Total Synthesis of (±)-Breynolide, an Aglycon Derivative of the Orally Active Hypocholesterolemic Agent Breynin A†

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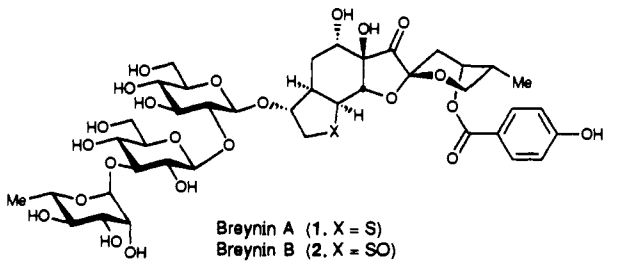
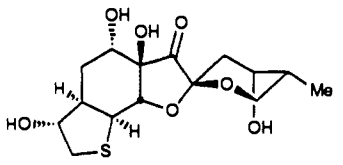
Abstract: The total synthesis of (±)-breynolide (**3**), an aglycon derivative of the potent, orally active hypocholesterolemic glycoside breynin A, has been achieved via a stereochemically linear strategy. The successful approach entailed union of the anion derived from **58** with aldehyde **54** followed by an anomerically driven spiroketalization–equilibration protocol. Aldehyde **54** derived from the bicyclo[2.2.2]octenol **12**; key transformations included chemoselective epoxide ring opening of **16** to furnish **17**, introduction of sulfur via 1,4-addition of thiolacetic acid and ring closure (i.e., **35** → **27**), and hydroboration of vinyl sulfide **52** to install the C(3) exo hydroxyl in **40**. Incorporation of the trans vicinal diol unit then exploited the strain in enone **68**. Also noteworthy is the end-game strategy, wherein differential deprotection of the three secondary hydroxyl groups will provide the flexibility required for elaboration of the biologically important glycosides.

Breynins A and B, novel sulfur-containing glycosides isolated[1] from the Taiwanese woody shrub *Breynia officinalis* Hemsl, display significant oral hypocholesterolemic activity.[2] Recently we[3] and Ohkuma et al.[4] independently established the complete linear trisaccharide structure **1** for breynin A; we also characterized

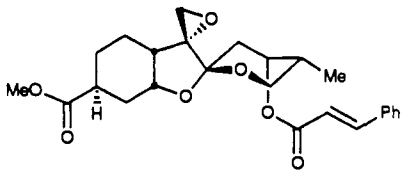


Breynin A (1, X = S)
Breynin B (2, X = SO)

breynin B as the α-sulfinyl derivative **2**.[3] In initial degradation studies, exhaustive hydrolysis of A afforded breynolide (**3**) along with D-glucose, L-rhamnose, and *p*-hydroxybenzoic acid.[1c] Single-crystal X-ray analysis then secured the formulation of **3**.[1a,b]



Breynolide (3)



Phyllanthocin (4)

Our interest in the breynins stems from their pharmacological potential as well as the structural similarity of **3** to phyllanthocin (**4**),[5a] the aglycon nucleus of the phyllanthoside antitumor agents[5b] which we have studied in depth. Not surprisingly, others in the synthetic community have also been attracted to the breynolide arena;[6] the first total synthesis of (+)-**3** was reported by Williams et al.[7] in 1990. In this full account, we record an alternate approach which recently culminated in a total synthesis of racemic breynolide.[8] Highlights include (1) a stereochemically linear strategy exploiting the anomerically driven spiroketalization–equilibration utilized to great advantage in our phyllanthocin venture;[9] (2) a chemoselective, regiocontrolled epoxide ring opening (i.e., **16** → **17**); (3) three-step construction of the cis-fused perhydrobenzothiophene ring system; and (4) development of an end game which will permit selective deprotection of the three secondary hydroxyl groups in **79** (Scheme XXIV), providing the flexibility required for the eventual elaboration of the biologically important glycosides.

Synthetic Plan. We sought to devise a breynolide strategy that would amplify our stereochemically linear[10] construction of phyllanthocin. A stereochemically linear approach employs a series of substrate-controlled operations to derive the relative configurations of all remaining stereocenters from the chirality of a racemic or scalemic starting material. Vis-à-vis a convergent synthetic design, such a strategy sometimes entails additional steps, but may nonetheless afford enhanced overall efficiency as only one chiral substrate is required. Importantly, a stereochemically linear synthesis of a racemate circumvents the formation of unwanted diastereomers that normally complicates the coupling of racemic fragments.

The phyllanthocin study suggested that the breynolide spiroketal intermediate **6** would be more stable than the diastereomer **7** (Scheme I), presumably manifesting the anomeric interactions[11]

† Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday.

(1) (a) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 2439. (b) Sasaki, K.; Hirata, Y. *Acta Crystallogr.* **1974**, *B30*, 1347. (c) Sakai, F.; Ohkuma, H.; Koshiyama, H.; Naito, T.; Koshiyama, H. *Chem. Pharm. Bull.* **1976**, *24*, 114. (d) Koshiyama, H.; Hatori, M.; Ohkuma, H.; Sakai, F.; Imanishi, H.; Ohbayashi, M.; Kawaguchi, H. *Ibid.* **1976**, *24*, 169.

(2) Trost, W. *IRCS Med. Sci.* **1986**, *14*, 905.

(3) Smith, A. B., III; Gallagher, R. T.; Keenan, T. P.; Furst, G. T.; Dormer, P. G. *Tetrahedron Lett.* **1991**, *32*, 6847.

(4) Ohkuma, H.; Tsuno, T.; Kowishi, M.; Naito, T.; Kawaguchi, H. *Chem. Pharm. Bull.* **1991**, *38*, 942.

(5) (a) Kupchan, S. M.; La Voie, E.; Branfman, A.; Fei, B.; Bright, W.; Bryan, R. *J. Am. Chem. Soc.* **1977**, *99*, 3199. (b) Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630 and references cited therein.

(6) Nishiyama, S.; Ikeda, Y.; Yoshida, S.; Yamaura, S. *Tetrahedron Lett.* **1989**, *30*, 105.

(7) Williams, D. R.; Jass, P.; Tse, H.; Gaston, R. *J. Am. Chem. Soc.* **1990**, *112*, 4552.

(8) Preliminary communication: Smith, A. B., III; Empfield, J. R.; Rivero, R. A.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 4037.

(9) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071. Also see: Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269.

(10) We have previously defined and discussed *stereochemically linear* strategies in connection with our synthesis of (+)-phyllanthocin.[9]

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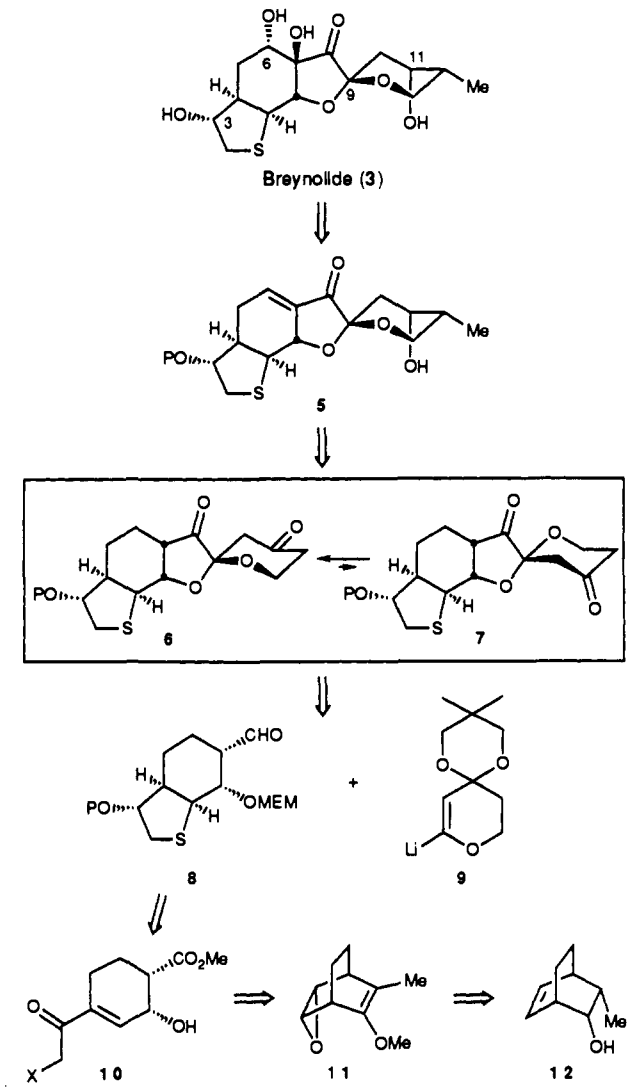
Scheme I

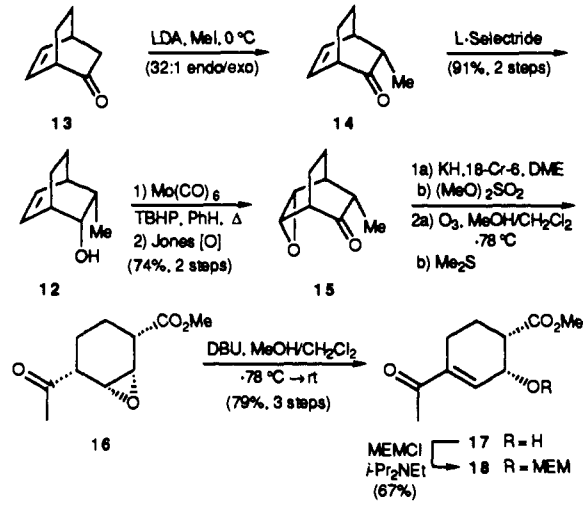


within the furanone and pyranone moieties. Either a kinetically controlled spiroketalization or the equilibration of **6** and **7** would thus be expected to furnish **6** selectively. This tactic became the cornerstone of our strategy.

The conversion of spiroketal **6** to (±)-breynolide would then require regio- and stereocontrolled introduction of the C(12) methyl group, chemo- and stereoselective reduction of the C(11) carbonyl to the axial alcohol, and incorporation of the C(6,7) trans vicinal diol. We envisioned that enone **5** could provide a suitable template for the potentially challenging generation of the diol moiety. Spiroketal **6** in turn would arise via coupling of the dihydropyranone derivative **9** with the cis-fused perhydrobenzothiophene aldehyde **8**, followed by the spiroketalization–equilibration protocol developed earlier. Generation of **8** would involve thioannulation of enone **10**, via 1,4-addition of a sulfur nucleophile to the enone and cyclization by displacement of an α-keto halide. We anticipated[12] introduction of sulfur anti to the adjacent hydroxyl, as required; the initial stereochemistry at C(4) would be inconsequential, as an equilibration would furnish the thermodynamically preferred cis-fused hydrindanone.[13] Finally, enone **10** would arise via ozonolysis of enol ether **11**, derived from the known [2.2.2]bicycle **12**,[14] followed by chemoselective epoxide opening.

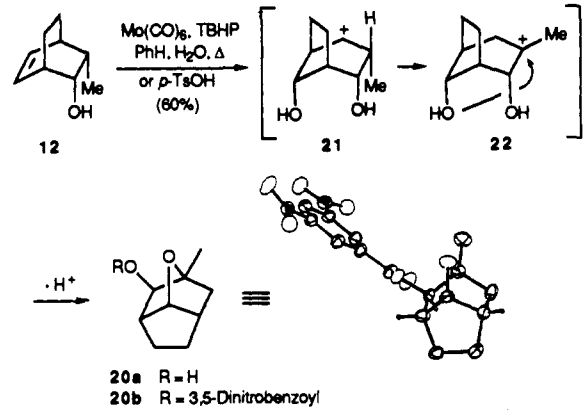
An Efficient, Stereocontrolled Preparation of Enone 18. As our point of departure, we developed a highly stereoselective sequence leading to the requisite alcohol **12**.[14] Methylation of the parent bicyclo[2.2.2]oct-5-en-2-one (**13**)[15] furnished **14** with 32:1 endo/exo selectivity (Scheme II). Reduction with L-Selectride then gave **12** in 91% yield for the two steps. Hydroxyl-directed epoxidation[16] of **12** and Jones oxidation[17] afforded epoxy ketone **15** (74%). Following O-methylation of **15** and ozonolysis/reduction of the enol ether, the resultant epoxy keto ester **16** underwent selective ring opening upon exposure to DBU, furnishing enone alcohol **17** in 79% yield overall from **15**. Finally, hydroxyl protection gave the MEM ether **18** (67%).

Scheme II



In preliminary epoxidation experiments, extended reaction times led to the unexpected tricyclic alcohol **20a** (Scheme III). Proof of structure was secured via single-crystal X-ray analysis of the derived 3,5-dinitrobenzoate. This novel rearrangement could also be induced by exposure of **19** to *p*-toluenesulfonic acid. As illustrated in Scheme III, a plausible mechanism for the formation

Scheme III



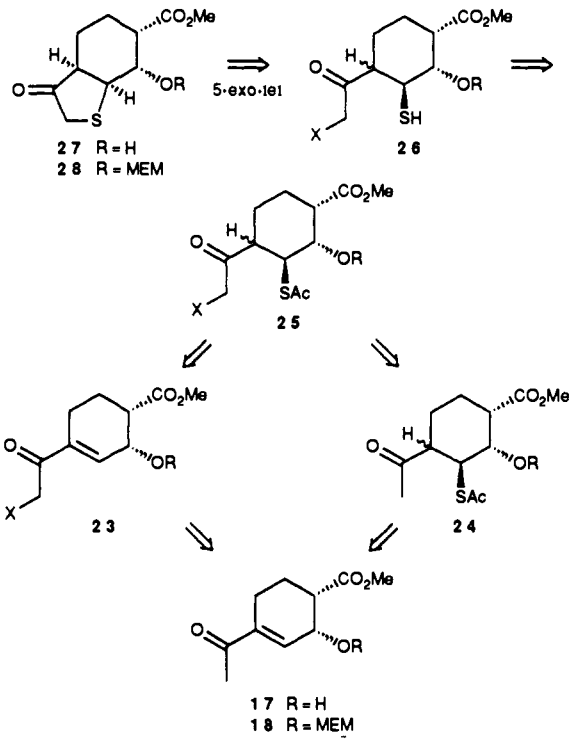
of **20a** involves initial epoxide opening with alkyl migration to give carbocation **21**. A 1,2-hydride shift would then generate **22**; cyclization of the latter would furnish **20a**. Importantly, this pathway could be suppressed by removing most of the water from the commercial aqueous solution of *tert*-butyl hydroperoxide via extraction with benzene.

Thioannulation: Generation of the Cis-Fused Perhydrobenzothiophene Ring System. Introduction of the sulfur atom and cyclization now entailed further functionalization of enone **17** or **18**. Here we envisioned two closely related approaches exploiting a favorable 5-*exo*-*tet* ring closure[18] (Scheme IV). Specifically, incorporation of sulfur either before or after installation of the leaving group (X = Br, Cl) α to the ketone would lead to in-

(11) For excellent reviews of the anomeric effect, see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: New York, 1983. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Hafner, K., Ed.; Springer-Verlag: Berlin, 1983.

(12) (a) Goering, H. L.; Relyea, D. I.; Larsen, D. W. *J. Am. Chem. Soc.* **1956**, *78*, 348. (b) Bordwell, F. G.; Hewlett, W. A. *J. Am. Chem. Soc.* **1957**, *79*, 3493. (c) LeBel, N. A.; DeBoer, A. *J. Am. Chem. Soc.* **1967**, *89*, 2784. (d) Readio, P. E.; Skell, P. S. *J. Org. Chem.* **1966**, *31*, 759. (e) Lebel, N. A.; Czaja, R. F.; DeBoer, A. *J. Org. Chem.* **1969**, *34*, 3112.

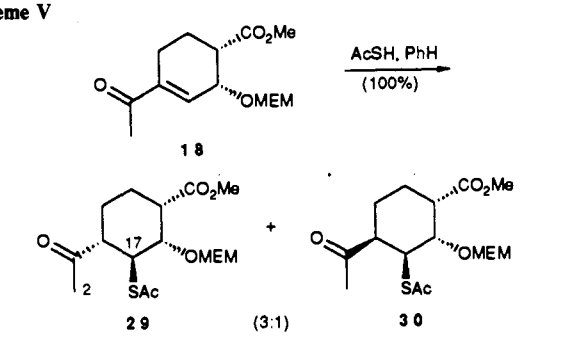
Scheme IV



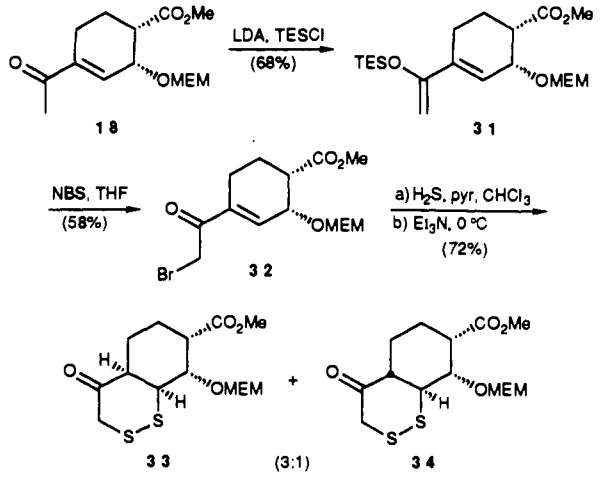
termediate **25**. After liberation of the thiol moiety, cyclization of **26** and equilibration would afford the thermodynamically preferred cis-fused ring system.

1,4-Addition of thiolacetic acid to enone **18** (Scheme V) uneventfully furnished a 3:1 mixture of **29** and **30**; both epimers embodied the requisite C(17) configuration, anticipated to arise via axial attack anti to the alkoxy and carbomethoxy groups. Subsequent incorporation of the C(2) halide proved to be problematic; we therefore elected to pursue our second alternative. Exposure of the kinetic silyl enol ether **31** to NBS effected α-bromination of ketone **18** (Scheme VI). Surprisingly, treatment

Scheme V



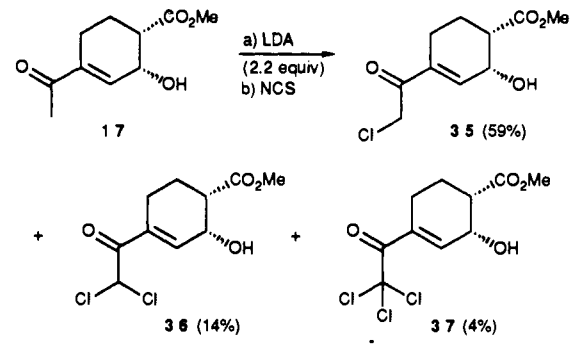
Scheme VI



of **32** with hydrogen sulfide generated disulfides **33** and **34** in good yield, whereas reaction of **32** with thiolacetic acid afforded a plethora of products.

At this juncture, we reasoned that the highly electrophilic α-bromo ketone moiety had interfered with the requisite 1,4-addition, and accordingly we sought to prepare the less reactive chloro analog (Scheme VII). NCS treatment of the dianion derived from **17** afforded chloride **35** in 59% yield, accompanied by minor

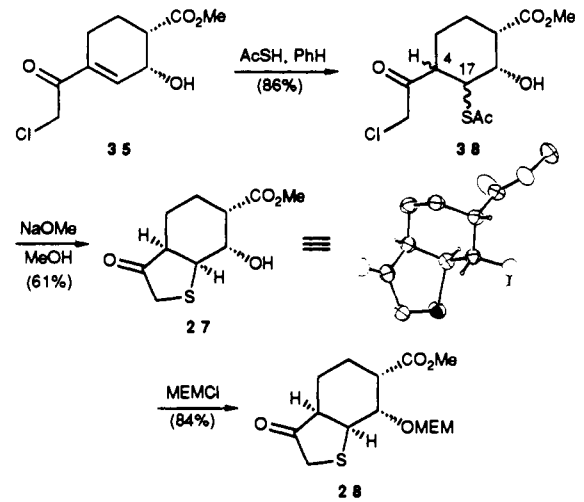
Scheme VII



amounts of the corresponding dichloro and trichloro enones **36** and **37**. Interestingly, chlorination of the MEM-protected substrate **18** was even less efficient.

1,4-Addition of thiolacetic acid to enone **35** gave thiolacetates **38** in 86% yield (Scheme VIII). Although ^{1}H NMR analysis revealed a mixture of epimers at C(4) and possibly at C(17), the major product clearly arose via attack anti to the hydroxyl as desired. Treatment of **38** with sodium methoxide then furnished **27** (61% yield); single-crystal X-ray analysis confirmed the requisite cis ring fusion. Finally, the alcohol was protected as MEM ether **28** (84%).

