Total Synthesis of (−)-Galbonolide B and the Determination of Its Absolute Stereochemistry

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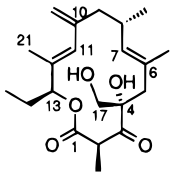
Abstract: Through a trans-lactonization reaction, galbonolide B (**1**) was converted to **3** with the chiral secondary alcohol at C13 exposed for derivatization. Two independent methods were employed to determine the absolute chirality at C13. Both of these methods established *S* chirality at C13. Since the relative stereochemistry of galbonolide B had been determined from the X-ray structure, the absolute stereochemistry of galbonolide B was therefore formally established to be structure **1**, which contradicted earlier speculations in the literature. A total synthesis of galbonolide B has been completed. A highly selective method was developed for the assembly of the peculiar diene unit using Martin's sulfurane reagent for the dehydration of the preceding tertiary alcohol **20**. The chiral center at C4 was installed by "contra-steric" enolate chemistry. A novel macro-Dieckmann cyclization was employed to generate the macrocycle. The desired configuration at C2 was obtained from the kinetic protonation of the corresponding enolate. Finally, a seldom used protecting group, 2,4,6-trimethylbenzylidene acetal, was employed for the glycol unit. It exhibited extremely facile hydrolysis under mildly acidic conditions without causing any decomposition of synthetic intermediates.

Galbonolide B was isolated as a fungal metabolite from *Micromonospora chalcea* by Otake[1] and from *Streptomyces galbus* by Achenbach[2] independently. It has been shown to exhibit potent activities against a large number of microorganisms, which include *Candida albicans* and *Rhodotorula rubra* that are associated with human infections and *Botrytis cinerea* and *Pseudomonas lachrymans* that are harmful to agriculture.[3] Galbonolide B has been shown to consist of a 14-membered ring with the connectivities of atoms as shown in structure **1**. Though there were speculations of the relative and absolute stereochemistries of galbonolide B from a series of NMR experiments, circular dichroism methods, and the Celmer model,[3] there was no definitive confirmation.



1: Galbonolide B

Galbonolide B is a rather unstable compound. As expected, the chiral center at C2 is readily susceptible to epimerization. Under basic conditions, trans-lactonization, involving the tertiary alcohol at C4, takes place rapidly. Additionally, the allylic lactone moiety shows sensitivity to acid.[3] A total synthesis of this compound will, therefore, serve as a useful tool to generate more stable analogs as potential antifungal agents. However, due to the peculiar diene system, four remote chiral centers and a 14-membered β-keto lactone containing a labile chiral center, galbonolide B poses a significant synthetic challenge.

The first part of this article describes the determination of the absolute stereochemistry of galbonolide B which corrects the previously published structure.[3] The second part details its total synthesis developed in this laboratory.

Determination of Absolute Stereochemistry

Though attempts to crystallize several derivatives of galbonolide B have failed, the Merck crystallography group has recently obtained an X-ray structure of this natural product,[4] through which the *relative* stereochemistry was assigned (Figure 1). Therefore, to determine the absolute stereochemistry, the absolute chirality at only one asymmetric center was required. The chiralities of the remaining three centers would follow.

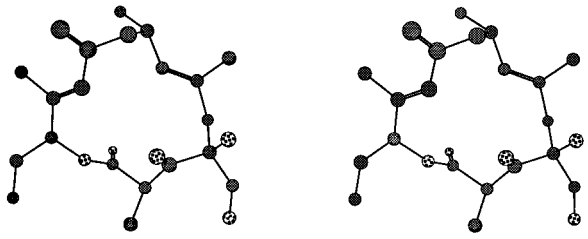


Figure 1. Stereoview of the X-ray structure of galbonolide B.

As mentioned earlier, facile trans-lactonization under basic conditions is one mode of decomposition of galbonolide B. This pathway turned out to be very useful for the determination of stereochemistry. Upon reaction with MeI, NaH in DMF, compound **3** was formed in 70% yield.[5] The IR stretches of 1749 and 1801 cm^{-1} supported the five-membered β-keto lactone moiety, confirming that trans-lactonization did indeed involve the tertiary alcohol at C4 instead of the primary alcohol at C17 which would generate the alternative six-membered β-keto lactone. Compound **3** was ideal for use in the determi-

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) Abe, Y.; Nakayama, H.; Shimazu, A.; Furihata, K.; Ikeda, K.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1810.

(2) Achenbach, H.; Muhlenfeld, A.; Fauth, U.; Zahner, H. *Tetrahedron Lett.* **1985**, *26*, 6167.

(3) Achenbach, H.; Muhlenfeld, A.; Fauth, U.; Zahner, H. *Ann. N. Y. Acad. Sci.* **1988**, *544*, 128. The speculated absolute stereochemistry was different from that shown in structure **1**.

(4) Unpublished results from Dr. Richard Ball of the Merck Crystallography Group in Rahway, NJ, who kindly provided the X-ray structure of galbonolide B.

(5) An authentic sample of galbonolide B was kindly provided by Dr. Guy Harris of Merck Research Laboratories, Rahway, NJ.

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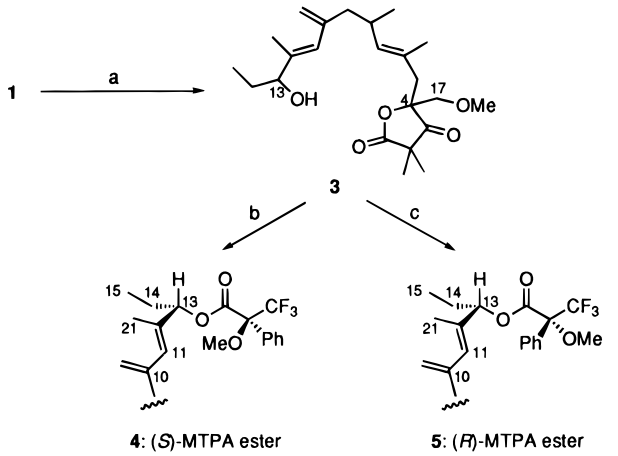
Scheme 1[a]



[a] Reagents and conditions: a. NaH, MeI, DMF, room temperature. b. (*R*)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, room temperature. c. (*S*)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, room temperature. If the chirality of C13 were *S* as drawn, with the shielding effects of the phenyl groups, one would predict an upfield shift of the protons on C11 and C21 from **4** to **5** and a downfield shift of the protons on C14 and C15. If the chirality were *R*, the opposite shifts would be predicted.

Table 1. Chemical Shifts of the Protons Adjacent to the (*S*)- and (*R*)-MTPA Esters Moieties (ppm)[a]

compd	C14−H	C15−H	C11−H	C21−H
4	1.60−1.76	0.80	5.88	1.72
5	1.65−1.80	0.88	5.80	1.62

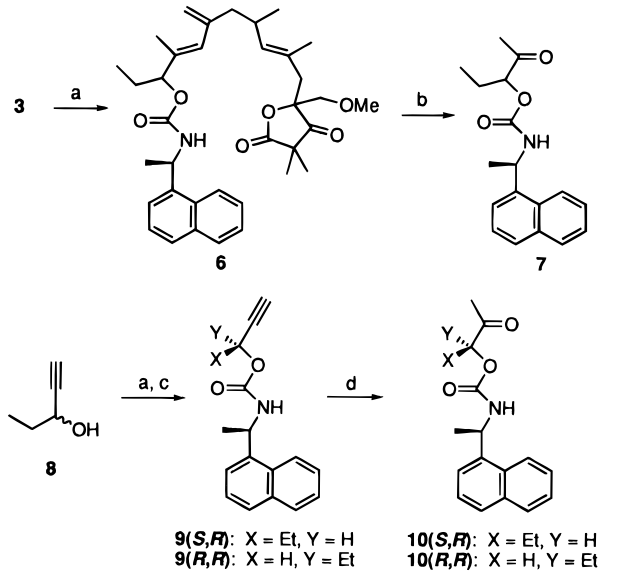
[a] Comparing the shifts of the relevant signals of **4** to **5**, the downfield shift of the protons on C14 and C15 and the upfield shift of those on C11 and C21 indicated *S*-chirality at C13. $CDCl_3$ was used as the solvent.

nation of stereochemistry for two reasons: (a) the chiral center at C2 was eliminated by the introduction of an additional methyl group, thus, preventing any complications from epimerization at C2; (b) the chiral secondary alcohol at C13 was exposed for derivatization while the two alcohols at C4 and C17 were masked in the form of a lactone and an ether respectively. Two independent methods have been performed on **3** to determine the configuration at C13—both proved its *S*-chirality.

