Articles

Stereocontrolled Synthesis of Cyclic Ethers by Intramolecular Hetero-Michael Addition. 5. Synthesis of All Diastereoisomers of 2,3,5,6-Tetrasubstituted Tetrahydropyrans

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A systematic approach to the enantiomeric synthesis of all possible diastereoisomers of 2,6-dialkyl-3,5-dioxytetrahydropyrans is described. The key step in the described methodology is the intramolecular cyclization of enantiomerically enriched (≥95% ee) 7-hydroxy-4-(benzoyloxy)-2,3-unsaturated esters. In fused systems, six of the eight diastereoisomers for one enantiomeric series were synthesized using this procedure as a key step. Using those with the suitable stereochemistry, the two left were synthesized by simple chemical transformations: in one case by the basic isomerization of the carbon with the (methoxycarbonyl)methyl substituent or by a Mitsunobu inversion of a secondary alcohol available from the benzoyloxy group, in the remaining one by a consecutive sequence of oxidation and reduction reactions again over the free secondary alcohol. The stereochemistry of the intramolecular hetero-Michael addition leading to 2,3-disubstituted tetrahydropyrans is highly predictable when kinetic conditions (low temperature and sodium or potassium bases) are used and can be rationalized by invoking a model of a chair-like transition state in which the benzoyloxy group is located in the equatorial mode and the stereochemical course of the approach of the α,β-unsaturated ester is controlled by the geometry of the double bond. As a rule of thumb, the cyclization using *E* double bonds yielded *cis*-2,3-disubstituted tetrahydropyrans, while (*Z*)-unsaturated esters yielded the *trans* compounds. This empirical rule is followed in highly substituted systems, leading to fused 2,3,5,6-tetrasubstituted tetrahydropyrans, with the same absolute configuration in the carbon where the nucleophilic oxygen is located and the one where the benzoyloxy group is located. Those systems having opposite configurations yield the same *trans*-2,3-disubstituted compound. The isomerization under thermodynamic conditions (room or higher temperature with excess of base) of the diastereoisomers with the (methoxycarbonyl)methyl substituent in the axial mode led quantitatively to those in which such a group was located equatorially. The scope and limitations of the method are described in both the synthesis of the unsaturated precursor and the stereochemistry reached in the cyclization step.

Introduction

The presence in nature of molecules with oxygenated heterocycles is receiving considerable attention considering their capacity of modification of the transport of the metallic cations Na^+, K^+, and Ca^{2+} through the lipidic membranes,[1,2] this activity being responsible for their antibiotic,[1] neurotoxic,[3] antiviral,[4] and cytotoxic action[5] and as growth regulators[1,6] or inhibitors of the level of cholesterol in blood,[7] etc. The structural diversity of this kind of molecules is very wide, but all have in common the presence of polysubstituted cyclic ethers, with a defined stereochemistry in the substituents and ring size changing from five to nine members.[8] A particularly interesting group of this kind of molecules, of which maitotoxin (Scheme 1) is one of the most outstanding examples, is a series of highly toxic complex molecules characterized by having fused cyclic ether units usually with a *trans* relationship between the two substituents (H or CH_3) in the fusion of the rings and a *syn* stereochemistry in the substituents (H or CH_3) close to the oxygen atom of the cycle.[9]

Although several methods[10] have been reported for the synthesis of cyclic ethers and of tetrahydropyrans, in particular new methodologies are desirable for the ste-

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(1) Wesley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Decker: New York, 1982; Vols. I and II.

(2) (a) Painter, G. R.; Presman, B. C. *Top. Curr. Chem.* **1982**, *101*, 83. (b) Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, *28*, 2817. (c) Smith, P. W.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7917.

(3) (a) Shimizu, Y. *Marine Natural Products*; Scheuer, P., Ed.; Academic Press: New York, 1978; Vol. I, p 1. (b) Ellis, S. *Toxicon* **1985**, *23*, 469.

(4) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.

(5) (a) Suzuki, T.; Suzuki, A.; Furusaki, T.; Matsumoto, A.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329. (b) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644.

(6) (a) Cohran, V. M. *Physiology of Fungi*; Wiley: New York, 1958. (b) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sanmakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210.

(7) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J. *Tetrahedron* **1982**, *38*, 1009.

(8) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, pp 131−257. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251; (d) **1986**, *3*, 1; (e) **1987**, *4*, 539; (f) **1988**, *5*, 613; (g) **1990**, *7*, 269; (h) **1991**, *8*, 97; (i) **1992**, *9*, 323; (j) **1993**, *10*, 497; (k) **1994**, *11*, 355; (l) **1995**, *12*, 223.

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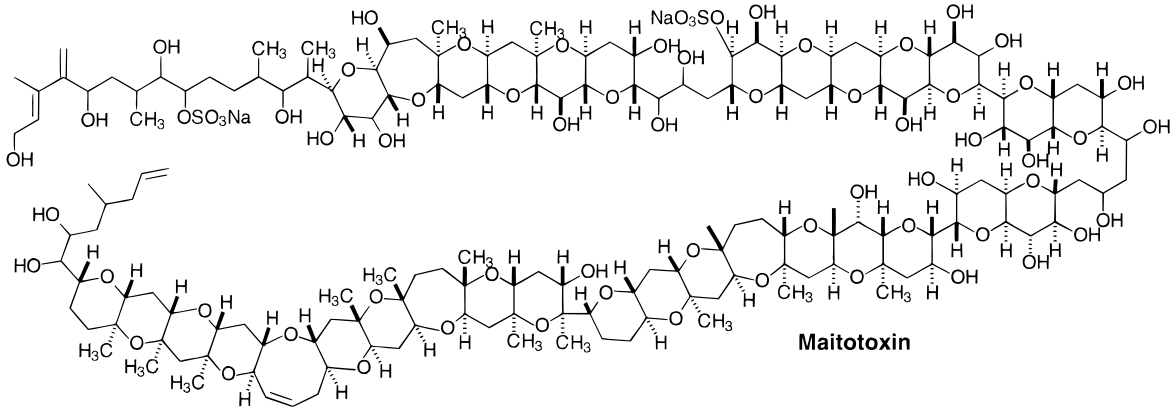
Scheme 1



reocontrolled synthesis of highly substituted rings. In this paper we discuss a particular approach based on the heteronuclear annelation by intramolecular alkoxide addition to γ-(benzoyloxy)-α,β-unsaturated esters. The intramolecular hetero-Michael addition, on the other hand, is known in carbohydrate chemistry.[11] In general terms such a cyclization in polyhydroxylic compounds leading to C-glycopyranosides seems to be a reaction in which the stereoselectivity is not controlled and which usually leads to an "epimeric mixture" which in basic conditions (even mild basic conditions) equilibrates to the more stable β-anomer with the C-1 substituent located equatorially.[12] In some cases, however, the intramolecular hetero-Michael cyclization of alkoxides over α,β-unsaturated esters can prove to be a stereoselective process, with the stereochemistry of the new stereocenter controlled by the configuration of the nucleophilic alkoxide,[13] the reaction conditions, and even the type of groups present in the linear precursors.[14] Stereoselectivity has also been observed when an unsaturated ketone is cyclized in a similar way.[15] In these cases, however, the stereochemistry in the final products is even more sensitive to the reaction conditions since acid equilibrium between both epimers has been reported.[16]

We considered the possibility that the double-bond geometry may play an important role in the transition state of this hetero-Michael addition. Although conjugate additions of organometallic reagents of γ-alkoxy-α,β-unsaturated carbonyl systems have been investigated,[17] to the best of our knowledge there are no similar studies with both (*E*)- and (*Z*)-α,β-unsaturated esters in the intramolecular hetero-Michael addition. Our synthetic approach could be considered to be based on the possible biogenetic route of some natural tetrahydropyranyl systems. In this sense, it had been proposed that the tetrahydropyranyl ring of the polyketide cladosporin is formed by an intramolecular hetero-Michael addition of a hydroxy group over an α,β-unsaturated carbonyl group.[18]

Results and Discussion

Synthesis of Isolated Tetrahydropyrans by Intramolecular Hetero-Michael Addition. Our research is focused on the study of the influence of both the stereochemistry of the chiral centers and the double-bond geometry in the cyclization of substituted chiral 7-hydroxy-4-(benzoyloxy)-2,3-unsaturated esters.[19] We began our studies with the linear models **9** and **11** with unambiguous absolute configuration of the secondary allylic center. The asymmetric induction was performed by the Katsuki−Sharpless asymmetric epoxidation[20] of a suitable allylic alcohol (**4**) obtained from 1,4-butanediol (Scheme 2). The enantiomerically enriched epoxy alcohol **5** was regioselectively opened using benzoic acid as nucleophile and Ti(OPr-*i*)$_4$ as acidic catalyst yielding the diol benzoate **6** with excellent regioselectivity (>100:1).[21] The oxidative cleavage with $NaIO_4$ led to the aldehyde **7** ready to be submitted to Wittig homologation. Thus, treatment of **7** with the sodium salt of trimethylphospho-

(9) (a) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060 and references cited therein. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. (c) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (d) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (e) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869. (f) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361. (g) Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448. (h) *Marine Toxins: Origin, Structure and Molecular Pharmacology*; Hall, S., Strichartz, G., Eds.; 1990; American Chemical Society: Washington, DC, ACS Symposium Series.

(10) (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Alvarez, E.; Candenas, M. L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953. (c) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, 1996.

(11) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522.

(12) (a) Allevi, P.; Anastasia, M.; Ciuffreda, C.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1275. (b) Bates, H. A.; Deng, P.-N. *J. Org. Chem.* **1983**, *48*, 4479. (c) Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 44. (d) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, E.; Yoshii, K. *J. Org. Chem.* **1992**, *57*, 2888.

(13) (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682. (b) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. (c) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279.

(14) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177.

(15) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (b) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843.

(16) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474.

(17) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652 and references cited therein.

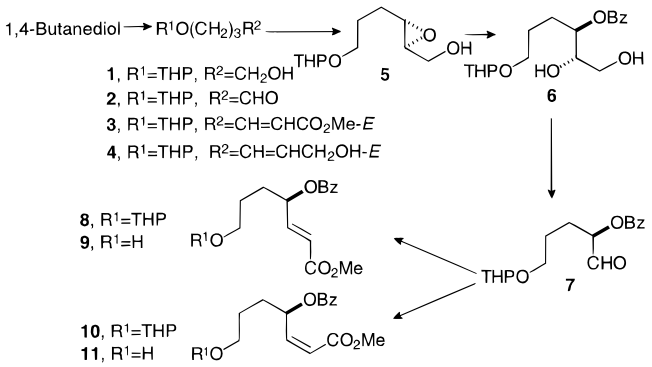
(18) Rawling, B. J.; Reese, P. B.; Ramer, S. E.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3382.

(19) For preliminary accounts of the matter, see: (a) Martín, V. S.; Núñez, M. T.; Ramírez, M. A.; Soler, M. A. *Tetrahedron Lett.* **1990**, *31*, 763. (b) Martín, V. S.; Palazón, J. M. *Tetrahedron Lett.* **1992**, *33*, 2399. (c) Palazón, J. M.; Soler, M. A.; Ramírez, M. A.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5467.

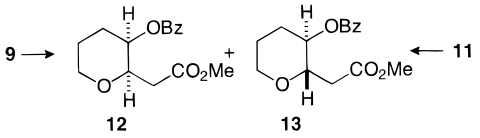
(20) Katsuki, T.; Martín, V. S. *Organic Reactions*; Paquette, L. A., et al., Eds.; Wiley: New York, 1996; Vol. 48, pp 1−299.

(21) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Palazón, J. M.; Añorbe, B.; Martín, V. S. *Tetrahedron Lett.* **1986**, *27*, 4987.

Scheme 2



Scheme 3



noacetate led to the *E*-unsaturated ester **8** with excellent *E*:*Z* selectivity (>20:1). In a similar manner, when **7** was submitted to the sodium salt of bis(phenoxy)[(methoxycarbonyl)methyl]phosphonate, the *Z* ester **11** was obtained almost exclusively (*Z*:*E*, >20:1).[22] Cleavage of the THP protecting group under standard acidic conditions gave the free alcohols **9** and **11**.

The cyclization reaction of both **9** and **11** was performed using different reaction conditions, changing base, solvent, and temperature. Gratifyingly, we found a good dependence between the geometry of the double bond in the α,β-unsaturated ester and the stereochemistry in the cyclization reaction (Scheme 3). As a rule of thumb, the cyclization using *E* double bonds yielded *cis*-2,3-disubstituted tetrahydropyrans, while (*Z*)-unsaturated esters yielded the *trans* compounds. As shown in Table 1, while the stereoselectivity in the cyclization of the (*E*)-unsaturated ester is strongly sensitive to the reaction conditions, the *trans*-2,3-disubstituted tetrahydropyran was the almost exclusively obtained product when the cyclization of the *Z* isomer was performed under any basic conditions. In general, we have found that potassium bases are the most convenient regarding stereochemistry and rate since in almost all the cases described in Table 1 the reactions were practically quantitative. Thus, when $LiN(TMS)_2$ was used as base, the cyclization reactions needed to proceed overnight at rt to be completed, while when $KN(TMS)_2$ was used the cyclizations were completed in less than 5 min even at −78 °C. The use of NaH at −78 °C also gave good stereoselectivity and yields (entry 6) although longer periods of time are required than with potassium salt.

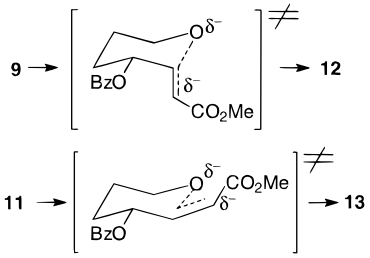
On the other hand, we found that at temperatures lower than 0 °C and using sodium and potassium bases none of the obtained products suffers further transformations to the other stereoisomer even after long periods of time (ca. 24 h). This result suggests to us that under such conditions the cyclization is a kinetically controlled reaction. In order to rationalize the stereochemical results, we have performed extensive calculations assuming only that the cyclization occurs by a chair-like transition state, obtaining a model summarized in Scheme 4 in which the energetically more favored transition

(22) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105.

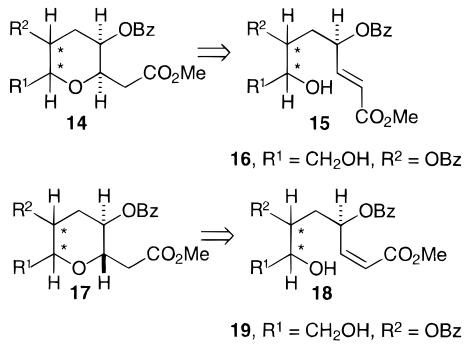
Table 1. Influence of the Reaction Conditions on Intramolecular Hetero-Michael Additions

entry	substrate	base	solvent	temp (°C)	**12**:**13**
1	**9**	NaH	THF	0	3:1
2		NaH	benzene	0	2:1
3		NaH	toluene	−78	8:1
4		NaH	CH_2Cl_2	0	2.5:1
5		NaH	CH_3CN	0	4:1
6		NaH	THF	−78	9:1
7		$LiN(TMS)_2$	toluene	rt	3:1
8		$NaN(TMS)_2$	toluene	0	3.3:1
9		$KN(TMS)_2$	THF	0	4.5:1
10		$KN(TMS)_2$	toluene	0	9:1
11		$KN(TMS)_2$	THF	−78	7:1
12		$KN(TMS)_2$	toluene	−78	9:1
13	**11**	NaH	THF	0	1:11
14		NaH	toluene	0	1:19
15		$LiN(TMS)_2$	toluene	rt	1:10
16		$NaN(TMS)_2$	toluene	0	1:10
17		$KN(TMS)_2$	toluene	0	1:20
18		$KN(TMS)_2$	toluene	−78	1:26
19		$KN(TMS)_2$	THF	−78	1:17

Scheme 4



Scheme 5



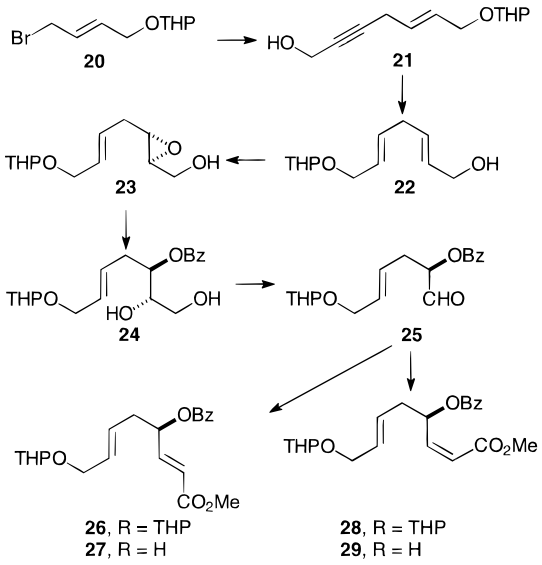
states reasonably explain our results.[23]

Taking into consideration the obtained results, we focused our interest on a possible approach to the stereoselective synthesis of isolated 2,3,5,6-tetrasubstituted tetrahydropyrans **14** and **17** in their enantiomeric forms by a procedure based on the cyclization of the suitable unsaturated precursors **15** and **18** (Scheme 5). Our interest in such a structural unit is based on the fact that it is widespread in a large number of highly active natural products[8] and its synthesis has not been properly solved to date from a general point of view.[10] On the other hand, we wanted to check the degree of accuracy of our proposed model in more complicated cases.

