the terminal nitrogen is the lowest energy pathway. The very slow rate of these reactions may be due to the low probability of the orbiting complex being able to enter the appropriate reaction channel.

Acknowledgments. The flowing afterglow experiments were carried out while one of us (J. H. Bowie) was on leave at the University of Colorado, Boulder. C. H. DePuy and R. Damrauer acknowledge the support of this work by N.S.F. Grants CHE-8503505 and CHE 83-13826, respectively. We thank the University of Adelaide Computing Centre for facilities.

Registry No. H_3Si^-, 15807-96-2; Me_3Si^-, 54711-92-1; CO_2, 124-38-9; COS, 463-58-1; CS_2, 75-15-0; SO_2, 7446-09-5; N_2O, 10024-97-2; MeNCO, 624-83-9; MeNCS, 556-61-6; H_3SiO^-, 43336-62-5; Me_3SiO^-, 41866-81-3; H_3SiS^-, 81429-19-8; Me_3SiS^-, 88657-58-3; H_3SiOSO, 104114-30-9; O_2, 7782-44-7; S, 7704-34-9; Si, 7440-21-3; $H_3SiCS_2^-$, 104092-12-8; $H_3SiCO_2^-$, 40058-48-8.

Communications to the Editor

Bridging of Macrocycles to Bicycles. New Synthetic Technology for the Construction of Cis- and Trans-Fused Oxopolycyclic Systems

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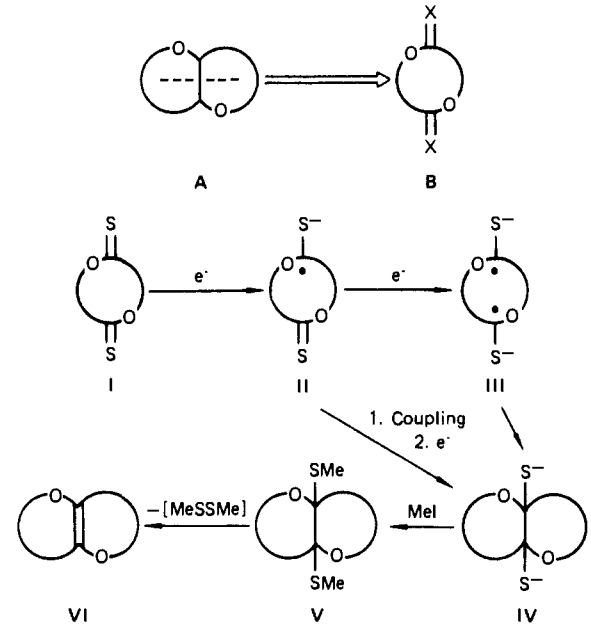
Cis- and trans-fused oxobicyclic and oxopolycyclic systems of type A (Scheme I) are becoming increasingly recognized as common structural features of marine and other natural products such as brevetoxins[1] (trans fusions) and halohydrins[2] (trans and cis fusions). A potentially efficient and economical retrosynthetic disconnection of the bicyclic system A would be the indicated rupture of the central C–C bond, suggesting the macrocycle B (Scheme I) as a precursor, since in the synthetic direction the construction of one bond would result in the simultaneous generation of two rings.[3] Based on this concept, a method for bridging macrocycles of type B that would allow stereoselective entry into both the cis- and trans-fused systems A was sought. Due to the relatively low reduction potential of the C=S bond[4] and the synthetic potential of sulfur for further chemical transformations, macrodithionolactones were chosen as starting materials. Our general strategy for bridging macrocycles to bicycles is depicted in Scheme I. Thus, it was anticipated that electron transfer to a thiocarbonyl group of the macrodithionolide system I would generate a radical anion (II), initiating a sequence leading to a bridged product (IV) as outlined in Scheme I. Quenching of the resulting dianion IV with an electrophile such as MeI was then expected to lead to a stable disulfide (V) which could be chemically manipulated[3b] to a variety of systems including the olefinic compounds VI and the cis- and trans-fused polycycles A (Scheme I).

As a model of the brevetoxin framework, the systems depicted in Scheme II were chosen to test these ideas. Thus, two enantiomeric hydroxy acids in the form of their benzyl derivatives **1a** and **1b** were synthesized[5] and utilized to construct the meso diolide

Scheme I[a]



[a] General concept for bridging macrocycles to bicycles by free radical coupling reactions.