Scheme VIII



Installation of the C(3) α Hydroxyl: A Major Obstacle. The synthesis of **28** established four of the five contiguous stereocenters in advanced aldehyde **8**; only conversion of the C(3) carbonyl to the α carbinol remained. Given the convex character of **28**, we

(13) Confalone, P. N.; Baggiolini, E.; Hennessy, B.; Pizzolato, G.; Uskokovic, M. R. *J. Org. Chem.* **1981**, *46*, 4923.

(14) Previous preparation: Willcott, M. R., III; Davis, R. E.; Holder, R. W. *J. Org. Chem.* **1975**, *40*, 1952. In this study both **12** and its diastereomers were required; accordingly, the modest stereoselectivity of the approach was not disadvantageous.

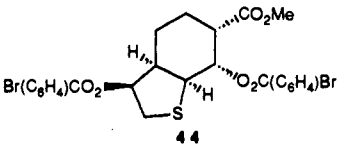
(15) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis* **1977**, 289.

(16) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(17) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

anticipated that hydride reduction would selectively provide the undesired β isomer. However, analysis of the solid-state conformation of **27** suggested that the α hydroxyl should be pseudoequatorial and, therefore, accessible via protocols affording the more stable epimer. To this end we explored numerous methods (Table I), but none provided more than minor amounts of the desired alcohol **40**. In fact, the best ratio was obtained with DIBAL, which furnished a 2.5:1 mixture of the unwanted β-alcohol **41** and the α-isomer **42** with concomitant ester reduction. Similarly, treatment of ketone **27** with $NaBH_4$ provided the corresponding diol with the undesired C(3) stereochemistry. Single-crystal X-ray analysis of the derived bis-*p*-bromobenzoate **44** not only confirmed the assigned structure but also revealed a pseudoequatorial disposition of the β hydroxyl, consistent with its predominance under both kinetic and thermodynamic control.



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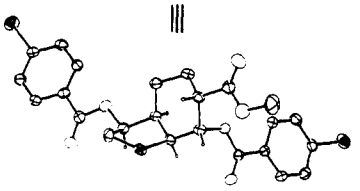
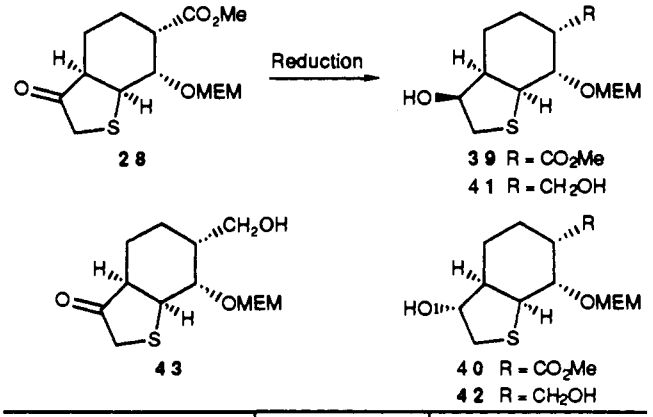


Table I. Reduction of Keto Ester **28**



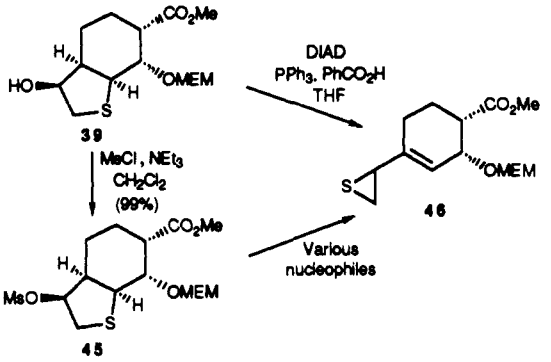
28 **39** R = CO_2Me; **41** R = CH_2OH

43 **40** R = CO_2Me; **42** R = CH_2OH

Conditions	Yield (%)	Products (Ratio)
$NaBH_4$, MeOH, -20 °C	90	**39**
$NaBH_4$, MeOH, $CeCl_3$	89	**39**
$NaBH_4$, DME, $MgCl_2$	80	**39**
$ZnBH_4$, Et_2O	83	**39**
$LiAl(O\text{-}t\text{-}Bu)_3H$	69	**39**
$Al(O\text{-}i\text{-}Pr)_3$, Acetone	62	**39** + **40** (>10:1)
LAH, THF	72	**41** + **42** (>10:1)
LAH, $AlCl_3$	63	**41** + **42** (>10:1)
$LiEt_3BH$	69	**41**
$LiBH_4$	81	**41**
REDAL	91	**41**
DIBAL, PhMe, -78 °C	78	**41** + **42** (4:1)
DIBAL, PhMe, 0 °C	94	**41** + **42** (2.5:1)
Li, NH_3, Et_2O	20 - 40	**43**

As $NaBH_4$ reduction of **28** effectively generated the undesired β alcohol **39**, an inversion of the C(3) configuration in the latter appeared to offer the obvious solution to our problem. However, neither the Mitsunobu[19] protocol nor reaction of the derived mesylate **45** with various oxygen nucleophiles led to the requisite alcohol (Scheme IX). Both approaches instead furnished a major product tentatively identified as the vinylic episulfide **46**, which presumably arose via intramolecular alkylation of sulfur followed by fragmentation of the resultant sulfonium ion.[20]

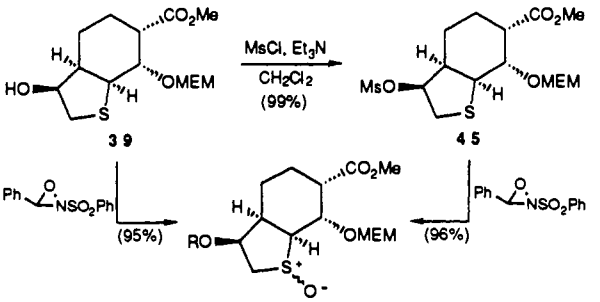
Scheme IX



39 **46** **45**

We inferred that this difficulty could be circumvented by reducing the nucleophilicity of the sulfur atom. Reversible oxidation to the sulfoxide offered an expeditious tactic, conveniently implemented via the Davis phenyl oxaziridine;[21a] in this fashion alcohol **39** and the derived mesylate **45** furnished **47** and **48**, respectively, both as mixtures of α and β sulfoxides (Scheme X). The α-sulfinyl configurations of the major isomers were established via a chemical correlation employing keto sulfoxide **49** (Scheme XI). Interestingly, the pentafluorophenyl oxaziridine[21b] afforded

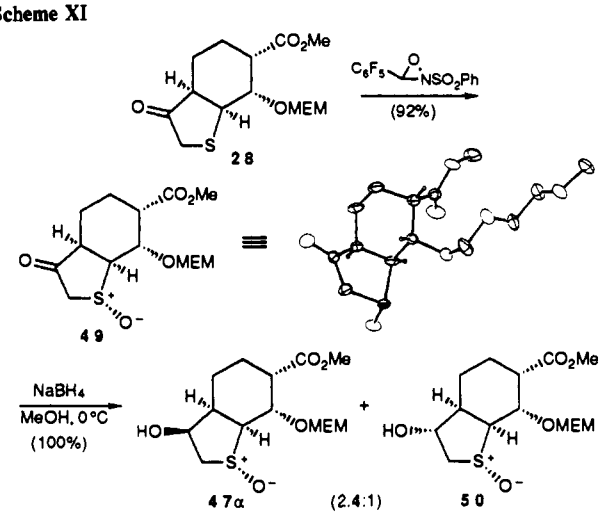
Scheme X



39 **45**

47 R = H (13:1 α/β)
48 R = Ms (10:1 α/β)

Scheme XI



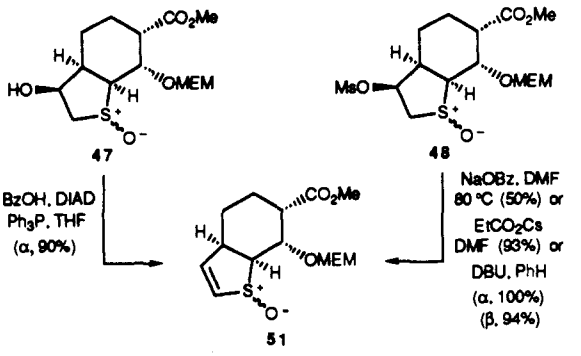
28 **49** **47α** **50**

the α sulfoxide exclusively; single-crystal X-ray analysis verified the stereochemical assignment. Sodium borohydride reduction of **49** then furnished **47α** and the α-hydroxy epimer **50** in a 2.4:1 ratio.

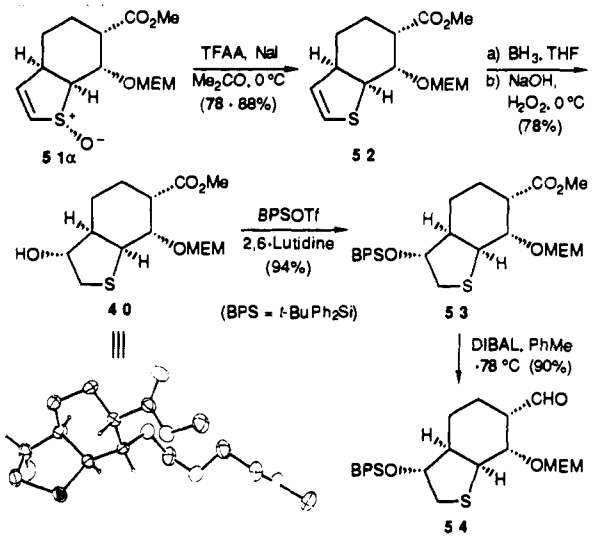
Attempted inversion of **47** and **48** furnished predominantly the vinyl sulfoxide **51** under a variety of conditions, even with nonbasic

nucleophiles such as cesium propionate (Scheme XII). This result, although unexpected, was not unproductive: after reduction[22] of **51α** to the vinyl sulfide **52** (Scheme XIII), hydroboration–oxidation, exploiting the convex topography of the substrate, efficiently generated the desired α alcohol **40**. Given the importance of this intermediate, proof of the C(3) stereochemistry was again secured by X-ray analysis. Importantly, the resultant five-step conversion of **39** to **40** (i.e., β carbinol **39** → mesylate **45** → sulfoxide **48** → alkene **51** → sulfide **52** → α alcohol **40**; Schemes X, XII, and XIII) could be achieved on a large scale in 59% overall yield. With the requisite C(3) stereochemistry intact, silylation followed by DIBAL reduction of the resultant ester (**53**) afforded advanced intermediate **54**.

Scheme XII



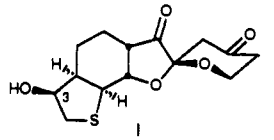
Scheme XIII



As an alternative to the C(3) hydroxyl inversion protocol described above, we explored the use of the α-sulfoxide moiety in **49** as a control element for selective reduction of the keto group. Here we envisioned that hydrogen bonding of the sulfinyl oxygen with a bulky alcohol might hinder hydride addition to the convex face of the substrate, enhancing formation of α-alcohol **50**. Unfortunately, only modest improvement was observed with alcohols such as MeOH, *t*-BuOH, and L-menthol.

(19) Mitsunobu, O. *Synthesis* **1981**, 1.

(20) Efforts to invert the C(3) hydroxyl in spiroketal i were likewise unproductive.



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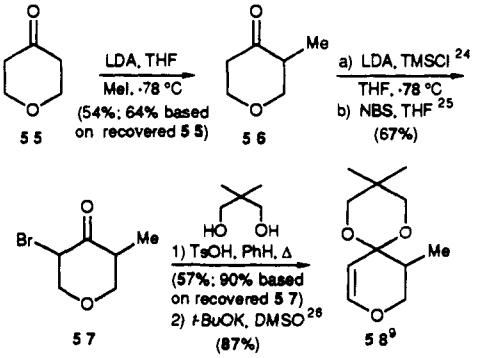
(21) (a) Davis, F. A.; Jenkins, R. H.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171. (b) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254.

(22) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404.

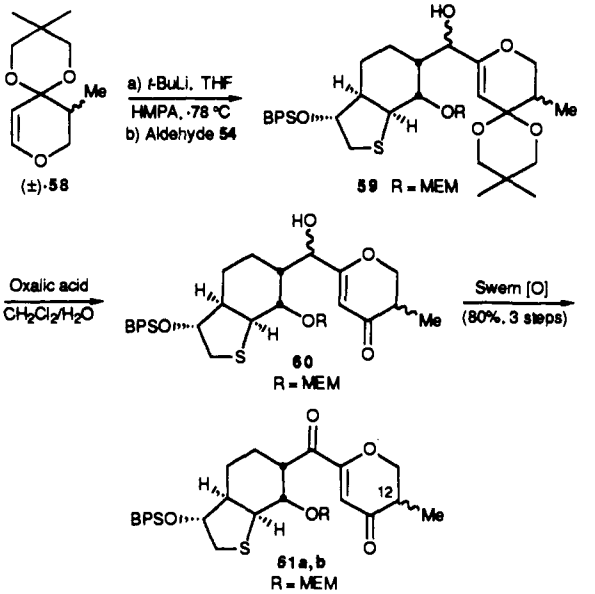
Spiroketal Formation: An Augmented Approach. We were now poised to couple aldehyde **54** with vinyl anion **9** (Scheme I), setting the stage for the spiroketalization protocol which proved highly successful in our phyllanthocin work.[23] However, as we looked ahead to the C(12) methylation of spiroketal diketone **6** and the attendant, potentially problematic issues of chemo- and regioselectivity, we became intrigued by the possibility of incorporating the methyl group prior to spiroketalization. In this scenario, our commitment to a stereochemically linear approach would necessitate the use of a racemic dihydropyran [i.e., (±)-**58**][9] for coupling with **54**, with subsequent equilibration of the C(12) stereocenter during the spiroketalization maneuver. The requisite methylated dihydropyran was readily prepared from tetrahydropyran-4-one (**55**) as outlined in Scheme XIV.

Scheme XIV



The enediones **61a,b**, substrates for the augmented spiroketalization, were generated as a 1:1 mixture of C(12) epimers via coupling of the vinyllithium derivative of **58** with aldehyde **54**, followed by deketalization and Swern oxidation[27] (Scheme XV). The overall yield for these three steps was 80%. We then executed our spiroketalization protocol, seeking to establish the C(9) and C(12) stereocenters concurrently. Indeed, upon removal of the MEM group with $ZnBr_2$ and exposure of the resultant alcohols to *p*-toluenesulfonic acid, spiroketalization with concomitant equilibration afforded the requisite diastereomer **62** in 53% yield, accompanied by three minor products (Scheme XVI).

Scheme XV



(23) For a detailed discussion of the original spiroketalization study, see ref 9.

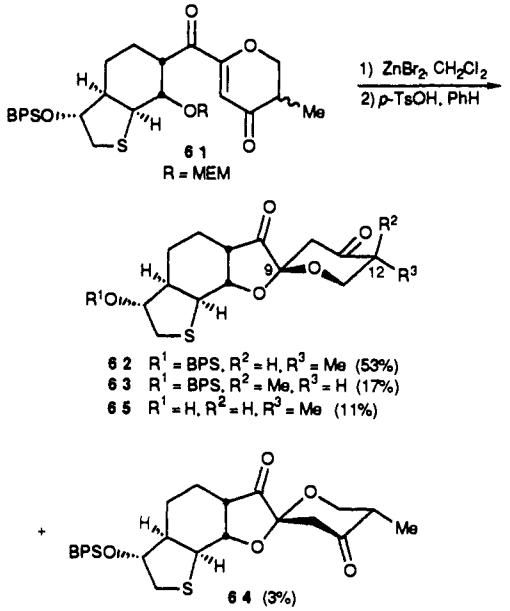
(24) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(25) (a) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, *194*. (b) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

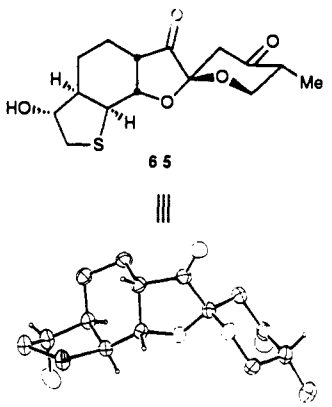
(26) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109.

(27) Mancuso, A.; Brownfain, D.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

Scheme XVI

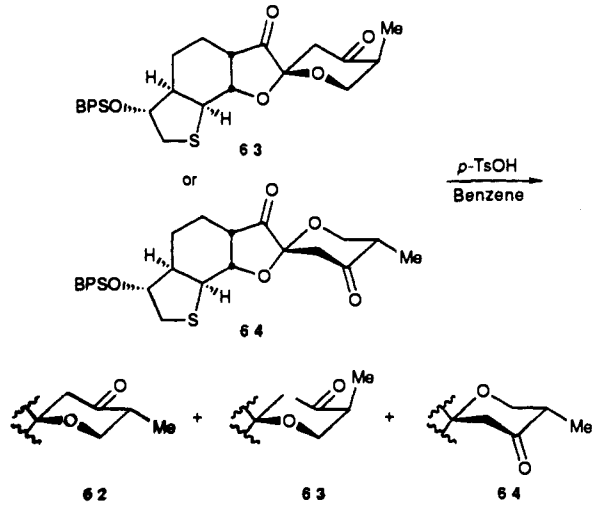


Spiroketal **63**, isolated in 17% yield, embodied the desired C(9) configuration with an axial C(12) methyl, whereas **64** (3% yield) proved to be epimeric with **62** at both C(9) and C(12). In addition, alcohol **65** was isolated in 11% yield and was readily converted



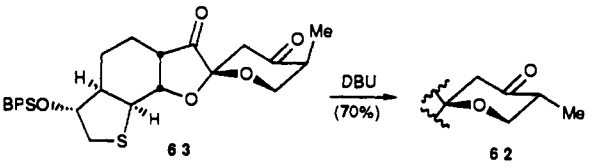
to **62** by silylation. Interestingly, the fourth possible spiroketal diastereomer was not detected. Resubmission of **63** and **64** to the reaction conditions regenerated the original ratio of **62**, **63**, and **64** in each case (Scheme XVII). Moreover, DBU treatment equilibrated the axial methyl in **63** to the more stable equatorial

Scheme XVII



orientation (Scheme XVIII). These transformations not only established that the cyclization was thermodynamically controlled

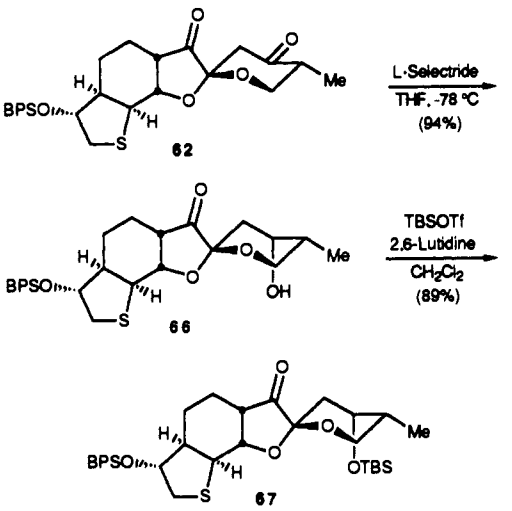
Scheme XVIII



but also converted essentially all of the material to the desired product. Initially the structures **62–64** derived from ^{1}H NMR analysis; the configuration of **62** was later confirmed via single-crystal X-ray analysis of the desilylated derivative **65**.

Generation of Enone 68 and Incorporation of the Trans Vicinal Diol Moiety. With the entire carbon framework of breynolide in hand, completion of the synthesis entailed selective reduction of the pyranone carbonyl to the corresponding axial alcohol and installation of the C(6,7) trans diol unit. The first objective was more easily realized. The C(11) pyranone ketone could be reduced chemoselectively by exploiting the sterically hindered environment of the furanone carbonyl, even though the latter was expected to be more electrophilic.[28] Thus, exposure of **62** to the bulky reducing agent L-Selectride afforded the axial alcohol **66** in 94% yield via equatorial attack[29] (Scheme XIX). Silylation then gave **67**.