First, the standard Mosher method was employed.[6] The (*S*)- and (*R*)-MTPA esters were obtained by treating **3** with the corresponding MTPA chlorides (*ca.* 80% yield). Assuming the chirality of C13 were *S*, the preferred conformations predicted from Mosher's model were drawn as shown in **4** and **5** (Scheme 1). As a result of the shielding effects of the phenyl group, from **4**((*S*)-MTPA ester) to **5**((*R*)-MTPA ester), one would expect an upfield shift of the protons on C11 and C21 and a downfield shift of the protons on C14 and C15. The opposite shifts would be observed if the chirality of C13 were *R*. The chemical shifts of the pertinent signals are tabulated in Table 1 and show that the chirality of C13 is indeed *S*.

In the second method (Scheme 2), carbamate **6** was formed from the reaction of **3** and (*R*)-1-(1-naphthyl)ethyl isocyanate (83% yield) and was subsequently degraded by Sharpless' method of oxidative cleavage to yield **7** (54% yield).[7] The diastereomeric carbamates **9(*S*,*R*)** and **9(*R*,*R*)** have been synthesized, separated, and characterized by Pirkle.[8] Using relatively mild and neutral conditions, the alkynes **9(*S*,*R*)** and **9(*R*,*R*)** were converted to the corresponding methyl ketones **10(*S*,*R*)**

Scheme 2[a]



[a] Reagents and conditions: a. (*R*)-1-(1-naphthyl)ethyl isocyanate, DMAP, toluene, reflux. b. $NaIO_4$, $RuCl_3$, $CCl_4-CH_3CN-H_2O$, room temperature. c. Chromatography. d. PhHgOH, $CHCl_3-H_2O$, reflux.

and **10(*R*,*R*)**, respectively, with PhHgOH in a refluxing $CHCl_3-H_2O$ mixture (*ca.* 87% yield).[9] By ^1H NMR comparison, the degradation product **7** was found to be identical to **10(*S*,*R*)** and different from **10(*R*,*R*)**.[10] Thus, the *S*-chirality of C13 was proven.

Since these two independent methods both established *S*-chirality at C13 and the relative stereochemistry of galbonolide B had already been confirmed by X-ray crystallography, the absolute stereochemistry of galbonolide B was therefore proven to be that as shown in structure **1**. Consequently, the earlier prediction on the absolute stereochemistry by others[3] was shown to be incorrect.

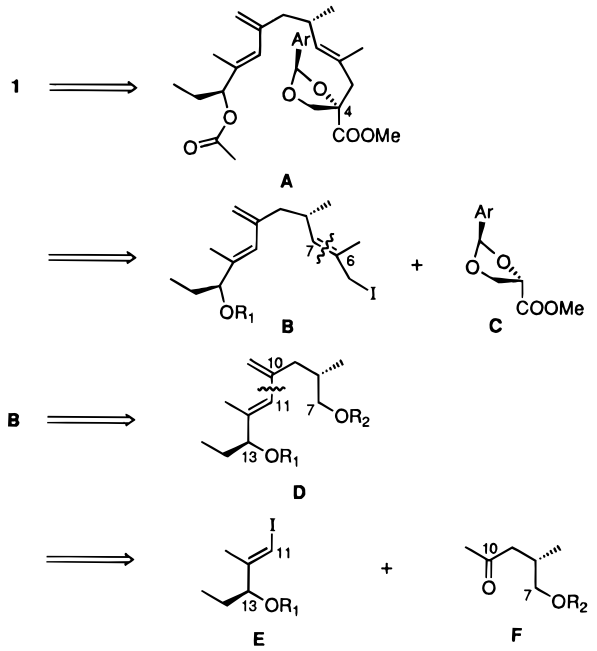
Total Synthesis

Retrosynthetically, to assemble the β-keto lactone moiety in a 14-membered ring, a novel macro-Dieckmann cyclization was planned on **A** (Scheme 3). The proper configuration at C4 of **A** could be achieved from a modification of Seebach's and Ladner's "contra-steric" enolate attack of **C** on **B**. The trisubstituted C6−C7 double bond of **B** could be installed from **D** through a suitable Wittig or Horner-Emmons' reaction. Noticing the two chiral centers in **D** were rather distant from each other, it would be intuitive to further disconnect the C10−C11 bond to **E** and **F**. This route not only involved simple and efficient assemblies of all carbon−carbon bonds but also allowed easy access to important analogs of galbonolide B through simple modifications.

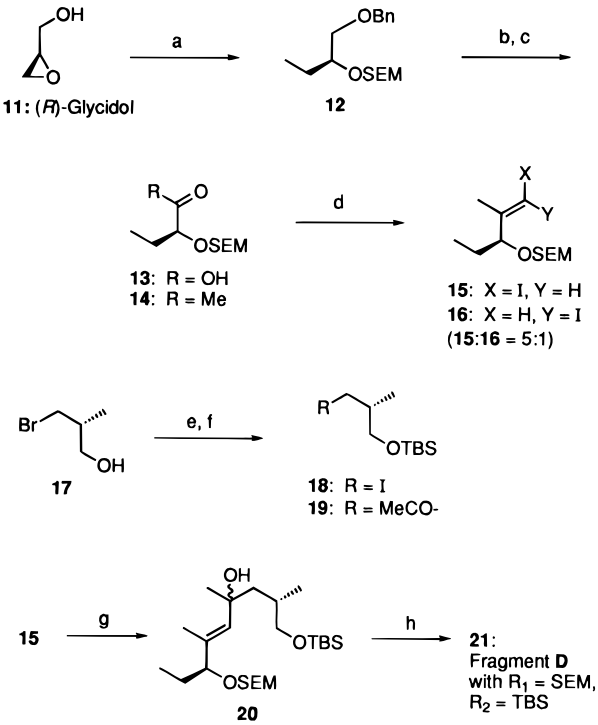
Fragments **E** and **F** were obtained from readily available chiral starting materials. (*R*)-Glycidol (**11**) was chosen as the starting material for **E** (Scheme 4). After benzylation (81%), the epoxide was selectively opened at the primary center by MeMgI and CuI in THF (97%). The secondary alcohol formed was protected as a SEM ether to give **12** (100%). Catalytic hydrogenolysis (96%) and subsequent PDC oxidation (75%) were employed to furnish the carboxylic acid **13**, which reacted with MeMgCl in ether to yield the methyl ketone **14** (92%).

(6) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(7) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(8) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839.
(9) Janout, V.; Regen, S. L. *J. Org. Chem.* **1982**, *47*, 3331.
(10) The most notable difference between the ^1H NMR of **10(*S*,*R*)** and that of **10(*R*,*R*)** is the signal corresponding to the methyl group next to the ketone. The former showed up at 2.09 ppm in $CDCl_3$, whereas the latter showed up at 2.17 ppm.

Scheme 3



Scheme 4[a]



[a] Reagents and conditions: a. 1. BnBr, NaH, DMF, room temperature. 2. MeMgI, CuI, THF, −78 °C. 3. SEMCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature. b. 1. H_2 (balloon), $Pd(OH)_2$ on C, THF−MeOH. 2. PDC, DMF, room temperature. c. MeMgCl, ether, 0 °C. d. CHI_3, $CrCl_2$, THF, 0 °C. e. 1. TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C. 2. LiI, THF, reflux. f. Ethyl vinyl ether, *t*-BuLi, THF, room temperature, followed by acid workup. g. 1. *t*-BuLi, ether, −78 °C. 2. Methyl ketone **19**, THF−ether, −78 °C. h. Martin's sulfurane reagent, CH_2Cl_2, room temperature.

