Conformational Diagnosis of Diethyl (4*S*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2*E*,6*E*-octadienedioate Based on the Stereochemical Outcomes of Representative Reactions As Compared with Those of Its 4,5-*O*-Isopropylidene Derivatives and on a Dichroic Exciton Chirality Method

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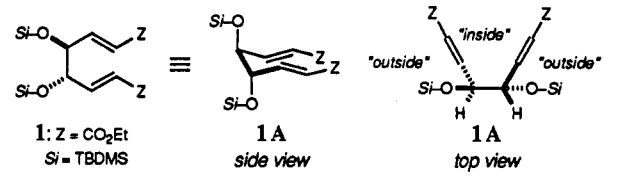
In order to gain more insight into the conformation of diethyl (4*S*,5*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-2*E*,6*E*-octadienedioate (1) experimentally, some appropriate reactions of 1 and its derivative (*S*,*S*)-3, which bears isopropylidene protecting groups, have been executed. The stereochemical outcomes of such reactions as the Diels–Alder reaction, osmium tetraoxide-catalyzed hydroxylation, conjugate addition with amines, and cyclopropanation with phosphonium ylides point to a rigid conformation (**1A**) in which the vicinal TBDMSO groups, the most bulky substituents, are arranged in an anti relationship, and, therefore, the enoate groups are forced to be gauche each other. A dichroic exciton chirality study has also provided clear-cut evidence for this rigid conformation.

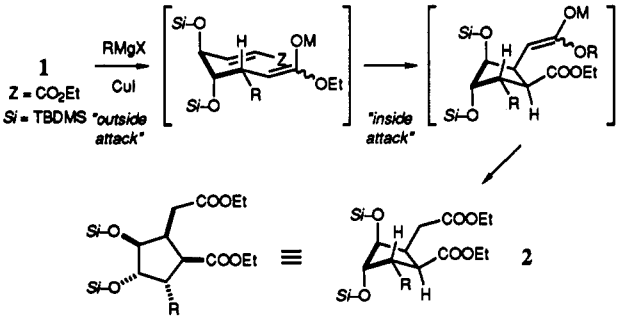
Introduction

Diastereofaces of carbon–carbon double bonds linked to the protected vicinal (4*S*,5*S*)-diol subunit of diethyl (4*S*,5*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-2*E*,6*E*-octadienedioate (1) have been differentiated with very high diastereomeric excess in not only carbon–carbon bond forming processes[1a,d-f] but also oxidative functionalizations.[1b,c] The first impressive stereocontrol realized with 1 was in a cyclopentane annelation through a double Michael process that involved initial "outside" nucleophilic attack by a RMgX–CuI complex followed by intramolecular "inside" nucleophilic attack by the resulting enolate. This process led to fully substituted cyclopentane derivatives **2** with very high optically purity (Scheme I).[1a]

These striking successes in stereocontrol of diverse organic reactions of 1 have necessarily turned our attention to the role of the ground-state conformation (**1A**) in the diastereofacial bias. The role of the ground state conformation can be deduced from the consideration of the preferred rotational isomer [**1B** ≪ **1A** *Newman* ≫ **1C**].[1a,2] Because **1A** entails the mutual shielding of a pair of the "inside" diastereofaces, a pair of the remaining homotopic diastereofaces exposed "outside" becomes susceptible to nucleophilic, electrophilic, and concerted processes with external reagents. We refer to this topological situation



Scheme I



as "*outside–inside bias*" (**1A** *top view*).[3a] When a functional group could be located properly for intramolecular attack or a reactive nucleophilic center such as an enolate could be generated at a specific location, the "*inside*" diastereofaces would be accessible as reaction sites, as described in the examples above. These reactions would

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(2) For a discussion of the stability order of rotamers, see (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill Inc.: New York, 1962; p 124–132. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; John Wiley and Sons, Inc.: New York, 1965; p 5–35. (b) Rüchardt, C.; Beckhaus, H.-D. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 529–538. (c) Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* **1989**, *25*, 1–97.

(3) (a) Saito, S.; Harunari, T.; Shimamura, N.; Asahara, M.; Moriwake, T. *Synlett*, **1992**, 325–326. (b) Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401–3404. (c) Yoda, H.; Katagiri, T.; Takabe, K. *Ibid.* **1991**, *32*, 6771–6774. (d) Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513–516.

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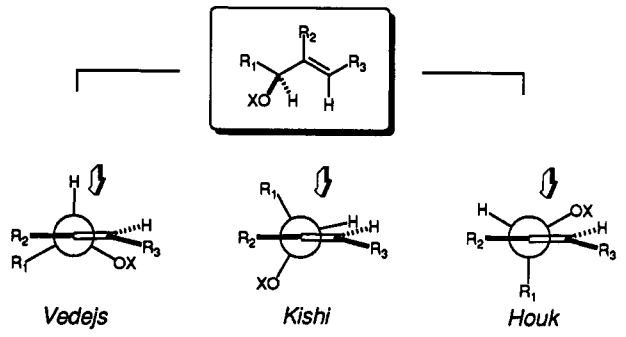
lead to carbacycles[1a,e] or heterocycles[1c] bearing multiple stereocenters that could not easily be obtained otherwise.

As an outgrowth of our interest in diverse organic reactions involving the differentiation of diastereomeric carbon–carbon double bonds, we examined the applicability of this vicinal diol controller strategy to the differentiation of diastereofaces of a carbonyl group of a β-keto ester substituent linked to the controller unit, and we had considerable success.[3]

In the meantime, Schreiber[4] has arrived at essentially the same molecular design. He employed a substrate in which the TBDMS groups of 1 were replaced with benzyl groups to construct a consecutive polyol array with the desired absolute configuration of Hikizimycin,[5] the most structurally complex member of the long-chain carbohydrate class of natural products. The desired stereocenters were introduced by a substrate-controlled diastereoselective osmylation process. However, the underlying concept of Schreiber's work seems to be different from ours, and he invokes his own synthetic concept, "*two-directional chain synthesis*".[6]

In general, stereochemical outcomes for reactions of allylic compounds have been predicted or accounted for by invoking one of the reasonable allylic ground-state or transition-state models proposed by Kishi,[7] Houk,[8] or Vedejs,[9] as shown below. Indeed, stereochemical outcomes

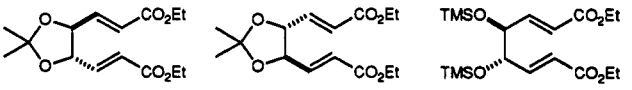


observed so far in the diastereoselective processes of 1 and related structures can be rationalized on the basis of either of the models, as far as the sense of diastereoselection is concerned. However, we believe that, for 1, the effect of the preferred rotational isomer distribution should be the overriding concern. Because 1 basically consists of a *dl*-ethane backbone, we should evaluate the most stable rotational isomer before considering the allylic models; otherwise we could not deduce its real conformation.

Accordingly, we feel that experimental, theoretical, or physical corroboration of conformation **1A** is required in order to establish "*outside-inside bias*" as a general concept. In this article, we compare the stereochemical outcomes of some representative reactions of 1 with those of the corresponding acetonide derivative (*S,S*)-**3**. On the basis of these comparisons, we discuss the stereochemical course of such reactions, the role that the unique structure of 1 plays in controlling the diastereoselection, and the conformation that is compatible with all these findings. We also present our effort to provide support for the so-deduced conformation of 1 based on dichroic exciton chirality[10] studies.

Results and Discussion

Stereochemical Outcomes of the Reactions of Silyl and Acetonide Derivatives. We considered Diels–Alder, osmylation, amine conjugate addition, and cyclopropanation reactions because some of these reactions for 1 had been previously reported,[1a,b,d] and the stereochemical outcomes of the Diels–Alder[11] and cyclopropanation[12] reactions of (*S,S*)-**3** or (*R,R*)-**3** were also available from the literature. These results are summarized in Table I together with additional results for related reactions of 1, (*S,S*)-**3**, and bis-trimethylsiloxy derivative **4**. The sub-



(*S,S*)-**3** (*R,R*)-**3** **4**

strates bearing vicinal silyloxy groups resulted in exclusive (>99% de) diastereoselection for every reaction examined, and, in every case, the sense of the diastereoselection could be predicted on the basis of "*outside–inside bias*".

Diels–Alder Reaction. The Diels–Alder reaction of (*R,R*)-**3** exhibited low selectivity (a 3:2 ratio of **6**/**7**) but afforded two of the three possible diastereoisomers,[11] whereas 1 afforded **5** as a single product.[1d] The reactivity of 1 was much lower than that of (*R,R*)-**3** probably because of the highly sterically crowded nature of 1's reaction centers, for which its conformational rigidity may be responsible. For instance, only one of two "*outside*" faces of 1 (one enoate group served as a dienophile) underwent a Diels–Alder reaction, which required a higher temperature (−20 °C) and a large excess of Lewis acid for a practical rate, whereas the same reaction of (*R,R*)-**3** proceeded efficiently at −70 °C at both enoate groups, although with low diastereoselectivity. The conformational rigidity of 1 also became evident in its reaction with 2-methyl-1,3-butadiene, which proceeded with very high % de (>99%) even at 80 °C.[1d]

Osmylation. Osmium tetraoxide-catalyzed (5 mol%) mono-dihydroxylations of (*S,S*)-**3** by means of a published procedure[13] using *N*-methylmorpholine *N*-oxide (2 equiv of NMO) as a cooxidant led to a separable mixture of diastereoisomeric tetraols **9** and **10** in a ratio 2:1. The osmylation of **3** contrasts markedly with that of **1**, which gave **8** exclusively. The absolute configurations of the stereogenic centers of **9** and **10** were confirmed both by

(4) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657–9659.
(5) Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.* **1971**, *24*, 259.
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(7) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (b) *Idem. Tetrahedron* **1984**, *40*, 2247–2255.
(8) (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882. (b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *Ibid.* **1986**, *108*, 2754–2755. (c) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117.
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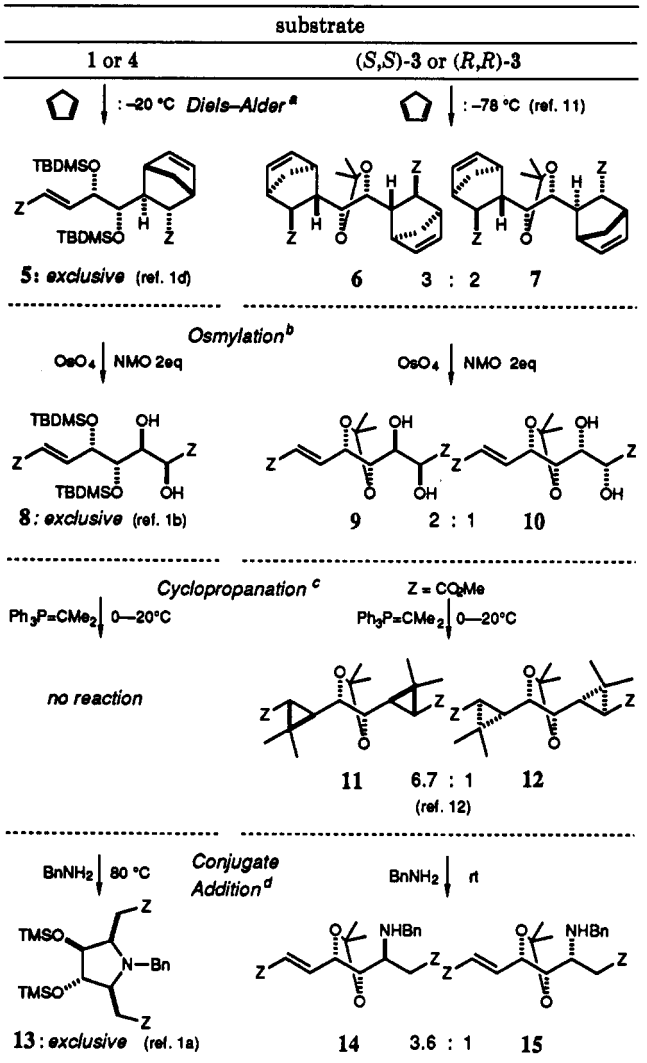
(11) Takano, S.; Kurotaki, A.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 3991–3992.
(12) Krief, A.; Dumont, W.; Pasav, P. *Tetrahedron Lett.* **1988**, *29*, 1079–1082.
(13) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. (b) Ray, R.; Matheson, D. S. *Ibid.* **1980**, *21*, 449–450.

