Intramolecularly Competitive Ireland-Claisen Rearrangements: Scope and Potential Applications to Natural Product Synthesis

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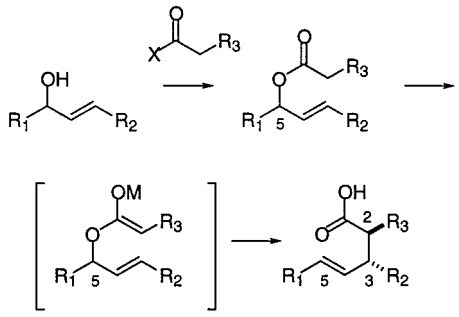
A variety of bis-allylic esters were prepared by vinylmetal addition to cycloalkenones followed by esterification either in situ or in a separate operation. For chiral cyclohexenones, the vinyl additions generally occurred with >10:1 diastereoselectivity. Although in some cases the bis-allylic esters proved to be sensitive to silica gel or other adsorbents, all of the esters examined could be isolated in acceptable purity. The Ireland-Claisen rearrangement of the bis-allylic esters occurred with complete regioselectivity via the exocyclic alkene. The alkene stereochemistry and the stereochemistry at C-2 and C-3 of the pentenoic acid products were consistent with a chairlike transition state in the rearrangement. Substituents at the carbons adjacent to the allylic carbinol carbon (i.e., C-2 or C-6 in cyclohexenone-derived substrates) directed the stereochemical course of the rearrangement. The rearrangements generally proceeded so as to place the larger of the C-2 or C-6 substituents in the pseudoequatorial position with respect to the chairlike transition state. For a bis-allylic ester bearing both a C-2-CH_3 and a C-6-OMEM substituent, the rearrangement product resulted from the nominally smaller OMEM substituent occupying a pseudoequatorial position with respect to the chairlike transition state.

Introduction

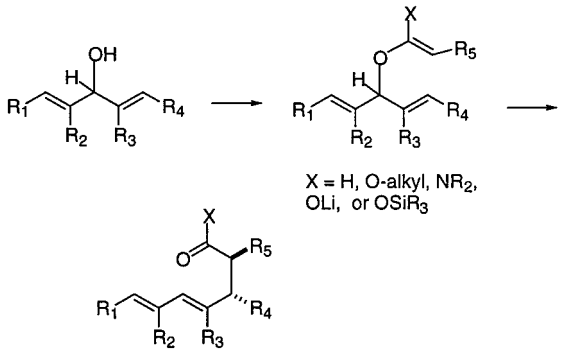
Since its development in the mid 1970s, the Ireland-Claisen rearrangement has become widely used in the synthesis of a diverse range of natural products and other targets (Scheme 1).[1,2] The popularity of the reaction is due to several factors: (i) the ease of preparation of the allylic ester reactants; (ii) the ability to control the *E*/*Z* geometry of the ester enolate and hence the relative stereochemistry between C-2 and C-3 of the pentenoic acid product; (iii) the generally high chirality transfer between the allylic stereocenter of the allyl ketene acetal (C-5, pentenoic acid numbering) and the newly formed stereocenter(s) at C-2 and C-3 of the pentenoic acid.

Claisen Rearrangements of Bis-allylic Substrates. Another noteworthy feature of the Claisen rearrangement is that the 1,2-transposition of the alkene may result in the formation of a new functional group array with different reactivity than the starting alkene. In particular, Claisen rearrangement of bis-allyl vinyl ethers and related compounds results in the formation of 1,3-dienes (Scheme 2). In 1965 Reed reported the first example of a Claisen rearrangement of a bis-allylic substrate.[3] The Claisen rearrangement of the bis-allyl vinyl ether derived from penta-1,4-dien-3-ol (R_1−R_5, X = H) afforded 4,6-heptadienal. Soon thereafter, Cresson et al. demonstrated that unsymmetrical bis-allyl vinyl ethers undergo Claisen rearrangement with moderate to high regioselectivity.[4] Parker and Farmar subsequently reported that Johnson, Eschenmoser, and Ireland variants of the Claisen rearrangement of unsymmetrical bis-

Scheme 1



Scheme 2



(1) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877; Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650−657.

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(3) (a) Reed, S. F., Jr. *J. Org. Chem.* **1965**, *30*, 1663−1665. (b) See also: Spino, C.; Crawford, J. *Tetrahedron Lett.* **1994**, *35*, 5559−5562; Baillie, L. C.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2487−2488 and ref 8b.

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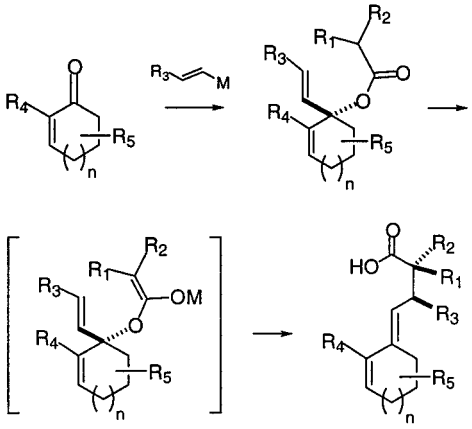
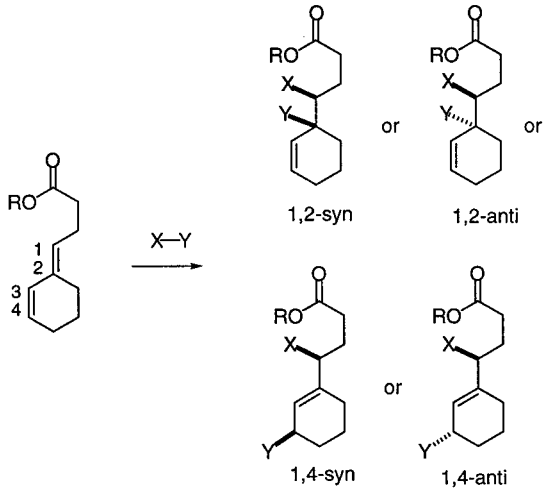
Scheme 3



Scheme 4



allylic substrates could be highly regio- and stereoselective.[5] Yamamoto et al. described a novel reagent-controlled Claisen rearrangement of bis-allyl vinyl ethers which resulted in regioselectivities opposite to those obtained in the thermal reaction.[6] Tanis et al. reported an Ireland-Claisen rearrangement of bis-allyl silyl ketene acetals in which the regioselectivity of the Ireland-Claisen rearrangement was strongly influenced by the substituents on the silyl group.[7]

In 1980 Hudlicky et al. used the Johnson-Claisen rearrangement of a bis-allyl ketene acetal in the synthesis of hirsutene, using the resulting diene to prepare a key vinylcyclopropane intermediate.[8] In 1986 Parker and Farmar employed the Ireland-Claisen rearrangement of a bis-allyl ketene acetal in the total synthesis of biflora-4,10(19),15-triene.[5b] The 1,3-diene formed in the Ireland-Claisen rearrangement was used in a subsequent intramolecular Diels–Alder reaction. In 1988 Wender et al. employed the Ireland-Claisen rearrangement of a bis-allylic ester in the synthesis of (+)-asteriscanolide.[9] The 1,3-diene was used in a [4 + 4] cycloaddition to install the cyclooctane ring.

In all of the above examples, the bis-allylic substrates were invariably derived from aldehydes or, in one case,[8c] an acyclic ketone. We became intrigued with the possibility of a variant of the Ireland-Claisen rearrangement in which the carbinol center of the bis-allylic ester would be contained within a cycloalkene ring (Scheme 3). The product of such a rearrangement occurring via the exocyclic alkene would be an alkylidene cycloalkene. Such adducts possess some attractive structural features. First, diastereoselective 1,2-addition of the exocyclic vinyl group[10] followed by Ireland-Claisen rearrangement could result in a net 1,*m*-stereocontrol ($m = 4-7$) between stereocenters endocyclic and exocyclic to the cycloalkene ring.

Second, the rigid diene framework might allow for the stereoselective addition of various reagents X–Y across the diene in either a 1,2- or 1,4-fashion (Scheme 4) (substituents are removed for clarity).[11] This would also enable the control of the relative stereochemistry of stereocenters which are endocyclic and exocyclic to the ring.

