Palladium-Catalyzed Enyne Cycloisomerization Reaction in an Asymmetric Approach to the Picrotoxane Sesquiterpenes. 2. Second-Generation Total Syntheses of Corianin, Picrotoxinin, Picrotin, and Methyl Picrotoxate

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Abstract: An alternative, more efficient synthesis of the picrotoxane core by palladium-catalyzed cycloisomerization of an enyne requires the design of a new catalyst system based upon 1,3-bis(dibenzophospholyl)-propane and 2-(diphenylphosphino)benzoic acid as ligands. Thus, unlike thermal processes which leave little opportunity to address failed reactions, the transition-metal-catalyzed reaction provides opportunities for catalyst modification to overcome limitations. In this way, a seven-step synthesis of the picrotoxane core from carvone emerges. The formation of the bislactone depends critically on the ring substitution pattern. A myriad of selective transannular cyclizations occur as a function of this substitution pattern. The bislactone serves as a pivotal intermediate to picrotoxinin, picrotin, and corianin. During the course of the manipulation of the oxidation pattern to create the correct bislactone, an intermediate generated also provides access to methyl picrotoxate. An improved sequence from the bislactone to corianin compared to the first generation evolves—in part derived from enhanced control of stereoselectivity in the functionalization of the double bond in the cyclohexenyl portion of the picrotoxane skeleton. Later in the sequence, a hydroxyl-directed chemoselective lactone reduction is employed using lithium triacetoxyborohydride. In the course of these studies, two reactions that involve substitution with retention of configuration occur in high yield as a result of the remarkable reactivity of this densely functionalized ring system.

The development of the palladium-catalyzed cycloisomerization of 1,6-enynes to methylenecyclopentanes provides a new opportunity to develop a synthetic strategy.[1] In the previous paper, we demonstrated the realization of a synthesis of the picrotaxane skeleton that provides an intermediate to picrotoxinin in less than half the number of steps of an earlier synthesis and completed the first synthesis of corianin (Figure 1). In considering some of the issues of manipulating the functionality of this densely functionalized ring system, we envisioned a second-generation strategy, which had two goals: (1) realization of an effective general strategy by total syntheses of picrotoxinin (**1**), picrotin (**2**), and methyl picrotoxate (**4**) and (2) development of an even more effective route to the picrotaxane skeleton.

Scheme 1 illustrates the key feature of this second-generation synthesis, which envisions tying the tertiary alcohol and the isopropenyl double bond together early in the synthesis. Rigidifying the enyne substrate **6** raises questions regarding the stereoelectronic requirements of the palladium-catalyzed cycloisomerization. This circumstance did indeed lead to difficulties in this key step. One major advantage of transition-metal-catalyzed reactions is the ability to alter significantly the behavior of the catalyst and thereby modify it for recalcitrant substrates. In this paper, we record the successful realization of this second-generation synthesis of the picrotaxane family.

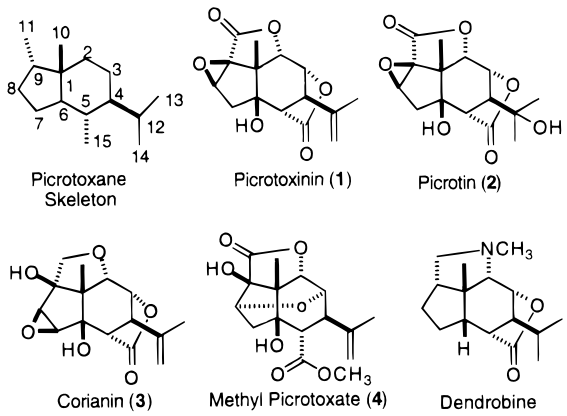
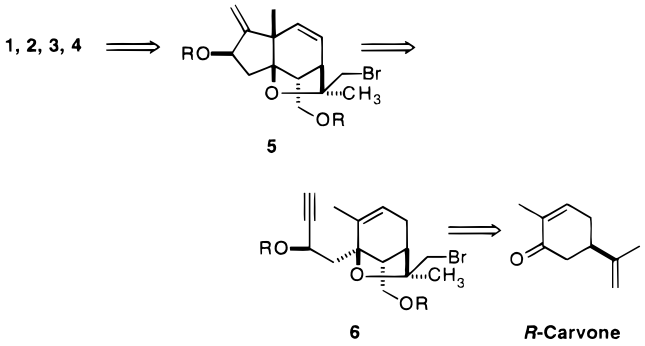


Figure 1. Some picrotoxane natural products.

Scheme 1. Second-Generation Retrosynthesis of the Picrotoxane Sesquiterpenes



(1) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255. Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 233.

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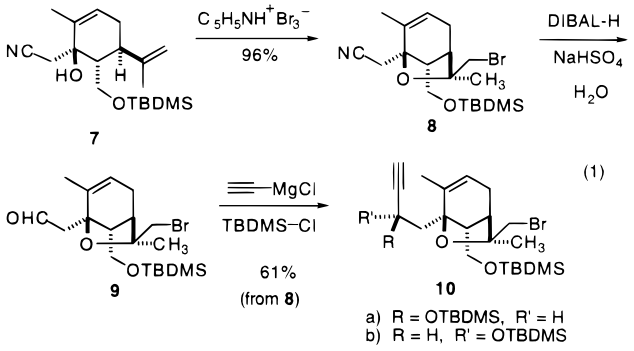
In the course of this study, we developed a new ligand system for the palladium-catalyzed enyne cycloisomerizations of sterically crowded substrates.

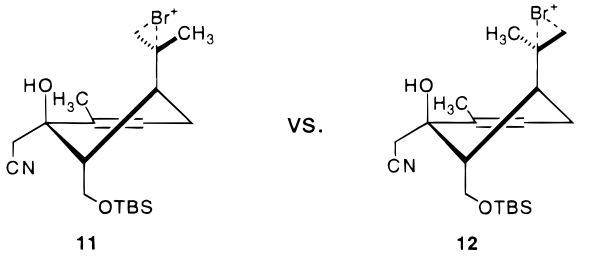
Preparation of Enyne Substrate

As in the first-generation synthesis, (*R*)-carvone was converted into the nitrile **7** in three steps and 44% overall yield. Equation 1 outlines the four-step sequence from this nitrile to



(1)

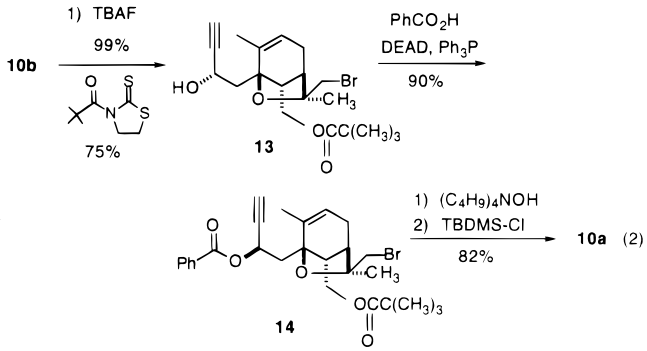
the enyne substrate. Bromoetherification, gratifyingly, gave a single isomeric product. The endo nature of the bromomethyl was subsequently proven by X-ray crystallography of a later intermediate. The smaller destabilization between the terminal methylene unit of the isopropenyl group and the cyclohexyl ring leading to cyclization via **11** compared to the corresponding eclipsing interaction between the methyl group of the isopropenyl substituent and the cyclohexane ring leading to cyclization via **12** favors the former pathway to generate the observed



product. The possible stabilization of the bromonium ion in **11** by the proximal cyclohexene double bond may also contribute to this selectivity.

Standard DIBAL-H reduction followed by acid hydrolysis formed the aldehyde **9** which, without purification, was immediately subjected to ethynylmagnesium chloride. The alcohols were capped with TBDMS−Cl to give a 2:1 ratio of the epimeric alcohols **10a** and **10b**, respectively. The relative stereochemistry was not established rigorously since it was irrelevant to the synthesis. It is tentatively assigned in the cycloisomerization product by comparison to analogous compounds.

The minor epimer could be converted to the major one on the basis of a Mitsunobu inversion[2] as outlined in eq 2. After desilylation, monoprotection was necessary to avoid cyclic ether formation. The 3-pivaloylthiazolidine-2-thione[3] allowed easy chemodifferentiation between a primary and a secondary alcohol to give hydroxy ester **13**, which participated smoothly in a standard Mitsunobu protocol to give the inverted benzoate **14**. Adjustment of the protecting groups to silyl completed the

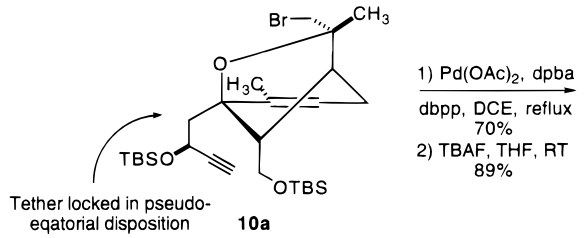


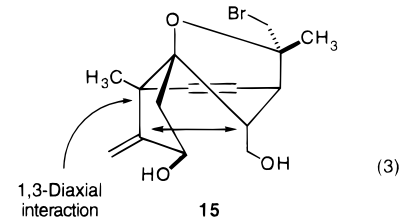
(2)

convergence to a single epimer, **10a**. The key cycloisomerization substrate is available in six steps from (*R*)-carvone by this sequence.

Cycloisomerization

Surprisingly, when enyne **10a** was subjected to conditions that affected smooth cycloisomerization of our related first-generation substrate, i.e., palladium acetate with *N*,*N*-bisbenzylideneethylenediamine (BBEDA) in 1,2-dichloroethane (DCE) at 55 °C, no conversion was observed. A telling result was obtained when the reaction was attempted using a catalyst derived from triphenylphosphine, acetic acid, and $Pd_2dba_3 \cdot CHCl_3$ (dba = dibenzylideneacetone). The product of alkyne dimerization resulted, indicating that coordination of the alkyne occurred but subsequent internal carbometalation of the cyclohexene was retarded. That the metal-coordinated butynyl tether is locked in a pseudoequatorial disposition makes its approach to the cyclohexenyl olefin difficult. This is exacerbated by the developing 1,3-diaxial interaction between the C15 (silyloxy)-methyl substituent and the incipient cyclopentenyl ring bond (see eq 3). Given this assessment of the problem, it seemed





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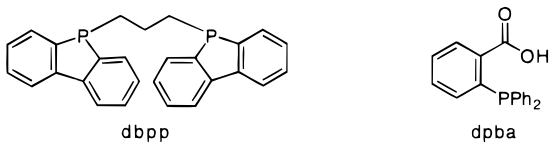
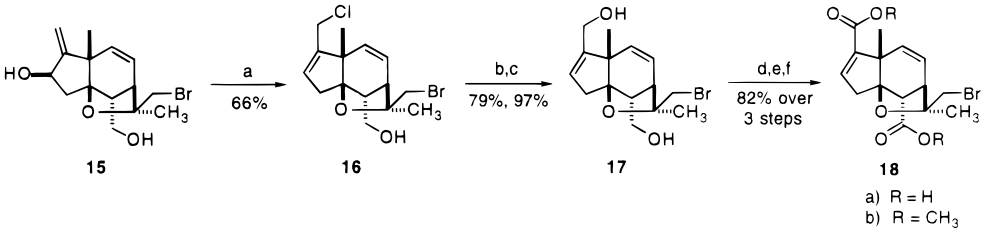


reasonable that if the steric demands of the catalyst were attenuated and its Lewis acidity increased, internal carbametalation of the olefin could be promoted over the dimerization pathway.