Table I. Comparison of the diastereoselectivity of the Diels-Alder, osmylation, cyclopropanation, and amine conjugate addition reactions of silyl and acetonide derivatives 1, 3, and 4



[a] For 1, Et_2AlCl/CH_2Cl_2/cyclopentadiene (10 equiv)/−20 °C for 48 h. For (*R,R*)-3, Et_2AlCl/CH_2Cl_2/cyclopentadiene (10 equiv)/−20 °C for 20 h. [b] OsO_4 (5 mol %)/Me_2CO–H_2O (5:1)/rt. [c] 2.5 equiv Ph_3PCMe_2/THF–hexane/0–20 °C/2 h. [d] $PhCH_2NH_2$ (15 equiv)/EtOH/80 °C for 48 h (4) or $PhCH_2NH_2$ (1.2 equiv)/EtOH/25 °C for 12 h [(*S,S*)-3].

chemical correlations as previously described[1b] and by the *J* value between H(5) and H(6) or that between H(6) and H(7).[14]

Cyclopropanation. The effects of the sterically crowded nature of 1 were again observed in the cyclopropanation reaction. The reaction of (*S,S*)-3 with isopropylidenetriphenylphosphorane has been reported to be easily effected at 0–20 °C within 2 h, giving rise to a mixture of cyclopropanecarboxylates 11 and 12 (74% de),[12] whereas the application of these conditions to 1, or even to 4, resulted in total recovery of the starting materials.

Conjugate Addition of Amines. The reaction of (*S,S*)-3 with 1 equiv of benzylamine took place even at room temperature and required a shorter reaction period than did 1, although a 3.6:1 mixture of amino diols 14 and 15 was obtained from 3.[15] In contrast, 1 is not susceptible to amine attack,[1a] and trimethylsilyl-protected dienedioate 4 was needed for the reaction to proceed. Surprisingly enough, 4 afforded exclusively pyrrolidine dicarboxylate 13,[16] even though an elevated temperature (80 °C) was required for the reaction to proceed at a practical rate (48 h for completion).

Scheme II

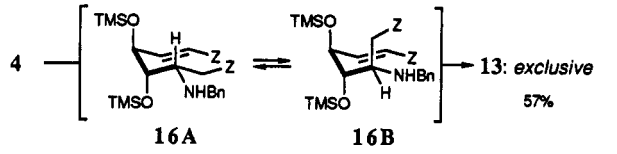


Table II. The Steric Effects of R_3Si and $R'NH_2$ on the Course of Conjugate Addition Reactions[a]

substrate: R	R′ (amine)	time/h	yield[b]/%	pyrrolidine[c]	ratio[d]
4: CH_3	Bn	48	57	**13**	>99
4: CH_3	$BnCH_2$	10	43	**19**	>99
17: C_2H_5	Bn	36	53	**20** + **22**	3:1
17: C_2H_5	$BnCH_2$	35	54	**21** + **23**	10:1

[a] Conducted with 15 equiv of amine in EtOH at 80 °C. [b] For chromatographically pure product. [c] For the structures determined by 500-MHz NMR analyses and chemical derivatization, see Scheme III and Experimental Section. [d] Determined by a proton-NMR analysis (500 MHz).

A plausible mechanism for the conjugate addition of amines to 4 should be noted (Scheme II). Benzylamine initially attacks the "*outside*" π-(C=C) face to give amino endioate **16A**. This intermediate must undergo a change in its conformation for the second-stage conjugate addition to take place. The second stage becomes possible when the σ-C(3)–C(4) bond of **16A** rotates to such a degree that the secondary *N*-benzylamino group reaches the specific location indicated by structure **16B**, at which point, the amine is capable of attacking the "inside" face of the remaining C=C bond. This mechanism is the only one leading to double amino-Michael product **13** as a single isomer with the indicated absolute configuration, if the two TMSO groups maintain an anti relationship throughout the course of the reaction.

The stereochemical outcomes of double amino-Michael reactions of 4 and 17 with various primary amines are worthy of note. The results are summarized in Table II. As can be quickly recognized from the ratios listed in Table II, a striking change in the product distribution was observed when either R on the silicon or R′ on the nitrogen atom was changed.

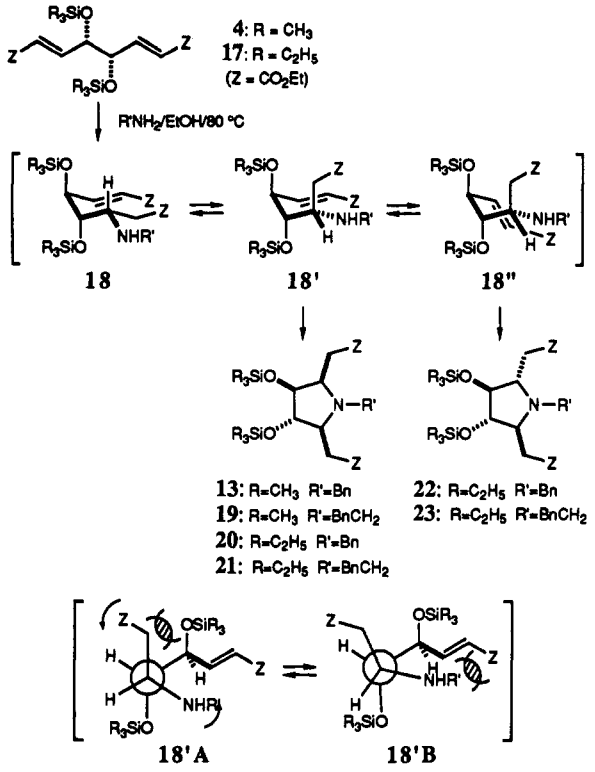
The formation of **22** and **23** indicates that the second-stage intramolecular conjugate addition proceeded in such a way that the incorporated amino group attacked the "outside face" of the remaining enoate function even though the process was intramolecular. This outcome can be rationalized on the basis of an unavoidable conformational constraint that emerged during the reaction. This constraint partially dictates the interconversion between amino enedioates 18′ and 18″. For example, when R_3 on the silicon atom is changed from CH_3 to C_2H_5, the nonbonded 1,3-diaxial-type repulsion between the R_3SiO and ZCH_2 groups at the stage of 18′ may increase

(14) $J_{H(6)-H(6)}$ and $J_{H(6)-H(7)}$ were 8.8 and 2.0 Hz for **9** and 5.4 and 3.4 Hz for **10**, respectively. The $J_{H(4)-H(5)}$-values for **9** and **10** (8.7 and 8.3 Hz, respectively) reflect the anti arrangement between C(4)-H and C(5)-H.

(15) For the determination of their structures, see the Experimental Section.

(16) The absolute structure of **13** was unambiguously confirmed by NOE experiments on the bicyclic lactone **34** (see Experimental Section), which could be derived from **13** via TMS-deprotection, lactonization, and acetylation (see the Experimental Section).

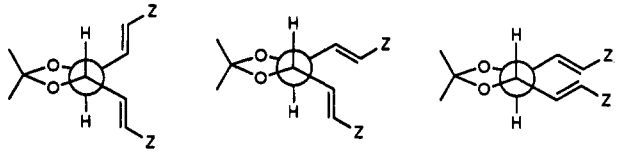
Scheme III



considerably; one consequence of the increased repulsion would be the movement of the R'HN group from the position indicated in 18'**A** to that in structure 18'**B** (Scheme III).

Conformation 18'**B** would also suffer from increased steric congestion between the amino and enoate groups, and, therefore, the conformational equilibrium between 18' and 18'' may significantly shift to the right. The shift would lead to an increase in the formation of pyrrolidine *anti*-dicarboxylate **22** or **23**. This is indeed observed: **20**/**22** = 3:1. The observed ratio 10:1 (**21**/**23**) in the case of 2-phenylethylamine, which is less sterically demanding than benzylamine, can be explained on the same basis. That **13** or **19** was exclusively formed from **4** irrespective of amine variation can be rationalized by concluding that, in this case, the interconversion between 18' and 18'' was not required because of the sterically less-demanding trimethylsilyl protecting group.

The possible conformations of (*S,S*)-**3**, illustrated below, are (*S,S*)-**3A**, (*S,S*)-**3B**, and (*S,S*)-**3C**. Both diastereomeric



π-(C=C) faces of **3A** and **3B** would be available for reactions, and, accordingly, moderate stereoselectivity would result. In contrast, conformation (*S,S*)-**3C** would provide a very high degree of diastereoselection with a sense opposite that of **1A** because (*S,S*)-**3C** is parallel to **1A** in terms of diastereofacial bias, although the opposite diastereofaces are exposed to the "outside".

The question as to the conformation of **3** has been answered by the experiments discussed above: *no efficient shielding of diastereofaces was observed in the above four representative reactions of (S,S)-3, and both diastereomeric π-(C=C) faces of the enoate groups of 3 were available for these processes, in sharp contrast to the cases of 1 and 4.* The diastereoselectivity observed for the reactions of the acetonide derivatives points not to (*S,S*)-**3C** but to (*S,S*)-**3A** or **-3B**, or both of them, although (*S,S*)-**3C** cannot necessarily be ruled out. The distinct differences in the stereochemical outcomes of the reactions of **1** and (*S,S*)-**3** or (*R,R*)-**3** strongly suggest that **1** has a conformation that allows for the carbon–carbon double bonds to be attacked from "*outside*" in every intermolecular process studies. Conformations **1B** and/or **1C** can reasonably be ruled out in this context, and only **1A** is compatible with both the very high diastereomeric excesses and the absolute configurations observed in the reactions discussed above. The rather lower reactivity of **1** probably stems from its conformational rigidity and the sterically demanding nature of its reaction centers.

Table III. CD and UV Data[a] and Conformations Estimated for 1, 24, (*S,S*)-3, and 25

substrate	$\Delta\epsilon^b$ (nm)	$\epsilon/10^4$ (nm)	conformation[c]
1	+1.2 (251)		**1A** (G^+)
	−11.0 (213)	1.70 (217)	
24	+0.8 (251)		
	−6.1 (218)	1.63 (217)	
(*S,S*)-**3**	−20.3 (220)	1.72 (216)	
25	+2.5 (212)	0.91 (215)	

[a] Measured in acetonitrile solution. [b] In $dm^3\,mol^{-1}\,cm^{-1}$. [c] See text.

Dichroic Exciton Chirality Method. In order to support the conclusions derived from the stereochemical studies mentioned above, we have executed conformational analyses based on the dichroic exciton chirality method. A recent publication[17] from the laboratory of one of the authors has revealed the conformational differences between (*R,R*)-tartaric acid esters and *N,N*-dialkylamides using the dibenzoate exciton chirality method.[10] Because the absolute configurations of the tartaric acid family are known, the spatial arrangement of each substituent on the stereocenters has been unequivocally determined.[17] We believed that this valuable method could be extended to **1** to provide physical corroboration in support of conformation **1A**. Accordingly, we carried out CD measurements on **1**, the corresponding diol **24**, (*S,S*)-**3**, and ethyl (4*S*)-4,5-*O*-isopropylidene-4,5-dihydroxy-2*E*-pentenoate (**25**) as well as a number of mono- and biscinnamates **26**–**31** for systematic comparison.[18] The results are summarized in Tables III (**1**, **3**, **24**, and **25**) and IV (**26**–**31**) together with the estimated conformations, and typical CD spectra of **1**, (*S,S*)-**3**, **24**, **27**, **29**, and **31** are illustrated in Figure 1.

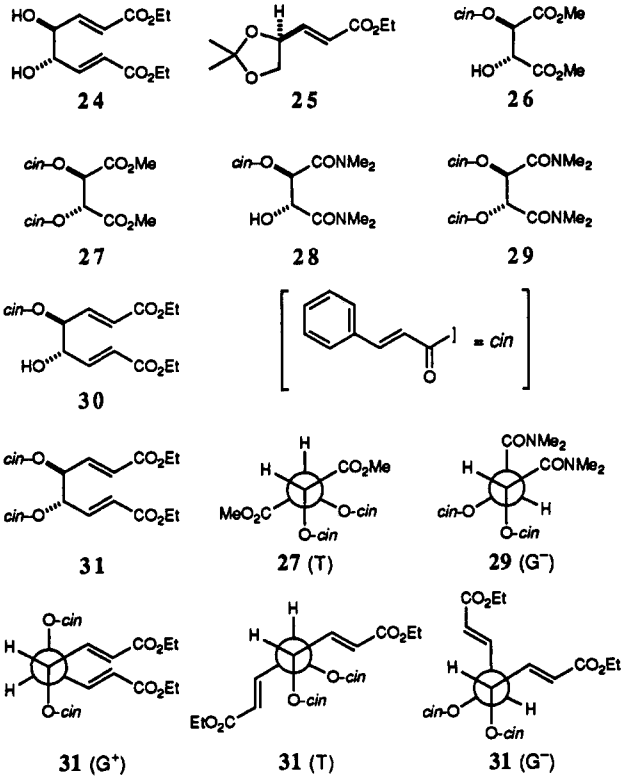
(17) Gawronski, J.; Gawronska, K.; Rychlewska, U. *Tetrahedron Lett.* **1989**, *30*, 6071–6074 and refs cited therein.

(18) For the synthesis of **1** (Z = CO_2Et), **24**, and (*S,S*)-**3**, see ref 1a and the Experimental Section. For a synthesis of **25** from (*R*)-glyceraldehyde acetonide, see (a) Minami, N., Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109–1111 and (b) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis*, **1986**, 403–406. For the preparation of the corresponding methyl enoate, see (c) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009–3012, (d) Mulzer, J.; Kappert, M.; Hutner, G.; Jibril, I. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 704–705, and (e) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284–291. For the preparation of **26** and **27** from (*R,R*)-dimethyl tartrate and of **28** and **29** from (*R,R*)-dimethyl tartramide, see Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301–325. Compounds **30** and **31** were prepared from **24** via cinnamoylation with the corresponding acid halides promoted by 4-(*N,N*-dimethylamino)pyridine in dichloromethane.