We envisioned that appropriately substituted pentenoic acids would be useful intermediates in the total synthesis of various natural product targets, including eunicellin diterpenes[12] such as eleutherobin[13,14] (**1**) and members of the eupomatilone family of lignans such as eupomatilone-6 (**2**) (Scheme 5).[15] The Ireland-Claisen rearrangement might be used to establish the C-7/C-8 stereochem-

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(12) For reviews, see: Wahlberg, I.; Eklund, A.-M. *Prog. Chem. Org. Nat. Prod.* **1992**, *60*, 1–141. Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531–556.

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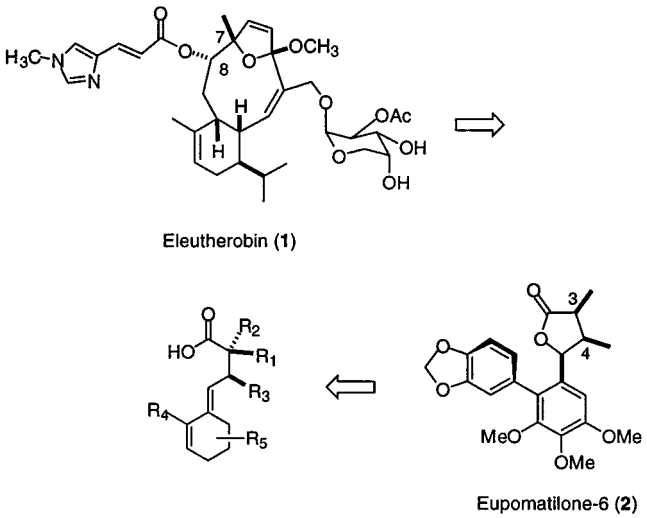
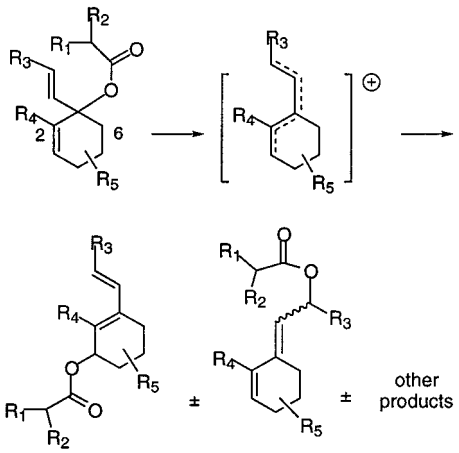
Scheme 5



Scheme 6



istry of eleutherobin and the C-3/C-4 stereochemistry of eupomatilone-6.

At the outset of this project, we recognized that there were four issues we would have to address: (i) synthesis and stability of the bis-allylic esters, (ii) regioselectivity of the Ireland-Claisen rearrangement, (iii) alkene stereoselectivity, and (iv) chirality transfer.

Interestingly, prior to our initial communication,[16] only one report of the synthesis of bis-allylic esters of the requisite type had been disclosed.[17] The desired bis-allylic ester reactants are not only tertiary, but would be further hindered by substitution at C-2 and/or C-6. Allylic rearrangement or decomposition of the bis-allylic esters or their alcohol precursors via the corresponding pentadienyl cation during their synthesis or purification was a concern (Scheme 6).[18] In the earlier report,[17] the esters were substituted with one or more electron-withdrawing groups, which would inductively suppress formation of the pentadienyl cation.

The desired regioselectivity, alkene stereoselectivity, and chirality transfer of the Ireland-Claisen rearrangement were rationalized by analysis of the possible transition states (Scheme 7).[19] Although both endocyclic[1,2] and exocyclic[20] Claisen rearrangements of substrates which lacked the competing alkene had been reported, we reasoned that the exocyclic rearrangement would be the favored pathway. Chair transition states **a** and **b** leading to the alkylidene cycloalkenes have fewer eclipsing and/or transannular interactions relative to transition states **c** and **d** leading to the endocyclic products.[19] We also reasoned that the preferred exocyclic transition state would depend on the substitution at C-2 and/or C-6 of the cyclohexene ring of the bis-allylic ester. The ring carbon with the larger substituent should adopt a pseudoequatorial disposition relative to the chairlike Claisen rearrangement transition state. Ketene acetals substituted at C-2 should rearrange predominantly through transition state **b** leading to the *E*-alkene, whereas those substituted at C-6 would rearrange through transitions state **a** leading to the *Z*-alkene (for the sake of uniformity *Z* and *E* will refer to the alkylidene stereochemistry with respect to the endocyclic alkene irrespective of CIP rules throughout this manuscript). Finally, chirality transfer from the C-1 carbinol center to the newly formed stereocenters should follow directly from the same chairlike transition states.

Results and Discussion

General Features of Bis-allylic Ester Synthesis. As expected, the bis-allylic ester precursors of the Ireland-Claisen rearrangement were sometimes prone to allylic rearrangement or decomposition. Endocyclic allylic rearrangement products were readily identifiable in the ^{1}H NMR spectra by the downfield shift of the conjugated exocyclic vinyl resonances relative to the bis-allylic isomer (cf. Scheme 6). Allylic rearrangement sometimes occurred during chromatography on silica gel or less acidic alternatives such as Florisil. Purification was generally achieved by rapid flash chromatography over alumina or over silica gel pretreated with 2−3% of ethylenediamine (see Experimental Section), although several of the esters were sufficiently pure to be used in the Claisen rearrangement without chromatography. In some cases allylic rearrangement products were obtained directly in the crude reaction mixtures during attempts at in situ acylation of the vinylmetal addition products. The allylic rearrangement was presumably catalyzed by metal salts. In those cases, the intermediate alcohols were isolated and the esters were prepared in a separate operation.

There proved to be no single general procedure that reliably afforded the bis-allylic esters. We have thus far developed three different procedures for their synthesis: (i) in situ acylation of the intermediate alkoxide resulting from vinylmetal addition to the cycloalkenone; (ii) treatment of the purified alcohol with strong base (^{n}BuLi or

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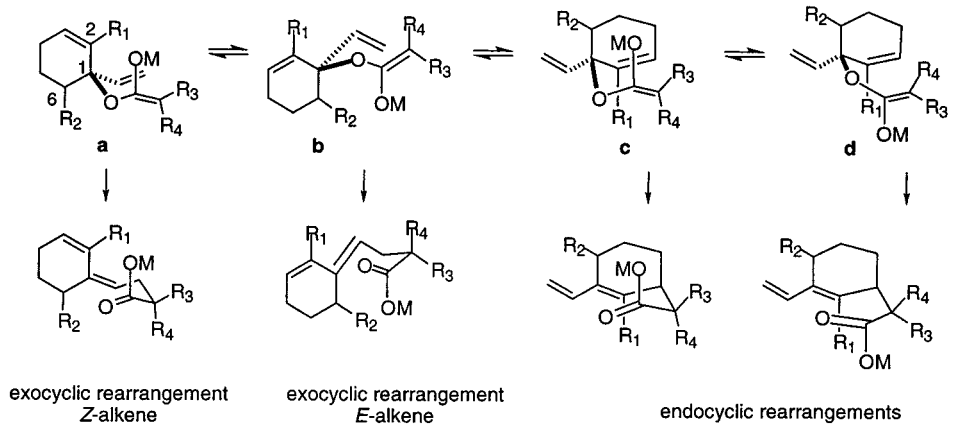
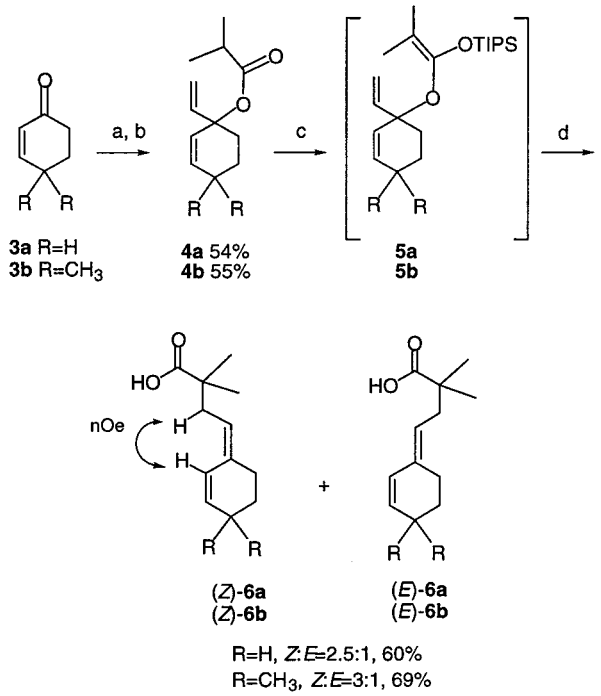
(19) (a) Ground state conformations are depicted rather than transition states for the sake of clarity. (b) The exocyclic boat transition states would be too high in energy due to severe flagpole interactions between the R_4 substituent and the cycloalkene ring.

