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Antimicrobial Algal Metabolites of Unusual Structure. Concise Synthesis of the Highly Oxygenated [4.4]Spirononene Dimethyl Gloiosiphone A by Ring Expansion of Dimethyl Squarate

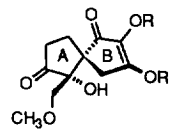
Claudio F. Sturino,† Pascale Doussot,‡ and Leo A. Paquette*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Dedicated with heartfelt congratulations to Professor Samuel Danishefsky on his receipt of the **Tetrahedron Prize** for 1996, a richly deserved recognition indeed.

Abstract: A synthesis of dimethyl gloiosiphone A (**2**) has been realized. The key step involves the boron trifluoride-catalyzed eliminative ring expansion of a 2'-(dimethoxymethyl)-1'-(cyclopenten-1'-yl)-4-hydroxy-2-cyclobuten-1-one, which was directly assembled by condensation of the appropriate cycloalkenyllithium with dimethyl squarate. Following arrival at spirocyclic diketone **17** in only two steps, the cyclopentenedione A-ring was subjected to controlled reductive removal of one carbonyl group. Subsequent oxidation of the enol ether to unsaturated aldehyde **21** set the stage for proper elaboration of the α-hydroxy ketone part structure in ring B. The spectral properties of the synthetic material were identical to those of natural **2**, which was originally isolated as a racemate. © 1997 Elsevier Science Ltd.

Every year in early summer, the temperate red marine algal species *Gloiosiphonia verticillaris* can be found in abundance along the Oregon coast. Its favored habitats are the low intertidal pools that are extensively scoured by sand. Since a large variety of novel marine natural products have been isolated from these life forms during the past twenty years, an Oregon State University group headed by Gerwick was moved to survey this organism for its biomedical potential.[1] When crude lipid extracts were discovered to exhibit potent antimicrobial activity against several *Staphylococcus, Bacillus*, and *Salmonella* species, efforts were intensified to characterize the responsible agent or agents. However, the instability of the compounds to chromatography caused most of the activity to be rapidly lost. This sensitivity was significantly reduced by prior treatment of



1, R = H
2, R = CH_3

†NSERC Postdoctoral Fellow, 1995-96. Present address: Department of Medicinal Chemistry, Allelix Biopharmaceuticals, Toronto, Ontario, Canada.

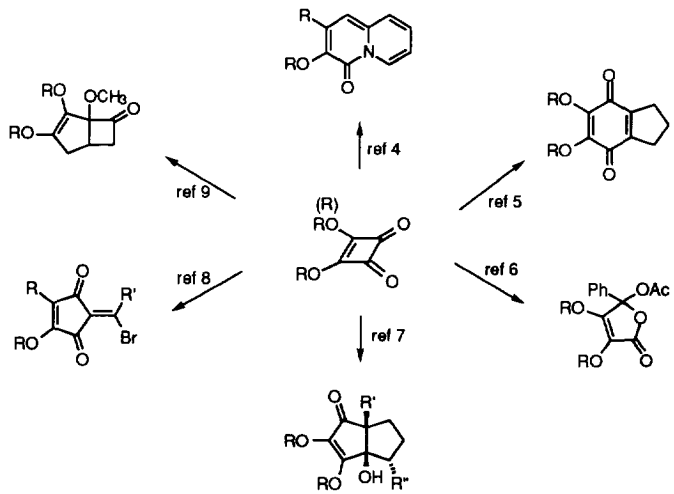
‡Postdoctoral Fellow of the Ministère de l'Enseignment Supérieur et de la Recherche (France).

the bioactive fractions with diazomethane. This process effects the O-methylation of the enolic protons of gloiosiphone A (**1**) to generate the somewhat more robust dimethyl derivative **2** with which it co-occurs. Both antimicrobial agents possess a new C_{10} carbon connectivity constituted of a 1-methylspiro[4.4]nonane network. The unprecedented nature of this ring system, its highly oxygenated substitution pattern, its ability to elicit a very significant pharmacologic response, and its occurrence in nature as the racemate were sufficient reasons for us to undertake the synthesis of **2** in as concise a manner as possible. Herein we report on the full details of this preparative study.[2]

RESULTS AND DISCUSSION

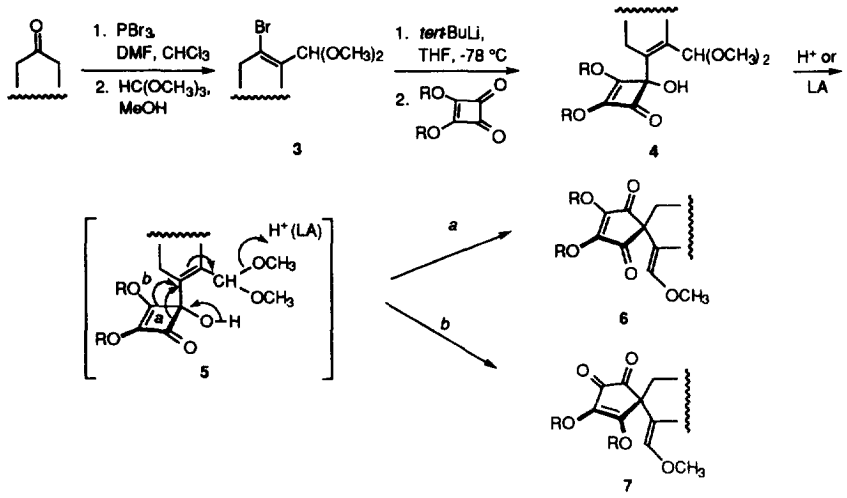
Development of a Strategy Based on Dimethyl Squarate. From the outset, the B ring of **2** was viewed by us to be a structural segment derivable by appropriate ring expansion of dimethyl squarate. The latent strain energy inherent in this and other closely related four-membered ring building blocks has been extensively exploited in recent years.[3] Particularly notable in the present context is the number of rearrangement reactions that eventuate in facile enlargement of the original squarate ring. Scheme 1 illustrates a selection of examples which have been recently documented.[4-9] None features conversion to a spirocyclic end-product. Therefore, new methods had necessarily to be developed for this purpose.