Employing Takai's procedure,[11] upon reaction with CHI_3 and $CrCl_2$ in THF, **14** was converted to the desired vinyl iodide **15** and the undesired isomer **16** in 5:1 ratio (61%).[12] The two vinyl iodides were separable by silica gel chromatography.

To prepare fragment **F**, the commercially available (*R*)-3-bromo-2-methyl-1-propanol (**17**) was used as the starting material. After protection of the alcohol as a TBS ether (100%), the bromide was displaced by iodide to function as a better leaving group (97%).[13] The umpolung, lithiated ethyl vinyl ether, was used to displace the iodide. After acid workup, the desired methyl ketone **19** was obtained (62%).[14]

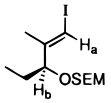
For the coupling of **15** and **19**, Li-I exchange was first performed on **15** with *tert*-butyllithium in ether. The vinyllithium species formed was then trapped with **19** to give diastereomeric **20** (84%). Upon the screening of a number of dehydrating conditions, Martin's sulfurane reagent[15] worked best and most efficiently to give the desired diene **21** in high yield (95%) and high selectivity (∼95:5 desired/undesired dienes). The SEM group was chosen as the protecting group for the alcohol at C13 because among all the protecting groups examined, only the vinyl iodides with MOM, MEM, BOM, and SEM groups underwent Li−I exchange successfully in step g of Scheme 4, and among these groups, only the SEM group had been successfully removed without the destruction of the diene system.

After selective removal of the TBS group in **21** with Et_4NF in DMF (84%) in the presence of the SEM ether (Scheme 5), the resultant alcohol was oxidized to the corresponding aldehyde by a standard Swern oxidation (93%). To install the C6−C7 trisubstituted double bond, a Horner−Emmon's reaction using the phosphonate **31** was employed. Among all the conditions attempted, the Roush−Masamune conditions[16] using LiCl, DBU in CH_3CN performed best to give the desired *E* alkene **24** as the only isomer observed (95%). The ethyl ester was subsequently reduced by DIBAL-H to the alcohol **32** (96%),[17] which was then converted to the iodo compound **25** by PPh_3, imidazole and I_2.[18]

To prepare for the next step, the commercially available acetonide **22** was first hydrolyzed to give the corresponding diol (81%), which was then treated with an aromatic aldehyde to give **23**. A modification of Seebach's and Ladner's "contrasteric" enolate chemistry was then carried out on **25**, which predicted the attack of the lithium enolate of **23** to take place on the same face of the five-membered ring as the Ar group.[19,20]

(11) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(12) The desired *E* geometry of **15** was confirmed by the NOE observed between H_a and H_b.



15

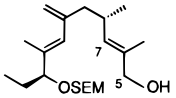
(13) If the bromide was not first displaced by iodide, reaction with lithiated ethyl vinyl ether was low-yielding.

(14) For example, see: Baldwin, J. E.; Hofle, G. A.; Lever, O. W. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(15) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

(16) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(17) The *E* geometry of the C6−C7 double bond of alcohol **32** was confirmed by the NOE observed between the proton on C7 and the 2H's on C5.

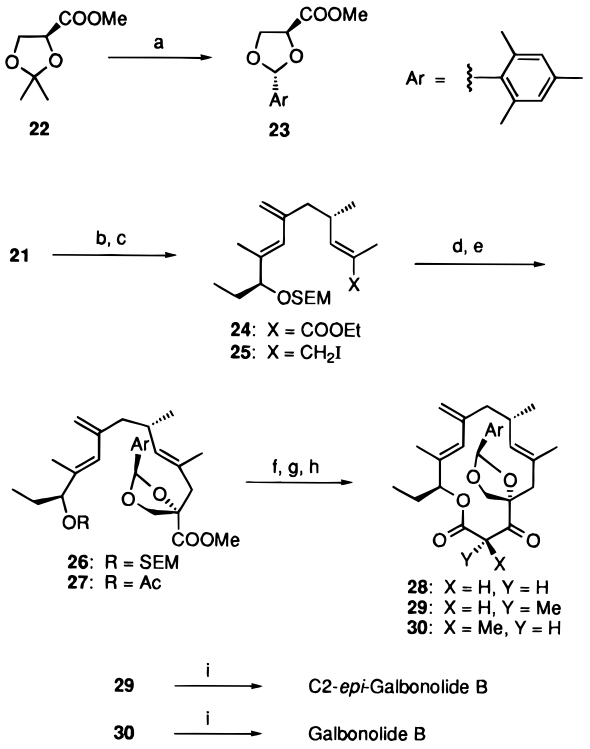


32

(18) For example, see: Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(19) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.

Scheme 5[a]



[a] Reagents and conditions: a. 1. *p*-TsOH, MeOH−H_2O, room temperature. 2. ArCHO, CSA, $CHCl_3$, Dean-Stark with 4A molecular sieves. b. 1. Et_4NF, DMF, room temperature. 2. $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C. 3. $(EtO)_2POCHMeCOOEt$ (**31**), LiCl, DBU, CH_3CN, 0 °C. c. 1. DIBAL-H, CH_2Cl_2, −78 °C. 2. PPh_3, imidazole, I_2, ether−CH_3CN, −30 °C. d. **23**, LiHMDS, THF−HMPA, −78 °C. e. 1. Et_4NF, DMSO, powdered molecular sieves, 90 °C. 2. CH_2N_2, ether, room temperature. 3. Ac_2O, pyridine, DMAP, room temperature. f. LiHMDS, THF, high-dilution, reflux. g. 1. KO*t*-Bu, DMF, 0 °C, 2. MeI. h. 1. KO*t*-Bu, DMF, 0 °C. 2. AcOH quench. i. AcOH-H_2O (2:1), room temperature.

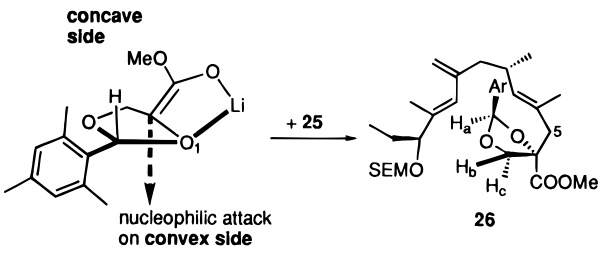
Indeed, upon the treatment of **23** with LiHMDS in a THF/HMPA solvent system, the lithium enolate reacted with **25** to furnish compound **26** (75% over two steps).[21] The SEM ether was then cleaved by Et_4NF in DMSO at 90 °C in the presence of powdered molecular sieves to generate the secondary alcohol at C13. The methyl ester of **26** was also cleaved in this reaction but it could be regenerated by the reaction of the resultant carboxylic acid with ethereal CH_2N_2 (52% over two steps). Acetylation of the secondary alcohol at C13 furnished compound **27** (99%). The stage was set for cyclization. A novel macro-Dieckmann cyclization was carried out. Reaction of **27** with LiHMDS in refluxing THF under high-dilution conditions successfully generated the cyclized product **28** (75%). It is noteworthy that the cyclization failed when the acetate in **27** was replaced by the analogous propionate. Therefore, the methyl group at C2 had to be installed after cyclization. To this end, compound **28** was first enolized with KO*t*-Bu in DMF. Trapping of the enolate with MeI gave a single isomer **29** (92%), indicating that the nucleophilic attack of the enolate was extremely stereoselective. The issue that remained was the stereochemistry of the C2 center of **29**. To determine that, the acetal would first need to be hydrolyzed. The hydrolyzed product could then be compared with galbonolide B and C2-*epi*-galbonolide B, both of which have been characterized.[22] The difficulty, however, lay in the hydrolysis of the acetal. A number of different Ar acetal protecting groups have been investigated. When the Ar group was Ph, 3-MeO-C_6H_4, or 4-Me-C_6H_4, it was found that the allylic lactone moiety was hydrolyzed preferentially. In an effort to enhance the hydrolysis of the acetal, 2-MeO-C_6H_4, 4-MeO-C_6H_4, and 4-PhO-C_6H_4 groups have been attempted. Unfortunately, they gave rise to severe instability of acetals **23**. Finally, a seldom used protecting group for 1,2-glycols, 2,4,6-trimethylbenzylidene acetal,[23] was employed because of three main reasons. Firstly, it gave rise to facile hydrolysis of **29**. Indeed, the hydrolysis was completed within 30 min in AcOH/H_2O (2:1 by volume) without causing any decompositions. Secondly, in step d involving the "contra-steric" enolate chemistry, the highest diastereoselectivity of enolate attack was obtained with this particular Ar group (20:1). Thirdly, none of the intermediates involving this 2,4,6-trimethylbenzylidene acetal were unstable. In fact, all of the intermediates were stable indefinitely at room temperature in the absence of acids. Thus, this rarely utilized protecting group for 1,2-glycols may prove very useful when conventional acetals fail to work satisfactorily.

