1.58 (ddd, 1 H, J = 4.4, 5.2, 15.5 Hz), 1.57 (s, 3 H), 1.23 (s, 3 H), 0.95 (m, 1 H), 0.87 (s, 3 H), 0.86 (s, 3 H), 0.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 212.58 (s), 174.02 (s), 139.01 (s), 137.75 (s), 133.72 (s), 130.81 (d), 130.04 (d), 129.82 (d), 129.01 (d), 128.78 (d), 128.07 (d), 125.66 (s), 78.97 (d), 68.89 (t), 64.89 (d), 62.61 (s), 46.71 (d), 46.20 (d), 46.20 (t), 43.97 (s), 40.60 (t), 37.01 (t), 34.65 (t), 33.67 (q), 25.84 (q), 19.82 (t), 17.98 (q), 14.94 (q); IR ($CHCl_3$) 1709, 1679 cm^{-1}; mass spectrum m/e 456 (32%, $M^+ - (CH_3)_3SiCH_2CH_2$), 438 (55%, $M^+ - (CH_3)_3SiCH_2CH_2 - H_2O$), 91 (100%); exact mass: calcd for $C_{30}H_{34}NO_3$ ($M^+ - (CH_3)_3SiCH_2CH_2$) 456.254, found 456.253.

35: ^{1}H NMR ($CDCl_3$ 470 MHz, in part) δ 7.4-7.0 (m, 10 H), 6.49 (s, 1 H), 5.41 (d, 1 H, J = 14.9 Hz), 4.57 (s, 1 H), 3.94 (m, 1 H), 3.47 (m, 1 H), 3.21 (dd, 1 H, J = 6.6, 7.7 Hz), 3.20 (d, 1 H, J = 14.9 Hz), 2.87 (dd, 1 H, J = 6.6, 13.3 Hz), 2.75 (dd, 1 H, J = 7.7, 13.3 Hz), 2.31 (m, 1 H), 1.97 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 169.35 (s), 145.58 (d), 138.94 (s), 138.70 (s), 134.11 (s), 131.11 (d), 130.14 (d), 129.85 (d), 129.41 (d), 128.54, 128.31, 127.14, 127.53, 97.95 (d), 72.29 (s), 66.85 (t), 59.68 (d), 49.59 (t), 47.38 (d), 44.36 (t), 35.33 (t), 34.19 (t), 33.35 (s), 29.91 (q), 29.76 (q), 19.67 (t), 18.18 (q), 16.04 (q); IR ($CHCl_3$) 1635 cm^{-1}; mass spectrum m/e 557 (3%, M^+), 438 (100%, $M^+ - (CH_3)_3SiCH_2CH_2 - H_2O$).

Acknowledgment. We thank the National Science Foundation (CHE 79-03953) and the National Institute of Health (AI-13073) for their generous support of this work. The carbon-13 NMR data reported in this investigation were obtained on the departmental CFT-20 and Varian XL 200 instruments provided by NSF Grants 7842 and CHE 800-4246. We thank Dr. Preston Conrad and Professor J. Grutzner for providing those spectra. We also thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 470-MHz ^{1}H NMR spectrometer and John Saddler and Phil Hamann for providing those spectra.

Registry No. 8, 13505-32-3; 9, 82495-70-3; **10**, 82495-71-4; **11**, 74974-70-2; **12**, 74974-71-3; **13-*Z***, 74974-72-4; **14-*Z***, 74974-74-6; **14-*E***, 74974-79-1; EL-**14-*E***, 82536-02-5; **15-*Z***, 74974-75-7; EL-**15-*Z***, 82535-49-7; **15-*E***, 74974-80-4; **16-*Z***, 74974-77-9; **16-*E***, 74974-78-0; **17**, 26487-92-3; EL-**18-*E***, 82495-72-5; **18-Z**, 82569-77-5; EL-**17**, 82495-73-6; EL-**20**, 82495-74-7; **21**, 76513-69-4; **229**, 4009-98-7; **226**, 82495-75-8; **23-*EZ***, 82495-76-9; **23-*ZZ***, 82495-77-0; **24-*EZ***, 82495-78-1; **24-*ZZ***, 82495-79-2; **25-*EZ***, 82495-80-5; **25-*ZZ***, 82495-81-6; **26-*EZ***, 82495-82-7; **26-*ZZ***, 82495-83-8; EL-**27-*ZE***, 82535-50-0; EL-**27-*EE***, 82535-51-1; EL-**28-*ZE***, 82535-52-2; DL-**28-*EE***, 82535-53-3; **29**, 82495-84-9; **30**, 74974-81-5; **31**, 82495-85-0; **32**, 82495-86-1; **33**, 74974-82-6; **34**, 82522-07-4; **35**, 82511-63-5; L-(-)-phenylalanine, 63-91-2.

Supplementary Material Available: Tables of ^{13}C NMR of amino dienes (2 pages). Ordering information is given on any current masthead page.

Conjugate Addition of β-Keto Ester Dianions to Vinyl Sulfones: A New Procedure for Seven-Ring Annulation. Synthesis of a Chiral Cytochalasin C Intermediate via an Intramolecular Diels-Alder Reaction of a Chiral *Z* Diene[1,2]

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Abstract: Conjugate addition reactions of dimethylhydrazone anions and β-keto ester dianions to a chiral sterically hindered vinyl sulfone are reported. Further functionalization of the resulting α-sulfonyl-stabilized anion by alkylation with allyl bromide followed by reductive desulfonylation, ozonolysis, and intramolecular aldol reaction provides an enolized α-carboalkoxy enone, the net result being a new annulation sequence for the synthesis of seven-membered rings. Determination of the relative stereochemistry of conformationally mobile cis- and trans-fused bicyclo[5.4.0] systems by combined Karplus/molecular mechanics calculations is described. Cyclization of a pair (**40**, **3**) of chiral *Z* dienes via an intramolecular Diels-Alder reaction stereospecifically affords chiral polycyclic adducts (**41**, **4**) that are potential precursors for cytochalasin C.

Pursuant to our goal of the total synthesis of *l*(-)-cytochalasin C (**5**), we wished to prepare the trans-fused bicyclo[5.4.0] system **3** and effect its cyclization to lactam **4**. Confidence in the viability of the *Z* diene bearing a chiral substituent at the pentadienylic center to serve as a cyclization substrate was bolstered by our earlier model studies.[1] Cyclization of diene **3** to lactam **4**[4] would *simultaneously create five new asymmetric relationships* induced by the specified C-3 center (the four-starred "standard" centers subject to Diels-Alder control as well as the ultimate relationship that results from the diene selecting a single diastereotopic face of the dienophile).

The plan for synthesis of the cyclization substrate **3** was based upon the union of the previously prepared chiral dienyl amine **1**[1] and oxocycloheptencarboxylic acid **2**. Synthesis of **2** was envisaged to arise from an annulation approach with chiral vinyl sulfone *d*-**8**, which in turn was to be prepared from the previously available racemic sulfide alcohol *dl*-**6**[5] (Scheme I).

Synthesis of Chiral Vinyl Sulfone *d*-8. Treatment of racemic sulfide alcohol *dl*-**6**[5] with 2 equiv of *m*-chloroperoxybenzoic acid in methylene chloride smoothly affords β-hydroxy sulfone *dl*-**7**. Subsequent reaction of *dl*-**7** with phosphorus oxychloride in pyridine provides *racemic* vinyl sulfone *dl*-**8**.

Sulfide alcohol *dl*-**6**[5] also provides a ready entry to the chiral vinyl sulfones *d*-**8** and *l*-**8**. Reaction of *dl*-**6** with excess neat α-phenethyl isocyanate[6] at 140 °C for 18 h affords a near-quantitave yield of the diastereomeric sulfide urethanes **9**/**10**. Although it was possible to purify urethane **9** by direct crystallization, it was more convenient to simply oxidize the crude **9**/**10** mixture with *m*-chloroperoxybenzoic acid to afford a mixture of sulfone urethanes **11**/**12**. Separation of the individual diastereomers **11** and **12** proved to be exceptionally convenient and could

(1) Cytochalasin Support Studies. 5. For paper 4, see: Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) Syntheses via Vinyl Sulfones. 9. For paper 8 in this series, see ref 5.
(3) Postdoctoral Research Associate.
(4) Lactam 4 is a potential substrate for enolate-promoted fragmentation to establish the macrocyclic moiety of cytochalasin C. See: Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567.
(5) Musser, A. K.; Fuchs, P. L. *J. Org. Chem.* **1982**, *47*, 3121.
(6) Gracheva, R. A.; Terent'ev, A. P.; Bezruchka, V. T. *Zh. Org. Khim., Engl. Transl.* **1969**, *5*, 1044.

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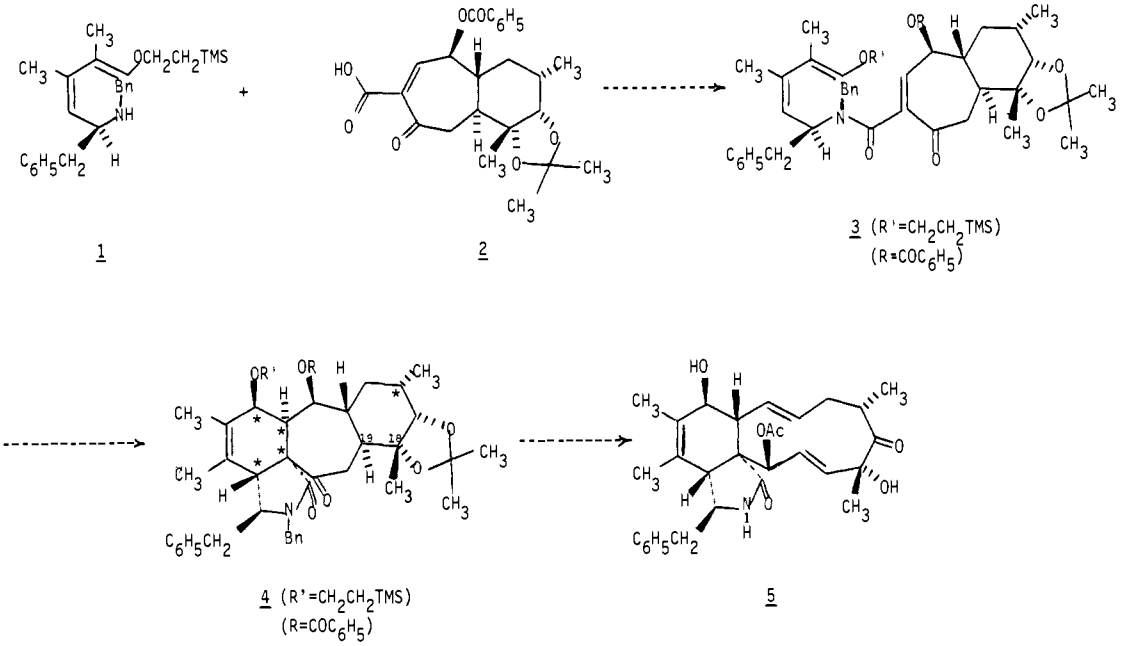
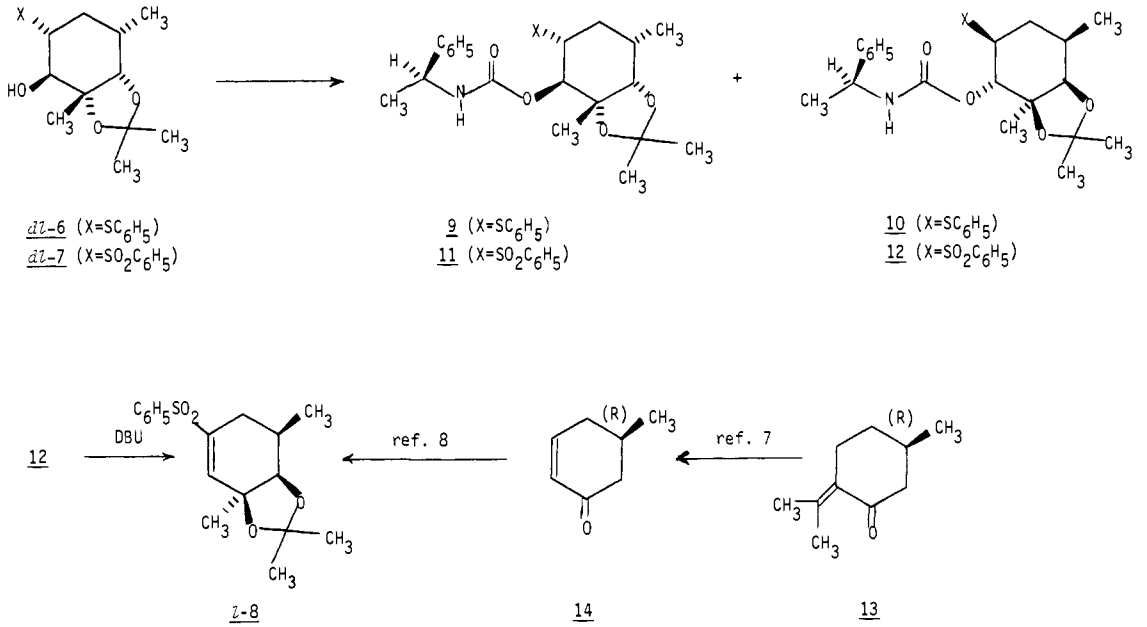
Scheme I



Scheme II



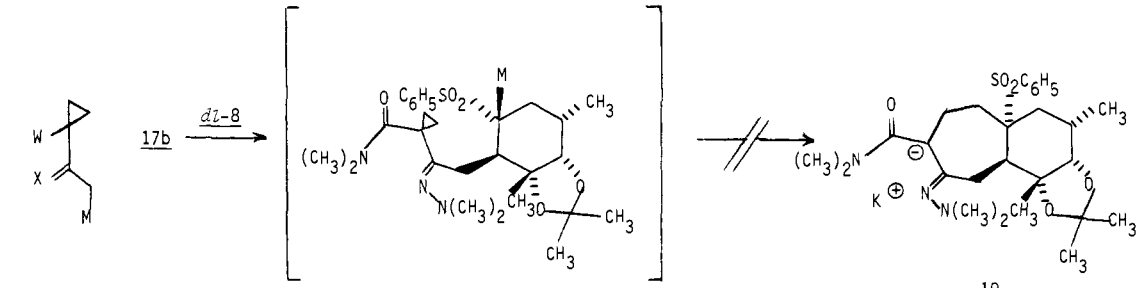
be done on a large scale by medium-pressure liquid chromatography. Separate treatment of **11** and **12** with DBU in hot THF afforded the pure enantiomers *d*-**8** and *l*-**8**, respectively. Assignment of the absolute configuration of *l*-**8** was established by direct comparison with an authentic sample[8] prepared from (*R*)-5-methylcyclohexenone **14**[7] (via (*R*)-pulegone **13**)[5] (Scheme II).

Seven-Ring Annulations with Vinyl Sulfone 8. Our previous success at affecting sequential conjugate addition/alkylation reactions with vinyl sulfones[2] prompted us to investigate extension of this strategy for the development of a seven-ring annulation process. The initial attempt at conversion of vinyl sulfone *dl*-**8** to the trans-fused bicyclo[5.4.0] system **2**[9] required for the proposed intramolecular Diels–Alder reaction (**3** → **4**) involved a conjugate addition/intramolecular homoconjugate addition sequence (**17** → **18** ⇝ **19**).

Conversion of keto acid **15**[10] to keto amide **16** followed by formation of the dimethylhydrazone derivative **17a** was accomplished via standard methods.[11,12] The indicated anti stereochemistry of the dimethylhydrazone moiety was established by comparison of the ^{13}C NMR chemical shifts of the "acetyl" methyl carbon and the quaternary cyclopropane carbon in compounds **16** and **17a**. The differential shielding increments ($\delta_{16} - \delta_{17a}$) of 12.1 ppm for the "acetyl" methyl group and 4.9 ppm for the quaternary carbon are in perfect accord with those values found in similar systems for the geometry in which the dimethylamino moiety is syn to the "acetyl" methyl group.[13]

(7) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.
(8) Hensel, M. J.; Fuchs, P. L., unpublished results.
(9) Inspection of models for the ultimate enolate-promited fragmentation[4] suggests that of the two trans-fused diastereomeric [5.4.0] systems, the one (**4**) in which the C-19 carbon has been formed from the same face as the C-18 methyl group appears to be a vastly more attractive substrate.
(10) Singh, R. K.; Danishefsky, S. *J. Org. Chem.* **1975**, *40*, 2969.
(11) Middlemas, E. D.; Quin, L. D. *J. Org. Chem.* **1979**, *44*, 2587.
(12) Moretti, I.; Torre, G. *Synthesis* **1970**, 141.
(13) Bunnell, C. A.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2614.