Table IV. CD and UV Data[a] and Conformations Estimated for Cinnamates 26–31

substrate	$\Delta\epsilon$[b] (nm)	$\epsilon/10^4$ (nm)	conformation[c]
26	−1.2 (274)	2.27 (279)	
	−4.5 (219)	1.45 (217)	
27	−26.9 (292), +13.4 (263)	4.22 (278)	**26** (T)
	−3.2 (223)	2.73 (217)	
28	−1.1 (285)	2.08 (278)	
	+3.2 (229), −3.4 (213)	1.88 (216)	
29	+42.3 (294), −44.7 (266)	4.40 (275)	**29** (G^-)
	+8.2 (225), −6.3 (212)	3.50 (217)	
30	−3.1 (275)	2.07 (278)	
	+2.6 (221)		
31	−9.8 (270)	4.22 (279)	**31** (G^+)
	+6.4 (210), +3.80 (216)	3.80 (216)	

[a] Measured in acetonitrile solution. [b] In $dm^3\,mol^{-1}\,cm^{-1}$. [c] See text.



O,O'-Bis(cinnamoyl)tartrate **27** is known to exist as conformer **27**(T),[17] and it gave a negative exciton Cotton effect, $\Delta\epsilon$ = −26.9 at 292 nm and $\Delta\epsilon$ = +13.4 at 263 nm, for the cinnamate system, accordingly (Table IV and Figure 1d). In contrast, *O,O'*-bis(cinnamoyl)tartramide **29** was characterized by a positive exciton Cotton effect, $\Delta\epsilon$ = +42.3 at 294 nm and $\Delta\epsilon$ = −47.7 at 266 nm, due to conformer **29**(G^-) (Table IV and Figure 1e).[17] As expected, monocinnamates **26** and **28** did not show a Cotton effect because of the absence of exciton coupling.

O,O'-Bis(cinnamoyl)dienedioate **31** displayed no exciton Cotton effect within the cinnamate dipole-allowed transition at around 280 nm and instead displayed a single negative Cotton effect, $\Delta\epsilon$ = −9.8 at 270 nm (Table IV and Figure 1f). Although this could be accounted for by a canceling of the contributions of conformers **31**(T) and **31**(G^-), we took it as evidence for the dominant contribution of conformer **31**(G^+) because no sign of the presence of conformations **31**(T) and **31**(G^-) has been detected by NMR diagnosis.[19] In conformer **31**(G^+), because of the coplanar arrangement of the two cinnamate chromophores, no bis-cinnamate exciton Cotton effect was observed. However, heterochromophoric coupling between the cinnamate and enoate chromophores is possible in **31**(G^+), leading to a negative exciton Cotton effect (i.e., a negative Cotton effect at 270 nm (cinnamate transition) and a positive Cotton effect at 210 nm (enoate transition)). Since the coupling between the two enoate chromophores in **31**(G^+) is expected to be weak, the CD of conformer **31**(G^+) should approximately be that of "doubled" CD of **30** and this is indeed the case (Table IV).

We have also analyzed the CD data of parent compounds **1** and **24**, which have enoate chromophores. The bis-enoate system in conformer **1A** should produce an exciton Cotton effect at around 215 nm. Only a single negative Cotton effect is this region is observed (Table III and Figure 1a). We believe that this is due to weak coupling between the two enoate chromophores. Although the three-bond system (=C—C—C—C=) in **1** has positive chirality, the actual chirality of the two-transition dipole is strongly dependent on the conformation of the substituents, in this case the enoate chromophores. For conformer **1A**, the chirality of the bis-enoate system, shown below as *s-trans*-**1**, is negative, and exciton coupling would result in a negative Cotton effect at around 215 nm. This is indeed observed. It is interesting that the CD spectra of **1** (Table III and Figure 1a) and **24** (Table III and Figure 1c) are essentially the same, which, however, does not necessarily mean that diol bis-enoate **24** has the same conformation as **1**. A possible intramolecular hydrogen bonding between the 4,5-dihydroxy groups of **24** apparently allows for the enoate groups to be in a gauche arrangement similar to the case of (*S,S*)-**3** shown in Figure 3, which results in a negative Cotton effect.

The CD spectra of two conformationally rigid derivatives, (*S,S*)-**3** and **25**, provide additional evidence for exciton coupling due to the bis-enoate chromophores. Whereas mono-enoate compound **25** gave a weak, positive Cotton effect at 212 nm, bis-enoate derivative (*S,S*)-**3** exhibited negative and much stronger Cotton effect at 220 nm, indicative of exciton coupling of the two enoate chromophores. If (*S,S*)-**3** exists as a conformer with an *s-trans* enoate group (Figure 3, upper), the stronger negative Cotton effect observed implies that the conformational equilibrium of (*S,S*)-**3** is shifted toward (*S,S*)-**3A** or (*S,S*)-**3B**. In contrast, if an *s-cis* enoate is present (Figure 3, lower), all of the three possible conformers should be consistent with the observed sign of the exciton coupling. The stereochemical outcomes observed for (*S,S*)-**3** shown in Table I did not indicate any dominant contribution of conformation (*S,S*)-**3C**, which, therefore, could possibly be excluded in this CD interpretation.

Thus, all results obtained from the dichroic exciton chirality experiments are consistent with the expectation that **1** exists as conformer **1A**, in which the most bulky substituents, the TBDMSO's, are anti to each other and the enoate chromophores are gauche.

NOE Experiments. It is worthy of note that, in support of the above conclusion, distinct NOE's, as shown below,

(19) The H[4(or 5)]-signal of **10** was a sharp, narrow-lined doublet of doublets with a $J_{H(4),H(5)}$ coupling constant of 4.3 Hz (see Experimental Section). NMR data for monocinnamates give additional support for conformational assignments; the $J_{H(4),H(5)}$ coupling constants are **26**, 2.1 Hz; **28**, 6.0 Hz; **30**, 5.3 Hz—as expected for conformations T, G^-, and G^+, respectively (see Hawkes, G. E.; Lewis, D. *J. Chem. Soc. Perkin Trans. 2* **1984**, 2073–2078 and Gillies, D. G.; Lewis, D. *Ibid.* **1985**, 1155–1159). Accordingly, the $J_{H(4),H(5)}$ coupling constant of **31** (4.3 Hz) is the closest to that (5.3 Hz) of **30**. In addition, the line shape of the H[4(or 5)] signal of **31** as mentioned above seems not to agree with the presence of both **31** (T) and **31** (G^-). This interpretation is reasonably consistent with the observation that the CD of **31** was that of "doubled" CD of **30** (see text).

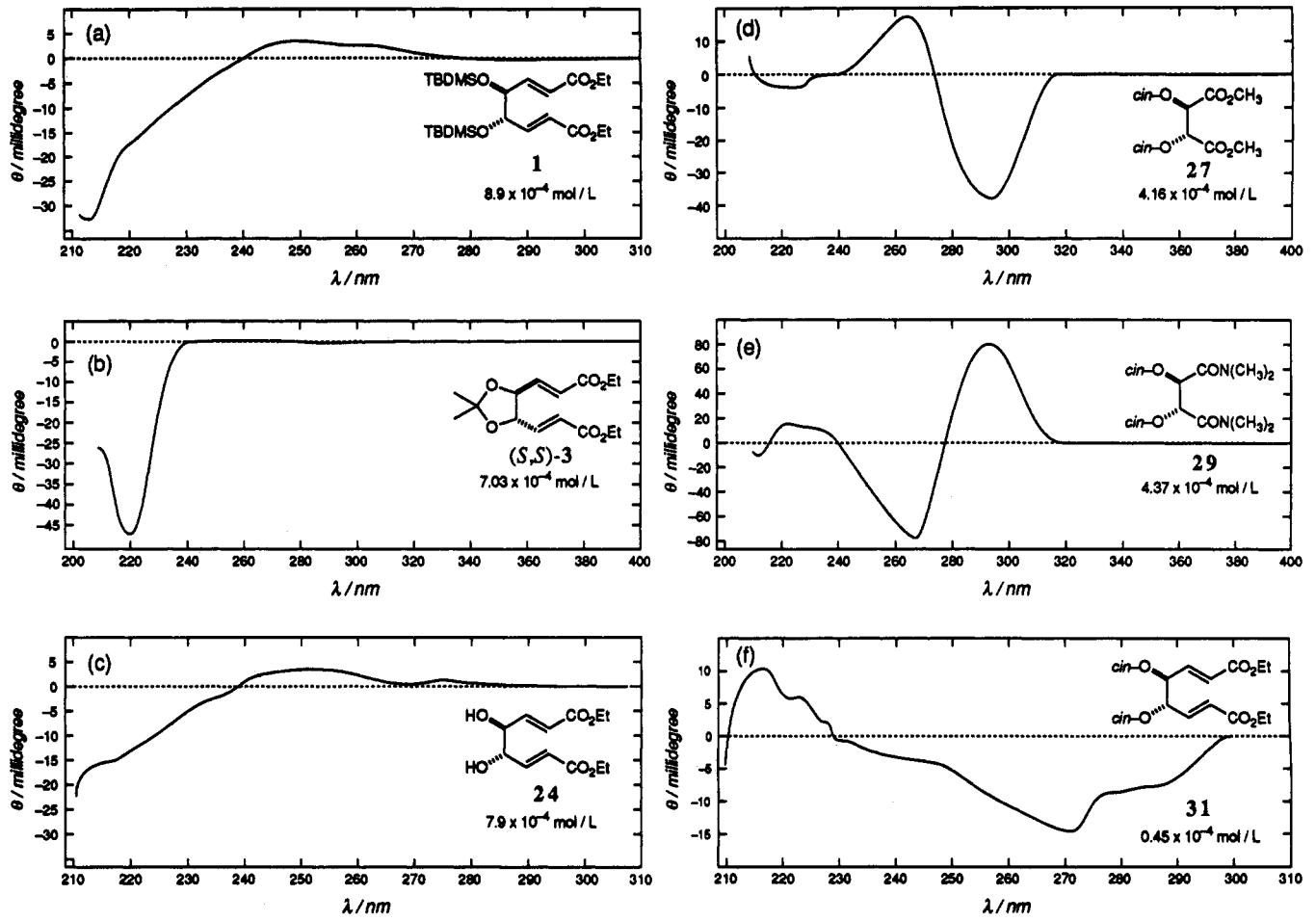


Figure 1. Representative CD spectra a–f for 1, (*S,S*)-3, 24, 27, 29, and 31, respectively, in which θ (millidegree) is plotted against wavelength λ (nm). Solvent = CH_3CN; temperature = 23 °C.

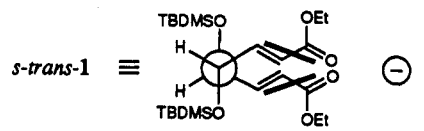


Figure 2. Possible coupling of electric transition moments (the thick lines) due to the enoate chromophore.

have been observed between the C(3)- and C(6)-hydrogens in compounds 8, 32,[1b] and 33,[3a] which bear a protected vicinal 4,5-diol unit. For such NOE's to occur, all these compounds must be in specific conformations in which the hydrogens concerned are in close proximity because they are separated by five σ-bonds. Both **1A**- and **1B**-type conformations are candidates. However, that the coupling constants ($J_{4,5}$) observed for 8, 32, and 33 are 4.5, 4.9, and 4.1 Hz, respectively, clearly suggests that the **1B**-type conformations are highly unlikely and, therefore, that the **1A**-type conformations must be responsible for the observed NOE's. In addition, one of the C(8)-hydrogens of 32 exhibited a 1.7% NOE when C(3)-H was irradiated even though these hydrogens are separated by seven bonds. Hence parent substrate 1, albeit not amenable to an NOE experiment because of its axially dissymmetric nature, should likewise exist in conformation **1A**.