Scheme 1



In a general sense, intermediates such as **3** and **4** appeared to be ideally suited for construction of the nucleus in **2** (Scheme 2). The bromo acetals, potentially available by Vilsmeier-Haack bromoformylation of ketone precursors[10-13] and subsequent acetalization with trimethyl orthoformate,[13] were anticipated to be amenable to halogen-metal exchange.[14] The resulting alkenyl anions in turn should undergo smooth 1,2-monoaddition to a squarate ester with formation of the heavily functionalized intemediates **4**. Under suitable Brönsted or Lewis acid catalysis, the expectation was that one of the methyl groups in **5** would experience ionization and generate an allylic methoxycarbenium ion. Of the two migratory events that would result in ring expansion, the first, labelled as *a*, involves the 1,2-shift of a carbonyl carbon and delivers the C_2-symmetric

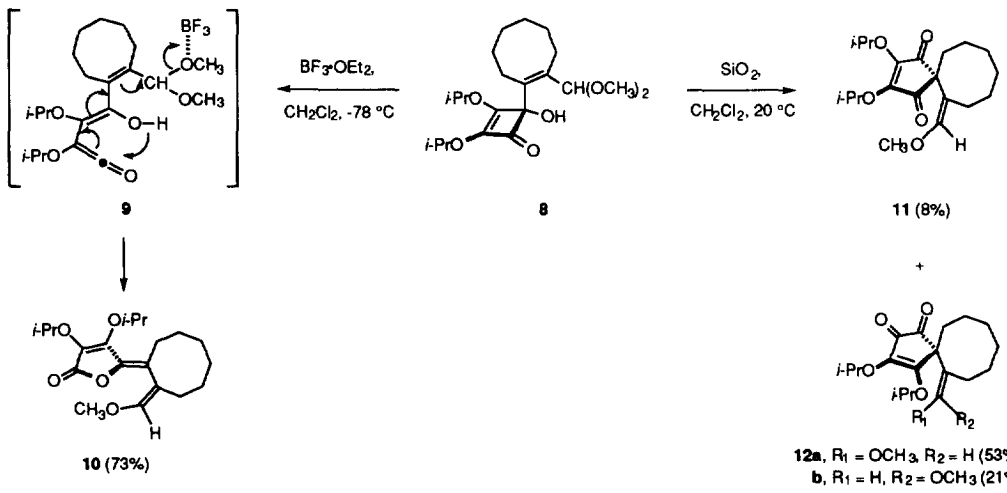
Scheme 2



diketone **6**. The second option *b* consists of the migration of a vinylic carbon and leads to α-diketone **7**. Trigonal carbons are involved in both structural reorganizations, and neither pathway can effectively skirt the delivery of a product containing a vinylogous ester functional group array.

Selected test experiments to evaluate the consequences of this intramolecular competition proved not to be particularly encouraging.[15] For example, exposure of **8** to boron trifluoride etherate in CH_2Cl_2 at -78 °C afforded **10** in 73% yield (Scheme 3). Evidently, these conditions result in complete bypassing of the desired ring expansions in favor of conrotatory opening of the hydroxycyclobutenone to give vinyl ketene **9** in which the bulky cyclooctenyl ring is positioned to the exterior. The enolic hydroxyl now finds itself syn to the electrophilic carbonyl, a situation which provides for concurrent formation of the lactone ring and stereocontrolled introduction of the vinyl ether.

Scheme 3

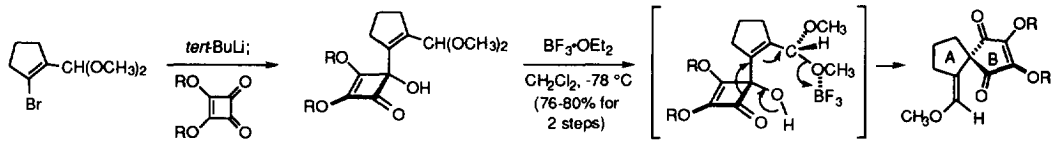


When **8** was subjected instead to the action of silica gel in CH_2Cl_2, ring expansion to give **11** proved that pathway *a* could indeed operate, although at a low level (8%) in this particular example. Transfer of the isopropoxy-substituted carbon to the incipient spirocyclic center was kinetically relevant, giving rise to both **12a** (53%) and **12b** (21%).

Although these and related results can correctly be construed not to be promising, we did note during these early studies *that product distributions were particularly sensitive to ring size*. Since arrival at **2** requires that the initial cycloalkenyl anion be five-membered, we proceeded with the original plan to utilize the ring expansion protocol for spirononene construction.