Scheme III

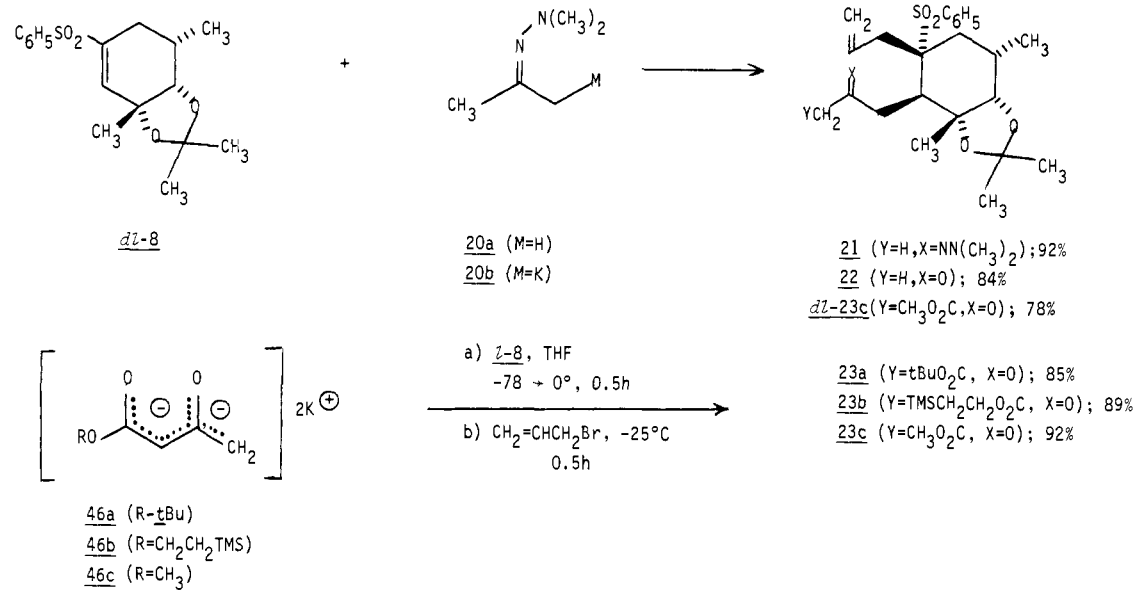


15 (W=CO_2H,X=O,M=H)
16 (W=$CON(CH_3)_2$,X=O,M=H)
17a (W=$CON(CH_3)_2$,X=$NN(CH_3)_2$,M=H)
17b (W=$CON(CH_3)_2$,X=$NN(CH_3)_2$,M=K)
17c (W=$CON(CH_3)_2$,X=$NN(CH_3)_2$,M=Li)

18a (M=H)
18b (M=K)

19

Scheme IV



dl-8

20a (M=H)
20b (M=K)

21 (Y=H,X=$NN(CH_3)_2$);92%
22 (Y=H,X=O); 84%
dl-23c(Y=CH_3O_2C,X=O); 78%

46a (R-tBu)
46b (R=CH_2CH_2TMS)
46c (R=CH_3)

a) l-8, THF
-78 → 0°, 0.5h
b) CH_2=$CHCH_2Br$, -25°C
0.5h

23a (Y=$tBuO_2C$, X=O); 85%
23b (Y=$TMSCH_2CH_2O_2C$, X=O); 89%
23c (Y=CH_3O_2C, X=O); 92%

Metalation of **17a** with LDA or KDA[14] affords metallo imine anions **17c** and **17b**, respectively. While **17c** is sufficiently nucleophilic to undergo conjugate addition reactions with simpler vinyl sulfones,[15] the more reactive **17b** is required for successful addition to the more hindered vinyl sulfone *dl*-**8**. Although adduct **18a** could be isolated in 89% yield after aqueous workup, no conditions could be found under which intermediate **18b** would undergo cyclization to the desired [5.4.0] system **19**. The failure of this reaction can undoubtly be attributed to the poor alignment between the sulfonyl-stabilized anion and the diactivated cyclopropane. This relationship corresponds to a "fused-mode" opening of the cyclopropane ring, and although examples are known,[16] they are quite rare. Nevertheless, this case represents an especially drastic example of the severity that sterochemical restrictions can place upon what otherwise would be expected to be an exceptionally exothermic process (Scheme III).

Encouraged with the facility by which the metallo imine anion **17b** added to vinyl sulfone *dl*-**8**, we modified our previous approach to substitute an *intermolecular* alkylation of the initially generated α-sulfonyl anion for the unsuccessful intramolecular step (**18b** ↛ **19**). Treatment of acetone dimethylhydrazone (**20a**) with KDA[14] in THF at −78 °C affords a solution of metallo imine **20b**. Addition of vinyl sulfone *dl*-**8** to a threefold excess of **20b** followed by quenching the resulting α-sulfonyl-stablized anion with allyl bromide affords a 92% yield of dimethylhydrazone **21** as a single crystalline diastereomer.[17] Carbonyl exchange with paraformaldehyde and boron trifluoride[18] serves to convert **21** to ketone **22**.[17] Treatment of ketone **22** with dimethyl carbonate in THF at reflux under basic conditions produces keto ester **23c** in 78% yield (Scheme IV).

A more preferable one-step method for synthesis of the chiral β-keto esters **23a–c**[19] involves conjugate addition of the dipotassium β-keto ester dianions **46a–c** (the precursor for **46b** being prepared via the Meldrum acid route[20]) to vinyl sulfone *l*-**8**[19] followed by in situ quenching with allyl bromide (Scheme IV).

Sequential treatment of keto esters **23a** or **23b** with 1 equiv each of potassium *tert*-butoxide and *tert*-butyl alcohol in dry THF (to protect the α-keto ester group as its potassium enolate[21]) followed

(14) (a) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794. (b) Gawley, R. E.; Termine, E.; Aube, J. *Tetrahedron Lett.* **1980**, 3115.
(15) Pyne, S. G.; Fuchs, P. L., unpublished results.
(16) For an in-depth discussion of the intramolecular homoconjugate addition reaction, see: Danishefsky, S. *Acc. Chem. Res.* **1978**, *12*, 66 and references therein.
(17) The stereochemistry indicated at the quaternary C-4 center should be regarded as tentative.
(18) Sacks, C. E.; Fuchs, P. L. *Synthesis* **1976**, 456.
(19) All reactions on chiral material have thus far been derived from the "unnatural" (6*R*) enantiomer *l*-**8**. While the compound names in the Experimental Section are correct for the 6*R* absolute configuration, *it should be noted that throughout the text all structures referred to by this footnote have been drawn in the opposite natural configuration to maintain consistency with the natural product.* Use of unnatural enantiomer *l*-**8** as a "model" for *d*-**8** offsets the disadvantage of having performed the resolution late in the synthetic sequence.
(20) Oilawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.
(21) The use of enolates as carbonyl protecting groups is an expedient that is finding increasing use in organic synthesis: Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4262 and references therein.

Scheme V

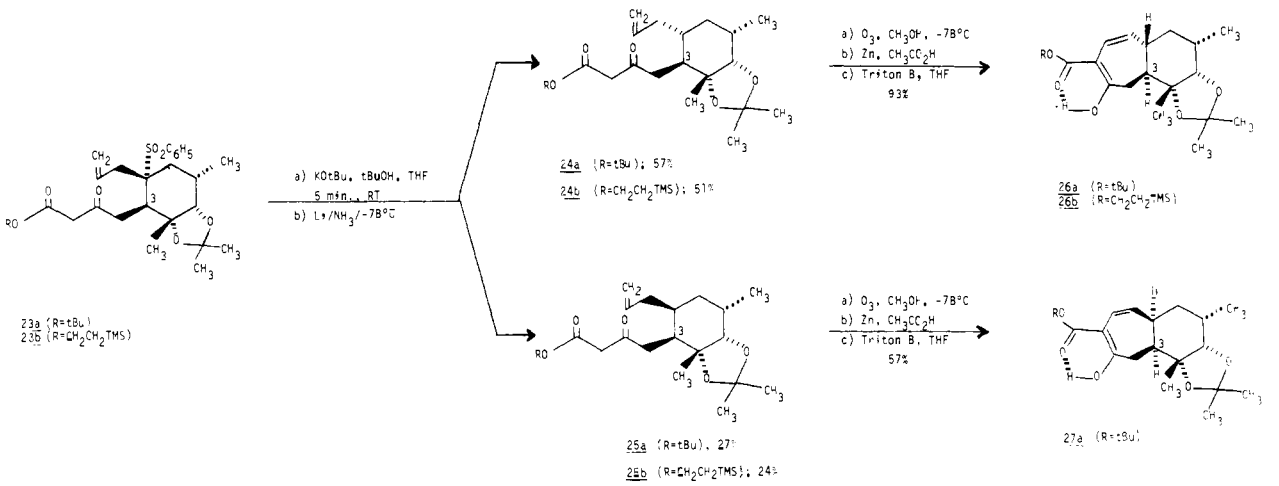


Table I. Calculated and Observed Coupling Constants

	J_{calcd}, Hz (ϕ_{calcd}, deg)				J_{obsd}, Hz
	26M[a]	26M'[a]	28M[a]	28M'[a]	26a
H_aH_f	12.8 (172)	12.9 (175)	12.4 (166)	12.8 (171)	12.5
H_aH_b	6.6 (132)	3.5 (62)	6.5 (131)	3.5 (61)	4.4
H_dH_f	2.0 (84)	11.2 (156)	7.3 (39)	2.0 (86)	4.3
H_eH_f	8.6 (31)	2.0 (86)	2.3 (76)	11.1 (155)	6.2
E_{calcd} kcal/mol	31.2	33.2	33.5	35.5	

	J_{calcd}, Hz (ϕ_{calcd}, deg)					J_{obsd}, Hz
	27M[b]	27M'[b]	29M[b]	29M'[b]	29M''[b]	27a
H_aH_f	6.4 (45)	3.8 (61)	6.0 (4)	3.1 (68)	4.4 (57)	6.4
H_aH_b	7.1 (135)	2.7 (97)	6.6 (4)	6.2 (18)	4.5 (47)	6.4
H_dH_f	12.3 (165)	3.1 (68)	8.6 (30)	5.2 (52)	2.6 (72)	11.0
H_eH_f	5.8 (48)	6.0 (47)	2.0 (83)	12.6 (168)	12.7 (170)	6.6
E_{calcd}, kcal/mol	34.1	35.6	37.7	37.8	38.2	

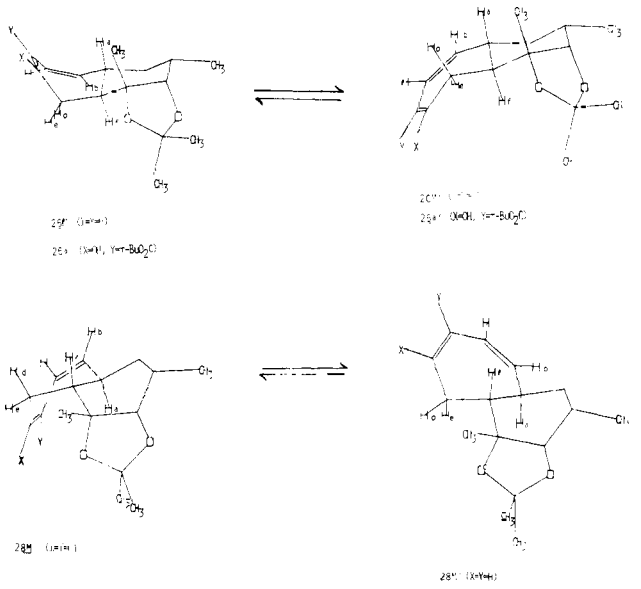
[a] Trans. [b] Cis.

by the addition of ammonia and reductive cleavage[22] of the sulfone moiety with lithium metal smoothly affords a 2.1:1 mixture of keto esters **24a**/**25a** and **24b**/**25b**, respectively.[19] Ozonolysis of the individual trans- (**24a,b**) and cis-substituted (**25a**) isomers followed by base-catalized cyclization of the crude ozonolysis mixture affords dienols **26a,b** and **27a**, respectively.[19] Presumably these reactions are occuring by a sequence that involves (1) an intramolecular aldol reaction to establish the seven-membered ring followed by (2) β elimination and enolization of the intermediate α-carboalkoxy enone to the thermodynamically preferred[23] dienol form (Scheme V).

Stereochemical Assignments. Since **26a** and **27a** are both ultimately derived from singly diastereomeric β-keto ester sulfone **23a** (**23a** → **24a** + **25a**; **24a** → **26a**, **25a** → **27a**, Scheme V), it is necessarily true that they both must have the same configuration at C-3. It is also clear from the 470-MHz NMR decoupling data (Table I) that **26a** has a trans ring fusion (J_{af} = 12.5 Hz) and **27a** has a cis ring fusion (J_{af} = 6.4 Hz).

The stereochemical assignment of **26a**, rather than the alternatively possible trans-fused isomer **28**, was initially based primarily upon a mechanistic consideration. Observations earlier in the synthetic sequence had shown that the reagents add stereospecifically to the β face of olefins possessing the sterically shielding *cis*-acetonide moiety.[5]

Scheme VI

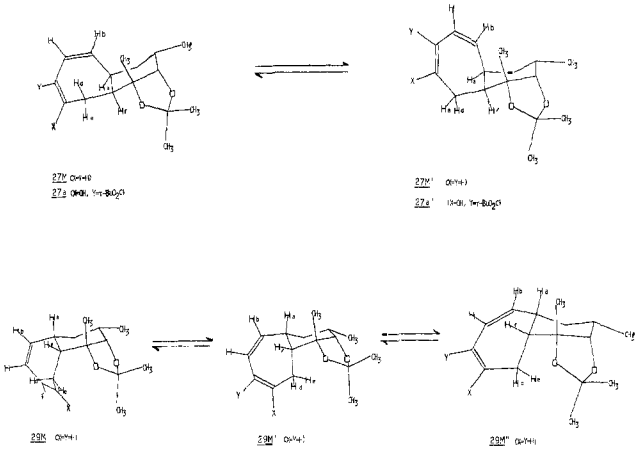


An unambiguous choice between the two trans isomers **26a** and **28** could not be made simply on the basis of the NMR decoupling evidence (Table I). The spectral assignments were complicated by the fact that in both possible configurational isomers (**26a**, **28**), the seven-membered ring diene moiety can readily undergo conformational isomerization between two seemingly quite reasonable

(22) Truce, W. E.; Tate, D. P.; Burdge, D. N. *J. Am. Chem. Soc.* **1960**, *82*, 2872.

(23) The hydrogen-bonded dienol from has previously been shown to predominate over the α-carboethoxyenone from by >20:1 in both the trans-fused and cis-fused parent bicyclo[5.4.0] systems [Clark, D. A. Ph.D. Thesis, Purdue University, 1978].

Scheme VII



forms. Evidence supporting the population of at least two such conformational forms can be inferred by inspection of the values of J_{df} and J_{ef}. If **26a** (**28**) had adopted a *single* conformation, then either J_{df} or J_{ef} should exhibit one very small coupling constant since in both conformational extrema there exists a dihedral angle close to 90°; the fact that *both* J_{df} and J_{ef} exhibit mid-range values strongly suggests that we are observing an *average* conformation.

In an effort to make a structural differentiation between **26a** and **28**, we elected to perform several theoretical calculations. Molecular mechanics calculations[24,25] on simplified models (**26M**, **28M**) of **26a** and **28** (Scheme VI) divested of both the enolic hydroxyl group and the ester moiety revealed several interesting features: (1) Both possible trans-fused bicyclo[5.4.0] systems possessed a pair of comparable energy conformers (**26M** ⇌ **26M′**; **28M** ⇌ **28M′**). Calculation of the relative energies of alternative conformations of the *six-membered ring* revealed no additional minima within 4–5 kcal/mol for either **26M′** or **28M′**. (2) Fitting the calculated bond angles for each of the model conformers (**26M**, **26M′**; **28M**, **28M′**) to the Karplus relationship[26] generated the calculated coupling constants displayed in Table I. (3) Solution of four simultaneous equations generates the observed coupling constants and reveals that an equilibrium mixture of 63 ± 5% **26M** and 37 ± 5% **26M′** would fit the observed coupling constants within 0.9 ± 0.1 Hz. Unfortunately, a mixture of 59 ± 5% **28M** and 41 ± 5% **27M′** will also generate the observed coupling constants of **26a** to within 1.0 ± 0.1 Hz. While the calculated energy difference of 2.0 kcal/mol between either **26M** and **26M′** (or **28M** and **28M′**) is substantially larger than the ca. 0.3 kcal/mol required for a 2:1 mixture, the qualitative agreement is reasonable considering that the model has neglected polar effects of the enolized β-keto ester moiety. Nevertheless, it is abundantly clear that *the spectral data do not allow the desired structural differentiation between* **26M** and **28M**.

