–hexane, R_f = 0.26; IR ($CHCl_3$, cm^{-1}) OH, 3660; 200 MHz NMR ($CDCl_3$) δ 11.39 (1 H, s), 7.95–7.75 (2 H, m), 7.55–7.20 (10 H, m), 6.95–6.65 (2 H, m), 5.61 (1 H, ddd, J = 16.1, 7.4, 4.0 Hz), 5.42 (1 H, ddd, J = 16.1, 8.4, 1.1 Hz), 4.56 (1 H, d, J = 11.2 Hz), 4.44 (1 H, d, J = 11.2 Hz), 4.14 (1 H, dd, J = 12.9, 5.4 Hz), 4.02 (1 H, dd, J = 7.3, 2.2 Hz), 3.59 (1 H, ddd, J = 7.3, 3.3, 3.3 Hz), 3.22 (1 H, dd, J = 7.3, 1.6 Hz), 2.57 (1 H, br d, J = 15.2 Hz), 2.45–2.25 (1 H, m), 2.20–1.85 (2 H, m), 1.65–0.90 (5 H, m), 1.20 (3 H, d, J = 7.1 Hz), 0.99 (3 H, d, J = 7.1 Hz), 0.98 (3 H, d, J = 6.6 Hz), 0.85 (9 H, s), 0.68 (3 H, t, J = 7.3 Hz), 0.11 (3 H, s), 0.07 (3 H, s).

Hydroxyalkyl Thiolactone 14. The *tert*-butyldimethylsilyl-protected thiolactone **13** (161.6 mg, 0.3206 mmol) in CH_3CN (6 mL) was treated with 48% HF (9 drops). This mixture was stirred for 1.75 h, then diluted with 50% ether–hexane (60 mL), and extracted with saturated $NaHCO_3$ (2 × 5 mL) and brine (1 × 4 mL). After the solvent was removed, the resulting oil was purified by flash chromatography (8 g, 5%:20% ethyl acetate–hexane) to give hydroxy thiolactone **14** (124.9 mg, 100%).

14. Oil; silica gel, 25% ethyl acetate–hexane, R_f = 0.31; MS, exact mass calcd for $C_{23}H_{34}O_3S_1$ = 390.222; found 390.2227, error = 1.7 ppm; IR (neat, cm^{-1}) OH, 3560; O=C—S, 1665; 270 MHz NMR ($CDCl_3$) δ 7.39–7.20 (5 H, m), 5.60 (1 H, dd, J = 15.8, 7.6 Hz), 5.32 (1 H, ddd, J = 15.8, 9.0, 5.6 Hz), 4.63 (1 H, d, J = 11.8 Hz), 4.53 (1 H, d, J = 11.8 Hz), 3.75–3.68 (1 H, m), 3.60–3.51 (1 H, m), 3.40 (1 H, d, J = 5.6 Hz), 3.07 (1 H, dq, J = 5.6, 7.1 Hz), 2.45 (1 H, ddd, J = 13.0, 5.6, 4.7 Hz), 2.24 (1 H, ddd, J = 13.0, 9.0, 9.0 Hz), 2.07–1.82 (2 H, m), 1.65–1.45 (4 H. m), 1.26 (3 H, d, J = 7.1 Hz), 1.11 (1 H, ddd, J = 13.9, 8.4, 2.2 Hz), 0.99 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 6.8 Hz), 0.95 (3 H, t, J = 7.5 Hz).

tert*-Butyldimethylsilyl Ether 4*.** *tert*-Butyldimethylsilyl triflate (0.14 Ml, 1.8 equiv) and 2,6-lutidine (0.13 mL, 3.6 equiv) were added to alcohol **3 (107 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 3 h, the reaction mixture was diluted with 20% ether–hexane (20 mL) and extracted with 10% H_2SO_4 (1 × 2 mL) and saturated $NaHCO_3$ (1 × 2 mL). A clear oil **4*** (123 mg, 88%) was isolated after purification by flash chromatography (5 g silica gel, 5% ether–hexane).

4*. Oil; silica gel, 5% ether–hexane, R_f = 048; MS, exact mass calcd for $C_{29}H_{50}O_2Si_1S_1$ = 490.3289; found 490.3301, error = 2.6 ppm; 200 MHz NMR ($CDCl_3$) δ 7.38–7.19 (5 H, m), 5.38–5.16 (2 H, m), 4.58 (1 H, d, J = 11.1 Hz), 4.50 (1 H, d, J = 11.1 Hz), 3.72 (1 H, ddd, J = 8.6, 3.5, 3.5 Hz), 2.80 (1 H, dd, J = 11.1, 2.9 Hz), 2.71 (1 H, d, J = 10.4 Hz), 2.62 (1 H, ddd, J = 11.1, 3.4, 1.3 Hz), 2.54–2.35 (2 H, m), 2.15–1.80 (3 H, m), 1.80–1.15 (5 H, m), 1.06 (3 H, d, J = 7.5 Hz), 1.02 (3 H, d, J = 7.5 Hz), 0.98 (3 H, d, J = 6.4 Hz), 0.91 (9 H, s), 0.90 (3 H, t, J = 6.8 Hz), 0.06 (3 H, s), 0.05 (3 H, s).

Sulfoxide 5*. To sulfide **4*** (140 mg, 0.30 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added a CH_2Cl_2 solution of *m*-chloroperbenzoic acid (65 mg in 2 mL, 1.0 equiv) via cannula over a 15-min period. The temperature was maintained at –78 °C for 3 h, followed by warming to –20 °C for 20 min. Dimethyl sulfide (3 drops) was added to quench excess peracid, and the cooling bath was removed. The reaction mixture was diluted with 50% ether–hexane (50 mL) and extracted with 10% NaOH (4 × 3 mL). After solvent removal, the resulting oil was purified by flash chromatography (5 g of silica gel, 30% ethyl acetate–hexane). A single sulfoxide diastereomer **5*** (135 mg, 88%) was isolated.

5*. Oil; silica gel, 50% ether–hexane, R_f = 0.34; MS, exact mass calcd for $C_{29}H_{50}O_3Si_1S_1$ = 506.3238; found 506.3245, error = 1.5 ppm; IR (neat, cm^{-1}) S=O, 1060; 200 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 5.23–5.01 (2 H, m), 4.62 (1 H, d, J = 11.0 Hz), 4.56 (1 H, d, J = 11.0 Hz), 4.13 (1 H, ddd, J = 9.7, 3.8, 2.0 Hz), 3.66 (1 H, d, J = 12.8 Hz), 2.97 (1 H, ddd, J = 11.5, 3.8, 0.9 Hz), 2.88 (1 H, d, J = 14.4 Hz), 2.81 (1 H, d, J = 9.7 Hz), 2.16–2.05 (2 H, m), 2.15 (1 H, dd, J = 12.8, 12.2 Hz), 2.01 (1 H, dq, J = 9.7, 5.7 Hz), 1.98–1.89 (1 H, m), 1.71 (1 H, ddq, 11.9, 2.0, 6.9), 1.56–1.30 (3 H, m), 1.33 (3 H, d, J = 5.7 Hz), 1.09 (3 H, d, J = 7.1 Hz), 0.95 (3 H, t, J = 6.9 Hz), 0.95 (3 H, d, J = 6.6 Hz), 0.89 (9 H, s), 0.10 (3 H, s), 0.08 (3 H, s).