Upon the hydrolysis of the 2,4,6-trimethylbenzylidene acetal of **29**, the product was found to be identical to C2-*epi*-galbonolide B, not galbonolide B. The fact that the enolate attack of **28** was very stereoselective suggested that the proton quench of the enolate of **29** could invert the stereochemistry. Indeed, the reaction of **29** with KO*t*-Bu in DMF, followed by AcOH quench, successfully inverted the stereocenter at C2 to yield **30**. Comparing the ^1H NMR of **29** and **30**, notable shifts of signals were observed, which suggested a significant change in the conformation of the macrocycle upon epimerization at C2. The subsequent hydrolysis of the acetal of **30** with AcOH/H_2O (2:1) successfully furnished galbonolide B. The synthetic material was identical to the natural product in all aspects, including spectroscopic data, optical rotation, and biological activity.

In summary, an efficient synthesis of galbonolide B has been developed. The final stage of the synthesis was highlighted by a novel macro-Dieckmann cyclization and the utilization of 2,4,6-trimethylbenzylidene acetal as a useful protecting group for 1,2-glycols. With slight modifications of this synthetic route, a number of analogs of galbonolide B have been synthesized for biological studies and will be reported elsewhere.

(20) Ladner, W. *Chem. Ber.* **1983**, *116*, 3413.

(21) To explain the "contra-steric" enolate attack, Seebach's model (ref 19) could be used, which predicted the chelation of Li and O_1, resulting in the folding of the enolate into a *cis*-fused five-membered ring system. Consequently, nucleophilic attack would preferentially take place on the less hindered convex side, *i.e.*, the same face as the Ar group. The fact that NOE was observed between H_a and H_c and between H_b and the 2 H's on C5 confirmed the structure of **26**.



(22) Galbonolide B and C2-*epi*-galbonolide B were found to be in equilibrium in conditions such as DMAP in CH_2Cl_2 or pyridine−water mixture and were characterized by Dr. Mark Greenlee and Ms. Regina Black of this department. Both compounds have also been reported in the literature, *e.g.*, see ref 3.

(23) An example of the use of 2,4,6-trimethylbenzylidene acetal as a protecting group for diols can be found in the following: Woodward, R. B. *et al. J. Am. Chem. Soc.* **1981**, *103*, 3213.

(24) Acetal **23** and it *cis* isomer were distinguished by NOE experiments. The latter showed a strong NOE between the benzylic proton and the proton next to the −COOMe moiety, whereas the former did not.

Experimental Section

General Methods. Reactions sensitive to moisture or air were performed under nitrogen using anhydrous solvents and reagents. Reagents and solvents were used as supplied otherwise. Na_2SO_4 was used for drying in the aqueous workups of reactions. ^1H and ^{13}C NMR spectra were obtained at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million, and residual solvent peaks were used as internal references. Coupling constants are reported in hertz. IR spectra were measured as films, and the wavenumbers are reported in cm^{-1}. Analytical TLC was performed with E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Preparative TLC (PTLC) separations were performed on E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.50 mm. Flash chromatography was performed with E. Merck Kieselgel 60 (230−400 mesh) silica gel. The experimental procedures for the preparations of **15** from **11**, **19** from **17**, and **23** from **22** are routine[24] and are provided as supporting information.

Trans-Lactonized Product 3. To a mixture of galbonolide B[5] (300 mg, 0.824 mmol) and MeI (0.51 mL, 8.19 mmol) in 7 mL of anhydrous DMF was added NaH (76 mg of 60% oil dispersion, 1.90 mmol). The mixture was stirred at room temperature for 1 h and was then concentrated *in vacuo*. After aqueous workup (CH_2Cl_2) and chromatography, 226.2 mg (70% yield) of **3** was obtained: $[\alpha]^{25}_D$ +37.5° (*c* 0.76, $CHCl_3$). IR 3477, 1801, 1749. ^1H NMR ($CDCl_3$) δ 0.85 (3H, d, J = 6.4), 0.86 (3H, t, J = 7.3), 1.19 (3H, s), 1.26 (3H, s), 1.54−1.61 (2H, m), 1.61 (3H, d, J = 1.4), 1.71 (3H, d, J = 1.4), 1.95 (1H, dd, J = 7.5, 13.3), 2.01 (1H, dd, J = 6.9, 13.3), 2.32 (1H, d, J = 14.2), 2.40 (1H, d, J = 14.2), 2.41 (1H, m), 3.26 (3H, s), 3.44 (1H, d, J = 10.1), 3.60 (1H, d, J = 10.1), 3.94 (1H, t, J = 6.4, 6.7), 4.82 (1H, s), 4.96 (1H, s), 5.08 (1H, d, J = 8.4), 5.73 (1H, d, J = 0.7). ^{13}C NMR ($CDCl_3$) δ 10.0, 13.3, 17.9, 20.0, 20.0, 21.2, 27.9, 31.6, 42.0, 44.4, 45.2, 59.4, 75.0, 79.1, 92.6, 115.3, 126.1, 126.6, 138.6, 139.8, 143.5, 177.6, 214.0. HRMS (EI) calcd for $C_{23}H_{36}O_5$ 392.2563, found 392.2587.

(*S*)-MTPA Ester 4. To a CH_2Cl_2 solution (4 mL) of **3** (20.0 mg, 0.051 mmol) and a catalytic amount of DMAP at −78 °C were added NEt_3 (0.4 mL, 2.87 mmol) and (*R*)-MTPA chloride (0.2 mL, 1.07 mmol). The mixture was allowed to warm to room temperature and was stirred overnight. Purification by PTLC gave 25.7 mg (83% yield) of **4**: $[\alpha]^{25}_D$ +11.3° (*c* 0.50, $CHCl_3$). IR 1799, 1755, 1653. ^1H NMR ($CDCl_3$) δ 0.80 (3H, t, J = 6.4), 0.81 (3H, d, J = 8.0), 1.18 (3H, s), 1.26 (3H, s), 1.58 (3H, d, J = 1.2), 1.72 (3H, d, J =1.2), 1.60−1.76 (2H, m), 1.91 (1H, dd, J = 8.5, 13.5), 2.03 (1H, dd, J = 6.1, 14.1), 2.31 (1H, d, J = 14.2), 2.36 (1H, m), 2.40 (1H, d, J =14.2), 3.26 (3H, s), 3.43 (1H, d, J =10.0), 3.48 (3H, s), 3.60 (1H, d, J = 10.0), 4.83 (1H, s), 5.01 (1H, s), 5.06 (1H, d, J = 9.4), 5.30 (1H, dd, J = 6.6, 7.1), 5.87 (1H, s), 7.31−7.50 (5H, m). ^{13}C NMR ($CDCl_3$) δ 9.6, 13.3, 17.8, 19.7, 20.0, 21.1, 25.4, 31.3, 41.9, 44.4, 45.0, 55.2, 59.4, 75.0, 83.7, 92.5, 116.1, 126.3, 127.4, 128.2, 128.3, 129.5, 130.9, 132.5, 134.3, 138.4, 142.9, 165.8, 177.6, 213.9. HRMS (EI) calcd for $C_{33}H_{43}F_3O_7$ 608.2961, found 608.2922.