Repetition of these same calculations for the minor cis-fused isomer **27a** and its configurational isomer **29** (models **27M**, **29M**, Scheme VII) provided the desired structure illucidation. In this instance, once again an equilibrium mixture involving a pair of conformational isomers (75 ± 5% **27M** ⇌ 25 ± 5% **27M′**) would generate the observed coupling constants of **27a** within 1.2 ± 0.1 Hz. Although the molecular mechanics calculations reveal three conformations (**29M**, **29M′**, **29M″**) of comparable energy for the alternative cis-fused bicyclo[5.4.0] system **29**, it can be shown that for all possible equilibrium combinations of these conformers, there is no mathematical solution that would generate the observed coupling constants of **27a** even allowing deviations as large as 5 Hz from the calculated coupling constants. Accordingly, we assigned the indicated structure to **27a** (and therefore by deduction, **26a** as well). The veracity of these assignments was later substantiated by the X-ray structure of **44**.

Oxidation of the trans-fused dienols **26a** and **26b** with MCPBA[27] yields a 6.2:1 mixture of hemiketals **30a,b** and γ-hydroxy enones **31a,b**, respectively.[19] Benzoylation of the **30a**/**31a** reaction mixture affords, in addition to the benzoate (**34a**) expected from minor alcohol **31a**, a mixture of "closed" (**32a**) and "open" (**33a**) benzoates from hemiketal **30a**.[19] The ratio of **32a**:**33a** could be changed from 5.8:1 to 1:5.7 by varying the conditions of the benzoylation reaction. Similar treatment of the cis-fused isomer **27a** afforded a pair of open γ-hydroxy enones (**35**/**36**) which upon benzoylation afforded the open benzoates **37**/**38** in a 6.4:1 ratio[19,28] (Scheme VIII).

The structural assignment of compounds **30**–**38** relies heavily upon a combination of homonuclear proton decoupling (at 470 Hz) and carbon-13 NMR. The trans ring fusion of compounds **30a**, **32a**, and **33a** is confirmed by direct observation of $J_{af} \simeq 11.5$ Hz (supplementary material, Table II), whereas the major component **35** (and its benzoate, **37**) from the MCPBA oxidation of the cis-dienol **27a** exhibits $J_{af} \simeq 5.1$ Hz, consistent with the assigned cis ring fusion (supplementary material, Table II).

The closed hemiketal **30a** and its benzoate ester **32a** were easily distinguished from the isomeric open enone alcohol (**31a**) and enone benzoates (**33a**, **34a**) by ^{13}C NMR (supplementary material, Table III). Particularly informative in this regard was the chemical shift of C-5 (the "carbonyl" carbon); in the closed isomers (**30a**, **32a**) this carbon resonates at 107–108 ppm (consistent with a carbon bearing two oxygen substitutents), whereas in the open isomers (**31a**, **33a**, **34a**) it exhibited resonance at 201–202 ppm, as is typical for enone carbonyl groups.

The specific stereochemistry at C-2 (the γ-oxygenated carbon) was also established by homonuclear spin decoupling at 470 MHz (see Table II, supplementary material). The assignments shown are also consistent with the chemical correlation of the closed alcohol **30a** with the mixture of open (**33a**) and closed (**32a**) benzoates.

The ease of formation of hemiketal **30a** (relative to the epimeric alcohol **31a**) probably relates to the fact that **30a** can exist in a chair conformation while **31a** would have to exist in the less preferred boat form (**31a′**). In the cis series, **35** does not undergo hemiketal formation since the carboxyl moiety of **35′** would suffer severe interactions with the axial methyl group of the cyclohexane ring (Scheme IX).

Acid-catalyzed (TFA/CH_3SO_3H) dealkylation of *tert*-butyl ester **32a** affords carboxylic acid **39** in 94% yield. Reaction of **39** with the chiral aminodiene **1** under the conditions previously employed for model system **1** produced amide **40**[1,29] (78%). Repetition of this two-reaction sequence with open enone **33a** similarly yields the open amide **3** (49% overall).

Heating a dilute solution of amide **40** in toluene at 110 °C for 36 h affords the closed lactam **41** (67%). Similar treatment of open amide **3** produces lactam **4** after only 14 h at 110 °C. It is not suprising that amide **40** undergoes cyclization at a slower rate than does **3**, but it is surprising that the rates are within a factor of 3. Apparently loss of the "activating" carbonyl group has been effectively offset by the reduced steric interactions present in the bicyclo[3.2.1] hemiketal portion of **40**. This makes the **40** → **41** transformation expecially remarkable, since with the amide

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(25) (a) Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *92*, 4786. (b) Skaarup, S; Boggs, J. E.; Skancke, P. N. *Tetrahedron*, **1976**, *32*, 1179. (c) Cole, A. R. M.; Mobay, G. N.; Osborne, G. A. *Spectrochim Acta, Part A* **1967**, 909. (d) Marais, D. J.; Sheppard, N.; Stoicheff, B. P. *Tetrahedron* **1962**, *17*, 163.

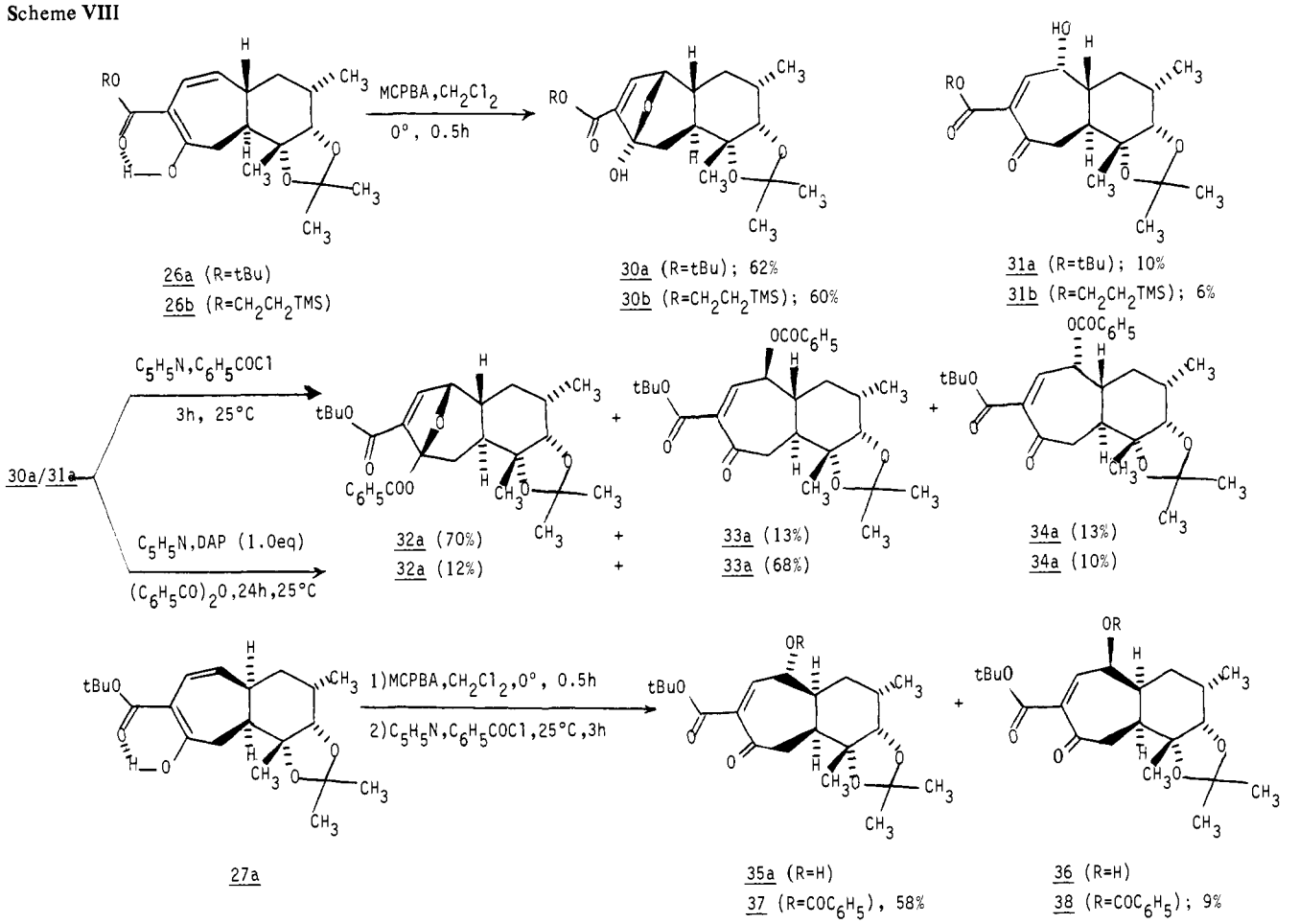
(26) (a) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195. (b) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 556.

(27) For leading references to the γ-oxygenation reaction of dienyl ethers, see: Suryawanshi, S. N.; Fuchs, P. L. *Tetrahedron, Lett.* **1981**, 4021.

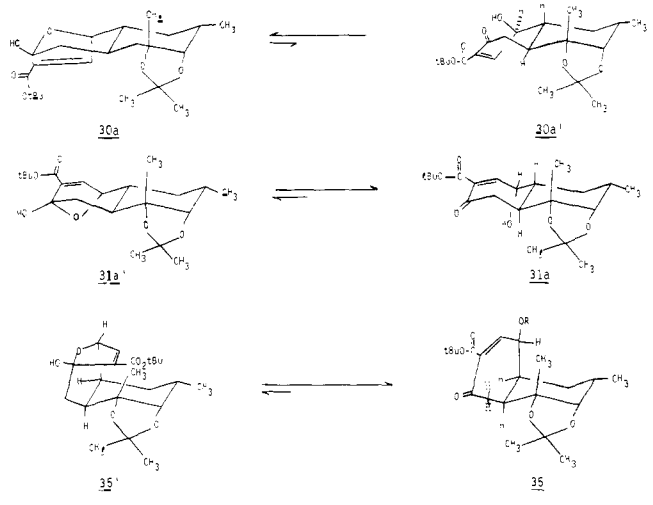
(28) MCPBA oxidation of enol **26b** followed by benzolylation with benzoyl chloride affords the analogous β-silylethyl ester **32b** as the major benzoate.[19] The β-silylethyl ester series ("b" series) converges with the *tert*-butyl ester series after the deprotection step to acid **39**. In general, yields have been higher with the *tert*-butyl series, but it is not clear at this point whether that was not simply related to the fact that the "a" series had been more extensively investigated.

(29) This sequence was actually carried out on the enantiomeric (*R*)-aminodiene (prepared from D(+)-phenylalanine) in order to remain in the totally enantiomeric [(3*R*,16*R*)-cytochalasin numbering] "model" series.[19]

Scheme VIII



Scheme IX



carbonyl substantially twisted out of conjugation from the dienophilic double bond and the ketone carbonyl lost through hemiketal formation, the cyclization is approaching that of an "unactivated" olefin (Scheme X).

Hydrolysis of the benzoate moiety of either the closed (**41**) or the open (**4**) Diels–Alder adducts affords the same closed hemiketal **42** (Scheme XI). Attempts to convert **42** to the prefragmentation substrate **46** under *basic* reaction conditions proved fruitless. However, it is possible to effect oxidative ring opening under acidic conditions since pyridinium chlorochromate[30] oxidation smoothly affords dione **43**, while chromium trioxide in pyridine[31] returns **42** unchanged. Selective[32] reduction of **43** to alcohol **44** (further characterized as benzoate **45**) stereospecifically yielded nicely crystalline material for the purposes of X-ray analysis.

The structural assignment of compounds **41–45** are based on ^{13}C NMR (supplementary material, Table IV) and proton-decoupled 470-MHz ^1H NMR (supplementary material, Table V). Establishment of the structure of **44** by X-ray interrelates the **41–45** series as well as confirms many earlier structural assignments. Similar to what was observed in the **30a–37** series, the ^{13}C NMR chemical shift values of the carbonyl carbon (supplementary material, Table IV) are a definitive characteristic for the determination of the open vs. closed keto/hemiketal question. The most striking observation in regard to the conformational aspects of these cyclic ring systems is the highly coupled nature of their molecular deformations. The dihedral relationship between H_j and H_k, which in large part defines the geometry of the cis-fused lactam/cyclohexene ring, exhibits coupling values at both extremes of the 0–8-Hz range. This suggests, in combination with the relative constancy of J_{ci} (4.8–7.0 Hz) for all six compounds examined, that the compounds are selecting between a flattened half-chair conformation of the cyclohexene ring (ii) and a boat form (iii). Half-chair conformation ii is also the form seen in the simpler model adducts.[1] The alternative boat form (i) is precluded by the magnitude of J_{ci}. The shift to form iii for the oxygen-bridged adducts **41** and **42** may be a consequence of torsional constraints imposed by the forced alignment of bonds a and b (Scheme XII).

X-ray Structure of Alcohol 44. Single-crystal X-ray analysis substantiated the structure assigned to **44** (Figure 1) (for bond

(30) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(31) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(32) Brown, H. C.; Krishnamurthly, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