Along these lines, moving from triphenylphosphine to 1,2-bis(diphenylphosphino)ethane (dppe), in conjunction with

(2) Mitsunobu, O. *Synthesis* **1981**, 1.
(3) Yamada, S. *Tetrahedron Lett.* **1992**, *33*, 2171.

Scheme 2. Allylic Isomerization and Oxidation of the Hydroxyl Functionality of **15**[a]

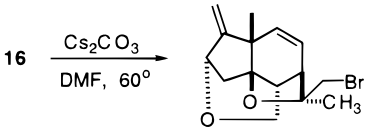


[a] Conditions: (a) $SOCl_2$, Pyr, Et_2O, 0 °C. (b) CsOAc, DMF, 60 °C. (c) K_2CO_3, MeOH, room temperature (rt). (d) DMSO, $(COCl)_2$, TEA, DCM. (e) $NaClO_2$, NaH_2PO_4, $H_2O-{}^tBuOH$, 2-methyl-but-2-ene. (f) CH_2N_2, Et_2O-acetone, rt.

$Pd(OAc)_2$, gave a promising yield of 37%. When dppe is combined with a ligand capable of internal proton delivery, 2-(diphenylphosphino)benzoic acid (dpba),[4] the yield increased to 43%. Tying back the diphenylphosphino moiety of dppe in the form of 1,3-bis(dibenzophospholyl)propane (dbpp)[5] creates an even smaller ligand. This modification not only opens up the active site of the catalyst but also modulates the electronics of the ligand such that it is a weaker σ-donor and stronger π-acceptor. The net effect is a smaller, more Lewis acidic ligand. The dbpp/dpba ligand system gave a gratifying yield of 70% with no observed dimer formation. The compatibility of the bromide functionality under conditions involving low-valent palladium is noteworthy. In seven steps, we have realized the most efficient route to the picrotoxane skeleton to date.

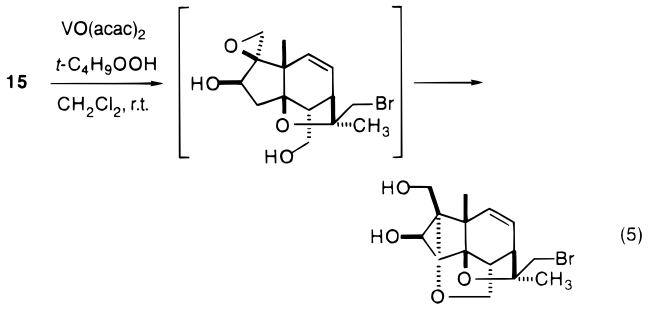
Chemo- and Stereoselective Oxygenation of Hydrindane 15

Having achieved concise construction of a suitably functionalized picrotoxane skeleton, placement of the requisite oxygen functionality was in order. This task began with installation of the C11 and C15 carboxylate moieties. The first stage required a 1,3-hydroxyl group shift (i.e., **15** to **17**, Scheme 2) which molecular modeling suggested was 2.7 kcal/mol exothermic. Nevertheless, equilibration methods failed. Allylic isomerization of hydrindane diol **15** was accomplished using a three-step protocol. Reaction of **15** with 400 mol % thionyl chloride in ether in the presence of 250 mol % pyridine proceeded chemoselectively in the presence of the C15 hydroxyl group to afford a 66% yield of the allylically isomerized chloride **16**.[6] Replacing the chloride by oxygen proved to be nontrivial as the hydroxy chloride **16** proved prone to cycloetherification as shown in eq 4. Exposure of the allyl chloride **16** to cesium



(4)

acetate in DMF at 60 °C smoothly afforded the corresponding allylic acetate in 79% yield[7] which was saponified in 97% yield to provide the allylically isomerized diol **17**. Concomitant oxidation of the diol functionality using the Swern modification of the Moffatt oxidation[8] followed by treatment with sodium chlorite[9] and, finally, ethereal diazomethane gave the dimethyl ester **18** in an 82% yield over the three-step sequence (Scheme 2). An alternative sequence envisioned hydroxyl-directed epoxidation followed by vicinal reductive elimination.[10] However, as shown in eq 5, the intermediate epoxide suffered ring opening



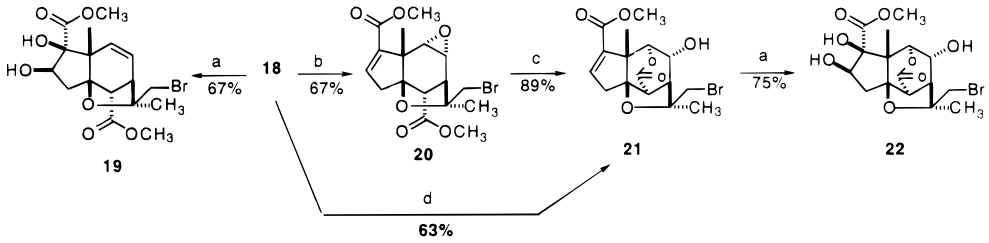
(5)

under the conditions of the epoxidation. This result, although disappointing from the point of view of our desired 1,3-hydroxyl transposition, served to support the stereochemistry of the secondary hydroxyl group. Upon formation of the β-epoxide, the rigid structure of the bromolactone places the primary hydroxyl group in a perfect alignment to effect S_N2 ring opening to form the tetrahydropyran ring.

As in our first-generation synthesis, all attempts to effect direct oxidative bislactonization of the diacid **18a** failed. For example, cis dihydroxylation with osmium tetroxide[11] of diene **18b** occurred at the C8−C9 electron-poor olefin to give **19**.[12] That steric hindrance might be responsible for this unusual selectivity was suggested by subsequent epoxidation studies. Attempts at oxidative lactonization of the acetonide or cyclic carbonate of this diol also failed, normally because of lack of reactivity of the C2−C3 alkene! Bromolactonization required the use of neat liquid bromine for any reaction but led to a six-membered ring lactone analogous to **21** (vide infra). As we began to explore methods for the stereoselective oxygenation of the olefin functionality, the unusual stereoelectronic aspects of the bicyclic core of the bromoether-containing substrates became apparent. As enoate **18b** was not susceptible to nucleophilic epoxidation, electrophilic epoxidation utilizing trifluoroperacetic acid[13] was attempted. Not surprisingly, reaction occurred at the electron-rich C2−C3 olefin to provide the epoxide **20** in 67% yield (see Scheme 3). As we anticipated, the diastereofacial selectivity of the epoxidation was dictated by the bromoether function, exclusively favoring reaction on the concave face of the hydrindane. Interestingly, the lactone **21** was isolated as a side product. This prompted us to determine

(4) Trost, B. M.; VanVranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(5) Affandi, S.; Green, R. L.; Hsieh, B. T.; Holt, M. S.; Nelson, J. H. *Synth. React. Inorg. Met.-Org. Chem.* **1987**, *17*, 307.
(6) Peglotti, J. A.; Young, W. G. *J. Am. Chem. Soc.* **1961**, *83*, 3251.
(7) Kruinga, W. H.; Strijtueen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.
(8) Omura, K.; Swern, D. *Tetrahedron* **1978**, 1651. Manusco, A. J.; Brownfain, D. S.; Swern, D. J. *J. Org. Chem.* **1979**, *44*, 4148.
(9) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091. Delcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(10) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1976**, *17*, 2621.
(11) Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
(12) Krische, M. J.; Trost, B. M. *Tetrahedron* **1998**, 3693.
(13) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

Scheme 3. Stereoselective Oxygenation of Diene **18**[a]



[a] Conditions: (a) OsO_4, Pyr, rt. (b) $(CF_3CO)_2O$, UHP, CH_2Cl_2, rt. (c) CH_2Cl_2, CF_3CO_2H, CSA, reflux. (d) $(CF_3CO)_2O$, UHP, DCM, CSA, reflux.

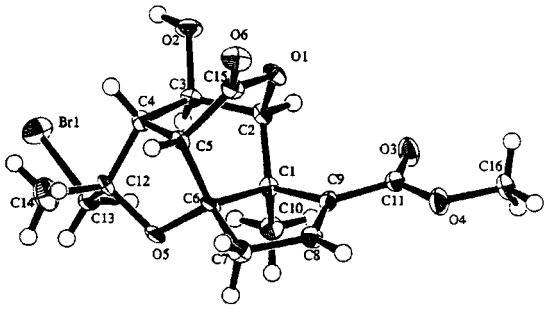
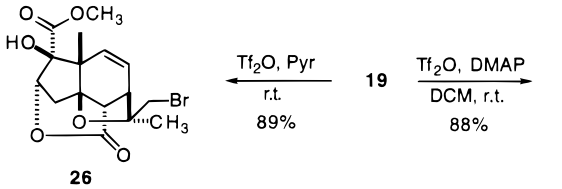
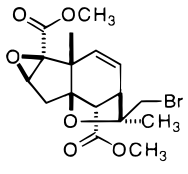


Figure 2. X-ray crystal structure of epoxide ring opening product **21**.

if the acid-promoted ring opening of epoxide **20** was possible. Indeed, exposure of **20** to acid in refluxing dichloromethane gave the lactone **21** in 89% yield. In fact, if the epoxidation reaction was conducted under more forcing conditions, tandem epoxidation−ring opening of **18** to **21** was effected in 63% yield. An X-ray structure confirmed the connectivity and stereochemistry of **21** (Figure 2). Thus, epoxide ring opening occurred with *retention* of configuration—an event that constitutes a cis dihydroxylation of the alkene. The reaction of **21** with osmium tetroxide exclusively occurred on the convex face of the enoate with respect to the hydrindane ring system to afford triol **22** in 75% yield.

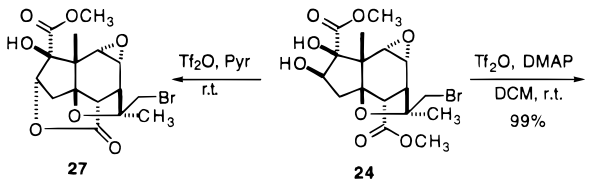
To obtain picrotoxinin from triol **22** required that the C8−C9 cis vicinal diol functionality be transformed to the corresponding glycidic epoxide and that the issue of lactone connectivity be addressed. In related studies, we established that an excellent yield of the desired epoxide **23** was obtained by subjecting diol **19** to triflic anhydride in methylene chloride in the presence of DMAP (eq 6). Under the same conditions,

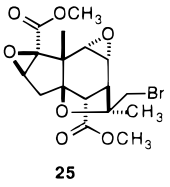




(6)

epoxydiol **24**, available by dihydroxylation of epoxide **20**, was converted quantitatively to the bisepoxide **25** (eq 7). In analogy to **19**, forming lactone **26** using triflic anhydride in pyridine, diol **24** forms lactone **27** under the same conditions. This observation further supports the earlier suggestion that the C5 ester is responsible for a double inversion mechanism whereby the initial triflate undergoes cyclization to an oxonium ion. In pyridine, demethylation dominates and lactone **26** or **27** is formed. On the other hand, in a less polar and less nucleophilic medium, methylene chloride, the neighboring hydroxyl group serves as a nucleophile to collapse to the epoxide.