Scheme XIX



Stereocontrolled introduction of the trans vicinal diol represented the final challenge. We evaluated a number of tactics, all of which involved unsaturation at C(6,7); the requisite enone **68** was readily elaborated in one step by treatment of the enolate derived from **67** with benzeneseleninyl chloride (Scheme XX).[30] Importantly, use of the latter reagent circumvented the potential problem of sulfur oxidation. We then explored a sequence involving conversion of **68** to allylic alcohol **69** and subsequent hydroboration. To this end, generation of the extended enolate of **68** with potassium bis(trimethylsilyl)amide (KHMDS) followed by hydroxylation with the Davis (+)-camphorsulfonyl oxaziridine[31] gave **69** in 81% yield. Unfortunately, attempted hydroboration–oxidation of the latter provided none of the expected diol **70**, but instead led predominantly to carbonyl reduction.

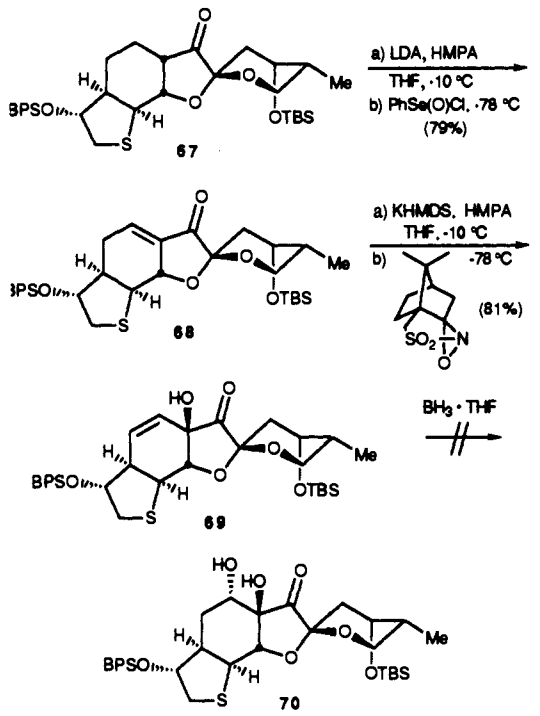
(28) In our phyllanthocin synthesis we demonstrated that the C(7) furanone carbonyl (phyllanthocin numbering) was considerably more electrophilic than the C(10) pyranone ketone; for discussion, see ref 9.

(29) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(30) (a) Ayrey, G.; Barnard, D.; Woodbridge, D. T. *J. Chem. Soc.* **1962**, 2089. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

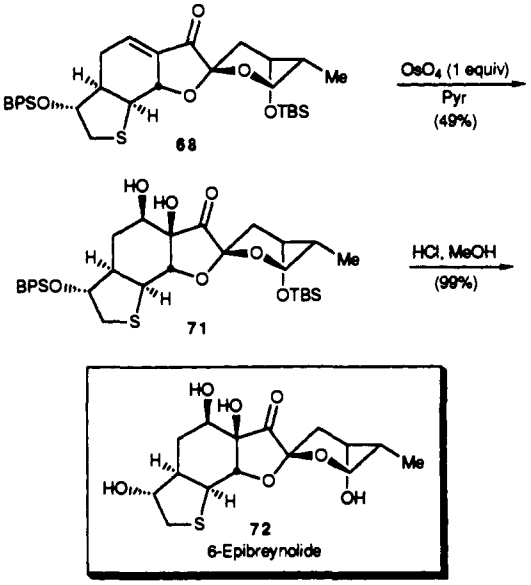
(31) Davis, F. A.; Hague, M. S. *J. Org. Chem.* **1986**, *51*, 4083.

Scheme XX



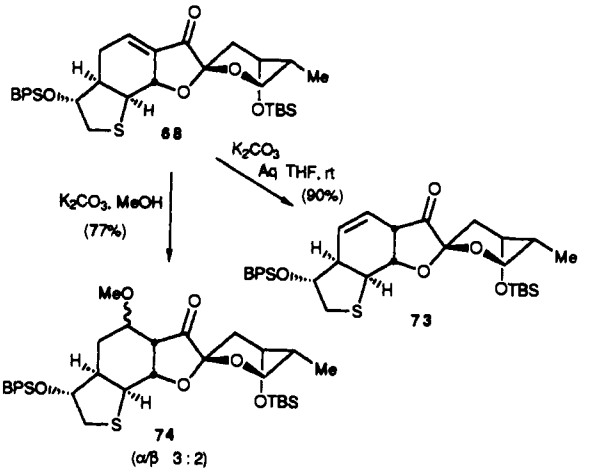
Our second approach required formation of the cis diol followed by inversion of the C(6) hydroxyl. Careful stoichiometric osmylation of **68** furnished cis diol **71** (Scheme XXI). The modest yield (ca. 50%) was not particularly surprising, as osmium tetraoxide readily oxidizes sulfide moieties. Desilylation with acidic methanol then afforded 6-epibreynolide (**72**) in 99% yield. However, we could not convert the C(6) β hydroxyl to the requisite α epimer; numerous approaches including retroaldol/aldol equilibration, oxidation/reduction, and Mitsunobu inversion[19] were explored to no avail.

Scheme XXI



At this juncture we fortuitously discovered that exposure of enone **68** to aqueous K_2CO_3 at room temperature induced facile isomerization to the β,γ isomer **73** (90% yield; Scheme XXII). This striking result was recognized as a manifestation of the strained architecture of the conjugated enone; the latter insight in turn suggested that **68** might also be susceptible to 1,4-addition of an oxygen nucleophile. This expectation was readily realized, as reaction with K_2CO_3 in methanol generated a 3:2 mixture of α and β adducts **74**α and **74**β. We envisioned that extension of

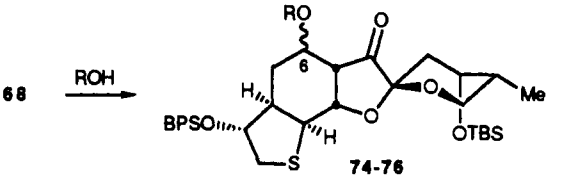
Scheme XXII



this process to a suitable alcohol could lead to successful introduction of the trans diol moiety.

Final Elaboration of (±)-Breynolide. To adapt the above conjugate addition to the introduction of a hydroxyl group, we examined a variety of alcohols whose ether adducts would be amenable to unmasking under mild conditions, in conjunction with several base catalysts (Table II). Strong bases (e.g., NaH) led to little or no 1,4-addition, but instead gave β,γ enone **73**. Sterically hindered alcohols reacted sluggishly, but the primary alcohols we investigated all added readily. Of the base catalysts studied, cesium carbonate proved most satisfactory in terms of yield and diastereoselectivity.

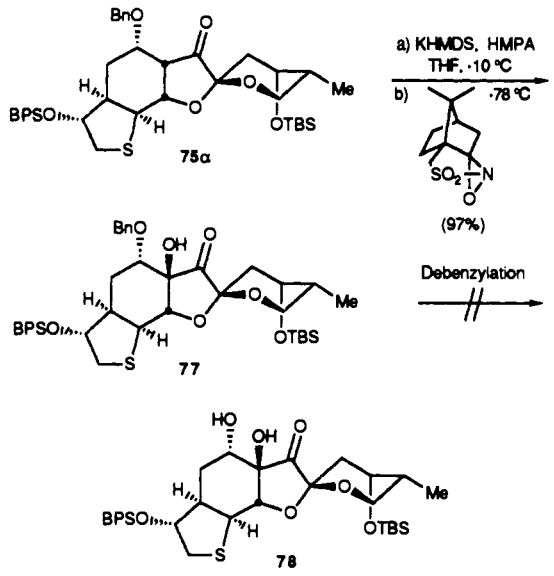
Table II. Conjugate Additions of ROH to Enone **68**



Nucleophile	Conditions	Yield (%)	α/β Ratio	Product
MeOH	K_2CO_3, 0 °C	77	3:2	**74**
Me_3SiOK	THF, 0 °C	< 10	–	
BnOH	NaH, RT	10	–	
BnOH	12 kbar	60	1:6	**75**
BnOH	K_2CO_3, rt	50	5:3	**75**
BnOH	K_2CO_3, 0 °C	80	2:3	**75**
BnOH	Cs_2CO_3, 0 °C	60	3:2	**75**
t-BuMe$_2$SiOH	Cs_2CO_3, 0 °C→rt	0	–	
t-BuOH	Cs_2CO_3, 0 °C→rt	0	–	
Allyl alcohol	Cs_2CO_3, 0 °C	80	3:1	**76**

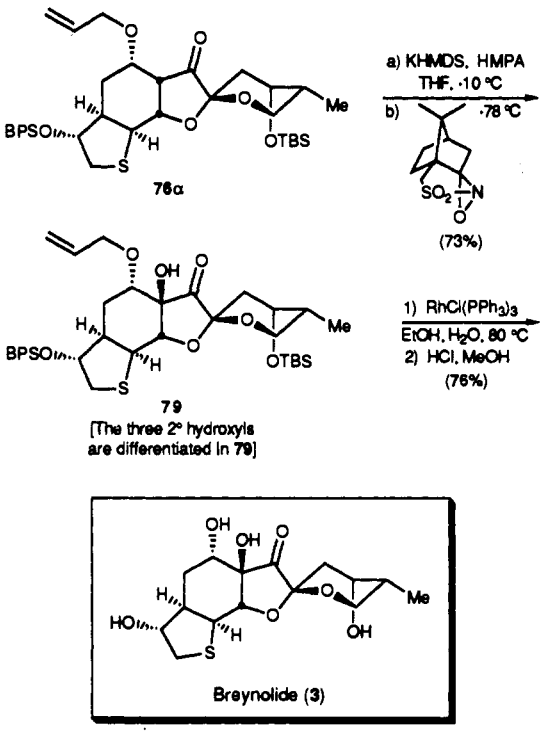
These encouraging observations notwithstanding, completion of the synthesis would still entail hydroxylation at C(7) as well as deprotection at C(6). Enolate hydroxylation appeared to comprise a direct and plausible approach to the former problem, as the strain in enone **68** was expected to reduce the propensity for a C(7) enolate to expel a C(6) alkoxy group. Indeed, oxidation of the enolate derived from benzyl alcohol adduct **75**α with the Davis (+)-camphorsulfonyl oxaziridine[31] furnished **77** in 97% yield (Scheme XXIII); β-elimination of the C(6) benzyloxy substituent occurred only upon warming the enolate solution to ambient temperature. Our excitement was short-lived, however, as we were unable to remove the benzyl protecting group. Numerous debenzylation protocols including hydrogenation with various catalysts, treatment with Lewis acids, and dissolving metal reductions invariably led to either recovery or destruction of the starting material.

Scheme XXIII



After exhausting these possibilities, we searched for an alternative oxygen nucleophile; ultimately, allyl alcohol proved successful. Cesium carbonate-promoted 1,4-addition of allyl alcohol to enone **68** furnished a 3:1 mixture of α and β adducts in 80% yield (Table II). Hydroxylation of the α epimer **76** at C(7) as before then gave the allyl-protected trans diol **79** (Scheme XXIV). Deallylation via Gigg's modification[32a] of the Corey method[32b] employed tris(triphenylphosphine)rhodium chloride to isomerize the allyl ether to the corresponding enol ether. Finally, vinyl ether hydrolysis and concomitant desilylation with aqueous HCl in methanol afforded synthetic (±)-breynolide, spectroscopically and chromatographically indistinguishable from a sample of (+)-**3** kindly provided by Professor Williams.[33]

Scheme XXIV



In summary, a reasonably concise, stereochemically linear total synthesis of breynolide has been achieved. Importantly, the three secondary hydroxyl groups in penultimate intermediate **79** are differentially protected; this substance therefore holds considerable promise as a precursor to the biologically active glycosides. Progress toward the total synthesis of the breynins will be reported in due course.

Experimental Section[34]

Alcohol 12. A solution of diisopropylamine (6.00 mL, 42.6 mmol) in THF (120 mL) was cooled to 0 °C and treated with *n*-BuLi (2.28 M in hexanes, 17.3 mL, 39.4 mmol). The solution was stirred at 0 °C for 30 min, and then a solution of **13**[15] (4.0 g, 32.8 mmol) in THF (70 mL) was added dropwise over 5 min. After 35 min the reaction was cooled to −78 °C. Methyl iodide (10.2 mL, 164 mmol) was added in one portion and the mixture warmed to 0 °C. After 2 h the reaction was quenched with aqueous NH_4Cl (25 mL), and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. GC analysis of the crude product showed a 32:1 endo/exo ratio. This material was normally used without purification. Flash chromatography with 10% Et_2O/pentane as eluant and removal of the solvent by distillation gave **14** (1.74 g, 40% yield) as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 6.41 (dd, J = 8.1, 0.6 Hz, 1 H), 6.14 (dd, J = 8.0, 1.6 Hz, 1 H), 3.11 (m, 1 H), 2.79 (m, 1 H), 2.1–2.4 (m, 5 H), 1.06 (d, J = 7.2 Hz, 3 H).

In a second experiment, the crude methylated ketone was dissolved in dry THF (100 mL) and the solution was cooled to −78 °C and treated with L-Selectride (1.0 M in THF, 42.6 mL). The reaction was warmed to 0 °C and monitored by TLC. After 2.5 h, the reaction was quenched with 10% NaOH (50 mL) followed by 30% aqueous H_2O_2 (30 mL) and the mixture warmed to ambient temperature. After 16 h, aqueous $NaHSO_3$ (50 mL) was added and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were concentrated in vacuo. Flash chromatography with 25% Et_2O/pentane as eluant furnished **12**[15] (4.1 g, 91% yield) as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 6.41 (apparent t, J = 7.7 Hz, 1 H), 6.12 (apparent t, J = 7.8 Hz, 1 H), 3.91 (m, 1 H), 2.76 (m, 1 H), 2.32 (m, 1 H), 1.94 (m, 1 H), 1.47–1.13 (m, 5 H), 0.87 (d, J = 7.4 Hz, 3 H).

Epoxide 19. A warmed solution (ca. 60 °C) of alcohol **12** (1.30 g, 9.42 mmol) and $Mo(CO)_6$ (150 mg, 0.57 mmol) in benzene (150 mL) was treated with 90% *tert*-butyl hydroperoxide (TBHP) (prepared by ex-

(32) (a) Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 277. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

(33) We thank Professor David R. Willams (University of Indiana) for a generous sample of (+)-breynolide.

(34) Materials and methods: All reactions were carried out under an argon atmosphere with solvents freshly distilled under argon and glassware flame-dried under vacuum, unless otherwise stated. Diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were distilled from sodium/benzophenone. Benzene was distilled from sodium. Dichloromethane was distilled from calcium hydride. Diisopropylamine, hexamethyldisilazane, triethylamine, *N,N*-diisopropylethylamine, and pyridine were distilled from calcium hydride and stored over KOH. Dimethyl sulfoxide and hexamethylphosphoramide were distilled from calcium hydride and stored over 4-Å molecular sieves. *n*-Butyllithium was standardized by titration with diphenylacetic acid or menthol/triphenylmethane. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck 0.25-mm precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise. Gas–liquid chromatography (GLC) analyses were performed with a Hewlett-Packard 5790A chromatograph equipped with a 25-m × 0.2-mm × 0.33-μm Hewlett-Packard Ultra 1 (cross-linked methyl silicone) column. Chromatograms were recorded with an HP 3390A integrator. High-performance liquid chromatography (HPLC) was performed with a Rainin or Waters system. The Waters analytical chromatograph was fitted with a Model 6000A solvent delivery system, a U6K injector, an R-400 refractive index detector or Model 440 absorbance detector, and a 4.6-mm × 25-cm column packed with 5-μ Ultrasphere-Si. The Rainin HPLC system was equipped with a Dynamax method manager, a Rabbit MPX solvent delivery system, a Rheodyne injector, and a Gilson Model 131 refractive index detector or Gilson Model 115 variable-wavelength UV detector. Columns measured 4.0, 10.0, or 25.0 mm × 25 cm with 8-μm, 60-Å normal-phase packing. Chromatographs were recorded with an HP 3390A integrator. Melting points were obtained on a Thomas-Hoover apparatus and were corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. ^1H NMR spectra were recorded on a Bruker WP-250 or AM-250 (250 MHz) or AM-500 (500 MHz) spectrometer; ^{13}C NMR spectra were recorded on a Bruker WH-250 or AM-500 instrument. ^1H and ^{13}C chemical shifts are reported as δ values relative to tetramethylsilane. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center with a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Labs, Madison, NJ.

tracting 70% TBHP with benzene; 1.44 mL, 10.4 mmol; for 70% TBHP: 7.2 mmol/mL).[35] The vigorously stirred reaction mixture was heated at reflux for 6 h, then cooled, quenched with 20% aqueous $Na_2S_2O_5$ solution, and extracted with diethyl ether (3 × 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 40% diethyl ether/pentane as eluant gave **19** (1.18 g, 81% yield) as a white semisolid: IR ($CHCl_3$) 3540 (m, br), 3010 (m), 2950 (s), 2882 (m), 1418 (m), 1115 (m), 1058 (s), 1048 (m), 918 (m), 837 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (dd, J = 3.2, 10.0 Hz, 1 H), 3.35 (apparent t, J = 4.7 Hz, 1 H), 3.29 (apparent t, J = 4.7 Hz, 1 H), 3.03 (br s, 1 H), 2.38 (d, J = 3.4 Hz, 1 H), 2.00 (d, J = 1.9 Hz, 1 H), 1.90–1.83 (m, 1 H), 1.63–1.54 (m, 1 H), 1.51–1.43 (m, 3 H), 1.02 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.4, 54.3, 52.5, 37.1, 35.0, 34.5, 23.6, 19.8, 13.7; high-resolution mass spectrum (CI, NH_3) m/z 155.1063 [$(M + H)^+$; calcd for $C_9H_{14}O_2$: 155.1072].

Ketone 15 via Oxidation of Alcohol 19. A solution of alcohol **19** (1.37 g, 8.9 mmol) in acetone (25 mL) was cooled to 0 °C, and Jones reagent [2.2 M CrO_3 in H_2SO_4(aq), 4.8 mL, 10.6 mmol] was added dropwise with vigorous stirring. The reaction was then quenched with 2-propanol. Solid $NaHCO_3$ was added until the pH reached 6.0, and the mixture was stirred vigorously at ambient temperature to break up solid chromium salts. The reaction mixture was then filtered through Florisil and the precipitate washed with acetone (ca. 75 mL). Following addition of 10% aqueous $NaHCO_3$ (50 mL), the acetone was evaporated in vacuo. Extraction with methylene chloride (3 × 50 mL), drying over $MgSO_4$, filtration, and concentration in vacuo furnished **15** (1.25 g, 92% yield) as an oil: IR ($CHCl_3$) 3018 (m), 2945 (s), 2884 (m), 1733 (s), 1220 (br, w), 1109 (m), 948 (m), 858 (m), 840 (m), 823 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.49–3.44 (m, 2 H), 2.87–2.85 (m, 1 H), 2.44 (dd, J = 2.4, 4.5 Hz, 1 H), 1.95 (qd, J = 1.9, 7.1 Hz, 1 H), 1.86–1.71 (m, 4 H), 1.14 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 52.1, 50.5, 46.4, 44.8, 34.9, 22.8, 18.8, 13.8; high-resolution mass spectrum (CI, NH_3) m/z 170.1167 [$(M + NH_4)^+$; calcd for $C_9H_{16}NO_2$: 170.1181].

Tricyclic Alcohol 20a. To a warmed solution of the homoallylic alcohol **12** (1.30 g, 9.42 mmol) and catalytic $Mo(CO)_6$ (150 mg, 0.57 mmol) in freshly distilled, dry benzene (150 mL) was added 70% *tert*-butyl hydroperoxide (1.44 mL, 1.1 equiv, 10.4 mmol; for 70% TBHP: 7.2 mmol/mL). The reaction mixture was stirred vigorously and heated to reflux for 6 h, then quenched with 20% aqueous $Na_2S_2O_5$, and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine, then dried with Na_2SO_4, and concentrated in vacuo. The residual oil was purified by flash chromatography using diethyl ether/pentane (4:6) as eluant to yield 870 mg (60%) of **20a** as a white semisolid: IR ($CHCl_3$) 3580 (w), 3440 (br, w), 3018 (m), 2970 (s), 2890 (m), 1452 (m), 1386 (m), 1132 (m), 1115 (m), 1065 (s), 1034 (w), 1009 (s), 980 (w), 907 (m), 817 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (apparent t, J = 6.1 Hz, 1 H), 3.24 (s, 1 H), 2.36–2.32 (m, 1 H), 2.11–2.05 (m, 2 H), 1.96–1.89 (m, 1 H), 1.80–1.56 (m, 4 H), 1.38 (s, 3 H), 1.02 (dd, J = 2.72, 12.79 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 85.2, 52.1, 41.1, 40.5, 28.0, 26.2, 15.6; high-resolution mass spectrum (CI, NH_3) m/z 172.1315 [$(M + NH_4)^+$; calcd for $C_9H_{18}NO_2$: 172.1337].