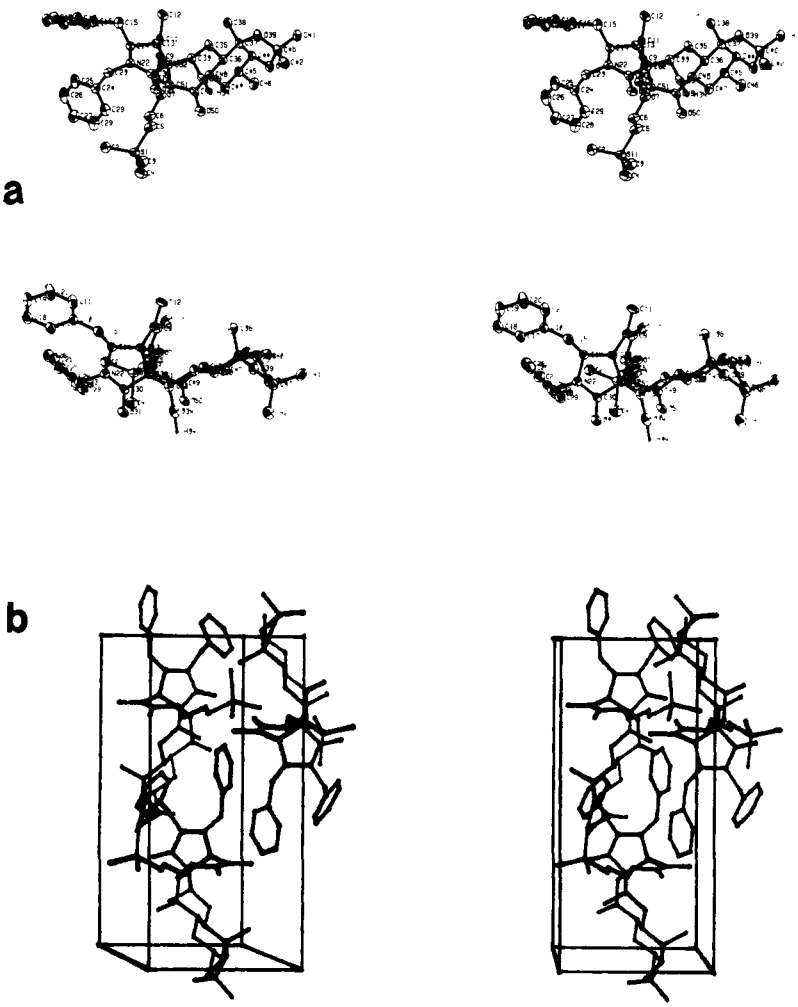
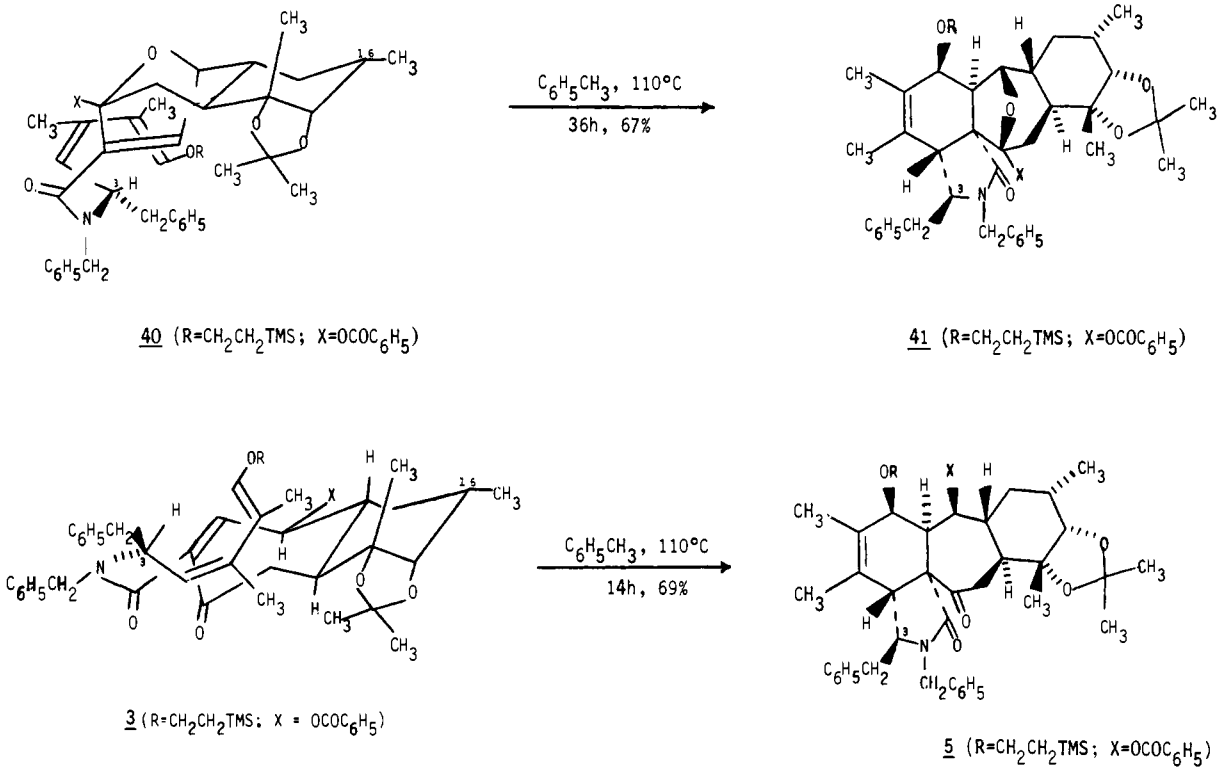
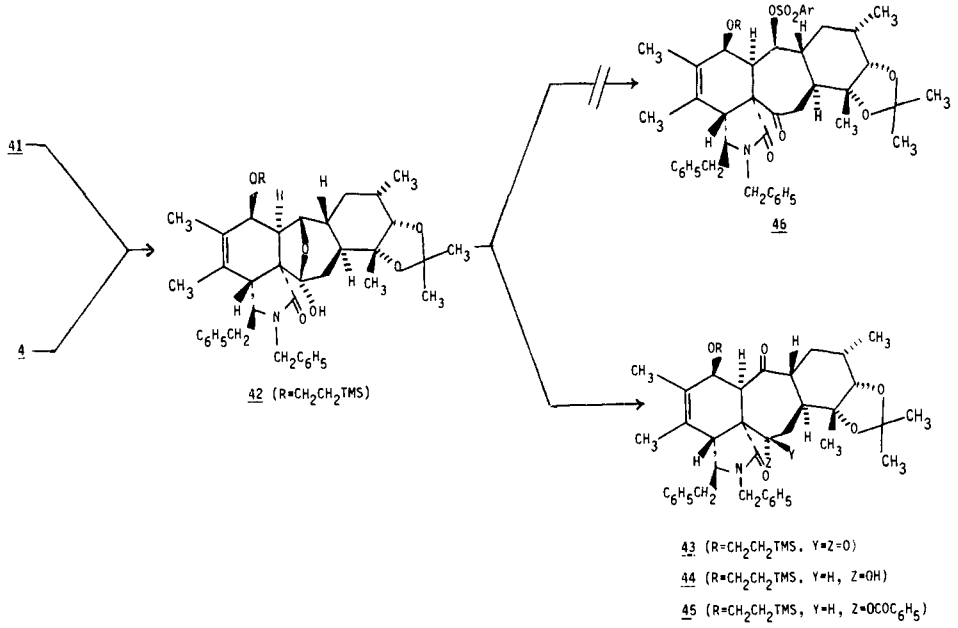


Figure 1. (a) Two stereo views of **44**. (b) Unit cell, **44**.

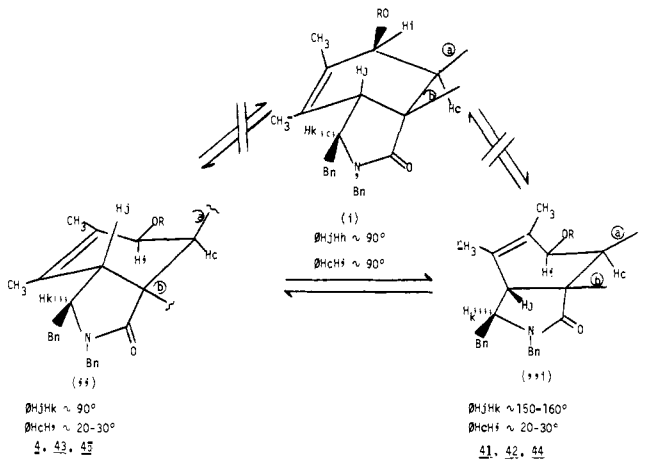
Scheme X



Scheme XI



Scheme XII



angles and bond distances for **44**, see Table VI, supplementary material).

Experimental Section

General Procedures. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer in chloroform solution unless otherwise stated. ^{1}H NMR spectra were recorded on either a Perkin-Elmer R-32, a Nicolet 360, or a Nicolet 470 instrument at 90, 360, and 470 MHz, respectively. The spectra were measured in deuteriochloroform, unless otherwise stated, relative to tetramethylsilane (0.00 ppm). Each signal is described in terms of chemical shift in ppm from tetramethylsilane, multiplicity, intensity, and coupling constant (Hz) in that order with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; q quartet; m, multiplet; br, broad, and $W_{1/2}$, width of peak at half-height. ^{13}C NMR spectra were recorded on a Varian CFT-20 instrument operating at 20 MHz or on a Varian XL200 operating at 50 MHz. The spectra were measured in deuteriochloroform solution, unless otherwise stated, relative to tetramethylsilane (0.00 ppm). Both ^{1}H-decoupled and off-resonance spectra were recorded. Mass spectra were recorded on a CEC-21-110-B high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 A. Exact-mass determinations were obtained on the CEC-21-110-B instrument. Microanalyses were performed by C. S. Yeh and M. Lam, Department of Chemistry, Purdue University.

Optical rotations were measured with a Rudolph Research Autopol III automatic polarimeter in chloroform solution (unless otherwise specified) at the sodium D line in a 10-cm long cell at the designated concentration in g per 100 mL.

All reaction were run under a positive pressure of nitrogen. All organic extracts were dried over anhydrous sodium sulfate, filtered, and then evaporated on a Buchi Rotavapor. Tetrahydrofuran (THF) and ether were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride, toluene, triethylamine, and pyridine were distilled from calcium hydride. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel plates (60 F-254). Preparative thick-layer chromatography (preparative TLC) was performed on 2 mm × 20 cm × 20 cm E. Merck precoated silica gel plates (60 F-254). Column chromatography was performed on silica gel 60–200 mesh obtained from Sargent-Welch.

***trans*,*cis*-3,5-Dimethyl-1-(phenylsulfonyl)-*trans*,*cis*,*cis*-2,3,4-trihydroxycyclohexane 3,4-Acetonide (*dl*-7).** A solution of sulfide alcohol (*dl*-**6**)[5] (3.44 g, 0.0112 mol) in 30 mL of methylene chloride was added dropwise to a solution of *m*-chloroperbenzoic acid (2.2 equiv) in 50 mL of methylene chloride at −10 °C. The white suspension was allowed to slowly warm to room temperature and to remain at that temperature for 1 h. The suspension was then washed with a 10% aqueous sodium bisulfite solution followed by several saturated aqueous sodium carbonate solutions. The organic layer was dried over magnesium sulfate and the solvent removed in vacuo. Recrystallization from ether and hexane afforded 3.50 g (92%) of *dl*-**7**: mp 176–177.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.06 (d, J = 6 Hz, 3 H), 1.26 (s, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.50–2.00 (m, 3 H), 3.02 (ddd, J = 11, 11, and 4 Hz, 1 H), 3.74 (s, 1 H), 3.77 (s, 1 H), 4.04 (d, J = 11 Hz, 1 H), 7.4–7.75 (m, 3 H), 7.80–8.06 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.35 (s), 134.07 (d), 129.13 (d), 108.41 (s), 83.39 (d, s) 72.31 (d), 65.34 (d), 30.24 (d), 28.29 (t), 27.89 (q), 26.91 (q), 17.64 (q), 16.90 (q); exact mass calcd for $C_{16}H_{21}O_5S$ ($M^+ - CH_3$), 325.111; found, 325.113.

***cis*-3,4-Dihydroxy-*trans*-3,5-dimethyl-1-(phenylsulfonyl)cyclohexene 3,4-Acetonide (*dl*-8).** Phosphorus oxychloride (2.03 mL, 22.2 mmol) was slowly added via a syringe to a solution of sulfone alcohol (*dl*-**7**) (2.16 g, 6.35 mmol) in 30 mL of pyridine under a nitrogen atmosphere. The colorless solution was heated to 110 °C and allowed to remain at that temperature for 3 h. After being cooled to room temperature, the solution was carefully poured onto ice. The aqueous suspension was washed several times with ether. The ether extracts were washed several times with saturated aqueous cupric sulfate solution. The ether solution was dried over magnesium sulfate and the solvent removed in vacuo. Recrystallization from ether and hexane afforded 1.85 g (91%) of *dl*-**8**, mp 112–113 °C; see experimental description of *d*-**8** for spectral data.

(1′*S*,1*S*,2*S*,3*R*,4*R*,6*S*)-2,6-Dimethyl-3-[(((1′-phenylethyl)amino)carbonyl)oxy]-4-(phenylthio)cyclohexane-1,2-diol 1,2-Acetonide (9) and (1′*S*,1*R*,2*R*,3*S*,4*S*,6*R*)-2,6-Dimethyl-3-[(((1′-phenylethyl)amino)carbonyl)oxy]-4-(phenylthio)cyclohexane-1,2-diol 1,2-Acetonide (10). A carefully deoxygenated mixture of sulfide *dl*-**6** (40 g, 0.13 mol) and (*S*)-(−)-α-methylbenzyl isocyanate[6] ($[\alpha]_D^{25}$ −11.2° (neat, 26.3 mL)) was heated to 140 °C for 18 h. Excess isocyanate was removed by distillation (water aspirator), and the crude product was dissolved in a small volume of methylene chloride and filtered through a short column of silica gel. The crude product (60 g) was usually used without further purification;

however pure diasteromer **9** could be obtained in 15% yield by crystallization of the **9/10** mixture from hexane: mp 138–139.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.5–7.1 (m, 10 H), 5.11 (d, 1 H, J = 12 Hz), 4.90 (m, 1 H), 3.78 (d, 1 H, J = 3 Hz), 3.03 (m, 1 H), 1.60 (s, 3 H), 1.43 (d, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 155.13 (s), 143.74 (s), 134.67 (s), 132.04 (d), 128.73 (d), 128.46 (d), 127.01 (d), 126.85 (d), 125.89 (d), 108.46 (s), 84.17 (d), 82.14 (s), 77.88 (d), 50.60 (d), 48.56 (d), 35.46 (t), 31.46 (t), 27.94 (q), 27.12 (q), 22.57 (q), 17.52 (q), 17.11 (q); mass spectrum, m/e 455 (3% $M^+ - CH_3$), 105 (100%); exact mass calcd for $C_{26}H_{33}NO_4S$, 455.213; found, 455.212.

(1′*S*,1*S*,2*S*,3*R*,4*R*,6*S*)-2,6-Dimethyl-3-[(((1′-phenylethyl)amino)carbonyl)oxy]-4-(phenylsulfonyl)cyclohexane-1,2-diol 1,2-Acetonide (11) and (1′*S*,1*R*,2*R*,3*S*,4*S*,6*R*)-2,6-Dimethyl-3-[(((1-phenylethyl)amino)carbonyl)oxy]-4-(phenylsulfonyl)cyclohexane-1,2-diol 1,2-Acetonide (12). To a solution of the diastereomers **9/10** (29 g, 63.73 mmol) in methylene chloride (250 mL) at −35 °C was added solid *m*-chloroperbenzoic acid (85%, 25.4 g, 128.2 mmol). After 10 min, the reaction mixture was warmed to 25 °C over a period of 1 h. The reaction mixture was then filtered, and the solution was washed with aqueous sodium bicarbonate and saturated NaCl solution and dried. The mixture of diastereoisomers **11** and **12** was separated by column chromatography on silica gel. Elution with 5% ethyl acetate–methylene chloride gave sulfone **12** (15.0 g, higher R_f) and sulfone **11** (14.3 g, lower R_f).

11: mp 88–89.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2 H); 7.6–7.2 (m, 8 H), 5.19 (d, 1 H, J = 11 Hz), 4.87 (m, 1 H), 3.66 (br s, 1 H), 2.2–1.5 (m, 3 H), 3.10 (m, 1 H), 1.51 (d, 3 H, J = 7 Hz), 1.45 (s, 6 H), 1.29 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 154.10 (s), 137.35 (s), 133.47 (s), 128.93 (d), 128.51 (d), 127.07 (d), 126.13 (d), 108.67 (s), 83.64 (d), 82.63 (s), 73.08 (d), 64.05 (d), 50.82 (d), 30.14 (t), 28.32 (d), 27.59 (q), 27.05 (q), 26.61 (q), 17.58 (q), 17.30 (q); mass spectrum, m/e 487 (6%, M^+), 105 (100%); exact mass calcd for $C_{26}H_{33}NO_6S$, 487.202; found, 487.204.

12: mp 74–76 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (dd, 2 H, J = 2, 8 Hz), 7.6–7.1 (m, 8 H), 5.36 (d, 1 H, J = 12 Hz), 4.87 (m, 1 H), 3.67 (d, 1 H, J = 3 Hz), 3.14 (m, 1 H), 2.3–1.5 (m, 3 H), 1.50 (d, 3 H, J = 7 Hz), 1.47 (s, 3 H), 1.28 (s, 3 H), 1.18 (s, 3 H), 1.04 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 154.21 (s), 143.07 (s), 138.44 (s), 133.51 (d), 128.98 (d), 128.91 (d), 128.48 (d), 127.15 (d), 126.12 (d), 108.69 (s), 83.56 (d), 82.52 (s), 73.01 (d), 63.75 (d), 50.76 (d), 30.07 (t), 28.32 (d), 27.58 (q), 27.05 (q), 27.05 (q), 22.34 (q), 17.55 (q), 17.44 (q); mass spectrum, m/e 487 (10%, M^+), 105 (100%); exact mass calcd for $C_{26}H_{33}NO_6S$, 487.202; found, 487.204.

(1*S*,2*R*,6*S*)-2,6-Dimethyl-4-(phenylsulfonyl)cyclohex-3-ene-1,2-diol 1,2-Acetonide (*d*-8) and (1*R*,2*S*,6*R*)-2,6-Dimethyl-4-(phenylsulfonyl)-cyclohex-3-ene-1,2-diol 1,2-Acetonide (*l*-8). A solution of the sulfone **11** (31 g, 63.73 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (14 mL, 93.6 mmol) in dry THF (200 mL) was heated to reflux for 16 h. The reaction mixture was then cooled, concentrated, and taken up in ether, washed with cold 5% hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated NaCl solution, and dried. The crude product was purified by column chromatography on silica gel.