In these particular cases, we can recognize that a protected vicinal (*S,S*)-diols incorporated into a *di*-1,1,2,2-tetrasubstituted ethane framework can play an important role in controlling the ground-state conformation by orienting themselves anti because of their steric bulk and

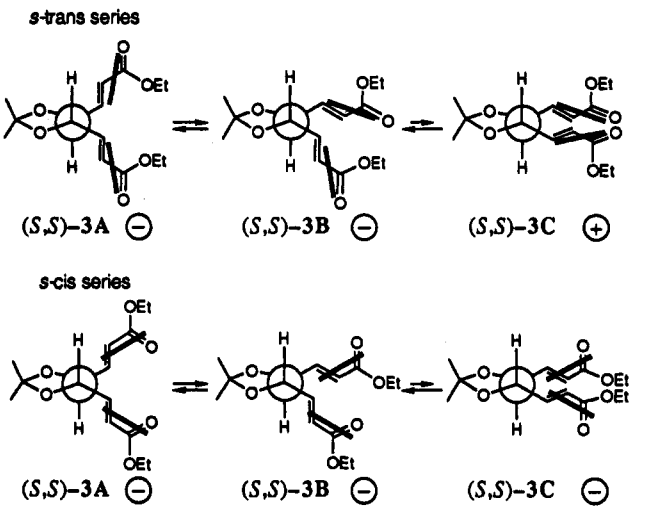
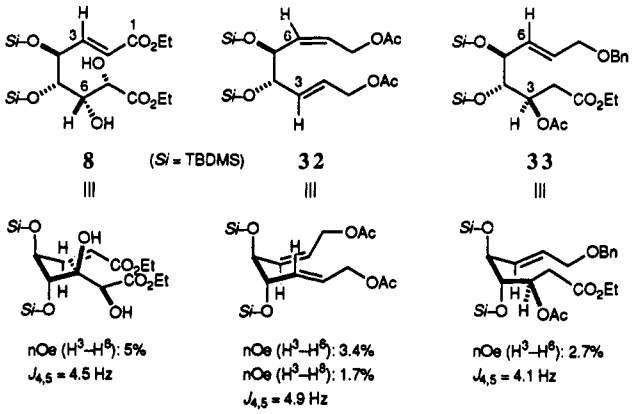


Figure 3. Possible coupling of electric transition moments (the thick lines) due to the enoate chromophore: the top row for the *s-trans*-conformation and the bottom row for *s-cis*-conformation (for simplicity, the *s-trans–s–cis* hybrid system is not shown).

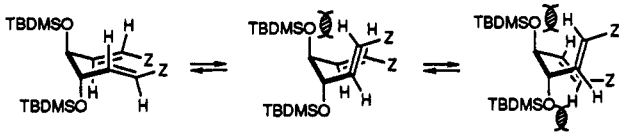
forcing the remaining substituents to arrange gauche to each other. Such topological characteristics could reasonably account for the perfect stereocontrol of, for instance, the previously reported osmylation of 1 on both sites of the enoate groups.[1b] This osmylation apparently involved 8 as the first-stage vicinal dihydroxylation product.



Concluding Remarks. All evidence obtained in this study indicates that the conformation of 1 should be **1A**.[20] However, the question may be raised as to how the Curtin–Hammett principle[21] applied to the present discussion. We are presently postulating that the barriers for rotational interconversion such as those for **1A** ↔ **1C** and **1B** ↔ **1C** are quite large[22] because these processes must suffer, respectively, from two extremely congested TBDMSO vs enoate eclipsing interactions (torsional strain) and from TBDMSO vs TBDMSO and enoate vs enoate eclipsing interactions, whereas a barrier to a rotation such as **1A** ↔ **1B** might relatively be small because this process suffers only from an enoate vs enoate eclipsing interaction. This postulation is consistent with discussions of the rotamer distribution of such related structures as 1,1,2,2-tetrabromoethane,[23] 2-tetra-*tert*-butylethane,[24] and *dl*-1,2-di-*tert*-butyl-1,2-bis(1-adamantyl)ethane.[2b] In particular, in the last case, that the two conformationally stable gauche rotamers of the *dl* isomer could be separated by mutual crystal selection attested to the high barrier separating the rotamers.

These interpretations would lead us to conclude that **1A** and/or **1B** should be responsible for the observed stereochemical outcomes. Conformer **1B** would provide stereochemical outcomes similar to those for (*S*,*S*)-**3** because of their conformational similarity: this, however, did not happen. Hence, we could exclude **1B** in this context and postulate that the reactions of 1 proceed via an early transition state that is close to **1A** in structure, although no physical proof for **1A** has been obtained and **1B** could not be completely ruled out. If this is the case, diastereoselective reactions of 1 must take allylic conformations **1A**, **1A′**, and **1A″** into account; **1A** may still be the most stable conformation because the others apparently suffer from nonbonded repulsion that is lacking in **1A** (Scheme IV).

Scheme IV



The present discussion has not taken any electronic effect into account and rests only on steric interactions. We believe that the diastereoselection of allylic carbon–carbon double bonds linked to oxygen-bearing stereocenters would primarily be governed by steric effects. Recent work by Vedejs[9] has systematically and conscientiously disclosed that this is most likely the case. In any event, the proposed vicinal diol subunit should provide a novel device for acyclic stereocontrol.

Experimental Section

General Methods. UV spectra were determined on a Shimadu UV 160 spectrophotometer. Circular dichroism (CD) spectra were determined on an Aviv Model 62 DS dichrograph. IR spectra were obtained with a Hitachi 215 grating infrared spectrophotometer or a Perkin-Elmer Model 580 instrument, and only the major absorptions are cited. The ^{1}H-NMR (500, 200, 100, and 80 MHz) and ^{13}C-NMR (126, 50, and 25 MHz) spectra were recorded on a Varian VXR-500, VXR-200, JEOL FX-100, or Tesla BS 587A instrument, with deuteriochloroform as a solvent. The chemical shifts are given in δ units relative to internal $CHCl_3$ (7.26 ppm for proton) or $CDCl_3$ (77 ppm for carbon-13) or tetramethylsilane (0 ppm). Splitting patterns are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Optical rotations were measured on a JASCO DIP-4 digital polarimeter using a 3.5 mm × 0.5 dm Pyrex cell. Mass spectra were obtained on a JEOL JMS-DX303 instrument operated either in the electron impact (EI) or fast atom bombardment (FAB) mode relying on a JMA-DA5000 mass data system.

Usual column chromatography was carried out with Merck silica gel 60-7743. Dichloromethane (CH_2Cl_2), acetonitrile, and pyridine were freshly distilled from P_2O_5 under argon. Triethylamine (Et_3N), benzene, and toluene were freshly distilled from CaH_2. Acetone was dried over anhydrous potassium carbonate and freshly distilled. Methanol was distilled from magnesium methoxide under argon. 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) was purchased from Fluka and was used as received. All reactions were executed under an atmosphere of dry argon in flame-dried glassware.

Diisopropyl L-2,3-*O*-Isopropylidenetartrate. To a stirred solution of diisopropyl L-tartrate (5.08 g, 21.7 mmol) and TsOH (10 mg) in benzene (20 mL) at rt was added dimethoxypropane (3.20 mL, 26.0 mmol). The mixture was heated at 80 °C (bath temperature) for about 3 h while the benzene–MeOH azeotrope was slowly removed through a Vigreux column equipped with a vacuum jacket. The reaction was cooled to room temperature and neutralized with anhydrous potassium carbonate (60 mg). The resulting suspension was subjected to a short-path column chromatography (SiO_2) with EtOAc–hexane (1:10) as an eluent. The combined fractions were concentrated under reduced pressure to given an oil. The oil was solidified as it was purified by distillation under vacuum (diisopropyl L-2,3-*O*-isopropylidenetartrate: 5.77 g, 97%): bp 78–86 °C/0.05 mmHg; mp 41.5–42.5 °C; $[\alpha]^{23}_D$ +42° (c 4.0, $CHCl_3$); IR ($CHCl_3$) 2910, 1735, 1430, 1350 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.22 (d, 12H, J = 6.3 Hz, 2 × $(CH_3)_2$), 1.41 (s, 6H, $C(CH_3)_2$), 4.60 (s, 2H, 2 × $CHCO_2R$), 5.03 (7 lines, 2H, J = 6.3 Hz, 2 × CO_2CH); ^{13}C NMR

(20) Calculated ΔH_f values for **1A**, **1B**, and **1C** were −367.2, −359.0, and −361.9 kcal/mol, respectively. (The values were calculated by the AM1 method within SYBYL molecular model software package of computer programs: Tripos Associates, St. Louis, MO 63117). Thus, the most stable conformation was shown to be **1A**: the calculations were carried out at Daicel Research Center, Himeji, Japan.

(21) (a) Curtin, D. Y. *Record Chem. Progr. Kresge-Hooker Sci. Lib.* **1954**, *15*, 111. (b) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill Inc.: New York, 1962; pp 151–152, 237–238.

(22) The barriers to rotations such as **1A** → **1C** or **1B** → **1C** have been calculated to be 53.9 and 51.4 kcal/mol, respectively. The calculations involved systematic bond rotation about the C(4)–C(5) bond of (*S*,*S*)-1 with an increment of 20°, and the heats of formation (ΔH_f) at each dihedral angle (θ = ∠C–C(OSi)–C(OSi)–C) were calculated [the AM1 method within SYBYL molecular model software package of computer programs (Tripos Associates, St. Louis, MO 63117)], while that for **1A** → **1B** has been estimated to be 12.4 kcal/mol: typical values for the heats of formation calculated; ΔH_f = −367.1 (θ = 60°, **1A**), −313.3 (θ = 140°), −361.9 (θ = 180°, **1C**), −314.8 (θ = 260°), −359.0 (θ = 300°, **1B**), and −354.7 (θ = 0°) kcal/mol.

(23) (a) Kagarise, R. E.; Rank, D. H. *Trans. Faraday Soc.* **1952**, *48*, 394–400. (b) Miyagawa, I.; Chiba, T.; Ikeda, S.; Morino, Y. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 218–222.

(24) (a) Brownstein, S.; Dunogues, J.; Lindsay, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 2073–2091. (b) Beckhaus, H. D.; Hellmann, G.; Rüchardt, C. *Chem. Ber.* **1978**, *111*, 72–83. (c) Hellmann, G.; Hellmann, S.; Beckhaus, H. D.; Rüchardt, C. *Chem. Ber.* **1982**, *115*, 3364–3383.

(50 MHz) δ 21.40 (q), 21.45 (q), 26.2 (q), 69.3 (d), 77.1 (d), 113.4 (s), 169.0 (s); exact mass calcd for $C_{13}H_{22}O_6$ (M^+) 274.1416, found 274.1390. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.80; H, 8.05.

Diethyl (4*S*,5*S*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2*E*,6*E*-octadienedioate [(*S*,*S*)-3]. To a stirred solution of diisopropyl L-2,3-*O*-isopropylidenetartrate (2.85 g, 10.4 mmol) in toluene (20 mL) at −78 °C was added DIBAL (21.6 mL/1 M in hexane; 21.6 mmol). After the mixture was stirred for 4 h at that temperature, a solution of ethyl diisopropylsodiophosphonoacetate (61.8 mmol) in THF was added to it with vigorous stirring at −78 °C. The mixture was stirred for 30 min and slowly warmed up to rt. The reaction was carefully quenched with water, and the resulting yellow suspension was filtered through a Celite pad. The pad was rinsed with several portions of CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated in vacuo to give a viscous oil, which was purified by column chromatography (SiO_2) to afford (*S*,*S*)-**3** (2.95 g, 98%): $[\alpha]^{27}_D$ −70.1° (*c* 2.40, $CHCl_3$); IR (film) 2990, 2900, 1720, 1660, 1470, 1460, 1460, 1350, cm^{-1}; UV (CH_3CN) λ_{max} 216 nm (ε, 17200); ^1H NMR (200 MHz) δ 1.27 (t, 6H, *J* = 7.2 Hz, 2 × CH_3), 1.43 (s, 6H, $C(CH_3)_2$), 4.18 (q, 4H, *J* = 7.2 Hz, 2 × OCH_2), 4.26 (m, 2H, 2 × OCH), 6.13 (dm, 2H, *J* = 16 Hz, 2 × C=$CHCO_2$), 6.85 (dm, 2H, *J* = 16 Hz, 2 × CH=CCO_2); ^{13}C NMR (50 MHz) δ 14.1 (q), 26.7 (q), 60.6 (t), 79.6 (d), 110.1 (s), 123.6 (d), 141.7 (d), 165.5 (s); exact mass (FAB) calcd for $C_{15}H_{23}O_6$ (M^+ + H) 299.1494, found 299.1488. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.15; H, 7.29.

Diethyl (4*S*,5*S*)-4,5-Dihydroxy-2*E*,6*E*-octadienedioate (24) and Diethyl (4*S*,5*S*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2*E*,6*E*-octadienedioate (1). To a solution of (*S*,*S*)-**3** (1.87 g, 6.27 mmol) in EtOH (150 mL) was added aqueous HCl (2 M, 6.5 mL), and the mixture was heated at 40 °C for 4 h. The reaction was cooled to 0 °C, saturated with NaCl, neutralized with Et_3N (1.8 mL), and extracted with CH_2Cl_2 (50 mL × 3). The combined CH_2Cl_2 solutions were dried (Na_2SO_4) and concentrated to give a pale yellow solid, which, on recrystallization from hexane–EtOAc (1:1), afforded the corresponding diol **24** (1.36 g, 84%). **24**: mp 67–68 °C; $[\alpha]^{22}_D$ + 61.9° (*c* 2.22, $CHCl_3$); IR ($CHCl_3$) 3620, 3410, 1720 (s), 1710, 1662, 1370, 1310 cm^{-1}; UV (CH_3CN) λ_{max} 217 nm (ε, 16300); ^1H NMR (200 MHz) δ 1.29 (t, 3H, *J* = 7.1 Hz), 3.00 (d, 1H, *J* = 4.7 Hz, OH), 4.20 (q, 2H, *J* = 7.1 Hz), 4.28 (m, 1H), 6.17 (dd, 1H, *J* = 15.7 Hz), 6.92 (distorted dm, 1H, *J* = 15.7 Hz); ^{13}C NMR (126 MHz) δ 14.1 (q), 60.7 (t), 73.4 (d), 123.2 (d), 145.0 (d), 166.1 (s); exact mass calcd for $C_{12}H_{18}O_6$ (M^+) 258.1103, found 258.1115.