Phosphine Oxide 9*. The sulfoxide **5*** (43.5 mg, 0.085 mmol) and 1,10-phenanthroline (0.2 mg) were dissolved in THF (1 mL) and cooled to –78 °C. Enough *n*-BuLi (1.0 M, 0.120 mL, 1.4 equiv) was added until a reddish-brown color persisted, and then 1.0 equiv more of *n*-BuLi was added via syringe. The anion was quenched 1 h later with chlorodiphenylphosphine (0.022 mL, 1.4 equiv). Twenty minutes later, iodine (17.4 mg, 0.8 equiv) in CH_2Cl_2 (2 mL) was added via syringe, and the reaction was stirred at 0 °C for 0.5 h, diluted with 50% ether–hexane (20 mL), and extracted with saturated $Na_2S_2O_3$ (3 × 2 mL) to remove the iodine. The oil obtained after solvent removal was purified by flash chromatography (6 g of silica gel, 30% ethyl acetate–hexane) to afford a single phosphine oxide diastereomer **9*** (49 mg, 79%).

9*. Oil; silica gel, 20% ethyl acetate, R_f = 0.44; MS, exact mass calcd for $C_{41}H_{59}O_3P_1Si_1S_1$ = 690.3678; found 690.3692, error = 2.1 ppm; IR (neat, cm^{-1}) P=O, 1135; 200 MHz NMR ($CDCl_3$) δ 8.34–7.15 (15 H, m), 5.39–5.25 (2 H, m), 4.42 (1 H, d, J = 11.5 Hz), 4.28 (1 H, d, J = 11.5 Hz), 3.66 (1 H, d, J = 11.0 Hz), 3.57 (1 H, dd, J = 11.2, 2.3 Hz), 3.16 (1 H, ddd, J = 7.6, 3.8, 3.8 Hz), 2.74 (1 H, d, J = 13.7 Hz), 2.70–2.41 (1 H, m), 2.22 (1 H, dd, J = 10.9, 3.8 Hz), 2.15–1.10 (7 H, m), 1.02 (3 H, d, J = 7.3 Hz), 1.02 (3 H, d, J = 7.3 Hz), 0.97 (3 H, d, J = 6.6 Hz), 0.80 (9 H, s), 0.70 (3 H, t, J = 7.3 Hz), –0.14 (3 H, s), –0.21 (3 H, s).

Thiolactone 13*. 1,10-Phenanthroline (0.2 mg) and the phosphine oxide **9*** (48.6 mg, 0.070 mmol) were cooled to –78 °C in THF (20 mL). Enough *t*-BuLi (0.54 M, 0.190 mL, 1.5 equiv) was added via syringe to obtain a persistent reddish color, and then 1.0 additional equiv was added. Two hours were provided for anion formation, and then the temperature was lowered to –120 °C (N_2/pentane). Oxygen (dried as before) was bubbled directly into the solvent via a 20 gauge stainless steel needle for 15 min (CAUTION: exit gases should be diluted with N_2 and the reaction performed behind a safety shield). Upon warming to –78 °C, the indicator color faded. Camphorsulfonic acid (17 mg, 1.5 equiv) in THF (0.3 mL) was used to neutralize the reaction mixture. The reaction mixture was added to hexane (10 mL) and extracted with 10% $NaHCO_3$ (2 × 3 mL). The solvent was removed, and the resulting oil was purified by flash chromatography (3 g, 20%:50%) ethyl acetate–hexane). Thiolactone **13*** (12 mg, 34%) and recovered starting material (8.5 mg, 16%) were the only products identified.

13*. Oil; silica gel, 3.33% ethyl acetate 6.67% CH_2Cl_2–hexane, R_f = 0.65; MS, no peak match, parent; M – *t*-Bu, 447.2389, calcd = 447.2389, error = 0.0 ppm, formula = $C_{29}H_{48}O_3Si_1S_1$; IR (neat, cm^{-1}) O=C—S, 1700, O=C—S, 1690; 200 MHz NMR ($CDCl_3$) δ 7.28–7.15 (5 H, m), 5.17 (1 H, ddd, J = 15.5, 8.6, 3.3 Hz), 5.08 (1 H, ddd, J = 15.5, 8.6, 4.5 Hz), 4.66 (1 H, d, J = 11.1 Hz), 4.60 (1 H, d, J = 11.1 Hz), 3.70 (1 H, ddd, J = 6.5, 6.5, 2.3 Hz), 3.62 (1 H, ddd, J = 12.5, 2.3, 2.3 Hz),

3.48 (1 H, dd, J = 9.7, 1.0 Hz), 3.10 (1 H, dq, J = 9.7, 6.8 Hz), 2.35 (1 H, ddd, J = 12.5, 4.5, 2.3 Hz), 2.05 (1 H, ddd, J = 12.5, 12.5, 8.6 Hz), 1.85–1.35 (6 H, m), 1.28 (3 H, d, J = 6.8 Hz), 1.05 (3 H, d, J = 6.8 Hz), 0.99 (3 H, d, J = 6.6 Hz), 0.88 (9 H, s), 0.86 (3 H, t, J = 7.7 Hz), 0.06 (3 H, s), 0.04 (3 H, s).

Hydroxyalkyl Thiolactone 14*. To the *tert*-butyldimethylsilyl ether of thiolactone **13*** (31 mg, 0.061 mmol) in acetonitrile (1 mL) was added 48% HF (4 drops). After stirring for 1.5 h, the reaction was diluted with 50% ether–hexane (20 mL) and extracted with saturated $NaHCO_3$ (1 × 3 mL) and brine (1 × 3 mL). Purification by flash chromatography (3 g, 10% ethyl acetate–hexane) gave hydroxy thiolactone **14*** (20.5 mg) in 85% yield.