Elution with 1:1 ether–hexane gave vinyl sulfone *d*-**8** (17.61 g, 86%) as a white crystalline solid: mp 93.5–94.5 °C; $[\alpha]^{25}_D$ 35.0° (c 0.161); ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, 2 H, J = 2, 8 Hz), 7.58 (m, 3 H), 6.66 (br s, 1 H, $W_{1/2}$ = 6 Hz), 3.74 (br s, 1 H, $W_{1/2}$ = 4 Hz), 1.37 (s, 3 H), 1.32 (s, 3 H), 1.11 (d, 3 H, J = 7 Hz), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.15 (s), 139.07 (s), 137.85 (d), 133.44 (d), 129.19 (d), 128.07 (d), 108.26 (s), 81.53 (d), 78.52 (s), 30.47 (d), 27.68 (q), 27.15 (q), 25.50 (t), 23.44 (q), 18.32 (q); mass spectrum, m/e 322 (1%, M^+), 307 (100%, $M^+ - CH_3$); exact mass calcd for $C_{16}H_{19}O_4S$ ($M^+ - CH_3$) 307.100; found, 307.103. Repetition of this sequence with sulfone **12** yields *l*-**8** ($[\alpha]^{25}_D$ −34.5° (c 0.164)).

***N*,*N*-Dimethyl-1-acetylcyclopropanecarboxamide (16).** To 1-acetylcyclopropane carboxylic acid[10] **15** (3.0 g, 23.4 mmol) in benzene (20 mL) was added hexamethylphosphorus triamide[11] (23.4 mmol, 4.3 mL) at such a rate as to maintain a gentle reflux. After room temperature was reached (ca. 1 h), the reaction mixture was poured into saturated sodium bicarbonate solution (20 mL), and the layers were separated. The aqueous phase was extracted with methylene chloride (3 × 20 mL), and the combined extracts were washed with water (2×) and saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent and distillation (58 °C/1 mm) afforded **16** (1.75 g, 50%): ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 6 H), 2.21 (s, 3 H), 1.48 (t, 2 H), 1.35 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 204.0 (s), 169.6 (s), 37.6 (s), 37.2 (q), 35.7 (q), 27.0 (q), 17.2 (t).

***anti*-*N*,*N*-Dimethyl-1-acetylcyclopropanecarboxamine Dimethylhydrazone (17a).** To a solution of keto amide **16** (1.54 g, 10.0 mmol) in methylene chloride (20 mL) was added dimethylhydrazine (2.7 mL, 35 mmol) and triethylamine (8.4 mL, 60 mmol). This solution was cooled to 6 °C, and titanium tetrachloride (0.66 mL, 6 mmol) in methylene chloride (2.5 mL) was added over the course of 1 h.[12] The resulting reaction mixture was allowed to warm to 25 °C and stir an additional 20 h. The reaction mixture was filtered through Celite/sodium sulfate. The resulting homogeneous solution was washed with water and saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent and distillation (89–90 °C (2.25 mm)) affords dimethylhydrazone **17a** (1.6 g, 77%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 6 H), 2.41 (s, 6 H), 1.93 (s, 3 H), 1.20 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 171.1 (s), 164.3 (s), 47.0 (q), 37.2 (q), 37.1 (q), 32.7 (s), 14.9 (q), 12.9 (t).

Assignment of the anti stereochemistry results from comparison of the ^{13}C chemical shifts for the "acetyl" methyl carbon and the quaternary cyclopropane carbon in compounds **16** and **17a** (Δ_{syn} α = 27.0 − 14.9 = 12.1 ppm and Δ_{anti} α' = 37.6 − 32.7 = 4.9 ppm).[13]

(1′*RS*,2′*RS*,3′*SR*,4′*SR*,6′*RS*)-*N*,*N*-Dimethyl-1-[1-(2,2-dimethyl-1,1-diazanedityl)-2-(2′,3′-dihydroxy-2′,4′-dimethyl-6′-(phenylsulfonyl)-cyclohexyl)ethyl]cyclopropanecarboxamide 2′,3′-Acetonide (18a). A suspension of potassium *tert*-butoxide (672 mg, 6 mmol) in THF (8 mL) was added to oil-free potassium hydride (ca. 10 mg) at 25 °C. After the solution was stirred for 15 min, the potassium hydride was allowed to settle. The potassium *tert*-butoxide suspension was then transferred via syringe to a fresh reaction vessel cooled to −78 °C. Diisopropylamine (0.38 mL, 2.8 mmol) and *n*-BuLi (2.2 mmol) were then added consecutively. After 10 min, **17a** (384 mg, 2 mmol) in THF (1.5 mL) was added over 2 min and stirring at −78 °C was continued for 1 h. A solution of the vinyl sulfone *dl*-**8** (225 mg, 0.7 mmol) in THF (1 mL) was added over 2 min, and the reaction mixture was warmed to 0 °C over 10 min. The resulting orange solution was stirred at 0 °C for 1 h, extracted into ether, and dried over sodium sulfate. Preparative TLC (ether) purification afforded **18a** as a white solid (325 mg, 89.5%). Recrystallization from ether afforded an analytical sample: mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (dd, J = 2, 8 Hz, 2 H), 7.60 (m, 3 H), 3.57 (d, J = 3 Hz, 1 H), 3.45 (dd, J = 14, 3 Hz, 1 H), 3.05 (s, 3 H), 2.95 (s, 3 H), 2.90 ($CH_XCH_ACH_B$, m, 1 H), 2.73 ($CH_XCH_ACH_B$, m, 1 H), 2.43 (s, 6 H), 1.55 (s, 3 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 0.92 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5 (s), 166.6 (s), 139.5 (s), 133.4 (d), 129.1 (d), 128.5 (d), 108.4 (d), 83.3 (d), 82.5 (s), 65.4 (d), 47.3 (q), 40.8 (d), 36.9 (q), 36.0 (q), 31.8 (s), 30.2 (t), 29.9 (d), 28.7 (q), 27.1 (q), 20.4 (q), 16.7 (t), 15.4 (t); mass spectrum, m/e 519 (100%, M^+); 475 (59% $M^+ - N(CH_3)_2$); 378 (63%, $M^+ - C_6H_5SO_2$). Anal. Found: C, 62.28, H, 8.12; N, 8.06; S, 6.27 ($C_{27}H_{41}N_3SO_5$ requires C, 62.40; H, 7.95; N, 8.09; S, 6.17%).

(1*SR*,2*RS*,3*RS*,4*RS*,6*SR*)-2,6-Dimethyl-4-(phenylsulfonyl)-4-(2-propenyl)-3-(2-oxopropyl)cyclohexane-1,2-diol 1,2-Acetonide, Dimethylhydrazone (21). To a solution of potassium *tert*-butoxide (2.08 g, 18.6 mmol) and diisopropylamine (1.35 mL, 9.6 mmol) in dry THF (30 mL) at −78 °C was added *n*-BuLi (9.3 mmol) over 10 min.

After 10 min, a solution of acetone dimethylhydrazone **20a** (0.837 g, 9.3 mmol) in THF (4 mL) was added. After 40 min, vinyl sulfone *dl*-**8** (1 g, 3.10 mmol) in THF (4 mL) was added, and the reaction mixture was warmed to −25 °C and stirred at that temperature for 10 min. Allyl bromide (0.84 mL, 9.6 mmol) was then added, and after 20 min at −25 °C the reaction mixture was poured into cold saturated aqueous ammonium chloride and extracted with ether (3×). Purification of the crude product on silica gel (60 g, 2:3 ether–hexane) gave **21** (1.32 g, 92%) as a white crystalline solid: mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, 2 H, J = 2, 8 Hz), 7.65 (m, 3 H), 6.05–5.55 (m, 1 H), 5.40–5.05 (m, 2 H), 3.81 (d, 1 H, J = 2.5 Hz), 2.45 (s, 6 H), 1.95 (s, 3 H), 1.80 (s, 3 H), 1.39 (s, 3 H), 1.27 (s, 3 H), 1.01 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) 166.96 (s), 137.66 (s), 133.66 (d), 131.06 (d), 130.00 (d), 128.87 (d), 121.21 (t), 107.19 (s), 84.13 (d), 83.35 (s), 70.81 (s), 46.79 (q), 44.44 (d), 40.08 (t), 35.94 (t), 32.14 (t), 28.53 (q), 27.16 (q), 26.35 (d), 21.56 (q), 18.47 (q), 16.69 (q); IR ($CHCl_3$) 1640 cm^{-1}; mass spectrum, m/e 462 (19% M^+), 447 (13%, $M^+ - CH_3$), 321 (100%, $M^+ - C_6H_5SO_2$); exact mass calcd for $C_{25}H_{38}N_2SO_4$, 462.255; found, 462.255.

(1*SR*,2*RS*,3*RS*,4*RS*,6*SR*)-2,6-Dimethyl-4-(phenylsulfonyl)-4-(2-propenyl)-3-(2-oxopropyl)cyclohexane-1,2-diol 1,2-Acetonide (22). To a solution of the dimethylhydrazone **21** (399 mg, 0.86 mmol) in aqueous acetone (2.6 mL of H_2O, 26 mL of acetone) was added paraformaldehyde (312 mg) and then boron trifluoride etherate (0.5 mL).[18] The reaction mixture was stirred at 25 °C for 48 h and then made basic by the addition of solid sodium bicarbonate and evaporated to dryness. The crude product was dissolved in ether, washed with water and saturated NaCl solution, and dried. The solution was concentrated and then filtered through a small plug of silica gel. The ketone **22** (306 mg, 84%) was obtained as a white solid: mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, 2 H, J = 2, 8 Hz), 7.66 (m, 3 H), 6.16–5.62 (m, 1 H), 5.23 (dd, 1 H, J = 2, 10 Hz), 5.17 (dd, 1 H, J = 2, 16 Hz), 3.83 (d, 1 H, J = 3 Hz), 3.20–2.70 (m, 6 H), 2.26 (s, 3 H), 1.72 (s, 3 H), 1.42 (s, 3 H), 1.31 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 208.25 (s),

137.45 (s), 133.82 (d), 130.70 (d), 130.12 (d), 128.98 (d), 121.52 (t), 107.84 (s), 83.31 (d), 82.65 (s), 70.31 (s), 43.20 (d), 40.45 (t), 39.67 (t), 32.28 (t), 30.81 (q), 27.79 (q), 27.23 (q), 26.41 (d), 21.36 (q), 18.47 (q); IR ($CHCl_3$) 1712 cm^{-1}; mass spectrum, *m/e* 420 (17%, M^+), 278 (100%, $M^+ - C_6H_5SO_2H$); exact mass calcd for $C_{23}H_{32}SO_5$, 420.197; found, 420.197.

(1*SR*,2*RS*,3*RS*,4*RS*,6*SR*)-2,6-Dimethyl-4-(phenylsulfonyl)-4-(2-propenyl)-3-[3-(methoxycarbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (23c). A mixture of the ketone **22** (310 mg, 0.738 mmol), dimethyl carbonate (0.6 mL), methanol (4 μL), and sodium hydride (80 mg) in dry THF (7 mL) was heated to reflux for a period of 2 h. The reaction mixture was cooled to 0 °C, quenched with methanol, and then poured into saturated ammonium chloride solution and extracted into ether. Purification of the crude product by preparative TLC (3:2 ether–hexane) gave 274 mg (78%) of **23c** as a white solid: mp 112–113 °C; ^1H NMR ($CDCl_3$) δ 7.84 (dd, 2 H, *J* = 2, 8 Hz), 7.65 (m, 3 H), 6.15–6.50 (m, 1 H), 5.23 (dd, 1 H, *J* = 2, 10 Hz), 5.04 (dd, 1 H, *J* = 2, 16 Hz), 3.87 (d, 1 H, *J* = 3 Hz), 3.73 (s, 3 H), 3.64 (s, 2 H), 3.3–2.6 (m, 6 H), 1.72 (s, 3 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 1.06 (d, 3 H, *J* = 7 Hz); IR ($CHCl_3$) 1745, 1720 cm^{-1}; mass spectrum, *m/e* 478 (7%, M^+), 453 (31%, $M^+ - CH_3$), 337 (23%, $M^+ - C_6H_5SO_2$), 101 (100%); exact mass calcd for $C_{25}H_{34}SO_7$, 478.203; found, 478.202.

(1*R*,2*S*,3*S*,4*S*,6*R*)-2,6-Dimethyl-4-(phenylsulfonyl)-4-(2-propenyl)-3-[3-(*tert*-butoxycarbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (23a). To a solution of potassium *tert*-butoxide (22 g, 196 mmol) and diisopropylamine (18.6 mL, 132.6 mmol) in THF (250 mL) at −78 °C was added *n*-BuLi (117 mmol) over 10 min. After 10 min, a solution of *tert*-butyl acetoacetate (10.28 g, 65.0 mmol) in THF (25 mL) was added over 15 min. After 40 min, a solution of the vinyl sulfone *l*-**8** (8.39 g, 26.0 mmol) in THF (25 mL) was added, and the −78 °C cooling bath was exchanged for an ice–water bath. After 40 min, the reaction mixture was cooled to −25 °C, and allyl bromide (5.9 mL, 67.6 mmol) was added. Stirring was continued at −25 °C for 30 min, and then the reaction mixture was poured into saturated aqueous ammonium chloride and ice and extracted into ether (3×). Purification of the crude product by chromatography on silica gel (200 g, 1:1 ether–hexane) and crystallization from 5% ether–hexane gave **23a** (11.44 g, 85%) as a white crystalline solid: mp 127–128 °C; $[\alpha]^{25}_D$ +15.1° (*c* 1.22); ^1H NMR ($CDCl_3$) δ 7.82 (dd, 2 H, *J* = 2, 8 Hz), 7.64 (m, 3 H), 6.15–5.6 (m, 1 H), 5.21 (dd, 1 H, *J* = 2, 10 Hz), 5.03 (dd, 1 H, *J* = 2, 16 Hz), 3.83 (d, 1 H, *J* = 3 Hz), 3.52 (s, 2 H), 1.71 (s, 3 H), 1.49 (s, 6 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 1.05 (d, 3 H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 202.77 (s), 166.49 (s), 137.40 (s), 133.81 (d), 130.55 (d), 130.07 (d), 128.96 (d), 121.62 (t), 107.91 (s), 83.19 (d), 82.46 (s), 81.51 (s), 70.01 (s), 51.27 (t), 44.12 (d), 40.51 (t), 38.76 (t), 32.32 (t), 28.03 (q), 27.72 (q), 27.18 (q), 26.37 (d), 21.26 (q), 18.44 (q); IR ($CHCl_3$) 1745, 1720 cm^{-1}; mass spectrum, *m/e* 505 (9%, $M^+ - CH_3$), 379 (48%, $M^+ - C_6H_5SO_2$), 323 (100%, $M^+ - C_6H_5SO_2 - C_4H_8$). Anal. Calcd for $C_{28}H_{40}SO_7$: C, 65.59; H, 7.74; S, 6.16. Found: C, 65.53; H, 7.66; S, 6.15.

2-(Trimethylsilyl)ethyl 3-Oxobutanoate. To Meldrum's acid (10 g, 69.44 mmol) and pyridine (11.3 mL, 2 equiv) in methylene chloride (200 mL) at 0 °C was added acetyl chloride (5.5 mL, 1.1 equiv) dropwise. After being stirred at 0 °C for 1 h and 25 °C for 1 h, the reaction mixture was washed with ice-cold 5% HCl and saturated sodium chloride solution, dried, and concentrated. The crude product was dissolved in 2 M K_2CO_3 and washed with ether. The aqueous phase was cooled to 0 °C, and acidified, and then extracted with methylene chloride. Evaporation gave 10.02 g (77%) of acetyl Meldrum's acid; ^1H NMR ($CDCl_3$) δ 15.59 (br s, 1 H), 2.67 (s, 3 H), 1.72 (s, 3 H).

A mixture of acetyl Meldrum's acid (10.02 g, 5.36 mmol) and 2-(trimethylsilyl)ethanol (Fluka, 7.6 g, 6.43 mmol) in benzene (50 mL) was heated to reflux for 12 h.[20] Distillation gave 2-(trimethylsilyl)ethyl 3-oxobutanoate (85%): bp 130 °C (20 mm) [lit. 50–50 °C (10 mm)]; ^1H NMR ($CDCl_3$) δ 4.19 ("t", 2 H), 3.37 (s, 2 H), 2.19 (s, 3 H), 0.96 ("t", 2 H).

(1*R*,2*S*,3*S*,4*S*,6*R*)-2,6-Dimethyl-4-(phenylsulfonyl)-4-(2-propenyl)-3-[3-((2-(trimethylsilyl)ethoxy)carbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (23b). In a similar manner to that described for the preparation of keto ester **23a**, 2-(trimethylsilyl)ethyl 3-oxobutanoate gave keto ester **23b** (89%): ^1H NMR ($CDCl_3$) δ 7.9–7.3 (m, 5 H), 6.05–5.50 (m, 1 H), 5.2–4.8 (m, 2 H), 4.16 (t, 2 H), 3.74 (d, 1 H, *J* = 3 Hz), 3.51 (s, 2 H), 1.62 (s, 3 H), 1.29 (s, 3 H), 1.19 (s, 3 H), 0.98 (s, 3 H), 0.95 (d, 3 H, *J* = 7 Hz).