The Cyclopentenyl Case Studies. The bromo acetal **13** required for dimethyl gloiosiphone A had recently been reported by Maezaki and co-workers.[13] Halogen-metal exchange within this readily available intermediate with *tert*-butyllithium at -78 °C provided the corresponding cycloalkenyl anion, which was directly treated in situ with **14a** or **14b**. The resulting keto alcohols **15a** and **15b**, respectively, were found to be difficult to purify and quickly decomposed on silica gel, even when triethylamine was added to the chromatography solvents (Scheme 4). Consequently, these α-hydroxy ketones were exposed without purification to the action of boron trifluoride etherate in CH_2Cl_2 at -78 °C. To our delight, both reactions proceeded unidirectionally with loss of methanol to deliver the desired spirocyclic end product. In addition, the exocyclic vinyl ether in **17a** (76%) and **17b** (80%) was introduced stereoselectively in the anti geometry. The high overall yields were realized by slow dropwise introduction of the Lewis acid promoter with constant monitoring of the progress of reaction by TLC. By means of this titration technique, any destruction of **17** by the boron trifluoride can be effectively skirted.

Scheme 4



13 14 15 16 17

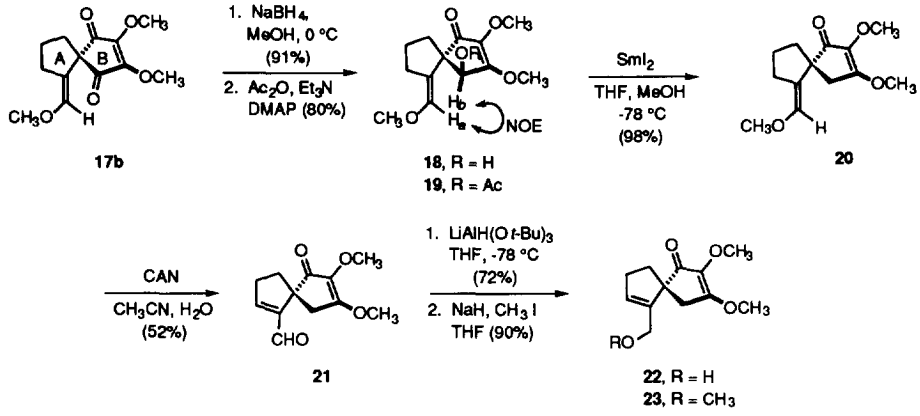
a, R = *i*-Pr; b, R = CH_3

The identification of **17a** and **17b** was notably facilitated by their C_s-symmetric nature. Additional characterization was made on the basis of COSY, NOE, and long-range DEPT analysis.

Evidently, many factors influence the relative efficiencies with which pathways *a* and *b* operate in **5**. Although the ring strain inherent in the cyclobutenone unit certainly exerts a very positive kinetic benefit to ring expansion, partitioning of the trigonal 1,2-shifts gives evidence of being controlled predominantly by the size of the pendant cycloalkenyl ring. In any event, with ample quantities of **17b** available, attention was now turned toward the synthesis of **2**.

Synthesis of Advanced Intermediate 23. To set the stage for appropriate oxygenation of the A ring in **17b**, it was first necessary to effect controlled reduction of either of the equivalent ketone carbonyls in its ring B. Breaking of the molecular symmetry at this stage held the prospect of facilitating proper introduction of the

Scheme 5



stereogenic center in ring A later in the synthesis. Consequently, **17b** was treated with 1 equiv of sodium borohydride in methanol at 0 °C (Scheme 5).[16] The single alcohol **18**, obtained in 91% yield, proved to be prone to decomposition even when stored in a freezer. Therefore, in order to avoid material loss, esterification usually followed promptly. Examination of the xanthate derivative was initially pursued with intention of accomplishing the subsequent chemospecific reductive removal of this substituent.[17] When this ploy was determined to be ineffectual, perhaps because of a latent sensitivity of the substrate to unwanted free radical processes, acetate **19** was prepared instead. NOE measurements performed on both the acetate and xanthate convincingly established the proximity of H_a to H_b. This finding requires that hydride delivery have occurred from that direction syn to the exocyclic double bond. Although the high diastereoselectivity is noteworthy, this stereochemical information is lost in the ensuing step involving careful treatment of **19** with samarium iodide in THF/methanol solution at -78 °C.[18] Clean reduction ensued to afford **20** in 98% yield.

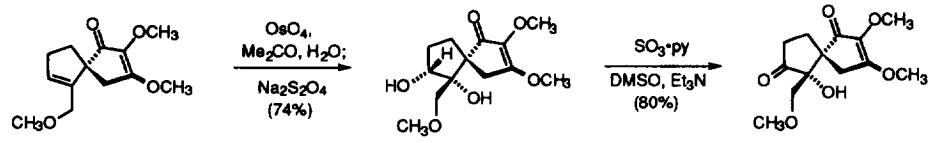
With completion of the chemical events required in ring B, efforts became focused on the introduction of unsaturation internal to ring A. Examination of a number of methods led to the selection of ceric ammonium nitrate in aqueous acetonitrile[19] as the oxidant of choice. Although the use of this reagent did prove to be problematical at times, attack at the enol ether double bond was undoubtedly favored kinetically. Although the conversion to **21** proved to be a chemoselective process, yields in excess of 52% were not realized because of competing decomposition.

The sensitivity exhibited by **21** is shared by alcohol **22**, which was obtained following treatment with lithium tri(*tert*-butoxy)aluminum hydride[20] at or below -78 °C. The use of sodium potassium tartrate in the workup of this reduction was found to be essential for the realization of good yields (72%).

At this juncture, **22** was transformed into its methyl ether **23**. Although this conversion could be realized with silver(I) oxide and methyl iodide in acetonitrile,[21] significantly higher yields were obtained with sodium hydride in THF.