With these ideas in mind, we primarily prepared some diastereoisomers of the unsaturated dibenzoates **16** and **19**, for which the allylic alcohols **27** and **29** were obtained in accordance with Scheme 6. Thus, the copper-catalyzed

(23) Ramírez, M. A.; Palazón, J. M.; Padrón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584.

Scheme 6

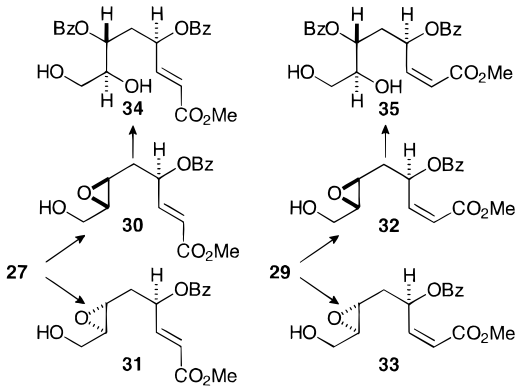


coupling[24] of the lithium salt of the *tert*-butyldiphenylsilyl-protected propargylic alcohol with the allylic bromide **20** yielded after silyl cleavage the enyne **21** which was reduced with $LiAlH_4$[25] to the corresponding bis-(*E*)-allylic alcohol **22** with excellent stereoselection, which when submitted to a similar sequence of reactions as those described above for the synthesis of **9** and **11** yielded through the aldehyde **25** the geometrical isomers **27** and **29**.

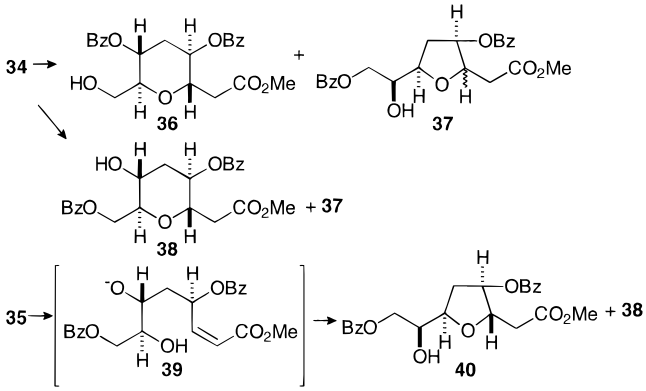
In order to obtain some of the diastereoisomers of **16**, both **27** and **29** were submitted to asymmetric epoxidation[20] using the enantiomers of diethyl tartrate. We found that while the reaction ran smoothly using (*R,R*)-(+)-DET to yield the expected epoxy alcohols **30** and **32** with excellent stereoselection (>20:1), any attempt to achieve the asymmetric epoxidation to obtain **31** and **33** using the enantiomeric chiral auxiliary was fruitless probably due to a carbonyl participation of the benzoate group.[26] On the other hand, other attempts to achieve the epoxidation using a non-enantioselective reagent such as MCPBA,[27] Ti(OPr-*i*)$_4$/TBHP[20b] or VO(acac)$_2$[28] led to an inseparable mixture of **30** and **31** (1:1) or **32** and **33** (1:1). The pure epoxides **30** and **32** were submitted to regioselective opening with benzoic acid as mentioned above, yielding smoothly the corresponding diol benzoates **34** and **35** ready to be cyclized (Scheme 7).

When **34** was submitted to 1.1 equiv of NaH, in THF, at −78 °C, the tetrahydropyran **36** was obtained in 73% yield and the diastereoisomeric mixture **37** in 20% yield. When more base was used (2.2 equiv), the transesterified benzoate **38** was isolated in 75% yield with the mixture **37** (15%). On the other hand, when the *Z* ester **35** was treated under similar basic conditions, the tetrahydrofuran **40** was obtained in 80% isolated yield with a small amount of **38**. Compound **40** was formed presumably via the anion **39** by a transesterification reaction (Scheme 8).

Scheme 7



Scheme 8



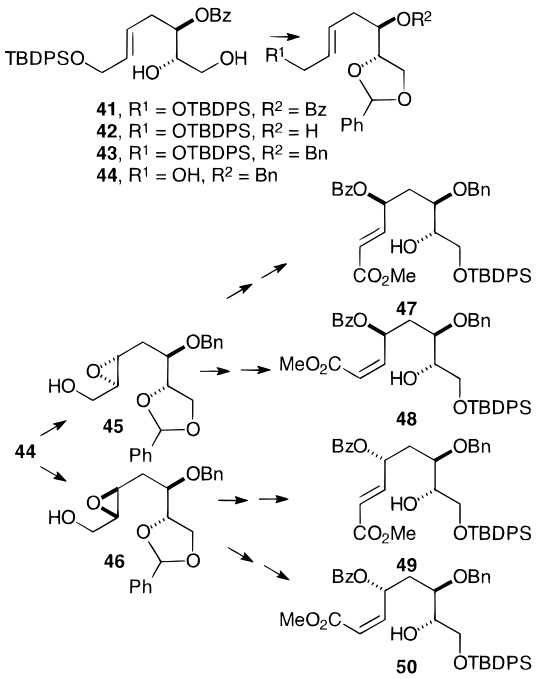
Although the synthesis of both **38** and **40** as pure enantiomers in high yields is a good synthetic result, the difficulty in synthesizing all the desired epoxides and the transesterification reactions which make it difficult to distinguish which is the actual nucleophile at any given moment led us to change the target for our studies in the hetero-Michael cyclization mainly by the proper choice of the suitable protecting group. Thus, **24**, used as a silyl-protected ether, was transformed into the benzylidene derivative **41** which, after cleavage of the benzoate group with NaOMe, was protected as the benzyl ether to obtain **43** in which cleavage of the silyl ether yielded the allylic alcohol **44**. Gratifyingly, the asymmetric epoxidation of **44** proceeded smoothly using both enantiomers of the tartrate esters, yielding the epoxides **45** and **46** used as described above to obtain the desired (*E*)- and (*Z*)-γ-alkoxy-α,β-unsaturated esters which, in order to ensure the nucleophilic position, were monoprotected as the primary TBDPS ethers **47**−**50** (Scheme 9).

When the obtained α,β-unsaturated esters were treated under basic conditions (NaH, THF) the results outlined in Scheme 10 were obtained. The cyclization of both **47** and **48** yielded the expected stereochemistry in accordance with the empirical rule, the (*Z*)-unsaturated ester yielding the *trans*-2,3-substituted tetrahydropyran **51** while the *E* compound afforded the *cis*-cyclic ether **52**. On the other hand, while **50** yielded the expected *trans*-substituted tetrahydropyran **54**, the cyclization of **49** afforded a mixture of **53** and **54** in a ratio of 1:4. Although this result was improved when different basic conditions were used [KN(TMS)$_2$, in toluene at −78 °C] affording a 1:1 mixture of **53** and **54**, the ratio suggested that again some adverse structural feature was forcing the system to follow a different stereochemical course.

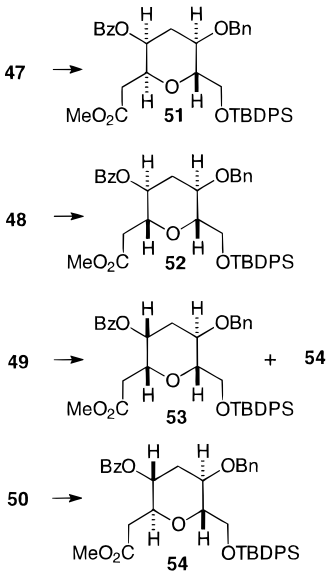
We conjecture that a possible explanation of the cases where the stereochemical course in the cyclization is

(24) Tagirachi, H.; Mathai, I. M.; Miller, S. I. *Org. Synth.* **1970**, *50*, 97.
(25) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988.
(26) Johnston, B. D.; Oehlschlager, A. C. *J. Org. Chem.* **1982**, *47*, 5384.
(27) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(28) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

Scheme 9



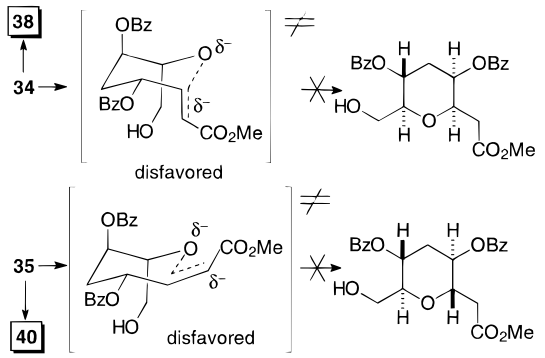
Scheme 10



different from that obtained in the models (Scheme 3**)** (cyclization of **34**, **35** and **49**) could be the presence of the additional groups located in disfavored conformational positions (*trans*-diaxial mode) that makes it difficult to reach the proposed chair-like transition state. Thus, the cyclization of **34** and **35** yielded respectively **38** and **40**, as the main products, instead of the expected products (Scheme 11). In such cases, a different mechanism could be possible.[23]

Synthesis of Fused Tetrahydropyrans. In order to ensure as much as possible the stereochemical pathway of the cyclization, we decided to perform our studies in compounds with a ring already present having a well-defined stereochemistry in the carbon where the nucleophilic hydroxy group is located and which furthermore would introduce some conformational restrictions in the cyclization reactions. On the other hand, this model would resemble even more the natural compound, which obviously is the final objective of our work. Consequently, in order to synthesize the necessary precursors to study the ring formation in a general way we decided to use both **12** and **13** as the starting point. Using a similar methodology to that described above we synthesized all the hydroxy-γ-(benzoyloxy)-α,β-unsaturated esters necessary for our study (Scheme 12). Interestingly, the asymmetric epoxidation of all the allylic alcohols could now be achieved with excellent stereoselection regardless of the chiral auxiliary used.

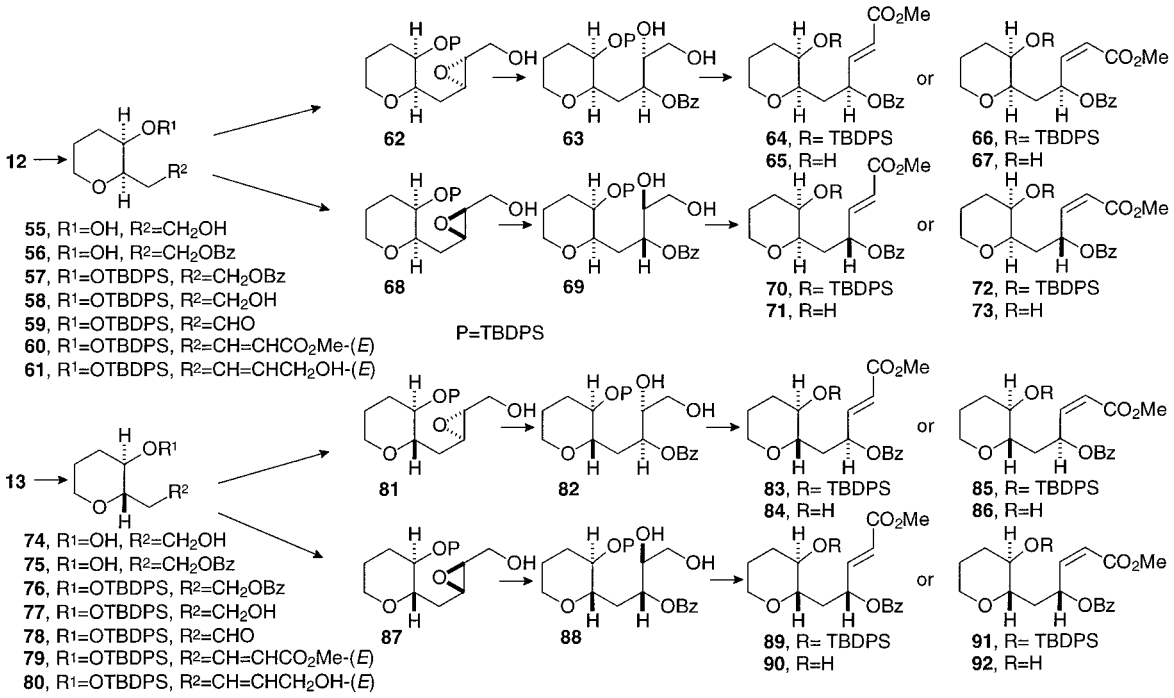
Scheme 11



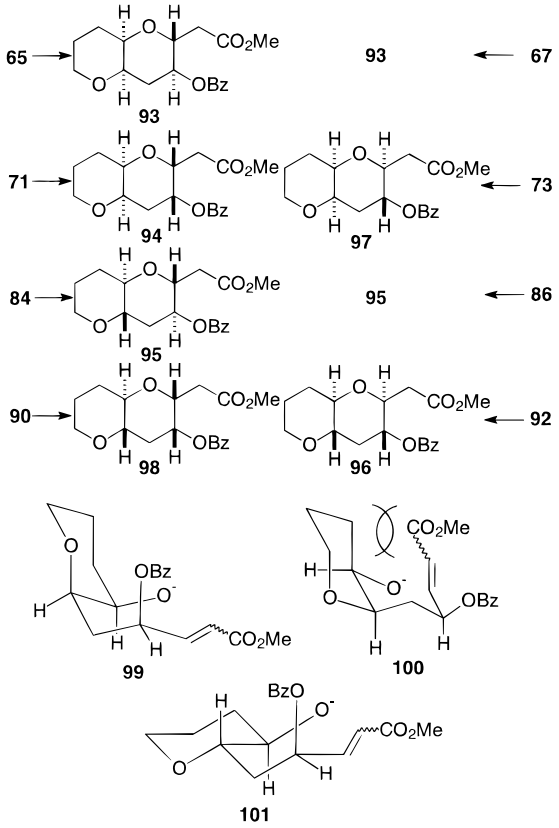
With the necessary precursors in our hands, we proceeded to systematically perform the cyclization using NaH as the base in THF at −78 °C. Although in all the cases the yields were good (>85%), we found two different behaviors regarding the obtained stereochemistry: those cases in which the carbon where the nucleophilic oxygen is located and the one where the benzoyloxy group is located have the same absolute configuration and those with opposite configuration. In the former the expected stereochemistry was obtained in accordance with the above-mentioned tendency: (*E*)-α,β-unsaturated esters led to the 2,3-*cis*-substituted tetrahydropyrans (**71** → **94**, **90** → **98**) while the *Z* esters gave the *trans*-isomers (**73** → **97**, **92** → **96**). In the latter, both (*E*)- and (*Z*)-α,β-unsaturated esters afforded the same 2,3-*trans*-disubstituted tetrahydropyran (**65** or **67** → **93**, **84** or **86** → **95**) (Scheme 13). In these cases the benzoyloxy group needs necessarily to be located in a pseudoaxial position (**99** and **101**) or the approach of the unsaturated system is disfavored by interaction with the preexisting ring (**100**), eliminating in both cases the possibility of reaching the proposed transition state (Scheme 4). In all cases, the yield and stereochemical results were practically similar using different bases, although the use of $KN(TMS)_2$ in toluene speeded up the reaction.