Benzoate Ester 20b. To a solution of tricyclic alcohol **20a** (500 mg, 3.25 mmol) in CH_2Cl_2 (2 mL) were added 3,5-dinitrobenzoic acid (700 mg, 1.02 equiv, 3.3 mmol), dicyclohexylcarbodiimide (700 mg, 1.02 equiv, 3.3 mmol), and a catalytic amount of DMAP (50 mg). The reaction mixture was stirred at room temperature for 30 min, after which time the resultant white precipitate (dicyclohexylurea) was filtered from the reaction mixture. The solid was washed with Et_2O (3 × 10 mL), and the combined organic layers were concentrated in vacuo to furnish a solid, which upon recrystallization from acetonitrile gave **20b** as a white solid (962 mg, 85%): mp 153–155 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.25–9.17 (m, 3 H), 4.80–4.74 (m, 2 H), 2.54–2.37 (m, 2 H), 2.04–1.50 (m, 9 H), 1.47 (s, 3 H), 1.44–1.02 (m, 3 H).

Hydroxy Enone 17. A suspension of KH (35% oil dispersion, 8.3 g, 2.0 equiv) in DME (75 mL) was cooled to 0 °C, and a solution of 18-crown-6 (4.0 g, 15.1 mmol) and epoxy ketone **15** (5.50 g, 36.2 mmol) in DME (35 mL) was added. The reaction mixture was stirred at 0 °C for 20 min and then at room temperature until hydrogen evolution ceased. The solution was warmed to 50 °C, and dimethyl sulfate (5.1 mL, 1.5 equiv) was added slowly with continued stirring. The reaction mixture was stirred for 30 min further at 50 °C, cooled to 0 °C, carefully quenched with saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 100 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo to a volume of ca. 20 mL. The resultant oil was dissolved in a mixture of MeOH and CH_2Cl_2 (1:1, 480 mL). The solution was cooled to −78 °C and treated with ozone until a blue color persisted. Dimethyl sulfide (ca. 30 mL) was added and the mixture allowed to warm to ambient temperature. After introduction of DBU (ca. 0.5 mL), the solution was stirred overnight and then concentrated in vacuo; high vacuum was employed to remove the DMSO. Flash chromatography with 45% EtOAc/hexanes as eluant afforded **17** (5.68 g, 79% yield) as an oil: IR ($CHCl_3$) 3600–3300 (m), 3010 (m), 2950 (m), 2880 (m), 2840 (w), 1740–1720 (s), 1675 (s), 1440 (m), 1380 (m), 1350 (m), 1300 (m), 1240 (s), 1160 (m), 1110 (m), 1065 (m), 1040 (m), 1015 (m), 995 (m), 960 (m), 940 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.00 (m, 2 H), 2.10–2.30 (m, 1 H), 2.32 (s, 3 H), 2.36–2.61 (m, 1 H), 2.73 (m, 1 H), 3.42 (d, J = 7.1 Hz, 1 H), 3.76 (s, 3 H), 4.64 (m, 1 H), 6.84 (dd, J = 3.9, 1.7 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 216.1252 [$(M + NH_4)^+$; calcd for $C_{10}H_{18}NO_4$: 216.1236].

MEM Ether 18. At ambient temperature, a solution of alcohol **17** (1.61 g, 8.13 mmol) in CH_2Cl_2 (5 mL) was treated with diisopropylethylamine (4.2 mL, 2.0 equiv) and MEM chloride (2.03 g, 16.2 mmol, 2 equiv). The reaction mixture was stirred for 24 h and then quenched with saturated $NaHCO_3$ solution. The resultant mixture was extracted with Et_2O (3 × 75 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 55% Et_2O/pentane as eluant gave **18** (1.53 g, 67% yield) as an oil: IR ($CHCl_3$) 3010 (m), 2950 (m), 2890 (m), 1740 (s), 1675 (s), 1650 (w), 1450 (m), 1430 (m), 1355 (m), 1300 (m), 1250 (s), 1220 (s), 1170 (m), 1100 (m), 1050 (s), 930 (m), 910 (m), 850 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.86 (m, 1 H), 2.07 (m, 2 H), 2.37 (s, 3 H), 2.61 (m, 2 H), 3.41 (s, 3 H), 3.58 (m, 3 H), 3.72 (s, 3 H), 3.82 (m, 1 H), 4.58 (apparent t, J = 4.7 Hz, 1 H), 4.71 (AB q, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 14.4 Hz, 2 H), 6.96 (d, J = 5.0 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 304.1779 [$(M + NH_4)^+$; calcd for $C_{14}H_{26}NO_6$: 304.1760].

Thiolacetates 29 and 30. A solution of enone **18** (35 mg, 0.13 mmol) in benzene (2 mL) was treated with thiolacetic acid (ca. 0.25 mL) and the mixture stirred at room temperature for 13 h. Following concentration in vacuo, three 15-mL portions of benzene were added and evaporated. Flash chromatography with 30% EtOAc/hexanes as eluant furnished cis adduct **30** (11 mg, 24% yield) (R_f 0.51, 50% EtOAc/hexanes, 2 elutions) and trans adduct **29** (34 mg, 76%) (R_f 0.44), both as oils.

30: IR ($CHCl_3$) 3010 (m), 2960 (s), 2890 (m), 1740 (s), 1719 (s), 1455 (m), 1440 (m), 1360 (m), 1315 (m), 1280 (m), 1240 (m), 1030 (s), 960 (m), 850 (m), 635 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20–1.42 (m, 2 H), 1.70–1.98 (m, 2 H), 2.12 (s, 3 H), 2.62 (br d, J = 11.4 Hz, 1 H), 3.13 (dt, J = 12.4, 3.4 Hz, 1 H), 3.41 (s, 3 H), 3.62 (m, 2 H), 3.68 (s, 3 H), 3.70–3.86 (m, 2 H), 4.18 (apparent t, J = 3.1 Hz, 1 H), 4.48 (m, 1 H), 4.89 (AB q, J_{AB} = 6.9 Hz, $\Delta\nu_{AB}$ = 6.9 Hz, 2 H); high resolution mass spectrum (CI, NH_3) m/z 287.0956 [$(M - C_3H_7O)^+$; calcd for $C_{16}H_{26}O_7S$: 287.0953].

29: IR ($CHCl_3$) 3020 (m), 3010 (m), 2950 (m), 1735 (s), 1710 (s), 1435 (m), 1355 (m), 1235 (m), 1170 (s), 1025 (s), 950 (m), 620 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.52 (m, 1 H), 1.73 (m, 1 H), 2.04 (m, 1 H), 2.18 (m, 1 H), 2.25 (s, 3 H), 2.34 (s, 3 H), 2.52 (br q, J = 6.4 Hz, 1 H), 2.79 (dt, J = 9.5, 5.4 Hz, 1 H), 3.37 (s, 3 H), 3.55 (m, 2 H), 3.60–3.72 (m, 2 H), 3.70 (s, 3 H), 4.06 (dd, J = 5.4, 3.3 Hz, 1 H), 4.59 (apparent t, J = 5.4 Hz, 1 H), 5.72 (AB q, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 34.3 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 380.1783 [$(M + NH_4)^+$; calcd for $C_{16}H_{30}NO_7S$: 380.1743].

Silyl Enol Ether 31. A solution of diisopropylamine (109 mg, 150 μL, 1.1 equiv) in THF (2 mL) was cooled to 0 °C and treated with *n*-BuLi (1.23 M in hexanes, 0.79 mL, 1.0 equiv). The solution was stirred for 30 min at 0 °C and then cooled to −78 °C. A solution of **18** (280 mg, 0.979 mmol) in THF (5 mL) was added and the reaction mixture stirred at −78 °C for 1 h. Following introduction of triethylsilyl chloride and triethylamine (1:1, 0.5 mL, excess), the reaction was warmed to ambient temperature and quenched with saturated $NaHCO_3$ solution. The resultant mixture was extracted with Et_2O (3 × 30 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 20% → 50% EtOAc/hexanes as eluant afforded **31** (113 mg, 29% yield) as an oil (R_f 0.58, 50% EtOAc/hexanes) and unreacted **18** (161 mg, 58% yield) (R_f 0.2). The yield of **31** corrected for recovered starting material was 68%. **31**: IR ($CHCl_3$) 3000 (m), 2960 (s), 2880 (s), 1740 (s), 1660 (w), 1630 (w), 1600 (m), 1450 (m), 1435 (m), 1410 (m), 1370 (m), 1310 (s), 1230 (s), 1170 (m), 1090 (m), 1030 (s), 900 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.72 (q, J = 6.4 Hz, 6 H), 1.01 (t, J = 6.4 Hz, 9 H), 1.91–2.18 (m, 3 H), 2.42 (m, 1 H), 2.58 (dt, J = 11.7, 4.0 Hz, 1 H), 3.41 (s, 3 H), 3.57 (m, 2 H), 3.68 (m, 2 H), 3.73 (s, 3 H), 4.33 (d, J = 1.3 Hz, 1 H), 4.50 (d, J = 1.3 Hz, 1 H), 4.55 (apparent t, J = 5.3 Hz, 1 H), 4.77 (AB q, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, 2 H), 6.40 (d, J = 5.3 Hz, 1 H);

(35) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

high-resolution mass spectrum (CI, NH_3) m/z 401.2336 [$(M + H)^+$; calcd for $C_{20}H_{37}O_6Si$: 401.2359].

α-Bromo Ketone 32. A solution of silyl enol ether **31** (33 mg, 0.083 mmol) in THF (1 mL) was cooled to 0 °C, and NBS (15 mg, 1.0 equiv) was added. The reaction was complete upon mixing as determined by TLC analysis. After concentration in vacuo, the product was purified by flash chromatography with 30% EtOAc/hexanes as eluant, affording **32** (17 mg, 56% yield) as an unstable oil: IR ($CHCl_3$) 3005 (m), 2929 (s), 2880 (m), 1740 (s), 1690 (m), 1670 (m), 1450 (m), 1435 (m), 1300 (m), 1240 (m), 1160 (m), 1090 (m), 1040 (s), 845 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.78 (m, 1 H), 2.10 (m, 2 H), 2.62 (m, 2 H), 3.43 (s, 3 H), 3.45–3.70 (m, 3 H), 3.74 (s, 3 H), 3.89 (m, 1 H), 4.32 (s, 2 H), 4.55 (apparent t, J = 4.6 Hz, 1 H), 4.81 (AB q, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 26.0 Hz, 2 H), 7.06 (d, J = 4.7 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 382.0921 [$(M + NH_4)^+$; calcd for $C_{14}H_{25}NO_6Br$: 382.0865].

Disulfides 33 and 34. A solution of α-bromo ketone **32** (20 mg, 0.086 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (5 mL) was cooled to 0 °C. H_2S was bubbled through the solution until TLC analysis indicated complete disappearance of **32**. Triethylamine (0.2 mL) was then added and the reaction mixture stirred for an additional 1 h. Concentration in vacuo and flash chromatography with 40% EtOAc/hexanes as eluant furnished **33** (16 mg, 54% yield) (R_f 0.39, 50% EtOAc/hexanes) and **34** (5.5 mg, 18% yield) (R_f 0.20) as oils.

33: IR ($CHCl_3$) 3020 (m), 3005 (m), 2950 (m), 2890 (m), 1730 (s), 1705 (s), 1450 (m), 1440 (m), 1390 (m), 1350 (m), 1240 (m), 1170 (s), 1100 (m), 1035 (s), 845 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.68 (m, 1 H), 1.88 (m, 1 H), 2.00–2.25 (m, 2 H), 2.96 (m, 1 H), 3.19 (m, 1 H), 3.40 (s, 3 H), 3.54–3.72 (m, 2 H), 3.57 (d, superimposed on m, J = 5.1 Hz, 2 H), 3.72–3.80 (m, 2 H), 3.73 (s, superimposed on m, 3 H), 4.30 (dd, J = 6.4, 3.9 Hz, 1 H), 4.42 (dd, J = 6.4, 3.9 Hz, 1 H), 4.79 (s, 2 H); high resolution mass spectrum (CI, NH_3) m/z 244.0248 [$(M - C_4H_{10}O_3)^+$; calcd for $C_{10}H_{12}O_3S_2$: 244.0252].

34: IR ($CHCl_3$) 3005 (m), 2950 (m), 2929 (m), 2890 (m), 1730 (s), 1700 (s), 1450 (m), 1440 (m), 1170 (m), 1105 (m), 1035 (s), 850 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.60–1.80 (m, 2 H), 1.91–2.12 (m, 2 H), 2.54 (dt, J = 2.8, 11.0 Hz, 1 H), 3.23 (m, 1 H), 3.30 (d, J = 12.9 Hz, 2 H), 3.41 (s, 3 H), 3.62 (m, 2 H), 3.68–3.88 (m, 3 H), 3.71 (s, superimposed on m, 3 H), 4.38 (apparent t, J = 11.0 Hz, 1 H), 4.81 (AB q, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 31.7 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 350.0820 (M^+; calcd for $C_{14}H_{22}O_6S_2$: 350.0858).

α-Chloro Ketone 35. A solution of diisopropylamine (1.27 g, 1.76 mL, 2.4 equiv) in THF (110 mL) was cooled to 0 °C and treated with *n*-BuLi (2.29 M in hexanes, 5.0 mL, 2.2 equiv). The solution was stirred at 0 °C for 20 min and then cooled to −78 °C. A solution of hydroxy enone **17** (1.04 g, 5.25 mmol) in THF (ca. 10 mL) was added slowly via a cannula. After 2 h at −78 °C, the rust-colored dianion was treated with a solution of NCS (1.40 g, 2.0 equiv) in THF (35 mL). The NCS solution was added as rapidly as possible without allowing the bath temperature to rise above −78 °C. The reaction mixture was stirred for 30 min further and then quenched with saturated NH_4Cl solution. After concentration in vacuo to a volume of ca. 40 mL, the mixture was extracted with Et_2O (3 × 60 mL) and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 43% EtOAc/hexanes as eluant gave trichloride **37** (67 mg, 4% yield) as an oil (R_f 0.60, 50% EtOAc/hexanes), dichloride **36** (197 mg, 14%) as an oil (R_f 0.50), α-chloro enone **35** (714 mg, 59%) as a solid (R_f 0.37), and unreacted **17** (218 mg, 21%). The yield of **35** corrected for recovered starting material was 74%.

35: mp 70 °C; IR ($CHCl_3$) 3600–3300 (m), 3010 (m), 2950 (m), 1730–1690 (s), 1635 (w), 1440 (m), 1230 (s), 1065 (m), 1020 (m), 900 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.93–2.08 (m, 2 H), 2.23 (m, 1 H), 2.45 (dt, J = 18.5, 4.1 Hz, 1 H), 2.78 (m, 1 H), 3.46 (d, J = 7.4 Hz, 1 H), 3.76 (s, 3 H), 4.47 (AB q, J_{AB} = 14.6 Hz, $\Delta\nu_{AB}$ = 10.3 Hz, 2 H), 4.63 (br m, 1 H), 6.82 (m, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 250.0857 [$(M + NH_4)^+$; calcd for $C_{10}ClH_{17}NO_4$: 250.0846].

Anal. Calcd for $C_{10}ClH_{13}O_4$: C, 51.62; H, 5.63. Found: C, 51.79; H, 5.57.

Cis-Fused Perhydrobenzothiophene 27. A solution of α-chloro enone **35** (1.0 g, 4.3 mmol) in benzene (8 mL) was treated with thiolacetic acid (5 mL, excess), and the reaction mixture was stirred at room temperature, exposed to air, for 5 h. After concentration in vacuo, several portions of benzene were added and evaporated. Flash chromatography with 30% EtOAc/hexanes as eluant provided a mixture of diastereomeric thiolacetates **38** (1.12 g, 84% yield). A solution of the latter material in MeOH (130 mL) was cooled to 0 °C. Following the addition of NaOMe (392 mg, 2.0 equiv), the solution was allowed to warm to ambient temperature and stirred for 4 h. The reaction mixture was then quenched with saturated NH_4Cl solution, concentrated in vacuo to a volume of ca. 15 mL, and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 35% EtOAc/hexanes as eluant furnished **27** (493 mg, 50% yield for 2 steps) as a white crystalline solid: mp 91 °C; IR ($CHCl_3$) 3600–3400 (w), 3010 (m), 2950 (m), 2920 (m), 2850 (m), 1735 (s), 1440 (m), 1230 (m), 1195 (m), 1170 (m), 1060 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.58 (m, 1 H), 1.73 (m, 1 H), 1.95–2.08 (m, 2 H), 2.82 (br m, 1 H), 3.28 (d, J = 6.1 Hz, 1 H), 3.34 (d, J = 7.7 Hz, 2 H), 3.55 (m, 1 H), 3.74 (s, 3 H), 3.84 (dd, J = 8.4, 6.1 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 231.0745 [$(M + H)^+$; calcd for $C_{10}H_{15}O_4S$: 231.0691].

Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13. Found: C, 52.24; H, 6.07.

MEM Ether 28. Alcohol **27** (321 mg, 1.39 mmol) and diisopropylethylamine (0.73 mL) were dissolved in CH_2Cl_2 (1.0 mL), and a catalytic amount of DMAP (ca. 5 mg) and MEMCl (364 mg, 0.32 mL, 2.0 equiv) were added. The reaction mixture was stirred at room temperature for 2 days and then quenched with saturated $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 × 15 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 28% EtOAc in hexanes as eluant afforded **28** (376 mg, 84% yield) as an oil: IR ($CHCl_3$) 3005 (m), 2960 (m), 2890 (m), 1735 (s), 1450 (m), 1430 (m), 1240 (m), 1175 (s), 1110 (s), 1045 (s), 840 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1 H), 1.81–1.00 (m, 3 H), 2.82 (br q, J = 6.5 Hz, 1 H), 3.07 (q, J = 6.3 Hz, 1 H), 3.33 (d, J = 4.8 Hz, 2 H), 3.38 (s, 3 H), 3.54 (m, 2 H), 3.63 (m, 2 H), 3.70 (s, 3 H), 3.83 (m, 1 H), 4.06 (dd, J = 8.0, 6.8 Hz, 1 H), 4.82 (s, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 318.1096 (M^+; calcd for $C_{14}H_{22}O_6S$: 318.1137).

Hydroxy Ester 39. A solution of ketone **28** (80 mg, 0.25 mmol) in MeOH (5 mL) was cooled to −20 °C, and $NaBH_4$ (10 mg) was added. After 10 min the reaction mixture was quenched with saturated NH_4Cl solution, concentrated in vacuo, and extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 60% EtOAc/hexanes gave **39** (70 mg, 87% yield) as an oil: IR ($CHCl_3$) 3600 (w), 3600–3300 (w), 3010 (m), 2960 (m), 2940 (m), 2900 (m), 1740 (s), 1460 (m), 1440 (m), 1380 (m), 1340 (m), 1330 (m), 1300 (m), 1265 (m), 1045 (s), 855 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (m, 1 H), 1.67 (br s, 1 H), 1.82 (m, 2 H), 1.93 (m, 1 H), 2.42 (m, 1 H), 2.74 (dd, J = 10.1, 9.1 Hz, 1 H), 3.04 (dd, J = 10.2, 7.1 Hz, 1 H), 3.10 (m, 1 H), 3.39 (s, 3 H), 3.55 (m, 2 H), 3.60–3.76 (m, 2 H), 3.69 (s, superimposed on m, 3 H), 3.82 (apparent t, J = 4.8 Hz, 1 H), 4.09 (apparent t, J = 3.2 Hz, 1 H), 4.42 (br m, 1 H), 4.72 (AB q, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 7.1 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 321.1418 (M^+; calcd for $C_{14}H_{24}O_6S$: 321.1372).

Keto Alcohol 43. Method A. A solution of keto ester **28** (9.0 mg, 0.028 mmol) in Et_2O (4.0 mL) was cooled to −78 °C. Ammonia (ca. 2.0 mL) was condensed into the solution, and a small piece of Li wire (ca. 25–30 mg) was added. After a blue color persisted for ca. 2 min, the reaction was quenched with saturated NH_4Cl solution. The NH_3 was allowed to evaporate, and the mixture was extracted several times with Et_2O (10 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 40% acetone/hexanes as eluant afforded **43** (3.0 mg, 37% yield).