Arrival at Dimethyl Gloiosiphone A. Quite unexpectedly, initial efforts to bring about the osmium tetraoxide-promoted regioselective dihydroxylation of **23** were unsuccessful. Starting ketone was seen to be readily consumed, but only baseline material remained after workup with sodium bisulfite. At this point, we carefully reexamined the hydrolysis step and ultimately discovered that the resulting osmate ether is rather

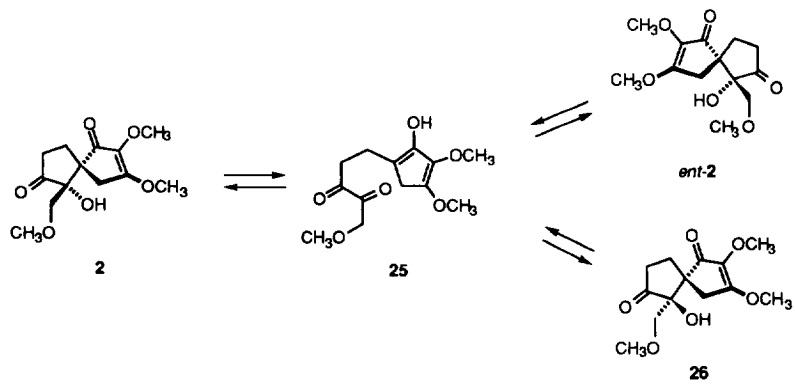
Scheme 6



recalcitrant to hydrolysis. However, cleavage can be effected with sodium dithionite at room temperature[22] during several hours. The only diol to result proved to be **24** (74%, Scheme 6), as established by NOE analysis (see Experimental Section). Thus, osmylation occurs diastereoselectively syn to the carbonyl, precisely as required in the target molecule.

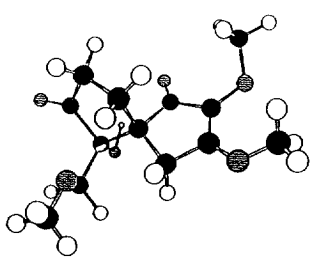
Oxidation of the secondary hydroxyl in **24** was necessary to reach **2**, but oxidants such as the Dess-Martin periodinane and tetrapropylammonium perruthenate led only to decomposition. However, the sulfur trioxidepyridine complex[23] proved to be adequately tolerant to deliver **2** in 80% yield. Although natural dimethyl gloiosiphone A has been described as a colorless oil, the synthetic material was isolated as a white crystalline solid, mp 107-108 °C. Despite the difference, the ^{1}H and ^{13}C NMR spectra of the two samples are identical. Since **2** occurs as a racemic compound, the crystallinity issue cannot be attributed to a proportion of enantiomers different from 50:50.

The absence of optical activity in natural **1** and **2** lends itself to interesting speculation. One possibility centers on the latent potential for ready and reversible retroaldol cleavage of the A ring as shown below. This conjecture centers about fragmentation of a specific interconnective spirononane bond with formation of **25**, an achiral α-diketone amenable to return with equal probability to **2** and to *ent*-**2** as a consequence of its matched electrophilic and nucleophilic sites. In actuality, **25** might also be expected to cyclize to racemic **26**, an unknown gloiosiphone diastereomer, but it evidently does not. The preference for reclosure to **2** and *ent*-**2** might, however, be attributed to inter-ring hydrogen bonding in this diastereomer.

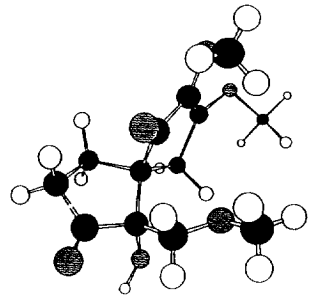


In order to gain further insight into the issue of thermodynamic stability, diastereomers **2** and **26** were minimized using the MacroModel 5.0 software package.[24] Each of the MM3 minimized structures were subjected to a Monte-Carlo multiconformational search, with resultant generation of 1000 conformations for each. This procedure was repeated several times with variation in the ring closure bond and torsion angles.

That global minimization had been reached was verified by the fact that the ten lowest conformations were generated multiple times. The lowest energy conformation from each Monte-Carlo search was subjected to a full-matrix Newton-Raphson minimization using the modified MM3 force field. The resultant finding is that **26** and not **2** is the more stable diastereomer! As originally proposed, **2** does indeed experience hydrogen bonding between the hydroxyl substituent and the carbonyl on the adjacent ring. However, this stabilizing effect is offset in **26** by virtue of an intra-ring hydrogen bond and by the absence of significant nonbonded steric interaction involving the $-CH_2OCH_3$ substituent and proximate methylene group from ring B as is found in **2**. This nonbonded steric compression may well govern the stereochemical course of the osymylation process that gives rise to **24**.



2

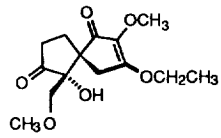


26

Total energy 42.22 kcal/mol 41.36 kcal/mol

ΔE = 0.86 kcal/mol

With this information in hand, we were motivated to undertake equilibration studies for the purpose of determining whether **2** could be isomerized to **26**. To this end, **2** was treated with potassium carbonate in methanol, but no evidence for isomerization materialized. Interestingly, if ethyl acetate was introduced prior to solvent evaporation, the β-methoxy group was subsequently exchanged for ethoxy and **27** was isolated in



27

76% yield. This transformation occurred more rapidly upon dissolution of **2** in ethanol containing K_2CO_3. The operation of a Michael addition-elimination scheme is thereby revealed without evidence of diastereomer equilibration. In this connection, the very close structural relationship enjoyed by **2** and **27** is clearly revealed from their high-field ^1H NMR spectra (Figure 1). The facts indicate therefore that the retroaldol-aldol process may be reluctant to operate. Definitive proof would require the resolution of **2** and direct observation of its racemization.