(1*R*,2*S*,3*R*,4*S*,6*R*)-2,6-Dimethyl-4-(2-propenyl)-3-[3-(*tert*-butoxycarbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (24a) and (1*R*,2*S*,3*R*,4*R*,6*R*)-2,6-Dimethyl-4-(2-propenyl)-3-[3-(*tert*-butoxycarbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (25a). To a solution of potassium *tert*-butoxide (5.21 g, 46.53 mmol) and dry *tert*-butyl alcohol (3.99 mL, 42.3 mmol) in dry THF (250 mL) at 0 °C was added a solution of sulfone **23a** (22 g, 42.3 mmol) in THF (50 mL). After 5 min, the solution was cooled to −78 °C and ammonia (1 L) was distilled into the reaction vessel from lithium. Lithium was then added in small pieces over 1.5 h until the persistance of a blue color (ca. 4 equiv of lithium). Isoprene was then added to destroy excess lithium, the ammonia was evaporated under a rapid stream of nitrogen, and the reaction mixture was poured into an ice–aqueous ammonium chloride mixture and finally extracted into ether (3×). Separation of **24a** from **25a** by MPLC (1:5 ethyl acetate–hexane) gave **25a** (4.20 g, higher R_f compound), **24a** (8.64 **g**), and a mixture (632 mg) of **24a** and **25**a (total 13.47 g, 84%).

24a: colorless oil; $[\alpha]^{25}_D$ +19.2° (*c* 1.50); ^1H NMR ($CDCl_3$) δ 5.95–5.35 (m, 1 H), 5.1–4.8 (m, 2 H), 3.62 (d, 1 H, *J* = 3 Hz), 3.38 (s, 2 H), 2.59 (d, 2 H, *J* = 6 Hz), 2.45 (s, 6 H), 1.43 (s, 3 H), 1.31 (s, 3 H), 1.13 (s, 3 H), 1.06 (d, 3 H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 202.21 (s), 166.46 (s), 136.99 (d), 116.35 (t), 107.39 (s), 83.73 (d), 81.92 (s), 81.68 (s), 50.85 (t), 42.43 (d), 41.70 (t), 39.02 (d), 37.87 (t), 34.96 (t), 31.23 (d), 28.41 (q), 28.00 (q), 27.18 (q), 18.49 (q), 18.22 (q); mass spectrum, *m/e* 380 (100%, M^+), 375 (99%, $M^+ - CH_3$); exact mass calcd for $C_{22}H_{36}O_5$ 380.271; found, 380.261.

25a: colorless oil; ^1H NMR ($CDCl_3$) δ 5.90–5.35 (m, 1 H), 5.1–4.8 (m, 2 H), 3.67 (d, 1 H, *J* = 3 Hz), 3.34 (s, 2 H), 1.45 (s, 6 H), 1.45 (s, 6 H), 1.44 (s, 3 H), 1.31 (s, 3 H), 1.17 (s, 3 H), 1.05 (d, 3 H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 202.74 (s), 166.42 (s), 138.10 (d), 115.76 (t), 107.28 (s), 83.78 (d), 81.71 (s), 80.67 (s), 50.83 (t), 41.32 (d), 40.35 (t), 35.44 (d), 31.80 (t), 30.50 (t), 28.35 (q), 28.02 (q), 27.14 (q), 26.29 (d), 21.64 (q), 18.47 (q); exact mass calcd for $C_{22}H_{36}O_5$, 380.271; found, 380.263.

(1*R*,2*S*,3*R*,4*S*,6*R*)-2,6-Dimethyl-4-(2-propenyl)-3-[3-((2-(trimethylsilyl)ethoxy)carbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (24b) and (1*R*,2*S*,3*R*,4*R*,6*R*)-2,6-Dimethyl-4-(2-propenyl)-3-[3-((2-(trimethylsilyl)ethoxy)carbonyl)-2-oxopropyl]cyclohexane-1,2-diol 1,2-Acetonide (25b). In a similar manner to that described for the preparation of keto esters **24a**/**24b**, reductive cleavage of **23b** gave **24b**/**25b** as colorless oils (75% yield, in a 2.1:1 ratio).

24b: ^1H NMR ($CDCl_3$) δ 5.8–5.3 (m, 1 H), 5.03–4.70 (m, 2 H), 4.12 (m, 2 H), 3.54 (d, 1 H, *J* = 4 Hz), 3.38 (s, 2 H), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.04 (s, 3 H), 0.97 (d, 1 H, *J* = 7 Hz).

25b: ^1H NMR ($CDCl_3$) δ 5.9–5.3 (m, 1 H), 5.1–4.8 (m, 2 H), 4.20 (m, 2 H), 3.66 (d, 1 H, *J* = 3 Hz), 3.40 (s, 2 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 1.12 (s, 3 H), 1.03 (d, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 424 (75%, M^+), 4.07 (25%), $M^+ - CH_3$), 91 (100%).

(1*R*,7*R*,9*R*,10*R*,11*S*)-*tert*-Butyl 3,10,11-Trihydroxy-9,11-dimethylbicyclo[5.4.0]undeca-3,5-diene-4-carboxylate 10,11-Acetonide (26a). Ozone (Welbach ozonator, 90 V, flow 0.02 ft^3 min^{-1}, 7 lb, of O_2 pressure) was bubbled through a solution of the olefin **24a** (3.39 g, 8.9 mmol) in dry methanol (80 mL) at −78 °C until a blue color persisted. Nitrogen was then bubbled through until excess ozone was removed (ca. 10 min), then glacial acetic acid (4.8 mL) was added, the cooling bath was removed, and activated zinc dust (3.5 g) was added portionwise over 10 min. After 20 min, water was added, and the solution was filtered and then extracted with ether (2×). The extract was washed with aqueous saturated sodium bicarbonate and saturated NaCl solution and dried. The crude product (3–4 spots by TLC analysis 1:1 ether–hexane, R_f 0.2–0.5) was dissolved in THF (80 mL) and treated with Triton B (2.41 M in CH_3OH, 3.7 mL) until no starting materials remained after about 15 min (product R_f 0.9, 1:1 ether–hexane). Saturated aqueous ammonium chloride was added, and the product was extracted into ether (2×). The crude product was purified by column chromatography on silica gel (100 g). Elution with 10% ether–hexane afforded enol **26a** (3.0 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ −68.3° (*c* 4.64); ^1H NMR ($CDCl_3$, 470 MHz) δ 13.21 (br s, 1 H), 6.12 (dd, 1 H, *J* = 4.4, 11.5 Hz), 5.49 (dd, 1 H, *J* = 1.7, 11.5 Hz), 3.64 (d, 1 H, *J* = 3.4 Hz), 2.63 (dd, 1 H, *J* = 4.3, 14.1 Hz), 2.33 (dd, 1 H, *J* = 6.2, 14.1 Hz), 2.16 (ddd, 1 H, *J* = 4.3, 6.2, 12.5 Hz), 2.05 (m, 1 H), 1.83 (m, 1 H), 1.51 (s, 6 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.22 (s, 3 H), 1.09 (d, 3 H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 178.68 (s), 171.86 (s), 130.16 (d), 121.87 (d), 107.17 (s), 100.42 (s), 83.36 (d), 82.25 (s), 81.45 (s), 50.33 (d), 41.13 (d), 36.41 (t), 33.72 (t), 32.07 (d), 28.72 (q), 28.33 (q), 27.15 (q), 18.03 (q), 17.50 (q); IR ($CHCl_3$) 1640, 1595 cm^{-1}; mass spectrum, *m/e* 364 (12%, M^+), 324 (62%), 291 (100%); exact mass calcd for $C_{21}H_{32}O_5$, 364.225; found, 364.223.

(1*R*,7*R*,9*R*,10*R*,11*S*)-β-2-(Trimethylsilyl)ethyl 3,10,11-Trihydroxy-9,11-dimethylbicyclo[5.4.0]undeca-3,5-diene-4-carboxylate 10,11-Acetonide (26b). In a similar manner to that described for preparation of **26a**, ozonolysis/aldol reaction of **24b** gives **26b** as a colorless oil (44%): ^1H NMR ($CDCl_3$) δ 6.08 (dd, 1 H, *J* = 1, 12 Hz), 5.35 (dd, 1 H, *J* = 4, 12 Hz), 4.21 (m, 2 H), 3.52 (d, 1 H, *J* = 3 Hz), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.01 (s, 3 H), 0.97 (d, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 408 (100%, M^+), 393 (80%, $M^+ - CH_3$).

(1*R*,7*S*,9*R*,10*R*,11*S*)-*tert*-Butyl 3,10,11-Trihydroxy-9,11-dimethylbicyclo[5.4.0]undeca-3,5-diene-4-carboxylate (27a). Treatment of the

olefin **25a** (590 mg, 1.55 mmol) in a similar manner to that described for the preparation of enol **26a** gave enol **27a** (322 mg, 57%): ^{1}H NMR ($CDCl_3$, 470 MHz) δ 13.1 (br s, 1 H), 6.10 (dd, 1 H, J = 1.9, 10.4 Hz), 5.66 (dd, 1 H, J = 6.4, 10.4 Hz), 3.63 (d, 1 H, 2.8 Hz), 2.59 (m, 1 H), 2.44 (d, 1 H, J = 11.0, 13.4 Hz), 2.33 (dd, J = 6.6, 13.4 Hz); ^{13}C NMR ($CDCl_3$) δ 179.28 (s), 171.40 (s), 130.75 (d), 124.37 (d), 107.60 (s), 101.90 (s), 84.24 (d), 81.46 (s), 81.26 (s), 54.34 (d), 38.89 (d), 33.69 (t), 30.88 (d), 28.34 (t), 28.34 (t), 28.34 (q), 27.66 (q), 27.12 (q), 22.30 (q), 18.69 (q); IR ($CHCl_3$) 1642, 1590 cm^{-1}; mass spectrum, m/e 364 (10%, M^+), 291 (100%); exact mass calcd for $C_{21}H_{32}O_5$, 364.225; found, 364.224.

Molecular Mechanics and Karplus Calculations on 26M–29M. Molecular mechanics calculations were performed by using a modification of the Allinger MM2 program.[24] The MM2 program has no parameters for conjugated dienes. For the present problem, it was necessary and sufficient to obtain reliable estimates for the torsional potential around the cis conformation of the diene fragment. For this purpose a new atom type was defined to treat the middle two carbons of the conjugated diene moiety with parameters chosen to reproduce the geometries and the torsional barrier of 1,3-butadiene.[25] We emphasize that these parameters were used for this specific problem and may not find general use on conjugated dienes. (These parameters can be obtained upon request.)

The coupling constants calculated were obtained from the Karplus relationships given by $J_{vic} = 7 - \cos\phi + 5\cos 2\phi$ for H–C(sp^3) – C(sp^3) – H^{26a} and $J = 6.6\cos^2\phi + 2.6\sin^2\phi$ [$0° \le \phi \le 90°$]; $J = 11.6\cos^2\phi + 2.6\sin^2\phi$ [$0° \le \phi \le 180°$] for H–C(sp^2) – H^{26b} coupling, respectively, where ϕ is the dihedral angle between the hydrogens. Percentage compositions were found by solving for X in equations of the form:

$$X(J_{1\text{calcd}} \pm \Delta) + (1 - X)(J_{2\text{calcd}} \pm \Delta) = J_{\text{obsd}}$$

with Δ ranging from 0.0 to 10.0 Hz in steps of 0.1 Hz.

(1*S*,2*R*,5*S*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 5,8,9-Trihydroxy-8,10-dimethyl-12-oxatricyclo[5.4.0.1^{2,5}]dodec-3-ene-4-carboxylate 8,9-Acetonide (30a) and (1*S*,2*S*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2,8,9-Trihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undeca-3-ene-4-carboxylate 8,9-Acetonide (31a). To a stirred mixture of 80% *m*-chloroperbenzoic acid (638 mg, 3.09 mmol) and solid sodium bicarbonate (620 mg, 7.38 mmol) in methylene chloride (25 mL) at 0 °C was added a solution of enol **26a** (900 mg, 2.47 mmol) in methylene chloride (10 mL) over 10 min. After a further 15 min, the solution was filtered through Celite, washed with aqueous sodium bisulfite and aqueous sodium bicarbonate, and dried. The crude product was purified by column chromatography on silica gel (30 g).

Elution with 10% ethyl acetate–hexane gave a mixture of **30a** and **31a** (6.14:1, 678 mg, 72%) as a white foam. **30a**: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 6.92 (d, 1 H, J = 1.5 Hz), 4.63 (dd, 1 H, J = 1, 1.5 Hz), 3.65 (d, 1 H, J = 3.2 Hz), 2.01 (dd, 1 H, J = 4.3, 11.7 Hz), 1.81 (m, 1 H), 1.62 (ddd, 1 H, J = 4.3, 11.4, 11.7 Hz), 1.56 (dd, 1 H, J = 11.7, 12.1 Hz), 1.49 (s, 9 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.08 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 162.53 (s), 141.18 (d), 139.96 (s), 107.16 (s), 107.06 (s), 83.70 (d), 81.66 (s), 81.25 (s), 79.78 (d), 40.88 (d), 36.92 (d), 31.97 (d), 31.21 (t), 29.61 (t), 28.64 (q), 28.02 (q), 27.12 (q), 18.55 (q), 18.19 (q); mass spectrum, m/e 380 (29%, M^+), 360 (100%, $M^+ - H_2O$), 324 (18%, $M^+ - C_4H_8$), 306 (12%, $M^+ - C_3H_6O_2$); exact mass calcd for $C_{21}H_{32}O_6$, 380.219; found, 380.217.

31a: ^{1}H NMR ($CDCl_3$, 470 MHz, in part) δ 6.95 (d, 1 H, J = 5.6 Hz), 4.61 (dd, 1 H, J = 5.9, 6.9 Hz), 3.70 (d, 1 H, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$, in part) δ 202.69 (s), 163.53 (s), 148.92 (d), 134.39 (s), 69.39 (d).

(1*S*,2*R*,5*S*,7*R*,8*S*,9*R*,10*R*)-2-(Trimethylsilyl)ethyl 5,8,9-Trihydroxy-8,10-dimethyl-12-oxatricyclo[5.4.0.1^{2,5}]dodec-3-ene-4-carboxylate 8,9-Acetonide (30b). In a manner similar to that for preparation of **26a**, MCPBA oxidation of **26b** affords a mixture of **30b** and **31b**. Chromatography affords a 55% yield of **30b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.89 (d, 1 H, J = 2.5 Hz), 4.54 (br s, 1 H, $W_{1/2}$ = 6 Hz), 4.18 (m, 2 H), 3.56 (d, 1 H, J = 3 Hz), 2.23 (s, 6 H), 1.01 (s, 3 H), 0.98 (d, 3 H, J = 7 Hz); mass spectrum, m/e 424 (14%, M^+), 409 (48%, $M^+ - CH_3$), 91 (100%).

(1*S*,2*R*,5*R*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 8,9-Dihydroxy-8,10-dimethyl-12-oxatricyclo[5.4.0.1^{2,5}]dodec-3-ene-4-carboxylate 8,9-Acetonide (32a), (1*S*,2*R*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2-(Benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undeca-3-ene-4-carboxylate 8,9-Acetonide (33a), and (1*S*,2*S*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2-(Benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undeca-3-ene-4-carboxylate 8,9-Acetonide (34a). (i) **Reaction of 30a/31a with Benzoyl Chloride in Pyridine.** To a solution of the alcohols **30a** and **31a** (678 mg, 1.78 mmol) in dry pyridine (10 mL) was added benzoyl chloride (0.52 mL, 4.45 mmol). After 3 h, water (0.5 mL) was added slowly dropwise and stirring was continued for 30 min. Ether was then added, and the solution was washed with ice-cold aqueous 5% hydrochloric acid, water, and saturated aqueous sodium bicarbonate. The crude product was purified by column chromatography on silica gel (40 g). Elution with 20% ether–hexane gave, in order of increasing elution time, benzoate **33a** (103 mg, 12%), benzoate **34a** (112 mg, 13%), and benzoate **32a** (603 mg, 70%).