To a precooled (0 °C) solution of **24** (1.80 g, 6.80 mmol) and Et_3N (3.8 mL, 27.2 mmol) in CH_2Cl_2 (15 mL), *tert*-butyldimethylsilyl triflate (3.3 mL, 14.3 mmol, 2.1 equiv) was added slowly. The reaction was continued at 0 °C–rt for 1 h, quenched by an addition of water, and extracted with CH_2Cl_2 (50 mL × 3). The combined CH_2Cl_2 solutions were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil, which, on column chromatography (SiO_2), afforded **1** (3.30 g, 99%): $[\alpha]^{26}_D$ −40.6° (*c* 0.99, $CHCl_3$); IR (film) 1725, 1660, 1470, 1460, 1389, 1364, 1300, 1261, 1175, 1125, 1046, 982, 830, 779 cm^{-1}; UV (CH_3CN) λ_{max} 217 nm (ε, 17000); ^1H NMR (100 MHz) δ 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.29 (t, 3H, CH_3), 4.11–4.23 (m, 2H, OCH_2), 4.36 (m, 1H, SiOCH), 5.97 (d, 1H, J_{trans} = 15.6 Hz, =$CHCO_2$), 6.94 (dq, 1H, J_{trans} = 15.6 Hz, CH=CCO_2); ^{13}C NMR (25 MHz) δ −5.0 (q), −4.8 (q), 14.2 (q), 18.1 (s), 25.8 (q), 60.3 (t), 74.4 (d), 122.0 (d), 146.2 (d), 166.3 (s); exact mass calcd for $C_{23}H_{43}O_6Si_2$ ($M^+ - CH_3$) 471.2598, found 471.2572. Anal. Calcd for $C_{24}H_{46}O_6Si_2$: C, 59.22; H, 9.53. Found: C, 59.15; H, 9.50.

Diethyl (4*S*,5*S*)-4,5-Bis[(trimethylsilyl)oxy]-(2*E*,6*E*)-octadienedioate (4). A mixture of **24** (0.194 g, 0.75 mmol), chlorotrimethylsilane (0.39 mL, 3 mmol), and Et_3N (0.62 mL, 4.5 mmol) in CH_2Cl_2 (1.3 mL) was stirred at 0 °C for 2 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated and purified by column chromatography on SiO_2 with hexane–EtOAc–Et_3N (86:9:5) to give **4** as a colorless oil (0.252 g, 83%): $[\alpha]^{24}_D$ −71.0° (*c* 1.24, $CHCl_3$); IR (film) 1730, 1718 (s), 1662, 1470, 1448, 1369, 1300, 1268, 1252, 1172, 1126, 1040, 985, 922, 900, 840, 755, 748 cm^{-1}; ^1H NMR (500 MHz) δ 0.11 (s, 9H, $Si(CH_3)_3$), 1.26 (t, 3H, CH_3), 4.11–4.21 (m, 2H, OCH_2), 4.24 (m, 1H, SiOCH), 5.97 (d, 1H, J_{trans} = 15.6 Hz, =$CHCO_2$), 6.91 (dq, 1H, J_{trans} = 15.6 Hz, CH=CCO_2); ^{13}C NMR (126 MHz) δ −0.05 (q), 14.2 (q), 60.4 (t), 74.5 (d), 122.1 (d), 146.2 (d), 166.3 (s); exact mass calcd for $C_{17}H_{31}O_6Si_2$ ($M^+ - CH_3$) 387.1659, found 387.1658. Anal. Calcd for $C_{18}H_{34}O_6Si_2$: C, 53.70; H, 8.51. Found: C, 53.72; H, 8.50.

Ethyl (1*S*,4*R*,5*S*,6*S*)-6-[(1′*S*,2′*S*)-1′,2′-Bis[(*tert*-butyldimethylsilyl)oxy]-4′-(ethoxycarbonyl)-3*E*-buten-1-yl]bicyclo-[2.2.1]hept-2-ene-5-carboxylate (5). A solution of **1** (0.197 g, 0.405 mmol) in CH_2Cl_2 (4 mL) was kept at −20 °C for 48 h in the presence of Et_2AlCl (1 M in CH_2Cl_2; 1.0 mL, 1.0 mmol) and excess cyclopentadiene (0.33 mL, 10 equiv). After the mixture was treated with 5% $NaHCO_3$ and worked up as usual, the crude product was purified by SiO_2 chromatography to give the cycloadduct (**5**) as a single isomer (0.364 g, 90% yield): IR (film) 2953, 2940, 2900, 2860, 1775, 1725, 1660 cm^{-1}; $[\alpha]^{26}_D$ −16.4° (*c* 1.50, $CHCl_3$): ^1H NMR ($CDCl_3$, 500 MHz) δ 0.057 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.93 (s, 9H), 1.18 (t, 3H, *J* = 7.0 Hz), 1.25–1.33 (m, 1H), 1.29 (t, 3H, *J* = 7.2 Hz), 1.60 (bd, 1H, *J* = 8.3 Hz), 2.06 (m, 1H), 2.66 (t, 3H, *J* = 3.4, 3.9 Hz), 2.97 (bs, 1H), 3.07 (bs, 1H), 3.71 (dd, 1H, *J* = 4.7, 6.7 Hz), 3.88–4.06 (dm, 2H), 4.18 (m, 2H), 4.36 (m, 1H), 5.87 (dd, 1H, *J* = 2.8, 5.5 Hz), 6.01 (dd, 1H, *J* = 2.3, 15.7 Hz), 6.22 (dd, 1H, *J* = 3.1, 5.5 Hz), 7.15 (dd, 1H, *J* = 3.2, 15.7 Hz); ^{13}C ($CDCl_3$, 126 MHz) δ −4.8 (2 × C), −4.7, −3.9, 14.1, 14.2, 17.9, 18.1, 25.8, 25.8, 44.0, 46.3, 46.8, 47.02, 47.09, 60.0, 60.2, 75.2, 78.3, 121.2, 133.4, 138.6, 147.0, 166.3, 173.9; exact mass calcd for $C_{28}H_{49}O_6Si_2$ ($M^+ - CH_3$) 537.3067, found 537.3061. Anal. Calcd for $C_{29}H_{52}O_6Si_2$: C, 63.01; H, 9.49. Found: C, 62.98; H, 9.50.

Compound **5** was subjected to (1) deprotection (Bu_4NF/THF/0 °C), (2) diol cleavage followed by reduction ($NaIO_4$/$NaHCO_3$/CH_2Cl_2/0 °C–rt and $NaBH_4$), and (3) ester reduction ($LiAlH_4$/THF/−40 °C) to afford known (1*S*,4*R*,5*S*,6*S*)-5,6-bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene exhibiting $[\alpha]^{26}_D$ −24.7° (*c* 0.80, $CHCl_3$) [lit.[25] $[\alpha]^{23}_D$ −23° (*c* 0.8, $CHCl_3$)].

Diethyl (4*S*,5*S*,6*S*,7*S*)-4,5-Bis-*O*-(*tert*-butyldimethylsilyl)-4,5,6,7-tetrahydroxy-2*E*-octenedioate (8). To a solution of **1** (90 mg, 0.186 mmol) in acetone–H_2O (5:1, 2.2 mL) at rt were added successively NMO (44 mg, 0.36 mmol) and a solution of OsO_4 in *t*-BuOH (5%; 0.05 mL = 5 mol %). The mixture was stirred at rt for 0.6 h; the reaction was quenched with saturated $NaHSO_3$ aqueous solution and then extracted with EtOAc (10 mL × 5). The combined EtOAc solutions were dried ($MgSO_4$) and concentrated to give a yellow oil, which, on column chromatography (SiO_2), gave **8** as a clear, colorless oil (91 mg, 94% yield): $[\alpha]^{25}_D$ −30.2° (*c* 1.24, $CHCl_3$). Acetylation of **8** with Ac_2O/DMAP/Et_3N at rt for 0.5 h afforded diethyl (4*S*,5*S*,6*S*,7*S*)-6,7-di-*O*-acetyl-4,5-bis-*O*-(*tert*-butyldimethylsilyl)-4,5,6,7-tetrahydroxy-2*E*-octenedioate (8-6,7-*O*,*O*′-diacetyl): R_f(TLC) = 0.45 as a single spot; $[\alpha]^{24}_D$ −21.3° (*c*, 1.14, $CHCl_3$); IR (film) 1764, 1753, 1745, 1720, 1715 (s), 1656, 1259, 1215 cm^{-1}; ^1H-NMR (500 MHz) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.92 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.00 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 4.06 (dd, *J* = 4.6, 6.6 Hz, 1H, C(5)-H), 4.10 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.18 (m, 2H, OCH_2), 4.42 (m, 1H, C(4)-H), 5.13 (d, *J* = 2.0, 1H, C(7)-H), 5.40 (dd, *J* = 2.0, 6.6 Hz, 1H, C(6)-H), 6.01 (dd, *J* = 2.1, 15.7 Hz, 1H, =C(2)-H), 7.12 (dd, *J* = 3.9, 15.7 Hz, 1H, =C(3)-H); ^{13}C NMR (126 MHz) δ −5.1 (q), −5.0 (q), −4.6 (q), −4.3 (q), 13.9 (q), 14.2 (q), 18.0 (s), 18.2 (s), 20.7 (q), 20.8 (q), 25.7 (s), 25.8 (q), 60.4 (t), 61.8 (t), 70.9 (d), 71.0 (d), 72.9 (d), 73.4 (d), 122.0 (d), 146.1 (d), 166.1 (s), 167.9 (S), 169.2 (s), 169.9 (s); exact mass (FAB) calcd for $C_{28}H_{52}O_{10}$ (M^+) 548.3560, found 548.3561. Anal. Calcd for $C_{28}H_{52}O_{10}$: C, 61.29; H, 9.55. Found: C, 61.15; H, 9.48.

Osmylation of (*S*,*S*)-3. To a solution of (*S*,*S*)-**3** (1.21 g, 4.06 mmol) in acetone–H_2O (5:1, 18 mL) at rt were added successively NMO (570 mg, 4.87 mmol) and a solution of OsO_4 in *t*-BuOH (10%; 0.2 mL = 2 mol %). The mixture was stirred at rt for 2.5 h; the reaction was quenched with saturated $NaHSO_3$ aqueous solution and then extracted with EtOAc (30 mL × 5). The combined EtOAc solutions were dried ($MgSO_4$) and concentrated to give a yellow oil, which, on column chromatography (SiO_2), gave **9** (529 mg) and **10** (265 mg) (total yield = 66%), without any overlap of the fractions, as clear, colorless oils; unchanged (*S*,*S*)-**3** (135 mg; 11%) was recovered. Acetylation of **9** and **10** under the

(25) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135–161.

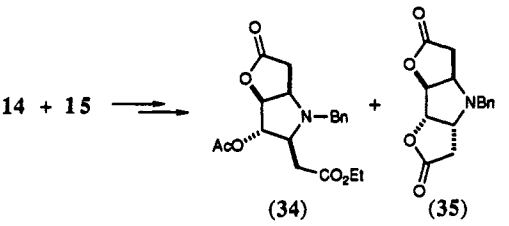
usual conditions (Ac_2O/DMAP/CH_2Cl_2) gave the corresponding diacetates, 9-(6,7-*O*,*O*'-diacetyl) [diethyl (4*S*,5*S*,6*S*,7*S*)-4,5-*O*-isopropylidene-6,7-bis(acetoxy)-4,5-dihydroxy-2*E*-octenedioate] and 10-(6,7-*O*,*O*'-diacetyl) [diethyl (4*S*,5*S*,6*R*,7*R*)-4,5-*O*-isoproopylidene-6,7-bis(acetoxy)-4,5-dihydroxy-2*E*-octenedioate], respectively, in high yields. 9-(6,7-*O*,*O*'-diacetyl): ^{1}H-NMR (500 MHz) δ 1.24 (t, J = 7.2 Hz, 3H, CCH_3), 1.27 (t, J = 7.2 Hz, 3H, CCH_3), 1.38 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 2.02 (s, 3H, O=CCH_3), 2.18 (s, 3H, O=CCH_3), 3.93 (dd, J = 7.4, 8.7 Hz, 1H, OC(5)H), 4.14–4.22 (m, 4H, OCH_2), 4.47 (m, 1H, OC(4)H), 5.30 (d, J = 2.0 Hz, 1H, AcOC(7)H), 5.50 (dd, J = 2.0, 8.8 Hz, 1H, AcOC(6)H), 6.05 (dd, J = 1.3, 15.6 Hz, 1H, =C(2)-H), 6.78 (dd, J = 5.9, 15.6 Hz, 1H, =C(3)-H); ^{13}C-NMR (126 MHz) δ 14.0 (q), 14.2 (q), 20.46 (q), 20.48 (q), 26.76 (q), 26.82 (q), 60.7 (t), 62.0 (t), 71.2 (d), 71.9 (d), 77.2 (d), 78.5 (d), 110.8 (s), 123.1 (d), 143.4 (d), 165.8 (s), 167.0 (s), 169.5 (s), 169.9 (s).