In summary, the first total synthesis of a gloiosiphone has been achieved in a highly stereocontrolled manner. The approach required ten steps and proceeded in 11.4% overall yield from dimethyl squarate. From the tactical vantage point, the latent potential of squarate esters must be underscored. In addition, the ability to

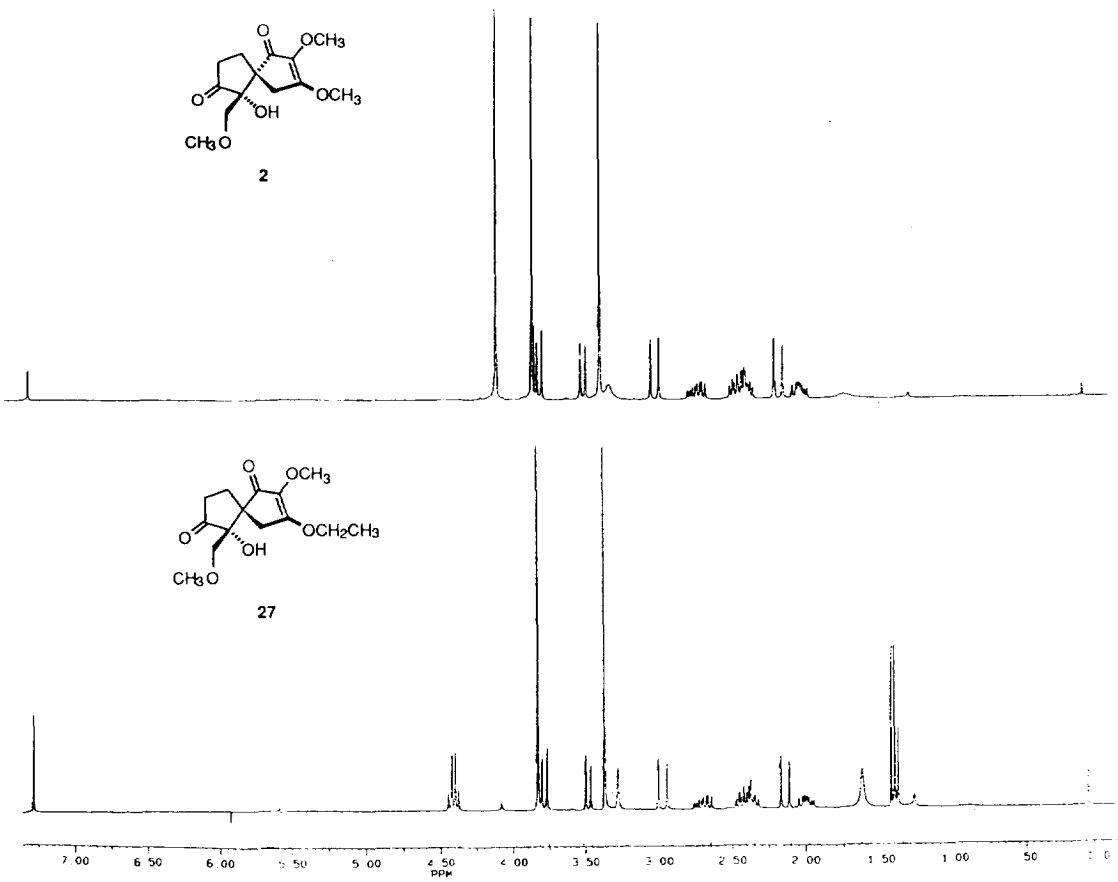


Figure 1. 300 MHz ^{1}H NMR spectra of **2** (top) and **27** (bottom) recorded in $CDCl_3$ solution.

accomplish chemo- and stereo-controlled transformations in small, densely oxygenated molecular frameworks has proven useful and perhaps will be found to be more widely applicable.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 instrument. High-field ^{1}H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 50 or 75 MHz on a Bruker AC-300 instrument as noted. Mass spectra were recorded on a Kratos MS-30 spectrometer at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark and Atlantic Microlab, Inc, Norcross, Georgia. All solvents were predried by standard methods. All reactions involving nonaqueous solutions were performed under an inert atmosphere. Unless otherwise indicated, all separations were carried out under flash chromatography

conditions on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents. The organic extracts were dried over anhydrous magnesium sulfate.

2-Bromo-1-cyclopentene-2-carboxaldehyde, Dimethyl Acetal (13). A cold (0 °C), magnetically stirred solution of DMF (95 mL) in dry $CHCl_3$ (300 mL) was treated dropwise with phosphorus tribromide (96 mL), followed 30 min later with cyclopentanone (30.4 g, 0.36 mol) dissolved in $CHCl_3$ (50 mL). The reaction mixture was stirred overnight at rt, poured onto ice (500 g), and neutralized with saturated $NaHCO_3$ solution. The product was extracted with ether, washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. The resulting orange oil was taken up in dry methanol (200 mL), treated with trimethyl orthoformate (200 mL) and camphorsulfonic acid (200 mg), and allowed to stir at rt overnight. After solvent evaporation, the residue was treated with solid potassium carbonate (300 mg), stirred, filtered, and distilled to give **13** (35.1 g, 44%) as a pale yellow liquid, bp 55-62 °C (2.5 Torr); ^1H NMR (200 MHz, $CDCl_3$) δ 4.90 (s, 1 H), 3.53 (s, 6 H), 2.57 (m, 2 H), 2.32 (m, 2 H), 1.86 (q, J = 6.0 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 137.7, 120.3, 101.9, 54.5, 40.3, 29.8, 21.5.