(ii) **Reaction of 36a/37a with Benzoic Anhydride and 4-(Dimethylamino)pyridine in Pyridine.** To a solution of the alcohols **30a** and **31a** (440 mg, 1.16 mmol)in dry pyridine (10 mL) was added 4-(dimethylamino)pyridine (144 mg, 1.16 mmol) and benzoic anhydride (784 mg, 3.48 mmol). After 24 h, water (0.5 mL) was added slowly dropwise, and stirring was continued for 30 min. Ether was then added, and the solution was washed with ice-cold aqueous 5% hydrochloric acid, water, and saturated aqueous sodium bicarbonate. The crude product was purified by column chromatography on silica gel (30 g). Elution with 20% ether–hexane gave, in order of increasing elution time, benzoate **33a** (386 mg, 68%), benzoate **34a** (55 mg, 10%), and benzoate **32a** (67 mg, 12%).

32a: $[\alpha]^{25}_D$ –67.8° (c 2.03); ^{1}H NMR ($CDCl_3$, 470 MHz) δ 6.93 (d, 1 H, J = 2.1 Hz), 4.80 (dd, 1 H, J = 2.1, 3.4 Hz), 3.68 (d, 1 H, J = 3.4 Hz), 2.18 (dd, 1 H, J = 4.4, 11.6 Hz), 1.88 (dd, 1 H, J = 11.6, 12.1 Hz), 1.83 (ddd, 1 H, J = 4.4, 11.5, 11.6 Hz), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 9 H), 1.29 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 164.23 (s), 160.93 (s), 139.84 (d), 137.0 (d), 133.23 (d), 130.23 (s), 129.86 (d), 128.34 (d), 108.19 (s), 107.17 (s), 83.71 (d), 81.22 (s), 81.04 (s), 80.85 (d), 40.03 (d), 36.84 (d), 31.93 (d), 30.92 (t), 28.65 (q), 28.10 (t), 27.84 (q), 27.15 (q), 18.61 (q), 18.20 (q); IR ($CHCl_3$) 1741, 1716 cm^{-1}; mass spectrum, m/e 484 (6%, M^+), 469 (28%, $M^+ - CH_3$), 428 (100%, $M^+ - C_4H_8$), 411 (47%, $M^+ - C_3H_2O_2$); exact mass calcd for $C_{28}H_{36}O_7$, 484.246; found, 484.245.

33a: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.24 (d, 1 H, J = 6.4 Hz), 5.58 (dd, 1 H, J = 2.3, 6.4 Hz), 3.69 (d, 1 H, J = 3.2 Hz), 2.85 (dd, 1 H, J = 2.8, 18.3 Hz), 2.60 (dd, 1 H, J = 11.6, 18.3 Hz), 2.17 (ddd, 1 H, J = 2.8, 11.3, 11.6 Hz), 1.91 (m, 1 H), 1.81 (dddd, J = 2.2, 2.3, 11.3, 12.6 Hz), 1.69 (ddd, J = 2.3, 3, 12.6 Hz), 1.46 (s, 9 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.17 (s, 3 H), 1.13 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 202.20 (s), 165.07 (s), 163.06 (s), 139.76 (s), 139.76 (d), 133.46 (d), 129.69 (d), 129.31 (s), 128.61 (d), 107.43 (s), 83.18 (d), 82.27 (s), 81.34 (s), 72.79 (d), 42.10 (d), 41.79 (d), 39.38 (t), 33.6. (t), 31.93 (d), 28.58 (q), 27.93 (q), 27.07 (q), 18.08 (q); IR ($CHCl_3$) 1740–1680 cm^{-1} (br band); mass spectrum, m/e 484 (5%, M^+), 428 (100%, $M^+ - C_4H_8$); exact mass calcd for $C_{28}H_{36}O_7$, 424.246; found, 484.243.

34a: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.05 (d, 1 H, J = 5.8 Hz), 5.80 (dd, 1 H, J = 5.8, 6.2 Hz), 3.69 (d, 1 H, J = 3.3 Hz), 2.89 (dd, 1 H, J = 0.9, 18.3 Hz), 2.36 (dd, 1 H, J = 11.7, 18.3 Hz), 1.49 (s, 9 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.13 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 201.16 (s), 165.32 (s), 164.84 (s), 142.15 (s), 142.15 (d), 133.54 (s), 133.25 (s), 129.76 (d), 128.64 (d), 107.42 (d), 83.31 (d), 82.32 (s), 81.35 (s), 72.61 (d), 41.57 (d), 39.97 (d), 39.80 (t), 31.98 (d), 30.83 (t), 28.62 (q), 27.99 (q), 27.11 (q), 18.15 (q), 18.02 (q); mass spectrum, m/e 484 (6%, M^+), 428 (100%, $M^+ - C_4H_8$); exact mass calcd for $C_{28}H_{36}O_7$, 484.246; found, 484.246.

MCPBA oxidation of enol **26b** followed by benzoylation with benzoyl chloride affords β-silylethyl ester **32b** as the major benzoate: ^{1}H NMR ($CDCl_3$) δ 8.07 (dd, 2 H, J = 2, 8 Hz), 7.49 (m, 3 H), 7.97 (d, 1 H, J = 2.5 Hz), 4.82 (br s, 1 H, $W_{1/2}$ = 6 Hz), 3.69 (d, 1 H, J = 3.02 Hz), 1.33 (s, 6 H), 1.25 (s, 3 H), 1.07 (d, 1 H, J = 7 Hz); mass spectrum, m/e 428 (2%, M^+), 406 (4%, $M^+ - C_6H_5CO_2H$), 105 (100%).

(1*R*,2*S*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2,8,9-Trihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undeca-3-ene-4-carboxylate 8,9-Acetonide (35) and (1*R*,2*R*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2,8,9-Trihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undeca-3-ene-4-carboxylate 8,9-Acetonide (36). Treatment of enol **27a** (200 mg, 0.549 mmol) in a similar manner to that described for the preparation of **30a/31a** gave an inseparable mixture of **35** and **36** (6.7:1, 140 mg, 67%).

35: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.15 (d, 1 H, J = 3.6 Hz), 4.37 (dd, 1 H, J = 3.6, 9.4 Hz), 3.81 (d, 1 H, J = 2.3 Hz), 2.65 (dd, 1 H, J = 5.3, 14.6 Hz), 2.51 (dd, 1 H, J = 10.9, 14.6 Hz), 2.35 (ddd, 1 H, J = 5.2, 5.3, 10.9 Hz), 1.81 (ddd, 1 H, J = 2.3, 6.6, 9.9 Hz), 1.77 (ddd, 1 H, J = 6.6, 12.4, 12.4 Hz), 1.66 (ddd, 1 H, J = 4.6, 9.9, 12.4 Hz), 1.51 (s, 9 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 1.01 (d,3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 201.41 (s), 163.49 (s), 150.82 (d), 134.89 (s), 107.79 (s), 83.55 (d), 82.28 (s), 81.55 (s), 71.66 (d), 42.81 (t), 40.30 (d), 39.75 (d), 29.60 (d), 28.99 (t), 28.69 (q), 28.01 (q), 26.56 (q), 24.35 (q), 18.75 (q); mass spectrum, m/e 380 (21%, M^+), 360 (100%, $M^+ - H_2O$); exact mass calcd for $C_{21}H_{32}O_6$, 380.219; found 380.218.

36: ^{1}H NMR ($CDCl_3$, 470 MHz, in part) δ 5.51 (dd, 1 H, J = 5.6, 7.0 Hz).

(1*R*,2*S*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2-(Benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undec-3-ene-4-carboxylate 8,9-Acetonide (37) and (1*R*,2*R*,7*R*,8*S*,9*R*,10*R*)-*tert*-Butyl 2-(Benzoyloxy)-8,9-di-

hydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undec-3-ene-4-carboxylate 8,9-Acetonide (38). Treatment of a mixture of alcohols **35** and **36** (120 mg, 0.316 mmol) with benzoyl chloride in pyridine in a similar manner to that described for the preparation of **32a**, **33a**, and **34a** gave an inseparable mixture of **37** and **38** (150 mg, 98%).

37: ^{1}H NMR ($CDCl_3$, 470 MHz), δ 7.08 (d, 1 H, J = 3.6 Hz), 5.86 (dd, 1 H, J = 3.6, 9.8 Hz), 3.79 (d, 1 H, J = 2.3 Hz), 2.78 (dd, 1 H, J = 6.4, 13.2 Hz), 2.71 (dd, 1 H, J = 10.6, 13.2 Hz), 2.51 (dddd, 1 H, J = 5.1, 5.6, 9.8, 11.9 Hz), 2.41 (ddd, 1 H, J = 5.1, 6.4, 10.6 Hz), 1.82 (ddd, 1 H, J = 2.3, 6.6, 9.9 Hz), 1.70 (ddd, 1 H, J = 6.6, 11.9, 13.7 Hz), 1.60 (ddd, J = 5.6, 9.9, 13.7 Hz), 1.48 (s, 9 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 0.99 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 202.46 (s), 163.50 (s), 160.59 (s), 142.25 (d), 138.03 (s), 137.64 (s), 133.55 (d), 129.84 (d), 128.60 (d), 107.97 (s), 83.52 (d), 82.40 (s), 81.25 (s), 71.73 (d), 43.12 (t), 39.80 (d), 38.58 (d), 28.43 (d), 28.29 (t), 28.02 (q), 27.43 (q), 26.55 (q), 23.81 (q), 18.63 (q); IR ($CHCl_3$) 1740–1680 cm^{-1} (br band).

38: ^{1}H NMR ($CDCl_3$, 470 MHz in part), 5.51 (dd, J = 5.6, 7.0 Hz).

(1*S*,2*R*,5*R*,7*R*,8*S*,9*R*,10*R*)-5-(Benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-12-oxatricyclo[5.4.0.1^{2,5}]dodeca-3-ene-4-carboxylic Acid (39). A solution of the ester **32a** (350 mg, 0.723 mmol) in dry methylene chloride (3 mL) was treated with trifluoroacetic acid (84 μL, 1.08 mmol) and methanesulfonic acid (20 μL, 0.3 mmol) at 25 °C. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL), washed with ice-cold saturated NaCl solution (3×), and then dried. Evaporation gave 292 mg (94%) of acid **39**: mp 231–232 °C; ^{1}H NMR ($CDCl_3$) 8.12 (dd, 2 H, J = 2, 7 Hz), 7.6–7.2 (m, 3 H), 7.11 (d, 1 H, J = 2 Hz), 4.83 (br s, 1 H, $W_{1/2}$ = 7 Hz), 3.68 (d, 1 H, J = 3 Hz); mass spectrum, m/e 428 (3%, M$^+$), 105 (100%); exact mass calcd for $C_{24}H_{28}O_7$, 428.183; found, 428.178.

(1*S*,2*R*,1′*R*,5*R*,7*R*,8*S*,9*R*,10*R*)-*N*-Benzyl-*N*-[1′-benzyl-3′,4′-dimethyl-5-[2-(trimethylsilyl)ethoxy]penta-2′,4′(*Z*,*E*)-dienyl]-5-(benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-12-oxatricyclo[5.4.0.1^{2,5}]dodec-3-ene-4-carboxamide 8,9-Acetonide (40). Treatment of the acid **39** (292 mg, 0.682 mmol) in a similar manner to that described for the preparation of **1**,[1] except the reaction was stirred at 25 °C for 1 h, gave amide **40** (433 mg, 78%) after purification on silica gel (30 g, 1:4 ether–hexane): ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, 2 H, J = 2, 8 Hz), 7.6–6.9 (m, 14 H), 6.01 (br s, 1 H), 5.49 (dd, 1 H, J = 2, 10 Hz); IR ($CHCl_3$) 1725, 1660–1590 (br band) cm^{-1}.

(1*S*,2*R*,7*R*,8*S*,9*R*,10*R*)-2-(Benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undec-3-ene-4-carboxylic Acid. A solution of the ester **33a** (210 mg, 0.43 mmol) in methylene chloride (3 mL) was treated with trifluororacetic acid (0.11 mL, 1.08 mmol) and methanesulfonic acid (30 μL, 0.45 mmol). After 2 h, the reaction mixture was diluted with ethyl acetate (20 mL), washed with ice-cold saturated NaCl solution (3×), and then dried. Evaporation gave 170 mg of the carboxylic acid (TLC analysis indicated a ca. 20% impurity).

(1*S*,2*R*,1′*R*,7*R*,8*S*,9*R*,10*R*)-*N*-Benzyl-*N*-[1′-benzyl-3′,4′-dimethyl-5-(2-(trimethylsilyl)ethoxy)penta-2′,4′(*E*,*Z*)-dienyl]-2-(benzoyloxy)-8,9-dihydroxy-8,10-dimethyl-5-oxobicyclo[5.4.0]undec-3-ene-4-carboxamide 8,9-Acetonide (3). Treatment of the crude acid (170 mg, 0.397 mmol) in a similar manner to that described for the preparation of **40** gave amide **3** (172 mg, 49% from **33a**) after purification by preparative TLC (1:1 ether–hexane): ^{1}H NMR ($CHCl_3$) δ 8.02 (dd, 2 H, J = 2, 8 Hz), 7.6–6.9 (m, 14 H), 6.30 (br s, 1 H), 5.35 (d, 1 H, J = 2, 10 Hz); IR ($CHCl_3$) 1730, 1670–1600 (br band) cm^{-1}.

(1*S*,2*R*,3*S*,5*R*,6*R*,7*S*,8*R*,10*R*,11*S*,14*R*,15*S*,18*R*)-10-(Benzoyloxy)-13,14-dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7-dihydroxy-5,7,16,17-tetramethyl-12-oxo-13-aza-19-oxapentacyclo[9.7.0.0^{2,10}.0^{3,8}.0^{11,15}]nonadec-16-ene 6,7-Acetonide (41). A solution of the amide **40** (433 mg, 0.53 mmol) in carefully deoxygenated toluene (45 mL) was heated to reflux for 36 h. The solution was concentrated, and the crude product was purified by column chromatography on silica gel (30 g). Elution with 20% ether–hexane gave **41** (293 mg, 67%) as a colorless oil: $[\alpha]^{25}_D$ −9.62° (c 0.67); ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.94 (d, 2 H, J = 7.2 Hz), 7.54–6.72 (m, 13 H), 5.31 (d, 1 H, J = 14.7 Hz), 3.78 (d, 1 H, J = 14.7 Hz), 3.76 (dd, 1 H, J = 1.9, 3.5 Hz), 3.64 (d, 1 H, J = 3.3 Hz), 3.49 (m, 1 H), 3.47 (d, 1 H, J = 4.9 Hz), 3.24 (dd, 1 H, J = 5.8, 12.1 Hz), 3.21 (m, 1 H), 3.07 (ddd, 1 H, J = 5.7, 7.6, 8.5 Hz), 3.07 (ddd, 1 H, J = 5.4, 7.6, 8.5 Hz), 2.88 (dd, 1 H, J = 1.9, 4.9 Hz), 2.83 (dd, 1 H, J = 5.7, 14.6), 2.79 (dd, 1 H, J = 5.4, 12.1 Hz), 2.58 (dd, 1 H, J = 8.5, 14.6 Hz), 2.39 (d, 1 H, J = 7.6 Hz), 1.79 (s, 3 H), 1.55 (s, 3 H), 1.30 (s, 3 H), 1.18 (s, 3 H), 1.10 (s, 3 H), 1.08 (d, 3 H, J = 6.8 Hz), 0.89 (m, 1 H), 0.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.03 (s), 163.22 (s), 137.23 (s), 136.94 (s), 133.22 (d), 130.90 (d), 129.76 (d), 129.42 (d), 128.43 (d), 124.42 (s), 126.59 (s), 112.42 (s), 107.74 (s), 84.07 (d), 81.38 (s), 76.91 (d), 76.08 (d), 67.80 (t), 61.06 (d), 58.62 (s), 47.74 (d), 45.49 (d), 44.52 (t), 40.93 (d), 40.67 (t), 38.56 (d), 34.73 (d), 31.94 (t), 30.57 (t), 28.15 (q), 27.37 (q), 19.60 (q), 18.68 (t), 18.45 (q), 17.83 (q), 13.95 (q), −1.20 (q); IR ($CHCl_3$) 1715, 1675 cm^{-1}; mass spectrum, m/e 698 (33%, M$^+$ − $(CH_3)_3SiCH_2CH_2$ − H_2O), 576 (7%, 698 − $C_6H_5CO_2H$), 105 (100%); exact mass calculated for $C_{45}H_{48}NO_6$ (M$^+$ − $C_5H_{15}SiO$), 698.348; found, 698.348.