(20) (a) Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2618−2628; *Ibid*, 2629−2635. Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 2095−2100. (b) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418−5420.

Scheme 7



Scheme 8[a]



[a] (a) Vinylmagnesium bromide, THF, −78 °C to rt; (b) NEt_3, DMAP, $(iPrCO)_2O$, CH_2Cl_2, rt; (c) (method i) KHMDS, TIPSOTf, ether, −78 °C to rt; (d) K_2CO_3, THF/MeOH, H_2O, 1 N HCl.

RMgBr) and an acylating reagent; (iii) acylation of the purified alcohol with an acylating reagent in the presence of tertiary amine and DMAP (vide infra).

Bis-allylic Ester Synthesis and Ireland-Claisen Rearrangements. We initially chose to examine the rearrangement of bis-allylic esters bearing no substituents at C-2 or C-6 (Scheme 8). Esters **4a**,**b** were prepared by addition of vinylmagnesium bromide to cyclohexenone (**3a**) or 4,4-dimethylcyclohexenone[21] (**3b**) to give the intermediate divinyl carbinols.[22] The purified alcohols were acylated in a separate operation to afford the desired esters **4a**,**b** in acceptable yield for the two steps. Esters **4a** and **4b** were treated with excess (ca. 2 equiv) potassium hexamethyldisilylamide (KHMDS) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) in ether at −78 °C, maintained for ca. 30 min at −78 °C, and then allowed to warm to room temperature over several hours. Although the TIPS esters were stable toward chromatography on silica gel, it was difficult to cleanly separate the TIPS ester from the side products resulting from hydrolysis of excess TIPSOTf (presumably TIPSOH). The desired pentenoic acids **6a**,**b** were isolated after hydrolysis of the silyl esters as mixtures of *Z*- and *E*-alkene isomers in reasonably good yield and modest alkene stereoselectivity.

Interestingly, the less stable *Z*-dienes proved to be the major products. The alkene geometry was confirmed by NOESY analysis of (*Z*)-**6b**. Equilibration of a 3:1 *Z*:*E* mixture of dienes **6b** by treatment with a catalytic amount of Ph_2S_2 and UV irradiation afforded a ca. 1:2.5 *Z*:*E* mixture. MM2 calculations predicted the *Z*-isomers to be ca. 0.5 kcal/mol higher in energy.[23]

To improve the stereoselectivity of the rearrangement, we then examined bis-allylic esters derived from C-2-substituted cycloalkenones. The 2-bromo cycloalkenones **7a**−**c** were prepared in a straightforward fashion from the parent enones.[17,24] We hoped that the 2-bromo substituent would not only direct the stereochemical course of the reaction, but would also serve as a flexible handle for functionalization of the resultant diene (vide infra).

Thus, 2-bromo cyclohexenyl esters **8a**,**b** were treated under rearrangement conditions analogous to those described above (Scheme 9). As before, only Claisen rearrangement via the exocyclic alkene was observed. To our satisfaction, only the *E*-alkene isomer was detected by ^1H NMR analysis of the crude reaction mixtures. Rearrangement of the 2-bromo cyclopentenyl ester **8c** gave the optimal yields upon treatment with KHMDS alone. For ester **8c**, use of TIPSOTf resulted in complex mixtures, possibly resulting from ionization of the ester or the silyl ketene acetal intermediate. The alkene geometry of acid **10b** was confirmed by its conversion to (*E*)-**6b** (vide infra, Scheme 19). In all subsequent examples that were substituted at C-2, only the *E*-alkene isomer was observed.

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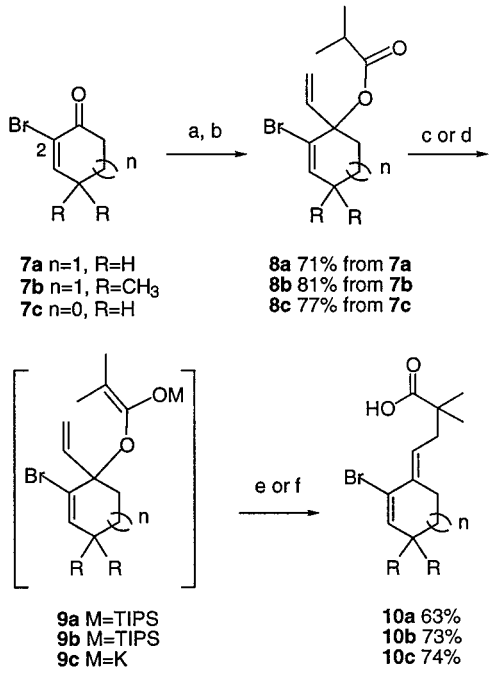
(24) (a) Enone **7a**: Smith, A. B., III; Brancca, S. J.; Pilla, N. N.; Gaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855−1869. (b) Enone **7b**: Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544−2550. (c) Enone **7c**: Guaciaro, M. A.; Wovkulich, P. M.; Smith, I., A. B. *Tetrahedron Lett.* **1978**, *47*, 4661−4664. See also, Sato, K.; Inoue, S.; Kuranami, S.-i. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1666−1669.

Scheme 9[a]



[a] (a) Vinylmagnesium bromide, $CeCl_3$, THF, 0 °C to rt; (b) vinylmagnesium bromide, $(RCO)_2O$, THF, 0 °C to rt; (c) ($n = 0$, R = H; $n = 1$, R = CH_3) (method ii) KHMDS, ether, −78 °C to rt; (d) ($n = 1$, R = H or CH_3) (method i) KHMDS, TIPSOTf, ether, −78 °C to rt; (e) ($n = 1$, R = H) K_2CO_3, THF/MeOH/H_2O, 1 N HCl; (f) ($n = 0$, R = H; $n = 1$, R = CH_3) 1 N HCl. (See Experimental Section for full details).

The high *E*-stereoselectivity observed in the 2-bromo series is consistent with the transition state analysis (Scheme 7). It is noteworthy that a relatively small functional group such as bromine can be used to direct the stereochemical course of the reaction, since it can be exchanged for both smaller or larger substituents by metal−halogen exchange or cross-coupling reactions (vide infra).

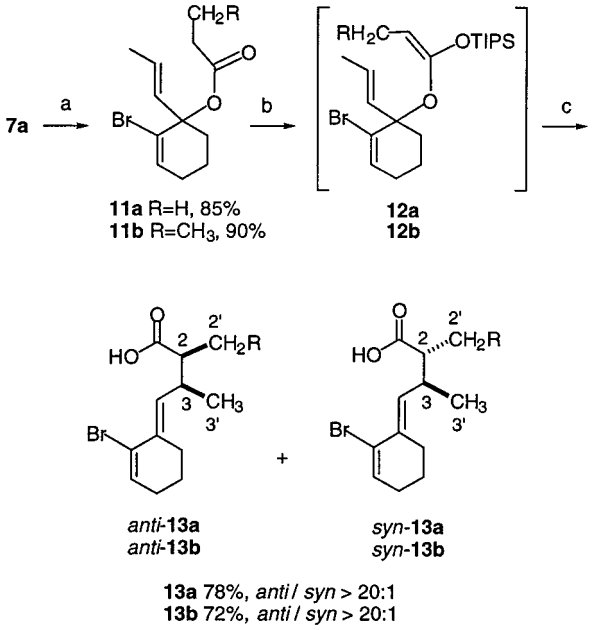
We next turned to the issue of relative stereocontrol using unsymmetrically substituted allyl ketene acetals (Scheme 10). (*E*)-Propenyllithium addition[25] to bromo ketone **7a** followed by in situ acylation with either propionic anhydride or *n*-butyryl chloride afforded the sensitive (*E*)-propenyl esters **11a**,**b**. Treatment as before with KHMDS and TIPSOTf yielded *anti*- and *syn*-dienes **13a**,**b** as >20:1 mixtures of *anti*/*syn* diastereomers as determined by ^{1}H NMR analysis of the crude reaction mixtures.