In order to fulfill the synthesis of the rest of the diastereoisomers, we considered the possibility of using the obtained products as precursors since the substituents present in such molecules may act as asymmetrical inductors in newly created stereocenters. Since the desired tetrasubstituted tetrahydropyrans have a secondary ester we pondered the synthesis of the new compounds by inversion of configuration in the suitable precursor of the carbon where such a functionality is located. Thus, **97** was completely reduced with $LiAlH_4$ and the resulting diol **102** was monoprotected as silyl ether (Scheme 14). The secondary alcohol **102** was oxidated with PCC to the corresponding ketone **104**, ready to be reduced. Satisfyingly, when **104** was treated with $LiAlH_4$ at −78 °C the *all-cis* tetrasubstituted tetrahydropyran **105** was obtained as the only detected diastereoisomer. However, when a similar sequence of reactions was applied to **96**, the reduction of **108** using a

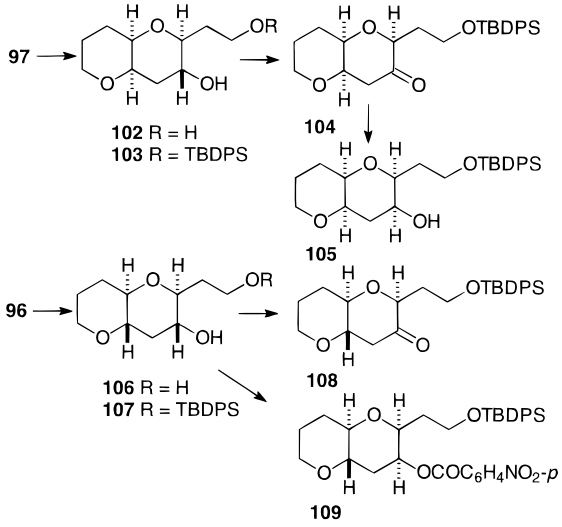
Scheme 12



Scheme 13



Scheme 14



myriad of reducing reagents yielded again **107** as the only diastereoisomer. Fortunately, when we performed Mitsunobu's methodology on **107** using *p*-nitrobenzoic acid as nucleophile and DIAD as activating agent,[29] the epimeric ester **109** was obtained in 78% yield. With these two sequences the synthesis of all possible diastereoisomers of 2,3,5,6-tetrasubstituted tetrahydropyrans were successfully accomplished, complementing the general methodology using the intramolecular hetero-Michael cyclization.

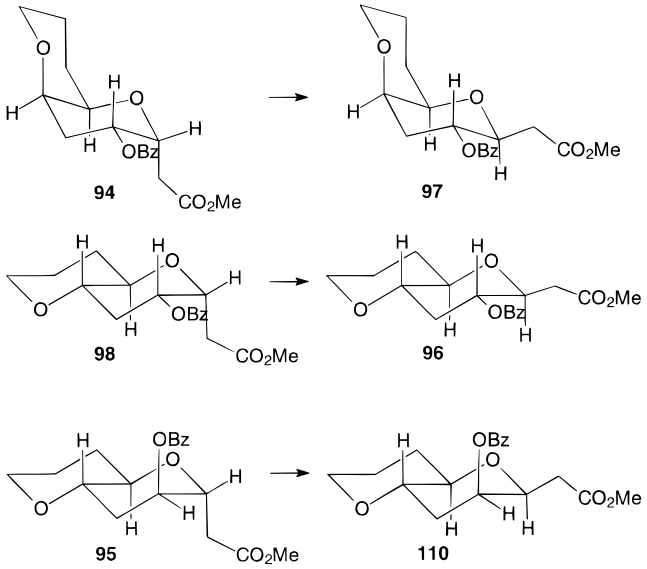
Although the chemistry described above permitted us to synthesize the eight possible diastereoisomers for each enantiomeric series, we wondered about the possibility of the basic isomerization of some of the obtained products in light of the known greater stability of the equatorial- relative to axial-substituted products.[12] Thus, we treated under such conditions the compounds **94**, **98**, and **95**, and gratifyingly in all the cases, complete isomerization of the axial (methoxycarbonyl)methyl group to the equatorial position was obtained (**97** and **96**) including **110** that could not be obtained by the use of kinetic cyclization conditions (Scheme 15).

Conclusions

The intramolecular hetero-Michael addition of 7-hydroxy-4-(benzoyloxy)-2,3-unsaturated esters has proved

(29) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (c) Hughes, M. S. *Org. React.* **1992**, *42*, 335.

Scheme 15



to be an excellent way to obtain substituted tetrahydropyrans of high stereochemical purity. The stereochemical course of the reaction depends on the reaction conditions. The method is particularly efficient when kinetic conditions are used (low temperatures and stoichiometric amounts of sodium or potassium bases) for the synthesis of fused rings. Thus, the synthesis of six of the eight possible diastereoisomers (only one enantiomeric series is considered) was possible by direct intramolecular hetero-Michael addition, while the remaining two were synthesized by simple chemical transformations using as starting material those diastereoisomers with the suitable stereochemistry. Using thermodynamic conditions (room temperature or higher and excess of base), the diastereoisomers with the (methoxycarbonyl)methyl substituent located in the axial mode isomerize to the equatorial position. The scope and limitations of the method have been described, the stereochemical course of the reaction being highly predictable. Thus, we found that under kinetic conditions, for those systems with the same absolute configuration for both the carbon on which the nucleophilic oxygen is located as well as the carbon vicinal to the α,β-unsaturated ester, the cyclization of *E*-unsaturated esters led to *cis*-2,3-disubstituted tetrahydropyran, while the reaction of *Z* esters afforded the *trans*-cyclic ether. In those systems with opposite absolute configuration for such carbon atoms, both *E*- and *Z*-unsaturated esters led to the same *trans*-2,3-disubstituted oxane. Although the methodology presented has been described only for one enantiomer series, the choice of the proper stereoisomer of the tartrate esters in the asymmetric epoxidation steps permits the control of the absolute configuration in the final products.

Experimental Section

Materials and methods are similar to those used in ref 30.

Preparation of 4-[(Tetrahydropyran-2-yl)oxy]butan-1-ol (1). To a stirred solution of commercially available 1,4-butanediol (7 g, 78 mmol) in dry CH_2Cl_2 (1 L) were added 3,4-dihydro-2*H*-pyran (3.2 mL, 35 mmol) and a catalytic amount of $OPCl_3$. The reaction was stirred at 0 °C until starting material was not detected by TLC. Then, Et_3N was added until pH ≈ 7 and the reaction mixture was poured into brine (350 mL). The mixture was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic phases were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography to yield **1** (8.1 g, 60% yield based on 1,4-butanediol) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 10 H), 3.01 (br s, 1 H), 3.39 (m, 2 H), 3.53 (t, *J* = 5.9 Hz, 2 H), 3.73 (m, 2 H), 4.49 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (t), 25.0 (t), 25.8 (t), 29.1 (t), 30.2 (t), 61.5 (t), 61.6 (t), 66.9 (t), 98.2 (d); IR ($CHCl_3$) (cm^{-1}) 3600, 3000, 2940, 1120; MS *m*/*z* (relative intensity) 175 $(M + 1)^+$ (5), 101 (19), 85 (100); HRMS calcd for $C_9H_{18}O_3$ $(M)^+$ 174.1256, found 174.1271.

General Method for the Preparation of (*E*)-α,β-Unsaturated Esters by the Knoevenagel Approach. Preparation of Methyl 6-[(Tetrahydropyran-2-yl)oxy]hex-2(*E*)-enoate (3). To a solution of alcohol **1** (9.54 g, 55 mmol) in dry CH_2Cl_2 (275 mL) under argon were sequentially added DMSO (36 mL, 0.7 mL × mmol), Et_3N (38 mL, 274 mmol), and SO_3·Py (26 g, 164 mmol) at rt. The mixture was stirred, and after 30 min TLC showed complete conversion. Then, to the reaction mixture was added 5% HCl aqueous solution (200 mL) and it was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield aldehyde **2** as an oil, which was used without further purification. To the crude were sequentially added pyridine (5.3 mL, 66 mmol), hemimalonate methyl ester (8.0 mL, 60 mmol), and a catalytic amount of piperidine (10 drops). This mixture was heated for 2 h in a water bath at 60 °C until TLC showed complete conversion. The mixture was diluted with Et_2O (30 mL) and washed with a 5% HCl aqueous solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography provided pure ester **3** (10.4 g, 83% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 4 H), 1.77 (m, 4 H), 2.25 (m, 2 H), 3.44 (m, 2 H), 3.69 (s, 3 H), 3.79 (m, 2 H), 4.54 (m, 1 H), 5.84 (ddd, *J* = 15.6, 15, 1.5 Hz, 1 H), 7.00 (ddd, *J* = 15.6, 6.9, 6.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.5 (t), 25.4 (t), 28.2 (t), 29.0 (t), 30.7 (t), 51.8 (q), 62.3 (t), 66.6 (t), 98.9 (d), 121.6 (d), 148.6 (d); IR ($CHCl_3$) (cm^{-1}) 2940, 1720, 1650, 1280; MS *m*/*z* (relative intensity) 227 $(M - 1)^+$ (1), 144 (10), 85 (100); HRMS calcd for $C_{12}H_{20}O_4$ $(M)^+$ 228.1361, found 228.1357.

General Method for the Reduction of Esters. Preparation of 6-[(Tetrahydropyran-2-yl)oxy]hex-2(*E*)-en-1-ol (4). To a stirred solution of **3** (10.2 g, 45 mmol) in Et_2O (450 mL) in an ice-cold bath was added slowly dropwise DIBAL (94 mL, 1.0 M in hexane, 94 mmol). After 30 min to the reaction mixture were sequentially added with stirring H_2O (13 mL), NaOH aqueous solution (15% w/v, 13 mL), and H_2O (39 mL). The mixture was allowed to reach rt, dried over $MgSO_4$, filtered through a pad of Celite, concentrated, and purified by silica gel column chromatography to yield **4** (7.84 g, 88% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 4 H), 1.71 (m, 4 H), 2.11 (m, 2 H), 3.46 (m, 2 H), 3.65 (m, 2 H), 3.77 (m, 2 H), 4.03 (s, 1 H), 4.53 (m, 1 H), 5.64 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.4 (t), 25.3 (t), 28.8 (t), 29.0 (t), 30.6 (t), 62.1 (t), 63.1 (t), 66.8 (t), 98.7 (d), 129.6 (d), 131.7 (d); IR ($CHCl_3$) (cm^{-1}) 3600, 2940, 1450, 1120; MS *m*/*z* (relative intensity) 199 $(M - 1)^+$ (1), 169 (4), 98 (28), 85 (100); HRMS calcd for $C_{11}H_{20}O_3$ $(M)^+$ 200.1412, found 200.1398.

General Asymmetric Epoxidation Procedure. Preparation of (2*R*,3*S*)-{3-[3-[(Tetrahydropyran-2-yl)oxy]propyl]-oxiranyl}methanol (5). Crushed, activated 3 Å molecular sieves (5 g) were added to stirred CH_2Cl_2 (325 mL) under argon. The flask was cooled to −20 °C, and $Ti(OPr\text{-}i)_4$ (11.6 mL, 39 mmol), (*R*,*R*)-(+)-diethyl tartrate (7.26 mL, 42.4 mmol), and **4** (7.64 g, 38 mmol) in CH_2Cl_2 (25 mL) were added sequentially with stirring. The mixture was stirred for 15 min, and *tert*-butyl hydroperoxide (13.6 mL, 5.2 M in isooctane, 71 mmol)[20b] was added slowly. After the addition, the reaction was maintained with stirring for 2 h. Tartaric acid aqueous solution (15% w/v, 250 mL) was added, and the stirring was continued until clear phases were reached (30 min). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were concentrated, diluted with ether (250 mL), and treated with a

(30) Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461.

precooled (0 °C) 15% NaOH aqueous solution (100 mL) and brine (100 mL). The two-phase mixture was stirred vigorously for 15 min at 0 °C. The organic phase was separated, and the aqueous phase extracted with ether (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, evaporated, and purified by silica gel column chromatography to yield **5** (6.7 g, 81% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 4 H), 1.69 (m, 6 H), 2.04 (br s, 1 H), 2.95 (m, 1 H), 2.98 (m, 1 H), 3.44 (m, 2 H), 3.70 (m, 1 H), 3.83 (m, 2 H), 3.89 (m, 1 H), 4.56 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 25.6 (t), 26.3 (t), 28.7 (t), 30.9 (t), 56.0 (d), 58.5 (d), 61.9 (t), 62.6 (t), 67.0 (t), 99.1 (d); IR ($CHCl_3$) (cm^{-1}) 3590, 2950, 1450, 1370; MS *m*/*z* (relative intensity) 217 $(M + 1)^+$ (8), 199 (38), 183 (67), 122 (18), 104 (100); HRMS calcd for $C_{11}H_{20}O_4$ $(M)^+$ 216.1361, found 216.1340.

General Procedure for the Regioselective Opening of 2,3-Epoxy 1-Alcohols with Benzoic Acid. Preparation of (1*R*)-1-[(1*S*)-1,2-Dihydroxyethyl]-4-[(tetrahydropyran-2-yl)oxy]butyl Benzoate (6). To a stirred solution of **5** (7.44 g, 34 mmol) in dry CH_2Cl_2 (350 mL) under argon were sequentially added benzoic acid (3.2 g, 26 mmol) and Ti(OPr-*i*)$_4$ (13mL, 42 mmol) at rt. The mixture was stirred for 15 min, and benzoic acid (3.2 g, 26 mmol) was added. After the addition, the mixture was stirred for 4 h. Tartaric acid aqueous solution (15% w/v, 250 mL) was added, and the solution was stirred until clear phases were reached (30 min). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$(2 × 50 mL) and brine (100 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography to yield **6** (9.31 g, 80% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.71 (m, 10 H), 3.39 (m, 2 H), 3.57 (m, 3 H), 3.74 (m, 2 H), 4.50 (m, 1 H), 5.12 (m, 1 H), 7.45 (m, 3 H), 7.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.6 (t), 25.4 (t), 27.4 (t), 30.6 (t), 62,4 (t), 62.9 (t), 67.1 (t), 67.3 (t), 73.1 (d), 74.7 (d), 99.0 (d), 128.3 (d), 128.4 (d), 129.7 (d), 130.0 (s), 133.2 (d), 166.6 (s); IR ($CHCl_3$) (cm^{-1}) 3600, 2950, 1700, 1120; MS *m*/*z* (relative intensity) 337 $(M - 1)^+$ (1), 115 (14), 104 (95), 84 (100); HRMS calcd for $C_{18}H_{26}O_6$ $(M)^+$ 338.1729, found 338.1713.

General Procedure for the Oxidative Cleavage of 3-Benzoyloxy 1,2-Diols. Preparation of (1*S*)-1-Formyl-4-[(tetrahydropyran-2-yl)oxy]butyl Benzoate (7). To a stirred solution of **6** (4 g, 12 mmol) in THF:H_2O (5:1, 70 mL) was added $NaIO_4$ (16.4 g, 77 mmol) at rt. After 2 h, the mixture was diluted with ether (175 mL) and the organic layer separated. The organic phase was washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated, yielding the crude aldehyde **7** as an oil, which was used without further purification.

General Procedure for the Preparation of γ-(Benzoyloxy)-(*E*)-α,β-unsaturated Esters. Preparation of Methyl (4*R*)-4-(Benzoyloxy)-7-[(tetrahydropyran-2-yl)oxy]hept-2(*E*)-enoate (8). To a suspension of NaH (0.46 g, 15 mmol, 80% in mineral oil) in benzene (500 mL) at 0 °C was slowly added trimethylphosphonoacetate (2.8 mL, 18 mmol) dissolved in benzene (50 mL). After complete addition the mixture was stirred for 5 min and the crude aldehyde **7** dissolved in benzene (50 mL) was added dropwise. The reaction mixture was stirred for 30 min, after which time TLC showed complete conversion to the unsaturated ester. The reaction was quenched with acetic acid (4 mL), diluted with ether (500 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (200 mL) and brine (200 mL). The water phases were extracted with ether (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography provided pure ester **8** (3.4 g, 80% yield from diol **6**) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 10 H), 3.46 (m, 2 H), 3.73 (s, 3 H), 3.80 (m, 2 H), 4.56 (s, 1 H), 5.73 (m, 1 H), 6.05 (dd, J = 14.9, J < 1 Hz, 1 H), 6.99 (dd, J = 14.9, 5.1 Hz, 1 H), 7.50 (m, 3 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.7 (t), 25.4 (t), 25.6 (t), 30.8 (t), 31.0 (t), 51.8 (q), 62.5 (t), 67.0 (t), 72.9 (d), 99.1 (d), 121.5 (d), 128.6 (d), 129.8 (d), 130.0 (s), 133.4 (d), 145.7 (d), 165.6 (s), 166.5 (s); IR ($CHCl_3$) (cm^{-1}) 2950, 1710, 1450, 1270; MS *m*/*z* (relative intensity) 361 $(M - 1)^+$ (1), 277 (12), 140 (20), 105 (100); HRMS calcd for $C_{20}H_{26}O_6$ $(M)^+$ 362.1729, found 362.1732.