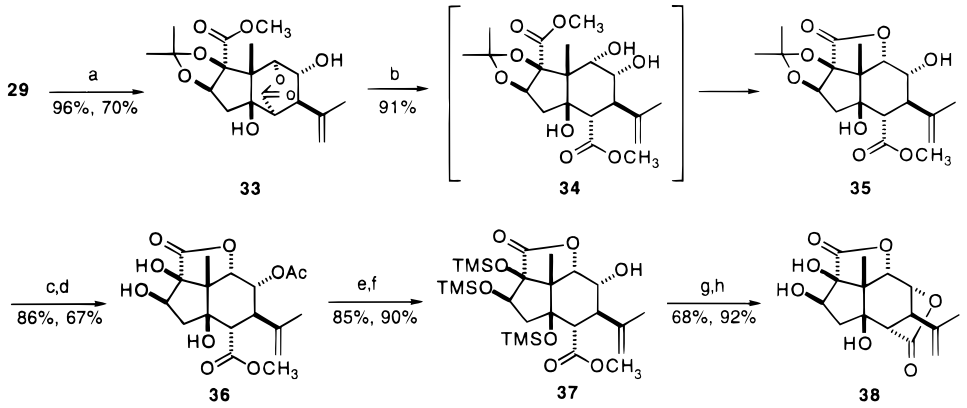
(7)

With the glycidic epoxide intact, its geometical influence was such that external reagents could now approach the cyclohexene, allowing for its stereoselective dihydroxylation. As noted previously,[12] dihydroxylation of epoxide **23** under catalytic osmium conditions failed and proceeded only sluggishly with a stoichiometric amount of osmium tetroxide in pyridine at 70 °C to form the lactone to the C2 hydroxyl group, i.e., **28**. Attempts to cyclize diepoxide **25** led only to ring opening of the 8,9-epoxide. Thus, neither **23** nor **25** proved promising with regard to reaching our target.

Our degradation studies[14] indicated that, with the bromoether intact, there exists an overwhelming thermodynamic preference for the undesired six-membered ring lactone evident in **28** relative to the corresponding bridged butyrolactone characteristic of picrotoxinin. Thus, having served its dual purpose in stereochemically directing the installation of the C2−C3 cis vicinal diol functionality and masking the isopropenyl olefin, the bromoether for a number of the intermediates prepared was cleaved by exposure to zinc dust[15] to generate the compounds shown in eqs 8−11. The conformational change accompanying the ring opening did not help to generate the correct lactone connectivity for compounds **30**−**32**. The key proved to be the choice of functionality at C8−C9. The cis vicinal cyclopentyl diol **29** was converted to the corresponding acetonide **33** in 70% yield (see Scheme 4). Saponification of **33** followed by treatment with ethereal diazomethane gave the monoester monolactone **35** in 91% yield, presumably via the intermediacy of the transient diester **34**. Interestingly, when the glycidic epoxide is intact, as in the known picrotoxinin degradation product dimethyl picrotoxinin dicarboxylate (vida supra), the lactone does not spontaneously form. This result also differs from the intermediate hydroxy ester derived from dihydroxylation of **23**.

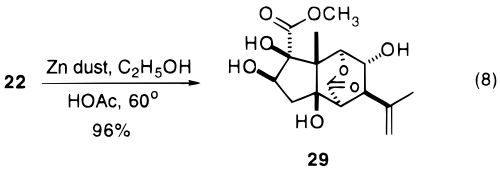
(14) Krische, M. J.; Trost, B. M. *Tetrahedron* **1998**, *54*, 7109.
(15) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *80*, 182.

Scheme 4. Formation of Bislactone **38**[a]



[a] Conditions: (a) DMP, acetone, TsOH(cat.), rt. (b) (i) KOH, MeOH, H_2O, rt. (ii) CH_2N_2, ether, 0 °C. (c) AcCl, DMAP, DCM, rt. (d) HCl, MeOH, H_2O, rt. (e) TMSOTf, DCM, lutidine, rt. (f) MeOH, catalytic NaCN, rt. (g) LHMDS, *t*-BuOH, $PhCH_3$, 100 °C. (h) HF, CH_3CN, H_2O, 100 °C.

The stage was now set for the formation of the bridged lactone. The direct lactonization of **35** under a variety of conditions failed even when the teritary alcohol at C6 was protected as the trimethylsilyl ether. Use of a cyclic carbonate in lieu of the acetonide in **35** also did not lead to lactonization. In accord with the results of our first-generation studies which involved a similar lactonization, it seems the acetonide restricts the confomational mobility of the system (Figure 3). With this in mind, the C3 hydroxyl group was acetylated in 86% yield and



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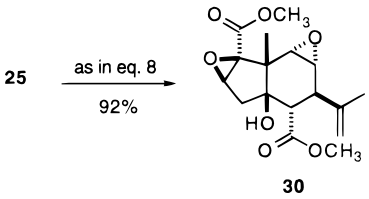

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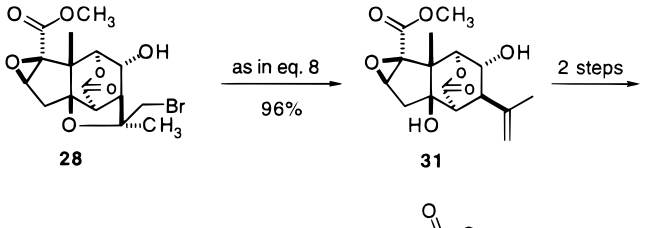
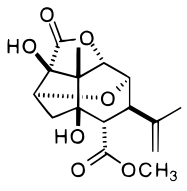
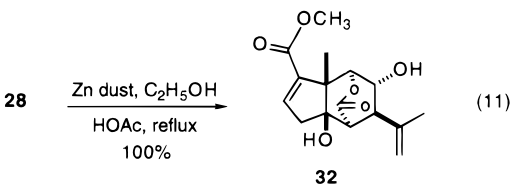




(10)

Methyl Picrotoxate



(11)

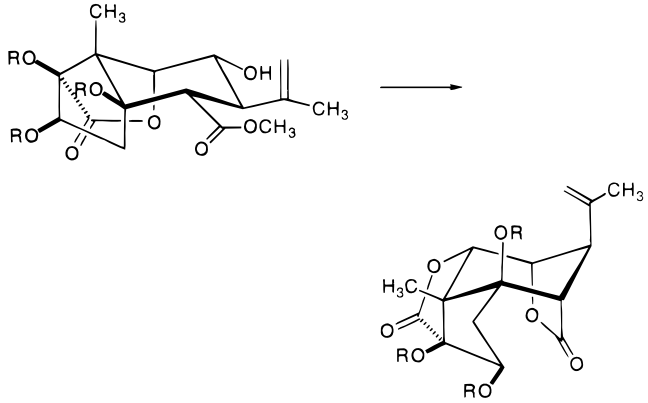


Figure 3. Conformational issues related to the lactonization of **38** and **40**.

the acetonide was removed by acid hydrolysis to afford triol **36** in 67% yield. Exhaustive trimethylsilylation of the hydroxyl functionality followed by sodium cyanide catalyzed deacylation proceeded in 85% and 90% yields, respectively, to afford lactonization substrate **37**. Replacing the acetonide with acyclic TMS ethers permitted cyclization under basic conditions to give our pivotal intermediate **38**.

Total Syntheses of Picrotoxinin, Corianin, and Methyl Picrotoxate

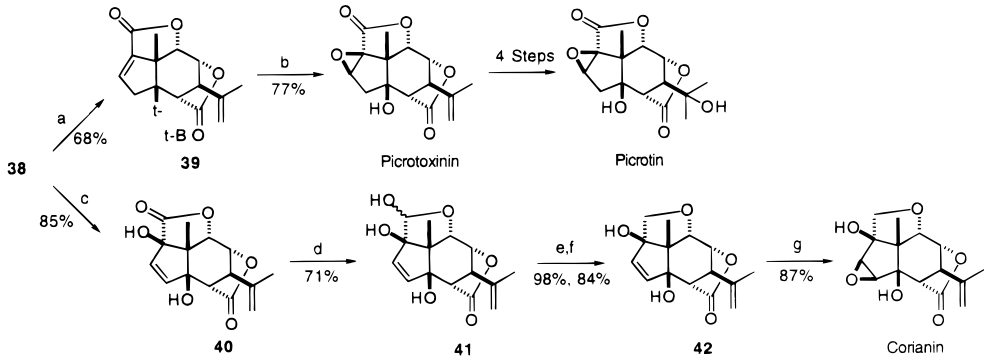
To demonstrate the generality of this strategy, syntheses of both picrotoxinin and corianin were completed from bislactone **38** as outlined in Scheme 5. Attempts to close the vicinal diol directly to the β-epoxide, as described in the conversion of diols **19** and **24** to epoxides **23** and **25**, were unsuccessful presumably due to the fact that the carbomethoxy substituent, now restricted in the form of the bridged lactone, could no longer participate in a double inversion mechanism. Dehydroxylation of **38** via an orthoaminal as described by Eastwood[16] occurred chemoselectively to form the strained alkene **39** in 68% yield. Nucleophilic epoxidation[17] gave picrotoxinin in 77% yield, identical in all respects to an authentic sample. The previous conversion of picrotoxinin to picrotin[18] makes this route a formal synthesis of the latter as well.

(16) Eastwood, F. W.; Harrington, K. J.; Josan, J. S.; Pura, J. L. *Tetrahedron Lett.* **1970**, *11*, 5223.

(17) Meth-Cohn, O.; Moore, C.; Talijaard, H. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663.

(18) Corey, E. J.; Pearce, H. *Tetrahedron Lett.* **1980**, *21*, 1823.

Scheme 5. Bifurcation of a Common Intermediate to Corianin and Picrotoxnin[a]



[a] Conditions: (a) $Me_2NCH(OMe)_2$, Ac_2O, 100 °C. (b) LHMDS, *t*-BuOOH, THF, 0 °C. (c) *N*-Methylimidazole, Tf_2O, 100 °C. (d) $LiBH_4$, AcOH, THF, 0 °C. (e) PhSH, TMSCl(cat.), CH_3CN, rt. (f) Ph_3SnH, AIBN(cat.), $PhCH_3$, reflux. (g) MCPBA, DCM, 0 °C.

Adjustment of the oxidation pattern to form corianin began with the chemoselective dehydration of **38** to alkene **40**, thus functionalizing the C7 position (see Scheme 5). Without the use of any protecting groups, the secondary alcohol was chemoselectively activated as its triflate and eliminated in situ in the presence of *N*-methylimidazole. The next stage required the removal of the carbonyl oxygen of the fused butyrolactone ring to form the tetrahydrofuran. This sequence was initiated by chemoselective hydroxyl-directed borohydride reduction[19] under acidic conditions of the α-hydroxybutyrolactone to the lactol **41** in 71% yield. To our knowledge, this represents the first example of chemoselective hydroxyl-directed lactone reduction using in situ generated lithium triacetoxyborohydride. Removal of the resultant hydroxyl group involved initial transformation to the corresponding phenyl sulfide under simple acid catalysis generated in situ by addition of trimethylsilyl chloride to thiophenol. Radical desulfurization[20] to ether **42** also proceeded with excellent chemoselectivity—notably without affecting either double bond. Completion of the sequence took advantage of hydroxyl direction whereby **42** was chemo- and stereoselectively epoxidized to give corianin, identical to an authentic sample.[21]

In the course of our studies on the chemo- and stereoselective oxygenation of **18**, we realized that we could rapidly access methyl picrotoxate. Methyl picrotoxate, first identified as a degradation product of picrotoxinin,[22] also occurs naturally as a constituent of the sea sponge *Spirastrella inconstans*.[23] Structurally, methyl picrotoxate differs from other picrotoxane sesquiterpenes due to the presence of a transannular ether linkage bridging C3 and C8 of the *cis*-hydrindane ring system in lieu of the lactone moiety typically bridging C3 and C5. Since we demonstrated that methanolysis of **28** to open the lactone to form dimethyl picrotoxinin dicarboxylate[24] followed by base-catalyzed cycloetherification generated methyl picrotoxate, this route also constitutes a synthesis of this natural product (eq 10).[12]

Conclusion

The palladium-catalyzed Alder-ene reaction differs from its thermal counterpart not only in that it proceeds under much milder conditions, thus allowing higher degrees of functionality to be tolerated in the substrates, but also in that the metal template may be tailored to achieve success if a given protocol fails, an opportunity lacking in thermal processes. The results herein highlight this strength through the realization of a more efficient strategy to the picrotoxane skeleton than previously practiced and the subsequent elaboration of this cycloisomerization product to the natural products picrotoxinin, picrotin, methyl picrotoxate, and corianin, the latter requiring the establishment of nine contiguous chiral centers around a hydrindane skeleton in which every carbon is asymmetrically substituted.