The *anti*/*syn* designation refers to the relative stereochemistry of the C-2 and C-3 substituents in the extended conformation of the pentenoic acid. The products are depicted in the conformation shown to emphasize the relationship to the natural product targets (cf. Scheme 5).

The stereochemistry of acid *anti*-**13a** was determined unambiguously by X-ray crystallographic analysis of the derived bromo lactone (see Experimental Section).[26] The stereochemical assignments of *syn*- and *anti*-**13a** and **13b** were further supported by comparison of the ^{13}C NMR spectra of the *syn*- and *anti*-isomers. The ^{13}C NMR shifts of the C-2′ and C-3′ carbons of the *anti*-isomer lie

(25) Tsui, H.-C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 9968−9977.
(26) Hong, S.-P.; McIntosh, M. C. *Tetrahedron* **2001**, *57*, 5055−5060.

Scheme 10[a]



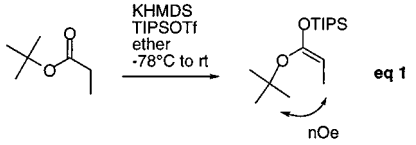
[a] (a) (*E*)-propenyllithium, THF, −78 °C to 0 °C; $(EtCO)_2$ or nPrCOCl, 0 °C to rt; (b) (method iii) KHMDS, TIPSOTf, ether, −78 °C; HOAc, −78 °C to rt; (c) TBAF, THF, 0 °C to rt; 1 N HCl.

downfield relative to those of the *syn*-isomers.[26] The stereochemistry of the silyl ketene acetal would therefore have to be *E* for *anti*-isomers **13a**,**b** to be the major products, assuming a chairlike transition state in the Ireland-Claisen rearrangement (cf. Scheme 7).[27]

In our initial studies of the rearrangements of esters such as **11a,** the diastereoselectivity of the reactions proved to be somewhat variable. After determining that the diastereoselectivity decreased as a function of reaction time, we discovered that excess base was epimerizing the TIPS ester product.[28] We had previously found that excess KHMDS and TIPSOTf (typically 2 equiv) were optimal for rapid silylketene acetal formation at −78 °C. To maintain the rapid silylketene acetal formation but avoid product epimerization, we treated the esters with KHMDS and TIPSOTf at −78 °C for ca. 15 min and then added HOAc at −78 °C to protonate the remaining base. High diastereoselectivities were reproducibly obtained using this modification.

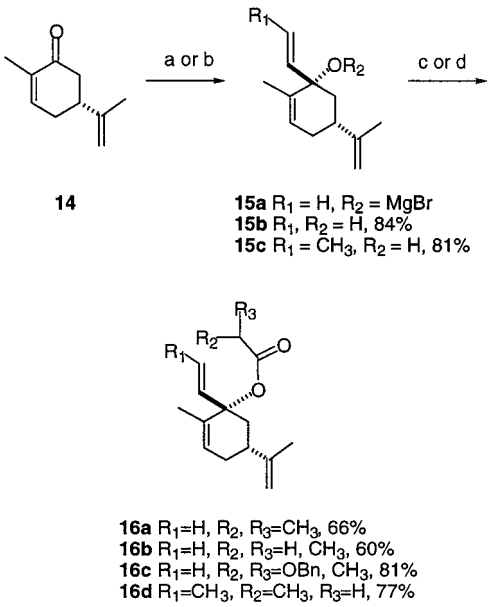
We next examined the rearrangement of several (*R*)-carvone-derived esters. We chose carvone for two reasons. First, it would allow us to determine the stability of bis-allylic esters substituted at C-2 with relatively electron-

(27) The *E*-stereochemistry of the bis-allyl silyl ketene acetal was supported by formation of the (*E*)-silylketene acetal of *tert*-butyl propionate under the same conditions (eq 1). NOESY analysis confirmed the proximity of the *t*-Bu and vinyl methyl groups.



(28) (a) In Ireland's seminal paper (ref 1a), he noted that C-2 trimethylsilyl esters of the pentenoic acid products were obtained as minor products of the rearrangement. The C-2 silylation was suggested to arise from enolization of the TMS ester product by excess amide base. (b) See also: Enev, V.; Stojanova, D.; Bienz, S. *Helv. Chim. Acta* **1996**, *79*, 891−404.

Scheme 11[a]



[a] (a) Vinylmagnesium bromide, THF, −78 °C to rt; (b) (*E*)-propenylmagnesium bromide, THF, −78 °C to rt; (c) $(iPrCO)_2O$; (d) $(EtCO)_2O$; (e) NEt_3, DMAP, *O*-benzyllactic acid chloride, CH_2Cl_2.

donating groups. Second, a carvone derivative would be the obvious choice for a starting material in the synthesis of the eunicellin diterpenes (cf. Scheme 5).[14]

A series of (*R*)-carvone-derived bis-allylic esters was prepared by addition of vinylmagnesium bromide or (*E*)-propenylMgBr to (*R*)-carvone (**14**), including vinyl isobutyrate **16a**, vinyl propionate **16b**, vinyl *O*-benzyl lactate **16c**, and (*E*)-propenyl propionate **16d** (Scheme 11). For the syntheses of esters **16a** and **16b**, the acylations could be performed in situ by treatment of the intermediate Mg alkoxide **15a** with the appropriate acylating reagent. For esters **16c** and **16d**, it was necessary to isolate the corresponding alcohols **15b** and **15c** and acylate under milder conditions. Ester **16c** was isolated as a mixture of epimers at the lactate ester stereocenter, although this was of no consequence, since the stereocenter was destroyed upon conversion to the silyl ketene acetal. In the case of propenyl propionate **16d**, the sensitivity of the ester precluded rigorous chromatographic purification. In the latter case, the purity of the ester was estimated to be ca. 90% based on ^{1}H NMR analysis of the product mixture after extractive workup.

The vinyl nucleophile additions to (*R*)-carvone (**14**) invariably occurred from the axial direction to yield the *trans* adducts as the major isomers. The stereochemistry of the addition products was supported by comparison of the ^{13}C NMR spectra of the two stereoisomers.[29]

Treatment of isobutyrate **16a** with KHMDS and TIPSOTf cleanly afforded only (*E*)-dienic acid **18a** in 58% yield after cleavage of the silyl ester (entry 1) (Table 1). Rearrangement of propionate ester **16b** as the potassium enolate **17b** gave a 1:1 mixture of diastereomers (entry 2). Approximately 10% of alcohol **15c** was also isolated from the reaction mixture and presumably resulted from ketene elimination. Use of KHMDS and TIPSOTf followed by quenching of the excess base with HOAc gave diene **18b** in 65% yield and with high chirality transfer (entry 3). The rearrangement occurred with at least 20:1 diastereoselectivity based on ^{1}H NMR analysis of the derived (*S*)-α-methylbenzyl amides (see Experimental Section). The ^{1}H NMR spectra of dienic acids **18b** and *epi*-**18b** proved to be almost identical. To determine the diastereoselectivity of the Ireland-Claisen rearrangements of ester **16b**, we prepared the (*S*)-α-methylbenzyl amides of a mixture of acids **18b** and *epi*-**18b**. The ^{1}H NMR spectra of the amides were readily distinguishable. The structure of dienic acid **18b** was ultimately determined by X-ray crystallographic analysis of the derived (*S*)-α-methylbenzyl amide. The Li ester enolate of **16b** underwent Ireland-Claisen rearrangement in higher yield albeit with lower diastereoselectivity (entry 4).