2 (C_i symmetry, esterification followed by debenzylation and macrolactonization[6]) which was then converted to the dithionolide **3** by Lawesson's reagent.[7] When **3** was exposed to sodium naphthalide in THF at −78 °C followed by quenching with CH_3I, the cis-bridged tetracycle **4**[8] (racemic mixture) was isolated as a major product. Dreiding molecular models suggest the syn relationship for the thiocarbonyl groups in **3** rather than the anti arrangement as the preferred conformation and hence this stereochemical outcome was not unexpected. Treatment of the disulfide **4** with *n*-Bu_3SnH in the presence of AIBN resulted in its high-yield conversion to the olefinic compound **5** (meso, C_i symmetry), the ORTEP drawing[9] of which is shown in Scheme II. Photolysis (Hanovia, UV quartz lamp. toluene) of **4** also led to the same product (**5**) in high yield. To enhance the usefulness

(1) Brevetoxin, A: Shimizu, Y.; Chou, H.-N.; Bando, H.; VanDuyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. Brevetoxin B: Lin, Y. Y.; Risk, M.; Ray, S. M.; VanEngen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

(2) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y., *J. Am. Chem. Soc.* **1985**, *107*, 4796. Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701.

(3) For our recent stepwise entries into oxo rings via C–O bond forming reactions, see (a) tetrahydropyrans: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. And oxocenes (b): Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468.

(4) Ohno, A. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977; Chapter 5, pp 189.

(5) These and the other compounds utilized to prepare the macrodithionolides shown in Table I were synthesized by standard methods either as described in ref 3a or from glucal triacetate.

(6) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(7) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. See also: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5087.

(8) The presence of two thiomethyl signals (250 MHz, $CDCl_3$, δ 2.03, 1.89) in the ^1H NMR spectrum of **4** proved the cis arrangement of the generated bridge. The ^1H NMR spectrum of **4** also showed the signal corresponding to the proton across the oxygen bridge and syn to the thiomethyl group at relatively low field (δ 4.21, ddd, J = 10.0, 10.0, 5.0 Hz). These observations were consistent and assisted in the tentative assignment of stereochemistry in the examples shown in Table I.

(9) We are indebted to Dr. Patrick J. Carrol of this department for solving this X-ray structure.

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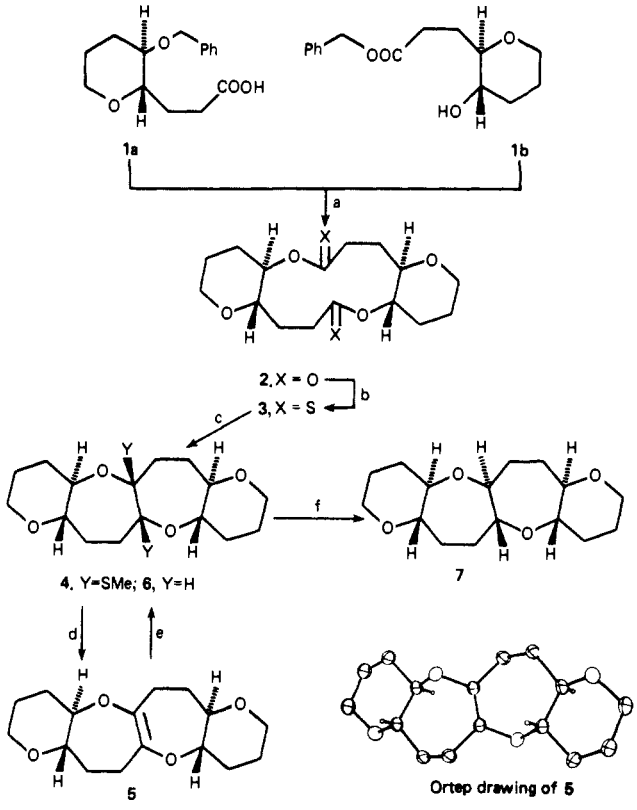
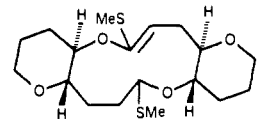
Scheme II[a]