The occurrence of natural products possessing the picrotoxane skeleton and exhibiting similar biological activities is noted in an increasingly diverse range of plant, animal, terrestrial, and marine life. Such ubiquitous distribution in such a diverse range of organisms underscores the fundamental role of the picrotoxanes in neurochemistry. Our efforts in this field are now directed toward extending our synthetic approach toward the recently discovered family of picrotoxane diterpenes, the picrodendrins.[25] Picrodendrin Q is the most potent picrotoxane to date. With IC_{50} values of 0.0075−6.0 μM for the inhibition of specific binding of [^{35}S]*tert*-butylbicyclophosphorothionate to rat brain cell membranes, picrodendrin Q is 27-fold more potent than picrotoxinin.[26]

Experimental Section[27]

a. Preparation of Enyne Cyclization Substrate (1*S*,3*S*,4*R*,8*R*)-1-(Cyanomethyl)-3,7-dimethyl-3-(bromomethyl)-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxobicyclo[3.2.1.]hept-6-ene (8). To a pyridine solution (0.2 M, 110 mL) of acetonitrile adduct **7** (7.55 g, 22.5 mmol, 100 mol %) at room temperature was added dropwise pyridinium bromide perbromide (7.91 g, 24.7 mmol, 110 mol %) in pyridine (45 mL, 0.5 M). After the addition was completed, the mixture was allowed to stir for 20 min. The yellow reaction mixture was then quenched with half-saturated $Na_2S_2O_4$ (100 mL) to give a clear solution and transferred to a separatory funnel. The aqueous layer was extracted with three 100 mL portions of ether. The combined organic extracts

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(20) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504.

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(24) Hormann, P. *Justus Liebigs Ann. Chem.* **1916**, *411*, 273.

(25) Picrodendrins C and D: Ohmoto, T.; Koike, K.; Fukuda, H.; Mitsunaga, K.; Ogata, K.; Kagei, K. *Chem. Pharm. Bull.* **1989**, *37*, 2988. Picrodendrins E, F, and I: Koike, K. Ohmoto, T.; Kawai, T.; Sato, T. *Phytochemistry* **1991**, *30*, 3353. Picrodendrins B, G, and J: Koike, K.; Fukuda, H.; Mitsunaga, K.; Ohmoto, T. *Chem. Pharm. Bull.* **1991**, *39*, 934. Picrodendrins K−R: Suzuki, Y.; Koike, K.; Ohmoto, T. *Phytochemistry* **1992**, *31*, 2059. Picrodendrins S and T: Koike, K.; Suzuki, Y.; Ohmoto, T. *Phytochemistry* **1994**, *35*, 701. Picrodendrins U, V and W: Nagahisa, M.; Koike, K.; Narita, M.; Ohmoto, T. *Tetrahedron* **1994**, *50*, 10859.

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(27) For the general experimental information, see: Trost, B. M.; Haffner, C.; Jebaratnam, D.; Krische, M. J.; Thomas, A. *J. Am. Chem. Soc.*, in press.

were washed with brine, dried ($MgSO_4$), filtered, evaporated, and chromatographed (SiO_2; 10% Et_2O in hexane) to give the title compound **8** (8.61 g, 20.77 mmol, 92%). $R_f = 0.35$ (1:1 $CHCl_3$/benzene). $[\alpha]_D = 1.38°$ (2.0% in CH_2Cl_2). IR (neat): 2250, 1650, 1470 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.48 (br s, 1H), 3.87 (dd, $J = 10.1$, 4.9 Hz, 1H), 3.69 (dd, $J_1 = J_2 = 9.5$ Hz, 1H), 3.42 (d, $J = 10.1$ Hz, 1H), 3.34 (d, $J = 10.0$ Hz, 1H), 2.87 (ddd, $J_1 = 9.4$, $J_2 = J_3 = 4.6$ Hz, 1H), 2.83 (d, $J = 16.4$ Hz, 1H), 2.74 (d, $J = 16.3$ Hz, 1H), 2.44 (br d, $J = 19.0$ Hz, 1H), 2.30 (br s, 1H), 2.10 (br d, $J = 18.1$ Hz, 1H), 1.65 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.3, 117.4, 84.5, 80.4, 61.7, 46.6, 42.9, 37.2, 25.8, 27.7, 25.1, 18.5, 18.1, −5.6, −5.7. HRMS: calcd for $C_{18}H_{29}Br^{81}NO_2Si$ [$M^+ - 15$] 401.1130, found 401.1111.

(1*R*,5*R*,6*S*/*R*,8*R*)-6-(Bromomethyl)-1-[2*R*/*S*-[(*tert*-butyldimethylsilyl)oxy]but-3-ynyl]-8-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,6-dimethyl-7-oxobicyclo[3.2.1]hept-2-ene (10). To a solution of **8** (5.2 g, 12.5 mmol, 100 mol %) in toluene (50 mL, 0.25 M) at −78 °C was slowly added DIBAL (50 mL of a 0.25 M solution in toluene, 12.5 mmol, 100 mol %) dropwise via an addition funnel. The reaction mixture was allowed to stir for 2 h, at which point the cooling bath was removed and half-saturated $NaHSO_4$(aq) was added dropwise via an addition funnel. The temperature of the reaction mixture should not be allowed to exceed 0 °C. Once the addition was complete, the reaction mixture was transferred to a separatory funnel containing ice cold diethyl ether and water. The reaction mixture was extracted twice with diethyl ether, and the combined extracts were dried (Na_2SO_4). The combined organic extracts containing the crude aldehyde were not evaporated, but added directly to a solution of chloromagnesium acetylide (50 mmol, 400 mol %) in THF (0.25 M with respect to the Grignard reacgent, 200 mL) at −20 °C via cannula. After transfer of the crude aldehyde was complete, the cooling bath was removed and the reaction mixture was allowed to stir for 0.5 h. The reaction mixture was partitioned between diethyl ether and half-saturated NH_4Cl, and the aqueous layer was extracted three times with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude residue was then dissolved in DMF (5 mL, 2.25 M with respect to **8**), and TBSCl (2.83 g, 18.7 mmol, 150 mol % with respect to **8**) and imidazole (2.12 g, 31.2 mmol, 250 mol % with respect to **8**) were added. The reaction mixture was heated to 60 °C and allowed to stir for 4 h, at which point the reaction mixture was charged onto a chromatographic column (SiO_2; 1:3, CH_2Cl_2/hexane). The title compounds **10a** (2.86 g, 5.1 mmol, 41% yield) and **10b** (1.40 g, 2.51 mmol, 20%) were obtained in a combined yield of 61% as a 2:1 mixture of epimers at the propargylic center.

Data for the Lower R_f Isomer. $R_f = 0.45$ (5% EtOAc in hexane). $[\alpha]_D = -24.5°$ ($c = 4$, CH_2Cl_2). IR (neat): 3300, 1470 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (br s, 1H), 4.69−4.72 (br d, $J = 8.0$ Hz, 1H), 3.72−3.77 (dd, $J = 5.0$, 9.5 Hz, 1H), 3.48−3.51 (d, $J = 10.0$ Hz, 1H), 3.45−3.51 (dd, $J_1 = J_2 = 9.9$ Hz, 1H), 2.85−2.90 (ddd, $J_1 = J_2 = 5.0$, $J = 10$, 1H), 2.39−2.40 (d, $J = 2.1$, 1H), 2.29−2.37 (M, 2H), 2.14−2.20 (dd, $J = 2.7$, 5.4 Hz,1H), 1.75−1.83 (dd, $J = 8.1$, 15.0 Hz, 1H), 1.60 (s, 3H), 1.44 (s, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 124.1, 86.7, 83.6, 80.8, 77.2, 77.1, 72.6, 60.4, 58.7, 45.3, 42.0, 41.2, 38.2, 26.0, 25.8, 25.7, 24.6, 18.7, 17.9, −4.3, −4.6, −5.6, −6.0. HRMS: calcd for $C_{18}H_{29}Br^{81}NO_2Si$ [$M^+ - 57$] 501.1679, found 501.1695.

Data for the Higher R_f Isomer. $R_f = 0.55$ (5% EtOAc in hexane). $[\alpha]_D = -24.0°$ ($c = 2$, CH_2Cl_2). IR (neat): 3310, 1470 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (br s, 1H), 4.59−4.62 (br d, $J = 8.9$ Hz, 1H), 3.81−3.85 (dd, $J = 4.9$, 9.7 Hz, 1H), 3.42−3.51 (d, $J = 9.89$ Hz, 1H), 3.44−3.50 (dd, $J_1 = J_2 = 2.0$ Hz, 1H), 3.32−3.36 (d, $J = 9.9$ Hz, 1H), 2.81−2.89 (ddd, $J_1 = J_2 = 5.1$, $J = 10.1$ Hz, 1H), 2.44 (s, 1H), 2.30−2.41 (m, 3H), 1.92−2.09 (m, 2H), 1.59 (s, 3H), 1.43 (s, 3H), 0.92 (s, 9H), 0.87 (s,9H), 0.35 (s,3H), 0.12 (s, 3H) (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 124.1, 86.7, 83.5, 80.4, 72.6, 60.3, 58.6, 45.5, 42.0, 41.4, 38.2, 25.8, 25.7, 25.6, 24.8, 18.6, 18.1, 18.0, −4.9, −5.2, −5.6, −5.7. Anal. Calcd for $C_{27}H_{49}Si_2O_3Br$: C, 58.14; H, 8.85. Found: C, 58.04; H, 8.79.

b. Compounds en Route from Enyne Cyclization Product Precursor 10a to Common Intermediate Bislactone Triol 38.

(1*R*,3*R*,5*S*,8*R*,9*S*,11*R*)-9-(Bromomethyl)-3-[(*tert*-butyldimethylsilyl)oxy]-11-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5,9-dimethyl-4-methylidine-10-oxotricyclo[6.2.1.0^{1,5}]undec-6-ene. To a dichloroethane solution (175 mL, 0.075 M) of **10a** (7.40 g, 13.26 mmol, 100 mol %) at room temperature were added bis(dibenzophospholyl)propane (541.8 mg, 1.32 mmol, 10 mol %), *o*-(diphenylphosphino)benzoic acid (407.7 mg, 1.32 mmol, 10 mol %), and palladium acetate (297 mg, 1.32 mmol, 10 mol %). The solution was stirred at room temperature for 20 min and was then gently refluxed for 21 h, at which point the solvent was removed in vacuo and the residue chromatographed (SiO_2; 1:4 CH_2Cl_2/hexane) to give the title compound in 70% yield (5.17 g, 9.28 mmol). $R_f = 0.45$ (1:1, CH_2Cl_2/hexane). $[\alpha]_D = -71.5°$ ($c = 2.28$, CH_2Cl_2). IR (neat): 1472, 1362, 1256 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.82−5.87 (m, 2H), 4.96 (s, 1H), 4.46−4.54 (m, 1H), 3.56−3.64 (m, 2H), 3.42−3.49 (dd, $J = 10.1$, 6.26 Hz, 1H), 3.46−3.48 (d, $J = 9.34$ Hz, 1H), 2.40−2.52 (m, 2H), 2.13−2.21 (m, 2H), 1.46 (s, 3H), 1.18 (s, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 134.1, 124.1, 111.5, 108.5, 89.1, 85.5, 77.3, 77.2, 76.9, 76.8, 76.8, 71.4, 60.9, 52.7, 50.4, 45.2, 41.5, 39.0, 25.7, 25.5, 25.2, 23.5, 18.1, 17.6, −4.8, −4.9, −5.7. HRMS: calcd for $C_{26}H_{46}Br^{81}O_3Si_2$ [$M^+ - 15$] 543.2148, found 543.2152.