One of the advantages of the Ireland variant of the Claisen rearrangement is the ability to control the relative stereochemistry of the pentenoic acid by control of the enolate geometry.[1,2] The epimeric dienic acid *epi*-**18b** was selectively obtained upon treatment of propionate **16b** with LDA in HMPA/THF, followed by addition of TMSCl (entry 5). The observed 1:5.2 **18b**:*epi*-**18b** diastereoselectivity is comparable to that obtained earlier by Ireland[1] and likely reflects the diastereoselectivity in the formation of the (*Z*)-enolate.

For the synthesis of eleutherobin and related eunicellin diterpenes, rearrangement of a lactate ester could be used to generate the tertiary carbinol center (C-7, eunicellin numbering, cf. Scheme 5). Treatment of vinyl *O*-benzyl lactate **16c** using KHMDS alone yielded a 2:1 mixture of tertiary ethers **18c** and *epi*-**18c** (entry 6). However, using the conditions recently reported by Langlois et al. (KHMDS, toluene, TMSCl), a 9.4:1 **18c**:*epi*-**18c** ratio was obtained (entry 7).[30] As Langlois reported, we found that the stereoselectivity improved when the solution of ester and KHMDS was allowed to stir for at least 20−30 min prior to addition of TMSCl. The optimal (9.4:1) selectivity was obtained when the solution was stirred for 90 min. Longer reaction times did not further increase the stereoselectivity. The stereochemistry of dienic acids **18c** and *epi*-**18c** was assigned using ^{1}H NMR spectroscopy of the derived (*S*)-α-methylbenzyl amides using the analysis of Trager et al.[31a] and Yabuuchi and Kusumi.[31b]

Installation of vicinal stereocenters also proceeded as anticipated (Scheme 12). Rearrangement of propenyl ester **16d** afforded *anti*-2,3-dimethyldiene **18d** in good yield with 10:1 *anti*/*syn* diastereoselectivity (entry 8). The stereochemistry of the products was assigned by comparison of the ^{13}C NMR spectra.[26]

The synthesis of dienic acids **18b**−**d** illustrates the ability to relay the stereochemistry of the C-5-isopropenyl group via carbonyl addition and Ireland-Claisen rearrangement to afford products with 1,5- and 1,6-relative stereocontrol. As a further example of remote stereocon-

(29) Although vinylmagnesium bromide additions to (*R*)-carvone yielded a single product, vinyllithium addition to (*R*)-carvone gave a 3:1 ratio of axial and equatorial addition products. This allowed for identification of the stereochemistry of the products by comparison of the ^{13}C NMR spectra (ref 29c). (b) Alcohol **15c** has been prepared previously by addition of dimethylsulfonium methylide to (*R*)-carvone (ref 10b). (c) The ^{13}C NMR spectra were compared to assign the stereochemistry: Buckwalter, B. L.; Burfitt, I. R.; Felkin, H.; Joly-Goudket, M.; Naemura, K.; Salomon, M. F.; Wenkert, E.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 6445−6450. See also: Lindsay, H. A.; Salisbury, C. L.; Cordes, W.; McIntosh, M. C. *Org. Lett.* **2001**, *3*, 4007−4010.

(30) Picoul, W.; Urchigui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797−4800.

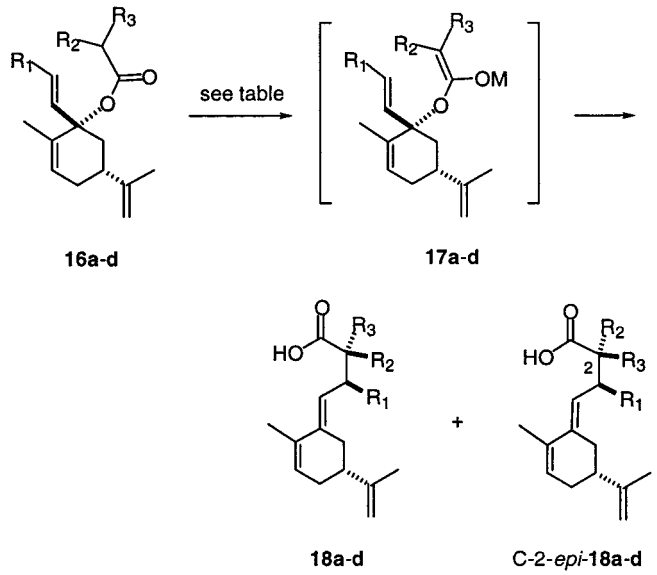
(31) (a) Valente, E. J.; Pohl, L. R.; Trager, W. F. *J. Org. Chem.* **1980**, *45*, 543−546. (b) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404.

Table 1. Ireland-Claisen Rearrangements of Esters 16a−d (Scheme 12)

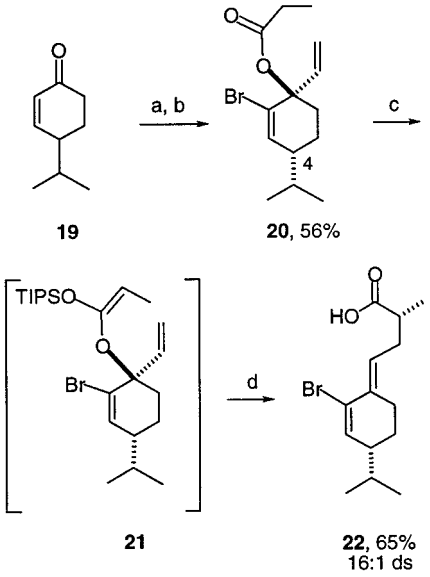
			16			**17**[a]			**18**			C-2-*epi*-**18**				
no.	method[b],[e]	compd	R_1	R_2	R_3	R_1	R_2	R_3	R_1	R_2	R_3	R_1	R_2	R_3	yield	**18**:*epi***18**
1	i	**a**	H	Me	Me	H	Me	Me	H	Me	Me	-	-	-	58	-
2	ii	**b**	H	Me	H	H	Me[c]	H[c]	H	Me	H	H	H	Me	85	1:1[d]
3	iii	**b**	H	Me	H	H	Me	H	H	Me	H	H	H	Me	65	> 20:1
4	iv	**b**	H	Me	H	H	Me	H	H	Me	H	H	H	Me	90	5:1
5	v	**b**	H	Me	H	H	H	Me	H	Me	H	H	H	Me	80	1:5.2
6	i	**c**	H	Me	OBn	H	Me	OBn	H	Me	OBn	H	OBn	Me	50	2:1
7	vi	**c**	H	Me	OBn	H	Me	OBn	H	Me	OBn	H	OBn	Me	84	9.4:1
8	iii	**d**	Me	Me	H	Me	Me	H	Me	Me	H	Me	H	Me	60	10:1

[a] The stereochemistry of the major isomer of the enolate or silyl ketene acetal is indicated. [b] Methods are numbered sequentially starting in Scheme 8. See Experimental Section for details on all methods. [c] Enolization was presumably unselective. [d] Accompanied by ca. 10% of alcohol **15b**. [e] Methods: (i) KHMDS, TIPSOTf, ether, −78 °C to room temperature; (ii) KHMDS, ether, −78 °C to room temperature; (iii) KHMDS, TIPSOTf, ether, −78 °C; HOAc, −78 °C to room temperature; (iv) LDA, THF, −78 °C to room temperature; (v) LDA, HMPA/THF, TMSCl, −78 °C to room temperature; (vi) KHMDS, $PhCH_3$, −78 °C, TMSCl, −78 °C to room temperature.

Scheme 12



Scheme 13[a]



[a] (a) Br_2, CH_2Cl_2, NEt_3; (b) vinylmagnesium bromide, ether, −78 °C to 0 °C; $(EtCO)_2O$; (c) (method iii) KHMDS, TIPSOTf, ether, −78 °C; HOAc, −78 °C to rt; (d) TBAF, THF, 0 °C to rt; 1 N HCl.

trol, we examined the rearrangement of 4-isopropyl ester **20**. The ester was prepared by axial-selective[29] vinylmagnesium bromide addition to 2-bromo-4-isopropylcyclohexenone (**19**) followed by in situ acylation. The ester was isolated as a 10:1 mixture of diastereomers, from which the major isomer **20** could be isolated by column chromatography. Treatment of ester **20** as above gave 16:1 diastereoselectivity for dienic acid **22** based on ^{1}H NMR analysis of the reaction mixture prior to TIPS ester cleavage (Scheme 13). The relative stereochemistry of dienic acid **22** was assigned by analogy to the dienic acids **11a** and **16d** (vide supra).