[a] Conditions, reagents, and yields. (a) 1.2 equiv of DCC, 1.2 equiv of DMAP, 0.3 equiv of CSA, CH_2Cl_2, 25 °C, 85% and then H_2, $Pd(OH)_2$ catalyst, EtOAc, 25 °C, 100% and then 1.5 equiv of pyrSSpyr, 1.5 equiv of PPh_3, toluene, reflux, 75%; (b) 1.5 equiv of Lawesson's reagent, toluene, reflux, 90%; (c) 2.2 equiv of Na–naphthalide, THF, −78 °C and then excess MeI, −78 → 25 °C, 80%; (d) 1.2 equiv of nBu_3SnH, 0.1 equiv of AIBN, toluene, reflux, 99%, or *hν*, toluene, 25 °C, 99%; (e) H_2, $Pd(OH)_2$ catalyst, EtOAc, 25 °C, 70% or 1.1 equiv of CF_3COOH, excess Et_3SiH, acidic alumina, CH_2Cl_2, 25 °C, 80%, or 1.1 equiv of CF_3COOH, excess $Na(CN)BH_3$, CH_2Cl_2, 90%; (f) 2.2 equiv of $AgBF_4$, excess Et_3SiH, CH_2Cl_2, 25 °C, 95%.

of this technology, conditions for the generation of the saturated systems **6** and **7** were sought and found. Thus, exposure of **5** to Et_3SiH in the presence of anhydrous protic acid or catalytic hydrogenation resulted in the selective and efficient generation of the cis compound **6**[10] (racemic mixture). On the other hand, use of Et_3SiH and $AgBF_4$ gave exclusively the trans-compound **7**[10] (meso, C_i symmetry) in excellent yield. Table I demonstrates the generality and scope of this new reaction in the construction of oxygenated polycyclic systems containing common and medium-size rings with flexible stereocontrol. Noteworthy is the successful bridging of mixed oxo dithionolide (entry 2), whereas oxo diolides failed to undergo this reaction under these or regular acyloin conditions.

In all cases shown in Table I only the indicated stereoisomer was detected.[11] In entries 3–7, however, a second product was isolated in varying amounts (see Table I) and identified by spectroscopic and chemical means as a macrocyclic system containing methylthio enol ester and methyl thioacetal groups of the type exemplified by structure **8**[12] obtained in 10% yield in entry 5 (Table I).

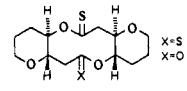
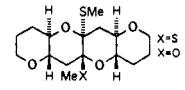
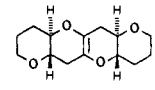
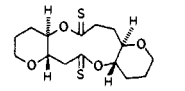
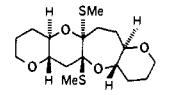
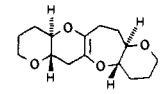
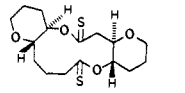
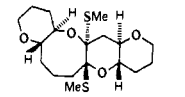
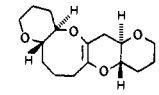
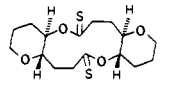
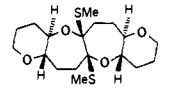
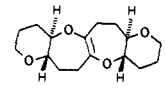
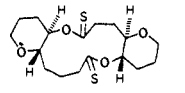
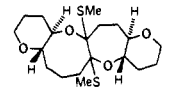
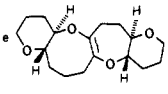
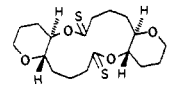
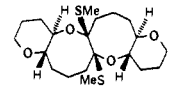
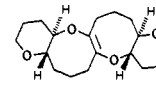


8

The described chemistry provides new and powerful technology for stereoselective construction of polycyclic systems including the complex marine natural products brevetoxins[1] and halohydrins.[2] Furthermore, this new coupling reaction parallels and complements the acyloin condensation[13] and the McMurry reaction[14] and may prove useful in other areas of synthetic chemistry. Extensions to the construction of other polycyclic systems including polyether, carbocyclic, and alkaloid skeletons are currently being planned.[15]

Acknowledgment. We express our many thanks to Drs. George Furst, John Dykins, and Patrick Carroll of this department for

Table I. Synthesis of Oxopolycyclic Systems by Bridging of Dithionolides

entry	substrate–dithionolides[a]	product–disulfide[b]	yield (%)[c]	product–olefin[d]	yield (%)
1			82		100
2			85		
3			78		98
4			45		99
5			80		99
6			53[e]		97
7			62		98

[a] These substances were optically active except for the meso ones (entries 1, 5, 7) and were prepared according to the conditions described in ref 3a and Scheme II. [b] Conditions: as described in Scheme IIc. [c] A macrocyclic by-product analogous to **8** was also found in entires 3–7: entry 3 (3%), entry **4** (45%), entry 5 (10%), entry 6 (44%), entry 7 (26%). [d] Conditions: as described in Scheme IId. [e] This product consisted of the two cis stereoisomers (ca. 1:1 ratio).