Method B. A solution of **28** (11 mg, 0.035 mmol) in THF (0.5 mL) was cooled to −78 °C and treated with $NaN(TMS)_2$ (1.0 M in THF, 50 μL, 1.4 equiv). The solution was stirred for 1.3 h, and ethereal LAH (1.0 M, 60 μL) was then added. The reaction mixture was warmed to room temperature while being stirred for 1 h and was quenched with H_2O (1 drop), 15% NaOH solution (1 drop), and H_2O (3 drops). The resultant mixture was diluted with Et_2O (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 30% acetone/hexanes as eluant furnished **43** (5.8 mg, 58% yield) as an unstable oil: IR ($CHCl_3$) 3600–3300 (m), 3010 (m), 2940 (m), 2900 (m), 1740 (s), 1455 (m), 1250 (m), 1160 (m), 1100 (m), 1040 (s), 910 (m), 850 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (m, 1 H), 1.55 (m, 1 H), 1.72 (m, 2 H), 1.89 (m, 1 H), 2.28 (m, 1 H), 2.73 (m, 1 H), 2.89 (br m, 1 H), 3.35 (s, 2 H), 3.40 (s, 3 H), 3.59 (m, 3 H), 3.74 (m, 2 H), 3.81 (m, 2 H), 4.81 (AB q, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 290.1215 (M^+; calcd for $C_{13}H_{22}O_5S$: 290.1118).

Mesylate 45. At ambient temperature a solution of alcohol **39** (73 mg, 0.23 mmol) and NEt_3 (0.25 mL) in CH_2Cl_2 (2.0 mL) was treated with a catalytic amount of DMAP (ca. 5 mg) and MsCl (4 drops, excess). After 5 min, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O (2 × 25 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 45% EtOAc/hexanes as eluant gave **45** (90 mg, 99% yield) as an oil: IR ($CHCl_3$) 3020 (m), 2950 (m),

2890 (m), 1740 (s), 1450 (m), 1440 (m), 1370–1330 (s), 1275 (s), 1240 (s), 1175 (s), 1110 (m), 1035 (s), 970 (m), 960 (m), 950 (m), 890 (s), 840 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.48 (m, 1 H), 1.78–1.97 (m, 3 H), 2.70 (m, 1 H), 3.00 (apparent t, J = 10.2 Hz, 1 H), 3.02 (dd, J = 7.5, 10.5 Hz, 1 H), 3.04 (m, 1 H), 3.05 (s, 3 H), 3.39 (s, 3 H), 3.57 (m, 2 H), 3.61 (m, 1 H), 3.69 (s, 3 H), 3.74 (m, 1 H), 3.86 (br t, J = 4.7 Hz, 1 H), 4.11 (apparent t, J = 3.0 Hz, 1 H), 4.72 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ 4.9 Hz, 2 H), 5.12 (m, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 323.0598 [(M − $C_3H_7O_2$)$^+$; calcd for $C_{15}H_{26}O_8S_2$: 323.0623].

Episulfide 46. Method A. A solution of alcohol **39** (35 mg, 0.11 mmol), $PhCO_2H$ (20 mg, 1.5 equiv), and PPh_3 (43 mg, 1.5 equiv) in THF (1 mL) was cooled to 0 °C and treated with diisopropyl azodicarboxylate (32 μL, 1.5 equiv). The mixture was warmed to room temperature and then concentrated in vacuo. Flash chromatography with 50% EtOAc/hexanes as eluant afforded **46** (22 mg, 67% yield).

Method B. Mesylate **45** (20 mg, 0.050 mmol) was dissolved in DMF (5 mL). NaOBz (30 mg, 5.2 equiv) was added, and the reaction mixture was stirred at 100 °C for 3 h. The mixture was then cooled, diluted with H_2O (ca. 3 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with 25% EtOAc/hexanes as eluant provided **46** (13 mg, 79% yield) as an oil: IR ($CHCl_3$) 3000 (m), 2950 (m), 2890 (m), 1730 (s), 1670 (w), 1450 (m), 1440 (m), 1390 (m), 1360 (m), 1240 (m), 1175 (s), 1100 (s), 1035 (s), 840 (m), 800 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.61 (m, 1 H), 2.05 (dq, J = 14.7, 3.8 Hz, 1 H), 2.41 (dd, J = 9.4, 2.3 Hz, 2 H), 3.23 (td, J = 5.3, 2.4 Hz, 1 H), 3.41 (s, 3 H), 3.61 (m, 2 H), 3.62–3.80 (m, 4 H), 3.68 (s, superimposed on m, 3 H), 3.86 (m, 1 H), 4.71 (br m, 1 H), 4.85 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 9.5 Hz, 2 H), 5.48 (br m, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 303.1242 (M^+; calcd for $C_{14}H_{23}O_5S$: 303.1266).

Hydroxy Sulfoxides 47α and 47β. A solution of sulfide **39** (1.24 g, 3.87 mmol) in methylene chloride (60 mL) was cooled to 0 °C, and solid (+)-2-(phenylsulfonyl)-3-phenyloxaziridine (1.10 g, 4.26 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1.5 h and then warmed to room temperature. Dimethyl sulfide (300 μL) was then added, and the mixture was concentrated in vacuo. Flash chromatography with 5% methanol/ethyl acetate as eluant gave **47α** (1.16 g, 89% yield) and **47β** (87 mg, 7%), both as white solids.

47α: mp 95.5–96.5 °C; IR ($CHCl_3$) 3070 (w), 3500–3160 (br, w), 3018 (s), 2958 (s), 2876 (m), 1737 (s), 1440 (m), 1276 (m), 1209 (s), 1172 (m), 1111–1100 (br, m), 1042 (s), 848 (w), 732 (s), 661 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96–4.92 (m, 1 H), 4.80 (AB q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 21.1 Hz, 2 H), 4.50 (dd, J = 3.8, 6.0 Hz, 1 H), 3.75–3.52 (m, 5 H), 3.71 (s, superimposed on m, 3 H), 3.39–3.38 (m, 1 H), 3.38 (s, superimposed on m, 3 H), 3.06 (br d, J = 3.2 Hz, 1 H), 2.97 (dd, J = 7.0, 14.1 Hz, 1 H), 2.88–2.82 (m, 2 H), 2.04–1.94 (m, 2 H), 1.89–1.80 (m, 1 H), 1.19–1.12 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 95.3, 75.0, 72.5, 71.6, 71.5, 67.6, 59.0, 58.4, 51.7, 44.2, 41.7, 21.6, 21.2; high-resolution mass spectrum (CI, NH_3) m/z 337.1340 [(M + H)$^+$; calcd for $C_{14}H_{25}O_7S$: 337.1322].

47β: mp 113.0–114.9 °C; IR ($CHCl_3$) 3500–3200 (br, w), 3019 (s), 2948 (m), 1735 (s), 1452 (w), 1441 (w), 1210 (s), 1178 (s), 1115–1101 (br, m), 1045 (s), 849 (w), 729 (s), 661 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 2 H), 4.63–4.58 (m, 1 H), 4.54 (dd, J = 5.1, 7.8 Hz, 1 H), 3.75–3.67 (m, 2 H), 3.71 (s, superimposed on m, 3 H), 3.60 (apparent t, J = 9.1 Hz, 1 H), 3.57–3.51 (m, 3 H), 3.42–3.35 (m, 1 H), 3.38 (s, superimposed on m, 3 H), 3.19 (dd, J = 4.0, 14.1 Hz, 1 H), 2.95 (dd, J = 5.2, 14.1 Hz, 1 H), 2.62–2.56 (m, 1 H), 2.16–2.10 (m, 1 H), 1.89–1.82 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 95.7, 78.8, 71.7, 71.6, 67.5, 62.9, 59.0, 57.2, 51.6, 44.2, 43.2, 23.1, 20.6; high resolution mass spectrum (CI, NH_3) m/z 337.1351 [(M + H)$^+$; calcd for $C_{14}H_{25}O_7S$: 337.1322].

Mesylates 48α and 48β. A solution of mesylate sulfide **45** (219 mg, 0.55 mmol) in freshly distilled methylene chloride (15 mL) cooled to 0 °C under an Ar atmosphere was treated with solid (+)-2-(phenylsulfonyl)-3-phenyloxaziridine (156 mg, 0.61 mmol). The reaction mixture was maintained at 0 °C with stirring for 1.5 h and then warmed to room temperature, and dimethyl sulfide was added (500 μL). The reaction mixture was then concentrated in vacuo and the resulting residue purified by flash column chromatography (7:93 methanol/ethyl acetate) to furnish 185 mg (88%) of **48α** and 18 mg (8.6%) of **48β**.

Sulfinyl Mesylate 48α. A solution of sulfinyl alcohol **47α** (34.5 mg, 103 μmol) in methylene chloride (1.0 mL) at ambient temperature was treated with triethylamine (250 μL), catalytic (dimethylamino)pyridine (10 mg), and methanesulfonyl chloride (40 μL, 0.52 mmol). After 2 min the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with methylene chloride (3 × 150 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 7% methanol/ethyl acetate as eluant gave **48α** (29.0 mg, 68% yield) as an oil: IR ($CHCl_3$) 3021 (m), 2958 (w), 2900 (w), 1741 (s), 1442 (w), 1375 (m), 1352 (m), 1213 (s), 1183 (s), 1136 (w), 1103 (m), 1050 (s), 1037 (sh, s), 958 (s), 911 (s), 882 (s), 744 (s), 662 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70–5.66 (m, 1 H), 4.79 (AB q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 27.4 Hz, 2 H), 4.62 (dd, J_1 = J_2 = 3.7 Hz, 1 H), 3.77–3.51 (m, 6 H), 3.72 (s, superimposed on m, 3 H), 3.40 (s, 3 H), 3.24 (dd, J = 8.2, 14.7 Hz, 1 H), 3.12–3.09 (m, 1 H), 3.07 (s, 3 H), 2.74 (dt, J = 3.6, 10.9 Hz, 1 H), 2.02–1.95 (m, 2 H), 1.94–1.84 (m, 1 H), 1.08–1.01 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 95.7, 80.1, 72.1, 71.7, 70.9, 67.8, 59.1, 54.8, 51.9, 44.0, 40.6, 38.4, 21.6, 20.6; high-resolution mass spectrum (CI, NH_3) m/z 415.1134 [(M + H)$^+$; calcd for $C_{15}H_{27}O_9S_2$: 415.1100].

Sulfinyl Mesylate 48β. A solution of sulfinyl alcohol **47β** (54 mg, 161 μmol) in methylene chloride (1.5 mL) at ambient temperature was treated with triethylamine (300 μL), catalytic (dimethylamino)pyridine (15 mg), and methanesulfonyl chloride (62 μL, 0.80 mmol). After 5 min the reaction was quenched and worked up as described above for **48α**. Flash chromatography with 6% methanol/ethyl acetate as eluant afforded **48β** (35.4 mg, 53% yield) as a white solid: mp 43.0–44.0 °C; IR ($CHCl_3$) 3019 (m), 2958 (w), 2898 (w), 1738 (m), 1441 (w), 1304 (w), 1212 (s), 1108 (m), 1038 (s), 740 (s), 662 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.15–5.10 (m, 1 H), 4.81 (AB q, J_{AB} = 7.4 Hz, $\Delta\nu_{AB}$ = 31.7 Hz, 2 H), 4.72 (apparent t, J = 3.0 Hz, 1 H), 3.97 (dd, J = 8.2, 14.5 Hz, 1 H), 3.78–3.75 (m, 1 H), 3.70 (s, 3 H), 3.58–3.48 (m, 3 H), 3.36 (s, 3 H), 3.28 (m, 1 H), 3.20 (m, 1 H), 3.10 (s, 3 H), 3.06 (apparent t, J = 6.0 Hz, 1 H), 2.97–2.90 (m, 1 H), 2.09–2.04 (m, 1 H), 1.98–1.89 (m, 1 H), 1.87–1.81 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 96.7, 78.3, 73.6, 71.7, 67.5, 59.5, 58.1, 51.6, 44.9, 41.1, 38.5, 21.4, 20.0; high-resolution mass spectrum (CI, NH_3) m/z 415.1124 [(M + H)$^+$; calcd for $C_{15}H_{27}O_9S_2$: 415.1100].

Keto α-Sulfoxide 49. A solution of ketone **28** (69 mg, 0.22 mmol) in methylene chloride (6 mL) was cooled to −23 °C and treated with *N*-(phenylsulfonyl)-3-(pentafluorophenyl)oxaziridine (91.4 mg, 0.26 mmol) in one portion. After 3 h, dimethyl sulfide (1 mL) was added and the reaction mixture warmed to ambient temperature. Concentration in vacuo and flash chromatography with 10% methanol/ethyl acetate as eluant furnished **49** (67 mg, 92% yield) as a white crystalline solid: mp 76.1–77.0 °C; IR ($CHCl_3$) 3009 (m), 2950 (m), 2890 (m), 1740 (s), 1450 (m), 1434 (m), 1365 (w), 1170 (s), 1104 (s), 1029 (s), 840 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 (d, J = 7.5 Hz, 1 H), 4.63 (d, J = 7.5 Hz, 1 H), 4.34–4.30 (m, 1 H), 3.87–3.83 (m, 1 H), 3.75–3.30 (m, 7 H), 3.72 (s, 3 H), 3.36 (s, 3 H), 3.14–3.11 (m, 1 H), 2.14–2.11 (m, 1 H), 1.97–1.90 (m, 2 H), 1.45–1.42 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 171.9, 92.9, 71.6, 70.0, 67.6, 64.0, 59.0, 57.1, 51.9, 43.9, 41.9, 23.2, 18.3; high-resolution mass spectrum (CI, NH_3) m/z 335.1107 [(M + H)$^+$; calcd for $C_{14}H_{23}O_7S$: 335.1164].

Sulfinyl Alcohols 47 and 50 via Reduction of Ketone 49. A solution of ketone **49** (17 mg, 0.051 mmol) in anhydrous methanol (3 mL) was cooled to 0 °C, and $NaBH_4$ (2.1 mg, 0.056 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Following concentration in vacuo, flash chromatography with 10% methanol/ethyl acetate as eluant afforded a 2.4:1 mixture of **47** and **50** (17 mg, 99% yield). Further purification by HPLC with 10% methanol/ethyl acetate as eluant then provided pure **47** as a white solid followed by **50** as a white solid.

47α: mp 95.5–96.5 °C; IR ($CHCl_3$) 3350 (br w), 3018 (s), 2958 (s), 2897 (m), 1738 (s), 1450 (w), 1441 (m), 1205 (s), 1173 (m), 1112 (m), 1042 (s), 731 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96–4.92 (m, 1 H), 4.79 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 21.1 Hz, 2 H), 3.75–3.37 (m, 6 H), 3.71 (s, superimposed on m, 3 H), 3.38 (s, superimposed on m, 3 H), 3.07 (br s, 1 H), 2.97 (dd, J = 6.9, 14.1 Hz, 1 H), 2.88–2.81 (m, 1 H), 2.00–1.78 (m, 3 H), 1.21–1.10 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 95.3, 75.0, 72.5, 71.6, 71.5, 67.6, 59.0, 58.4, 51.7, 44.2, 41.7, 21.6, 21.1; high-resolution mass spectrum (CI, NH_3) m/z 337.1341 [(M + H)$^+$; calcd for $C_{14}H_{25}O_7S$: 337.1321].

50: mp 120.0–120.5 °C; IR ($CHCl_3$) 3380 (br, m), 2998 (m), 2848 (m), 2892 (m), 1738 (s), 1448 (m), 1436 (m), 1306 (m), 1272 (m), 1231 (m), 1170 (m), 1132 (m), 1104 (m), 1032 (s), 840 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 39.0 Hz, 2 H), 4.60 (br s, 1 H), 4.38 (br s, 1 H), 4.13 (br s, 1 H), 3.84–3.81 (m, 1 H), 3.71 (s, 3 H), 3.69–3.52 (m, 5 H), 3.38 (s, 3 H), 2.97 (d, J = 14.8 Hz, 1 H), 2.79–2.70 (m, 2 H), 1.92–1.76 (m, 3 H), 0.87–0.83 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 95.5, 76.3, 72.2, 71.9, 71.1, 67.6, 59.1, 51.8, 45.3, 43.9, 24.2, 20.7; high-resolution mass spectrum (CI, NH_3) m/z 337.1308 [(M + H)$^+$; calcd for $C_{14}H_{25}O_7S$: 337.1321].

Vinyl Sulfoxide 51α. Method A. A solution of mesylate **48α** (490 mg, 1.18 mmol) in benzene (25 mL) was cooled to 0 °C, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (194 μL, 1.3 mmol) was added. The reaction mixture was then warmed to ambient temperature and stirred for

3 h. Concentration in vacuo followed by flash chromatography with 10% methanol/ethyl acetate as eluant gave **51α** (379 mg, quantitative).

Method B. A solution of alcohol **47α** (1.03 g, 3.07 mmol) in methylene chloride (25 mL) at ambient temperature was treated with triethylamine (5 mL), catalytic (dimethylamino)pyridine (50 mg), and methanesulfonyl chloride (1.2 mL, 15.3 mmol). After 5 min, DBU (2 mL) was added. The reaction mixture was stirred for 1 h further and then quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with methylene chloride (3 × 150 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 10% methanol/ethyl acetate as eluant provided **51α** (880 mg, 90% yield) as a white solid: mp 85.0–85.5 °C; IR ($CHCl_3$) 3014 (m), 2956 (w), 2896 (w), 1740 (s), 1439 (w), 1208 (s), 1170 (w), 1110 (w), 1030 (s), 730 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65 (dd, J = 3.1, 6.2 Hz, 1 H), 6.58 (dd, J = 1.6, 6.2 Hz, 1 H), 4.78 (AB q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 24.3 Hz, 2 H), 4.33 (dd, J = 4.1, 5.4 Hz, 1 H), 3.77–3.65 (m, 3 H), 3.73 (s, superimposed on m, 3 H), 3.58–3.53 (m, 3 H), 3.37 (s, 3 H), 2.90–2.87 (m, 1 H), 2.05–1.92 (m, 2 H), 1.78–1.73 (m, 1 H), 1.25–1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 145.7, 133.7, 95.2, 72.2, 71.6, 70.8, 67.7, 58.9, 51.8, 43.9, 41.9, 27.3, 21.2; high-resolution mass spectrum (CI, NH_3) m/z 319.1181 [(M + H)$^+$; calcd for $C_{14}H_{23}O_6S$: 319.1215].

Vinyl Sulfoxide 51β. A solution of mesylate **48β** (2.8 mg, 6.8 μmol) in benzene (0.5 mL) was cooled to 0 °C and treated with DBU (25 μL). The reaction mixture was then warmed to room temperature and stirred for 3 h. Concentration in vacuo and flash chromatography with 10% methanol/ethyl acetate as eluant then gave **51β** (2.0 mg, 94% yield) as a white solid: mp 43.0–44.0 °C; IR ($CHCl_3$) 3016 (m), 2952 (w), 2895 (w), 1736 (s), 1438 (w), 1210 (s), 1105 (m), 1032 (s), 732 (s), 660 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, J = 2.7, 6.1 Hz, 1 H), 6.77 (d, J = 6.1 Hz, 1 H), 4.93 (br s, 1 H), 4.83 (AB q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 22.0 Hz, 2 H), 3.75–3.47 (m, 4 H), 3.70 (s, superimposed on m, 3 H), 3.33 (s, 3 H), 3.19–3.15 (m, 2 H), 3.00 (dt, J = 4.1, 10.9 Hz, 1 H), 2.19–2.14 (m, 1 H), 2.01–1.86 (m, 2 H), 1.48–1.40 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 149.9, 133.2, 96.1, 72.5, 71.6, 67.5, 60.5, 59.0, 51.6, 45.2, 44.0, 30.2, 20.7; high-resolution mass spectrum (CI, NH_3) m/z 319.1242 [(M + H)$^+$; calcd for $C_{14}H_{23}O_6S$: 319.1215].

Vinyl Sulfide 52. A solution of sulfoxide **51α** (15.0 mg, 47 μmol) in acetone (0.5 mL) was treated with NaI (17 mg, 113 μmol, dried azeotropically with benzene) and cooled to 0 °C. After addition of trifluoroacetic anhydride (9.3 μL, 66 μmol), the resultant dark red solution was stirred for 5 min. Diethyl ether (10 mL) followed by 10% sodium thiosulfate solution (10 mL) was then added. The aqueous phase was extracted with methylene chloride (2 × 20 mL) and then with ethyl acetate (20 mL). The combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 20% ethyl acetate/hexanes as eluant furnished **52** (10.0 mg, 71% yield) as a white solid: mp 37.0–37.8 °C.