14*. Oil; silica gel, 20% ethyl acetate, R_f = 0.58; MS, exact mass calcd for $C_{23}H_{34}O_3S_1$ = 390.222; found 390.2262, error = 10.7 ppm; IR (neat, cm^{-1}) SH, 2585, O=C—O, 1729; 200 MHz NMR ($CDCl_3$) δ 7.42–7.28 (5 H, m), 5.55 (1 H, ddd, J = 15.2, 9.5, 5.3 Hz), 5.20–5.11 (1 H, m), 5.11 (1 H, ddd, J = 15.2, 9.5, 1.3 Hz), 4.65 (2 H, d, J = 12.0 Hz), 3.81 (1 H, dd, J = 6.8, 3.1 Hz), 3.12 (1 H, dddd, J = 10.1, 6.5, 2.4, 1.8 Hz), 2.71 (1 H, dq, J = 6.8, 6.8 Hz), 2.60–2.40 (2 H, m), 2.39 (1 H, ddd, J = 14.0, 9.5, 2.4 Hz), 2.18–1.45 (5 H, m), 1.40 (1 H, d, J = 10.1 Hz), 1.29 (3 H, d, J = 7.3 Hz), 0.99 (3 H, d, J = 7.1 Hz), 0.95 (3 H, d, J = 7.5 Hz), 0.87 (3 H, t, J = 6.8 Hz).

Transacylation of Hydroxy Thiolactones 14 and 14*. Lactone 16. Hydroxy thiolactone **14** (23.5 mg, 0.0603 mmol) was combined with camphorsulfonic acid (31 mg, 2.2 equiv, recrystallized from benzene) in dry benzene (5 mL). A condenser was attached and sealed with Teflon tape to keep out water. The reaction was heated to 70 °C for 72 h. The crude reaction was passed through a silica gel pipet plug (0.5 g, 20% ether–hexane), and the solvent was removed. The resulting oil was further purified by flash chromatography (4 g of silica gel, 5%:30% ether–hexane) to give the desired lactone **16** (15.0 mg, 63%) and recovered starting material (1.1 mg, 4%).

16. Oil; silica gel, 25% ether–hexane, R_f = 0.46; MS, exact mass calcd for $C_{23}H_{34}O_3S_1$ = 390.222; found 390.2229, error = 2.3 ppm; IR (neat, cm^{-1}) SH, 2575, O=C—O, 1738; 270 MHz NMR ($CDCl_3$) δ 7.45–7.19 (5 H, m), 5.51 (1 H, ddd, J = 15.5, 6.6, 6.6 Hz), 5.43 (1 H, dd, J = 15.5, 7.1 Hz), 4.68 (1 H, ddd, J = 9.6, 3.3, 3.3 Hz), 4.65 (2 H, s), 3.44 (1 H, d, J = 10.4 Hz), 3.27 (1 H, dddd, J = 8.6, 8.3, 3.3, 2.7 Hz), 2.71 (1 H, dq, J = 10.4, 6.9 Hz), 2.51 (1 H, ddd, J = 14.0, 8.6, 6.6 Hz), 2.25 (1 H, ddd, J = 14.0, 6.6, 2.7 Hz), 2.10–1.80 (2 H, m), 1.75–1.05 (4 H, m), 1.66 (1 H, d, J = 8.3 Hz), 1.26 (3 H, d, J = 6.9 Hz), 1.05 (3 H, d, J = 6.9 Hz), 0.98 (3 H, d, J = 6.9 Hz), 0.92 (3 H, t, J = 7.4 Hz).

Lactone 16*. Hydroxy thiolactone **14*** (18.8 mg) and camphorsulfonic acid (recrystallized from benzene, 34 mg) were combined in dry benzene (5 mL) and heated to 70 °C under a reflux condenser. After 36 h, the reaction was cooled to room temperature, and the crude reaction mixture was filtered through a silica gel pipet plug (0.5 g, 20% ether–hexane) to remove the acid catalyst. Purification by flash chromatography (1.5 g, 10% ethyl acetate–hexane) gave the desired lactone **16*** (14.8 mg) in 79% isolated yield.

16*. Oil; silica gel, 20% ethyl acetate, R_f = 0.58; MS, exact mass calcd for $C_{23}H_{34}O_3S_1$ = 390.222; found 390.2262, error = 10.7 ppm; IR (neat, cm^{-1}) SH, 2585, O=C—O, 1729; 200 MHz NMR ($CDCl_3$) δ 7.42–7.28 (5 H, m), 5.55 (1 H, ddd, J = 15.2, 9.5, 5.3 Hz), 5.20–5.11 (1 H, m), 5.11 (1 H, ddd, J = 15.2, 9.5, 1.3 Hz), 4.65 (2 H, d, J = 12.0 Hz), 3.81 (1 H, dd, J = 6.8, 3.1 Hz), 3.12 (1 H, dddd, J = 10.1, 6.5, 2.4, 1.8 Hz), 2.71 (1 H, dq, J = 6.8, 6.8 Hz), 2.60–2.40 (2 H, m), 2.39 (1 H, ddd, J = 14.0, 9.5, 2.4 Hz), 2.18–1.45 (5 H, m), 1.40 (1 H, d, J = 10.1 Hz), 1.29 (3 H, d, J = 7.3 Hz), 0.99 (3 H, d, J = 7.1 Hz), 0.95 (3 H, d, J = 7.5 Hz), 0.87 (3 H, t, J = 6.8 Hz).

Phenacyl Sulfide 17*. Thiol **16*** (14.8 mg, 0.038 mmol) was dissolved in CH_2Cl_2 (0.1 mL) and CH_3CN (0.2 mL) and then cooled to −5 °C. 2,6-Lutidine (0.007 mL, 1.5 equiv) and phenacyl triflate[8] (11.2 mg, 1.1 equiv) were added to the thiol, and the cooling bath was removed. The reaction was stirred for 2.5 h, and then the crude reaction mixture was passed through a silica gel pipet plug (0.5 g, 20% ether–hexane). After solvent removal, the oil was purified by preparative thin-layer chromatography to give the phenacyl sulfide **17*** (14.5 mg, 75%).

17*. Oil; silica gel, 6.3% ether 12.7% CH_2Cl_2–hexane, R_f = 0.43; MS, exact mass calcd for $C_{31}H_{40}O_4S_1$ = 508.2638; found 508.2649, error = 2.3 ppm; IR (neat, cm^{-1}) O=C—O, 1736, Ph—C=O, 1685; 200 MHz NMR ($CDCl_3$) δ 8.00–7.15 (10 H, m), 5.56 (1 H, ddd, J = 15.5, 9.7, 5.2 Hz), 5.15–5.07 (1 H, m), 5.11 (1 H, dd, J = 15.5, 9.4 Hz), 4.61 (2 H, s), 3.88 (1 H, d, J = 14.0 Hz), 3.75 (1 H, dd, J = 6.6, 3.0 Hz), 3.70 (1 H, d, J = 14.0 Hz), 3.12 (1 H, ddd, J = 7.0, 1.8, 1.6 Hz), 2.67 (1 H, dq, J = 6.6, 7.2 Hz), 2.56 (1 H, ddd, J = 14.5, 7.0, 5.2 Hz), 2.26 (1 H, ddd, J = 14.5, 9.7, 1.8 Hz), 2.15–1.80 (2 H, m), 1.80–1.35 (2 H, m), 1.30–1.05 (2 H, m), 1.24 (3 H, d, J = 7.2 Hz), 0.95 (3 H, d, J = 6.0 Hz), 0.93 (3 H, d, J = 6.6 Hz), 0.79 (3 H, t, J = 7.4 Hz).