With the high alkene stereoselectivity and chirality transfer of the Ireland-Claisen rearrangement established for esters derived from C-2-substituted cycloalkenones, we turned our attention to the influence of substitution at C-6 (Scheme 14). Ester **24** was prepared by vinyl addition and acylation of aldol adduct **23**.[32] The stereochemistry of the vinyl addition to enone **23** could not be unambiguously determined by NMR analysis. The extremely high diastereoselectivity of the addition precluded determination of the structure by comparison of the ^{13}C NMR spectra.[29] The product is presumed to result from axial addition of the vinyl cerium reagent to the cyclohexenone conformation with the C-6-substituent disposed equatorially.[33] Ester **24** was too sensitive to rigorously purify by chromatography, but the crude product was of sufficient purity (>90% based on ^{1}H NMR analysis after extractive workup) to use in the rearrangement step.

Rearrangement of ester **24** afforded only (*Z*)-diene **26**. The reversal of alkene stereoselectivity was consistent with the transition state model (cf. Scheme 7). In this case the large group at C-6 would be disposed in a pseudoequatorial position with respect to the Ireland-Claisen chairlike transition state.

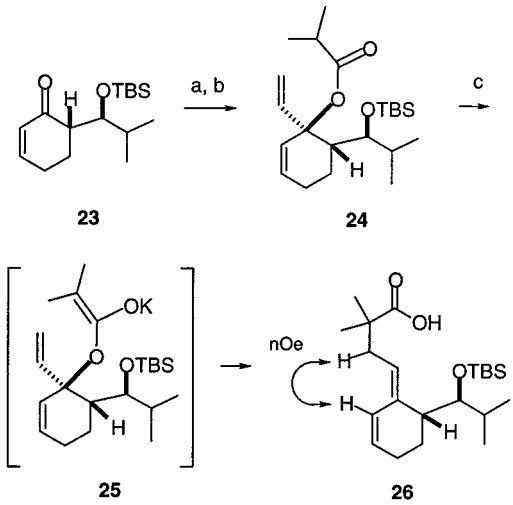
We were also interested in examining the effect of a C-6 oxygen substituent. The Ireland-Claisen rearrangement product would be a protected allylic alcohol, which could eventually serve as a leaving group and/or a directing group for functionalization of the allylic alkene. The C-6 OMEM cyclohexenone **28** was prepared from the known 6-hydroxycyclohexenone[34] (**27**) (Scheme 15). Vinyllithium addition to 6-OMEM cyclohexenone **28** followed by in situ acylation with either isobutyric or propionic anhydride afforded chromatographically sepa-

(32) Martin, S. F.; White, J. B. *Tetrahedron Lett.* **1982**, *23*, 23−26.

(33) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183−6192.

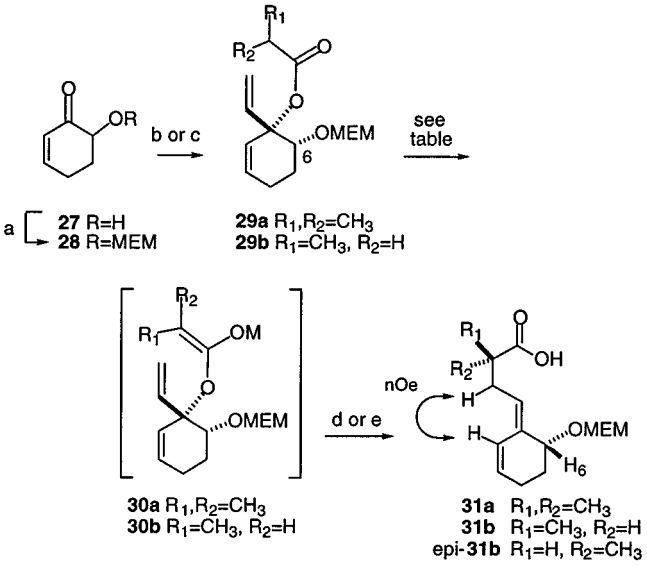
(34) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−1602.

Scheme 14[a]



[a] (a) Vinylmagnesium bromide, $CeCl_3$, THF, −78 °C to rt, 71%; (b) vinylmagnesium bromide, $(iPrCO)_2O$, THF, −78 °C to rt, 94%; (c) (method ii) KHMDS, ether, −78 °C to rt, 65%.

Scheme 15[a]



[a] (a) MEMCl, DIPEA, CH_2Cl_2, 65%; (b) vinyllithium, THF, −78 °C to rt, $(iPrCO)_2O$, 65%; (c) vinyllithium, THF, −78 °C to rt, $(EtCO)_2O$, 63%; (d) 1 N HCl; (e) TBAF, THF.

rable 3:1 mixtures of *syn*- and *anti*-esters.[35] Isobutyrate ester **29a** was treated with LDA to afford (*Z*)-diene **31a** as a single alkene isomer based on ^{1}H NMR analysis of the crude reaction mixture (Table 2). Rearrangement of propionate ester **29b** using either LDA or KHMDS/TIPSOTf/HOAc afforded (*Z*)-diene **31b**, with 9.5:1 and 11:1 diastereoselectivity, respectively. The relative stereochemistry of dienic acid **31b** was assigned by analogy to the dienic acids **11a** and **16d** (vide supra).

Because the ^{1}H NMR spectra of acids **31b** and *epi*-**31b** were indistinguishable, the ratio of diastereomers was determined by ^{1}H NMR via integration of the C-6 protons of the derived *p*-NO_2-benzamides (see Experimental Section). The stereochemistry of the exocyclic alkene was confirmed by NOESY analysis of propionate **31b**.

(35) The stereochemistry of esters **29a** and **29b** was assigned by correlation to the X-ray structure of the analogous alkyne addition products (See Supporting Information for full details).

On the basis of the innovative work of Krafft et al.,[36] we anticipated that a coordinating substituent at C-6 might serve to overcome the steric bias and enforce the formation of an (*E*)-alkene (Scheme 16). Unfortunately, all attempts at a chelation-controlled Claisen rearrangement using the optimal Krafft conditions ($ClMgNEt_2$, HMPA, or DMPU) or variations thereof yielded only the nonchelation product, recovered starting material, allylic rearrangement products, or complex reaction mixtures depending on the conditions employed. Both the *syn* and *anti* diols with either MEM or ethoxymethyl protecting groups were examined. The examples reported by Krafft were acyclic.[36] Apparently the conformations required for the chelated Ireland-Claisen rearrangement in such cyclic systems were not readily accessible.

Having established that substitution at either C-2 or C-6 could be used to direct the stereochemical course of the reaction, we next examined the possibility of stereoselective Ireland-Claisen rearrangements of a 2,6-disubstituted derivative. Rearrangement of such disubstituted derivatives would be useful for application to the synthesis of the eunicellin diterpenes as well as other targets (cf. Scheme 5). We again chose a protected oxygen as the C-6 substituent.

Thus, Rubottom oxidation[34,37] of (*S*)-carvone (**32**) yielded TMS ether **33** with 5−7:1 diastereoselectivity favoring the desired *trans*-isomer (Scheme 17). The *trans* stereochemistry was essential to direct the subsequent equatorial addition of the vinyl nucleophile. TMS ether **33** proved to be too labile in the carbonyl addition reaction, so it was converted to TBS ether **34**. Addition of vinyllithium proceeded with 10:1 diastereoselectivity to afford principally the equatorial addition product, alcohol **35**. The stereochemical assignment was confirmed unambiguously by X-ray crystallographic analysis of alcohol **35** (See Supporting Information). The bulky TBS protecting group was exchanged for a MEM group and the resulting alcohol acylated via the lithium alkoxide to afford isobutyrate **36**.

To our satisfaction, Ireland-Claisen rearrangement yielded a single diene product. Surprisingly, the alkene isomer proved to be diene (*Z*)-**37**. The stereochemistry was confirmed by NOESY analysis of the derived methyl ester (*Z*)-**38**. The alkene was quantitatively isomerized to (*E*)-**38** upon treatment with a catalytic amount of Ph_2S_2 in $CDCl_3$ and irradiation with a sun lamp.