(*R*)-MTPA Ester 5. The same procedure for the synthesis of **4** was followed with the use of (*S*)-MTPA chloride. From 10.5 mg of **3**, 13.2 mg (81% yield) of **5** was obtained: $[\alpha]^{25}_D$ +80.1° (*c* 0.47, $CHCl_3$). IR 1799, 1755, 1653. ^1H NMR ($CDCl_3$) δ 0.83 (3H, d, J = 6.9), 0.88 (3H, t, J = 7.6), 1.18 (3H, s), 1.26 (3H, s), 1.56 (1H, d, J =1.2), 1.62 (1H, d, J = 1.2), 1.65−1.80 (2H, m), 1.90 (1H, dd, J = 8.7, 13.5), 2.01 (1H, dd, J = 6.0, 13.5), 2.32 (1H, d, J = 14.2), 2.38 (1H, m), 2.41 (1H, d, J = 14.2), 3.27 (3H, s), 3.44 (1H, d, J = 10.1), 3.54 (3H, s), 3.60 (1H, d, J = 10.1), 4.80 (1H, s), 4.99 (1H, s), 5.07 (1H, d, J = 9.2), 5.24 (1H, t, J = 7.1), 5.80 (1H, s), 7.30−7.50 (5H, m). ^{13}C NMR ($CDCl_3$) δ 10.0, 13.1, 17.9, 19.8, 20.1, 21.2, 25.5, 31.4, 42.0, 44.5, 45.1, 55.6, 59.5, 75.1, 83.9, 92.7, 116.0, 126.4, 126.7, 127.3, 128.3, 128.4, 129.6, 130.9, 134.3, 138.6, 143.0, 165.8, 177.7, 214.0. HRMS (EI) calcd for $C_{33}H_{43}F_3O_7$ 608.2961, found 608.2919.

Carbamate 6. To a solution of **3** (21.7 mg, 0.055 mmol) in toluene (5 mL) were added (*R*)-1-(1-naphthyl)ethyl isocyanate (0.10 mL, 0.567 mmol) and a catalytic amount of DMAP. The mixture was refluxed overnight. After concentration *in vacuo* and purification by PTLC, 27.1 mg (83% yield) of **6** was obtained: $[\alpha]^{25}_D$ +43.5° (*c* 0.42, $CHCl_3$). IR 3353, 1799, 1755, 1712. ^1H NMR ($CDCl_3$) 0.79 (3H, d, J = 5.3), 0.86 (3H, br), 1.16 (3H, s), 1.25 (3H, s), 1.53 (3H, s), 1.60−1.66 (6H, br), 1.90 (1H, dd, J = 7.7, 14.2), 1.96 (1H, dd, J = 7.7, 14.2), 2.26 (1H, d, J = 12.2), 2.34 (1H, m), 2.36 (1H, d, J = 12.2), 3.25 (3H, s), 3.40 (1H, d, J = 9.7), 3.56 (1H, d, J = 9.7), 4.79 (1H, s), 4.94 (1H, s), 4.96 (1H, m), 5.02 (1H, m), 5.60 (1H, br), 5.71 (1H, s), 7.40−8.10 (9H, m). ^{13}C NMR ($CDCl_3$) δ 9.8, 13.8, 17.8, 19.9, 21.2, 21.5, 25.9, 31.4, 42.0, 44.4, 45.1, 46.5, 59.4, 75.0, 80.8, 92.6, 115.3, 122.2, 123.3, 125.2, 125.7, 126.1, 126.4, 127.9, 128.2, 128.8, 133.9, 135.9, 138.5, 143.4, 155.1, 177.6, 213.9. HRMS (EI) calcd for $C_{36}H_{47}N_1O_6$ 589.3403, found 589.3405.

Degradation Product 7. To a solution of carbamate **6** (4.0 mg, 0.0068 mmol) in CCl_4 (1 mL) and CH_3CN (1 mL) were added H_2O (1.5 mL), $NaIO_4$ (14 mg, 0.065 mmol), and $RuCl_3$ (0.2 mg, 0.001 mmol). The mixture was stirred at room temperature for 4 h. After aqueous workup (CH_2Cl_2) and purification by PTLC, 1.1 mg (54% yield) of degradation product **7** was obtained. Its spectroscopic data was found to be the same as **10(*S*,*R*)** as described below.

Methyl Ketone 10(*S*,*R*) and 10(*R*,*R*). The alkynes **9(*S*,*R*)** and **9-(*R*,*R*)** were prepared and characterized according to Pirkle's procedure.[8] To a solution of **9(*S*,*R*)** (102.7 mg, 0.365 mmol) in $CHCl_3$ (8 mL) was added PhHgOH (129.2 mg, 0.438 mmol). The mixture was refluxed for 2 h, after which H_2O (8 mL) was added. The mixture was refluxed overnight. After aqueous workup ($CHCl_3$) and chromatography, 94.0 mg (86% yield) of **10(*S*,*R*)** was obtained: $[\alpha]^{25}_D$ +22.6° (*c* 0.51, $CHCl_3$). IR 3332, 1712. ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.3), 1.67 (3H, d, J = 6.7), 1.66−1.84 (2H, m), 2.09 (3H, s), 4.89 (1H, dd, J = 4.8, 7.1), 5.19 (1H, d, J = 7.6), 5.6 (1H, dq, J = 7.6, 6.7), 7.42−8.10 (7H, m). ^{13}C NMR ($CDCl_3$) δ 9.5, 21.4, 24.0, 26.0, 46.8, 80.2, 122.2, 123.2, 125.2, 125.8, 126.5, 128.4, 128.8, 130.9, 134.0, 138.2, 155.0, 206.7. HRMS (EI) calcd for $C_{18}H_{21}N_1O_3$ 299.1521, found 299.1545. Using the same procedure, 76.9 mg (89% yield) of **10-(*R*,*R*)** was obtained from 81.2 mg of **9(*R*,*R*)**: $[\alpha]^{25}_D$ +4.8° (*c* 0.41, $CHCl_3$). IR 3332, 1712. ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.4), 1.67 (3H, d, J = 6.7), 1.65−1.83 (2H, m), 2.17 (3H, s), 4.91 (1H, dd, J = 4.6, 7.6), 5.22 (1H, d, J = 7.1), 5.64 (1H, dq, J = 7.1, 6.7), 7.42−8.12 (7H, m). ^{13}C NMR ($CDCl_3$) δ 9.4, 21.6, 23.9, 26.3, 46.8, 79.9, 122.2, 123.1, 125.3, 125.8, 126.5, 128.3, 128.9, 130.8, 133.9, 138.5, 155.0, 206.5. HRMS (EI) calcd for $C_{18}H_{21}N_1O_3$ 299.1521, found 299.1545.

Diene 21. To a solution of **15** (32 g, 0.090 mol) in anhydrous ether (400 mL) at −78 °C was added *t*-BuLi (116 mL of a 1.7 M solution in pentane, 0.197 mol). The mixture was stirred at −78 °C for 90 min. Methyl ketone **19** (12.3 g , 53.5 mmol) in 100 mL of THF was added at −78 °C. The mixture was stirred at −78 °C for 2 h and was warmed up to room temperature. After aqueous workup (CH_2Cl_2) and chromatography, 20.73 g (84% yield based on **19**) of tertiary alcohol **20** was obtained, which was used directly in the next step.