Ketolactone 21*. Phenacyl sulfide **17*** (4.0 mg, 0.0079 mmol) was dissolved in benzene (0.9 mL) and combined with the *tert*-butyldimethylsilyl nitronate **19**[9] (0.075 mL of a 30 mg/mL benzene solution, 1.5 equiv). Sunlamp irradiation through a 5% $CuSO_4$ filter was performed for 20 min. The yellow solution was filtered through a silica gel pipet (0.5 g, 20% ether–hexane) to give, upon solvent removal, a gummy oil which was dissolved in THF (1 mL). The solution was treated with 2 drops of anhydrous triethylamine–HF (1:1 mixture of HF to TEA which was dried by removal of water with a toluene azeotrope) and stirred for 3 h. The crude reaction mixture was passed through a silica gel pipet plug (0.5 g, 20% ether–hexane). Preparative thin-layer chromatography (6.67% ether, 3.33% CH_2Cl_2, 90% hexane) was used to purify ketolactone **21*** (2.5 mg, 85%).

21*. Oil; silica gel, 6.3% ether + 12.7% CH_2Cl_2 in hexane, R_f = 0.41; MS, exact mass calcd for $C_{23}H_{32}O_4$ = 372.2292; found 372.2281, error = 3 ppm; IR (neat, cm^{-1}) O=C, 1745, O=C, 1738; 270 MHz NMR ($CDCl_3$) δ 7.38–7.20 (5 H, m), 5.28–5.14 (2 H, m), 4.77 (1 H, dd, J = 6.9, 6.9 Hz), 4.61 (1 H, d, J = 11.4 Hz), 4.58 (1 H, d, J = 11.4 Hz), 3.55 (1 H, dd, J = 8.6, 1.2 Hz), 3.26 (1 H, ddd, J = 12.5, 5.9, 3.1 Hz), 3.05 (1 H, dd, J = 12.5, 2.2 Hz), 2.68 (1 H, dq, J = 8.6, 7.2 Hz), 2.01–1.82 (4 H, m), 1.40–1.25 (1 H, m), 1.32 (3 H, d, J = 7.2 Hz), 1.12 (1 H, ddd, J = 14.4, 6.9, 2.2 Hz), 1.02 (3 H, d, J = 6.9 Hz), 0.96 (3 H, d, J = 6.9 Hz), 0.89 (3 H, t, J = 7.4 Hz).

Phenacyl Sulfide 17. Thiol **16** (19.8 mg, 0.0508 mmol) and 2,6-lutidine (0.016 mL, 2.5 equiv) were dissolved in CH_2Cl_2 (0.4 mL) and CH_3CN (0.4 mL). After cooling to 0 °C, phenacyl triflate[9] (20.5 mg, 1.5 equiv) in CH_2Cl_2 (0.2 mL) was added to the mixture. The reaction was maintained at 0 °C for 2 h and then warmed to room temperature. The crude mixture was passed through a silica gel pipet plug (0.5 g, 20% ether–hexane) and further purified on a silica gel pipet column (1 g, 5% ether–hexane). Phenacyl sulfide **17** (22.4 mg, 87%) was isolated as a clear oil.

17. Silica gel, 25% ether–hexane, R_f = 0.27; MS, exact mass calcd for $C_{31}H_{40}O_4S_1$ = 508.2638; found 508.2646, error = 1.7 ppm; IR (neat, cm^{-1}) O=C, 1734, O=C—Ph, 1685, C=C, 1609; 200 MHz NMR ($CDCl_3$) δ 8.00–7.93 (2 H, m), 7.65–7.15 (8 H, m), 5.45 (1 H, ddd, J = 15.5, 6.7, 6.3 Hz), 5.34 (1 H, dd, J = 15.5, 7.4 Hz), 4.78 (1 H, ddd, J = 9.8, 3.5, 3.5 Hz), 4.64 (2 H, s), 4.01 (1 H, d, J = 14.3 Hz), 3.90 (1 H, d, J = 14.3 Hz), 3.45 (1 H, d, J = 10.6 Hz), 3.21 (1 H, ddd, J = 8.8, 3.5, 2.0 Hz), 2.68 (1 H, dq, J = 10.6, 6.8 Hz), 2.48 (1 H, ddd, J = 14.1, 8.8, 6.7 Hz), 2.18 (1 H, ddd, J = 14.4, 6.3, 2.0 Hz), 2.05–1.80 (1 H, m), 1.80–1.60 (2 H, m), 1.47 (1 H, dq, J = 9.5, 6.8 Hz), 1.40 (1 H, d, J = 12.5 Hz), 1.24 (3 H, d, J = 6.8 Hz), 1.14 (1 H, ddd, J = 12.5, 9.5, 2.8 Hz), 1.07 (3 H, d, J = 6.8 Hz), 0.97 (3 H, d, J = 6.6 Hz), 0.88 (3 H, t, J = 7.1 Hz).

Ketolactone 21. Phenacyl sulfide **17** (11.8 mg, 0.023 mmol) and the *tert*-butyldimethylsilyl nitronate ester of nitroethane (10.0 mg in 0.1 mL of benzene, 2 equiv) were combined in benzene (2 mL). The mixture was irradiated with a sunlamp for 40 min. The crude reaction mixture was passed through a silica gel pipet plug (20% ether–hexane). The solvent was removed, and the gummy oil was dissolved in THF (2 mL) and cooled to −18 °C. Tetrabutylammonium fluoride (1.0 M solution in THF, 0.023 mL, 1.0 equiv) was added via syringe, and the reaction was stirred for 20 min. The crude reaction mixture was passed through a silica gel pipet plug (0.5 g, 20% ether–hexane) and further purified by preparative thin-layer chromatography (10% ether, 20% CH_2Cl_2, 70% hexane) to give the desired ketone **21** (6.4 mg, 74%).