General Procedure To Cleave THP Ethers. Preparation of Methyl (4*R*)-4-(Benzoyloxy)-7-hydroxyhept-2(*E*)-enoate (9). To a stirred mixture of **8** (3.54 g, 9.8 mmol) in MeOH (100 mL) was added concentrated HCl until pH ≈ 1. The reaction mixture was monitored by TLC, and after 5 min there was complete conversion. Et_3N was added until pH ≈ 7, and the reaction mixture was stirred for 5 min. After evaporation of the solvent, the obtained crude was purified by silica gel column chromatography to yield **9** (2.6 g, 95% yield) as an oil: $[\alpha]^{25}_D = -52.5$ (*c* 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 2 H), 1.91 (m, 2 H), 3.66 (m, 2 H), 3.69 (s, 3 H), 5.68 (m, 1 H), 6.00 (dd, J = 15.6, 1.5 Hz, 1 H), 6.93 (dd, J = 15.6, 5.1 Hz, 1 H), 7.46 (m, 3 H), 8.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.8 (t), 30.2 (t), 51.6 (q), 61.7 (t), 72.6 (d), 121.1 (d), 128.4 (d), 129.5 (d), 130.0 (s), 133.2 (d), 145.5 (d), 165.5 (s), 166.4 (s); IR ($CHCl_3$) (cm^{-1}) 2900, 2780, 1670, 1385; MS *m*/*z* (relative intensity) 277 $(M - 1)^+$ (1), 156 (13), 124 (15), 105 (100); HRMS calcd for $C_{15}H_{18}O_5$ $(M)^+$ 278.1154, found 278.1125.

General Procedure for the Preparation of γ-(Benzoyloxy)-(*Z*)-α,β-unsaturated Esters. Preparation of Methyl (4*R*)-4-(Benzoyloxy)-7-[(tetrahydropyran-2-yl)oxy]hept-2(*Z*)-enoate (10). To a suspension of NaH (520 mg, 17 mmol, 80% in mineral oil) in THF (850 mL) at 0 °C was added slowly bis(phenoxy)[(methoxycarbonyl)methyl]phosphonate (6.1 g, 20 mmol). After complete addition the mixture was stirred for 5 min and cooled down to −78 °C and the crude aldehyde **7** dissolved in THF (150 mL) was added dropwise. The reaction mixture was stirred for 30 min, allowing the temperature to raise until rt, after which time TLC showed complete conversion to the unsaturated ester. The reaction was quenched with acetic acid (4 mL), diluted with ether (500 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (200 mL) and brine (200 mL). The aqueous phases were extracted with ether (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography provided pure ester **10** (4.1 g, 85% yield based on diol **6**) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 10 H), 3.46 (m, 2 H), 3.75 (s, 3 H), 3.81 (m, 2 H), 4.58 (m, 1 H), 5,88 (dd, J = 11.6, 1.0 Hz, 1 H), 6.21 (dd, J = 11.6, 7.8 Hz, 1 H), 6.46 (m, 1 H), 7.46 (m, 3 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 25.7 (t), 30.9 (t), 31.0 (t), 31.1 (t), 51.6 (q), 62.5 (t), 67.2 (t), 72.2 (d), 99.0 (d), 120.6 (d), 128.5 (d), 129.7 (d), 130.0 (s), 133.1 (d), 147.5 (d), 165.5 (s), 166.1 (s); IR ($CHCl_3$) (cm^{-1}) 2950, 1710, 1270, 1180; MS *m*/*z* (relative intensity) 362 $(M)^+$ (1), 276 (36), 104 (100), 85 (100); HRMS calcd for $C_{20}H_{26}O_6$ $(M)^+$ 362.1729, found 362.1727.

Preparation of Methyl (4*R*)-4-(Benzoyloxy)-7-hydroxyhept-2(*Z*)-enoate (11). The general THP cleavage procedure was applied to **10** on a 3.54 g (10 mmol) scale, obtaining **11** (2.58 g, 95% yield) as an oil: $[\alpha]^{25}_D = -29.9$ (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 2 H), 1.93 (m, 2 H), 3.74 (m, 2 H), 3.76 (s, 3 H), 5.89 (dd, J = 11.4, 1.1 Hz, 1 H), 6.26 (dd, J = 11.4, 7.4 Hz, 1 H), 6.48 (m, 1 H), 7.48 (m, 3 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.3 (t), 30.4 (t), 51.7 (q), 62.0 (t), 71.9 (d), 120.3 (d), 128.5 (d), 129.8 (d), 130.0 (s), 133.2 (d), 148.2 (d), 165.5 (s), 166.1 (s); IR ($CHCl_3$) (cm^{-1}) 2900, 1670, 1385, 1130; MS *m*/*z* (relative intensity) 278 $(M)^+$ (1), 156 (75), 137 (47), 105 (100); HRMS calcd for $C_{15}H_{18}O_5$ $(M)^+$ 278.1154, found 278.1145.

General Procedure for the Cyclization of 7-Hydroxy-4-(benzoyloxy)-2,3-unsaturated Esters. Preparation of (2*R*)- and 2(*S*)-(1*R*)-2-[(Methoxycarbonyl)methyl]tetrahydropyran-3-yl Benzoates (12 and 13). To a suspension of NaH (35 mg, 80% in mineral oil, 1.2 mmol) in dry THF (7 mL) at −78 °C was added slowly **9** (300 mg, 1.1 mmol) in THF (3 mL). The reaction was stirred for 4 h, after which TLC showed complete conversion. Then to the reaction mixture was added AcOH (50 μL) and H_2O (5 mL), and it was extracted with ether (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography, yielding **12** (254 mg, 85% yield) and **13** (28 mg, 9% yield), both as oils. Compound **12**: $[\alpha]^{25}_D = -19.7$ (*c*

0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (m, 1 H), 1.32 (m, 1 H), 1.76 (m, 1 H), 1.92 (m, 1 H), 2.56 (dd, J = 16.0, 8.5 Hz, 1 H), 2.64 (dd, J = 16.0, 4.9 Hz, 1 H), 3.20 (ddd, J = 11.7, 11.7, <1 Hz, 1 H), 3.35 (s, 3 H), 3.82 (ddd, J = 11.7, 4.5, 2.2 Hz, 1 H), 3.96 (ddd, J = 8.5, 4.9, <1 Hz, 1 H), 5.13 (dd, J = 3.0, <1 Hz, 1 H), 7.40 (m, 2 H), 7.53 (m, 1 H), 8.25 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.7 (t), 28.0 (t), 37.4 (t), 51.8 (q), 68.8 (t), 69.2 (d), 75.0 (d), 128.5 (d), 129.7 (d), 130.0 (s), 133.2 (d), 166.0 (s), 171.4 (s); IR ($CHCl_3$) (cm^{-1}) 2940, 2830, 1720, 1270; MS m/z (relative intensity) 279 $(M + 1)^+$ (3), 156 (72), 105 (100); HRMS calcd for $C_{15}H_{19}O_5$ $(M + 1)^+$ 279.1232, found 279.1230. Compound **13**: $[\alpha]^{25}_D = -37.1$ (c 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.74 (m, 3 H), 2.32 (m, 1 H), 2.49 (dd, J = 15.0, 4.5 Hz, 1 H), 2.71 (dd, J = 15.0, 7.9 Hz, 1 H), 3.09 (ddd, J = 11.6, 11.1, 2.4 Hz, 1 H), 3.31 (s, 3 H), 3.62 (m, 1 H), 4.07 (ddd, J = 9.4, 7.9, 4.5 Hz, 1 H), 4.94 (m, 1 H), 7.40 (m, 2 H), 7.52 (m, 1 H), 8.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.2 (t), 29.5 (t), 38.1 (t), 51.8 (q), 68.0 (t), 72.3 (d), 76.6 (d), 128.5 (d), 129.7 (d), 130.0 (s), 133.3 (d), 165.6 (s), 171.6 (s); IR ($CHCl_3$) (cm^{-1}) 2940, 2830, 1720, 1270; MS m/z (relative intensity) 279 $(M + 1)^+$ (1), 156 (55), 105 (100); HRMS calcd for $C_{15}H_{19}O_5$ $(M + 1)^+$ 279.1232, found 279.1222.

Preparation of (1*R*,2*S*)-2-[(Methoxycarbonyl)methyl]-tetrahydropyran-3-yl Benzoate (13). The cyclization procedure described above to obtain **12** and **13** was applied to **11** on a 3.54 g (9.8 mmol) scale for 2 h at 0 °C, yielding **13** (3.36 g, 95% yield).

Preparation of 2-[[4-Bromobut-2(*E*)-enyl]oxy]tetrahydropyran (20). To a stirred solution of 4-[(tetrahydropyran-2-yl)oxy]but-2(*E*)-en-1-ol[31] (4.0 g, 23.2 mmol) in dry CH_2Cl_2 (250 mL) were added Et_3N (6.5 mL, 46 mmol) and MsCl (2.52 mL, 26 mmol) at 0 °C. After 15 min, the mixture was poured into brine (200 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (1 × 100 mL), dried, and concentrated, yielding an oil of the crude mesylate, which was used without purification.

To a suspension of LiBr (3.03 g, 35 mmol) in DMF (240 mL) under argon was added the crude mesylate in DMF (5 mL) at 0 °C. The reaction mixture was stirred for 2 h and diluted with ether (200 mL). The mixture was poured into H_2O (500 mL) and extracted with ether (3 × 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography of the crude product on silica gel gave **20** (4.81 g, 88% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.57 (m, 6 H), 3.41 (m, 1 H), 3.72 (m, 1 H), 3.91 (m, 3 H), 4.16 (m, 1 H), 4.53 (t, J = 3.2 Hz, 1 H), 5.83 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 25.4 (t), 30.5 (t), 31.6 (t), 62.0 (t), 66.2 (t), 98.0 (d), 128.1 (d), 131.7 (d); IR ($CHCl_3$) (cm^{-1}) 3012, 2946, 1125; MS m/z (relative intensity) 235 $(M)^+$ (1), 135 (18), 85 (100); HRMS calcd for $C_9H_{15}O_2$ $(M - 80)^+$ 155.1055, found 155.1072.

Preparation of 7-[(Tetrahydropyran-2-yl)oxy]hept-5(*E*)-en-2-yn-1-ol (21). Ethylmagnesium bromide (32 mL, 1.5 M in THF, 48 mmol) was added dropwise to a solution of propargyl alcohol (1.36 g, 24.3 mmol) in THF (25 mL) at rt. The mixture was heated at 40 °C for 50 min and then cooled again to 0 °C. A catalytic amount of copper(I) chloride (100 mg, 1 mmol) was added to the mixture, followed by **20** (3.8 g, 16.2 mmol). After being warmed to rt and stirred for 12 h, the reaction mixture was quenched sequentially with water (10 mL) and a saturated aqueous solution of NH_4Cl (100 mL).The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography to afford **21** (2.56 g, 75% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.52 (m, 6 H), 2.88 (m, 2 H), 3.45 (m, 1 H), 3.76 (m, 1 H), 3.91 (m, 1 H), 4.22 (m, 3 H), 4.61 (t, J = 3.5 Hz, 1 H), 5.67 (m, 1 H), 5.81 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 21.7 (t), 25.4 (t), 30.2 (t), 50.8 (t), 62.0 (t), 67.0 (t), 80.8 (s), 82.7 (s), 97.8 (d), 127.2 (d), 128.1 (d); IR ($CHCl_3$) (cm^{-1}) 3425, 3001, 2943, 1131; MS m/z (relative intensity) 210 $(M)^+$ (1), 101 (8), 85 (100); HRMS calcd for $C_8H_{14}O_2$ $(M - 68)^+$ 142.0942, found 142.0915.

Preparation of 7-[(Tetrahydropyran-2-yl)oxy]hepta-2(*E*),5(*E*)-dien-1-ol (22). To a stirred suspension of $LiAlH_4$ (460 mg, 12 mmol) in dry THF (125 mL) was added dropwise **21** (2.35 g, 11 mmol) in THF (5 mL) at −78 °C. The reaction was stirred for 4 h and quenched sequentially with water (0.5 mL), a 15% NaOH aqueous solution (0.5 mL), and H_2O (1.5 mL). The mixture was allowed to warm to rt, stirred additionally for 0.5 h, and dried with $MgSO_4$. The mixture was filtered through a pad of Celite, and the solution was concentrated and purified by silica gel chromatography to give **22** (1.9 g, 81% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.44−1.77 (br s, 6 H), 2.34 (s, 1 H), 2.75 (m, 2 H), 3.46 (m, 1 H) 3.87 (m, 2 H), 4.03 (d, J = 4.0 Hz, 2 H), 4.15 (dd, J = 11.7, 2.2 Hz, 1 H), 4.59 (t, J = 3.2 Hz, 1 H), 5.59 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.2 (t), 25.2 (t), 30.4 (t), 34.7 (t), 62.0 (t), 63.1 (t), 67.4 (t), 97.6 (d), 127.2 (d), 129.6 (d), 130.2 (d), 131.5 (d); IR ($CHCl_3$) (cm^{-1}) 3416, 2946, 1622, 1352, 1118; MS m/z (relative intensity) 213 $(M + 1)^+$ (1), 110 (6), 93 (23), 85 (100); HRMS calcd for $C_{12}H_{20}O_3$ $(M)^+$ 212.2902, found 212.1387.

Preparation of (2*R*,3*S*)-{3-[4-[(Tetrahydropyran-2-yl)-oxy]but-2(*E*)-enyl]oxiranyl}methanol (23). The general asymmetric epoxidation procedure using (*R*,*R*)-(+)-DET as a chiral auxiliary was used on **22** on a 1.8 g (8.5 mmol) scale for 2 h, yielding **23** (1.55 g, 80% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.63 (s, 6 H), 2.33 (t, J = 5.0 Hz, 2 H), 2.45 (br s, 1 H), 2.97 (m, 2 H), 3.56 (m, 1 H), 3.61 (d, J = 4.5 Hz, 1 H), 3.87 (m, 2 H), 4.15 (dd, J = 11.7, 2.2 Hz, 1 H), 4.60 (t, J = 3.2 Hz, 1 H), 3.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.9 (t), 25.8 (t), 31.0 (t), 34.7 (t), 50.3 (d), 55.2 (d), 61.9 (t), 62.7 (t), 67.9 (t), 98.4 (d), 128.0 (d), 130.0 (d); IR ($CHCl_3$) (cm^{-1}) 3400, 2900, 1720, 1110; MS m/z (relative intensity) 229 $(M + 1)^+$ (1), 93 (23), 85 (100); HRMS calcd for $C_{12}H_{20}O_4$ $(M)^+$ 228.2896, found 228.2791.

Preparation of (1*R*)-1-[(1*S*)-1,2-Dihydroxyethyl]-5-[(tetrahydropyran-2-yl)oxy]pent-3(*E*)-enyl Benzoate (24). The general procedure for the opening of 2,3-epoxy 1-alcohols was applied to **23** on a 1.45 g (6.4 mmol) scale, yielding **24** (1.87 g, 84% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.57 (m, 6 H), 2.58 (m, 2 H), 3.39 (m, 1 H), 3.72 (m, 2 H), 3.84 (m, 2 H), 4.05 (t, J = 11.3 Hz, 1 H), 4.51 (d, J = 10.8 Hz, 1 H), 4.70 (br s, 2 H), 5.15 (m, 1 H), 5.68 (m, 2 H), 7.37 (m, 3 H), 7.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.1 (t), 19.4 (t), 19.6 (t), 24.9 (t), 25.1 (t), 30.3 (t), 33.4 (t), 33.5 (t), 61.9 (t), 62.8 (t), 67.1 (t), 69.2 (t), 69.7 (t), 97.3 (d), 97.4 (d), 99.7 (d), 100.2 (d), 126.7 (d), 128.2 (d), 129.4 (d), 129.8 (d), 130.0 (s), 132.5 (d), 133.0 (d), 166.5 (s); IR ($CHCl_3$) (cm^{-1}) 3650, 3400, 2850, 1700; MS m/z (relative intensity) 351 $(M + 1)^+$ (1), 249 (27), 229 (30), 105 (100); HRMS calcd for $C_{19}H_{26}O_6$ $(M)^+$ 350.4134, found 350.4083.