10-(6,7-*O*,*O*'-diacetyl): ^{1}H NMR (500 MHz) δ 1.25 (t, J = 7.2 Hz, 3H, CCH_3), 1.27 (t, J = 7.2 Hz, 3H, CCH_3), 1.39 (s, 6H, acetonide 2 × CH_3), 2.09 (s, 3H, O=CCH_3), 2.14 (s, 3H, O=CCH_3), 4.07 (dd, J = 5.4, 8.3 Hz, 1H, OC(5)H), 4.18–4.22 (m, 4H, OCH_2), 4.48 (bt, J = 7.3 Hz, 1H, OC(4)H), 5.24 (d, J = 3.4 Hz, 1H, AcOC-(7)H), 5.54 (dd, J = 3.4, 5.4 Hz, 1H, AcOC(6)H), 6.10 (d, J = 15.6 Hz, 1H, =C(2)-H), 6.78 (dd, J = 6.3, 15.6 Hz, 1H, =C(3)-H); ^{13}C-NMR (126 MHz) δ 14.0 (q), 14.2 (q), 20.5 (q), 20.6 (q), 26.6 (q), 26.7 (q), 60.7 (t), 62.1 (t), 69.7 (d), 70.8 (d), 76.4 (d), 78.5 (d), 110.8 (s), 123.9 (d), 142.9 (d), 165.6 (s), 166.8 (s), 169.6 (s), 169.7 (s).

(2*R*,3*S*,4*S*,5*S*)-1-Benzyl-2,5-bis[(ethoxycarbonyl)methyl]-3,4-bis[(trimethylsilyl)oxy]pyrrolidine (13). A mixture of 4 (0.196 g, 0.489 mmol), benzylamine (0.90 mL, 15 eq), and EtOH (1 mL) was heated at 80 °C for 48 h. The mixture was evaporated under high vacuum (0.1 mmHg) and the residual oil was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 86:9:5) to afford rather unstable **13** (0.141 mg, 57%). Since **13** was rather unstable, its physical data were collected very quickly after the column chromatography: $[\alpha]^{24}_D$ −21.0° (*c* 1.96, $CHCl_3$); IR (film) 1730 (s), 1722, 1635, 1488, 1445, 1362, 1255, 1245, 1170, 1120, 1075, 1020, 980, 892, 855, 835, 745 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.07 (s, 9H, $Si(CH_3)_3$), 0.10 (s, 9H, $Si(CH_3)_3$), 1.18 (t, 3H, CH_3), 1.20 (t, 3H, CH_3), 2.22 (dd, 1H, J_{gem} = 15.2 Hz, J_{vic} = 5.4 Hz, C(5)-C*H*H), 2.29 (dd, 1H, J_{gem} = 16.4 Hz, J_{vic} = 5.1 Hz, C(2)-C*H*H), 2.52 (dd, 1H, J_{gem} = 15.2 Hz, J_{vic} = 8.8 Hz, C(5)-CH*H*), 2.59 (dd, 1H, J_{gem} = 16.4 Hz, J_{vic} = 8.8 Hz, C(2)-CH*H*), 3.11 (m, 1H, 5-H), 3.51 (m, 1H, 2-H), 3.79 (d, 1H, J_{gem} = 14.0 Hz, C*H*HPh), 3.84 (d, 1H, J_{gem} = 14.0 Hz, CH*H*Ph), 3.85 (m, 1H, 4-H), 3.98 (m, 1H, 3-H), 4.00–4.07 (m, 4H, 2 × OCH_2), 7.23–7.32 (m, 5H, ArH); ^{13}C NMR (126 MHz) δ 14.1 (q), 35.8 (t), 37.8 (t), 56.2 (t), 61.3 (t), 62.4 (d), 67.8 (d), 80.8 (d), 88.0 (d), 127.8 (d), 128.7 (d), 128.9 (d), 136.8 (s), 173.2 (s), 175.7 (s).

Amine Conjugate Addition to (*S*,*S*)-3. To a solution of (*S*,*S*)-**3** (60 mg, 0.20 mmol) in ethanol (0.5 mL) at 25 °C was added benzylamine (0.025 mL, 1.2 equiv), and the solution was stirred at that temperature for 12 h. The usual workup and purification by column chromatography (SiO_2) gave an inseparable mixture of **14** and **15** (72 mg) in 89% yield. NMR analyses of this mixture, however, made the assignments of both ^{1}H- and ^{13}C-signals of the major isomer and ^{13}C signals of the minor isomer possible. **14** (major): ^{1}H NMR (500 MHz) δ 1.25 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 1.39 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 2.59 (d, J = 6.4 Hz, 2H, C(7)H_2-CO), 3.15 (td, J = 3.1, 6.3 Hz, C(6)H-N), 3.74 (d, J = 13.0 Hz, 1H, C*H*HPh), 3.86 (dd, J = 3.2, 8.2 Hz, 1H, C(5)H-O), 3.94 (d, J = 13.0 Hz, 1H, CH*H*Ph), 4.10–4.22 (m, 4H, 2 × OCH_2), 4.67 (ddd, J = 1.4, 5.8, 8.2 Hz, 1H, OC(4)H), 5.96 (dd, J = 1.5, 15.6 Hz, 1H, =C(2)-H), 6.85 (dd, J = 5.8, 15.6 Hz, 1H, =C(3)-H), 7.22–7.35 (m, 5H, ArH); ^{13}C-NMR (126 MHz) δ 14.1 (q), 14.2 (q), 26.7 (q), 27.0 (q), 36.5 (t), 51.2 (t), 53.0 (d), 60.5 (t), 60.6 (t), 76.5 (d), 82.1 (d), 109.8 (s), 122.7 (d), 127.2 (d), 128.3 (d), 128.4 (d), 144.5 (d), 145.7 (s), 165.9 (s), 171.8 (s). **15** (minor): ^{13}C-NMR (126 MHz) δ 14.19 (q), 14.21 (q), 26.6 (q), 27.0 (q), 35.1 (t), 51.1 (t), 56.3 (d), 60.5 (t), 60.6 (t), 78.8 (d), 81.9 (d), 109.8 (s), 121.7 (d), 127.1 (d), 128.2 (d), 128.4 (d), 139.7 (d), 140.0 (s), 166.2 (s), 171.9 (s).

Deprotection (HCl in EtOH) of the silyl groups of the product mixture (14 + 15) and subsequent basification (K_2CO_3 in EtOH) were followed by facile intramolecular amine Michael addition and lactonization processes to afford a mixture of pyrrolidine mono- and bis-lactone derivatives, which were separated by column chromatography (SiO_2). Acetylation of the monolactone under the usual conditions gave an acetylated product which was identical in all respects to **34**. The bis-lactone pyrrolidine was confirmed to be C_2-symmetric and the structure denoted as **35** on the basis of NMR and mass spectral experiments. **35**:



(34) (35)

^{1}H-NMR (500 MHz) δ 2.50 (dd, J = 7.0, 18.1 Hz, 2H, 2 × C(O)-C*H*H), 2.63 (dd, J = 3.2, 18.1 Hz, 2H, 2 × C(O)CH*H*), 3.51 (d, J = 13.4 Hz, 1H, NCH*H*Ph), 3.92 (d, J = 13.4 Hz, 1H, NC*H*HPh), 3.95 (td, J = 3.2, 6.7 Hz, 2H, 2 × N-CH), 4.95 (d, J = 5.9 Hz, 2H, 2 × OCH), 7.22–7.35 (m, 5H, Ar-H); ^{13}C NMR (126 MHz) δ 31.0 (t), 52.2 (t), 60.1 (d), 84.4 (d), 128.0 (d), 128.4 (d), 128.8 (d), 136.1 (s), 174.4 (s); exact mass calcd for $C_{15}H_{15}O_4N$ (M^+) 273.1001, found 273.1011.

Diethyl (4*S*,5*S*)-4,5-Bis[(triethylsilyl)oxy]-(2*E*,6*E*)-octadienedioate (17). A mixture of **24** (0.422 g, 1.63 mmol), chlorotriethylsilane (0.66 mL, 3.91 mmol), and C_5H_5N (2 mL) was stirred at 20 °C for 2 h. The mixture was filtered through a Celite pad, concentrated, and purified by column chromatography on SiO_2 with hexane–EtOAc (10:1) to give **17** as a colorless oil (0.793 g, 99%): $[\alpha]^{24}_D$ −68.3° (*c* 1.13, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.61 (q, 12H, J = 7.9 Hz, 6 × $SiCH_2$), 0.95 (t, 18H, J = 7.9 Hz, 6 × $SiCCH_3$), 1.27 (t, 6H, J = 7.1 Hz, 2 × $OCCH_3$), 4.17 (m, 4H, 2 × OCH_2), 4.35 (m, 2H, 2 × SiOCH), 5.97 (dm, 2H, J_{trans} = 15.6 Hz, =$CHCO_2$), 6.93 (dm, 2H, J_{trans} = 15.6 Hz, CH=CCO_2); ^{13}C NMR (50 MHz) δ 4.7 (t), 6.7 (q), 14.2 (q), 60.3 (t), 74.4 (d), 121.9 (d), 146.3 (d), 166.3 (s); exact mass calcd for $C_{22}H_{41}O_6Si_2$ (M^+ − C_2H_5) 457.2442, found 457.2440. Anal. Calcd for $C_{24}H_{46}O_6Si_2$: C, 59.22; H, 9.52. Found: C, 59.18; H, 9.50.

Amine Conjugate Addition to 4 and 17. All reactions of **4** and **17** (ca. 0.5 mmol) with amines such as benzylamine or 2-phenylethylamine (15 equiv) were carried out at 80 °C in EtOH (1 mL) as a solvent (see Table II). After completion of the reactions (monitored by TLC), the mixture was treated under high vacuum (0.1 mmHg) to remove the solvent and the unchanged amine, and the residual oil was purified by column chromatography (SiO_2; hexane–EtOAc–Et_3N for products from **4** and hexane–EtOAc for products from **17**). All runs were accompanied by considerable ester aminolysis. The reaction of **17** with benzylamine or 2-phenylethylamine gave a mixture of **20** and **22** or **21** and **23** in 50–60% yield, respectively. These mixtures were difficult to separate (SiO_2). NMR (analyses [^{1}H (500 MHz) and ^{13}C (126 MHz) including 2D or NOE experiments] turned out to be useful for determining both the isomer ratios and structures. The deprotection of the silyl groups of these mixtures led to separable **34**-type monolactone pyrrolidine derivatives and C_2-symmetric 3,4-dihydroxypyrrolidine diesters (**22** or **23**; $R_3SiO- \rightarrow HO-$), which were crucial for the structure determination.

(2*R*,3*S*,4*S*,5*S*)-1-(2'-Phenylethyl)-2,5-bis[(ethoxycarbonyl)methyl]-3,4-bis[(trimethylsilyl)oxy]pyrrolidine (19): $[\alpha]^{24}_D$ −24.7° (*c* 1.49, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.08 (s, 9H, $Si(CH_3)_3$), 0.11 (s, 9H, $Si(CH_3)_3$), 1.23 (t, 3H, CH_3), 1.25 (t, 3H, CH_3), 2.38 (dd, 1H, J_{gem} = 16.2 Hz, J_{vic} = 4.8 Hz, C(O)C*H*H), 2.46 (dd, 1H, J_{gem} = 15.0 Hz, J_{vic} = 5.0 Hz, C(O)C*H*H), 2.61 (dd, 1H, J_{gem} = 16.2 Hz, J_{vic} = 8.8 Hz, C(O)CH*H*), 2.64 (dd, 1H, J_{gem} = 15.0 Hz, J_{vic} = 9.2 Hz, C(O)CH*H*), 2.67–2.92 (m, 4H, NCH_2CH_2-Ph), 3.15 (m, 1H, 2(or 5)-H), 3.47 (dt, 1H, J = 4.4, 8.8 Hz, 5(or 2)-H), 3.88 (t, 1H, J = 2.2 Hz, 3(or 4)-H), 3.98 (m, 1H, 4(or 3)-H), 4.06–4.18 (m, 4H, 2 × OCH_2), 7.15–7.28 (m, 5H, ArH); ^{13}C NMR (126 MHz) δ 0.05 (q), 0.3 (q), 14.2 (q), 14.3 (q), 33.6 (t), 34.6 (t), 39.8 (t), 55.6 (t), 60.1 (t), 60.2 (t), 62.0 (d), 67.4 (d), 78.3 (d), 79.4 (d), 125.9 (d), 128.3 (d), 128.7 (d), 140.4 (s), 172.3 (s), 172.7 (s); exact mass calcd for $C_{25}H_{42}O_6NSi_2$ (M^+ − CH_3) 508.2550, found 508.2548.