21. Oil; silica gel, 1:2:7 ether–CH_2Cl_2–hexane, R_f = 0.40; MS, exact mass calcd for $C_{23}H_{32}O_4$ = 372.2292; found = 372.2298, error = 1.6 ppm; IR (neat, cm^{-1}) O=C, 1738, O=C, 1720; 270 MHz NMR ($CDCl_3$) δ 7.40–7.25 (5 H, m), 5.31 (1 H, ddd, J = 15.0, 9.5, 1.9 Hz), 5.15 (1 H, ddd, J = 15.0, 10.3, 3.3 Hz), 5.09 (1 H, dd, J = 8.0, 6.0 Hz), 4.65 (1 H, d, J = 11.0 Hz), 4.62 (1 H, d, J = 11.0 Hz), 3.47 (1 H, d, J = 10.4 Hz), 3.45 (1 H, dd, J = 11.3, 10.3 Hz), 2.88 (1 H, ddd, J = 11.3, 3.3, 1.9 Hz), 2.64 (1 H, dq, J = 10.5, 7.1 Hz), 1.99–1.80 (1 H, m), 1.81–1.65 (2 H, m), 1.55–1.21 (3 H, m), 1.30 (3 H, d, J = 7.1 Hz), 1.06 (3 H, d, J = 7.1 Hz), 0.97 (3 H, d, J = 6.6 Hz), 0.92 (3 H, t, J = 7.4 Hz).

Preparation of Epoxide 23. Ketolactone **21** (14.4 mg, 0.039 mmol) and *m*-chloroperbenzoic acid (12.1 mg, 1.8 equiv) were dissolved in CH_2Cl_2 (0.6 mL) and stirred at room temperature for 12 h. Additional peracid (5 mg, 0.8 equiv) was added after 12 h. After 24 h, the reaction mixture was diluted with ether (25 mL) and extracted with saturated K_2CO_3 (4 × 5 mL). The solvent was removed, and the resulting oil was purified by preparative thin-layer chromatography (5% ethyl acetate–hexane) to give a single epoxide diastereomer **23** (42.1 mg, 80%).

23. Oil, silica gel, 1:2:7 ether–CH_2Cl_2–hexane, R_f = 0.19; MS, exact mass calcd for $C_{23}H_{32}O_5$ = 388.2241; found 388.2263, error = 5.6 ppm; IR (neat, cm^{-1}) O=C, 1740, O=C, 1730; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 5.19 (1 H, dd, J = 7.4, 7.1 Hz), 4.66 (1 H, d, J =

11.2 Hz), 4.64 (1 H, d, J = 11.2 Hz), 3.46 (1 H, d, J = 10.4 Hz), 2.86 (1 H, dq, J = 10.4, 6.8 Hz), 2.81 (1 H, dd, J = 9.6, 1.6 Hz), 2.79 (1 H, dd, J = 11.3, 1.8 Hz), 2.66 (1 H, dd, J = 11.3, 8.3 Hz), 2.44 (1 H, dd, J = 8.3, 1.8 Hz), 1.90–1.40 (4 H, m), 1.40–1.00 (2 H, m), 1.32 (3 H, d, J = 6.8 Hz), 1.06 (3 H, d, J = 5.6 Hz), 1.00 (3 H, d, J = 6.5 Hz), 0.90 (3 H, t, J = 7.4 Hz).

Hydroxy Lactone 24 and Hemiketal 25. Keto epoxide **23** (7.2 mg) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C. Diazabicyclononane (0.05 mL, excess) was added via syringe. The reaction was stirred at −78 °C for 0.5 h, warmed to −30 °C for 2 h, and finally allowed to warm to room temperature for 0.5 h. The reaction mixture was diluted with 50% ether–hexane (20 mL) and washed with 10% H_2SO_4 (2 × 2 mL). The solvent was removed to yield an oil which was purified on a silica gel pipet column (1 g, 20% ethyl acetate–hexane). Alcohols **24** and **25** (6.7 mg, 93%, 4:1 ratio by NMR) were separated by high-pressure liquid chromatography (flow rate = 5.0 mL/min, **24** retention time = 11.3 min, **25** retention time = 13.1 min) after combining several experiments.

24. Solid, mp 103.5–104.5 °C (crystallized from ether–hexane); MS, no peak match, parent; M + 1, 389.2325, calcd = 389.2328, error = 0.8 ppm, formula = $C_{23}H_{32}O_5$; IR (neat, cm^{-1}) OH, 3420; O=C—O, 1750; O=C—C=C, 1660; 270 MHz NMR ($CDCl_3$) δ 7.41–7.20 (5 H, m), 6.63 (1 H, dd, J = 16.4, 6.0 Hz), 6.31 (1 H, dd, J = 16.4, 1.2 Hz), 4.98 (1 H, dd, J = 8.0, 6.3 Hz), 4.67 (1 H, d, J = 11.0 Hz), 4.61 (1 H, d, J = 11.0 Hz), 3.93 (1 H, dd, J = 6.0, 6.0 Hz), 3.49 (1 H, dd, J = 10.1, 1.6 Hz), 2.82 (1 H, dq, J = 10.1, 7.0 Hz), 1.95–1.50 (5 H, m), 1.50–1.01 (2 H, m), 1.33 (3 H, d, J = 7.0 Hz), 1.08 (3 H, d, J = 6.3 Hz), 1.06 (3 H, d, J = 6.9 Hz), 1.00 (3 H, t, J = 7.4 Hz).

25. Solid, mp 122–123 °C (crystallized from ether–hexane); MS, no peak match, parent; M − 18, 370.2175, calcd = 370.2144, error = 8.5 ppm, formula = $C_{23}H_{32}O_5$; IR (CH_2Cl_2, cm^{-1}) OH, 3695, O=C, 1745; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 6.14 (1 H, d, J = 6.3 Hz), 6.01 (1 H, dd, J = 6.3, 2.7 Hz), 5.01 (1 H, dd, J = 10.4, 2.9 Hz), 4.99–4.90 (1 H, m), 4.67 (1 H, d, J = 11.0 Hz), 4.62 (1 H, d, J = 11.0 Hz), 3.37 (1 H, dd, J = 9.5, 1.8 Hz), 2.74 (1 H, dq, J = 9.5, 6.7 Hz), 2.32 (1 H, s), 2.12–1.85 (2 H, m), 1.85–0.68 (4 H, m), 1.28 (3 H, d, J = 6.7 Hz), 1.03 (3 H, d, J = 6.8 Hz), 0.94 (3 H, d, J = 7.6 Hz), 0.92 (3 H, t, J = 7.4 Hz).