Similarly, treatment of the epimeric sulfoxide **51β** (3.2 mg, 10.0 μmol) with NaI (3.6 mg, 24.0 μmol) and trifluoroacetic anhydride (2.0 μL, 14.0 μmol) in acetone (100 μL) gave **52** (2.1 mg, 70% yield): IR ($CHCl_3$) 3018 (m), 2954 (m), 2928 (m), 2892 (m), 1734 (s), 1438 (w), 1268 (m), 1209 (s), 1171 (m), 1158 (m), 1108 (s), 1039 (s), 730 (s), 661 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (dd, J = 1.5, 6.0 Hz, 1 H), 5.64 (dd, J = 2.8, 6.0 Hz, 1 H), 4.76 (AB q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 16.2 Hz, 2 H), 4.12 (apparent t, J = 4.8 Hz, 1 H), 4.03 (dd, J = 5.4, 6.9 Hz, 1 H), 3.73–3.64 (m, 2 H), 3.70 (s, superimposed on m, 3 H), 3.55–3.53 (m, 2 H), 3.38 (s, 3 H), 3.01–2.97 (m, 2 H), 1.83–1.72 (m, 3 H), 1.52–1.46 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 128.4, 125.2, 95.6, 75.2, 71.7, 67.3, 59.0, 53.2, 51.6, 44.2, 43.3, 24.2, 20.8; high-resolution mass spectrum (CI, NH_3) m/z 302.1168 (M$^+$; calcd for $C_{14}H_{22}O_5S$: 302.1138).

Alcohol 40. Method A. A solution of vinyl sulfide **52** (8.0 mg, 26.7 μmol) in THF (1.5 mL) at ambient temperature was treated dropwise with BH_3·THF (1 M in THF, 107 μL, 107 μmol). After 3 h, TLC analysis revealed the disappearance of **52**. Following dilution with THF (1.0 mL), the solution was cooled to 0 °C and 10% aqueous NaOH (1.0 mL) was slowly added dropwise followed by 30% aqueous H_2O_2 (170 μL, excess). The ice bath was then removed and the mixture vigorously stirred. After 0.5 h the reaction was quenched at 0 °C with 10% aqueous $NaHSO_3$ solution and extracted with diethyl ether (10 mL) and then with ethyl acetate (10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 65% ethyl acetate/hexanes afforded **40** (6.6 mg, 77% yield). The product solidified in the freezer. Recrystallization from Et_2O/petroleum ether (low boiling point) gave a white solid, mp 70.0–70.4 °C.

Method B. A mixture of sulfoxides **51α** and **51β** (13:1, 320 mg, 1.01 mmol) was dissolved in dry acetone (6.0 mL), and NaI (453 mg, 3.02 mmol) was added. The mixture was cooled to 0 °C and treated with solid $NaHSO_3$ (250 mg), followed by dropwise addition of trifluoroacetic anhydride (242 μL, 1.70 mmol). After 75 s, the reaction mixture was diluted with diethyl ether (15 mL) and quenched with 10% aqueous sodium thiosulfate solution. The aqueous phase was extracted with methylene chloride (100 mL) and then with diethyl ether (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, and the product was purified by chromatography on neutral alumina with 25% ethyl acetate/hexanes as eluant. The recovered starting material was then resubmitted to the same reaction conditions, and the products were combined. The crude vinyl sulfide was dissolved in THF (10.0 mL). The solution was cooled to 0 °C and treated dropwise with BH_3·THF (1.0 M in THF, 4.0 mL, 4.02 mmol). The reaction mixture was stirred at 0 °C for 45 min and then warmed to room temperature. After 3 h TLC analysis revealed the disappearance of the vinyl sulfide. The mixture was cooled to −23 °C and diluted with THF (10 mL), followed by slow addition of 10% aqueous NaOH (ca. 2.5 M, 14.5 mL, 36.2 mmol). After warming to 0 °C, 30% H_2O_2 (ca. 8.8 M, 2.1 mL, 18.1 mmol) was slowly added with vigorous stirring. The reaction mixture was then stirred at room temperature for 1 h, cooled to 0 °C, and quenched with aqueous $NaHSO_3$. The pH was adjusted to 6.0 by addition of solid $NaHSO_3$, and the mixture was stirred for 1 h. Sodium chloride was then added, and the aqueous phase was extracted with ethyl acetate (100 mL) followed by methylene chloride (100 mL). The combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 65% ethyl acetate/hexanes as eluant furnished **40** (195 mg, 61% yield for 2 steps) as a white solid: IR ($CHCl_3$) 3560–3260 (br, w), 3016 (m), 2946 (s), 2895 (m), 1733 (s), 1438 (m), 1368 (w), 1309 (w), 1278 (m), 1242 (m), 1206 (s), 1171 (m), 1160 (m), 1135 (s), 1109 (s), 1090 (s), 1041 (s), 910 (w), 842 (w), 728 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 9.5 Hz, 2 H), 4.29–4.27 (m, 2 H), 4.23–4.22 (m, 1 H), 3.85–3.81 (m, 1 H), 3.69 (s, 3 H), 3.58–3.52 (m, 3 H), 3.38 (s, 3 H), 3.17 (dd, J = 4.3, 11.9 Hz, 1 H), 3.08–3.04 (m, 1 H), 2.85 (d, J = 11.9 Hz, 1 H), 2.41–2.36 (m, 1 H), 2.28 (d, J = 5.1 Hz, 1 H), 1.86–1.81 (m, 2 H), 1.58–1.54 (m, 1 H), 1.14–1.05 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 96.1, 78.7, 75.6, 72.0, 67.2, 59.1, 51.6, 48.0, 46.1, 41.8, 38.5, 23.3, 20.4; high-resolution mass spectrum (CI, NH_3) m/z 338.1673 [(M + NH_4)$^+$; calcd for $C_{14}H_{28}NO_6S$: 338.1637].

Silyl Ether 53. A solution of alcohol **40** (1.01 g, 3.16 mmol) in methylene chloride (25 mL) was cooled to 0 °C and treated with 2,6-lutidine (3.65 mL, 31.6 mmol) and *tert*-butyldiphenylsilyl trifluoromethanesulfonate (2.45 g, 6.32 mmol). The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 2 h and then was quenched with saturated $NaHCO_3$ solution. After the addition of methylene chloride (100 mL), the pH of the aqueous phase was adjusted to ca. 7.0 with 1 M HCl. The aqueous phase was extracted with methylene chloride (3 × 150 mL), and the combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 20% ethyl acetate/hexanes as eluant afforded **53** (1.66 g, 94% yield) as a clear, colorless oil: IR ($CHCl_3$) 3018 (m), 2942 (s), 2900 (m), 2860 (m), 1738 (s), 1471 (m), 1441 (m), 1429 (m), 1362 (m), 1314 (m), 1272 (m), 1198 (m), 1160 (m), 1138 (s), 1108 (s), 1070 (s), 1038 (s), 900 (m), 845 (w), 818 (m), 695 (s), 604 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.36 (m, 10 H), 4.77 (AB q, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 26.6 Hz, 2 H), 4.30 (apparent t, J = 2.7 Hz, 1 H), 4.24–4.23 (m, 1 H), 4.18–4.17 (m, 1 H), 3.73–3.61 (m, 2 H), 3.67 (s, superimposed on m, 3 H), 3.54–3.46 (m, 2 H), 3.36 (s, 3 H), 3.06–3.02 (m, 1 H), 2.90 (dd, J = 4.1, 11.6 Hz, 1 H), 2.74 (d, J = 11.6 Hz, 1 H), 2.35–2.31 (m, 1 H), 1.75–1.68 (m, 2 H), 1.32–1.28 (m, 1 H), 1.06 (s, 9 H), 0.99–0.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 135.7, 129.9, 129.8, 127.8, 127.7, 95.3, 80.1, 74.1, 71.7, 67.3, 59.0, 51.5, 48.5, 46.5, 41.8, 38.4, 26.9, 23.0, 20.3, 19.1; high-resolution mass spectrum (CI, NH_3) m/z 576.2823 [(M + NH_4)$^+$; calcd for $C_{30}H_{46}NO_6SSi$: 576.2815].

Aldehyde 54. A solution of methyl ester **53** (240 mg, 0.43 mmol) in toluene (7 mL) was cooled to −78 °C and treated with DIBAL (1 M in hexanes, 0.49 mL, 1.15 equiv). For TLC monitoring, aliquots were quenched with methanol and reduced with $NaBH_4$ because ester **53** and aldehyde **54** were not resolved. After 45 min at −78 °C, the reaction was quenched with methanol and warmed to room temperature. A saturated solution of Rochelle's salt was added and the mixture extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 70% hexanes/ethyl acetate as eluant gave **54** (204 mg, 90% yield) as a white solid accompanied by the alcohol derived from overreduction (25 mg, 10% yield). **54**: mp 85.0–87.0 °C; IR ($CHCl_3$) 3001 (m), 2924 (s), 2884 (m), 2850 (m), 1724 (s), 1468 (w), 1422 (m), 1203 (s), 1134 (s), 1107 (s), 1032 (s), 903 (s), 730 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.67–7.36 (m, 10 H), 4.77 (AB q, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 76.6 Hz, 2 H), 4.44 (br s, 1 H), 4.24 (d, J = 3.8 Hz, 1 H), 4.16 (br s, 1 H), 3.69–3.50 (m, 2 H), 3.50–3.48 (m, 2 H), 3.37 (s, 3 H), 2.94–2.90 (m, 2 H), 2.76 (d, J = 11.6 Hz, 1 H), 2.35–2.31 (m, 1 H),

1.75–1.61 (m, 2 H), 1.34–1.26 (m, 1 H), 1.07 (s, 9 H), 0.99–0.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 135.6, 133.5, 129.8, 127.7, 127.6, 94.6, 80.0, 72.1, 71.6, 67.5, 59.0, 48.7, 47.8, 46.9, 38.5, 27.0, 22.7, 19.1, 18.4; high-resolution mass spectrum (CI, NH_3) *m/z* 546.2690 [(M + NH_4)$^+$; calcd for $C_{29}H_{44}NO_5SSi$: 546.2754].

Enedione 61. A solution of dihydropyran **58** (568 mg, 2.87 mmol) in THF (18 mL) was cooled to −78 °C, and *tert*-butyllithium (1.7 M in pentane, 1.49 mL, 2.5 mmol) was added dropwise over 1 min. The reaction mixture was stirred for 5 min further at −78 °C and then warmed to 0 °C. After 1.5 h the anion solution was cooled to −78 °C, and a cold (0 °C) solution of aldehyde **54** (606 mg, 1.15 mmol) and HMPA (399 μL) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 30 min and at 0 °C for 10 min and then was quenched with saturated NH_4Cl solution. The aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. The resultant oil was taken up in methylene chloride (50 mL) and treated with saturated aqueous oxalic acid (15 mL) at ambient temperature with vigorous stirring. The reaction was monitored by TLC and was complete after 1 h. Water (10 mL) was added, and the aqueous phase was extracted with methylene chloride (3 × 100 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 42:58 ethyl acetate/hexanes as eluant afforded a mixture of the four isomeric alcohols. The alcohols were combined and oxidized as follows. A solution of oxalyl chloride (200 μL, 2.3 mmol) in methylene chloride (10 mL) was cooled to −78 °C and treated with DMSO (326 μL, 4.6 mmol). The mixture was stirred for 30 min at −78 °C, and then a cold (−78 °C) solution of the alcohols (1.15 mmol) in methylene chloride (10 mL) was added via a cannula. After 30 min triethylamine (959 μL, 6.9 mmol) was added, and the mixture was warmed to ambient temperature and monitored by TLC. After 45 min, the reaction was quenched with 10% aqueous $NaHCO_3$ solution and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 25% ethyl acetate/hexanes as eluant gave a 1:1 mixture of **61a** and **61b** (559 mg, 80% yield for three steps). The diastereomers were separated by HPLC.

61a: oil; IR ($CHCl_3$) 2938 (s), 2870 (m), 2863 (m), 1710 (m), 1682 (s), 1602 (w), 1461 (w), 1429 (w), 1353 (m), 1309 (w), 1363 (w), 1184 (w), 1137 (s), 1107 (s), 1054 (s), 1032 (s), 900 (w), 819 (w), 697 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.36 (m, 10 H), 6.03 (s, 1 H), 4.76 (d, *J* = 7.4 Hz, 1 H), 4.62–4.58 (m, 2 H), 4.39 (br s, 1 H), 4.25–4.21 (m, 2 H), 4.16 (apparent t, *J* = 3.7 Hz, 1 H), 3.73 (dt, *J* = 2.5, 12.0 Hz, 1 H), 3.56–3.52 (m, 2 H), 3.46–3.36 (m, 2 H), 3.32 (s, 3 H), 2.96 (dd, *J* = 3.9, 11.6 Hz, 1 H), 2.78 (d, *J* = 11.6 Hz, 1 H), 2.67–2.62 (m, 1 H), 2.36–2.32 (m, 1 H), 1.84 (qd, *J* = 12.7, 3.4 Hz, 1 H), 1.55–1.48 (m, 1 H), 1.34–1.31 (m, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 1.06 (s, 9 H), 0.95 (qd, *J* = 3.7, 12.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 195.9, 135.7, 129.9, 129.8, 127.8, 127.7, 105.2, 94.8, 80.1, 73.0, 71.6, 67.6, 59.0, 48.6, 46.5, 39.3, 38.5, 26.9, 22.8, 19.3, 19.2, 10.8; high-resolution mass spectrum (CI, NH_3) *m/z* 639.2820 [(M + H)$^+$; calcd for $C_{35}H_{47}O_7SSi$: 639.2811].

61b: oil; IR ($CHCl_3$) 3002 (w), 2937 (s), 2885 (m), 2862 (m), 1712 (m), 1682 (s), 1601 (w), 1462 (w), 1429 (w), 1354 (m), 1311 (w), 1266 (w), 1187 (w), 1138 (s), 1108 (s), 1077 (s), 1034 (s), 900 (w), 847 (w), 819 (w), 698 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.36 (m, 10 H), 6.04 (s, 1 H), 4.76 (d, *J* = 7.4 Hz, 1 H), 4.63 (dd, *J* = 5.3, 11.4 Hz, 1 H), 4.58 (d, *J* = 7.4 Hz, 1 H), 4.44 (br s, 1 H), 4.25 (br d, *J* = 3.5 Hz, 1 H), 4.18–4.13 (m, 2 H), 3.74 (dt, *J* = 2.8, 11.9 Hz, 1 H), 3.55–3.53 (m, 2 H), 3.46–3.42 (m, 1 H), 3.39–3.35 (m, 1 H), 3.31 (s, 1 H), 2.96 (dd, *J* = 4.1, 11.6 Hz, 1 H), 2.78 (d, *J* = 11.6 Hz, 1 H), 2.69–2.66 (m, 1 H), 2.35–2.32 (m, 1 H), 1.84 (qd, *J* = 12.6, 3.4 Hz, 1 H), 1.51–1.48 (m, 1 H), 1.34–1.30 (m, 1 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 1.06 (s, 9 H), 0.95 (dq, *J* = 12.8, 3.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 195.9, 162.9, 135.7, 133.8, 129.9, 129.8, 127.8, 127.7, 94.7, 80.1, 73.6, 72.7, 71.6, 67.7, 58.9, 48.4, 46.5, 44.8, 39.3, 38.5, 26.9, 22.7, 19.2, 19.1, 10.6; high-resolution mass spectrum (CI, NH_3) *m/z* 639.2773 [(M + H)$^+$; calcd for $C_{35}H_{47}O_7SSi$: 639.2811].

Spiroketals 62–65. A solution of enediones **61a,b** (1:1 mixture, 123 mg, 0.20 mmol) in methylene chloride (10 mL) was treated with freshly powdered $ZnBr_2$ (546 mg, 2.4 mmol) in one portion. The reaction mixture was vigorously stirred at ambient temperature for 18 h, cooled to 0 °C, and quenched slowly with 10% aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with a saturated aqueous solution of EDTA, dried over K_2CO_3, filtered, and concentrated in vacuo. The crude product was dried azeotropically with benzene, redissolved in benzene (7 mL), and treated with TsOH·H_2O (20 mg, 0.1 mmol). The solution was stirred at ambient temperature for 48 h, then cooled to 0 °C, diluted with diethyl ether (10 mL), and quenched with 10% aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether (3 × 30 mL), and the combined organic solutions were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 20% → 50% diethyl ether/pentane as eluant furnished **62** and **63** as one fraction, followed by **64** (3.6 mg, 3%) and **65** (7.0 mg, 11%). HPLC (11% ethyl acetate/hexanes) then furnished **63** (19.3 mg, 17%) and **62** (58.1 mg, 53%).

62: solid, mp 179.3–180.2 °C; IR ($CHCl_3$) 2939 (s), 2893 (m), 2863 (s), 1774 (s), 1728 (s), 1468 (w), 1431 (w), 1387 (w), 1328 (w), 1303 (w), 1232 (w), 1170 (s), 1132 (s), 1111 (s), 1104 (s), 1091 (s), 1061 (s), 971 (s), 931 (w), 820 (w), 697 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.36 (m, 10 H), 4.35 (br d, *J* = 3.7 Hz, 1 H), 4.30 (br d, *J* = 3.3 Hz, 1 H), 4.18 (br d, *J* = 4.1 Hz, 1 H), 4.00 (dd, *J* = 7.0, 11.1 Hz, 1 H), 3.86 (apparent t, *J* = 11.3 Hz, 1 H), 2.95 (dd, *J* = 0.6, 14.6 Hz, 1 H), 2.79 (dd, *J* = 3.9, 11.7 Hz, 1 H), 2.77–2.65 (m, 3 H), 2.32 (d, *J* = 14.6 Hz, 1 H), 2.25–2.21 (m, 1 H), 1.76–1.73 (m, 1 H), 1.26–0.94 (m, 3 H), 1.09 (d, 9 H), 1.04 (d, superimposed on m, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 205.1, 135.7, 133.7, 133.4, 129.9, 129.8, 128.3, 127.8, 127.7, 102.6, 81.3, 72.8, 66.5, 45.9, 45.6, 44.8, 41.1, 37.9, 26.9, 22.3, 22.0, 19.1, 9.0; high-resolution mass spectrum (CI, NH_3) *m/z* 568.2553 [(M + NH_4)$^+$; calcd for $C_{31}H_{42}NO_5SSi$: 568.2518].

Anal. Calcd for $C_{31}H_{38}O_5SSi$: C, 67.60; H, 6.84. Found: C, 67.41; H, 6.84.

63: oil; IR ($CHCl_3$) 3019 (w), 2972 (s), 2948 (s), 2909 (m), 2870 (m), 1781 (s), 1737 (s), 1478 (w), 1435 (m), 1391 (w), 1371 (w), 1308 (m), 1246–1200 (br, m), 1138 (s), 1120 (s), 1111 (s), 1099 (s), 1068 (s), 1051 (s), 984 (s), 932 (m), 915 (s), 823 (m), 704 (s), 680 (s), 610 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.36 (m, 10 H), 4.64 (dd, *J* = 1.0, 4.3 Hz, 1 H), 4.30 (br d, *J* = 3.3 Hz, 1 H), 4.23 (dd, *J* = 5.0, 11.5 Hz, 1 H), 4.20 (dd, *J* = 1.3, 5.1 Hz, 1 H), 3.68 (dd, *J* = 5.7, 11.5 Hz, 1 H), 2.85 (d, *J* = 15.5 Hz, 1 H), 2.80 (dd, *J* = 3.9, 11.6 Hz, 1 H), 2.71–2.67 (m, 2 H), 2.63–2.59 (m, 1 H), 2.43 (dd, *J* = 1.0, 15.5 Hz, 1 H), 2.23–2.19 (m, 1 H), 1.78–1.73 (m, 1 H), 1.26–0.94 (m, 3 H), 1.21 (d, superimposed on m, *J* = 7.1 Hz, 3 H), 1.08 (s, superimposed on m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 206.0, 143.2, 135.7, 133.7, 133.4, 129.9, 129.8, 128.3, 127.8, 100.9, 81.3, 73.3, 66.1, 46.0, 45.7, 44.3, 43.8, 41.2, 37.9, 29.4, 26.9, 22.4, 22.0, 19.2, 13.0; high-resolution mass spectrum (CI, NH_3) *m/z* 568.2569 [(M + NH_4)$^+$; calcd for $C_{31}H_{42}NO_5SSi$: 568.25553].