To a solution of **20** (20 g, 43.5 mmol) in CH_2Cl_2 (400 mL) at room temperature was added Martin's sulfurane reagent until TLC analysis of the mixture indicated the completion of the reaction. The mixture was then concentrated *in vacuo* and chromatographed to give 18.26 g (95% yield) of diene **21** and its diene isomers (95:5). A small amount was further purified by PTLC to give an analytical sample: $[\alpha]^{25}_D$ −35.1° (*c* 0.84, $CHCl_3$). IR 1622. ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.00 (3H, s), 0.01 (3H, s), 0.80 (3H, d, J = 6.6), 0.86 (3H, t, J = 7.3), 0.87 (9H, s), 0.88−0.94 (2H, m), 1.50−1.65 (2H, m), 1.64−1.70 (1H, m), 1.69 (3H, d, J = 1.4), 1.77 (1H, dd, J = 8.7, 13.3), 2.26 (1H, dd, J = 5.2, 13.3), 3.35 (1H, dd, J = 6.2, 9.8), 3.39 (1H, dd, J = 5.7, 9.8), 3.49 (1H, m), 3.74 (1H, m), 3.84 (1H, t, J = 7.0), 4.57 (2H, AB q, J = 6.7), 4.86 (1H, s), 4.99 (1H, d, J = 0.9), 5.74 (1H, s). ^{13}C NMR ($CDCl_3$) δ −5.4, −5.0, −1.4, 10.4, 12.7, 16.4, 18.1, 25.7, 25.9, 26.6, 34.5, 41.6, 65.1, 67.9, 83.3, 91.7, 115.1, 129.5, 136.5, 144.0.

Desilylated 21. To a solution of **21** (9.8 g, 0.022 mol) in DMF (250 mL) was added Et_4NF (16.5 g, 0.111 mol). The mixture was stirred at room temperature overnight and was then concentrated *in vacuo*. After aqueous workup (ether) and chromatography, 6.1 g (84% yield) of desilylated-**21** was obtained: $[\alpha]^{25}_D$ −78.4° (*c* 0.58, $CHCl_3$). IR 3454, 1629. ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.86 (3H, d, J = 3.2), 0.87 (3H, t, J = 3.7), 0.92 (2H, m), 1.50−1.66 (2H, m), 1.69 (3H, d, J = 1.2), 1.71 (1H, m), 1.88 (1H, dd, J = 8.2, 13.5), 2.23 (1H, dd, J = 6.0, 13.5), 3.42 (1H, dd, J = 5.9, 10.7), 3.46 (1H, dd, J = 5.8, 10.7), 3.50 (1H, m), 3.73 (1H, m), 3.85 (1H, t, J = 7.0), 4.57 (2H, AB q, J = 6.8), 4.88 (1H, s), 5.03, (1H, d, J = 0.9), 5.76 (1H, s). ^{13}C

NMR ($CDCl_3$) δ −1.3, 10.7, 13.0, 16.7, 18.9, 27.6, 35.7, 42.8, 66.2, 68.2, 84.8, 92.8, 115.9, 130.8, 137.9, 145.3. HRMS (EI) calcd for $C_{18}H_{36}Si_1O_3$ 328.2344, found 328.2499.

Ethyl Ester 24. To a solution of oxalyl chloride (5.6 mL, 0.064 mol) in CH_2Cl_2 (150 mL) at −78 °C was slowly added DMSO (6.1 mL, 0.086 mol). The mixture was stirred at −78 °C for 15 min. To this mixture was added desilylated **21** (3.5 g, 0.011 mol) in 50 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 1 h, and NEt_3 (14.9 mL, 0.107 mol) was added. The mixture was stirred at −78 °C for another 15 min. After aqueous workup (CH_2Cl_2) and chromatography, 3.24 g (93% yield) of the aldehyde was obtained, which was used directly in the next step.

To a mixture of LiCl (1.69 g, 0.040 mol) and phosphonate **31** (8.52 mL, 0.040 mol) in CH_3CN (100 mL) was added DBU (4.46 mL, 0.030 mol). The mixture was stirred at room temperature until a clear solution was obtained and was then cooled to 0 °C. To this mixture was added the aldehyde obtained above (3.24 g, 9.94 mmol) in 30 mL of CH_3CN. The mixture was stirred at 0 °C for another hour and was concentrated *in vacuo*. After aqueous workup (CH_2Cl_2) and chromatography, 3.87 g (95% yield) of **24** was obtained: $[\alpha]^{25}_D$ −21.6° (*c* 0.38, $CHCl_3$). IR 1644, 1712. ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.87 (3H, t, J = 7.4), 0.92 (2H, m), 0.95 (3H, d, J = 6.9), 1.27 (3H, t, J = 7.1), 1.50−1.65 (2H, m), 1.66 (3H, s), 1.77 (3H, s), 2.06 (1H, dd, J = 7.5, 13.5), 2.13 (1H, dd, J = 6.9, 13.5), 2.58 (1H, m), 3.49 (1H, m), 3.74 (1H, m), 3.85 (1H, t, J = 6.9), 4.16 (2H, AB q, J = 7.2), 4.57 (2H, AB q, J = 6.7), 4.86 (1H, s), 5.00 (1H, d, J = 1.1), 5.73 (1H, s), 6.51 (1H, d, J = 9.9). ^{13}C NMR ($CDCl_3$) δ −1.4, 10.4, 12.4, 12.8, 14.3, 18.1, 19.4, 26.6, 32.1, 44.7, 60.4, 65.1, 83.1, 91.7, 115.7, 126.4, 129.0, 137.2, 142.9, 147.2, 168.4. HRMS (EI) calcd for $C_{23}H_{42}Si_1O_4$ 410.2762, found 410.2752.

Alcohol 32. To a solution of **24** (3.60 g, 8.78 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added DIBAL-H (44 mL of a 1 M solution in hexanes, 44 mmol). The mixture was stirred at −78 °C for 2 h. EtOAc (20 mL) was added to quench the excess DIBAL-H. The mixture was warmed to room temperature. MeOH (10 mL) was added at 0 °C, followed by saturated NH_4Cl solution (300 mL) and cold 1 N HCl (100 mL). After aqueous workup and chromatography, 3.10 g (96% yield) of the desired alcohol **32** was obtained: $[\alpha]^{25}_D$ −48.5° (*c* 0.48, $CHCl_3$). IR 3413, 1621. ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.87 (3H, t, J = 7.3), 0.89 (3H, d, J = 6.4), 0.92 (2H, m), 1.50−1.65 (2H, m), 1.60 (3H, d, J = 0.9), 1.66 (3H, d, J = 1.2), 1.99−2.08 (2H, m), 2.48 (1H, m), 3.50 (1H, m), 3.74 (1H, m), 3.86 (1H, t, J = 6.8), 3.94 (2H, s), 4.58 (2H, AB q, J = 6.8), 4.84 (1H, s), 4.98 (1H, s), 5.18 (1H, d, J = 9.4), 5.75 (1H, s). ^{13}C NMR ($CDCl_3$) δ −1.4, 10.4, 12.7, 13.7, 18.1, 20.5, 26.5, 31.4, 45.6, 65.1, 68.8, 83.2, 91.5, 115.2, 129.7, 132.0, 133.4, 136.4, 143.8.

Iodo Compound 25. To a mixture of the alcohol obtained above (1.05 g, 2.85 mmol), PPh_3 (1.50 g, 5.72 mmol) and imidazole (389 mg, 5.72 mmol) in ether (30 mL) and CH_3CN (10 mL) at −30 °C was added I_2 (1.45 g, 5.71 mmol). The mixture was stirred at −30 °C for 30 min and was then filtered through a plug of silica gel. The filtrate was concentrated *in vacuo* and the crude iodo compound **25** obtained (1.50 g) was used in the next step directly without further purification.