Ethyl (4*S*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2*E*-pentenoate (25). To a suspension of 1,2:5,6-*O*-bis(isopropylidene)-D-mannitol[26] (1.27 g, 4.85 mmol) in 5% $NaHCO_3$ aqueous solution (13 mL) at 0 °C was added dropwise a solution of $NaIO_4$ (1.25 g) in H_2O (3.5 mL) under vigorous stirring. The mixture was stirred at rt for 1 h and cooled again to 0 °C. To this cold mixture was added ethyl diisopropylphosphonoacetate (2.6 mL), and then a solution of K_2CO_3 (13.7 g in 15 mL H_2O) was added. The mixture was stirred overnight at 0–rt, diluted with H_2O, filtered through a Celite pad, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator to give an oil (*E*/*Z* = 183/1 on capillary GLC), which, after column chromatography [SiO_2, hexane–EtOAc (5:1)] and a short-path distillation [bp 88 °C (air-bath temp)/1 mmHg] afforded **25** as a colorless oil (1.48 g, 76%). **25**: $[\alpha]^{19}_D$ +42.4° (*c* 6.50, $CHCl_3$) [lit.[18b] $[\alpha]^{20}_D$ +43.3° (*c* 0.5, $CHCl_3$)]; IR (film) 2980, 1720, 1670, 1370, 1300, 1260, 1215, 1180, 1155, 1060, 1035, 980, 850 cm^{-1}; UV (CH_3CN) λ_{max} 215 nm (ϵ, 9100); ^{1}H NMR (200 MHz) δ 1.27 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.39 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.66 (dd, 1H, *J* = 8.4, 7.1 Hz, OC*H*H), 4.18 (q, 2H, *J* = 7.1 Hz, CO_2CH_2), 4.18 (m, 1H, OCH*H*, overlapped with the strong CO_2CH_2 quartet), 4.65 (m, 1H, OCH), 6.09 (dd, 1H, *J* = 15.6, 1.4 Hz, CH=C*H*CO_2R), 6.86 (dd, 1H, *J* = 15.6, 5.7 Hz, C*H*=CHCO_2R); ^{13}C NMR (126 MHz) δ 14.2 (q), 25.7 (q), 26.4 (q), 60.5 (t), 68.8 (t), 74.9 (d), 110.1 (s), 122.4 (d), 144.6 (d), 165.9 (s).

General Procedure for the Preparation of Monocinnamoyl Derivatives of the Diols. Synthesis of Diethyl (4*S*,5*S*)-4-(Cinnamoyloxy)-5-hydroxy-2*E*,6*E*-octadienedioate (30). To a solution of cinnamoyl chloride (0.0097 g, 0.0058 mmol, 0.5 equiv) in CH_2Cl_2 (1 mL) at 25 °C under argon was added a solution of **24** (0.030 g, 0.116 mmol) in CH_2Cl_2 (2 mL) dropwise with stirring over a period of 3 min. After 10 min of stirring, pyridine (5.2 mL, 0.064 mmol, 0.55 equiv) was added over a period of 1 min. The solution was stirred at 25 °C for 3 days, and then it was diluted with CH_2Cl_2 (10 mL) and extracted with 5% aqueous HCl solution. The organic layer was separated, washed with brine (2 mL), and dried over Na_2SO_4. The product was isolated by column chromatography [SiO_2, CH_2Cl_2–MeOH (98:2)]. Obtained was 0.011 g (24.4% yield or 56.1% yield based on the amount of **24** consumed) of the product as a viscous oil. Isolated also was the starting diol (0.017 g). Substituting pyridine for DMAP furnished the monocinnamate in a higher yield (48.8%), and the reaction time was shorter (overnight). **30**: $[\alpha]^{20}_D$ −77.0° (*c* 2.28, $CHCl_3$); IR (film) 3470, 3060, 3030, 2980, 2940, 1715, 1660, 1640, 1450, 1370, 1310, 1280, 1180, 1160, 1040, 980, 770 cm^{-1}; UV (CH_3CN) λ_{max} 278 nm (ϵ, 20700); ^{1}H NMR (200 MHz) δ 1.29 (t, 6H, *J* = 7.1 Hz, CH_3), 2.60 (d, 1H, *J* = 5.9 Hz, OH), 4.21 (q, 4H, *J* = 7.1 Hz, OCH_2), 4.58 (m, 1H, HOC*H*), 5.63 (td, 1H, *J* = 5.3, 1.6 Hz, CO_2CHC=), 6.10 (dd, 1H, *J* = 15.7, 1.6 Hz, HOCHHC=C*H*CO_2,), 6.19 (dd, *J* = 15.7, 1.6 Hz, CO_2-CHCH=C*H*CO_2), 6.48 (d, 1H, *J* = 16.1 Hz, PhCH=C*H*), 6.94 (dd, 1H, *J* = 15.7, 4.4 Hz, HOCH*H*C=CHCO_2), 6.96 (dd, 1H, *J* = 15.7, 5.3 Hz, CO_2CHC*H*=CHCO_2), 7.35–7.59 (m, 5H, ArH), 7.76 (d, 1H, *J* = 16.1 Hz, PhCH=); ^{13}C NMR (126 MHz) δ 14.2 (2 × q), 60.7 (t), 60.8 (t), 71.8 (d), 74.3 (d), 116.6 (d), 123.6 (d), 124.4 (d), 128.3 (d), 129.0 (d), 130.8 (d), 133.9 (s), 140.7 (d), 143.9 (d), 146.7 (d), 165.5 (s), 165.6 (s), 165.8 (s).

Dimethyl (2*R*,3*R*)-*O*-Cinnamoyltartrate (26): 47.4% yield, viscous oil; $[\alpha]^{20}_D$ −18.7° (*c* 1.86, $CHCl_3$); IR (film) 3490, 3060, 3030, 2950, 1745, 1720, 1635, 1450, 1435, 1350, 1330, 1310, 1220, 1200, 1160, 1070, 980, 860, 765 cm^{-1}; UV (CH_3CN) λ_{max} 217 nm (ϵ, 14500), 279 nm (ϵ, 22700); ^{1}H NMR (200 MHz) δ 3.23 (d, *J* = 7.6 Hz, OH), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.82 (dd, 1H, *J* = 7.5, 2.2 Hz, HO-CH), 5.60 (d, 1H, *J* = 2.2 Hz, CO_2-CH-CO_2), 6.52 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 7.35–7.59 (m, 5H, ArH), 7.75 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH); ^{13}C NMR (126 MHz) δ 52.9 (q), 53.3 (q), 70.6 (d), 72.9 (d), 116.1 (d), 128.3 (d), 128.9 (d), 130.8 (d), 133.9 (s), 146.9 (d), 165.5 (s), 167.2 (s), 171.2 (s).

(2*R*,3*R*)-2-(cinnamoyloxy)-3-hydroxy-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (Bis-tartramide Monocinnamate) (28): 42.4% yield, colorless oil; $[\alpha]^{20}_D$ −19.6° (*c* 1.64, $CHCl_3$); IR (film) 3370, 3060, 3000, 2940, 1715, 1645, 1500, 1450, 1400, 1330, 1250, 1200, 1160, 1060, 980, 770 cm^{-1}; UV (CH_3CN) λ_{max} 216 nm (ϵ, 18800), 278 nm (ϵ, 20800); ^{1}H NMR (200 MHz) δ 2.97 (s, 3H, $CONCH_3$), 2.98 (s, 3H, $CONCH_3$), 3.14 (s, 3H, $CONCH_3$), 3.17 (s, 3H, $CONCH_3$), 3.63 (d, 1H, *J* = 8.5 Hz, OH), 4.93 (dd, 1H, *J* = 8.5, 5.8 Hz, OHC*H*), 5.78 (d, 1H, *J* = 5.8 Hz, CO_2CH), 6.51 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 7.23–7.58 (m, 5H, ArH), 7.75 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH); ^{13}C NMR (126 MHz) δ 36.0 (q), 36.2 (q), 37.1 (q), 37.3 (q), 69.0 (d), 72.4 (d), 116.6 (d), 128.2 (d), 128.9 (d), 130.6 (d), 134.1 (s), 146.6 (d), 166.1 (s), 167.3 (s), 170.2 (s).

General Procedure for the Preparation of Bis-cinnamoyl Derivatives of the Diols. Diethyl (4*S*,5*S*)-4,5-Bis(cinnamoyloxy)-2*E*,6*E*-octadienedioate (31). To a solution of cinnamoyl chloride (0.027 g, 0.163 mmol, 2.1 equiv) in CH_2Cl_2 (1 mL) at 25 °C under argon was added dropwise over a period of 3 min a solution of **24** (0.020 g, 0.077 mmol) in CH_2Cl_2 (1 mL) with stirring. After 10 min of stirring, a solution of DMAP (0.020 g, 0.163 mmol, 2.1 equiv) in CH_2Cl_2 (1 mL) was added dropwise over a 3-min period. After an overnight stirring at 25 °C, the product was isolated by column chromatography (SiO_2, CH_2Cl_2). Product **31** (0.039 g, 97% yield) was obtained as a viscous oil. **31**: $[\alpha]^{20}_D$ −102° (*c* 1.00, $CHCl_3$); IR (film) 3050, 2980, 2930, 1730, 1710, 1665, 1640, 1450, 1365, 1260, 1240, 1180, 1150, 980, 760 cm^{-1}; UV (CH_3CN) λ_{max} 216 nm (ϵ, 38000), 279 nm (ϵ, 42200); ^{1}H NMR (200 MHz) δ 1.28 (t, 3H, *J* = 7.0 Hz, CH_3), 4.21 (q, 2H, *J* = 7.0 Hz, OCH_2), 5.82 (m, 1H, OCH), 6.12 (dd, 1H, *J* = 15.5, 1.3 Hz, =$CHCO_2$), 6.49 (d, 1H, *J* = 16.0 Hz, =HC-O), 6.94 (dm, 1H, *J* = 15.5 Hz, CC*H*=CHCO_2R), 7.36–7.58 (m, 5H, ArH), 7.75 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH); ^{13}C NMR (126 MHz) δ 14.2 (q), 60.8 (t), 71.9 (d), 116.6 (d), 124.8 (d), 128.3 (d), 128.9 (d), 130.8 (d), 134.0 (s), 146.7 (d), 165.3 (s), 165.3 (s).

Dimethyl (2*R*,3*R*)-2,3-*O*-Bis(cinnamoyl)tartrate (27): 99% yield, viscous oil; $[\alpha]^{20}_D$ −166° (*c* 1.95, $CHCl_3$); IR (film) 3060, 3030, 2960, 1765, 1720, 1630, 1450, 1350, 1330, 1310, 1270, 1200, 1140, 1070, 980, 870, 770 cm^{-1}; UV (CH_3CN) λ_{max} 217 nm (ϵ, 27300), 278 nm (ϵ, 42200); ^{1}H NMR (200 MHz) δ 3.80 (s, 3H, CO_2CH_3), 5.90 (s, 1H, OCH), 6.58 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 7.36–7.60 (m, 5H, ArH), 7.79 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH); ^{13}C NMR (126 MHz) δ 53.1 (q), 71.0 (d), 116.1 (d), 128.4 (d), 128.9 (d), 130.8 (d), 134.0 (s), 147.1 (d), 165.5 (s), 166.5 (s).

(2*R*,3*R*)-2,3-Bis(cinnamoyloxy)-*N*,*N*,*N*′,*N*′-Tetramethylsuccinamide (29): 97% yield, colorless solid; mp 203–204 °C; $[\alpha]^{20}_D$ +179° (*c* 3.43, $CHCl_3$); IR (KBr) 3060, 2930, 1720, 1710, 1665, 1640, 1490, 1450, 1345, 1310, 1270, 1260, 1205, 1155, 1055, 1030, 970, 760 cm^{-1}; UV (CH_3CN) λ_{max} 217 nm (ϵ, 35000), 275 nm (ϵ, 44000); ^{1}H NMR (200 MHz) δ 2.96 (s, 3H, CH_3NCH_3), 3.22 (s, 3H, CH_3NCH_3), 6.23 (s, 1H, OCH), 6.42 (d, 1H, *J* = 16.0 Hz, Ph-CH=C*H*), 7.30–7.50 (m, 5H, ArH), 7.79 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH); ^{13}C NMR (126 MHz) δ 335.9 (q), 37.4 (q), 69.5 (d), 116.5 (d), 128.2 (d), 128.8 (d), 130.6 (d), 134.0 (s), 146.6 (d), 165.7 (s), 166.9 (s).