Preparation of (1*R*)-1-[2-(Methoxycarbonyl)-(*E*)-vinyl]--5-[(tetrahydropyran-2-yl)oxy]pent-3(*E*)-enyl Benzoate (26). The general procedure to transform 3-benzoyloxy 1,2-diols into γ-(benzoyloxy)-(*E*)-α,β-unsaturated esters was applied to **24** on a 1.67 g (4.8 mmol) scale, yielding **26** (1.57 g, 88% yield based on diol **24**) as an oil: ^1H NMR ($CDCl_3$) δ 1.63 (m, 6 H), 2.58 (t, J = 5.5 Hz, 2 H), 3.44 (m, 2 H), 3.73 (s, 3 H), 3.88 (m, 1 H), 4.17 (m, 1 H), 4.57 (m, 1 H), 5.72 (m, 3 H), 6.04 (dd, J = 15.8, 1.6 Hz, 1 H), 6.98 (dd, J = 15.8, 5.0 Hz, 1 H), 7.48 (m, 3 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.4 (t), 25.4 (t), 30.6 (t), 36.9 (t), 51.6 (q), 62.1 (t), 67.0 (t), 72.1 (d), 97.7 (d), 121.7 (d), 126.7 (d), 128.4 (d), 129.6 (d), 130.0 (s), 131.1 (d), 133.2 (d), 141.9 (d), 165.5 (s), 166.2 (s); IR ($CHCl_3$) (cm^{-1}) 2900, 1700, 1660, 1240; MS m/z (relative intensity) 343 $(M - 31)^+$ (2), 273 (62), 151 (69), 105 (100); HRMS calcd for $C_{21}H_{26}O_6$ $(M)^+$ 374.1668, found 374.1665.

Preparation of (1*R*)-5-Hydroxy-1-[2-(methoxycarbonyl)-(*E*)-vinyl]pent-3(*E*)-enyl Benzoate (27). The general procedure for THP cleavage was applied to **26** on a 1.45 g (3.9 mmol) scale, yielding **27** (1.07 g, 95% yield) as an oil: $[\alpha]^{25}_D = -45.1$ (c 1.96, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.87 (s, 1 H), 2.62 (t, J = 6.5 Hz, 2 H), 3.77 (s, 3 H), 4.11 (d, J = 4.9 Hz, 2 H), 5.77 (m, 3 H), 6.09 (dd, J = 15.8, 1.6 Hz, 1 H), 7.01 (dd, J = 15.8, 5.0 Hz, 1 H), 7.41 (m, 2 H), 7.61 (m, 1 H), 8.08 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.3 (t), 52.2 (q), 63.5 (t), 72.6 (d), 122.0 (d), 125.8 (d), 128.9 (d), 130.0 (s), 133.7 (d), 134.1 (d), 145.3 (d), 165.8 (s), 166.8 (s); IR ($CHCl_3$) (cm^{-1}) 3400, 2900, 1710, 1650; MS m/z (relative intensity) 291 $(M + 1)^+$ (1), 151 (10), 105 (100); HRMS calcd for $C_{16}H_{18}O_5$ $(M)^+$ 290.1104, found 260.1110.

**Preparation of (1*R*)-1-[2-(Methoxycarbonyl)-(*Z*)-vinyl]-

(31) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

-5-[(tetrahydropyran-2-yl)oxy]pent-3(*Z*)-enyl Benzoate (28). The general procedure to transform 3-benzoyloxy-1,2-diols into γ-(benzoyloxy)-(*Z*)-α,β-unsaturated esters was applied to diol **24**, yielding **28** (2.95 g, 87% yield based on diol **24**) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 6 H), 2.67 (t, J = 5.8 Hz, 2 H), 3.49 (m, 2 H), 3.80 (s, 3 H), 3.90 (m, 1 H), 4.21 (m, 1 H), 4.62 (m, 1 H), 5.80 (m, 3 H), 5.94 (dd, J = 11.6, 0.5 Hz, 1 H), 6.26 (m, 1 H), 7.40 (m, 2 H), 7.60 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 25.8 (t), 31.0 (t), 37.4 (t), 51.9 (q), 62.6 (t), 67.6 (t), 72.0 (d), 98.0 (d), 120.8 (d), 128.2 (d), 128.33 (s), 128.9 (d), 130.0 (s), 130.7 (d), 133.5 (d) 147.6 (d), 165.5 (s), 166.2 (s); IR ($CHCl_3$) (cm^{-1}) 2900, 1710, 1640, 1440; MS *m*/*z* (relative intensity) 343 $(M - 31)^+$ (2), 273 (62), 151 (69), 105 (100); HRMS calcd for $C_{21}H_{26}O_6$ $(M)^+$ 374.1668, found 374.1665.

Preparation of (1*R*)-5-Hydroxy-1-[2-(methoxycarbonyl)-(*Z*)-vinyl]pent-3(*E*)-enyl Benzoate (29). The general procedure for THP cleavage was applied to **28** on a 1.39 g (3.7 mmol) scale, yielding **29** (1.02 g, 95% yield) as an oil: $[\alpha]^{25}_D$ = −60.0 (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 1 H), 2.61 (t, J = 4.2 Hz, 2 H), 3.75 (s, 3 H), 4.06 (d, J = 2.6 Hz, 2 H), 5.77 (m, 2 H), 5.90 (dd, J = 11.7, 1.4 Hz, 1 H), 6.23 (dd, J = 11.7, 7.8 Hz, 1 H), 6.48 (m, 1 H), 7.38 (m, 2 H), 7.55 (m, 1 H), 8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.3 (t), 52.0 (q), 63.5 (t), 72.0 (d), 120.8 (d), 126.5 (d), 128.9 (d), 129.8 (d), 130.0 (s), 133.4 (d), 147.3 (d), 165.5 (s), 166.3 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 2900, 1710, 1655; MS *m*/*z* (relative intensity) 291 $(M + 1)^+$ (1), 151 (10), 105 (100); HRMS calcd for $C_{16}H_{18}O_5$ $(M)^+$ 290.1104, found 290.1115.

Preparation of (1*R*)-1-[(2*R*,3*S*)-[3-(Hydroxymethyl)-oxiranyl]methyl]-3-(methoxycarbonyl)-2(*E*)-allyl Benzoate (30). The general asymmetric epoxidation procedure using (*R*,*R*)-DET as chiral auxiliary was used on **27** on a 1.01 g scale (3.5 mmol) for 2 h, yielding **30** (850 mg, 80% yield) as an oil: $[\alpha]^{25}_D$ = −55.2 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.14 (m, 2 H), 2.96 (m, 1 H), 3.09 (m, 1 H), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.85 (m, 1 H), 5.87 (d, J = 5.2 Hz, 1 H), 6.12 (dd, J = 16.0, 1.6 Hz, 1 H), 7.03 (dd, J = 15.6, 4.8 Hz, 1 H), 7.45 (m, 2 H), 7.58 (m, 1 H), 8.06 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 36.7 (t), 52.2 (q), 52.5 (d), 52.4 (d), 61.8 (t), 71.2 (d), 122.2 (d), 128.9 (d), 128.9 (d), 129.8 (d), 130.1 (s), 133.8 (d), 144.9 (d), 165.8 (s), 166.6 (s); IR ($CHCl_3$) (cm^{-1}) 3650, 3450, 1720, 1660; MS *m*/*z* (relative intensity) 307 $(M + 1)^+$ (1), 166 (16), 105 (100); HRMS calcd for $C_{16}H_{18}O_6$ $(M)^+$ 306.1044, found 306.1045.

Preparation of (1*R*)-1-[(2*R*,3*S*)-[3-(Hydroxymethyl)-oxiranyl]methyl]-3-(methoxycarbonyl)-2(*Z*)-allyl Benzoate (32). The general asymmetric epoxidation procedure using (*R*,*R*)-DET as chiral auxiliary was used on **29** on a 950 mg scale (3.3 mmol) for 2 h, yielding **32** (793 mg, 79% yield) as an oil: $[\alpha]^{25}_D$ = −43.7 (*c* 2.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 1 H), 2.10 (m, 1 H), 2.25 (m, 1 H), 3.10 (m, 1 H), 3.20 (m, 1 H), 3.67 (dd, J = 11.7, 4.1 Hz, 1 H), 3.81 (s, 3 H), 3.91 (dd, J = 12.2, 2.9 Hz, 1 H), 5.99 (d, J = 11.6 Hz, 1 H), 6.36 (dd, J = 11.6, 7.7 Hz, 1 H), 7.50 (m, 2 H), 7.62 (m, 1 H), 8.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.0 (t), 52.1 (q), 53.3 (d), 58.2 (d), 62.0 (t), 71.0 (d), 120.9 (d), 121.2 (s), 128.9 (d), 130.1 (s), 133.7 (d), 147.4 (d), 165.5 (s), 166.6 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 1710, 1640, 1100; MS *m*/*z* (relative intensity) 307 $(M + 1)^+$ (1), 166 (16), 105 (100), 77 (80); HRMS calcd for $C_{16}H_{18}O_6$ $(M)^+$ 306.1044, found 306.1050.

Preparation of (1*R*)-1-[(2*R*,3*S*)-2-(Benzoyloxy)-3,4-dihydroxybutyl]-3-[(methoxycarbonyl)-2(*E*)-allyl Benzoate (34). The general procedure to obtain 3-benzoyloxy 1,2-diols was applied to **30** on a 840 mg scale (2.7 mmol), yielding **34** (1.0 g, 87% yield) as an oil: $[\alpha]^{25}_D$ = +26.0 (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.31 (m, 1 H), 2.55 (m, 1 H), 3.15 (br s, 2 H), 3.60 (m, 1 H), 3.74 (s, 3 H), 3.77 (m, 2 H), 5.23 (m, 1 H), 5.86 (m, 1 H), 6.06 (dd, J = 15.7, 1.6 Hz, 1 H), 7.00 (dd, J = 15.7, 5.0 Hz, 1 H), 7.49 (m, 4 H), 7.52 (m, 2 H), 7.94 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.6 (t), 51.6 (q), 62.4 (t), 69.8 (d), 70.6 (d), 72.6 (d), 121.5 (d), 129.2 (d), 129.5 (d), 130.0 (s), 133.2 (d), 133.3 (d), 145.0 (d), 165.3 (s), 166.2 (s), 166.5 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 1710, 1660, 1100; MS *m*/*z* (relative intensity) 429 $(M + 1)^+$ (1), 166 (37), 141 (86), 105 (100); HRMS calcd for $C_{23}H_{24}O_8$ $(M)^+$ 428.1392, found 428.1395.

Preparation of (1*R*)-1-[(2*R*,3*S*)-2-(Benzoyloxy)-3,4-dihydroxybutyl)]-3-(methoxycarbonyl)-2(*Z*)-allyl Benzoate (35). The general procedure used above for the opening of 2,3-epoxy 1-alcohols was applied to **32** on a 705 mg (2.3 mmol) scale, yielding **35** (787 mg, 80% yield) as an oil: $[\alpha]^{25}_D$ = −26.2 (*c* 2.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.35 (m, 1 H), 2.63 (m, 1 H), 2.90 (br s, 1 H), 3.65 (m, 2 H), 3.75 (s, 3 H), 3.97 (m, 1 H), 5.21 (m, 1 H), 5.89 (dd, J = 11.3, 1.5 Hz, 1 H), 6.29 (dd, J = 11.1, 6.9 Hz, 1 H), 6.69 (m, 1 H), 7.20 (m, 4 H), 7.42 (m, 2 H), 7.80 (m, 2 H), 7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 34.6 (t), 52.2 (q), 63.2 (t), 69.3 (d), 71.7 (d), 72.4 (d), 120.5 (d), 128.7 (d), 130.0 (s), 130.3 (s), 133.4 (d), 133.6 (d), 147.5 (s), 148.5 (d), 166.2 (s), 166.7 (s), 167.2 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 1710, 1660, 1430; MS *m*/*z* (relative intensity) 429 $(M + 1)^+$ (1), 141 (32), 105 (100); HRMS calcd for $C_{23}H_{24}O_6$ $(M)^+$ 428.1392, found 428.1390.

Preparation of (2*S*,3*R*,5*R*,6*S*)-5-(Benzoyloxy)-6-(hydroxymethyl)-2-[(methoxycarbonyl)methyl]tetrahydropyran-3-yl Benzoate (36). The general cyclization procedure described was applied to **34** on a 210 mg (0.5 mmol) scale using 1.1 equiv of NaH (16 mg, 0.54 mmol, 80% in mineral oil), yielding **36** (150 mg, 71% yield) as an oil: $[\alpha]^{25}_D$ = +5.0 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.25 (m, 1 H), 2.44 (m, 1 H), 2.75 (t, J = 2.0 Hz, 2 H), 2.90 (m, 1 H), 3.73 (s, 3 H), 4.02 (d, J = 9.2 Hz, 1 H), 4.10 (m, 1 H), 4.40 (d, J = 7.6 Hz, 1 H), 5.28 (m, 2 H), 7.46 (m, 4 H), 7.59 (m, 2 H), 8.04 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 31.5 (t), 36.2 (t), 52.6 (q), 59.9 (t), 68.2 (d), 69.4 (d), 69.7 (d), 75.5 (d), 128.9 (d), 128.9 (d), 130.0 (s), 130.1 (s), 133.6 (d), 133.8 (d), 165.9 (s), 166.1 (s), 172.2 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 3000, 1710, 1485; MS *m*/*z* (relative intensity) 429 $(M + 1)^+$ (1), 166 (15), 141 (27), 105 (100); HRMS calcd for $C_{23}H_{23}O_8$ $(M - 1)^+$ 427.1393, found 427.1388.

Preparation of (2*S*,3*R*,5*R*,6*S*)-6-[(Benzoyloxy)methyl]-5-hydroxy-2-[(methoxycarbonyl)methyl]tetrahydropyran-3-yl Benzoate (38). The general cyclization procedure described above was applied to **34** on a 200 mg (0.47 mmol) scale using 2.1 equiv of NaH (30 mg, 1.0 mmol, 80% in mineral oil), yielding **38** (150 mg, 75% yield) as an oil: $[\alpha]^{25}_D$ = +5.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 1 H), 2.30 (m, 1 H), 2.65 (dd, J = 14.8, 5.2 Hz, 1 H), 2.88 (dd, J = 14.8, 9.6 Hz, 1 H), 3.05 (d, J = 4.7 Hz, 1 H), 3.71 (s, 3 H), 3.85 (m, 1 H), 3.95 (m, 1 H), 4.41 (dd, J = 12.1, 2.0 Hz, 1 H), 4.89 (dd, J = 12.1, 4.1 Hz, 1 H), 5.22 (m, 2 H), 7.28 (m, 2 H), 7.45 (m, 3 H), 7.60 (m, 1 H), 7.93 (m, 2 H), 8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 35.7 (t), 52.4 (q), 63.2 (d), 64.2 (t), 71.2 (d), 72.5 (d), 74.5 (d), 128.7 (d), 128.9 (d), 130.0 (s), 130.3 (d), 133.6 (d), 133.8 (d), 165.9 (s), 166.1 (s), 172.2 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 3000, 1710, 1470; MS *m*/*z* (relative intensity) 429 $(M + 1)^+$ (1), 397 (3), 141 (27), 105 (100), 77 (20); HRMS calcd for $C_{23}H_{23}O_8$ $(M - 1)^+$ 427.1393, found 427.1388.

Preparation (2*S*,3*R*,5R)-5-[2(*S*)-(Benzoyloxy)-1-hydroxyethyl]-2-[(methoxycarbonyl)methyl]tetrahydro-furan-3-yl Benzoate (40). The general cyclization procedure described above was applied to **35** on a 250 mg (0.6 mmol) scale using NaH (36 mg, 1.2 mmol, 80% in mineral oil), yielding **38** (32 mg, 13% yield) and **40** (199 mg, 80% yield) both as oils. Compound **40**: $[\alpha]^{25}_D$ = −6.1 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 1 H), 2.58 (m, 1 H), 2.68 (m, 2 H), 3.71 (s, 3 H), 4.17 (br s, 1 H), 4.26 (t, J = 6.1 Hz, 1 H), 4.39 (dd, J = 11.7, 6.2 Hz, 1 H), 4.55 (dd, J = 11.8, 3.6 Hz, 1 H), 4.60 (m, 1 H), 5.37 (m, 1 H), 7.45 (m, 4 H), 7.58 (m, 2 H), 8.04 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 32.8 (t), 38.3 (t), 52.3 (q), 66.6 (t), 71.6 (d), 78.5 (d), 78.7 (d), 80.9 (d), 128.8 (d), 128.9 (s), 129.0 (s), 130.0 (s), 130.1 (s), 133.7 (d), 133.7 (d), 166.5 (s), 167.3 (s), 171.1 (s); IR ($CHCl_3$) (cm^{-1}) 3450, 3000, 1710, 1470; MS *m*/*z* (relative intensity) 429 $(M + 1)^+$ (1), 105 (100), 84 (100); HRMS calcd for $C_{23}H_{23}O_8$ $(M - 1)^+$ 427.1393, found 427.1388.