This unexpected result clearly implies preferential rearrangement through chair transition state $\mathbf{39}_{ax}$ with the C-2 methyl substituent disposed pseudoaxially rather than the pseudoequatorially as in transition state $\mathbf{39}_{eq}$ (Scheme 18).[20] This is surprising, since the methyl group is twice as large as the structurally analogous OMe group as measured by axial strain (1.7 [CH_3] vs 0.85 kcal/mol [OMe]).[38] Perhaps the orientation of the OMEM group in transition state $\mathbf{39}_{eq}$ is such that the steric interaction between it and the OTIPS group is substantially greater than that between the C-2 methyl and the OTIPS group in transition state $\mathbf{39}_{ax}$. Further studies are underway to elucidate the reasons surrounding the *Z*-selectivity.

(36) Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093−5101.

(37) The synthesis of trimethylsilyloxycarvone **33** has been reported, although no experimental details were disclosed: Hirai, Y.; Ito, K.; Nagaoka, H. *Heterocycles* **1998**, *48*, 235−238. See also, Schulz, M.; Kluge, R.; Schüβler, M.; Hoffman, G. *Tetrahedron* **1995**, *51*, 3175−3180.

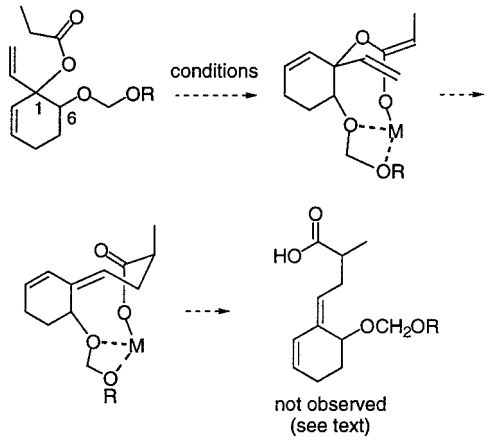
(38) Hirsch, J. A. *Topics Stereochem.* **1967**, *1*, 199−222.

Table 2. Ireland-Claisen Rearrangements of Esters 29a,b

			29		**30**[a]		**31**		C-2-*epi*-**31**			
no.	method[b,c]	compd	R_1	R_2	R_1	R_2	R_1	R_2	R_1	R_2	yield	**31**:*epi*-**31**
1	vii	**a**	Me	Me	Me	Me	Me	Me	-	-	70	-
2	vii	**b**	H	Me	Me	H	Me	H	H	Me	61	9.5:1
3	iii	**b**	H	Me	Me	H	Me	H	H	Me	79	11:1

[a] The stereochemistry of the major isomer of the enolate or silyl ketene acetal is indicated. [b] Methods are numbered sequentially from Scheme 8. See Experimental Section for details on all methods. [c] Methods: (iii) KHMDS, TIPSOTf, ether, −78 °C; HOAc, −78 °C to room temperature; (vii) LDA, THF, −78 °C to −10 °C; HOAc.

Scheme 16



Substitution Reactions of Bromo Dienic Acids. To illustrate the synthetic utility of the bromodienic acids, we briefly examined substitutions of the vinyl bromide of bromo diene **10b** (Scheme 19). Treatment of bromo diene **10b** with excess ^{n}BuLi yielded the presumed intermediate dilithio diene **41**. Protonation of lithio diene **41** yielded isomerically pure dienic acid (*E*)-**6b**, while addition of isobutyraldehyde gave allylic alcohol **42**.

Conclusions

We have found that a variety of C-2- and/or C-6-substituted cyclic bis-allylic esters can be synthesized and isolated in good to excellent yield with moderate to high diastereoselectivity. The bis-allylic esters undergo Ireland-Claisen rearrangement to afford alkylidene cycloalkenes with control of both alkene geometry and the C-2 and C-3 stereocenters of the pentenoic acid products. The stereochemical outcome of the rearrangement can be directed by substitution at either or both of the carbons adjacent to the tertiary carbinol center. Further studies are underway to exploit the Claisen rearrangement strategy in total synthesis.[39]

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, or Alfa Aesar Organics and used as received unless otherwise specified. Tetrahydrofuran (THF), ether, and CH_2Cl_2 were purified with alumina using the Solv-Tek ST-002 solvent purification system. All ^{1}H and ^{13}C NMR spectra were obtained at 270 and 67.9 MHz, respectively. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ.

Extractive workup is defined as extraction of the reaction mixture and the indicated aqueous solution three times with ether, washing of the combined organic extracts with saturated NaCl solution, drying of the extracts over anhydrous $MgSO_4$, and concentration in vacuo.

In those cases in which silica gel was treated with ethylenediamine, the following procedure was used. A mixture of ca. 5 mL of ethylenediamine and 100 mL of hexane was stirred for ca. 5 min. The ethylenediamine-saturated hexane was decanted from the undissolved ethylenediamine and diluted with the ethyl acetate until the desired solvent ratio was obtained. The resulting solution was mixed with silica gel and the slurry used in column chromatography.

The Ireland-Claisen rearrangement methods are numbered sequentially beginning in Scheme 8 (see text).

Ester 4a. Vinylmagnesium bromide (120 mL, 1 M in THF, 120 mmol) was added to a solution of cyclohexenone (**3a**) (9.6 g, 100 mmol) in ether (400 mL) at −78 °C. The resulting mixture was allowed to warm to room temperature over 1 h. The mixture was poured into saturated NH_4Cl solution and the crude product isolated by extractive workup. The crude material was distilled (35−42 °C/0.1 mmHg) to give the alcohol[22,40] as a colorless oil (7.34 g, 60%): IR (film) 3373, 2936 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60−1.80 (m, 5H), 2.00 (m, 2H), 5.06 (dd, J = 1.2, 10.5 Hz, 1H), 5.20 (dd, J = 1.2, 17.4 Hz, 1H), 5.52 (dd, J = 10.1, 1.8 Hz, 1H), 5.84 (dt, J = 9.7, 3.6 Hz, 1H), 5.93 (dd, J = 10.5, 17.6 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 19.03, 25.03, 36.34, 71.01, 113.02, 130.24, 131.10, 144.26.

To a solution of the alcohol (450 mg, 3.64 mmol) in CH_2Cl_2 (2 mL) were added NEt_3 (2.0 mL, 14.54 mmol), DMAP (10 mg, 0.08 mmol), and isobutyric anhydride (1.8 mL, 1.72 g, 11.05 mmol). The reaction mixture was stirred 3 d at room temperature, poured into saturated $NaHCO_3$ solution, and washed with 1 N aqueous ethylenediamine (to facilitate removal of excess anhydride) and the crude product isolated by extractive workup to afford ester **4a** as colorless oil (0.67 g, 90%): IR (film) 2937, 1733, 1155 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09 (d, J = 7.1 Hz, 6H), 1.50−1.80 (m, 3H), 1.90−2.15 (m, 3H), 2.44 (sept, J = 7.1 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 5.12 (d, J = 16.6 Hz, 1H), 5.92 (dt, J = 10.1, 3.6 Hz, 1H), 6.00−6.10 (m, 2H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 18.48, 18.98, 24.92, 34.40, 34.60, 79.20, 114.11, 127.73, 131.91, 141.51, 175.94; MS (*m*/*z*) 194, 151, 123, 107, 91, 79, 71; HRMS calcd for $C_{12}H_{18}O_2$ 194.13068, found 194.12983.