64: oil; IR ($CHCl_3$) 2980 (sh), 2961 (s), 2892 (m), 2861 (m), 1774 (s), 1728 (s), 1463 (w), 1430 (m), 1387 (w), 1331 (w), 1262 (w), 1228–1207 (br, w), 1667 (m), 1110 (s), 1080 (s), 1061 (sh), 991 (m), 938 (w), 850 (w), 819 (w), 698 (m), 603 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.37 (m, 10 H), 4.26 (apparent t, *J* = 6.7 Hz, 1 H), 4.12 (dd, *J* = 5.3, 10.9 Hz, 1 H), 4.03–3.76 (m, 2 H), 2.80 (dd, *J* = 0.6, 14.3 Hz, 1 H), 2.78–2.64 (m, 4 H), 2.34–2.28 (m, 2 H), 1.86–1.76 (m, 1 H), 1.64–1.56 (m, 2 H), 1.19–0.87 (m, 1 H), 1.07 (s, superimposed on m, 9 H), 1.00 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 204.8, 135.8, 133.6, 133.4, 130.0, 127.8, 127.7, 102.7, 80.1, 77.3, 67.6, 46.6, 45.6, 45.4, 44.8, 43.7, 37.1, 26.9, 22.8, 21.0, 19.2, 9.0, 0.0; high-resolution mass spectrum (CI, NH_3) *m/z* 568.2543 [(M + NH_4)$^+$; calcd for $C_{31}H_{42}NO_5SSi$: 568.2553].

65: solid, mp 146.0–146.5; IR ($CHCl_3$) 2980 (w), 2942 (m), 2892 (w), 1773 (s), 1727 (s), 1449 (w), 1383 (w), 1328 (w), 1232 (m), 1218 (m), 1171 (m), 1151 (m), 1091 (m), 1052 (m), 1024 (m), 971 (s), 928 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (d, *J* = 3.4 Hz, 1 H), 4.38 (br s, 1 H), 4.05 (d, *J* = 4.6 Hz, 1 H), 4.00 (dd, *J* = 7.0, 11.1 Hz, 1 H), 3.78 (apparent t, *J* = 11.3 Hz, 1 H), 3.10 (dd, *J* = 4.0, 12.0 Hz, 1 H), 2.96 (dd, *J* = 0.9, 14.6 Hz, 1 H), 2.81 (d, *J* = 12.0 Hz, 1 H), 2.77–2.72 (m, 2 H), 2.30 (d, *J* = 14.5 Hz, 1 H), 2.34–2.28 (m, 1 H), 1.88–1.82 (m, 1 H), 1.75 (br s, 1 H), 1.51–1.46 (m, 1 H), 1.22 (qd, *J* = 12.7, 3.1 Hz, 1 H), 1.15 (qd, *J* = 12.4, 2.9 Hz, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 204.9, 102.6, 79.9, 72.8, 66.6, 45.7, 45.4, 45.2, 44.8, 41.1, 37.8, 22.2, 22.1, 9.0; high-resolution mass spectrum (CI, NH_3) *m/z* 330.1357 [(M + NH_4)$^+$; calcd for $C_{15}H_{24}NO_5S$: 330.1375].

Equilibration of Spiroketals 63 and 64. Spiroketal **63** (6.0 mg, 0.011 mmol) was dissolved in THF (2 mL) at ambient temperature and treated with DBU (0.4 mL). The reaction mixture was stirred at room temperature for 16 h, diluted with H_2O (1 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 10% ethyl acetate/hexanes as eluant gave a 4:1 mixture of **62** and **63** (5.9 mg, 98% yield). HPLC with 11% ethyl acetate/hexanes as eluant then provided **62** (4.2 mg, 70% yield) as an oil.

Both **63** and **64** were independently resubmitted to the spiroketalization conditions (TsOH, benzene). HPLC analysis with 11% EtOAc/hexanes as eluant revealed the following ratios of **62**, **63**, and **64**: from **63**, 17.9:5.4:1.0; from **64**, 13.5:4.5:1.0.

Spiroketal 62 via Silylation of 65. A solution of alcohol **65** (4.1 mg, 0.013 mmol) in methylene chloride (1 mL) was cooled to 0 °C, and

2,6-lutidine (14.6 μL, 0.13 mmol) and *tert*-butyldiphenylsilyl trifluoromethanesulfonate (9.8 μL, 0.026 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 2 h. Concentration in vacuo and flash chromatography with 10% → 50% ethyl acetate/hexanes as eluant provided **62** (4.5 mg, 66% yield) as an oil.

Alcohol 66. A solution of spiroketal **62** (55.0 mg, 0.10 mmol) in THF (3.0 mL) was cooled to −78 °C. A solution of L-Selectride (1 M in THF, 107 μL, 0.105 mmol) was diluted with THF (0.5 mL) and added dropwise over ca. 15 min via a syringe pump. The reaction mixture was stirred at −78 °C for an additional 15 min and then treated with THF (7.0 mL), H_2O (7.0 mL), and acetic acid (1.5 mL). The resultant mixture was warmed to room temperature for 30 min. The aqueous phase was then extracted with diethyl ether (3 × 25 mL), and the combined organic solutions were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 1:9 → 1:5 ethyl acetate/hexanes as eluant afforded **66** (51.7 mg, 94% yield) as an oil: IR ($CHCl_3$) 3550 (m), 2960 (sh), 2938 (s), 2860 (m), 1770 (s), 1462 (w), 1427 (m), 1387 (w), 1362 (w), 1330 (w), 1278 (w), 1151 (m), 1134 (s), 1121 (s), 1057 (s), 1007 (m), 972 (m), 940 (m), 927 (m), 862 (w), 819 (w), 693 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.28 (m, 10 H), 4.51 (d, *J* = 3.8 Hz, 1 H), 4.20 (d, *J* = 3.5 Hz, 1 H), 4.13 (d, *J* = 4.8 Hz, 1 H), 3.82 (m, 1 H), 3.70 (app t, *J* = 11.7 Hz, 1 H), 3.44 (dd, *J* = 4.9, 11.6 Hz, 1 H), 2.74–2.71 (m, 2 H), 2.61 (d, *J* = 11.6 Hz, 1 H), 2.57–2.53 (m, 1 H), 2.16–2.13 (m, 1 H), 2.08 (dd, *J* = 3.3, 14.1 Hz, 1 H), 1.85–1.83 (m, 1 H), 1.68 (dd, *J* = 3.2, 14.1 Hz, 1 H), 1.66–1.63 (m, 1 H), 1.47–0.88 (m, 3 H), 0.99 (s, superimposed on m, 9 H), 0.85 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 135.7, 133.6, 130.0, 129.9, 128.3, 127.8, 127.7, 97.4, 81.3, 73.5, 67.3, 61.9, 46.2, 45.8, 41.2, 37.9, 35.8, 34.3, 26.9, 22.2, 22.0, 19.1, 13.0; high-resolution mass spectrum (CI, NH_3) *m/z* 570.2697 [(M + NH_4)$^+$; calcd for $C_{31}H_{44}NO_5SSi$: 570.2711].

Silyl Ether 67. A solution of alcohol **66** (20.0 mg, 0.036 mmol) and 2,6-lutidine (0.5 mL) in methylene chloride (3 mL) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl triflate (150 μL, 0.65 mmol). The mixture was stirred at 0 °C for 15 min and then warmed to room temperature. After 2 h, the reaction was quenched at 0 °C with aqueous $NaHCO_3$. After dilution with methylene chloride (10 mL), 10% aqueous HCl was added until the pH of the aqueous layer reached ca. 7. The aqueous phase was then extracted with diethyl ether (3 × 5 mL), and the combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 10% ethyl acetate/hexanes as eluant gave **67** (21.0 mg, 89% yield) as an oil: IR ($CHCl_3$) 2960 (s), 2938 (s), 2883 (m), 2858 (s), 1767 (s), 1461 (w), 1428 (w), 1360 (w), 1250 (w), 1161 (m), 1138 (m), 1102 (m), 1059 (s), 978 (m), 892 (m), 838 (m), 695 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.37 (m, 10 H), 4.56 (d, *J* = 4.2 Hz, 1 H), 4.30 (d, *J* = 3.4 Hz, 1 H), 4.27 (d, *J* = 4.8 Hz, 1 H), 4.00 (dd, *J* = 3.0, 5.9 Hz, 1 H), 3.92 (app t, *J* = 9.7 Hz, 1 H), 3.38 (dd, *J* = 4.0, 10.8 Hz, 1 H), 2.74 (dd, *J* = 3.9, 10.8 Hz, 1 H), 2.63–2.59 (m, 1 H), 2.59 (d, superimposed on m, *J* = 16.3 Hz, 1 H), 2.35–2.31 (m, 1 H), 2.03 (dd, *J* = 3.3, 14.4 Hz, 1 H), 1.89–1.84 (m, 1 H), 1.75–1.70 (m, 1 H), 1.65 (dd, *J* = 3.6, 14.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 135.8, 129.8, 128.3, 127.7, 127.6, 98.9, 81.7, 72.5, 68.9, 62.5, 46.3, 46.0, 41.4, 37.7, 36.4, 35.0, 27.0, 25.8, 22.4, 19.2, 18.2, 13.2, −4.1, −5.1; high-resolution mass spectrum (CI, NH_3) *m/z* 667.3308 [(M + H)$^+$; calcd for $C_{37}H_{55}O_5SSi_2$: 667.3308].

Enone 68. A solution of ketone **67** (9.1 mg, 13.7 μmol) in THF (1.5 mL) was treated with HMPA (0.5 mL) and cooled to −10 °C. LDA in THF (0.5 M, 150 μL, 75 μmol) was added and the mixture stirred at −10 °C for 1.5 h. A second portion of LDA (20 μL, 10 μmol) was then introduced and the reaction mixture cooled to −78 °C. Following addition of benzeneseleninyl chloride (28.4 mg, 137 μmol) in THF (0.3 mL), the reaction mixture was stirred for 8 min further and quenched with aqueous NH_4Cl solution. Diethyl ether (2 mL) and dimethyl sulfide (0.5 mL) were added, and the mixture was warmed to ambient temperature. The aqueous phase was extracted with diethyl ether (3 × 30 mL), and the combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 5% ethyl acetate/hexanes as eluant gave **68** (7.2 mg, 79% yield) as an oil: IR ($CHCl_3$) 2962 (s), 2939 (s), 2882 (m), 2862 (s), 1746 (s), 1671 (s), 1472 (m), 1463 (m), 1429 (m), 1362 (w), 1252 (m), 1161 (s), 1141 (s), 1114 (s), 1058 (s), 1010 (s), 980 (m), 939 (w), 909 (w), 890 (m), 857 (m), 843 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.36 (m, 10 H), 6.85–6.83 (m, 1 H), 4.33 (dd, *J* = 1.9, 8.7 Hz, 1 H), 4.08–4.05 (m, 1 H), 4.02 (dd, *J* = 3.3, 6.5 Hz, 1 H), 3.92 (app t, *J* = 10.6 Hz, 1 H), 3.37 (dd, *J* = 4.0, 10.6 Hz, 1 H), 2.96 (app t, *J* = 8.3 Hz, 1 H), 2.73 (dd, *J* = 8.6, 10.3 Hz, 1 H), 2.65–2.53 (m, 3 H), 2.41–2.36 (m, 1 H), 2.03 (dd, *J* = 3.4, 14.2 Hz, 1 H), 1.86–1.83 (m, 1 H), 1.59 (dd, *J* = 4.1, 14.2 Hz, 1 H), 1.07 (s, 9 H), 0.91 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 135.8, 135.7, 135.5, 134.0, 133.5, 133.1, 130.1, 130.0, 127.9, 127.7, 99.4, 79.0, 78.8, 66.7, 63.1, 46.4, 45.2, 35.3, 34.9, 27.6, 27.0, 25.8, 19.3, 13.0, −4.5, −5.0; high-resolution mass spectrum (CI, NH_3) *m/z* 665.3077 [(M + H)$^+$; calcd for $C_{37}H_{53}O_5SSi_2$: 665.3152].

Allylic Alcohol 69. A solution of enone **68** (4.0 mg, 6.0 μmol) in THF (1.0 mL) was cooled to −10 °C and treated with HMPA (0.250 mL) followed by potassium bis(trimethylsilyl)amide (0.5 M in toluene, 48 μL, 24 μmol). The reaction mixture was stirred at −10 °C for 1 h and then cooled to −78 °C. The Davis (+)-camphorsulfonyl oxaziridine[31] (11.0 mg, 48 μmol) was added, and after 25 min further at −78 °C the reaction was quenched with aqueous NH_4Cl. Following addition of dimethyl sulfide (2 mL) and warming to room temperature, the aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 20:1 hexanes/ethyl acetate as eluant provided **69** (3.3 mg, 81% yield) as a colorless oil: IR ($CHCl_3$) 2960 (s), 2921 (s), 2857 (m), 1782 (s), 1461 (m), 1427 (m), 1350 (w), 1310 (w), 1246 (m), 1160 (s), 1128 (m), 1109 (s), 1052 (s), 988 (s), 897 (m), 829 (m), 691 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93–7.38 (m, 10 H), 5.54 (d, *J* = 10.0 Hz, 1 H), 5.40 (d, *J* = 10.0 Hz, 1 H), 4.66 (s, 1 H), 4.51 (s, 1 H), 4.46 (m, 1 H), 3.98 (d, *J* = 2.9 Hz, 1 H), 3.92 (app t, *J* = 10.6 Hz, 1 H), 3.45 (dd, *J* = 4.0, 10.8 Hz, 1 H), 3.03 (d, *J* = 4.6 Hz, 1 H), 2.96 (s, 1 H), 2.64 (dd, *J* = 2.7, 11.5 Hz, 1 H), 2.52 (d, *J* = 11.5 Hz, 1 H), 1.97 (dd, *J* = 3.2, 14.2 Hz, 1 H), 1.90–1.87 (m, 1 H), 1.58 (dd, *J* = 3.7, 14.2 Hz, 1 H), 1.11 (s, 9 H), 0.92 (s, 9), 0.85 (d, *J* = 13.0 Hz, 3 H), 0.04 (s, 6 H); high-resolution mass spectrum (CI, NH_3) *m/z* 698.3385 [(M + NH_4)$^+$; calcd for $C_{37}H_{56}NO_6SSi_2$: 698.3367].

Cis Diol 71. A solution of enone **68** (6.0 mg, 9.0 μmol) in dry pyridine (1 mL) was treated with osmium tetraoxide (0.031 M in diethyl ether, 0.28 mL, 8.6 μmol) at ambient temperature. After ca. 2 h, TLC analysis revealed consumption of the enone. Pyridine (1 mL) and aqueous $NaHSO_3$ were added, and the mixture was stirred for 30 min. Following extraction with chloroform (3 × 5 mL), the combined organic solutions were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 10% → 50% ethyl acetate/hexanes as eluant afforded **71** (3.1 mg, 49% yield) as a colorless oil: IR ($CHCl_3$) 3530 (br, w), 2924 (s), 2853 (m), 1775 (m), 1458 (m), 1420 (m), 1350 (m), 1242 (br, m), 1222 (m), 1101 (m), 1040 (s), 970 (m), 892 (m), 825 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.38 (m, 10 H), 4.57 (s, 1 H), 4.38 (d, *J* = 3.2 Hz, 1 H), 4.24 (m, 1 H), 3.99 (d, *J* = 2.8 Hz, 1 H), 3.93 (app t, *J* = 10.9 Hz, 1 H), 3.61 (dd, *J* = 3.6, 11.8 Hz, 1 H), 3.43 (dd, *J* = 3.8, 10.9 Hz, 1 H), 3.16 (br s, 1 H), 2.90–2.87 (m, 1 H), 2.64 (d, *J* = 12.0 Hz, 1 H), 2.60–2.58 (m, 1 H), 2.07 (dd, *J* = 3.2, 14.2 Hz, 1 H), 1.93–1.88 (m, 1 H), 1.72 (dd, *J* = 3.5, 14.2 Hz, 1 H), 1.45–1.42 (m, 1 H), 1.32 (dd, *J* = 12.7, 25.1 Hz, 1 H), 1.10 (s, 9 H), 0.90 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H); high-resolution mass spectrum (CI, NH_3) *m/z* 716.3421 [(M + NH_4)$^+$; calcd for $C_{37}H_{58}NO_7SSi_2$: 716.3473].

6-Epibreynolide (72). Diol **71** (3.1 mg, 4.44 μmol) was dissolved in methanol (1.5 mL) at ambient temperature and treated with concentrated HCl (0.25 mL). The reaction mixture was stirred for 18 h and then concentrated in vacuo. Flash chromatography with 10% methanol/chloroform as eluant gave **72** (1.5 mg, 99% yield) as an oil: IR (KBr) 3368 (br, s), 2958 (s), 2928 (s), 2854 (m), 1778 (m), 1732 (m), 1666 (m), 1463 (m), 1439 (m), 1409 (m), 1284 (m), 1122 (s), 1101 (m), 1045 (s), 1013 (s), 981 (m), 872 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 4.40 (br s, 2 H), 4.29 (d, *J* = 2.2 Hz, 1 H), 4.14 (d, *J* = 3.3 Hz, 1 H), 4.03 (d, *J* = 4.9 Hz, 1 H), 4.01 (dd, *J* = 1.2, 7.0 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.81 (app t, *J* = 11.1 Hz, 1 H), 3.75–3.70 (m, 1 H), 3.45 (dd, *J* = 4.5, 11.1 Hz, 1 H), 3.23 (d, *J* = 7.3 Hz, 1 H), 3.16 (dd, *J* = 4.4, 11.5 Hz, 1 H), 2.86–2.82 (m, 1 H), 2.56–2.52 (m, 1 H), 2.00 (dd, *J* = 3.7, 14.2 Hz, 1 H), 1.88–1.85 (m, 1 H), 1.80 (dd, *J* = 3.7, 14.2 Hz, 1 H), 1.64–1.56 (m, 1 H), 1.47–1.43 (m, 1 H), 0.87 (d, *J* = 7.0 Hz, 3 H); high-resolution mass spectrum (CI, NH_3) *m/z* 364.1451 [(M + NH_4)$^+$; calcd for $C_{15}H_{26}NO_7S$: 364.1430].

β,γ-Enone 73. A solution of enone **68** (1.0 mg, 1.5 μmol) in THF (1 mL) was cooled to 0 °C and treated with saturated aqueous potassium carbonate (0.75 mL). The mixture was allowed to slowly warm to room temperature. After 24 h ether (5 mL) was added and the aqueous layer extracted wtih diethyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 10% ethyl acetate/hexanes as eluant afforded **73** (0.90 mg, 90% yield) as an oil: IR ($CHCl_3$) 3020 (m), 2963 (s), 2939 (s), 2863 (s), 1770 (s), 1462 (m), 1429 (m), 1250 (m), 1165 (m), 1112 (m), 1061 (s), 984 (m), 832 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72–7.30 (m, 10 H), 5.51–5.48 (m, 1 H), 5.24–5.21 (m, 1 H), 4.78–4.76 (m, 1 H), 4.43 (br s, 1 H), 4.34–4.33 (m, 1 H), 3.98 (d, *J* = 2.9 Hz, 1 H), 3.91 (app t, *J* = 10.7 Hz, 1 H), 3.38 (dd, *J* = 4.0, 10.7 Hz, 1 H), 3.29–3.26 (m, 1 H), 2.96 (br s, 1 H), 2.65 (dd, *J* = 3.1, 11.4 Hz, 1 H), 2.50 (d, *J* = 11.4 Hz, 1 H), 1.98 (dd, *J* = 3.3, 14.2 Hz, 1 H), 1.87–1.83

(m, 1 H), 1.57 (dd, J = 3.7, 14.2 Hz, 1 H), 1.10 (s, 9 H), 0.92 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 665.3121 [$(M + H)^+$; calcd for $C_{37}H_{53}O_5SSi_2$: 665.3152].

β-Methoxy Ketone 74. A solution of enone **68** (1.9 mg, 2.86 μmol) in methanol (1 mL) was cooled to 0 °C and treated with saturated aqueous K_2CO_3 (0.5 mL). After 5 min the reaction was quenched with saturated NH_4Cl solution and the mixture extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 5% ethyl acetate/hexanes as eluant gave **74α** (1.0 mg, 50% yield) and **74β** (0.54 mg, 27%), both as colorless oils.