Bicyclic Ether 27. Benzyl ether **23** (4.6 mg), camphorsulfonic acid (3.3 mg, 1.0 equiv), and 10% Pd/C (12 mg) were combined in toluene (0.2 mL). 1,4-Cyclohexadiene (Aldrich, 0.05 mL) was added, and the mixture was heated at 90 °C for 0.5 h. After cooling to room temperature, the reaction mixture was passed through a silica gel plug (0.5 mg, 20% ethyl acetate–hexane). The oil resulting from solvent removal was purified by preparative thin-layer chromatography (20% ether–hexane) to give bicyclic ether **27** (2.8 mg, 60%). Oil; silica gel, 20% ethyl acetate–hexane, R_f = 0.42; MS, exact mass calcd for $C_{16}H_{26}O_5$ = 298.1773; found 298.178, error = 2.4 ppm; IR (neat, cm^{-1}) OH, 3510, O=C, 1735, O=C, 1700; 270 MHz NMR ($CDCl_3$) δ 5.47 (1 H, dd, J = 7.7, 7.1 Hz), 3.76 (1 H, dddd, J = 11.7, 9.3, 3.3, 3.3 Hz), 3.28 (1 H, dd, J = 10.4, 5.7 Hz), 3.21 (1 H, d, J = 11.7 Hz), 3.11 (1 H, dd, J = 15.5, 3.3 Hz), 2.93 (1 H, dq, J = 5.7, 7.1 Hz), 2.52 (1 H, dd, J = 9.5, 9.3 Hz), 2.32 (1 H, dd, J = 15.5, 3.3 Hz), 1.90–1.10 (6 H, m), 1.12 (3 H, d, J = 7.1 Hz), 0.94 (3 H, d, J = 6.4 Hz), 0.89 (3 H, t, J = 7.3 Hz), 0.79 (3 H, d, J = 6.4 Hz).

Grignard Additions to Enone 24. Diol Lactones 30 and 29. Enone **24** (4.4 mg, 0.0113 mmol) in toluene (2.0 mL) which had been cooled to −78 °C was treated with MeMgI in toluene (0.8 M, 0.05 mL, 3.3 equiv, prepared by evaporating a conventional MeMgI/ether solution under a nitrogen stream and extracting the residue with dry toluene). The disappearance of the enone was monitored by TLC. Additional portions of MeMgI in toluene (0.04 mL each time) were added to the enone at 10, 20, 50, 60, and 70 min. Ten minutes after the last MeMgI addition, the reaction was warmed to 0 °C for 20 min and then quenched with 5% NH_4Cl (3 mL). The reaction mixture was diluted with ether (20 mL), and the organic layer was separated and dried over $MgSO_4$. After solvent removal, the resulting oil was purified by preparative thin-layer chromatography (20% ethyl acetate–40% hexane–40% dichloromethane) to give the 1,2-addition products **30** (R_f 0.15) and **29** (R_f 0.3), total 2.5 mg (55%), in a 7:1 ratio by NMR integration. Also isolated were two diastereomeric 1,4-addition products **31a,b** (0.9 mg, 19%) in a 5:4 ratio.

30. Solid, mp 135–138 °C (crystallized from ether–hexane); MS, no peak match, parent; M − 18, 386.2422, calcd = 386.2457, error = 11.6 ppm, formula = $C_{24}H_{36}O_5$; IR (CH_2Cl_2, cm^{-1}) OH, 3405, C=C, 1730, O=C, 1710; 270 MHz NMR ($CDCl_3$) δ 7.38–7.20 (5 H, m), 5.76–5.63 (2 H, m), 4.77 (1 H, dd, J = 11.0, 2.4 Hz), 4.66 (1 H, d, J = 11.0 Hz), 4.60 (1 H, d, J = 11.0 Hz), 4.01 (1 H, dd, J = 4.2, 3.1 Hz), 3.47 (1 H, dd, J = 10.3, 1.5 Hz), 2.70 (1 H, dq, J = 10.3, 6.8 Hz), 2.42–2.20 (1 H, m), 1.95–1.70 (2 H, m), 1.70–1.40 (4 H, m), 1.40–1.10 (1 H, m), 1.30 (3 H, s), 1.28 (3 H, d, J = 7.7 Hz), 1.10 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 7.1 Hz), 0.91 (3 H, t, J = 7.4 Hz).

29. Solid, mp 128–130 °C (crystallized from ether–hexane); IR (CH_2Cl_2, cm^{-1}) OH, 3500, O=C, 1730; 270 MHz NMR ($CDCl_3$) δ 7.35–7.20 (5 H, m), 5.83 (1 H, dd, J = 15.7, 2.4 Hz), 5.66 (1 H, dd, J = 15.7, 2.1 Hz), 4.91 (1 H, dd, J = 7.4, 6.2 Hz), 4.66 (1 H, d, J = 10.7 Hz), 4.61 (1 H, d, J = 10.7 Hz), 4.24 (1 H, s), 3.47 (1 H, dd, J = 10.4, 2.1 Hz), 2.74 (1 H, dq, J = 10.4, 6.8 Hz), 2.11–1.89 (2 H, m), 1.82–1.65 (2 H, m), 1.65–1.15 (4 H, m), 1.29 (3 H, d, J = 6.8 Hz), 1.25 (3 H, s), 1.11 (3 H, d, J = 6.8 Hz), 0.94 (3 H, d, J = 7.1 Hz), 0.88 (3 H, t, J = 7.3 Hz).

31a. Oil; silica gel, 1:2:2 ethyl acetate–CH_2Cl_2–hexane, R_f = 0.50; MS, exact mass calcd for $C_{24}H_{36}O_5$ = 404.2553; found 404.2563, error = 2.4 ppm; IR (neat, cm^{-1}) O=C, 1749, O=C, 1731, OH, 3415; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 4.86 (1 H, dd, J = 11.0, 2.7 Hz), 4.63 (2 H, d, J = 11.3 Hz), 4.21 (1 H, dd, J = 9.0, 4.2 Hz), 3.49 (1 H, dd, J = 8.3, 2.7 Hz), 2.80 (1 H, dd, J = 14.2, 7.1 Hz), 2.77 (1 H, dq, J = 8.3, 7.1 Hz), 1.95–1.80 (3 H, m), 1.85–1.65 (2 H, m), 1.55–0.80 (4 H, m), 1.30 (3 H, d, J = 7.1 Hz), 1.13 (3 H, d, J = 7.4 Hz), 0.99 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 7.7 Hz), 0.92 (3 H, t, J = 7.4 Hz).