(1*R*,3*R*,5*S*,8*R*,9*S*,11*R*)-9-(Bromomethyl)-5,9-dimethyl-3-hydroxy-11-(hydroxymethyl)-4-methylidine-10-oxotricyclo[6.2.1.0^{1,5}]undec-6-ene (15). To a solution of the above bis(TBS) ether (989 mg, 1.77 mmol, 100 mol %) in THF (7 mL, 0.25 M) at room temperature was added TBAF (5.3 mL of a 1 M solution in THF, 5.3 mmol, 300 mol %). The reaction mixture was allowed to stir for 22 h, at which point it was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$), evaporated, and chromatographed (SiO_2; 70% ethyl acetate in hexane) to provide the title compound **15** (518 mg) in 89% yield. $R_f = 0.25$ (70% ethyl acetate in hexane). Mp = 144−145 °C. $[\alpha]_D = -120.9°$ ($c = 2.1$, CH_2Cl_2). IR (neat): 3500−3250, 3100, 1450, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.93−5.85 (m, 1H), 5.15 (s, 1H), 5.01 (s, 1H), 4.61−4.57 (t, $J = 6.92$ Hz, 1H), 3.71−3.66 (A part of ABX system, dd, $J = 8.34$, 10.64, 1H), 3.59 (A part of AB system, d, $J = 9.73$ Hz, 1H), 3.51−3.47 (B part of ABX system, dd, $J = 5.73$ Hz, 10.68, 1H), 3.35 (B part of AB system, d, $J = 9.39$ Hz, 1H), 2.60 (m, 1H), 2.51 (m, 1H), 2.31−2.26 (A part of ABX system, dd, $J = 8.17$, 13.74 Hz, 1H), 2.22−2.17 (B part of ABX system, dd, $J = 7.02$, 14.04 Hz, 1H), 1.49 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.8, 133.9, 124.0, 109.4, 88.9, 85.9, 70.9, 59.9, 52.2, 50.3, 44.8, 40.1, 38.7, 25.2, 24.2. HRMS: calcd for $C_{15}H_{21}Br^{81}O_3$ [$M^+ - 15$] 315.0419, found 315.0398.

(1*R*,5*S*,8*R*,9*S*,11*R*)-9-(Bromomethyl)-4-(chloromethyl)-5,9-dimethyl-11-(hydroxymethyl)-10-oxotricyclo[6.2.1.0^{1,5}]undec-3,6-diene (16). To a −78 °C solution of the allyl alcohol **15** (670 mg, 2.03 mmol, 100 mol %) in ether (40 mL, 0.05 M) was added pyridine (413 mL, 5.08 mmol, 250 mol %) followed by thionyl chloride (593 mL, 8.14 mmol, 400 mol %). The cooling bath was removed, and the reaction mixture was allowed to stir for 1.5 h. The reaction mixture was diluted with ether (40 mL), and water (40 mL) was added. The aqueous layer was extracted with ether, and the combined organic layers were dried ($MgSO_4$) and evaporated. The crude allyl chloride was chromatographed (SiO_2; 30% ethyl acetate in hexane) to provide the title compound **16** in 66% yield. $R_f = 0.2$ (30% ethyl acetate in hexane). $[\alpha]_D = -21.3°$ ($c = 3.5$, CH_2Cl_2). IR (neat): 3500−3200, 1450, 1262 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (d, $J = 3.0$ Hz, 2H), 5.63 (br s, 1H), 4.05 (s, 2H), 3.63−3.52 (m, 3H), 3.40−3.37 (d, $J = 9.43$ Hz, 1H), 2.75−2.71 (d, $J = 16.41$ Hz, 1H), 2.60−2.56 (m, 2H), 2.27−2.22 (d, $J = 16.24$ Hz, 1H), 1.52 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 132.7, 125.9, 125.5, 91.6, 86.3, 60.8, 52.5, 52.1, 43.5, 40.1, 38.9, 36.4, 25.2, 20.3. HRMS: calcd for $C_{15}O_{20}ClBr^{81}O_2$ [$M^+ - 128$] 220.1226, found 220.1241.

(1*R*,5*S*,8*R*,9*S*,11*R*)-9-(Bromomethyl)-4-(acetoxymethyl)-5,9-dimethyl-11-(hydroxymethyl)-2-oxotricyclo[6.2.1.0^{1,5}]undec-3,6-diene. To a solution of the allyl chloride **16** (47.5 mg, 0.136 mmol, 100 mol %) in DMF (1.3 mL, 0.1 M) was added cesium acetate (52 mg, 0.272 mmol, 200 mol %). The reaction vessel was placed in a 60 °C oil bath and was allowed to stir for 16 h, at which point the reaction mixture was charged directly onto a chromatographic column (SiO_2; 30% ethyl

acetate in hexane) to provide the title compound (40 mg, 0.107 mmol) in 79% yield. $R_f = 0.35$ (50% ethyl acetate in hexane). $[\alpha]_D = -33.4°$ ($c = 3.7$, CH_2Cl_2). IR (neat): 3600−3300, 1740, 1450, 1375 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.91−5.88 (A part of ABX system, dd, J = 6.31, 9.40 Hz, 1 H), 5.80−5.78 (A part of ABX system, d, $J = 9.46$ Hz, 1H), 5.50 (br s, 1H), 4.57 (A part of AB system, d, $J = 1.22$ Hz, 1H), 4.55 (B part of AB system, d, $J = 1.22$, 1H), 3.57−3.49 (m, 3H), 3.38−3.35 (d, $J = 9.36$ Hz, 1H), 2.73−2.68 (A part of AB system, d, $J = 16.1$ Hz, 1H), 2.57−2.54 (m, 2H), 2.24−2.19 (B part of AB system, d, $J = 16.18$ Hz, 1H), 2.06 (s, 3H), 1.50 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 143.5, 132.5, 125.4, 123.7, 91.6, 86.2, 61.0, 60.7, 52.3, 43.7, 39.0, 36.6, 25.4, 20.9, 20.3. HRMS: calcd for $C_{17}O_{23}Br^{81}O_4$ [$M^+ - 59$] 312.0550, found 312.0521.

(1*R*,5*S*,8*R*,9*S*,11*R*)-9-(bromomethyl)-4,11-bis(hydroxymethyl)-5,9-dimethyl-10-oxotricyclo[6.2.1.0^{1,5}]undec-3,6-diene (17). To a methanolic solution (942 mL, 0.1 M) of the above acetate (35 mg, 0.0942 mmol, 100 mol %) at room temperature was added potassium carbonate (130 mg, 0.942 mmol, 1000 mol %). The mixture was allowed to stir for 30 min, at which point the reaction mixture was partitioned between ether and water. The aqueous layer was extracted three times with ether, and the combined organic layers were dried ($MgSO_4$) and evaporated to give the crude title compound (30 mg, 97% yield) as a white solid. $R_f = 0.25$ (70% EtOAc in hexane). Mp = 136−137 °C. $[\alpha]_D = -2.3°$ ($c = 3.5$, CH_2Cl_2). IR (neat): 3600−3200, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.90−5.84 (m, 2H), 5.47 (br s, 1H), 4.17 (s, 2H), 3.60−3.54 (m, 3H), 3.39 (d, $J = 9.36$ Hz, 1H), 2.74−2.70 (br d, J = 16.04 Hz, 1H), 2.59−2.54 (m, 2H), 2.25−2.20 (br d, $J = 16.10$ Hz, 1H), 1.52 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 133.1, 125.3, 120.6, 91.8, 86.2, 61.1, 59.6, 52.2, 52.0, 43.7, 38.9, 36.4, 25.2, 20.3. Anal. Calcd for $C_{15}H_{21}P_3Br$: C, 54.72; H, 6.43. Found: C, 54.55; H, 6.42.

(1*R*,5*S*,8*R*,9*S*,11*R*)-9-(Bromomethyl)-4,11-dicarbomethoxy-5,9-dimethyl-10-oxotricyclo[6.2.1.0^{1,5}]undec-3,6-diene (18b). To a −78 °C solution of oxyallyl chloride (834 mL, 9.56 mmol, 1000 mol %) in methylene chloride (90 mL) was added DMSO (1.35 mL, 19.1 mmol, 2000 mol %). The reaction mixture was allowed to stir for 2 min. A solution of hydrindan diol **17** (315 mg, 0.956 mmol, 100 mol %) in methylene chloride (26 mL) was then added. The reaction mixture was allowed to stir for 15 min, at which point triethylamine (6.66 mL, 47.8 mmol, 5000 mol %) was added and the cooling bath was removed. Once at room temperature, water was added and the mixture was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give the crude aldehyde which was immediately dissolved in *tert*-butyl alcohol (20 mL) and 2-methyl-2-butene (2 mL, 19.1 mmol, 2000 mol %). An aqueous solution (8 mL H_2O) of sodium chlorite (1.03 g, 11.4 mmol, 1200 mol %) and sodium dihydrogen phosphate (1.12 g, 8.12 mmol, 850 mol %) was then added, and the reaction mixture was allowed to stir at room temperatire for 3.5 h. The reaction mixture was partitioned between ether and saturated $NaHSO_4$(aq). The aqueous layer was extracted with ether, and the combined organic layers were evaporated to approximately 20 mL. An ethereal solution of diazomethane was then added dropwise to the crude diacid **18a** until a yellow color persisted. Acetic acid was added to quench the excess diazomethane, and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with half-saturated $NaHCO_3$(aq), dried ($MgSO_4$), evaporated, and chromatographed (SiO_2; 15% ethyl acetate in hexane) to give the diester **18b** (291 mg) in 79% yield from the diol **17** as a clear oil.

The diacid **18a** was isolated prior to the addition of diazomethane as follows: the organic layer was evaporated and the residue of the crude diacid **18a** dissolved in half-saturated K_2CO_3(aq). The aqueous layer was washed with ether, acidified with concentrated phosphoric acid, and extracted with dichloromethane. Benzene was added for the purpose of azeotropic drying, and the organic layer was subjected to rotary evaporation. After drying on high vacuum, the acid **18a** obtained by this protocol was pure as evidenced by ^1H NMR.