(1*S*,2*R*,3*S*,5*R*,6*R*,7*S*,8*R*,11*R*,14*R*,15*S*,18*R*)-2-(Benzoyloxy)-13,14-dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7-dihydroxy-5,7,16,17-tetramethyl-10,12-dioxo-13-azatetracyclo[9.7.0.0^{3,8}.0^{11,15}]octadec-16-ene 6,7-Acetonide (4). A solution of the amide **3** (140 mg, 0.171 mmol) in carefully deoxygenated toluene (14 mL) was heated to reflux for 12 h. The solution was concentrated, and the crude product was purified by column chromatography on silica gel (20 g). Elution with 20% ether–hexane gave **4** (96 mg, 69%) as a colorless oil: $[\alpha]^{25}_D$ −74.3° (c 1.46); ^{1}H NMR ($CDCl_3$, 470 MHz in part) δ 7.67 (d, 2 H, J = 7.2 Hz), 7.5–7.0 (m, 13 H), 5.47 (s, 1 H), 5.06 (d, J = 15.1 Hz, 1 H), 3.89 (d, 1 H, J = 15.1 Hz), 3.61 (d, 1 H, J = 3.6 Hz), 3.60 (m, 1 H), 3.56 (d, 1 H, J = 4.8 Hz), 3.47 (dd, 1 H, J = 1, 4.82 Hz), 3.34 (m, 1 H), 3.13 (dd, 1 H, J = 2.6, 18.5 Hz), 3.07 (br s, 1 H, J = 1 Hz), 2.61 (dd, 1 H, J = 13.3, 18.5 Hz), 1.79 (m, 1 H), 1.68 (s, 6 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.07 (d, 3 H, J = 6.9 Hz), 1.04 (s, 3 H), 0.93 (m, 1 H), 0.87 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 209.45 (s), 172.12 (s), 164.80 (s), 137.93 (s), 136.16 (s), 132.92 (d), 129.95 (d), 129.42 (d), 129.07 (s), 128.67 (d), 128.50 (d), 128.24 (d), 127.75 (s), 126.64 (s), 107.85 (s), 83.48 (d), 81.55 (s), 75.20 (d), 73.30 (d), 67.74 (t), 65.42 (s), 65.12 (d), 45.84 (d), 45.42 (d), 45.15 (t), 42.71 (t), 39.64 (t), 38.94 (t), 38.54 (d), 33.52 (d), 31.55 (t), 28.50 (q), 27.26 (q), 18.60 (t), 18.26 (q), 17.40 (q), 16.53 (q), 13.3 (q), −1.17 (q); IR ($CHCl_3$) 1715, 1675 cm^{-1}; mass spectrum, m/e 817 (8%, M$^+$), 716 (10% M$^+$ − $(CH_3)_3SiCH_2CH_2$), 698 (6%, 716 − H_2O), 105 (100%); exact mass calcd for $C_{45}H_{50}NO_7$ (M$^+$ − $C_5H_{13}Si$), 716.359; found, 716.361.

(1*S*,2*R*,3*S*,5*R*,6*R*,7*S*,8*R*,10*R*,11*S*,14*R*,15*S*,18*R*)-13,14-Dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7,10-trihydroxy-5,7,16,17-tetramethyl-12-oxo-13-aza-19-oxapentacyclo[9.7.0.0^{2,10}.0^{3,8}.0^{11,15}]nonadec-16-ene 6,7-Acetonide (42). (i) **From Benzoate 4.** A mixture of the benzoate **4** (100 mg, 0.139 mmol), aqueous potassium carbonate solution (1 M, 1.0 mL), THF (1 mL), and methanol (3 mL) was stirred at 25 °C for 4 h. The volatiles were then evaporated, ether was added, and the solution was washed with saturated aqueous sodium bicarbonate solution. Evaporation gave 77 mg (93%) of alcohol **42**.

(ii) **From Benzoate 41.** Benzoate **41** (5 mg) was treated with 1 mL of a solution prepared by adding water (12 L) to a solution of potassium *tert*-butoxide (266 mg) in ether (5 mL). After 20 h at 25 °C, the reaction mixture was diluted with ether (5 mL), washed with cold water, and dried. Evaporation gave (4 mg, 96%) identical by TLC (R_f 0.4, 1:1 ethyl acetate–hexane) and ^{1}H NMR (470 MHz) with that obtained from **4** above.

42: mp 60–63 °C; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.35–6.95 (m, 10 H), 5.17 (d, 1 H, J = 15 Hz), 3.74 (d, 1 H, J = 15 Hz), 3.65 (dd, 1 H, J = 2, 3.5 Hz), 3.63 (d, 1 H, J = 3.5 Hz), 3.50 (m, 1 H), 3.49 (d, 1 H, J = 5 Hz), 3.24 (m, 1 H), 3.13 (ddd, 1 H, J = 6, 7, 8 Hz), 2.96 (dd, 1 H, J = 6, 15 Hz), 2.86 (dd, 1 H, J = 8, 15 Hz), 2.83 (dd, 1 H, J = 3.5, 5 Hz), 2.71 (dd, 1 H, J = 5, 12 Hz), 2.64 (d, 1 H, J = 7 Hz), 2.63 (dd, 1 H, J = 6, 12 Hz), 1.73 (s, 3 H), 1.59 (s, 3 H), 1.42 (s, 3 H), 1.32 (s, 3 H), 1.14 (s, 3 H), 1.08 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 174.57 (s), 137.59 (s), 136.97 (s), 129.64 (d), 129.30 (d), 128.55 (d), 128.19 (d), 127.47 (s), 126.67 (s), 107.61 (s), 104.57 (s), 84.10 (d), 81.49 (s), 76.87 (d), 76.30 (d), 67.90 (t), 61.18 (d), 58.42 (s), 46.81 (d), 44.58 (d), 43.69 (t), 40.91 (d), 40.34 (t), 39.07 (d), 34.75 (d), 31.88 (t), 30.59 (t), 28.20 (q), 27.40 (q), 19.78 (q), 18.61 (t), 18.54 (q), 17.84 (q), 13.89 (q), −1.18 (q); IR ($CHCl_3$) 3600–3100, 1678 cm^{-1}; mass spectrum, m/e 594 (14%, M$^+$ − $(CH_3)_3SiCH_2CH_2$ − H_2O), 303 (19%), 91 (100%); exact mass calcd for $C_{38}H_{44}NO_5$ (M$^+$ − $(CH_3)_3SiCH_2CH_2$ − H_2O), 594.322; found, 594,318.

(1*R*,3*S*,5*R*,6*R*,7*S*,8*R*,11*S*,14*R*,15*S*,18*R*)-13,14-Dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7-dihydroxy-5,7,16,17-tetramethyl-2,10,12-trioxo-13-azatetracyclo[9.7.0.0^{3,8}.0^{11,15}]octadec-16-ene 6,7-Acetonide (43). A mixture of the alcohol **42** (87 mg, 0.122 mmol), pyridinium chlorochromate (128 mg, 0.6 mmol), sodium acetate (50 mg, 0.6 mmol), and 4-Å molecular sieves (ca. 10 pellets) in dry methylene chloride (5 mL) was stirred at 25 °C for 4 h. The reaction mixture was poured into saturated NaCl solution and extracted into methylene chloride (3×). The extracts were washed with saturated NaCl solution (2×), concentrated, and then filtered through a small pad of silica gel (10 g). Elution with ether gave pure dione **43** (73 mg, 85%): ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.35–7.00 (m, 10 H), 5.07 (d, 1 H, J = 15.1 Hz), 4.28 (d, 1 H, J = 4.9 Hz), 3.91 (d, 1 H, J = 15.1 Hz), 3.73 (d, 1 H, J = 4.9 Hz), 3.68 (m, 1 H), 3.67 (d, 1 H, J = 3.3 Hz), 3.44 (m, 1 H), 3.30 (ddd, 1 H, J = 1, 4.8, 13.0 Hz), 3.26 (dd, 1 H, J = 8.5, 15.4 Hz), 2.97 (dd, 1 H, J = 4.8, 13.0 Hz), 2.73 (br s, 1 H, J = 1 Hz), 2.70 (dd, 1 H, J = 10.2, 13.0 Hz), 2.54 (dd, 1 H, J = 3.5, 15.4 Hz), 2.07 (ddd, 1 H, J = 3.1, 3.3, 11.9 Hz), 1.82 (m, 1 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 1.36 (s, 3 H), 1.20 (s, 3 H),

1.09 (d, 3 H, J = 7 Hz), 0.95 (m, 1 H), 0.89 (m, 1 H), 0.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.90 (s), 206.49 (s), 170.18 (s), 137.53 (s), 135.88 (s), 131.19 (d), 128.74 (d), 127.86 (d), 126.91 (s), 124.71 (s), 107.99 (s), 83.35 (d), 81.74 (s), 75.45 (d), 68.03 (t), 64.15 (s), 64.01 (d), 54.58 (d), 47.61 (d), 43.37 (t), 42.73 (d), 40.22 (t), 40.08 (d), 38.77 (d), 32.43 (t), 31.56 (t), 28.77 (q), 27.10 (q), 18.75 (t), 17.95 (q), 17.62 (q), 16.92 (q), 13.57 (q), -1.29 (q); IR ($CHCl_3$) 1708, 1689 cm^{-1}; mass spectrum, m/e 711 (14%, M^+), 610 (4%, $M^+ - (CH_3)_3SiCH_2CH_2$), 592 (6%, 610 - H_2O), 91 (100%); exact mass calcd for $C_{43}H_{57}SiNO_6$, 711.395; found, 711.392.

(1*R*,3*S*,5*R*,6*R*,7*S*,8*R*,10*R*,11*S*,14*R*,15*S*,18*R*)-13,14-Dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7,10-trihydroxy-5,7,16,17-tetramethyl-2,12-dioxo-13-azatetracyclo[9.7.0.0^{3,8}.0^{11,15}]octadec-16-ene 6,7-Acetonide (44). To a solution of the dione **43** (114 mg, 0.16 mmol) in dry THF (5 mL) at -78 °C was added L-Selectride (1 M in THF, 0.18 mL, 0.18 mmol). After 1 h, 5% aqueous sodium hydroxide (0.5 mL) was added, and the reaction mixture was warmed to 0 °C (ice bath). Aqueous 30% hydrogen peroxide (0.5 mL) was added dropwise over 5 min. After 10 min at 0 °C, the reaction mixture was poured into water and extracted with ether (3×). The crude product was purified by column chromatography on silica gel (15 g). Elution with 1:1 ether-hexane gave alcohol **44** (82 mg, 72%) as a white solid: mp 61-62 °C; IR ($CHCl_3$) 3600-3200, 1700, 1666 cm^{-1}; mass spectrum, m/e 612 (9%, $M^+ - (CH_3)_3SiCH_2CH_2$), 594 (6%, $M^+ - (CH_3)_3SiCH_2CH_2 - H_2O$), 91 (100%); exact mass calcd for $C_{38}H_{44}NO_5$ ($M^+ - (CH_3)_3SiCH_2CH_2 - H_2O$), 594.322; found, 594.320.

44: ^1H NMR ($CDCl_3$, 470 MHz in part) δ 7.45-7.0 (m, 10 H), 5.23 (d, 1 H, J = 14.7 Hz), 3.87 (d, 1 H, J = 14.7 Hz), 3.54 (d, 1 H, J = 2.9 Hz), 3.21 (ddd, 1 H, J = 4.9, 5.1, 6.6 Hz), 3.15 (m, 1 H), 3.05 (dd, 1 H, J = 5.1, 14.6 Hz), 2.88 (dd, 1 H, J = 4.9, 14.6 Hz), 2.12 (d, 1 H, J = 6.6 Hz), 1.62 (s, 3 H), 1.49 (s, 3 H), 1.45 (s, 3 H), 1.28 (s, 3 H), 1.04 (d, 3 H, J = 6.8 Hz), 0.99 (s, 3 H).

(1*R*,3*S*,5*R*,6*R*,7*S*,8*R*,10*R*,11*S*,14*R*,15*S*,18*R*)-13,14-Dibenzyl-18-(2-(trimethylsilyl)ethoxy)-6,7,10-trihydroxy-5,7,16,17-tetramethyl-2,12-dioxo-13-azatetracyclo[9.7.0.0^{3,8}.0^{11,15}]octadec-16-ene 6,7-Acetonide (45). The alcohol **44** (30 mg,; 04 mmol) was treated with benzoyl chloride (12 mmol) in pyridine (1 mL) at 25 °C for 4 h. The crude product was purified by column chromatography on silica gel (10 g). Elution with 1:1 ether-hexane gave benzoate **45** (32 mg, 92%): ^1H NMR ($CDCl_3$, 470 MHz) δ 8.08 (dd, 2 H, J = 2, 8 Hz), 7.60-6.85 (m, 13 H), 5.33 (dd, 1 H, J = 3.2, 8.0 Hz), 5.00 (d, J = 14.9 Hz), 4.16 d, 1 H, J = 5.26 Hz), 3.92 (d, 1 H, J = 14.9 Hz), 3.65 (m, 1 H), 3.62 (d, 1 H, J = 5.6 Hz), 3.61 (d, 1 H J = 3.3 Hz), 3.39 (m, 1 H), 3.08 (ddd, 1 H, J = 1, 5.5, 7.9 Hz), 2.96 (dd, 1 H, J = 5.5, 13.9 Hz), 2.67 (dd, 1 H, J = 7.9, 13.9 Hz), 2.23 (br s, 1 H, J = 1 Hz), 1.60 (s, 3 H), 1.33 (s, 3 H), 1.25 (s, 3 H), 1.10 (s, 3 H), 1.06 (d, 3 H, J = 6.8 Hz), 1.03 (s, 3 H); mass spectrum, m/e 716 (23%, $M^+ - (CH_3)_3SiCH_2CH_2$), 698 (11%, $M^+ - (CH_3)_3SiCH_2CH_2 - H_2O$), 576 (8%, 698 - $C_6H_5CO_2H$), 105 (100%); exact mass calcd for $C_{45}H_{50}NO_7$ ($M^+ - C_5H_{13}Si$), 716.359; found, 716.362.

X-ray of 44. Crystals suitable for an X-ray analysis were grown from a pentane solution. The crystal used a right parallelopiped with dimensions 0.4 × 0.3 × 0.15 mm. Preliminary oscillation and Weissenberg photographs indicated orthorhombic symmetry, and the subsequent examination of systematic absences in the intensity data showed the space group to be $P2_12_12_1$. Unit cell dimensions and their associated standard deviations were derived from a least-squares fit to the setting angles of 15 three-dimensional reflections measured on a Syntex P-3 automated diffractometer equipped with a graphite monochromator. Crystallographic data are a = 8.748 (9) Å, b = 18.66 (3) Å, c = 25.57 (6) Å; V = 4175.3 Å^3; Z = 4; ρ_{calcd} = 1.098, $\rho_{exptl} \geq$ 1.0; $F(000)$ = 1544; μ = 7.71 cm^{-1}; λ(Cu K_{21}) = 1.5418 Å.

Intensity data were collected by using the θ-2θ scanning mode with a variable scan rate of 2° min^{-1} to 29° min^{-1} depending on the reflection intensity. Background counting time was equal to the scan time. Three standard reflections were monitored for every 50 reflections, and although they showed no systematic variations, they did decrease by 1.8% over the entire data-collection time interval. A total of 6432 reflections were collected, and only 4467 intensities for which $F_o > 3\sigma(F_o)$ were used in the solution and refinement of the structure. The data set was corrected for Lorentz and polarization effects and for the decay in intensity, but not for absorption effects.

The direct method program MULTAN[33] served to locate the silicon atom and six other carbon atoms. Several cycles of blocked-diagonal least-squares refinement followed by the calculation of difference Fourier maps quickly revealed all the non-hydrogen atoms. Full-matrix least-squares refinements of all the positional and anisotropic thermal parameters produced convergence, with $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$ both equal to 0.169. All 59 hydrogen atoms were refined with constrained bond angles and bond distances. Refinement was terminated when all the shift/error ratio for the positional and anisotropic thermal parameters for non-hydrogen atoms (isotropic thermal parameters for hydrogen atoms) were less than 0.5.

Final R_1 and R_2 were both 0.078. Anomalous dispersion effects of all non-hydrogen atoms were included in the calculation of F_c by using $\Delta f'$ and $\Delta f''$ calculated by Doyle and Turner.[34] The atomic scattering factors were taken from Cromer and Liberman.[35] A list of all interatomic distances and angles, atomic coordinate with their thermal parameters and estimated standard deviations, and the observed and calculated structure factor amplitudes are available.

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Supplementary Material Available: Table of all atomic positional and thermal parameters, all interatomic distances and angles, and a listing of observed and calculated structure amplitudes of $C_{43}H_{59}NO_6Si$ (9 pages). Ordering information is given on any current masthead page.

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