Preparation of (2*S*,3*S*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldiphenylsiloxy)methyl]-2-[(methoxycarbonyl)-methyl]tetrahydropyran-3-yl Benzoate (51). The general cyclization method was applied to **47** on a 75 mg (0.11 mmol) scale to afford **51** (68 mg, 91% yield) as an oil: $[\alpha]^{25}_D$ = −21.7 (*c* 0.82, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 1.24 (s, 9 H), 1.85 (ddd, J = 12.9, 9.1, 9.1 Hz, 1 H), 2.20 (ddd, J = 12.9, 4.6, 4.6 Hz, 1 H), 2.62 (dd, J = 15.3, 5.8 Hz, 1 H), 2.80 (dd, J = 15.3, 8.4 Hz, 1 H), 3.33 (s, 3 H), 3.54 (m, 1 H), 3.86 (m, 1 H), 4.00 (d, J = 3.6 Hz, 2 H), 4.21 (d, J = 11.7 Hz, 1 H), 4.35 (d, J = 11.7 Hz, 1 H), 4.79 (m, 1 H), 5.33 (ddd, J = 9.1, 4.6, 4.6 Hz, 1 H), 7.08 (m, 2

H), 7.19 (m, 6 H), 7.29 (m, 6 H), 7.88 (m, 4 H), 8.16 (m, 2 H); ^{13}C NMR (C_6D_6) δ 19.2 (s), 26.8 (q), 29.4 (t), 33.5 (t), 51.0 (q), 63.6 (t), 68.4 (d), 69.9 (d), 70.5 (t), 71.5 (d), 74.7 (d), 129.7 (d), 129.8 (d), 130.4 (s), 132.7 (d), 133.5 (s), 133.7 (s), 135.8 (d), 135.9 (d), 138.7 (s), 165.1 (s), 170.4 (s); IR ($CHCl_3$) (cm^{-1}) 3018, 2954, 1730, 1274; MS *m*/*z* (relative intensity) 595 $(M - 57)^+$ (1), 105 (77), 91 (100). Anal. Calcd for $C_{39}H_{44}O_7Si$: C, 71.75; H, 6.79. Found: C, 71.53; H, 6.80.

Preparation of (2*R*,3*S*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldiphenylsiloxy)methyl]-2-[(methoxycarbonyl)-methyl]tetrahydropyran-3-yl Benzoate (52). The general cyclization method was applied to **48** on a 96 mg (0.15 mmol) scale to afford **52** (84 mg, 88% yield) as an oil: $[\alpha]^{25}_D = -0.7$ (*c* 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9 H), 1.69 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1 H), 2.56 (dd, *J* = 15.4, 8.2 Hz, 1 H), 2.67 (dd, *J* = 15.4, 4.0 Hz, 1 H), 2.87 (ddd, *J* = 11.4, 4.7, 4.7 Hz, 1 H), 3.46 (m, 1 H), 3.6 (s, 3 H), 3.84 (m, 1 H), 3.95 (d, *J* = 3.2 Hz, 2 H), 4.05 (m, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.67 (d, *J* = 11.3 Hz, 1 H), 4.88 (m, 1 H), 7.28 (m, 4 H), 7.42 (m, 9 H), 7.59 (m, 1 H), 7.73 (m, 4 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 26.7 (q), 26.8 (q), 35.2 (t), 37.8 (t), 51.7 (q), 62.9 (t), 71 (d), 71.6 (t), 71.7 (d), 75.9 (d), 81.4 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.4 (d), 129.5 (d), 129.7 (d), 130.0 (s), 133.3 (d), 133.4 (d), 133.8 (s), 135.6 (d), 135.8 (d), 138.0 (s), 165.5 (s), 171.2 (s); IR ($CHCl_3$) (cm^{-1}) 3020, 2954, 1720, 1274; MS *m*/*z* (relative intensity) 595 $(M - 57)^+$ (1), 199 (23), 163 (28), 105 (100). Anal. Calcd for $C_{39}H_{44}O_7Si$: C, 71.75; H, 6.79. Found: C, 71.43; H, 6.96.

Preparation of (2*S*,3*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldiphenylsiloxy)methyl]-2-[(methoxycarbonyl)-methyl]tetrahydropyran-3-yl Benzoate and Benzoic acid (2*R*,3*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldiphenylsiloxy)-methyl]-2-[(methoxycarbonyl)methyl]tetrahydropyran-3-yl Ester (53 + 54). The general cyclization method was applied to **49** on a 100 mg (0.15 mmol) scale to afford **53** + **54** (90 mg, 90% yield) as an oil: ^{1}H NMR (C_6D_6) δ 1.24 (s, 9 H), 1.28 (s, 9 H), 1.95 (m, 2 H), 2.25 (m, 2 H), 2.33 (dd, *J* = 14.8, 5.1 Hz, 1 H), 2.50 (dd, *J* = 14.9, 5.4 Hz, 1 H), 2.62 (dd, *J* = 14.8, 9.1 Hz, 1 H), 2.73 (dd, *J* = 14.9, 8.1 Hz, 1 H), 3.35 (s, 3 H), 3.40 (s, 3 H), 3.85 (m, 1 H), 3.99 (m, 4 H), 4.11 (m, 2 H), 4.29 (d, *J* = 11.9 Hz, 1 H), 4.37 (d, *J* = 11.9 Hz, 2 H), 4.46 (d, *J* = 11.9 Hz, 1 H), 4.67 (m, 1 H), 5.32 (m, 1 H), 5.36 (m, 1 H), 7.10−7.36 (m, 30H), 7.84 (m, 2 H), 7.90 (m, 4 H), 8.01 (m, 1 H), 8.24 (m, 2 H), 8.30 (m, 1 H); ^{13}C NMR (C_6D_6) δ 19.3 (s), 19.4 (s), 26.8 (q), 29.8 (t), 29.9 (t), 36.0 (t), 36.5 (t), 51.0 (q), 63.3 (t), 63.4 (t), 70.6 (d), 70.7 (d), 71.0 (t), 71.9 (d), 74.7 (d), 74.8 (d), 81.5 (d), 127.0 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.6 (d), 129.1 (d), 129.5 (d), 129.6 (d), 129.7 (d), 129.8 (d), 130.4 (s), 130.6 (s), 132.8 (d), 132.9 (d), 133.3 (d), 133.6 (d), 133.7 (d), 135.7 (d), 136.0 (d), 136.1 (d), 138.7 (s), 165.2 (s), 165.4 (s), 170.1 (s), 170.3 (s); IR ($CHCl_3$) (cm^{-1}) 3020, 2954, 2932, 1730; MS *m*/*z* (relative intensity) 595 $(M - 57)^+$ (1), 199 (25), 167 (21), 105 (100). Anal. Calcd for $C_{39}H_{44}O_7Si$: C, 71.75; H, 6.79. Found: C, 71.54, H, 6.82.

Preparation of (2*R*,3*R*,5*R*,6*S*)-5-(Benzyloxy)-6-[(*tert*-butyldiphenylsiloxy)methyl]-2-[(methoxycarbonyl)-methyl]tetrahydropyran-3-yl Benzoate (54). The general cyclization method was applied to **50** on a 100 mg (0.15 mmol) scale to afford **54** (91 mg, 91% yield) as an oil: $[\alpha]^{25}_D = +19.3$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 1.24 (s, 9 H), 1.95 (m, 1 H), 2.25 (m, 1 H), 2.33 (dd, *J* = 14.8, 5.1 Hz, 1 H), 2.62 (dd, *J* = 14.8, 9.1 Hz, 1 H), 3.35 (s, 3 H), 3.85 (m, 1 H), 3.99 (m, 2 H), 4.10 (m, 1 H), 4.36 (d, *J* = 11.8 Hz, 1 H), 4.46 (d, *J* = 11.8 Hz, 1 H), 4.68 (m, 1 H), 5.31 (m, 1 H), 7.21 (m, 8 H), 7.30 (m, 5 H), 7.76 (m, 1 H), 7.84 (m, 2 H), 7.90 (m, 2 H), 8.25 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 26.8 (q), 29.8 (t), 36.0 (t), 51.0 (q), 63.4 (t), 70.6 (t), 71.0 (d), 71.9 (d), 74.8 (d), 81.5 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 129.5 (d), 129.6 (d), 129.8 (d), 130.6 (d), 132.8 (s), 135.7 (d), 135.9 (d), 136.1 (d), 138.7 (s), 165.5 (s), 171.2 (s); IR ($CHCl_3$) (cm^{-1}) 3020, 2954, 1730, 1274; MS *m*/*z* (relative intensity) 595 $(M - 57)^+$ (1), 243 (10), 199 (25), 105 (100). Anal. Calcd for $C_{39}H_{44}O_7Si$: C, 71.75; H, 6.79. Found: C, 71.50, H, 6.95.

Preparation of (2*S*,3*R*)-2-(2-Hydroxyethyl)tetrahydropyran-3-ol (74). The general method for the reduction of esters was applied to **13** on a 2.26 g (8 mmol) scale using $LiAlH_4$ (12 mL, 1.0 M in ether, 12 mmol) to afford **74** (850 mg, 73% yield) as a solid: mp = 58−59 °C; $[\alpha]^{25}_D = -32.3$ (*c* 2.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 1 H), 1.60 (m, 2 H), 1.76 (m, 1 H), 2.01 (m, 1 H), 2.08 (dd, *J* = 12.0, 2.4 Hz, 1 H), 3.16 (m, 1 H), 3.29 (m, 2 H), 3.34 (br s, 1 H), 3.77 (m, 2 H), 3.87 (d, *J* = 10.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.4 (t), 32.5 (t), 35.3 (t), 60.5 (t), 67.6 (t), 70.1 (d), 82.5 (d); IR ($CHCl_3$) (cm^{-1}) 3619, 3413, 2942, 1090; MS *m*/*z* (relative intensity) 147 $(M + 1)^+$ (3), 128 (41), 89 (48), 75 (100). Anal. Calcd for $C_7H_{14}O_3$: C, 57.50; H, 9.66. Found: C, 57.17; H, 9.58.

General Method for Benzoylation. Preparation of 2-[(2*S*,3*R*)-3-Hydroxytetrahydropyran-2-yl]ethyl Benzoate (75). To a solution of diol **74** (850 mg, 6 mmol) in dry CH_2Cl_2 (58 mL) were sequentially added Et_3N (4 mL, 29 mmol) and benzoyl chloride (1.4 mL, 12 mmol) at 0 °C. The reaction was stirred for 1 h, after which time TLC showed complete conversion. Then the mixture was washed with a 5% HCl aqueous solution (50 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel column chromatography provided pure ester **75** (1.35 g, 93% yield) as an oil: $[\alpha]^{25}_D = -35.7$ (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 1 H), 1.65 (m, 2 H), 1.86 (m, 1 H), 2.10 (dd, *J* = 12.4, 3.2 Hz, 1 H), 2.35 (m, 1 H), 2.82 (br s, 1 H), 3.19 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1 H), 3.33 (m, 2 H), 3.87 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.46 (m, 2 H), 7.40 (m, 2 H), 7.52 (m, 1 H), 8.03 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (t), 31.4 (t), 32.9 (t), 61.9 (t), 67.5 (t), 70.3 (d), 79.4 (d), 128.3 (d), 129.5 (d), 130.3 (s), 132.8 (d), 166.7 (s); IR ($CHCl_3$) (cm^{-1}) 3477, 2944, 1716, 1271; MS *m*/*z* (relative intensity) 251 $(M + 1)^+$ (1), 110 (42), 105 (100). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.25. Found: C, 67.02; H, 7.18.

General Method for Silyl Protection. Preparation of 2-[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]ethyl Benzoate (76). To a stirred solution of **75** (1.2 g, 4.8 mmol) in dry CH_2Cl_2 (25 mL) under argon were added imidazole (652 mg, 9.6 mmol) and *tert*-butylchlorodiphenylsilane (1.4 mL, 5.3 mmol) sequentially added at rt. After 12 h TLC showed complete conversion. Then the mixture was diluted with CH_2Cl_2 (25 mL) and washed with a 5% HCl aqueous solution (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, and the crude was purified by silica gel column chromatography to yield **76** (1.98 g, 85% yield) as an oil: $[\alpha]^{25}_D = -23.1$ (*c* 2.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.44 (m, 3 H), 1.58 (m, 1 H), 1.85 (m, 1 H), 2.44 (m, 1 H), 3.28 (dd, *J* = 11.0 Hz, 1 H), 3.33 (dd, *J* = 9.0, 9.0 Hz, 1 H), 3.41 (m, 1 H), 3.78 (d, *J* = 11.0 Hz, 1 H), 4.40 (m, 2 H), 7.40 (m, 8 H), 7.57 (m, 1 H), 7.69 (m, 4 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.5 (t), 27.0 (q), 31.6 (t), 33.3 (t), 62.0 (t), 67.6 (t), 72.2 (d), 79.5 (d), 127.4 (d), 127.7 (d), 128.3 (d), 129.6 (d), 129.7 (d), 130.7 (s), 132.7 (d), 133.6 (s), 134.5 (s), 135.9 (d), 166.6 (s); IR ($CHCl_3$) (cm^{-1}) 3073, 2961, 1715, 1270; MS *m*/*z* (relative intensity) 431 $(M - 57)^+$ (21), 309 (25), 303 (100), 105 (100). Anal. Calcd for $C_{30}H_{36}O_4Si$: C, 73.73; H, 7.43. Found: C, 73.64; H, 7.36.

General Method for Benzoate Cleavage. Preparation of 2-[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]ethanol (77). To a stirred solution of **76** (1.8 g, 3.7 mmol) in dry CH_2Cl_2 (40 mL) were added NaH (125 mg, 4.1 mmol, 80% in mineral oil) and dry MeOH (0.25 mL, 7.4 mmol) at rt. After 5 min the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography to afford **77** (1.36 g, 96% yield) as an oil: $[\alpha]^{25}_D = -27.9$ (*c* 2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.41 (m, 2 H), 1.59 (m, 1 H), 1.81 (m, 1 H), 2.16 (m, 1 H), 2.71 (m, 1 H), 3.29 (m, 1 H), 3.43 (m, 2 H), 3.72 (m, 2 H), 3.79 (dd, *J* = 9.3, 2.0 Hz, 1 H), 7.40 (m, 6 H), 7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.3 (t), 27.0 (q), 33.1 (t), 33.9 (t), 61.7 (t), 67.6 (t), 71.8 (d), 83.7 (d), 127.5 (d), 127.7 (d), 129.6 (d), 129.8 (d), 133.5 (s), 134.5 (s), 135.9 (d); IR ($CHCl_3$) (cm^{-1}) 3510, 3071, 2954, 1471; MS *m*/*z* (relative intensity) 327 $(M - 57)^+$ (19), 269 (43), 249 (31), 199

(100). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.84; H, 8.39. Found: C, 71.89; H, 8.52.

Preparation of Methyl 4-[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]but-2(*E*)-enoate (79). The general method for the preparation of (*E*)-α,β-unsaturated esters was applied to **77** on a 1.1 g (2.9 mmol) scale to afford **79** (1.1 g, 89% yield) as an oil: $[\alpha]^{25}_D = +2.41$ (*c* 2.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.48 (m, 3 H), 1.85 (m, 1 H), 2.17 (ddd, *J* = 15.2, 7.6, 7.6 Hz, 1 H), 2.81 (dd, *J* = 15.2, 2.0 Hz, 1 H), 3.28 (m, 2 H), 3.38 (m, 1 H), 3.72 (s, 3 H), 3.78 (d, *J* = 11.3 Hz, 1 H), 5.83 (d, *J* = 15.7 Hz, 1 H), 6.98 (ddd, *J* = 15.7, 7.1, 7.1 Hz, 1 H), 7.41 (m, 6 H), 7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.4 (t), 27.0 (q), 33.3 (t), 35.0 (t), 51.3 (q), 67.7 (t), 71.9 (d), 81.4 (d), 122.6 (d), 127.4 (d), 127.7 (d), 129.7 (d), 129.8 (d), 133.4 (s), 134.3 (s), 135.7 (d), 135.9 (d), 146.6 (d), 166.9 (s); IR ($CHCl_3$) (cm^{-1}) 3009, 2952, 2859, 1717; MS *m*/*z* (relative intensity) 381 $(M - 57)^+$ (100), 213 (35), 199 (55). Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.20; H, 7.82. Found: C, 71.34; H, 7.83.