Data for the Diacid. $R_f = 0.4$ (1% AcOH in EtOAc). $[\alpha]_D = -27.8°$ ($c = 1$, acetone). IR (neat): 3300−2500, 1732, 1682, 1426, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (dd, $J = 1.86$, 3.39 Hz, 1H), 6.26−6.24 (A part of ABX system, d, $J = 9.70$ Hz, 1H), 6.12−6.10 (B part of ABX system, dd, $J = 6.78$, 9.73 Hz, 1H), 3.60−3.57 (A part of AB system, d, $J = 9.46$ Hz, 1H), 3.39−3.36 (B part of AB system, d, 9.49 Hz, 1H), 3.25 (d, $J = 2.68$ Hz, 1H), 2.97−2.92 (A part of ABX system, d, $J = 17.94$ Hz, 1H), 2.81−2.79 (dd, $J = 3.34$, 6.65 Hz, 1H), 2.77−2.71 (B part of ABX system, dd, $J = 3.36$, 18.01 Hz, 1H), 1.51 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (300 MHz, d_6-acetone): δ 170.2, 164.7, 141.3, 140.7, 132.8, 127.0, 92.8, 85.5, 54.4, 52.3, 43.7, 39.0, 37.5, 24.8, 20.6. HRMS: calcd for $C_{15}H_{17}Br^{81}O_5$ [M^+] 358.0239, found 358.0214.

Data for the Diester. $R_f = 0.6$ (30% EtOAc in hexane). $[\alpha]_D = -17.9°$ ($c = 2$, CH_2Cl_2). IR (neat): 1750, 1702, 1611, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.58 (br s, 1H), 6.21−6.24 (A part of ABX system, d, $J = 9.61$ Hz, 1H), 6.04−6.10 (BX part of ABX system, dd, $J = 9.61$, 6.75 Hz, 1H), 3.69 (s, 3H), 3.58−3.61 (A part of AB system, d, $J = 9.46$ Hz, 1H), 3.52 (s, 3H), 3.35−3.38 (B part of AB system, d, $J = 9.49$ Hz, 1 H), 3.18−3.19 (d, $J = 2.75$ Hz, 1H), 2.85−2.91 (A part of ABX system, d, $J = 17.58$ Hz, 1H), 2.73−2.77 (dd, J = 3,57, 6.81 Hz, 1H), 2.61−2.68 (BX part of ABX system, dd, J = 3.30, 17.58 Hz, 1H), 1.49 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 163.9, 140.3, 140.1, 132.4, 126.2, 92.9, 86.3, 54.1, 52.2, 51.5, 51.3, 43.4, 38.2, 37.7, 25.4, 20.7. HRMS: calcd for $C_{17}H_{21}Br^{81}O_5$ [M^+] 386.0551, found 386.0554.

Epoxide 20. To a flask charged with diester **18** (2.76 g, 0.718 mmol, 100 mol %) and urea−hydrogen peroxide complex (1.35 g, 14.3 mmol, 2000 mol %) was added dichloroethane (14.3 mL, 0.05 M) followed by trifluoroacetic anhydride (1.01 mL, 7.18 mmol, 1000 mol %). The reaction mixture was allowed to stir at room temperature for 3 h, at which point the reaction mixture was partitioned between dichloromethane and half-saturated $NaHCO_3$(aq). The aqueous layer was extracted with dichloromethane, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (SiO_2; 20% ethyl acetate in hexane) to afford the title compound **20** (170 mg, 0.424 mmol, 59 mol %) in 67% yield based on recovered **18** (40 mg, 14 mol %). $R_f = 0.3$ (30% EtOAc in hexane). Mp = 168−170 °C. $[\alpha]_D = -58.0°$ ($c = 1$, CH_2Cl_2). IR (neat): 1742, 1715, 1630, 1436, 1345, 1233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (br s, 1H), 3.76 (s, 3.5H), 3.73 (s, 0.5H), 3.63 (s, 3H), 3.52 (dd, $J_1 = J_2 = 3.93$ Hz, 1H), 3.46 (d, $J = 10.04$ Hz, 1H), 3.42 (d, $J = 3.83$ Hz, 1H), 3.11 (dd, $J_1 = J_2 = 3.97$ Hz, 1H), 2.84 (br s, 1.5H), 2.79 (s, 0.5 H), 2.51 (dd, $J_1 = 3.35$, $J_2 = 17.7$ Hz, 1H), 1.54 (s, 3H), 1.22 (S, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.8, 168.6, 164.1, 141.4, 137.6, 89.3, 82.9, 54.0, 51.5, 51.4, 51.0, 49.5, 43.1, 38.8, 36.3, 26.9, 20.5. Anal. Calcd for $C_{17}H_{21}BrO_6$: C, 50.88; H, 5.27. Found: C, 50.62; H, 5.30.

8,9-Deoxy-β-bromopicrotoxinic Acid Methyl Ester (21). Preparation from Epoxide 20. To a flask charged with the epoxide **20** (100 mg, 0.249 mmol, 100 mol %) and (*S*)-camphorsulfonic acid was added dichloromethane (2.5 mL, 0.1 M) followed by trifluoroacetic acid (121 μL, 1.24 mmol, 500 mol %). The reaction was gently heated at reflux for 30 min, at which point the reaction mixture was charged onto a chromatographic column (SiO_2; 30% ethyl acetate in hexane). The title compound **21** was obtained as a white solid (79.1 mg, mmol) in 82% yield. The solid may be recrystallized from dichloromethane to yield clear prisms.

Preparation from Diene 18. To a flask charged with diene **18** (42 mg, 0.11 mmol, 100 mol %) and urea−hygrogen peroxide complex (205 mg, 2.18 mmol, 2000 mol %) was added dichloroethane (2.2 mL, 0.05 M) followed by trifluoroacetic anhydride (154 μL, 7.18 mmol, 1000 mol %). The reaction mixture was allowed to stir for 30 min at room temperature, at which point (*S*)-camphorsulfonic acid was added and the reaction mixture gently refluxed for 3 h. The reaction mixture was charged onto a chromatographic column (SiO_2; 30% ethyl acetate in hexane), and the lactone **21** (26.8 mg, 0.0692 mmol) was obtained as a white solid in 63% yield. The solid may be recrystallized from dichloromethane to yield clear prisms. $R_f = 0.25$ (40% ethyl acetate in hexane). Mp = 193−195 °C. $[\alpha]_D = -102°$ ($c = 1$, CH_2Cl_2). IR (neat): 3580, 1760, 1735, 1370 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (br s, 1H). 5.07 (d, $J = 2.4$ Hz, 1H), 4.27 (br s, 1H), 3.74 (s, 3H), 3.52−3.55 (A part of AB system, d, $J = 10.69$ Hz, 1H), 3.45−3.48 (B part of AB system, d, $J = 10.65$ Hz, 1H), 3.20 (d, $J = 3.97$ Hz, 1H), 2.84−2.89 (dd, $J = 2.2$, 19.2 Hz, 1H), 2.62−2.68 (dd, $J = 3.05$, 19.1 Hz, 1H), 2.48 (d, $J = 4.03$ Hz, 1H), 1.52 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 163.2, 141.2, 137.5, 91.5, 83.8, 79.5,

65.8, 53.6, 52.9, 51.7, 51.2, 39.5, 35.6, 25.9, 15.6. HRMS: calcd for $C_{16}H_{10}Br^{81}O_6$ [M^+] 388.03445, found 388.0362.

8,9-Dihydroxy-*β*-bromopicrotoxinic Acid Methyl Ester 22. To a solution of **21** (1.29 g, 3.33 mmol, 100 mol %) in pyridine (33 mL, 0.1 M) was added osmium tetroxide (1.48 g, 5.82 mmol, 175 mol %). The reaction mixture was allowed to stir for 24 h, at which point the volatiles were removed and the residue was dissolved in MeOH−H_2O (3:1). Sodium bisulfite (10 g) was added, and the mixture was stirred at 60 °C for 1 h, at which point the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The crude product was pure by ^{1}H NMR spectroscopy. R_f = 0.35 (70% ethyl acetate in hexane). $[\alpha]_D = -5.5°$ (c = 0.84, CH_3OH). IR (neat): 3400, 1780, 1720, 1440 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.6 (m, 2H), 4.3 (br m, 2H), 3.71 (s, 3H), 3.6 (br s, 1H), 3.43 (s, 2H), 3.27 (s, 1H), 2.8 (s, 1H), 2.68−2.73 (A part of ABX system, dd, J = 14.3, 8.2 Hz, 1H), 2.19−2.24 (B part of ABX system, dd, J = 14.3, 7.5 Hz, 1H), 1.51 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 169.8, 87.4, 82.2, 81.2, 77.2, 69.8, 65.8, 52.3, 51.2, 49.5, 42.1, 35.7, 26.7, 14.4. HRMS: calcd for $C_{16}H_{21}Br^{81}O_8$ [M^+] 422.0399, found 422.0386.

(1*R*,2*R*,4*R*,5*S*,6*R*,7*R*,10*S*,11*R*)-2,4,5,11-Tetrahydroxy-10-isopropenyl-6-methyl-9-oxo-8-oxatricyclo[5.2.2.0^{2,6}]undecane-5-carboxylic Acid Methyl Ester (29). To a solution of the bromoether triol **22** (2.04 g, 4.8 mmol, 100 mol %) in methanol was added acetic acid (2.7 mL, 48 mmol, 1000 mol %) followed by zinc dust (6.3 g, 96 mmol, 2000 mol %). The reaction mixture was placed in a 60 °C temperature bath and allowed to stir for 90 min, at which point the reaction mixture was diluted with ethyl acetate, filtered, and evaporated onto silica. Column chromatography provided the tetraol **29** (1.59 g, 4.6 mmol) in 96% yield. The tetraol **29** may be recrystallized from chloroform−methanol to yield clear prisms. R_f = 0.5 (neat ethyl acetate). Mp = 240−242 °C. $[\alpha]_D = -55°$ (c = 3.5, pyridine). IR (neat): 3500, 1746, 1733, 1641 cm^{-1}. ^{1}H NMR (300 MHz, d_4-methanol): δ 4.98 (br s, 1H), 4.56 (br s, 1H), 4.40 (dd, J_1 = 11.32, J_2 = 7.20 Hz, 1H), 4.27 (br s, 1H), 3.78 (s, 3H), 3.00 (d, J = 2.26 Hz, 1H), 2.25 (br s, 1H), 2.18 (dd, A part of ABX system, J_1 = 13.4, J_2 = 7.23 Hz, 1H), 1.99 (dd, B part of ABX system, J_1 = 13.4, J_2 = 11.4 Hz, 1H), 1.86 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 173.3, 144.4, 109.3, 87.3, 85.8, 77.0, 72.0, 67.3, 54.4, 54.2, 51.6, 50.7, 48.5, 22.8. Anal. Calcd for $C_{16}H_{22}O_8$: C, 56.13; H, 6.48. Found: C, 56.24; H, 6.42.

"8,9-Dihydroxy-α-picrotoxinic Acid Methyl Ester Acetonide" (33). To a solution of tetraol **29** (1.59 g, 4.64 mmol, 100 mol %) in acetone (92 mL, 0.05 M) at room temperature was added dimethoxypropane (11.4 mL, 93 mmol, 2000 mol %) followed by (*S*)-camphorsulfonic acid (107 mg, 0.46 mmol, 10 mol %). The reaction mixture was allowed to stir for 14 h, at which point it was partitioned between ethyl acetate and half-saturated $NaHCO_3$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 40% ethyl acetate in hexane) afforded the acetonide **33** (1.25 g, 3.3 mmol) as a crystalline solid in 70% yield along with a >10% yield of the product of acid-catalyzed cycloetherification of the tertiary hydroxyl grouping onto the isopropenyl moiety. R_f = 0.6 (70% ethyl acetate in hexane). Mp = 252 °C. $[\alpha]_D = -25°$ (c = 1.7, acetone). IR (neat): 3400, 1725, 1702, 1648, 1450, 1306 cm^{-1}. ^{1}H NMR (400 MHz, d_6-acetone): δ 5.01 (br s, 1H), 4.85 (s, 3H), 4.77 (dd, J_1 = J_2 = 8.24 Hz, 1H), 4.59 (br s, 1H), 4.41 (br s, 1H), 4.32 (s, 1H), 4.20 (s, 1H), 3.76 (s, 3H), 2.95 (s, 1H), 2.39 (dd, A part of ABX system, J_1 = 14.4, J_2 = 8.0 Hz, 1H), 2.30 (br s, 1H), 2.08 (dd, B part of ABX system, J_1 = 13.77, J_2 = 8.6 Hz, 1H), 1.85 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, d_6-acetone): δ 173.6, 171.4, 144.2, 112.6, 109.8, 94.8, 86.7, 80.4, 79.8, 66.7, 53.9, 53.4, 52.4, 49.7, 48.1, 29.2, 27.6, 22.5, 13.5. HRMS: calcd for $C_{19}H_{26}O_8$ [M^+] 382.1628, found 382.1615.