74α: IR ($CHCl_3$) 3000 (w), 2924 (s), 2856 (s), 1767 (s), 1457 (w), 1421 (w), 1250 (m), 1226 (m), 1211 (m), 1198 (s), 1136 (m), 1100 (s), 1056 (s), 918 (w), 810 (br, m), 692 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.38 (m, 10 H), 4.64 (d, J = 3.9 Hz, 1 H), 4.33 (d, J = 3.0 Hz, 1 H), 4.21 (d, J = 4.9 Hz, 1 H), 4.00 (d, J = 2.6 Hz, 1 H), 3.90 (app t, J = 10.9 Hz, 1 H), 3.39 (dd, J = 4.0, 10.9 Hz, 1 H), 3.29 (s, 3 H), 3.07 (td, J = 11.4, 3.8 Hz, 1 H), 2.77 (dd, J = 4.0, 11.9 Hz, 1 H), 2.61–2.58 (m, 2 H), 2.48–2.43 (m, 1 H), 2.09 (dd, J = 2.9, 13.9 Hz, 1 H), 1.91–1.88 (m, 2 H), 1.67–1.63 (m, 2 H), 1.10 (s, 9 H), 1.04–0.94 (m, 1 H), 0.91 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 697.3458 [$(M + H)^+$; calcd for $C_{38}H_{57}O_6SSi_2$: 697.3414].

74β: IR ($CHCl_3$) 2927 (s), 2858 (s), 1770 (s), 1460 (m), 1423 (m), 1356 (w), 1248 (m), 1161 (m), 1123 (m), 1091 (s), 1061 (s), 980 (m), 892 (m), 827 (m), 692 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.37 (m, 10 H), 4.54 (d, J = 5.1 Hz, 1 H), 4.33 (d, J = 4.4 Hz, 1 H), 4.0 (m, 1 H), 3.88 (apparent t, J = 10.6 Hz, 1 H), 3.73–3.70 (m, 1 H), 3.38 (dd, J = 4.1, 10.6 Hz, 1 H), 3.05 (s, 3 H), 2.77 (dd, J = 4.1, 11.8 Hz, 1 H), 2.67–2.57 (m, 3 H), 1.87–1.83 (m, 3 H), 1.60–1.54 (m, 1 H), 1.10 (s, 9 H), 0.98–0.93 (m, 1 H), 0.90 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 697.3383 [$(M + H)^+$; calcd for $C_{38}H_{57}O_6SSi_2$: 697.3414].

β-Benzyloxy Ketones 75α and 75β. A stirred solution of enone **68** (3.0 mg, 4.5 μmol) in dry benzyl alcohol (1.5 mL) was cooled to 0 °C and treated with dry Cs_2CO_3. After 2 h at 0 °C, the reaction was quenched with pH 7.0 buffer and the mixture extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 4% ethyl acetate/hexanes as eluant provided a mixture of **75α** and **75β** accompanied by olefin **73** (0.6 mg, 21% yield). Further purification by HPLC with 12.5:1 hexanes/ethyl acetate as eluant gave **75α** (1.5 mg, 43% yield) and **75β** (0.6 mg, 17%), both as colorless oils.

75α: IR ($CHCl_3$) 2961 (s), 2952 (s), 2858 (s), 1770 (s), 1590 (br, m), 1461 (m), 1425 (m), 1352 (w), 1247 (m), 1159 (m), 1121 (m), 1100 (m), 1062 (s), 980 (m), 890 (m), 825 (m), 788 (m), 692 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.16 (m, 15 H), 4.55 (d, J = 5.3 Hz, 1 H), 4.36–4.33 (m, 2 H), 4.23 (AB q, J_{AB} = 10.9 Hz, $\Delta\nu_{AB}$ = 75.7 Hz, 2 H), 4.02–4.00 (m, 1 H), 3.87–3.78 (m, 2 H), 3.33 (dd, J = 4.0, 10.8 Hz, 1 H), 2.78–2.63 (m, 4 H), 1.83–1.78 (m, 1 H), 1.75 (dd, J = 3.3, 14.4 Hz, 1 H), 1.60–1.50 (m, 2 H), 1.11 (s, 9 H), 1.07–1.00 (m, 1 H), 0.82 (s, 9 H), 0.80 (d, J = 6.9 Hz, 3 H), –0.14 (s, 3 H), –0.15 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 790.3967 [$(M + NH_4)^+$; calcd for $C_{40}H_{64}NO_6SSi_2$: 790.3993].

75β: IR ($CHCl_3$) 2965 (s), 2923 (s), 2857 (s), 1768 (s), 1587 (br, w), 1460 (m), 1422 (m), 1357 (m), 1247 (m), 1160 (s), 1138 (s), 1100 (s), 1058 (s), 977 (w), 919 (w), 829 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.25 (m, 15 H), 4.60 (d, J = 3.2 Hz, 1 H), 4.48 (AB q, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 108.6 Hz, 2 H), 4.33 (d, J = 3.7 Hz, 1 H), 4.16 (d, J = 4.9 Hz, 1 H), 3.89 (d, J = 2.8 Hz, 1 H), 3.85 (apparent t, J = 10.9 Hz, 1 H), 3.34 (dd, J = 4.0, 10.9 Hz, 1 H), 3.25 (td, J = 11.0, 3.5 Hz, 1 H), 2.80 (dd, J = 4.0, 11.8 Hz, 1 H), 2.65 (dd, J = 4.3, 10.4 Hz, 1 H), 2.62 (d, J = 11.8 Hz, 1 H), 2.42–2.38 (m, 1 H), 1.87–1.82 (m, 2 H), 1.66 (dt, J = 3.8, 7.7 Hz, 1 H), 1.21 (dd, J = 3.5, 14.3 Hz, 1 H), 1.13–1.03 (m, 1 H), 1.09 (s, superimposed on m, 9 H), 0.87 (s, 9 H), 0.81 (d, J = 6.9 Hz, 3 H), 0.00 (s, 3 H), –0.01 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 790.1681 [$(M + H)^+$; calcd for $C_{40}H_{64}NO_6SSi_2$: 790.3967].

α-Hydroxy-β-benzyloxy Ketone 77. A solution of ketone **75α** (1.2 mg, 1.5 μmol) in THF (1 mL) was cooled to –78 °C and treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene, 60 μL, 20 equiv). The reaction mixture was stirred at –78 °C for 45 min, and then a solution of the Davis (+)-camphorsulfonyl oxaziridine[31] (25 mg, 109 μmol, 73 equiv) in THF (0.5 mL) was added. After an additional 40 min at –78 °C, the mixture was warmed to 0 °C and stirred for 45 min further. The reaction was quenched with saturated NH_4Cl solution. Dimethyl sulfide (2 mL) was added, and the resultant mixture was then warmed to ambient temperature for 1 h. The aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 4:1 hexanes/ethyl acetate as eluant afforded **77** (1.2 mg, 97% yield) as an oil: IR ($CHCl_3$) 3370 (br), 2946 (s), 2857 (m), 1780 (m), 1590 (br s), 1460 (m), 1424 (m), 1249 (m), 1122 (s), 1108 (s), 1050 (s), 980 (w), 828 (m), 793 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.16 (m, 15 H), 4.39 (s, 1 H), 4.35 (d, J = 4.1 Hz, 1 H), 4.23 (AB q, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 79.5 Hz, 2 H), 3.86 (apparent t, J = 10.9 Hz, 1 H), 3.82 (m, 1 H), 3.69 (br s, 1 H), 3.36 (dd, J = 3.7, 10.9 Hz, 1 H), 2.84 (dd, J = 3.2, 11.9 Hz, 1 H), 2.76–2.72 (m, 1 H), 2.67 (d, J = 11.9 Hz, 1 H), 2.59 (s, 1 H), 2.38–2.29 (m, 1 H), 1.84–1.80 (m, 1 H), 1.79–1.72 (m, 2 H), 1.63–1.60 (m, 1 H), 1.40–1.36 (m, 1 H), 1.12 (s, 9 H), 0.82 (s, 9 H), 0.81 (d, J = 8.9 Hz, 3 H), –0.14 (s, 6 H); high-resolution mass spectrum (CI, NH_3) m/z 806.3891 [$(M + NH_4)^+$; calcd for $C_{44}H_{64}NO_7SSi_2$: 806.3942].

β-Allyloxy Ketones 76α and 76β. Enone **68** (6.0 mg, 9.0 μmol) was dried azeotropically with benzene and dissolved in allyl alcohol (3 mL, dried by filtration through activated neutral alumina). The solution was cooled to 0 °C and treated with powdered cesium carbonate (25 mg, 76.9 μmol) in one portion. After 15 min the reaction was quenched with pH 7.0 buffer solution. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. Flash chromatography with 5% ethyl acetate/hexanes as eluant followed by purification via HPLC with 5% ethyl acetate/hexanes as eluant then afforded **76α** (3.7 mg, 57% yield) and **76β** (1.5 mg, 23%).

76α: oil; IR ($CHCl_3$) 2960 (s), 2938 (s), 2892 (m), 2864 (s), 1773 (s), 1462 (m), 1429 (m), 1360 (w), 1249 (m), 1162 (m), 1145 (m), 1128 (m), 1103 (m), 1063 (s), 982 (m), 928 (w), 896 (m), 830 (m), 696 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.36 (m, 10 H), 5.77–5.70 (m, 1 H), 5.19–5.10 (m, 2 H), 4.55 (d, J = 5.4 Hz, 1 H), 4.35–4.33 (m, 2 H), 3.98–3.97 (m, 1 H), 3.90–3.85 (m, 2 H), 3.78 (dd, J = 5.7, 12.1 Hz, 1 H), 3.63 (dd, J = 6.0, 12.1 Hz, 1 H), 3.37 (dd, J = 4.0, 10.8 Hz, 1 H), 2.78 (dd, J = 4.0, 11.8 Hz, 1 H), 2.67–2.64 (m, 3 H), 1.88–1.80 (m, 3 H), 1.53–1.50 (m, 1 H), 1.10 (s, 9 H), 1.02–0.91 (m, 1 H), 0.89 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 135.9, 135.8, 134.5, 133.8, 133.6, 129.8, 129.7, 127.7, 117.3, 99.5, 81.8, 72.7, 71.7, 70.4, 67.0, 62.6, 46.8, 45.3, 40.2, 38.0, 35.2, 34.1, 27.0, 25.9, 25.4, 19.1, 18.2, 13.2, –4.0, –5.2; high-resolution mass spectrum (CI, NH_3) m/z 723.3600 [$(M + H)^+$; calcd for $C_{40}H_{58}O_6SSi_2$: 723.3570].

76β: oil; IR ($CHCl_3$) 3018 (w), 2962 (s), 2938 (s), 2894 (m), 2832 (s), 1761 (s), 1463 (w), 1439 (m), 1362 (w), 1251 (m), 1228 (m), 1200 (m), 1161 (m), 1142 (m), 1103 (m), 1061 (s), 1003 (w), 980 (w), 921 (m), 832 (m), 697 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.38 (m, 10 H), 5.82–5.74 (m, 1 H), 5.22–5.14 (m, 2 H), 4.63 (d, J = 3.9 Hz, 1 H), 4.32 (d, J = 3.5 Hz, 1 H), 4.20 (d, J = 4.3 Hz, 1 H), 4.03–3.99 (m, 2 H), 3.91–3.84 (m, 2 H), 3.40 (dd, J = 4.1, 10.9 Hz, 1 H), 3.25 (td, J = 3.7, 14.4 Hz, 1 H), 2.78 (dd, J = 3.9, 15.7 Hz, 1 H), 2.63–2.60 (m, 2 H), 2.46–2.43 (m, 1 H), 2.04 (dd, J = 3.2, 14.1 Hz, 1 H), 1.90–1.86 (m, 1 H), 1.65 (dd, J = 3.7, 14.1 Hz, 1 H), 1.59–1.55 (m, 1 H), 1.10 (s, 9 H), 1.07–1.02 (m, 1 H), 0.91 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 135.8, 134.8, 129.9, 127.8, 127.7, 117.7, 81.8, 74.7, 72.3. 70.1, 66.9, 62.7, 48.3, 46.8, 46.0, 37.8, 36.6, 34.9, 28.9, 27.0, 25.8, 18.2, 13.2, –4.0; high-resolution mass spectrum (CI, NH_3) m/z 723.3661 [$(M + H)^+$; calcd for $C_{40}H_{58}O_6SSi_2$: 723.3570].

α-Hydroxy-β-allyloxy Ketone 79. A solution of ketone **76α** (2.0 mg, 2.77 μmol) in THF (2.2 mL) was cooled to –78 °C and treated with potassium bis(trimethylsilyl)amide (1.0 M in toluene, 125 μL, 45 equiv). The reaction mixture was stirred at –78 °C for 45 min, and then a solution of the Davis (+)-camphorsulfonyl oxaziridine[31] (30 mg, 131 μmol, 47 equiv) in THF (0.2 mL) was added. After 40 min at –78 °C, the mixture was warmed to 0 °C and stirred for 45 min further. The excess oxaziridine was reduced by addition of dimethyl sulfide (1 mL) followed by warming to room temperature for 30 min. The reaction mixture was then cooled to 0 °C and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography with 20% ethyl acetate/hexanes as eluant gave **79** (1.5 mg, 73% yield) as an oil: IR ($CHCl_3$) 3540 (w), 3018 (m), 2937 (s), 2890 (m), 2862 (s), 1787 (m), 1462 (m), 1429 (m), 1360 (m), 1251 (m), 1162 (m), 1131 (m), 1103 (s), 1088 (s), 1058 (s), 981 (m), 900 (m), 830 (m), 694 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00–7.37 (m, 10 H), 5.76–5.68 (m, 1 H), 5.19–5.13 (m, 2 H), 4.39 (s, 1 H), 4.37 (d, J = 3.7 Hz, 1 H), 4.34 (d, J = 4.6 Hz, 1 H), 3.98–3.96 (m, 1 H), 3.89 (apparent t, J = 10.7 Hz, 1 H), 3.81 (dd J = 5.8, 12.0 Hz, 1 H), 3.63 (dd, J = 6.3, 12.0 Hz, 1 H), 3.59 (s, 1 H), 3.40 (dd, J = 4.0, 10.9 Hz, 1 H), 2.86 (dd, J = 4.0, 11.9 Hz, 1 H), 2.70–2.57 (m, 2 H), 1.93–1.84 (m, 3 H), 1.47–1.31 (m, 2 H), 1.11 (s, 9 H), 0.88 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.07 (s, 3 H), 0.02 (s,

3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 135.8, 135.7, 134.1, 133.8, 133.5, 129.9, 129.8, 127.7, 118.1, 99.3, 81.7, 77.9, 75.2, 74.1, 70.7, 66.8, 62.5, 45.6, 40.8, 38.1, 35.0, 34.3, 27.0, 25.8, 22.3, 19.1, 18.2, 13.2, -4.01, -5.25; high-resolution mass spectrum (CI, NH_3) m/z 756.3742 [(M + NH_4)$^+$; calcd for $C_{40}H_{62}NO_7SSi_2$: 756.3786].

(±)-Breynolide (3). Allyl ether **79** (3.1 mg, 4.2 μmol) was dissolved in 90% EtOH. DABCO (2 mg, 17.8 μmol, 4.2 equiv) was added, and the mixture was warmed to 80 °C. Following the introduction of $RhCl(PPh_3)_3$ (1.0 mg, 1.0 μmol, 0.26 equiv), the reaction mixture was stirred for 15 min, cooled to room temperature, and quenched with pH 7.0 buffer solution. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic solutions were concentrated in vacuo. The crude enol ether was taken up in methanol (1 mL), and concentrated HCl (300 μL) was added. The resultant mixture was stirred at ambient temperature for 18 h and then concentrated in vacuo. HPLC with 1:11.5 methanol/chloroform as eluant furnished (±)-breynolide (3) (1.1 mg, 76% yield) as an oil: IR (KBr) 3369 (br, s), 2960 (m), 2932 (s), 1782 (s), 1607 (m), 1464 (m), 1429 (m), 1412 (m), 1389 (m), 1339 (m), 1236 (m), 1163 (s), 1126 (s), 1086 (s), 1056 (s), 1045 (s), 1031 (s), 1018 (s), 982 (s), 868 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 4.65 (s, 1 H), 4.40-4.39 (m, 1 H), 4.33 (s, 1 H), 4.15 (d, J = 5.5 Hz, 1 H), 4.12 (d, J = 5.2 Hz, 1 H), 4.08 (d, J = 3.3 Hz, 1 H), 4.00 (br s, 1 H), 3.86-3.85 (m, 1 H), 3.77 (apparent t, J = 11.2 Hz, 1 H), 3.43 (dd, J = 4.4, 11.2 Hz, 1 H), 3.11 (dd, J = 4.0, 11.4 Hz, 1 H), 3.08 (d, J = 8.0 Hz, 1 H), 2.82-2.73 (m, 2 H), 1.95 (dd, J = 3.9, 14.1 Hz, 1 H), 1.88 (dd, J = 3.5, 14.1 Hz, 1 H), 1.84-1.81 (m, 1 H), 1.71 (td, J = 13.6, 2.2 Hz, 1 H), 1.50 (dt, J = 3.8, 13.5 Hz, 1 H), 0.87 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 211.8, 160.1, 80.4, 77.0, 75.4, 71.0, 67.1, 62.6, 46.2, 40.9, 38.4, 35.3, 34.6, 27.9, 13.0; high-resolution mass spectrum (CI, NH_3) m/z 364.1417 [(M + NH_4)$^+$; calcd for $C_{15}H_{26}NO_7S$: 364.1430].

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Supplementary Material Available: Tables of experimental details, positional parameters, and thermal parameters for X-ray analyses of **20b**, **27**, **40**, **44**, **49**, and **65** (41 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Calyculin A

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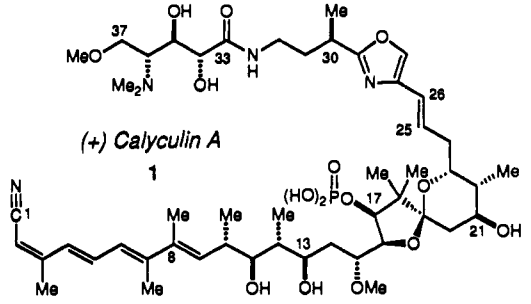
Abstract: A convergent asymmetric synthesis of the marine natural product calyculin A has been accomplished through the union of the two subunits comprising the C_1-C_{25} and C_{26}-C_{37} portions of the molecule. These fragments were constructed utilizing auxiliary-based asymmetric aldol, alkylation, hydroxylation, and Michael reactions to establish 10 of the 15 stereogenic centers. The remaining chirality was incorporated through internal asymmetric induction. Stereoselective Wittig coupling of the two fragments and subsequent deprotection provided synthetic calyculin A. The spectral properties of the synthetic material were in complete agreement with those of the natural material except for the optical rotation which was equal and opposite in sign to that of the natural material. The absolute configuration of (-)-calyculin A has thus been shown to be opposite to that illustrated in structure **1**.

Calyculin A (**1**) was isolated in 1986 by Fusetani and co-workers from the marine sponge *Discodermia calyx*.[2] Its relative stereostructure was determined by X-ray analysis. Degradation



of the natural product by acidic hydrolysis allowed the isolation of a fragment corresponding to the C_{33}-C_{37} γ-amino acid.[3] Comparison of the circular dichroism spectrum of this fragment to those of simple (*S*)-α-hydroxy acids led to a tentative assignment of the absolute configuration of (-)-calyculin A as being enantiomeric to that illustrated in structure **1**. A recent unambiguous synthesis of this degradation product by Shioiri and co-workers confirmed the Fusetani absolute configuration assignment.[4]

Interest in *D. calyx* and its active components was prompted by its activity in the anti-cell-division assay using fertilized starfish eggs and in cytotoxicity tests against P388 and L1210 leukemia cells.[5] It has since been demonstrated that calyculin A is a potent inhibitor of protein phosphatases 1 and 2a, two of the four major protein-serine/threonine phosphatases, with IC_{50} values on the order of 1 nM.[6] This activity profile was shown to be similar to that of the marine natural product okadaic acid.[7] The activity of both compounds is fully complementary to and equipotent with that of the phorbol ester class of protein kinase C activators in

(1) Taken, in part, from the Ph.D. Thesis of J. R. Gage, Harvard University, 1991.
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