31b. Oil; silica gel, 1:2:2 ethyl acetate–CH_2Cl_2–hexane, R_f = 0.41; MS, exact mass calcd for $C_{24}H_{36}O_5$ = 404.2553; found 404.254, error = 3.2 ppm; IR (neat, cm^{-1}) O=C, 1749, O=C, 1732, OH, 3485; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 4.78 (1 H, dd, J = 10.7, 2.7 Hz), 4.69 (1 H, d, J = 11.0 Hz), 4.63 (1 H, d, J = 11.0 Hz), 3.89 (1 H, dd, J = 7.1, 4.2 Hz), 3.42 (1 H, dd, J = 9.4, 1.8 Hz), 2.79 (1 H, dq, J = 9.4, 6.8 Hz), 2.47 (1 H, dd, J = 13.3, 10.7 Hz), 2.26–2.06 (1 H, m); 1.98–1.75 (1 H, m), 1.74 (1 H, dd, J = 13.3, 6.7 Hz), 1.55–1.39 (1 H, m), 1.39–1.15 (3 H, m), 1.32 (3 H, d, J = 6.8 Hz), 1.10 (3 H, d, J = 6.8 Hz); 1.10–0.72 (2 H, m), 1.03 (3 H, d, J = 7.1 Hz), 0.91 (3 H, d, J = 7.4 Hz), 0.88 (3 H, d, J = 7.4 Hz).

***tert*-Butyldimethylsilyl Ether 28.** Hydroxy enone **24** (1.0 mg, 0.0026 mmol) in CH_2Cl_2 (0.25 mL) at 0 °C was treated with 2,6-lutidine (0.010 mL) and *tert*-butyldimethylsilyl triflate (0.005 mL). After 15 min, the reaction mixture was diluted with ether (20 mL) and washed with 10% H_2SO_4 (2 × 2 mL). The solvent was removed to give an oil which was purified by preparative thin-layer chromatography (10% ethyl acetate–hexane) to give **28** (1.2 mg, quantitative).

28. Oil; silica gel, 1:2:2 ethyl acetate–CH_2Cl_2–hexane, R_f = 0.48; IR (neat, cm^{-1}) O=C, 1745, O=C, 1721, O=C—C=C, 1655; 270 MHz NMR ($CDCl_3$) δ 7.40–7.20 (5 H, m), 6.60 (1 H, dd, J = 16.6, 5.0 Hz), 6.22 (1 H, dd, J = 16.6, 1.2 Hz), 5.00 (1 H, dd, J = 8.7, 5.6 Hz), 4.66 (1 H, d, J = 11.2 Hz), 4.60 (1 H, d, J = 11.2 Hz), 3.95 (1 H, ddd, J = 6.2, 5.0, 1.2 Hz), 3.49 (1 H, dd, J = 10.0, 2.1 Hz), 2.81 (1 H, dq, J = 10.0, 7.0 Hz), 1.95–1.60 (3 H, m), 1.42–1.10 (3 H, m), 1.32 (3 H, d, J = 7.0 Hz), 1.08 (3 H, d, J = 6.6 Hz), 1.00 (3 H, t, J = 7.4 Hz), 0.98 (3 H, d, J = 7.7 Hz), 0.88 (9 H, s), 0.05 (3 H, s), 0.03 (3 H, s).

Grignard Addition to *tert*-Butyldimethylsilyl Ether 28. To the TBS ether **28** (1.2 mg, 0.0026 mmol) in toluene (0.7 mL) at −78 °C was added MeMgI (ether-free toluene solution 1.0 M, 0.015 mL). Additional portions of Grignard solution were added at 15 min (0.01 mL), 25 min (0.015 mL), and at 35 min (0.015 mL), and then the cooling bath was removed. The reaction was quenched 10 min later. The oil resulting from solvent removal was redissolved in THF (1.0 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M THF solution, 0.015 mL) was added, and 10 min later the reaction mixture was diluted with ether (10 mL) and washed with water (1 × 2 mL). Purification by preparative thin-layer chromatography (30% ethyl acetate–hexane) gave a mixture of diols **30** and **29** (0.7 mg, 60%) in a 1:7 ratio by NMR integration.

Preparation of *d,l*-Methynolide (38) and *d,l*-C_{10}-*epi*-Methynolide (37). Enone Alcohol 36. Diol **30** (5.1 mg, 0.0126 mmol) in CH_2Cl_2 (0.6 mL) was treated with pyridinium chlorochromate (9.1 mg). After 1.5 h, ether (1 mL) was added, and the mixture was passed through a silica gel pipet plug (0.5 g, 20% ethyl acetate–hexane). Purification by preparative thin-layer chromatography (30% ethyl acetate–hexane) gave **36** (4.0 mg, 78%).

36. Oil; silica gel, 1:2:1 ethyl acetate–CH_2Cl_2–hexane, R_f = 0.35; MS, exact mass calcd for $C_{24}H_{34}O_5$ = 402.2397; found 402.2428, error = 7.7 ppm; IR (neat, cm^{-1}) OH, 3460; O=C, 1725, O=C—C=C, 1695, O=C—C=C, 1640; 270 MHz NMR ($CDCl_3$) δ 7.35–7.25 (5 H, m), 6.56 (1 H, d, J = 16.0 Hz), 6.43 (1 H, d, J = 16.0 Hz), 4.75 (1 H, dd, J = 10.9, 2.3 Hz), 4.65 (1 H, d, J = 11.0 Hz), 4.61 (1 H, d, J = 11.0 Hz), 3.47 (1 H, dd, J = 10.5, 1.0 Hz), 2.74 (1 H, dq, J = 10.5, 7.0 Hz), 2.05–1.95 (1 H, m), 1.92 (1 H, ddd, J = 14.1, 7.4, 2.3 Hz), 1.86–1.20 (5 H, m), 1.34 (3 H, s), 1.32 (3 H, d, J = 7.0 Hz), 1.17 (3 H, d, J = 7.0 Hz), 1.05 (3 H, d, J = 6.4 Hz), 0.89 (3 H, t, J = 7.4 Hz).

Enone Alcohol 35. Diol **29** (3.0 mg, 0.0074 mmol) in CH_2Cl_2 (0.6 mL) was treated with pyridinium chlorochromate (4.8 mg). After 3 h, the reaction was worked up and purified as described above to give enone **35** (2.5 mg, 84%).

35. Oil; silica gel, 1:2:2 ethyl acetate–CH_2Cl_2–hexane, R_f = 0.29; IR (neat, cm^{-1}) OH, 3610, O=C, 1750, O=C, 1715, O=C—C=C, 1660;

270 MHz NMR ($CDCl_2$) δ 7.40-7.30 (5 H, m), 6.64 (1 H, d, J = 15.4 Hz), 6.43 (1 H, d, J = 15.4 Hz), 4.83 (1 H, dd, J = 8.4, 5.5 Hz), 4.65 (1 H, d, J = 11.0 Hz), 4.61 (1 H, d, J = 11.0 Hz), 3.47 (1 H, dd, J = 10.5, 1.1 Hz), 2.79 (1 H, dq, J = 10.5, 7.1 Hz), 2.62-2.48 (1 H, m), 1.94 (1 H, s), 1.82-1.62 (3 H, m), 1.49-1.19 (2 H, m), 1.33 (3 H, s), 1.32 (3 H, d, J = 6.8 Hz), 1.20 (3 H, d, J = 7.1 Hz), 1.05 (3 H, d, J = 6.5 Hz), 0.89 (3 H, t, J = 7.4 Hz).