Monoester Monolactone 35. To a solution of the acetonide **33** (68 mg, 0.17 mmol, 100 mol %) in methanol−water (3:1, 3.5 mL, 0.05 M) was added potassium hydroxide (249 mg, 4.25 mmol, 2500 mol %). The reaction mixture was heated to 70 °C for 22 h, at which point it was partitioned between ethyl acetate and $NaHSO_4$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were concentrated to a volume of 20 mL. An ethereal solution of diazomethane was added until a yellow color persisted. Acetic acid was added to quench the excess diazomethane, and the reaction mixture was partitioned between ethyl acetate and half-saturated $NaHCO_3$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The crude oil was subjected to column chromatography (SiO_2; 25% ethyl acetate in hexanes) to provide the title compound **35** (62.3 mg, 0.15 mmol) as a crystalline solid in 91% yield over the two-step sequence. R_f = 0.25 (30% ethyl acetate in hexane). Mp = 163−165 °C $[\alpha]_D = 52.4°$ (c = 0.5, acetone). IR (neat): 3525, 2940, 1785, 1737, 1648, 1436, 1382, 1131 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.89 (s, 1H), 4.70 (d, J = 4.18 Hz, 1H), 4.44 (d, J = 4.70 Hz, 1H), 3.85 (br m, 1H), 3.65 (s, 3H), 2.99 (s, 1H), 2.76−2.80 (d, J = 12.3 Hz, 1H), 2.56−2.63 (dd, J_1 = J_2 = 10.50 Hz, 1H), 2.46−2.53 (A part of ABX system, dd, J = 16.33, 4.24 Hz, 1H), 2.28−2.33 (B part of ABX system, d, J = 16.48 Hz, 1H), 2.20 (br m, 1H), 1.76 (s, 3H). 1.57 (s, 3H), 1.55 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 171.4, 141.6, 116.3, 115.0, 93.1, 86.9, 85.4, 84.2, 69.1, 51.8, 51.6, 51.4, 46.8, 37.4, 26.5, 24.9, 19.1, 17.6. HRMS: calcd for $C_{18}H_{23}O_8$ [M^+ − 15] 367.1392, found 367.1387.

Triol 36. To a solution of diol **35** (348 mg, 0.91 mmol, 100 mol %) in dichloromethane (18 mL, 0.05 M) was added DMAP (1.11 g, 9.1 mmol, 1000 mol %) followed by acetyl chloride (647 μL, 0.91 mmol, 1000 mol %). The reaction mixture was allowed to stir at room temperature for 3 h, at which point it was partitioned between ethyl acetate and $NaHSO_4$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 30% ethyl acetate in hexanes) provided the acetate of acetonide **36** (331 mg, 0.78 mmol) as a crystalline solid in 86% yield. R_f = 0.7 (50% ethyl acetate in hexane). Mp = 186−187 °C. $[\alpha]_D = 55.8$ (c = 0.77, acetone). IR (neat): 3554, 1786, 1743, 1733, 1648, 1369 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (dd, J_1 = 11.0, J_2 = 4.95 Hz, 1H), 4.94 (br s, 1H), 4.87 (br s, 1H), 4.72 (d, J = 4.12 Hz, 1H), 4.48 (d, J = 4.88 Hz, 1H), 3.67 (s, 3H), 3.09 (s, 1H), 2.86 (d, J = 12.37 Hz, 1H), 2.76 (dd, J_1 = J_2 = 12.36 Hz, 1H), 2.45 (dd, AX part of ABX system, J_1 = 16.5, J_2 = 4.3 Hz, 1H), 2.32 (d, B part of ABX system, J = 16.5 Hz, 1H), 2.06 (s, 3H), 1.71 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 171.2, 169.9, 141.0, 115.9, 115.2, 92.8, 87.0, 84.0, 82.5, 77.2, 69.9, 51.9, 51.6, 43.6, 37.2, 26.5, 24.9, 20.6, 19.9, 17.5. HRMS: calcd for $C_{21}H_{28}O_9$ [M^+ − 15] 409.1498, found 409.1514.

To a THF solution (1 mL, 0.05 M) of acetoxy acetonide (22 mg, 0.052 mmol, 100 mol %) at room temperature was added HCl(aq) (1 mL, 4 M). The reaction mixture was allowed to stir for 4.5 h, at which point the reaction mixture was partitioned between ethyl acetate and brine. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 60% ethyl acetate in hexane) afforded the triol **36** (13.3 mg, 0.034 mmol) in 67% yield as a viscous oil. R_f = 0.2 (50% ethyl acetate in hexane). $[\alpha]_D = 92.8°$ (c = 1.33, acetone). IR (neat): 3450, 2035, 1780, 1738, 1648, 1437, 1373, 1235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (dd, J_1 = 11.6, J_2 = 3.57 Hz, 1H), 4.95 (s, 1H), 4.86 (s, 1H), 4.53 (d, J = 3.48 Hz, 1H), 4.24 (br s, 1H), 3.70 (s, 3H), 2.87 (d, J = 12.6 Hz, 1H), 2.74 (dd, J_1 = J_2 = 12.4 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 2H), 1.72 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, d_6-acetone): δ 177.2, 171.7, 170.3, 142.7, 115.7, 86.9, 83.7, 83.2, 77.2, 71.3, 53.7, 53.4, 51.5, 43.4, 40.2, 40.2, 20.6, 19.7, 16.2. MS: *m/z* (rel intens) 384 (15.0), 366 (17.5), 348 (47.9), 181 (64.8), 127 (100). HRMS: calcd for $C_{18}H_{24}O_9$ [M^+] 384.1420, found 384.1419.

Tris(trimethylsilyl ether) 37. To a solution of the triol **36** (141 mg, 0.36 mmol, 100 mol %) in dichloromethane (3.6 mL, 0.1 M) at room temperature was added 2,6-lutidine (635 μL, 5.4 mmol, 1500 mol %) followed by trimethylsilyl triflate (700 μL, 3.6 mmol, 1000 mol %). The reaction mixture was allowed to stir for 2.5 h, at which point the reaction mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 5% ethyl

acetate in hexane) afforded the acetate of tris(silyl ether) **37** (184 mg, 0.30 mmol) in 85% yield as a crystalline solid. $R_f = 0.8$ (30% ethyl acetate in hexane). Mp = 192−195 °C. $[\alpha]_D = 87.1$ ($c = 0.5$, acetone). IR (neat): 2956, 1770, 1738, 1648, 1233, 844 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.05 (dd, $J_1 = 11.8$, $J_2 = 3.0$ Hz, 1H), 4.89 (br s, 1H), 4.81 (br s, 1H), 4.43 (d, $J = 2.90$ Hz, 1H), 4.26 (br s, 1H), 3.62 (s, 3H), 2.88 (d, $J = 12.8$ Hz, 1H), 2.70 (dd, $J_1 = J_2 = 12.3$ Hz, 1H), 2.05 (s, 3H), 1.88 (s, 2H), 1.66 (s, 3H), 1.12 (s, 3H), 0.19 (s, 9H), 0.16 (s, 9H), 0.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 171.0, 170.3, 141.1, 115.8, 88.3, 84.8, 83.8, 77.2, 70.5, 56.9, 55.4, 51.4, 42.3, 41.0, 20.8, 19.4, 18.0, 2.7, 1.6, 0.9. MS: *m/z* (rel intens) 600 (1.8), 585 (13.6), 482 (13.4), 147 (27.0), 73 (100). HRMS: calcd for $C_{27}H_{48}O_9Si_3$ [M^+] 600.2606, found 600.2597.

To a solution of the above acetate (97 mg, 0.161 mmol, 100 mol %) in THF−methanol (3:1, 3.2 mL, 0.05 M) was added powdered potassium cyanide (5.25 mg, 0.08 mmol, 50 mol %). The reaction mixture was allowed to stir for 4.5 h, at which point the reaction mixture was evaporated onto silica gel. Column chromatography (SiO_2; 5% ethyl acetate in hexane) afforded the hydroxy ester **37** (62 mg, 68.7 mol %) as a crystalline solid and recovered starting material (31 mg, 32 mol %). The yield based on recovered starting material is 90%. $R_f = 0.6$ (30% ethyl acetate in hexane). Mp = 187−188 °C. $[\alpha]_D = 87°$ ($c = 0.2$, acetone). IR (neat): 3564, 1776, 1739, 1648 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.97 (br s, 1H), 4.85 (br s, 1H), 4.49 (d, $J = 3.24$ Hz, 1H), 3.78 (br m, 1H), 3.61 (s, 3H), 2.80 (d, $J = 12.6$ Hz, 1H), 2.48 (dd, $J_1 = J_2 = 12.2$ Hz, 1H), 1.97 (d, A part of ABX system, $J = 15.4$ Hz, 1H), 1.86 (dd, B part of ABX system, $J_1 = 15.8$, $J_2 = 4.12$ Hz, 1H), 1.75 (s, 3H), 1.09 (s, 3H), 0.21 (s, 9H), 0.16 (s, 9H), 0.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 171.2, 141.5, 116.9, 88.6, 86.5, 85.0, 77.2, 77.1, 69.0, 56.6, 55.1, 51.3, 45.8, 40.9, 18.1, 2.6, 1.7, 0.9. HRMS: calcd for $C_{25}H_{46}O_8Si_3$ [$M^+ - 15$] 543.2265, found 543.2264.

Bislactone 38. To a solution of hydroxy ester **37** (72.4 mg, 0.129 mmol, 100 mol %) in toluene−*tert*-butyl alcohol (4:1, 2.5 mL, 0.05 M) at room temperature was added lithium hexamethyldisilamide (64 μL, 1 M solution in hexane, 0.0645 mmol, 50 mol %). The reaction vessel was placed in a 100 °C oil bath and allowed to stir for 1 h, at which point the reaction mixture was removed from the bath, allowed to cool to ambient temperature, and partitioned between diethyl ether and half-saturated NH_4Cl(aq). The aqueous layer was extracted with diethyl ether, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 5% → 20% ethyl acetate in hexane) afforded the silyl ether of the bislactone **38** (46.3 mg, 0.0837 mmol) as a white foam in 68% yield. $R_f = 0.8$ (30% ethyl acetate in hexane). $[\alpha]_D = 4.5$ ($c = 0.4$, $CHCl_3$). IR (neat): 2958, 1784, 1648, 1254, 1116, 1027, 842 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.00 (m, 2H), 4.85 (br s, 1H), 4.55 (d, $J = 4.12$ Hz, 1H), 3.94 (dd, $J_1 = 12.4$, $J_2 = 5.9$ Hz, 1H), 3.32 (br m, 1H), 2.88 (d, $J = 4.12$ Hz, 1H), 2.52 (dd, A part of ABX system, $J_1 = 12.2$, $J_2 = 6.0$ Hz, 1H), 2.29 (dd, B part of ABX system, $J_2 = J_2 = 12.4$ Hz, 1H), 1.87 (s, 3H), 1.08 (s, 3H), 0.20 (s, 9H), 0.18 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 173.6, 138.8, 113.6, 85.0, 80.8, 77.2, 76.7, 72.0, 53.7, 53.1, 48.3, 46.1, 22.7, 21.6, 2.2, 2.1, −0.2. HRMS: calcd for $C_{24}H_{42}O_7Si_3$ [M^+] 526.2238, found 526.2254.