2,3-Dimethoxy-6-[(E)-methoxymethylene]spiro[4.4]non-2-ene-1,4-dione (17b). A cold (-78 °C) solution of **13** (1.1 g, 5.0 mmol) in dry THF (40 mL) was treated dropwise with *tert*-butyllithium (5.9 mL of 1.7 M in pentane, 10.6 mmol) and stirred for 10 min at this temperature, at which point dimethyl squarate (0.6 g, 4.2 mmol) in anhydrous THF (25 mL) was introduced via cannula. After 30 min, the reaction mixture was quenched with saturated $NaHCO_3$ solution, allowed to warm to 20 °C, and poured into a separatory funnel containing ethyl acetate (100 mL) and water (100 mL). The separated aqueous phase was extracted with ethyl acetate (4 x 100 mL) and the combined organic solutions were washed with brine, dried, and concentrated.

The oil so obtained was dissolved in CH_2Cl_2 (150 mL), cooled to -78 °C under N_2 and treated dropwise with boron trifluoride etherate via syringe. This addition was continued until TLC analysis indicated the absence of starting material. A total of 0.5 mL was added. Following a quench with saturated $NaHCO_3$ solution (20 mL) and warming to 20 °C, the mixture was poured into a separatory funnel containing CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic solutions were washed with brine, dried, and evaporated. The residue was recrystallized from 20% ethyl acetate in petroleum ether (15 mL) to provide 0.85 g (80%) of **17b** as a yellow solid, mp 118 °C; IR ($CHCl_3$, cm^{-1}) 1744, 1686, 1625; ^1H NMR (300 MHz, C_6D_6) δ 5.72 (t, J = 2.4 Hz, 1 H), 3.77 (s, 6 H), 2.95 (s, 3 H), 2.64-2.56 (m, 2 H), 1.99-1.84 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 195.9 (2 C), 151.8 (2 C), 142.4, 12.4, 59.2, 59.1 (2 C), 58.6, 34.3, 29.2, 25.3; MS *m/z* (M^+) calcd 252.0998, obsd 252.0998.

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.13; H, 6.43.

Entirely comparable reaction with diisopropyl squarate gave **17a** in 80% overall yield as a yellow oil: IR (neat, cm^{-1}) 1744, 1682, 1612; ^1H NMR (300 MHz, C_6D_6) δ 5.79 (t, J = 2.3 Hz, 1 H), 5.53 (heptet, J = 6.0 Hz, 2 H), 2.97 (s, 3 H), 2.62 (td, J = 7.0, 2.3 Hz, 2 H), 2.02 (t, J = 7.0 Hz, 2 H), 1.89 (quintet, J = 7.0 Hz, 2 H), 1.12 (d, J = 6.0 Hz, 6 H), 1.11 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 196.1 (2 C), 122.9, 151.7 (2 C), 142.4, 74.0 (2 C), 59.2, 58.7, 34.1, 29.3, 25.4, 22.9 (4 C); MS *m/z* (M^+) calcd 308.1624, obsd 308.1623.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.20; H, 7.85. Found: C, 66.08; H, 8.06.

(4R,5R*)-4-Hydroxy-2,3-dimethoxy-6-[(E)-methoxymethylene]spiro[4.4]non-2-en-1-one Acetate (19).* A solution of **17b** (450 mg, 1.79 mmol) in dry methanol (10 mL) and THF (2 mL) was treated with sodium borohydride (70 mg, 1.79 mmol) at 0 °C, stirred for 1 h at this temperature, and quenched with saturated $NaHCO_3$ solution (10 mL). The product was extracted into ethyl acetate (4 x 30 ml), dried, and freed of solvent. The residue was purified by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether containing 2% triethylamine) to furnish 410 mg (91%) of **18** as a clear, colorless oil.

To a solution of **18** (1.32 g, 5.2 mmol) in CH_2Cl_2 (20 mL) containing triethylamine (1.5 mL, 10.4 mmol) and DMAP (10 mg) was added acetic anhydride (1.0 mL, 10.4 mmol). The reaction mixture was stirred for 1 h, concentrated, and subjected to chromatography on silica gel (elution with 25% ethyl acetate in petroleum ether containing 2% triethylamine). There was isolated 1.22 g (80%) of **19** as a white solid, mp 83-84 °C; IR ($CHCl_3$, cm^{-1}) 1741, 1713, 1681, 1644, 1462; ^1H NMR (300 MHz, C_6D_6) δ 5.82 (t, J = 2.5 Hz, 1 H), 3.81 (s, 3 H), 3.60 (s, 3 H), 3.13 (s, 3 H), 2.74-2.55 (m, 2 H), 2.34 (d, J = 16.9 Hz, 1 H), 2.24-2.15 (m, 1 H), 2.19 (d, J = 16.9 Hz, 1 H), 2.00-1.91 (m, 1 H), 1.57-1.35 (m, 2 H); ^{13}C NMR (50 MHz, C_6D_6) ppm 200.5, 169.5, 162.5, 145.0, 137.6, 118.3, 75.2, 59.2, 59.0, 58.8, 58.4, 40.4, 29.2, 24.3, 20.6; MS *m/z* (M^+) calcd 296.1254, obsd 296.1262.

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.72; H, 6.82.