Methyl Ester 26. To a mixture of the crude iodo compound **25** obtained above (1.50 g) and acetal **23** (5.71 g, 22.8 mmol) in THF (150 mL) and HMPA (50 mL) at −78 °C was added LiHMDS (25.7 mL of a 1 M solution in THF, 25.7 mmol). The mixture was stirred at −78 °C for 1 h. After aqueous workup and chromatography, 1.28 g (75% from **32**) of **26** was obtained: $[\alpha]^{25}_D$ −28.2° (*c* 0.65, EtOAc). IR 1749, 1614. ^{1}H NMR (C_6D_6) δ −0.01 (9H, s), 0.93 (3H, t, J = 7.3), 0.93 (3H, d, J = 7.1), 0.94 (2H, m), 1.57 (1H, m), 1.75 (1H, m), 1.77 (3H, s), 1.77 (3H, s), 1.93 (1H, dd, J = 8.2, 13.2), 2.07 (3H, s), 2.15 (1H, dd, J = 5.7, 13.2), 2.47 (6H, s), 2.54 (1H, d, J = 13.8), 2.58 (1H, m), 2.65 (1H, d, J = 13.8), 3.40 (3H, s), 3.52 (1H, m), 3.83 (1H, m), 3.83 (1H, d, J = 8.3), 3.99 (1H, t, J = 6.7), 4.3 (1H, d, J = 8.3), 4.59 (1H, d, J = 6.8), 4.74 (1H, d, J = 6.8), 4.95 (1H, s), 5.04 (1H, s), 5.12 (1H, d, J = 9.1), 5.86 (1H, s), 6.46 (1H, s), 6.69 (2H, s). ^{13}C NMR (C_6D_6) δ −1.3, 10.6, 13.0, 17.4, 18.3, 20.2, 20.3, 20.9, 27.1, 31.4, 46.0, 46.2, 51.5, 65.2, 73.2, 83.3, 85.3, 92.1, 103.6, 115.4, 128.3, 128.6, 129.6, 130.4, 136.1, 137.5, 138.5, 138.7, 144.1, 173.0. HRMS (EI) calcd for $C_{35}H_{56}Si_1O_6$ 600.3756, found 600.3800.

Deprotected 26. To a solution of **26** (467 mg, 0.778 mmol) in DMSO (20 mL) were added Et_4NF (1.16 g, 7.77 mmol) and 2 g of powdered 4 Å molecular sieves. The mixture was stirred at 90 °C overnight and was then acidified with 1 N HCl. After aqueous workup (ether) and concentration *in vacuo*, the mixture was dissolved in ether (20 mL) to which ethereal CH_2N_2 was added until a steady yellow color was obtained. The mixture was stirred for another 5 min, and nitrogen was passed through the mixture to remove the excess CH_2N_2. The mixture was concentrated *in vacuo* and chromatographed to give 190.2 mg (52% yield from **26**) of the deprotected compound: $[\alpha]^{25}_D$ +7.6° (*c* 0.29, EtOAc). IR 3477, 1741, 1610. ^{1}H NMR (C_6D_6) δ 0.84 (3H, t, J = 7.5), 0.93 (3H, d, J = 6.6), 1.47 (2H, m), 1.71 (3H, s), 1.72 (3H, s), 1.98 (1H, dd, J = 7.3, 13.5), 2.07 (3H, s), 2.12 (1H, dd, J = 6.6, 13.5), 2.47 (6H, s), 2.52 (1H, d, J = 13.9), 2.53 (1H, m), 2.64 (1H, d, J = 13.9), 3.38 (3H, s), 3.74 (1H, t, J = 6.4), 3.82 (1H, d, J = 8.1), 4.28 (1H, J = 8.1), 4.93 (1H, s), 5.03 (1H, s), 5.11 (1H, d, J = 9.4), 5.80 (1H, s), 6.46 (1H, s), 6.70 (2H, s). ^{13}C NMR (C_6D_6) δ 10.2, 13.6, 17.4, 20.3, 20.6, 20.9, 28.3, 31.6, 46.1, 46.2, 51.6, 73.3, 78.8, 85.3, 103.7, 115.1, 126.3, 128.3, 128.6, 129.6, 130.4, 136.0, 138.5, 138.8, 140.8, 144.4, 173.1. HRMS (EI) calcd for $C_{29}H_{42}O_5$ 470.3032, found 470.3080.

Acetate 27. The deprotected compound obtained above (165.2 mg, 0.351 mmol) was dissolved in 10 mL of pyridine and 5 mL of acetic anhydride. DMAP (10 mg, 0.082 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo* and chromatographed to give 178.2 mg (99% yield) of **27**: $[\alpha]^{25}_D$ +1.4° (*c* 0.18, EtOAc). IR 1733, 1610. ^{1}H NMR (C_6D_6) δ 0.76 (3H, t, J = 7.5), 0.90 (3H, d, J = 6.7), 1.46−1.63 (2H, m), 1.67 (3H, s), 1.75 (3H, s), 1.76 (3H, s), 1.92 (1H, dd, J = 8.0, 13.5), 2.07 (3H, s), 2.10 (1H, dd, J = 6.4, 13.5), 2.46 (6H, s), 2.54 (1H, d, J = 14.0), 2.55 (1H, m), 2.64 (1H, d, J = 14.0), 3.39 (3H, s), 3.83 (1H, d, J = 8.3), 4.30 (1H, d, J = 8.3), 4.91 (1H, s), 5.01 (1H, s), 5.10 (1H, d, J = 9.4), 5.22 (1H, t, J = 6.9), 5.92 (1H, s), 6.46 (1H, s), 6.69 (2H, s). ^{13}C NMR (C_6D_6) δ 9.96, 13.8, 17.3, 20.3, 20.7, 20.9, 26.0, 31.4, 45.9, 46.2, 51.5, 73.2, 80.4, 85.3, 103.6, 115.5, 128.3, 128.6, 129.1, 129.7, 130.4, 136.0, 136.0, 138.5, 138.7, 143.9, 169.3, 173.0. HRMS (EI) calcd for $C_{31}H_{44}O_6$ 512.3138, found 512.3126.

Cyclization Product 28. To a solution of **27** (91.2 mg, 0.178 mmol) in THF (100 mL) at 0 °C was added LiHMDS (1.07 mL of a 1 M THF solution, 1.07 mmol). This mixture was added over 1 h to a two-necked flask containing 100 mL of THF under reflux. After the addition was complete, the mixture was stirred under reflux for another hour. The mixture was concentrated *in vacuo*. After aqueous workup and purification by PTLC, 64.1 mg (75% yield) of **28** was obtained: $[\alpha]^{25}_D$ −7.5° (*c* 0.067, EtOAc). IR 1742, 1712, 1607. ^{1}H NMR (C_6D_6) δ 0.85 (3H, t, J = 7.5), 0.91 (3H, d, J = 6.7), 1.46 (1H, m), 1.47 (3H, s), 1.58 (3H, s), 1.62 (1H, m), 1.98 (1H, dd, J = 8.5, 13.1), 2.07 (3H, s), 2.27 (1H, dd, J = 2.5, 13.1), 2.32 (6H, s), 2.56 (1H, m), 2.6 (2H, AB q, J = 14.4), 3.23 (1H, d, J = 16.2), 3.91 (1H, d, J = 8.3), 3.95 (1H, d, J = 16.2), 4.15 (1H, d, J = 8.3), 4.87 (1H, s), 5.01 (1H, d, J = 2.0), 5.19 (1H, d, J = 9.2), 5.38 (1H, dd, J = 4.2, 7.4), 5.89 (1H, s), 6.02 (1H, d, J = 1.3), 6.69 (2H, s). ^{13}C NMR (C_6D_6) δ 9.5, 15.8, 16.3, 20.3, 20.9, 21.1, 26.4, 33.8, 45.6, 45.6, 47.2, 72.1, 77.9, 88.9, 102.0, 115.3, 126.4, 127.6, 128.3, 130.4, 134.2, 137.1, 138.3, 139.0, 144.2, 165.4, 204.0. HRMS (EI) calcd for $C_{30}H_{40}O_5$ 480.2876, found 480.2900.