To an acetonitrile solution (1.2 mL, 0.05 M) of the above tris(silyl ether) of **38** (33.4 mg, 0.063 mmol, 100 mol %) at ambient temperature and in a Teflon reaction vessel was added HF(aq) (600 μL of a 48% solution in water, approximately 15 mmol, 4200 mol %). The reaction vessel was placed in a 100 °C oil bath and the reaction mixture allowed to stir for 30 min, at which point it was partitioned between ethyl acetate and half-saturated $NaHCO_3$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 40% → 60% ethyl acetate in hexane) afforded the bislactone triol **38** (18.1 mg, 0.0583 mmol) as a white foam in 92% yield. $R_f = 0.3$ (60% ethyl acetate in hexane). $[\alpha]_D = -15.3°$ ($c = 1.6$, CH_2Cl_2). IR (neat): 3400, 1777, 1770, 1648, 1454, 1307 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.11 (br s, 1H), 5.07 (dd, $J_1 = J_2 = 4.28$ Hz, 1H), 4.92 (br s, 1H), 4.66 (d, $J = 3.97$ Hz, 1H), 4.15−4.19 (dd, $J = 12.01$, 6.27 Hz, 1H), 3.40 (br s, 1H), 3.06 (d, $J = 4.28$ Hz, 1H), 2.80−2.85 (A part of ABX system, dd, $J = 13.29$, 6.31 Hz, 1H), 195−2.02 (B part of ABX system, dd, $J = 12.2$, 13.3 Hz, 1H), 1.93 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, d_5-pyridine): δ 177.4, 176.3, 140.5, 113.2, 82.7, 81.8, 77.7, 74.7, 70.9, 53.1, 52.4, 49.0, 48.4, 22.9, 20.6. HRMS: calcd for $C_{15}H_{18}O_7$ [M^+] 310.1053, found 310.1042.

c. Synthesis of Picrotoxinin from Bislactone 38 and Related Structures. "8,9-Deoxypicrotoxinin" (39). To a dichloroethane solution (650 μL, 0.1 M) of bislactone triol **38** (20 mg, 0.0644 mmol, 100 mol %) at room temperature was added DMF−dimethyl acetal (342 μL, 0.257 mmol, 400 mol %). The reaction mixture was allowed to stir for 1 h, at which point the reaction mixture evaporated and the crude residue was dissolved in acetic anhydride (650 μL, 0.1 M). The reaction mixture was placed in a 100 °C temperature bath and stirred for 2 h. The reaction mixture was removed from the bath and allowed to reach ambient temperature. The residue was diluted with dichloromethane and charged onto a chromatographic column (SiO_2; 40% → 50% ethyl acetate in hexane). The enoate **39** (12.2 mg, 0.044 mmol) was obtained in 68% yield as a clear oil. $R_f = 0.4$ (60% ethyl acetate in hexane). $[\alpha]_D = 120°$ ($c = 2.75$, acetone). IR (neat): 3450, 1784, 1760, 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.38 (br s, 1H), 5.06 (s, 1H), 4.97 (dd, $J = 4.34$, 3.66 Hz, 1H), 4.82 (s, 1H), 4.70 (d, $J = 3.36$ Hz, 1H), 3.38 (br s, 1H), 3.26−3.32 (A part of ABX system, dd, $J = 17.88$, 3.73 Hz, 1H), 3.07−3.12 (B part of ABX system, d, $J = 17.94$ Hz, 1H), 2.90 (d, $J = 4.58$ Hz,1H), 2.65 (br s, 1H), 1.93 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 163.6, 142.2, 140.0, 134.9, 113.3, 83.3, 79.3, 78.0, 53.6, 49.6, 49.3, 49.0, 23.2, 19.2. HRMS: calcd for $C_{15}H_{16}O_5$ [M^+] 276.0997, found 276.0998.

Picrotoxinin. To a THF solution (600 μL, 0.2 M) of the enoate **39** (34 mg, 0.123 mmol, 100 mol %) at −78 °C was added *tert*-butyl hydroperoxide (174 μL of a 3 M solution in isooctane, 0.31 mmol, 250 mol %). The reaction vessel was transferred to an ice bath, and the reaction mixture was allowed to stir for 1 h, at which point the reaction mixture was partitioned between ethyl acetate and half-saturated NH_4Cl(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 30% ethyl acetate in hexane) afforded picrotoxinin (27.7 mg, 0.095 mmol) in 77% yield. $R_f = 0.5$ (60% ethyl acetate in hexane). $[\alpha]_D = 1.7°$ ($c = 1$, methanol). IR (neat): 3464, 1785, 1766, 1650, 1303 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.08 (m, 2H), 4.90 (d, $J = 3.48$ Hz, 1H), 4.83 (br s, 1H), 3.71 (d, $J = 3.30$ Hz, 1H), 3.43 (br m, 1H), 2.89−2.98 (m, 2H), 2.25 (s, 1H), 1.95−2.02 (d, $J = 15.20$ Hz, 1H), 1.9 (s, 3H), 1.2 (s, 3H). ^{13}C NMR (50 MHz, d_8-THF): δ 176.7, 171.8, 141.8, 112.1, 86.7, 81.8, 78.9, 73.6, 63.0, 52.4, 50.3, 49.7, 47.9, 23.2, 16.7.

Diene 40. To a solution of bislactone triol **38** (70 mg, 0.225 mmol, 100 mol %) in *N*-methylimidazole (2.2 mL, 0.1 M) was added triflic anhydride (151 μL, 0.88 mmol, 400 mol %). The reaction vessel was placed in a 100 °C temperature bath and allowed to stir for 1 h, at which point the reaction mixture was partitioned between ethyl acetate and half-saturated $NaHSO_4$(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Column chromatography (SiO_2; 40% → 70% ethyl acetate in hexane) afforded the title compound **40** (56.2 mg, 0.192 mmol) in 85% yield as a clear viscous oil. $R_f = 0.2$ (60% ethyl acetate in hexane). $[\alpha]_D = 90.0°$ ($c = 3.5$, acetone). IR (neat): 3450, 2985, 1770, 1646 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.25 (A part of AB system, d, $J = 5.56$ Hz, 1H), 5.86 (B part of AB system, d, $J = 5.60$ Hz, 1H), 5.15 (br s, 1H), 5.10 (dd, $J_1 = J_2 = 4.58$ Hz, 1H), 5.05 (br s, 1H), 4.75 (d, $J = 4.75$ Hz, 1H), 3.46 (br s, 1H), 3.26 (d, $J = 3.96$ Hz, 1H), 1.96 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 174.7, 142.5, 138.5, 130.1, 115.1, 88.5, 82.7, 76.9, 52.2, 50.5, 47.3, 22.3, 19.5. HRMS: calcd for $C_{15}H_{16}O_8$ [M^+] 292.0946, found 292.0950.

Lactol 41. To a test tube charged with lithium borohydride (16.3 mg, 0.75 mmol, 2000 mol %) was added THF (750 μL, 0.05 M with respect to **40**). The reaction vessel was placed in an ice bath, and acetic acid (43 μL, 0.75 mmol, 2000 mol %) was added to the mixture. After 2 min, a solution of bislactone **40** (11.0 mg, 0.0376 mmol, 100 mol %) in THF (750 μL, 0.05 M) was added, and the reaction mixture was allowed to stir for 30 min, at which point the reaction mixture was partitioned between ethyl acetate and half-saturated NH_4Cl(aq). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated onto silica

gel. Column chromatography (SiO_2; 50% → 70% ethyl acetate in hexane) afforded the monolactone monolactol **41** (7.9 mg, 0.0268 mmol) as a clear viscous oil. Lactol **41** is initially obtained as an equal mixture of epimers at the lactol carbon which, upon standing in chloroform, is converted to a single epimer. The data for this thermodynamic isomer are presented below. $R_f = 0.2$ (70% ethyl acetate in hexane). $[\alpha]_D = 54.4°$ ($c = 1.78$, acetone). IR (neat): 3450, 1769, 1646, 1380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.16 (d, $J = 5.7$ Hz, 1H), 5.77 (d, $J = 5.7$ Hz, 1H), 5.31 (s, 1H), 5.05 (m, 2H), 4.97 (s, 1H), 4.49 (d, $J = 4.9$ Hz, 1H), 3.37 (br s, 1H), 3.18 (d, $J = 3.9$ Hz, 1H), 2.75 (br s, 1H), 3.63 (br s, 1H) 1.93 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 141.5, 139.3, 132.3, 114.4, 97.7, 92.8, 81.8, 81.7, 78.1, 52.4, 50.5, 48.5, 22.3, 19.8. HRMS: calcd for $C_{15}H_{18}O_6$ [M^+] 294.1103, found 294.1113.

7,8-Deoxycorianin (42). To a solution of **41** (31 mg, 0.1 mmol, 100 mol %) in acetonitrile (500 μL, 0.2 M) at room temperature was added thiophenol (500 μL, 0.2 M) followed by trimethylsilyl chloride (12 μL, 0.1 mmol, mol %). The reaction mixture was allowed to stir for 20 h, at which point the reaction mixture was charged onto a chromatographic column (SiO_2; 40% → 70% ethyl acetate in hexane). The corresponding phenylthiolactol (38 mg, 0.098 mmol) was obtained in 98% yield and was taken on directly to the conditions for radical desulfurization.

To a reaction vessel charged with the above thiolactol (35 mg, 0.09 mmol, 100 mol %) and triphenyltin hydride (63 mg, 0.18 mmol, 200 mol %) was added toluene followed by AIBN (3 mg, 0.024 mmol, 20 mol %). The reaction vessel was placed in a 125 °C oil bath, and the reaction mixture was allowed to stir for 1.5 h, at which point the reaction mixture was charged onto a chromatographic column (SiO_2; 50% → 60% ethyl acetate in hexane). The cyclic ether **45** (21 mg, 0.075 mmol) was obtained in 84% yield. $R_f = 0.2$ (50% ethyl acetate in hexane). $[\alpha]_D = 27°$ ($c = 1.24$ methanol). IR (neat): 3450, 1765, 1643, 1177, 1053 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.0 (A part of AB system, d, $J = 5.84$ Hz, 1H), 5.8 (B part of AB system, d, $J = 5.70$ Hz, 1H), 5.0 (m, 2H), 4.95 (br s, 1H), 4.32 (d, $J = 4.25$ Hz, 1H), 4.0 (A part of AB system, d, $J = 10.07$ Hz, 1H), 3.8 (B part of AB system, d, $J = 10.07$ Hz, 1H), 3.33 (br m, 1H), 3.15 (d, $J = 3.66$ Hz, 1H), 1.93 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 139.5, 138.3, 133.8, 114.0, 94.8, 84.0, 81.6, 80.1, 78.1, 57.2, 50.6, 49.2, 22.6, 19.5. HMRS: calcd for $C_{15}H_{18}O_5$ [M^+] 278.1154, found 278.1152.

Supporting Information Available: Experimental details for the Mitsunobu inversion sequence and saponification−silylation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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