Preparation of 4-[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)-tetrahydropyran-2-yl]but-2(*E*)-en-1-ol (80). The general method for reduction of esters was applied to **79** on a 1.1 g (2.5 mmol) scale using DIBAL (5.6 mL, 1.0 M in hexane, 5.6 mmol) to afford **80** (800 mg, 78% yield) as an oil: $[\alpha]^{25}_D = -10.2$ (*c* 2.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2 H), 1.62 (m, 1 H), 1.81 (m, 1 H), 2.07 (m, 1 H), 2.70 (m, 1 H), 3.24 (m, 2 H), 3.38 (m, 1 H), 3.78 (d, *J* = 11.2 Hz, 1 H), 4.05 (d, *J* = 3.9 Hz, 2 H), 5.65, (m, 2 H), 7.39 (m, 6 H), 7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.4 (t), 27.0 (q), 33.3 (t), 34.9 (t), 63.6 (t), 67.6 (t), 71.8 (d), 82.2 (d), 127.4 (d), 127.6 (d), 129.6 (d), 129.7 (d), 131.0 (d), 133.6 (s), 134.5 (s), 136.0 (d); IR ($CHCl_3$) (cm^{-1}) 3458, 3071, 2944, 1684; MS *m*/*z* (relative intensity) 353 $(M - 57)^+$ (4), 299 (28), 199 (100), 105 (100), 77 (37). Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.18; H, 8.36.

Preparation of (2*R*,3*S*)-{3-[[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]methyl]oxiranyl}-methanol (87). The general asymmetric epoxidation procedure using as chiral auxiliary (*R*,*R*)-(+)-DET was used on **80** on a 1.6 g (3.9 mmol) scale for 2 h, yielding **87** (1.3 g, 80% yield) as an oil: $[\alpha]^{25}_D = -34.4$ (*c* 2.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 1.47 (m, 3 H), 1.85 (m, 2 H), 2.09 (m, 1 H), 2.87 (m, 1 H), 3.08 (m, 1 H), 3.31 (dd, *J* = 11.3, 11.3 Hz, 1 H), 3.37 (m, 2 H), 3.57 (d, *J* = 11.2 Hz, 1 H), 3.79 (m, 1 H), 3.85 (d, *J* = 12.7 Hz, 1 H), 7.40 (m, 6 H), 7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 25.5 (t), 26.9 (q), 33.3 (t), 34.6 (t), 53.3 (d), 59.0 (d), 61. 8 (t), 67.6 (t), 72.2 (d), 80.0 (d), 127.4 (d), 127.6 (d), 129.8 (d), 133.5 (s), 134.4 (s), 135.9 (d); IR ($CHCl_3$) (cm^{-1}) 3510, 3077, 2935, 1729; MS *m*/*z* (relative intensity) 369 $(M - 57)^+$ (3), 199 (100), 135 (48), 97 (73). Anal. Calcd for $C_{25}H_{34}O_4Si$ C, 70.39; H, 8.04. Found C, 70.34; H, 8.26.

Preparation of (1*R*,2*R*)-1-[[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]methyl]-2,3-dihydroxypropyl Benzoate (88). The general procedure for the opening of 2,3-epoxy 1-alcohols was applied to **87** on a 1.2 g (2.8 mmol) scale, yielding **88** (1.34 g, 87% yield) as an oil: $[\alpha]^{25}_D = -38.0$ (*c* 2.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.45 (m, 3 H), 1.80 (m, 2 H), 2.51 (br s, 1 H), 2.59 (dd, *J* = 15.5, 3.9 Hz, 1 H), 3.37 (m, 2 H), 3.57 (m, 2 H), 3.76 (m, 2 H), 3.90 (d, *J* = 2.6 Hz, 1 H), 5.26 (m, 1 H), 7.33 (m, 4 H), 7.43 (m, 4 H), 7.56 (m, 1 H), 7.63 (m, 4 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.1 (s), 25.2 (t), 26.8 (q), 32.5 (t), 33.2 (t), 63.5 (t), 67.6 (t), 71.4 (d), 71.8 (d), 72.0 (d), 79.2 (d), 127.3 (d), 127.7 (d), 128.3 (d), 129.6 (d), 130.1 (s), 133.1 (d), 133.3 (s), 134.3 (s), 135.7 (d), 166.0 (s); IR ($CHCl_3$) (cm^{-1}) 3449, 2944, 1716, 1272; MS *m*/*z* (relative intensity) 492 $(M - 57)^+$ (3), 199 (27), 135 (22), 105 (100). Anal. Calcd for $C_{32}H_{40}O_6Si$ C, 70.04; H, 7.35. Found C, 70.06; H, 7.42.

Preparation of (1*R*)-1-[[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]methyl]-3-(methoxycarbonyl)-(*E*)-allyl Benzoate (89). The general procedure to transform 3-benzoyloxy 1,2-diols into γ-(benzoyloxy)-(*E*)-α,β-unsaturated esters was applied to **88** on a 1.2 g (2.8 mmol) scale, yielding **89** (1.14 g, 71% yield) as an oil: $[\alpha]^{25}_D = -27.2$ (*c* 2.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 1.44 (m, 3 H), 1.70 (m, 1 H), 1.83 (m, 1 H), 2.35 (m, 1 H), 3.24 (m, 2 H), 3.39 (m, 1 H), 3.70 (d, *J* = 11.5 Hz, 1 H), 3.77 (s, 3 H), 5.85 (m, 1 H), 6.06 (d, *J* = 15.7 Hz, 1 H), 7.00 (dd, *J* = 15.7, 5.6 Hz, 1 H), 7.40 (m, 8 H), 7.57 (m, 1 H), 7.66 (m, 4 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 25.3 (t), 27.0 (s), 33.2 (t), 36.7 (t), 51.6 (q), 67.3 (t), 71.2 (d), 72.1 (d), 79.4 (d), 121.2 (d), 127.5 (d), 127.7 (d), 128.3 (d), 129.6 (d), 130.2 (s), 133.0 (d), 133.5 (s), 134.2 (s), 135.9 (d), 145.6 (d), 165.4 (s), 166.5 (s); IR ($CHCl_3$) (cm^{-1}) 3075, 2957, 1719, 1659; MS *m*/*z* (relative intensity) 515 $(M - 57)^+$ (4), 303 (48), 105 (100). Anal. Calcd for $C_{34}H_{40}O_6Si$ C, 71.30; H, 7.04. Found C, 71.05; H, 7.19.

General Method for Silyl Cleavage. Preparation of (1*R*)-1-[[(2*S*,3*R*)-3-Hydroxytetrahydropyran-2-yl]methyl]--3-(methoxycarbonyl)-(*E*)-allyl Benzoate (90). To a stirred mixture of **89** (750 mg, 1.3 mmol) in CH_3CN (10 mL) was added HF (3 mL, 48% in aqueous solution) at rt. The reaction was stirred for 12 h, until TLC showed complete conversion. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography to afford **90** (400 mg, 92% yield) as an oil: $[\alpha]^{25}_D = -58.1$ (*c* 1.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 1 H), 1.63 (m, 2 H), 2.04 (m, 2 H), 2.18 (br s, 1 H), 2.31 (m, 1 H), 3.14 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1 H), 3.24 (m, 2 H), 3.34 (m, 1 H), 3.72 (s, 3 H), 3.81 (m, 1 H), 5.89 (m, 1 H), 6.07 (d, *J* = 15.7 Hz, 1 H), 7.03 (dd, *J* = 15.7, 5.5 Hz, 1 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 32.9 (t), 36.6 (t), 51.7 (q), 67.5 (t), 70.8 (d), 71.0 (d), 79.2 (d), 121.2 (d), 128.4 (d), 129.7 (d), 129.9 (s), 133.1 (d), 145.5 (d), 165.6 (s), 166.5 (s); IR ($CHCl_3$) (cm^{-1}) 3529, 2948, 1718, 1659; MS *m*/*z* (relative intensity) 335 $(M + 1)^+$ (1), 213 (39), 105 (99), 71 (100). Anal. Calcd for $C_{18}H_{22}O_6$ C, 64.64; H, 6.64. Found C, 64.42; H, 6.76.

Preparation of (1*R*)-1-[[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsiloxy)tetrahydropyran-2-yl]methyl]-3-(methoxycarbonyl)-(*Z*)-allyl Benzoate (91). The general procedure to transform 3-benzoyloxy 1,2-diols into γ-(benzoyloxy)-(*Z*)-α,β-unsaturated esters was applied to **88** on a 1.2 g (2.8 mmol) scale, yielding **91** (1.2 g, 75% yield) as an oil: $[\alpha]^{25}_D = -30.7$ (*c* 1.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 1.75 (m, 1 H), 1.44 (m, 3 H), 1.79 (m, 1 H), 2.52 (dd, *J* = 14.5, 6.3 Hz, 1 H), 3.23 (dd, *J* = 10.7,10.7 Hz, 1 H), 3.43 (m, 2 H), 3.67 (d, *J* = 11.4 Hz, 1 H), 3.76 (s, 3 H), 5.89 (d, *J* = 11.7 Hz, 1 H), 6.27 (dd, *J* = 11.7, 8.4 Hz, 1 H), 6.68 (m, 1 H), 7.36 (m, 4 H), 7.43 (m, 4 H), 7.54 (m, 1 H), 7.68 (m, 4 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.3 (t), 27.0 (q), 33.2 (t), 36.5 (t), 51.4 (q), 67.2 (d), 70.3 (d), 71.9 (d), 79.8 (d), 119.9 (d), 127.4 (d), 127.6 (d), 128.3 (d), 129.6 (d), 130.6 (s), 132.7 (d), 133.6 (s), 134.5 (s), 135.8 (d), 147.0 (d), 165.7 (s), 165.8 (s); IR ($CHCl_3$) (cm^{-1}) 3071, 2955, 1719, 1652; MS *m*/*z* (relative intensity) 515 $(M - 57)^+$ (30), 303 (52), 105 (100). Anal. Calcd for $C_{34}H_{40}O_6Si$ C, 71.30; H, 7.04. Found C, 71.23; H, 7.29.

Preparation of (1*R*)-1-[[(2*S*,3*R*)-3-Hydroxytetrahydropyran-2-yl]methyl]-3-(methoxycarbonyl)-(*Z*)-allyl Benzoate (92). Using the procedure described above to cleave silyl ethers, **91** (835 mg, 1.46 mmol) yielded **92** (458 mg, 94% yield) as an oil: $[\alpha]^{25}_D = -54.0$ (*c* 2.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 1 H), 1.64 (m, 2 H), 2.08 (m, 2 H), 2.30 (ddd, *J* = 14.6, 4.4, 4.4 Hz, 1 H), 2.67 (br s, 1 H), 3.28 (m, 2 H), 3.40 (m, 1 H), 3.75 (s, 3 H), 3.81 (d, *J* = 9.9 Hz, 1 H), 5.88 (d, *J* = 11.6 Hz, 1 H), 6.29 (dd, *J* = 11.6, 7.8 Hz, 1 H), 6.62 (dd, *J* = 12.4, 7.5 Hz, 1 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 32.6 (t), 37.8 (t), 51.7 (q), 67.5 (t), 70.8 (d), 71.0 (d), 79.4 (d), 119.7 (d), 128.3 (d), 129.6 (d), 130.2 (s), 133.0 (d), 148.1 (d), 166.0 (s), 166.2 (s); IR ($CHCl_3$) (cm^{-1}) 3516, 2948, 1716, 1645; MS *m*/*z* (relative intensity) 335 $(M + 1)^+$ (2), 213 (76), 105 (100), 77 (100). Anal. Calcd for $C_{18}H_{22}O_6$ C, 64.64; H, 6.64. Found C, 64.56; H, 6.88.

Preparation of (2*R*,3*S*,4a*R*,8a*R*)-2-[(Methoxycarbonyl)-methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (93). The general cyclization method was applied to **67** (85 mg, 0.25 mmol) to afford **93** (74 mg, 87% yield) as an oil: $[\alpha]^{25}_D = +44.1$ (*c* 2.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 1 H), 1.68 (m, 1 H), 1.95 (m, 2 H), 2.15 (m, 2 H), 2.63 (m, 2 H), 3.47 (m, 1 H), 3.67 (s, 3 H), 3.75 (m, 1 H), 3.82 (m, 2 H), 4.46 (ddd, *J* = 8.9, 5.2, 5.2 Hz, 1 H), 4.90 (dd, *J* = 10.4, 5.2 Hz, 1 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.1 (t), 26.2 (t), 28.9 (t), 36.3 (t), 51.8 (q), 65.1 (t), 66.9 (d), 69.1 (d),

69.9 (d), 70.9 (d), 128.2 (d), 129.7 (d), 130.2 (s), 132.9 (d), 165.7 (s), 170.9 (s); IR ($CHCl_3$) (cm^{-1}) 3019, 2948, 1716, 1277; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (6), 212 (44), 303 (40), 105 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.46; H, 7.02.

Preparation of (2*R*,3*R*,4a*R*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (94). The general cyclization method was applied to **71** (112 mg, 0.3 mmol) to afford **94** (101 mg, 90% yield) as an oil: $[\alpha]^{25}_D = +46.3$ (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (d, $J = 5.2$ Hz, 1 H), 1.64 (ddd, $J = 12.8, 12.8, 3.4$ Hz, 1 H), 1.92 (m, 3 H), 2.22 (m, 1 H), 2.65 (dd, $J = 14.9, 5.2$ Hz, 1 H), 2.83 (dd, $J = 14.9, 9.2$ Hz, 1 H), 3.43 (ddd, $J = 11.2, 11.2, 2.0$ Hz, 1 H), 3.59 (s, 3 H), 3.68 (s, 1 H), 3.73 (s, 1 H), 3.95 (d, $J = 10.9$ Hz, 1 H), 4.73 (m, 1 H), 5.60 (m, 1 H), 7.42 (m, 2 H), 7.54 (m, 1 H), 7.97 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 27.5 (t), 30.0 (t), 32.5 (t), 51.8 (q), 65.1 (d), 66.8 (d), 67.3 (t), 70.2 (d), 72.3 (d), 128.3 (d), 129.6 (d), 129.9 (s), 133.1 (d), 165.2 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3013, 2955, 1723, 1271; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (3), 212 (53), 111 (27), 105 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.91; H, 6.73.

Preparation of (2*R*,3*S*,4a*S*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (95). The general cyclization method was applied to **86** (94 mg, 0.28 mmol) to afford **95** (83 mg, 88% yield) as a solid: mp = 88−89 °C; $[\alpha]^{25}_D = +6.7$ (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.54 (m, 1 H), 1.76 (m, 2 H), 1.87 (m, 1 H), 1.96 (m, 1 H), 2.25 (dd, $J = 11.2, 2.9$ Hz, 1 H), 2.65 (dd, $J = 14.7, 6.0$ Hz, 1 H), 2.93 (dd, $J = 14.7, 9.3$ Hz, 1 H), 3.42 (m, 3 H), 3.73 (s, 3 H), 3.92 (dd, $J = 11.3, 1.7$ Hz, 1 H), 4.49 (dd, $J = 9.3, 6.1$ Hz, 1 H), 5.21 (dd, $J = 2.3, 2.3$ Hz, 1 H), 7.44 (m, 2 H), 7.58 (m, 1 H), 8.06 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.7 (t), 29.4 (t), 30.3 (t), 35.1 (t), 52.0 (q), 68.1 (t), 70.9 (d), 71.7 (d), 72.8 (d), 74.4 (d), 128.3 (d), 129.7 (d), 130.0 (s), 133.1 (d), 165.6 (s), 170.3 (s); IR ($CHCl_3$) (cm^{-1}) 3026, 2948, 1716, 1275; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (10), 212 (79), 105 (100), 77 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.63; H, 6.59.