***d,l*-Methynolide (38).** Enone alcohol **36** (3.4 mg, 0.0085 mmol) was debenzylated according to the method of Yonemitsu et al.[15c] with 2,6-dichloro-2,5-dicyano-1,4-benzoquinone (DDQ, 12 mg) and water (0.03 mL) which were combined in CH_2Cl_2 (0.6 mL). After stirring for 4 h, 1,4-cyclohexadiene (0.1 mL) was added to convert the excess DDQ into the dihydroquinone. The reaction mixture was diluted with ether (20 mL) and washed with saturated $NaHCO_3$ (5 × 3 mL) to remove the hydroquinone. Purification by preparative thin-layer chromatography (30% ethyl acetate-hexane) gave synthetic *d,l*-methynolide (2.0 mg, 77%).

38. Solid, mp dec 189-194 °C (crystallized from ether-hexane); MS, no peak match, parent; $M - H_2O$, 294.1827, calcd = 294.1831, error = 1.4 ppm formula = $C_{17}H_{28}O_5$; IR (neat, cm^{-1}) OH, 3620, C=O, 1745, C=O, 1705, C=C-C=O, 1645; 500 MHz NMR ($CDCl_3$) δ 6.59 (1 H, d, J = 16.3 Hz), 6.34 (1 H, d, J = 16.3 Hz), 4.78 (1 H, dd, J = 11.2, 2.2 Hz), 3.58 (1 H, d, J = 10.3 Hz), 2.61 (1 H, dq, J = 10.3, 6.9 Hz), 2.60-2.51 (1 H, m), 1.99 (1 H, s), 1.91 (1 H, ddq, 14.2, 2.2, 6.9), 1.68-1.48 (3 H, m), 1.40-1.15 (2 H, m), 1.38 (3 H, s), 1.34 (3 H, d, J = 6.9 Hz), 1.20 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 6.3 Hz), 0.91 (3 H, t, J = 7.3 Hz).

***d,l*-C_{10}-*epi*-Methynolide (37).** Hydroxy enone benzyl ether **35** (2.4 mg, 0.0062 mmol) was debenzylated under exactly the same conditions as described for debenzylation of **36**. The product was purified by PTLC (30% ethyl acetate-hexane) to give *d,l*-C_{10}-*epi*-methynolide (1.3 mg, 68%).

37. Solid, mp 165-166 °C (crystallized from ether-hexane); MS, exact mass calcd for $C_{17}H_{28}O_5$ = 312.1929, found 312.1923, error = 2 ppm; IR (neat, cm^{-1}) OH, 3460, C=O, 1720, 1650; 500 MHz NMR ($CDCl_3$, ppm) 6.67 (1 H, d, J = 15.3 Hz), 6.46 (1 H, d, J = 15.3 Hz), 4.86 (1 H, dd, J = 8.1, 5.8 Hz), 3.58 (1 H, br d, J = 10.4 Hz), 2.67 (1 H, dq, J = 10.4, 6.8 Hz), 2.56 (1 H, ddq, J = 6.9, 3.6, 7.1), 1.95 (1 H, br s), 1.82-1.74 (2 H, m), 1.67-1.49 (2 H, m), 1.52-1.32 (2 H, m), 1.36 (3 H, s), 1.33 (3 H, d, J = 6.8 Hz), 1.23 (3 H, d, J = 7.1 Hz), 1.01 (3 H, d, J = 5.9 Hz), 0.91 (3 H, t, J = 7.4 Hz).

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Catalytic Cyclophanes. 4. Supramolecular Catalysis of Benzoin Condensations by a Thiazolium Cyclophane[1,2]

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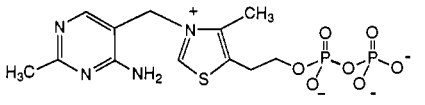
Abstract: As a model for thiamine pyrophosphate dependent ligases, the thiazolium-bridged cyclophane **1** was prepared in a 14-step synthesis. Compound **1** was designed to catalyze the benzoin condensation, and its macrocyclic cavity provides in aqueous and organic solutions a binding site for the two benzaldehyde molecules that react to give benzoin. In macrobicycle **1**, the thiazolium residue is connected to the binding site by two side arms, which limits the number of unproductive conformations of the catalytic residue. As a catalyst for the benzoin condensation, **1** is superior to the thiazolium derivative **3** without a macrocyclic binding site. For benzoin condensations catalyzed by **1**, high turnovers and very high yields in benzoin formation, catalysis of the back reaction, and sigmoid saturation kinetics plots suggesting the formation of a 1:2 Michaelis-Menten complex are observed. The surprisingly high catalytic activity of the thiazolium-bridged diphenylmethane spacer **2** is best explained by its potential for binding benzaldehyde at its niche binding site. The thiazolium-catalyzed benzoin condensation is investigated as a function of solvent polarity, of base concentration, and of buffer strength. Cyclophane **1** catalyzes the furoin condensation. Specific large enhancements of the H/D-exchange rate at C-2′ of the thiazolium ring in **1** are observed in aqueous buffers. They are best explained by a micropolarity effect of the cavity of **1** on the (kinetic) acidity of the proton at this position.

In recent years, novel reagents and catalysts for chemical processes have been developed by covalently anchoring coenzymes and coenzyme analogues to the binding sites of cyclodextrins,[3a] synthetic receptors,[3b-e] and semisynthetic enzymes.[4] Thiamin pyrophosphate (TPP, **1**)[5] participates as the essential cofactor in



TPP

numerous enzymatic reactions involving formation and breakage of carbon-carbon bonds, e.g., in the transketolase-catalyzed formation and cleavage of carbohydrates in the pentose phosphate pathway.[6] Since the pioneering work of Breslow in the 1950s,[7] it is well established that the catalytic action of TPP is mainly due to the thiazolium ring and that simple thiazolium ions catalyze many of the enzymatic transformations, e.g., acetoin condensations, in the absence of the enzymes.[8-11] The pyrophosphate part of

(1) Dedicated to the memory of Professor Emil T. Kaiser.

(2) For parts 1-3 in this series, see: (a) Preliminary communication of parts of this work: Lutter, H.-D.; Diederich, F. *Angew. Chem.* **1986**, *96*, 1125-1127; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125-1127. (b) Diederich, F.; Schürmann, G.; Chao, I. *J. Org. Chem.* **1988**, *53*, 2744-2757. (c) Jimenez, L.; Diederich, F. *Tetrahedron Lett.* **1989**, *30*, 2759-2762.

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