(10) The stereochemical assignments of **6** and **7** were based on ^1H (250 MHz, $CDCl_3$) and ^{13}C NMR (50.3 MHz, C_6D_6) spectral data. Thus, the cis compound **6** exhibited 16 ^{13}C signals, whereas the trans compound **7** showed only 8 signals as expected from symmetry considerations. Furthermore, **7** was tentatively distinguished from the other *trans* isomer (obtained as a minor product in the hydrogenation of **5** by Pd-catalyzed reduction) by comparison of the 7,7-ring junction proton signals for the two compounds. Dreiding molecular models of these systems suggest an axial arrangement for the 7,7-fusion protons in the trans compound **7**, whereas in the isomeric trans compound these protons occupy equatorial positions as reflected in the downfield chemical shift of the corresponding signals in their ^1H NMR spectra [**7** δ 4.30 br d, J = 8.0 Hz; other isomer δ 4.52 br s]. The coupling constants of these protons with the adjacent methylene protons were in accord with the relative arrangement of these protons as indicated by molecular models.

(11) Except in entry **1** in which a small amount (<5%) of the corresponding cis isomer was isolated.

(12) The methylthio enol ester grouping in this compound was suggested by a ^1H NMR signals (250 MHz, $CDCl_3$, δ 5.30, d, J = 11.0 Hz, ^1H, 2.21, s, 3 H), ^{13}C NMR signals (50.3 MHz, C_6D_6, δ 150.30 and 115.63), IR absorption (neat, ν_{max} 1640 cm^{-1}), and UV absorptions (CH_2Cl_2, λ_{max} 232, 245 mm) in addition to its facile conversion to a lactone functionality under mildly acidic conditions. The methylthio acetal group was evident from ^1H NMR signals (δ 4.42, d, J = 12.2 Hz, 1 H, 2.01, s, 3 H) and a ^{13}C signal (δ 84.51).

(13) For a review, see: Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.

(14) For a review, see: McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405.

(15) All new compounds exhibited satisfactory special and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

their superb NMR, mass spectroscopic, and X-ray crystallographic assistance and useful comments. We also thank Professor Kurt Mislow, Princeton University, for stimulating discussions concerning stereochemical consequences in this work. This work was financially supported by the National Institutes of Health, Merck Sharp and Dohme, and Hoffman-La Roche.

Registry No. 1a, 103710-72-1; **1b**, 103710-73-2; **2**, 103710-74-3; **3**, 103710-75-4; **3** (analogue 1), 103710-80-1; **3** (analogue 2), 103710-81-2; **3** (analogue 3), 103710-82-3; **3** (analogue 4), 103710-83-4; **3** (analogue 6), 103710-84-5; **3** (analogue 7), 103710-85-6; **4**, 103710-76-5; **4** (analogue 1), 103710-86-7; **4** (analogue 2), 103710-87-8; **4** (analogue 3), 103710-88-9; **4** (analogue 4), 103710-89-0; **4** (analogue 6) (isomer 1), 103710-90-3; **4** (analogue 6) (isomer 2), 103774-02-3; **4** (analogue 7), 103710-91-4; **5**, 103710-77-6; **5** (analogue 1), 103710-93-6; **5** (analogue 3), 103710-94-7; **5** (analogue 4), 103710-95-8; **5** (analogue 6), 103710-96-9; **5** (analogue 7), 103710-97-0; **6**, 103710-78-7; **7**, 103774-01-2; **8**, 103710-79-8; **8** (analogue 4), 103694-13-9; **8** (analogue 6), 103694-15-1; **8** (analogue 7), 103710-92-5.

Supplementary Material Available: Experimental procedure (**3** → **4**), listing of ^1H and ^{13}C NMR, IR, and mass spectroscopic data for compounds **4**–**7**, and X-ray crystallographic analysis data for compound **5** (8 pages). Ordering information is given on any current masthead page.