Preparation of (2*S*,3*R*,4a*S*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (96). The general cyclization method was applied to **92** (108 mg, 0.32 mmol) to afford **96** (96 mg, 89% yield) as a solid: mp = 76−77 °C; $[\alpha]^{25}_D = -39.2$ (*c* 3.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (m, 1 H), 1.70 (m, 3 H), 2.08 (dd, $J = 12.0, 2.8$ Hz, 1 H), 2.51 (dd, $J = 15.6, 8.2$ Hz, 1 H), 2.55 (m, 1 H), 2.62 (dd, $J = 15.6, 4.0$ Hz, 1 H), 3.13 (ddd, $J = 10.4, 10.4, 4.0$ Hz, 2 H), 3.40 (m, 1 H), 3.59 (s, 3 H), 3.92 (dd, $J = 9.2, 2.0$ Hz, 1 H), 4.02 (ddd, $J = 8.2, 8.2, 4.0$ Hz, 1 H), 4.91 (ddd, $J = 10.4, 10.4, 4.8$ Hz, 1 H), 7.45 (m, 2 H), 7.58 (m, 1 H), 8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.3 (t), 29.1 (t), 35.5 (t), 37.7 (t), 51.7 (q), 67.9 (t), 71.0 (d), 76.2 (d), 78.1 (d), 128.3 (d), 128.5 (d), 129.6 (d), 129.7 (s), 133.3 (d), 165.3 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3026, 2952, 2872, 1721; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (1), 212 (43), 105 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.48; H, 6.65.

Preparation of (2*S*,3*R*,4a*R*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (97). The general cyclization method was applied to **73** (92 mg, 0.27 mmol) to afford **97** (81 mg, 88% yield) as a solid: mp = 82−83 °C; $[\alpha]^{25}_D = -22.1$ (*c* 1.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (m, 1 H), 1.62 (ddd, $J = 12.1, 12.1, 4.4$ Hz, 1 H), 1.74 (ddd, $J = 11.3, 11.3, 3.3$ Hz, 1 H), 1.96 (m, 2 H), 2.44 (dd, $J = 13.1, 4.8$ Hz, 1 H), 2.60 (m, 2 H), 3.40 (dd, $J = 11.3, 11.3$ Hz, 1 H), 3.54 (s, 1 H), 3.58 (s, 3 H), 3.99 (m, 2 H), 5.13 (m, 1 H), 7.41 (m, 2 H), 7.54 (m, 1 H), 7.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.4(t), 28.3 (t), 35.4 (t), 38.0 (t), 51.5 (q), 68.1 (t), 69.1 (d), 72.3 (d), 73.3 (d), 76.1 (d), 128.3 (d), 129.6 (d), 129.9 (s), 133.0 (d), 165.2 (s), 171.7 (s); IR ($CHCl_3$) (cm^{-1}) 3003, 2957, 1718, 1266; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (2), 212 (98), 139 (45), 105 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.72; H, 6.73.

Preparation of (2*R*,3*R*,4a*S*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (98). The general cyclization method was applied to **90** (98 mg, 0.29 mmol) to afford **98** (88 mg, 90% yield) as a solid: mp = 79−80 °C; $[\alpha]^{25}_D = +28.6$ (*c* 3.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (m, 1 H), 1.76 (m, 2 H), 1.97 (dd, $J = 12.0, 3.2$ Hz, 1 H), 2.33 (ddd, $J = 12.0, 4.4, 4.4$ Hz, 1 H), 2.76 (dd, $J = 14.8, 5.6$ Hz, 1 H), 2.90 (dd, $J = 14.8, 8.8$ Hz, 1 H), 3.11 (m, 1 H), 3.29 (m, 1 H), 3.40 (ddd, $J = 11.6, 11.6, 4.4$ Hz, 1 H), 3.59 (s, 3 H), 3.91 (dd, $J = 11.2, 4.0$ Hz, 1 H), 4.69 (dd, $J = 5.6, 2.8$ Hz, 1 H), 5.39 (ddd, $J = 12.8, 5.2, 5.2$ Hz, 1 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 7.97 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.9 (t), 29.7 (t), 31.2 (t), 32.7 (t), 52.2 (q), 68.4 (t), 68.9 (d), 70.7 (d), 71.0 (d), 77.0 (d), 128.8 (d), 130.0 (s), 130.0 (d), 133.7 (d), 165.4 (s), 170.7 (d); IR ($CHCl_3$) (cm^{-1}) 3026, 2953, 1723, 1271; MS *m/z* (relative intensity) 335 $(M + 1)^+$ (7), 212 (27), 105 (100), 77 (83). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.82; H, 6.56.

Preparation of (2*S*,3*R*,4a*R*,8a*R*)-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]octahydropyrano[3,2-*b*]pyran-3-ol (103). The general method for reduction of esters was applied to **97** on a 180 mg (0.54 mmol) scale using $LiAlH_4$ (1.1 mL, 1.0 M in ether, 1.1 mmol) to afford **102** as an oil. The crude was dissolved in dry CH_2Cl_2 (5 mL) under argon, and imidazole (110 mg, 1.6 mmol) and *tert*-butylchlorodiphenylsilane (0.3 mL, 1.1 mmol) were sequentially added at rt. After 1 h TLC showed complete conversion. The solvent was evaporated, and the crude was purified by silica gel column chromatography to yield **103** (170 mg, 72% yield based on **97**) as an oil: $[\alpha]^{25}_D = -8.9$ (*c* 1.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.26 (dd, $J = 7.3, 7.3$ Hz, 1 H), 1.61 (m, 2 H), 1.89 (m, 3 H), 2.04 (m, 1 H), 2.27 (dd, $J = 10.4, 3.0$ Hz, 1 H), 3.24 (m, 1 H), 3.37 (s, 1 H), 3.42 (dd, $J = 12.4, 12.4$ Hz, 1 H), 3.55 (s, 1 H), 3.79 (m, 1 H), 3.85 (m, 2 H), 3.98 (dd, $J = 11.4, 2.1$ Hz, 1 H), 7.41 (m, 4 H), 7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (s), 20.6 (t), 26.7 (q), 28.6 (t), 36.5 (t), 38.0 (t), 61.0 (t), 66.3 (d), 68.2 (t), 71.8 (d), 74.0 (d), 80.5 (d), 127.7 (d), 129.7 (d), 133.0 (s), 135.5 (d); IR ($CHCl_3$) (cm^{-1}) 3394, 3006, 2956, 1426; MS *m/z* (relative intensity) 383 $(M - 57)^+$ (7), 365 (48), 199 (100), 149 (95). Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.24. Found: C, 70.96; H, 8.48.

Preparation of (2*S*,4a*R*,8a*R*)-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]hexahydropyrano[3,2-*b*]pyran-3-one (104). To a stirred solution of **103** (146 mg, 0.3 mmol) in dry CH_2Cl_2 (1.5 mL) were sequentially added NaOAc (5 mg, 0.07 mmol) and PCC (140 mg, 0.7 mmol) at rt. The reaction was stirred overnight until TLC showed complete conversion. After this time the reaction mixture was diluted with ether (10 mL), filtered through a pad of Celite, concentrated, and purified by silica gel column chromatography to afford **104** (130 mg, 90% yield) as an oil: $[\alpha]^{25}_D = -6.5$ (*c* 2.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.30 (dd, $J = 11.2, 2.1$ Hz, 1 H), 1.76 (m, 2 H), 1.94 (m, 1 H), 2.03 (dd, $J = 13.1, 3.2$ Hz, 1 H), 2.27 (m, 1 H), 2.60 (dd, $J = 4.3, 4.3$ Hz, 2 H), 3.45 (ddd, $J = 12.5, 12.5, 2.3$ Hz, 1 H), 3.79 (m, 2 H), 3.90 (m, 2 H), 3.97 (dd, $J = 11.2, 4.4$ Hz, 1 H), 4.11 (m, 1 H), 7.40 (m, 4 H), 7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 20.2 (t), 26.8 (q), 28.2 (t), 32.1 (t), 44.8 (t), 59.6 (t), 68.2 (t), 71.3 (d), 76.0 (d), 78.5 (d), 127.5 (d), 129.5 (d), 133.9 (s), 134.0 (s), 135.5 (d), 206.0 (s); IR ($CHCl_3$) (cm^{-1}) 3077, 2959, 1729, 1428; MS *m/z* (relative intensity) 381 $(M - 57)^+$ (15), 303 (55), 199 (100), Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.20; H, 7.82. Found: C, 71.04; H, 7.88.

Preparation of (2*S*,3*S*,4a*R*,8a*R*)-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]octahydropyrano[3,2-*b*]pyran-3-ol (105). To a stirred solution of **104** (80 mg, 0.18 mmol) in dry ether (1.5 mL) was added $LiAlH_4$ (0.1 mL, 1.0 M in ether, 0.1 mmol) at −78 °C. After 5 min, H_2O (0.1 mL), a 15% aqueous NaOH solution (0.1 mL), and H_2O (0.3 mL) were sequentially added to the reaction mixture with vigorous stirring. The mixture was allowed to reach rt, dried over $MgSO_4$, filtered through a pad of Celite, concentrated, and purified by silica gel column chromatography to yield **105** (68 mg, 85% yield) as an oil: $[\alpha]^{25}_D = -17.1$ (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.29 (m, 1 H), 1.62 (m, 1 H), 1.77 (d, $J = 13.7$ Hz, 1 H), 1.85 (m, 1 H), 1.98 (m, 3 H), 2.17 (d, $J = 13.7$ Hz, 1 H), 3.37 (dd, $J = 11.5$ Hz, 1 H), 3.40 (s, 1 H), 3.47 (s, 1 H), 3.51 (s, 1 H), 3.62 (dd, $J = 8.5, 4.6$ Hz, 1 H), 3.79 (m, 1 H), 3.88 (m, 1 H), 4.00 (dd, $J = 11.3, 2.1$ Hz, 1 H), 7.39 (m, 6 H), 7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 20.6 (t), 26.9 (q), 29.0 (t), 34.9 (t), 35.8 (t), 60.3 (t), 66.4 (d), 68.6 (t), 72.3 (d), 73.1 (d), 76.3 (d), 127.5 (d), 129.5 (d), 134.0 (s), 135.4 (d); IR ($CHCl_3$) (cm^{-1}) 3503, 3077, 2957, 1426; MS *m/z* (relative intensity) 441 (M +

1)$^+$ (1), 199 (67), 149 (92), 55 (100). Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.24. Found: C, 70.51; H, 8.20.

Preparation of (2*S*,3*R*,4a*S*,8a*R*)-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]octahydropyrano[3,2-*b*]pyran-3-ol (107). The general method for reduction of esters was applied to **96** on a 100 mg (0.3 mmol) scale using $LiAlH_4$ (0.4 mL, 1.0 M in ether, 0.4 mmol) to afford **106** as an oil. The crude was dissolved in dry CH_2Cl_2 (3 mL) under argon, and imidazole (60 mg, 0.9 mmol) and *tert*-butylchlorodiphenylsilane (0.15 mL, 0.6 mmol) were added at rt. After 1 h TLC showed complete conversion. The solvent was evaporated, and the crude was purified by silica gel column chromatography to yield **107** (99 mg, 75% yield based on **96**) as an oil: $[\alpha]^{25}_D = -16.5$ (*c* 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.26 (s, 1 H), 1.39 (m, 1 H), 1.50 (m, 1 H), 1.70 (m, 1 H), 1.83 (m, 1 H), 2.00 (m, 2 H), 2.39 (m, 1 H), 2.98 (m, 2 H), 3.27 (m, 1 H), 3.78 (m, 1 H), 3.53 (m, 1 H), 3.84 (dd, J = 4.1, 4.1 Hz, 2 H), 3.92 (d, J = 10.5 Hz, 1 H), 7.41 (m, 6 H), 7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.1 (s), 25.5 (t), 26.7 (q), 29.2 (t), 36.3 (t), 38.4 (t), 61.0 (t), 67.8 (t), 69.9 (d), 77.0 (d), 77.6 (d), 80.7 (d), 127.7 (d), 129.8 (d), 133.0 (s), 135.5 (d); IR ($CHCl_3$) (cm^{-1}) 3374, 3010, 2933, 1110; MS *m*/*z* (relative intensity) 383 (M − 57)$^+$ (16), 199 (55), 97 (100). Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.24. Found: C, 70.86; H, 8.41.

Preparation of (2*S*,3*S*,4a*S*,8a*R*)-2-(2-Hydroxyethyl)octahydropyrano[3,2-*b*]pyran-3-yl 4-Nitro-benzoate (109). To a stirred solution of **107** (40 mg, 0.1 mmol) in dry benzene (1 mL) were sequentially added Ph_3P (52 mg, 0.2 mmol), *p*-nitrobenzoic acid (30 mg, 0.18 mmol), and diisopropyl azodicarboxylate (0.04 mL, 0.2 mmol) at rt. The stirred mixture was maintained for 5 h at 50 °C after which time it was concentrated and the crude purified by silica gel column chromatography to give **109** (46 mg, 78% yield) as an oil: $[\alpha]^{25}_D = -7.3$ (*c* 0.92, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 1.06 (s, 9 H), 1.26 (m, 2 H), 1.57 (m, 2 H), 1.75 (m, 2 H), 2.34 (d, J = 10.2 Hz, 1 H), 3.10 (m, 1 H), 3.30 (m, 1 H), 3.42 (m, 1 H), 3.74 (m, 1 H), 3.84 (m, 1 H), 3.93 (m, 2 H), 5.30 (s, 1 H), 7.28 (m, 6 H), 7.70 (m, 4 H), 7.83 (m, 4 H); ^{13}C NMR (C_6D_6) δ 19.2 (s), 25.6 (t), 26.8 (q), 29.6 (t), 34.6 (t), 34.7 (t), 60.3 (t), 67.7 (t), 72.9 (d), 74.7 (d), 74.8 (d), 78.4 (d), 123.2 (d), 129.7 (d), 130.3 (d), 133.9 (s), 135.0 (s), 135.6 (d), 150.4 (s), 163.6 (s); IR ($CHCl_3$) (cm^{-1}) 3568, 2955, 1720, 1271; MS *m*/*z* (relative intensity) 532 (M − 57)$^+$ (2), 167 (52), 150 (33), 97 (100). Anal. Calcd for $C_{33}H_{39}NO_7$: C, 67.20; H, 6.67; N, 2.38. Found: C, 66.96; H, 7.02; N, 2.36.

Preparation of (2*S*,3*S*,4a*S*,8a*R*)-2-[(Methoxycarbonyl)methyl]octahydropyrano[3,2-*b*]pyran-3-yl Benzoate (110). To a solution of the fused bicycle **95** (45 mg, 0.13 mmol) in dry THF (1.3 mL) was added NaH (12 mg, 0.4 mmol, 80% in mineral oil) at rt. The reaction mixture was stirred for 12 h, after which time TLC showed complete conversion. Then to the reaction mixture were sequentially added HOAc (50 μL) and H_2O (5 mL). The mixture was extracted with ether (3 × 10 mL), and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography, yielding **110** (39 mg, 90% yield) as an oil: $[\alpha]^{25}_D = +12.0$ (*c* 1.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 1 H), 1.76 (m, 2 H), 1.82 (ddd, J = 12.8, 12.8, 2.8 Hz, 1 H), 2.07 (m, 1 H), 2.35 (ddd, J = 13.8, 3.4, 3.4 Hz, 1 H), 2.51 (dd, J = 16.1, 5.2 Hz, 1 H), 2.64 (dd, J = 16.1, 8.1 Hz, 1 H), 3.20 (ddd, J = 10.8, 10.8, 4.2 Hz, 1 H), 3.33 (m, 1 H), 3.40 (m, 1 H), 3.66 (s, 3 H), 3.90 (dd, J = 13.3, 3.6 Hz, 1 H), 4.13 (m, 1 H), 5.35 (s, 1 H), 7.46 (m, 2 H), 7.58 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 29.2 (t), 34.4 (t), 36.5 (t), 51.8 (q), 68.0 (t), 70.9 (d), 74.2 (d), 74.9 (d), 78.4 (d), 128.4 (d), 129.7 (d), 129.9 (s), 133.2 (d), 165.7 (s), 171.1 (s); IR ($CHCl_3$) (cm^{-1}) 3023, 2954, 1716; MS *m*/*z* (relative intensity) 335 (M + 1)$^+$ (1), 111 (98), 105 (100). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.64. Found: C, 64.49; H, 6.83.

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Supporting Information Available: NMR spectra for the compounds **1**, **3**−**6**, **8**−**13**, **20**−**24**, **26**−**30**, **32**, **34**−**36**, **38**, **40**, **93**−**98**, **105**, and **110** and experimental details for the synthesis of **44**−**50**, **55**−**73**, and **81**−**86** (58 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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