2,3-Dimethoxy-6-[(E)-methoxymethylene]spiro[4.4]non-2-en-1-one (20). A solution of **19** (267 mg, 0.90 mmol) in THF (10 mL) and methanol (2 mL) was deoxygenated by bubbling N_2 through for ca 10 min, cooled to -78 °C, and treated with samarium iodide solution (72.5 mL of ca 0.1 M, 7.25 mmol) in THF. The reaction mixture was allowed to warm to 0 °C, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine, dried, and concentrated to leave a residue which was chromatographed on silica gel (elution with 7% ethyl acetate in petroleum ether) to give 211 mg (98%) of **20** as a white solid, mp 76-77 °C; IR ($CHCl_3$, cm^{-1}) 1710, 1645, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (t, J = 2.5 Hz, 1 H), 4.03 (s, 3 H), 3.84 (s, 3 H), 3.53 (s, 3 H), 2.49 (s, 2 H), 2.44-2.39 (m, 2 H), 2.06-1.90 (m, 2 H), 1.70-1.54 (m, 2 H); ^{13}C NMR (50 MHz, C_6D_6) ppm 201.8, 168.2, 140.6, 134.6, 125.3, 59.0, 57.8, 52.8, 41.9, 39.5, 28.5, 24.3; MS *m/z* (M^+) calcd 238.1200, obsd 238.1207.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.58; H, 7.65.

6-(Hydroxymethyl)-2,3-dimethoxyspiro[4.4]nona-2,6-dien-1-one (22). A magnetically stirred solution of **20** (940 mg, 3.95 mmol) in acetonitrile (60 mL) and water (6 mL) was cooled to -10 °C and treated portionwise with ceric ammonium nitrate (4.32 g, 7.88 mmol). After 1 h at this temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL), allowed to stir for 10 min, and extracted with ethyl acetate (4 x 75 mL). The combined organic layers were washed with brine (25 mL), dried, and concentrated. The residual black oil was subjected to flash chromatography on silica gel (elution with 60% ethyl acetate in petroleum ether containing 2% triethylamine) to give 460 mg (52%) of **21** which because of its instability was therefore immediately reduced.

A cold (-78 °C) solution of **21** (26.7 mg, 0.12 mmol) in THF (5 mL) was treated with lithium tri-*tert*-butoxyaluminum hydride (0.12 mL of 1.0 M in THF), allowed to stir at this temperature for 1 h prior to warming to 20 °C, and quenched with saturated $NaHCO_3$ (10 mL) and sodium potassium tartrate solutions (10

mL). The product was partitioned between ethyl acetate (20 mL) and water (10 mL), and the aqueous phase was extracted with ethyl acetate (5 x 20 mL). The combined organic layers were dried and concentrated to leave a residue which was purified chromatographically (silica gel, elution with 50% ethyl acetate in petroleum ether containing 2% triethylamine). There was isolated 19.3 mg (72%) of **22** as a clear colorless oil that slowly solidified on prolonged storage in the freezer; mp 97-100 °C; IR ($CHCl_3$, cm^{-1}) 3448, 1696, 1619, 1401; ^1H NMR (300 MHz, C_6D_6) δ 5.68 (s, 1 H), 3.94 (br s, 2 H), 3.73 (s, 3 H), 3.50 (s, 3 H), 2.47 (d, J = 17.2 Hz, 1 H), 2.44-2.29 (m, 2 H), 2.17-2.05 (m, 1 H), 2.00 (d, J = 17.1 Hz, 1 H), 1.86 (br s, 1 H), 1.71-1.45 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.0, 169.3, 145.6, 135.2, 130.0, 59.6, 59.0, 57.83, 57.80, 37.7, 37.1, 30.7; MS *m/z* (M^+) calcd 224.1044, obsd 224.1039.

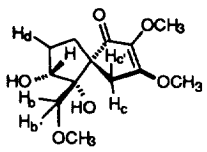
Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.29; H, 7.22.

2,3-Dimethoxy-6-(methoxymethyl)spiro[4.4]nona-2,6-dien-1-one (23). A. Use of Silver(I) Oxide. A mixture of **22** (276 mg, 1.24 mmol), methyl iodide (10 mL), and silver oxide (1.44 g, 6.21 mmol) in acetonitrile (10 mL) was stirred in the dark for 24 h, treated with an additional 1.44 g (6.21 mmol) of silver oxide, and agitated 36 h more. The reaction mixture was filtered through a pad of Celite (washing with ethyl acetate), and the filtrate was concentrated. Flash chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether containing 2% triethylamine) delivered 180 mg (61%) of **23** as a clear colorless oil; IR ($CHCl_3$, cm^{-1}) 1703, 1630, 1460; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (t, J = 1.3 Hz, 1 H), 4.02 (s, 3 H), 3.98-3.69 (m, 2 H), 3.80 (s, 3 H), 3.21 (s, 3 H), 2.78 (d, J = 17.2 Hz, 1 H), 2.51-2.32 (m, 3 H), 2.42 (d, J = 17.3 Hz, 1 H), 1.84-1.76 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.5, 170.1, 141.2, 134.8, 132.8, 69.0, 59.2, 58.04, 57.95, 57.8, 37.1, 36.8, 30.6; MS *m/z* (M^+) calcd 138.1200, obsd 238.1215.

B. By Means of Sodium Hydride. A solution of **22** (14.4 mg, 0.064 mmol) in dry THF (2 mL) was cooled to 0 °C and treated with excess methyl iodide (0.5 mL) and excess sodium hydride (60 mg). After being stirred for 45 min, the mixture was quenched slowly with water and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. Elution of the residue through a pipette containing silica gel with 60% hexanes in ethyl acetate afforded **23** (14 mg, 90%) as a colorlesss oil identical to the material obtained in part A.