Compound 29. To a solution of **28** (32.0 mg, 0.0667 mmol) in anhydrous DMF (2.5 mL) at 0 °C was added KO*t*-Bu (0.077 mL of a 1 M THF solution, 0.077 mmol). The mixture was stirred at 0 °C for 10 min. MeI (0.021 mL, 0.337 mmol) was added at 0 °C and stirring was continued for 1 h. The mixture was concentrated *in vacuo* and was purifed by PTLC to give 30.3 mg (92% yield) of **29**: $[\alpha]^{25}_D$ +20.2° (*c* 0.19, EtOAc). IR 1749, 1712, 1607. ^{1}H NMR (C_6D_6) δ 0.76 (3H, t, J = 7.3), 0.85 (3H, d, J = 6.9), 1.46 (3H, d, J = 6.9), 1.51 (3H, s), 1.52 (2H, m), 1.56 (3H, s), 1.84 (1H, dd, J = 10.6, 12.8), 2.07 (3H, s), 2.08 (1H, dd, J = 2.7, 12.8), 2.39 (6H, s), 2.40 (1H, m), 2.71 (1H, d, J = 16.5), 3.0 (1H, d, J = 16.5), 4.05 (1H, d, J = 8.7), 4.26 (1H, q, J = 6.9), 4.75 (1H, s), 4.78 (1H, d, J = 8.4), 4.98 (1H, d, J = 2.0), 5.00 (1H, d, J = 9.6), 5.27 (1H, t, J = 6.3), 5.96 (1H, s), 6.07 (1H, s), 6.70 (2H, s). ^{13}C NMR (C_6D_6) δ 9.5, 15.3, 16.1, 18.9, 20.4, 20.9, 22.4, 26.1, 35.8, 43.7, 45.6, 47.0, 69.7, 79.8, 88.2, 102.6, 114.5, 127.7, 128.3,

129.0, 130.5, 134.2, 134.2, 138.3, 139.1, 145.9, 169.1, 206.7. HRMS (EI) calcd for $C_{31}H_{42}O_5$ 494.3032, found 494.3007.

Compound 30. To a solution of **29** (9.8 mg, 0.020 mmol) in DMF (1 mL) at 0 °C was added KO*t*-Bu (0.030 mL of a 1 M THF solution, 0.030 mmol). The mixture was stirred at 0 °C for 10 min. Glacial AcOH (0.010 mL, 0.175 mmol) was added, and the mixture was concentrated *in vacuo* and purifed by PTLC to give 9.1 mg (93% yield) of compound **30**: $[\alpha]^{25}_D$ −99.4° (*c* 0.14, EtOAc). IR 1742, 1712, 1607. ^{1}H NMR (C_6D_6) δ 0.86 (3H, d, J = 7.0), 0.87 (3H, t, J = 7.6), 1.30 (3H, d, J = 6.8), 1.55 (2H, m), 1.72 (3H, s), 1.82 (3H, s), 2.03 (1H, dd, J = 7.8, 13.3), 2.06 (3H, s), 2.29 (1H, br d, J = 13.3), 2.38 (1H, d, J = 14.2), 2.45 (6H, s), 2.46 (1H, m), 3.06 (1H, d, J = 14.2), 3.53 (1H, q, J = 6.9), 3.62 (1H, d, J = 8.7), 3.90 (1H, d, J = 8.7), 4.80 (1H, s), 4.92 (1H, t, J = 6.1), 4.97 (1H, s), 5.32 (1H, d, J = 9.4), 5.99 (1H, s), 6.16 (1H, s), 6.68 (2H, s). ^{13}C NMR (C_6D_6) δ 10.0, 16.1, 16.2, 18.5, 19.7, 20.3, 20.9, 26.6, 32.7, 43.7, 45.6, 50.5, 72.0, 80.7, 91.1, 103.1, 116.3, 127.0, 128.5, 129.5, 130.4, 134.7, 136.3, 138.4, 138.8, 144.7, 167.6, 202.5. HRMS (EI) calcd for $C_{31}H_{42}O_5$ 494.3032, found 494.3018.

Synthetic C2-*epi*-Galbonolide B. Compound **29** (6.6 mg, 0.0134 mmol) was dissolved in 2 mL of glacial AcOH and 1 mL of H_2O. The mixture was stirred at room temperature for 30 min. It was then concentrated *in vacuo* and purified by PTLC to give 4.7 mg (97% yield) of C2-*epi*-galbonolide B: $[\alpha]^{25}_D$ −2.1° (*c* 0.20, EtOAc). IR 3484, 1735, 1712, 1614. ^{1}H NMR (CD_3OD) δ 0.84 (3H, t, J = 7.4), 0.87 (3H, d, J = 6.9), 1.16 (3H, d, J = 7.1), 1.56 (3H, s), 1.66 (2H, m), 1.75 (3H, s), 1.92 (1H, dd, J = 10.6, 12.8), 2.14 (1H, d, J = 14.0), 2.26 (1H, dd, J = 3.2, 12.8), 2.38 (1H, d, J = 14.0), 2.44 (1H, m), 3.52 (1H, d, J = 10.8), 3.63 (1H, d, J = 10.8), 3.85 (1H, q, J = 7.1), 4.87 (1H, s), 4.93 (1H, t, J = 6.9), 5.05 (1H, s), 5.14 (1H, d, J = 9.0), 5.87 (1H, s). ^{13}C NMR (CD_3OD) δ 10.1, 13.1, 14.6, 18.0, 22.0, 26.5, 36.4, 45.8, 46.9, 51.4, 70.0, 81.5, 83.1, 116.8, 130.3, 132.5, 136.1, 139.8, 145.9, 169.6, 173.6, 213.1. HRMS (EI) calcd for $C_{21}H_{32}O_5$ 364.2250, found 364.2288.

Synthetic Galbonolide B. Compound **30** (6.7 mg, 0.0136 mmol) was dissolved in 2 mL of glacial AcOH and 1 mL of H_2O. The mixture was stirred at room temperature for 30 min. It was then concentrated *in vacuo* and purified by PTLC to give 4.7 mg (95% yield) of synthetic galbonolide B: $[\alpha]^{25}_D$ −95.3° (*c* 0.22, EtOAc). IR 3469, 1734, 1712, 1614. ^{1}H NMR (CD_3OD) δ 0.70 (3H, d, J = 6.8), 0.90 (3H, t, J = 7.4), 1.39 (3H, d, J = 6.9), 1.60−1.74 (2H, m), 1.61 (3H, d, J = 1.3), 1.75 (3H, d, J = 1.3), 1.99 (1H, d, J = 13.9), 2.08 (1H, dd, J = 7.6, 13.0), 2.18 (1H, br d, J = 13.0), 2.46 (1H, m), 2.65 (1H, d, J = 13.9), 3.54 (1H, d, J = 11.7), 3.88 (1H, d, J = 11.7), 3.94 (1H, q, J = 7.0), 4.74 (1H, s), 4.81 (1H, dd, J = 4.3, 7.9), 4.94 (1H, d, J = 8.5), 4.97 (1H, s), 5.62 (1H, s). ^{13}C NMR (CD_3OD) δ 10.3, 15.7, 16.3, 19.1, 19.6, 27.4, 33.9, 42.6, 46.5, 51.1, 69.0, 82.0, 85.6, 117.1, 128.2, 129.6, 136.1, 137.6, 145.3, 170.4, 209.9. HRMS (EI) calcd for $C_{21}H_{32}O_5$ 364.2250, found 364.2257.

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Supporting Information Available: Experimental procedures for the preparations of **15** from **11**, **19** from **17**, and **23** from **22** and ^{1}H and ^{13}C NMR spectra of all characterized compounds and NOE difference spectra for compounds **15**, **26**, and **32** (65 pages). See any current masthead page for ordering and Internet access instructions.

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