Total Synthesis of (-)-Xylomollin

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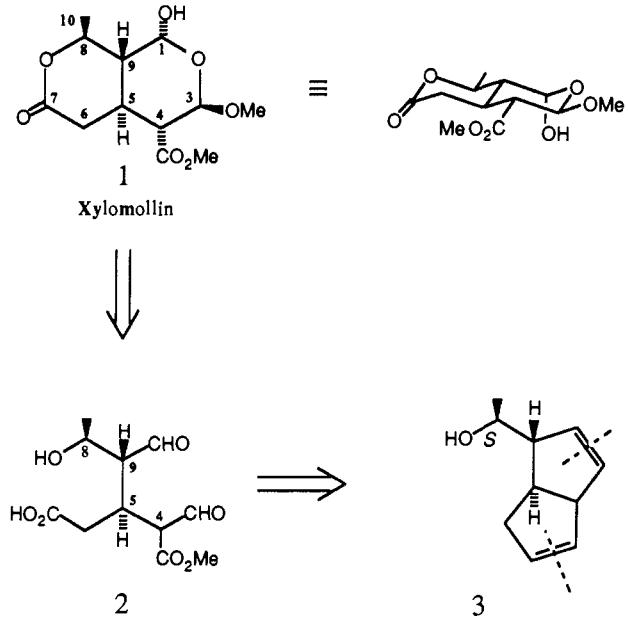
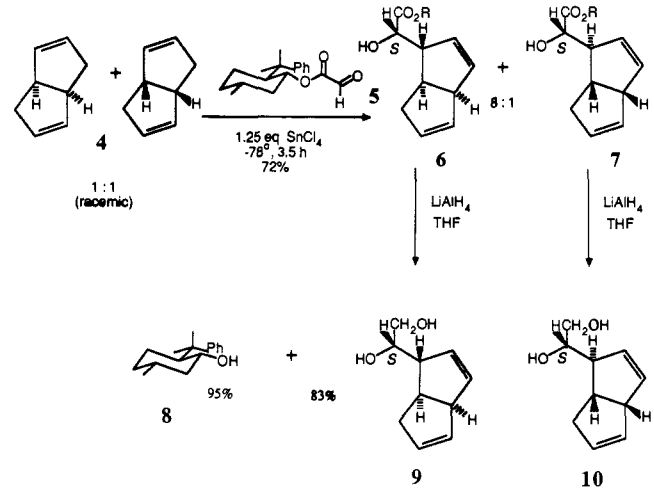
In 1976 Kubo and Nakanishi[1] described the isolation and characterization of the iridoid terpene xylomollin. Interest was immediately drawn to this compound because of its demonstrated biological activity as an insect antifeedant and as a decoupler of respiration in rat liver mitochondria and because xylomollin was the first and as of this date is the only iridoid terpene with the trans relative configuration at carbons 5 and 9.[2,3] We wish to describe here a short and efficient entry into this terpene system (Scheme I).[4]

In 1982 we communicated[5] a powerful tool for the control of absolute stereochemistry and further studies[6] expanded the scope of this method and placed it among the few practical transformations that form carbon–carbon bonds with high levels of asymmetric induction. The homoallylic alcohol functionality formed in this reaction represents a versatile synthetic building block that can be elaborated in a variety of ways. In the present context the aldol subunit present in the natural product (best visualized in **2**, the unraveled form of xylomollin) could be readily prepared by oxidative cleavage of such a homoallylic alcohol. This would provide the opportunity to create both the C-1 and C-3 aldehyde functionalities simultaneously. Such a retrosynthetic reconnection can be coupled with the joining of the carbomethoxy group carbon and C-7, leading to **3** as a key synthetic intermediate (Scheme II).

Scheme I



Scheme II



Synthesis of the homoallylic alcohol **3** was accomplished by an ene reaction between the glyoxylate **5** and 1 equiv of the racemic, bicyclic diene **4**.[7] Control of stereochemistry in this reaction led to production of two adducts (**6** and **7**)[8] in a ratio of 8:1[9] and a combined yield of 72%. The separated adducts were independently reduced to glycols **9** and **10**, respectively. Further conversion of **9** to **3** required reduction of the primary carbinol carbon to a methyl group with simultaneous inversion of stereochemistry at the secondary carbinol carbon. This was accomplished by sequence (b) shown in Scheme III involving protection of the primary hydroxyl followed by tosylation of the secondary hydroxyl group, removal of the silyl protecting group to form an intermediate epoxide with inversion, and reduction of the epoxide with lithium triethylborohydride. The minor ene adduct **10** was converted by an alternate sequence that effected that same reduction without inversion of stereochemistry (a, Scheme III) to a homoallylic alcohol (**11**) that was identical with **3** except for absolute stereochemistry, thus establishing the stereochemical relationship

(1) Kubo, I.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704.
(2) Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S.; Helbling, A. M. *Abstracts of Papers*, 175th National Meeting of the American Chemical Society, Anaheim, CA, March, 1978; American Chemical Society: Washington, DC, 1978; ORGN 176.
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(9) The ratio of diastereomers was unchanged when a 10-fold excess of diene was used.

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