(5R,6R*,7R*)-6,7-Dihydroxy-2,3-dimethoxy-6-(methoxymethyl)spiro[4.4]non-2-en-1-one (24).* Into a solution of **23** (76 mg, 0.32 mmol) in acetone (10 mL) and water (1 mL) was introduced osmium tetraoxide (81 mg, 0.32 mmol), and the mixture was stirred at rt for 2 h prior to quenching with 20% aqueous sodium dithionite solution (5 mL). After an additional 3 h of agitation, the acetone was removed under reduced pressure, and the residue was diluted with brine (10 mL) and extracted with ethyl acetate (7 x 30 mL). The combined organic layers were washed with brine (5 mL), dried, and concentrated. The residue was subjected to flash chromatography on silica gel (elution with ethyl acetate) to furnish 64 mg (74%) of **24** as a viscous colorless oil; IR ($CHCl_3$, cm^{-1}) 3446, 1697, 1621, 1460; ^1H NMR (300 MHz, C_6D_6) δ 4.83-4.78 (m, 1 H), 3.66 (s, 3 H), 3.50 (br s, 1 H), 3.45 (s, 3 H), 3.40 (d, J = 9.4 Hz, 1 H), 3.31 (d, J = 9.4 Hz, 1 H), 3.14 (d, J = 17.7 Hz, 1 H), 2.88 (s, 3 H), 2.41-2.35 (m, 1 H), 1.98 (d, J = 17.8 Hz, 1 H), 1.87-1.75 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 202.0, 171.1, 133.9, 80.3, 75.8, 65.8, 59.6, 59.3, 57.9, 56.2, 32.9, 32.7, 29.3; MS *m/z* (M^+) calcd 272.1254, obsd 272.1244.

Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 56.80; H, 7.70.



Irradiate	Observe	% NOE
H_a	H_d	5.9
H_a	H_b, $H_{b'}$	4.9
H_b, $H_{b'}$	H_a	3.7
H_c	$H_{c'}$	29.5
$H_{c'}$	H_c	26.2
H_a,$H_{b'}$	H_c	1.4

Dimethyl Gloiosiphone A (2). To a magnetically stirred solution of **24** (34 mg, 0.13 mmol) and triethylamine (0.2 mL) in DMSO (4 mL) was added the sulfur trioxide-pyridine complex (101 mg, 0.63 mmol) in several portions over a period of several minutes. After 45 min, the reaction mixture was poured into a separatory funnel containing ethyl acetate (20 mL) and brine (20 mL). The aqueous layer was extracted with ethyl acetate (4 x 50 mL). The separated organic layers were washed with brine (10 mL), dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 70% ethyl acetate in petroleum ether) provided 27 mg (80%) of **2** as a white solid, mp 107-108 °C; IR ($CHCl_3$, cm^{-1}) 3434, 1732, 1702, 1624, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3 H), 3.80 (s, 3 H), 3.75 (d, J = 10.5 Hz, 1 H), 3.45 (d, J = 10.5 Hz, 1 H), 3.34 (s, 3 H), 3.29 (br s, 1 H), 2.96 (d, J = 17.0 Hz, 1 H), 2.74-2.61 (m, 1 H), 2.45-2.29 (m, 2 H), 2.12 (d, J = 17.0 Hz, 1 H), 2.02-1.92 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.5, 199.9, 170.9, 134.6, 80.3, 71.8, 59.7, 59.4, 58.2, 52.9, 32.3, 32.0, 28.5; MS *m/z* (M^+) calcd 270.1098, obsd 270.1102.

(5R,6R*)-3-Ethoxy-6-hydroxy-2-methoxy-6-(methoxymethyl)spiro[4.4]non-2-ene-1,7-dione (26).* *A. From K_2CO_3 in Ethyl Acetate.* A solution of **2** (4.1 mg, 0.015 mmol) in methanol (2 mL) containing potassium carbonate (30.1 mg, 0.22 mmol) was stirred at rt for 2 days. At this point, TLC analysis indicated no change in the starting material. The reaction mixture was diluted with ethyl acetate (10 mL) and concentrated on a rotary evaporator. TLC analysis of the concentrate now indicated that no **2** remained. The less polar product was purified by flash chromatography (silica gel, elution with ethyl acetate) to give 3.1 mg (76%) of **26** as a clear, colorless oil; IR ($CHCl_3$, cm^{-1}) 3456, 1753, 1696, 1619, 1445; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 3.76 (d, J = 10.5 Hz, 1 H), 3.46 (d, J = 10.5 Hz, 1 H), 3.32 (s, 3 H), 3.26 (s, 1 H), 2.95 (d, J = 17.0 Hz, 1 H), 2.74-2.62 (m, 1 H), 2.45-2.30 (m, 2 H), 2.12 (d, J = 17.0 Hz, 1 H), 2.02-1.92 (m, 1 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.5, 199.9, 170.3, 134.4, 80.3, 71.8, 67.1, 59.7, 59.3, 52.8, 21.4, 32.3, 28.5, 15.3; MS *m/z* (M^+) calcd 284.1254, obsd 284.1257.

B. From K_2CO_3 in Ethanol. A solution of **2** (9.8 mg, 0.037 mmol) in ethanol (2 mL) containing potassium carbonate (33.5 mg, 0.24 mmol) was stirred at rt for 2 days and concentrated. The residue was taken up in ethyl acetate (10 mL), filtered, and evaporated. Purification of the residue by flash chromatography as described above afforded 7.4 mg (72%) of **26**, identical in all respects to the material produced in part A.

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