(4*S*,5*S*)-1,8-Di-*O*-acetyl-4,5-bis-*O*-(*tert*-butyldimethylsilyl)-(2*E*,6*Z*)-octadiene-1,4,5,8-tetraol (32). A solution of 1-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-L-threitol (5.80 g, 21 mmol) in CH_2Cl_2 (10 mL) at −78 °C was treated successively with the Swern reagent, prepared from $(COCl)_2$ (4.4 mL, 50 mmol) and DMSO (7.1 mL, 108 mmol) in CH_2Cl_2 (20 mL), and Et_3N (40 mL) to afford the corresponding aldehyde. To a solution of the crude aldehyde in MeOH (20 mL) was added powdered Ph_3P=$CHCO_2Me$ (8.4 g, 25 mmol) in one portion, and the mixture was stirred at 40 °C for 1.5 h. Evaporation of the MeOH gave an oil, from which triphenylphosphine oxide was separated by passing through a short SiO_2 column to afford the condensation product. This crude enoate was dissolved in THF (10 mL), and to the THF solution was added a solution of *n*-Bu_4NF (1 M in THF; 21 mL). The mixture was stirred at rt for 1 h. The reaction was diluted with H_2O (5 mL) and extracted with Et_2O (25 mL × 3). The combined ether extracts were dried ($MgSO_4$) and concentrated to afford an oil, from which, by careful column chromatography (SiO_2; 60 g), pure (*Z*)-enoate was obtained in 49% yield (2.2 g) together with the (*E*)-isomer (0.75 g, 16% yield). The (*Z*)-isomer (651 mg, 3 mmol) was oxidized with the Swern reagent to afford the corresponding aldehyde, which was condensed with (*i*-PrO)$_2$P(O)C(Na)HCO_2Me (0.28 mmol) in THF at 0 °C for 3 h to afford pure (*E*,*Z*)-bis-enoate (551 mg, 80% yield

(26) Kuszmann, J.; Tomori, E.; Meerwald, I. *Carbohydr. Res.* **1984**, *128*, 87–99.

based on the amount of consumed aldehyde; 95 mg of the aldehyde, recovered) after purification by SiO_2 column chromatography: $[\alpha]^{27}_D$ +33.1° (c 3.73, $CHCl_3$). A series of routine reactions involving DIBAL reduction, acetylation, deacetonidation, and silylation of the resulting diol led to **32** (543 mg, 74% yield for four steps): $[\alpha]^{26}_D$ +6.50° (c 2.34, $CHCl_3$); IR (film) 1740, 1644, 1250, 1225 cm^{-1}; ^1H NMR (500 MHz) δ 0.003 (s, 3H), 0.01 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 2.026 (s, 3H), 2.033 (s, 3H), 4.12 (m, 1H, C(4)-H), 4.34 (m, 1H, C(5)-H), 4.50 (ddd, J_{gem} = 13.2 Hz, J_{vic} = 5.5 Hz, $J_{HCC=CH}$ = 1.5 Hz, C(8)-*H*H), 4.54 (d, J = 5.9 Hz, 2H, C(1)-H_2), 4.71 (ddd, J_{gem} = 13.2 Hz, J_{vic} = 8.4 Hz, $J_{HCC=CH}$ = 1.3 Hz, C(8)-H*H*), 5.43 (m, 1H, C(6)-(*Z*)-CH=C), 5.57 (m, 1H, C(7)-(*Z*)-C=CH), 5.71 (dtd, J = 15.6, 5.9 Hz, 1H, C(2)-(*E*)-CH=C); 5.79 (dd, J = 15.6, 4.9 Hz, 1H, C(3)-(*E*)-C=CH); ^{13}C-NMR (126 MHz) δ −4.8 (q), −4.7 (q), −4.6 (q), 18.0 (q), 18.2 (q), 20.9 (s), 25.7 (q), 25.8 (q), 60.9 (t), 64.4 (t), 71.9 (d), 75.7 (d), 125.3 (d), 125.4 (d), 133.4 (d), 133.5 (d), 170.7 (s), 170.8 (s). Anal. Calcd for $C_{24}H_{46}O_6Si_2$: C, 59.22; H, 9.52. Found: C, 59.23; H, 9.50.

Ethyl (3*R*,4*S*,5*S*)-3-*O*-Acetyl-4,5-Bis-*O*-(*tert*-butyldimethylsilyl)-8-*O*-benzyl-3,4,5,8-tetrahydroxy-6*E*-octenoate (33). A solution of 1-*O*-(*p*-methoxybenzyl)-2,3-*O*-isopropylidene-L-threitol was oxidized under Swern conditions to the corresponding aldehyde, which was condensed with $(i\text{-}PrO)_2P(O)C(Na)HCO_2Et$. The resulting (*E*)-enoate (1.56 g, 4.46 mmol) was reduced with DIBAL (hexane–THF/−78 °C/3 h) to the corresponding allylic alcohol (72%), in which the hydroxyl group was protected as a benzyl ether (NaH/BnBr/DMF/−40–0 °C/2 h) (90%). Then, the acetonide group was deprotected [90% AcOH (7 mL)–MeOH (9 mL)/85 °C/10 h] to give a diol (90%), which was again protected as a bis(TBDMS)-ether (TBDMSOTf/Et_3N/CH_2Cl_2/0–20 °C/20 min) (99%). The bis(TBDMS)-ether (0.375 g, 0.803 mmol) was treated with DDQ (0.371 g, 1.17 mmol) in CH_2Cl_2 (5 mL) in the presence of water (0.25 mL) to remove the PMB-protecting group. The resulting alcohol (454 mg, 83%) was oxidized to an aldehyde under Swern conditions, which was quickly purified through a short column packed with SiO_2. This aldehyde was dissolved in CH_2Cl_2 (4.5 mL) and treated with ethyl diazoacetate (0.271 g, 2.41 mmol) in the presence of $SnCl_2$ (15 mg, 0.08 mmol) (25 °C, overnight) to give the corresponding enolizable β-oxo ester (200 mg, 45% in two steps) according to the procedure of Holmquist and Roskamp.[27]

To a pre-cooled (−78 °C) solution of the (4*S*,5*S*)-4,5-bis-(TBDMSO)-β-oxo ester (108 mg, 0.196 mmol) in THF (1.5 mL) was added $NaBH_4$ (5.6 mg, 0.59 mmol), and the mixture was stirred at −78—40 °C for 20 h. The reaction was quenched with an aqueous NH_4Cl solution and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried (Na_2SO_4), filtered, and concentrated to give an oil, which was purified by a SiO_2 column to give the corresponding β-hydroxy ester (86 mg, 79%). This alcohol was acetylated as usual (Ac_2O/DMAP/CH_2Cl_2/rt/30 min) to give **33** (85 mg, 94%): $[\alpha]^{25}_D$ −33.9° (c 3.53, $CHCl_3$); ^1H NMR (500 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.085 (s, 3H), 0.092 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 1.20 (t, J = 7.0 Hz, 3H), 1.98 (s, 3H, $COCH_3$), 2.52 (dd, J = 8.2, 15.7 Hz, 1H, AcOCC*H*HCO), 2.86 (dd, J = 4.3, 15.7 Hz, 1H, AcOCCH*H*CO), 3.83 (dd, J = 4.1, 6.9 Hz, 1H, AcOCCHOSi), 4.01–4.13 (m, 4H, OCH_2Me and $=CCH_2OBn$), 4.29 (m, 1H, =CCHOSi), 5.28 (m, 1H, AcOCH), 5.82 (dtd, J = 1.6, 5.8, 15.6 Hz, 1H, =CHCOBn), 5.97 (dd, J = 4.3, 15.6 Hz, 1H, SiOCCH=), 7.26–7.38 (m, 5H, ArH); ^{13}C NMR (126 MHz) δ −4.8, −4.7, −4.4, 14.1, 17.9, 18.1, 21.2, 25.7, 25.9, 36.3, 60.5, 70.2, 70.8, 71.7, 73.9, 74.7, 127.2, 127.5, 127.7, 128.3, 131.3, 138.4, 169.7, 170.6; exact mass (FAB) calcd for $C_{31}H_{49}O_7Si_2$ (M^+) 589.3017, found 589.3011. Anal. Calcd for $C_{31}H_{49}O_7Si_2$ C, 63.12; H, 8.37. Found: C, 63.01; H, 8.22.

(1*R*,3*S*,4*S*,5*S*)-4-Acetoxy-2-benzyl-3-[(ethoxycarbonyl)-methyl]-2-aza-6-oxa-7-oxabicyclo[3.3.0]octane (34). A mixture of **13** (0.179 g, 0.351 mmol) and Bu_4NF (1.0 M: 1.76 mL, 5 equiv) in THF (15 mL) was stirred at 0 °C for 50 min. The reaction was quenched by water and extracted with EtOAc. The organic solution was washed with saturated brine, dried (Na_2SO_4), and concentrated to give the very unstable bicyclic lactone alcohol as an oil. (1*R*,3*S*,4*S*,5*S*)-2-benzyl-3-[(ethoxycarbonyl)-methyl]-4-hydroxy-2-aza-6-oxa-7-oxobicyclo[3.3.0]octane (**36**): ^1H NMR (500 MHz) δ 1.24 (t, 3H, CH_3), 2.12 (d, 1H, J_{gem} = 18.1 Hz, 8-*H*H), 2.38 (dd, J_{gem} = 18.1 Hz, J_{vic} = 6.5 Hz, 8-H*H*), 2.47 (dd, 1H, J_{gem} = 16.9 Hz, J_{vic} = 9.9 Hz, C(3)-C*H*H), 2.78 (dd, 1H, J_{gem} = 16.9 Hz, J_{vic} = 3.6 Hz, C(3)-CH*H*), 2.93 (m, 1H, 4-H), 3.55 (bt, 1H, J = 6.3 Hz, 1-H), 3.56 (d, 1H, J_{gem} = 14.1 Hz, C*H*HPh), 3.72 (bs, 1H, exchangeable with D_2O), 3.83 (d, 1H, J_{gem} = 14.1 Hz, CH*H*Ph), 4.11–4.17 (m, 3H, OCH_2 and 4-H), 4.67 (dd, 1H, $J_{5,1}$ = 6.3 Hz, $J_{5,4}$ = 1.9 Hz, 5H), 7.48–7.32 (m, 5H, ArH); ^{13}C NMR (126 MHz) δ 14.1 (q), 35.8 (t), 37.8 (t), 56.2 (t), 61.3 (t), 62.4 (d), 67.8 (d), 80.8 (d), 88.0 (d), 127.8 (d), 128.7 (d), 128.9 (d), 136.8 (s), 173.2 (s), 175.7 (s).

Even when kept in a refrigerator, this alcohol decomposed to give a mixture. Accordingly, the crude lactone alcohol was immediately converted into the corresponding acetate in the usual manner. Thus, to a solution of the crude lactone alcohol in CH_2Cl_2 (0.8 mL) were added acetic anhydride (30 μL) and 4-(dimethylamino)pyridine (37 mg), and the mixture was stirred at rt for 30 min. The reaction was partitioned between water (5 mL) and ether (10 mL), and the aqueous solution was extracted with ether (10 mL × 2). The combined ether extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an oil, which, on column chromatography (SiO_2, hexane–EtOAc = 1:2), afforded stable **34** (*vide supra*) (77.1 mg, 61%): $[\alpha]^{24}_D$ −47.6° (c 1.42, $CHCl_3$); IR (film) 1782, 1741, 1735, 1368, 1232, 1245, 1182, 1165, 1042, cm^{-1}; ^1H NMR (500 MHz) δ 1.21 (t, 3H, CH_3), 2.05 (S, 3h, $COCH_3$), 2.10 (d, 1H, J_{gem} = 18.0 Hz, 8-*H*H), 2.35 (dd, 1H, J_{gem} = 18.0 Hz, J_{vic} = 6.3 Hz, 8-H*H*), 2.59 (dd, 1H, J_{gem} = 15.6 Hz, J_{vic} = 6.3 Hz, C(3)-C*H*H), 2.62 (dd, 1H, J_{gem} = 15.6 Hz, J_{vic} = 5.4 Hz, C(3)-CH*H*), 3.29 (m, 1H, 3-H), 3.58-3.61 (m, 1H, 1-H), 3.60 (d, 1H, J_{gem} = 13.9 Hz, C*H*HPh), 3.93 (d, 1H, J_{gem} = 13.9 Hz, CH*H*Ph), 4.03–4.12 (m, 2H, OCH_2), 4.66 (dd, 1H, J = 1.8 Hz, 6.1 Hz, 5-H), 5.21 (dd, 1H, J = 1.8 Hz, 5.7 Hz, 4-H), 7.18–7.29 (m, 5H, ArH); ^{13}C NMR (126 MHz) δ 14.1 (q), 20.8 (q), 35.9 (t), 37.8 (t), 56.7 (t), 60.8 (t), 62.7 (d), 65.7 (d), 79.8 (d), 85.7 (d), 127.8 (d), 128.6 (d), 129.0 (d), 136.9 (s), 169.7 (s), 170.9 (s), 175.1 (s); exact mass calcd for $C_{19}H_{23}O_6N$ (M^+) 361.1525, found 361.1542.

CD Spectral Measurements. Solutions of **1**, (*S*,*S*)-**3**, and **24–31** in acetonitrile (4×10^{-4}–1×10^{-3} mol/L) were employed for CD spectral analyses. All measurements were carried out at rt (23 °C), and CD curves were plotted using the AVIV 680S V3.3r software.

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Supplementary Material Available: Copies of NMR spectra (^1H and ^{13}C) for compounds that have no combustion analysis (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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