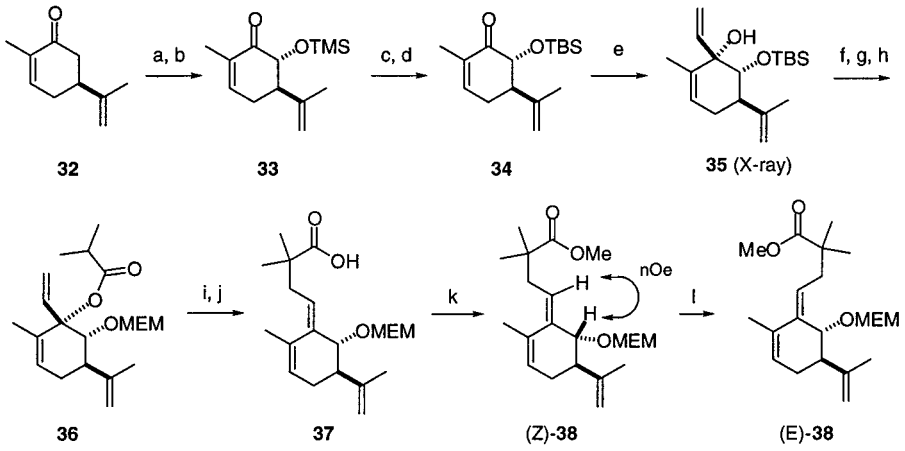
Acid 6a. (Method i). KHMDS (5.76 mL, 0.5 M in toluene, 2.88 mmol) was added to a solution of ester **4a** (138 mg, 0.71 mmol) in ether (20 mL) at −78 °C, followed by TIPSOTf (0.8 mL, 2.98 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was poured into saturated $NaHCO_3$ solution and the crude product isolated by extractive workup. The crude material was mixed with methanol (30 mL), THF (10 mL), water (10 mL), and K_2CO_3 (1 g). The reaction mixture was stirred for 2 h at room temperature, concentrated in vacuo, and diluted with saturated NaCl solution and 1 N HCl and the crude product isolated by extractive workup. The crude material was purified by flash chromatography on silica gel with 25/75 ethyl acetate/hexane to give acid **6a** as a colorless oil (84 mg, 60%, Z:E = 2.5:1). (*E*)-**6a**:[41] IR (film) 2927 (m) 1696 cm^{-1}; ^{1}H NMR (270

(39) Hong, S.-p.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19−21.

(40) Spectral data are given here since they were not supplied in the earlier report of the synthesis of the alcohol (ref 22).

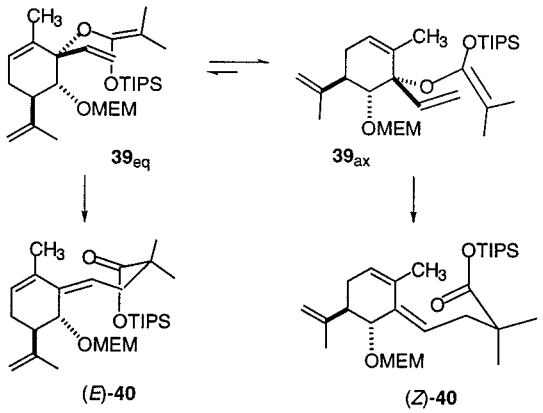
(41) Spectral data for the pure *E*-isomers were obtained by reduction of (*E*)-**10a** or (*E*)-**10b** (cf. Scheme 19).

Scheme 17[a]

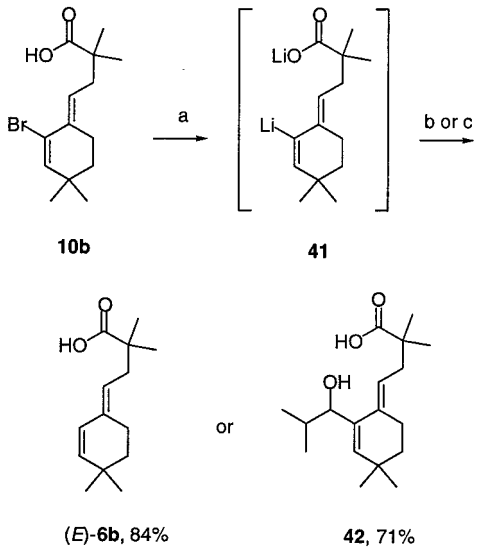


[a] (a) LDA, THF, TMSCl, −78 °C to rt; (b) mCPBA, CH_2Cl_2, 0 °C, 5−7:1 ds, 85%; (c) HF, CH_3CN, 0 °C to rt, 60%; (d) TBSCl, DMF, imidazole, 92%; (e) vinyllithium, THF, −78 °C to rt, 10 h, 10:1 ds, 70%; (f) TBAF, THF; (g) MEMCl, DIPEA, CH_2Cl_2; (h) vinylmagnesium bromide, $(iPrCO)_2O$, THF, 55−60% from **35**. (i) (method i) KHMDS, TIPSOTf, −78 °C to rt; (j) TBAF, THF, 0 °C; (k) CH_2N_2, ether, 0 °C to rt, 5 min; (l) Ph_2S_2, *hν*, $CDCl_3$.

Scheme 18



Scheme 19[a]



[a] (a) ^{n}BuLi, THF, −78 °C; (b) HOAc; (c) isobutyraldehyde.

MHz,$CDCl_3$) δ 1.19 (s, 6H), 1.66 (quint, J = 6.1 Hz, 2H), 2.09 (m, 2H), 2.30 (m, 2H), 2.34 (d, J = 7.7 Hz, 2H), 5.20 (t, J = 7.7 Hz, 1H), 5.70 (dt, J = 9.9, 5.0 Hz, 1H), 6.03 (d, J = 9.9 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 22.56, 24.68, 25.49, 25.69, 37.74, 42.83, 121.85, 128.09, 131.15, 137.54, 183.70; MS (*m*/*z*) 79, 91, 107, 194; HRMS calcd for $C_{12}H_{18}O_2$ 194.13068, found 194.13001.

Ester 8a. Anhydrous $CeCl_3$ (24.0 mL, 0.40 M in THF, 9.6 mmol) was added to ketone **7a** (1.70 g. 9.71 mmol) in THF (10 mL) at room temperature and the resulting mixture stirred for 1 h. Vinylmagnesium bromide (19.4 mL, 1 M in THF, 19.4 mmol) was added to the mixture at 0 °C. After 10 min, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was poured into saturated NH_4Cl solution and the crude product isolated by extractive workup. The residue was purified by flash chromatography over silica gel with 20/80 ethyl acetate/hexane to give the corresponding alcohol[17] as colorless oil (1.37 g, 71%).

To a solution of the alcohol (150 mg, 0.74 mmol) in 30 mL of THF at 0 °C was added vinylmagnesium bromide (1.1 mL, 1 M in THF, 1.1 mmol) followed by isobutyric anhydride (0.37 mL, 0.35 g, 2.23 mmol). After 1 h, the mixture was poured into saturated $NaHCO_3$ solution and extracted three times with ether. The combined organic phases were washed with aqueous 1 N ethylenediamine (to facilitate removal of excess anhydride) and with water three times. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography over Florisil with 20/80 ethyl acetate/hexane to give ester **8a** as yellow oil (0.20 g, 100%): IR (film) 2935, 1738, 1154 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (d, J = 4.9 Hz, 3H), 1.18 (d, J = 4.9 Hz, 3H), 1.60−1.80 (m, 2H), 1.97−2.23 (m, 2H), 2.23−2.40 (m, 1H), 2.50−2.80 (m, 2H), 5.26 (d, J = 10.9 Hz, 1H), 5.29 (d, J = 17.4, 1H), 5.90 (dd, J = 10.9, 17.4 Hz, 1H), 6.30 (m, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 18.98, 19.09, 19.43, 27.38, 32.56, 34.89, 82.22, 115.99, 123.44, 133.79, 137.79, 175.22; MS (*m*/*z*) 194, 193, 187, 185, 123, 106, 105, 71; HRMS calcd for $C_{12}H_{17}BrO_2$ 272.04119, found 272.04036.

Ester 8b. Vinylmagnesium bromide (14.3 mL, 1 M in THF, 14.3 mmol) was added to a solution 4,4-dimethyl-2-bromocyclohexen-1-one (**8b**)[24b] (1.46 g, 7.2 mmol) in THF (100 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature over 30 min, isobutyric anhydride (3.56 mL, 3.40 g, 21.5 mmol) added, and the reaction mixture stirred for 2 h. The mixture was poured into saturated $NaHCO_3$ solution and extracted three times with ether. The combined organic phases were washed with aqueous 1 N ethylenediamine (to facilitate removal of excess anhydride) and washed with water three times. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give ester **8b** as a yellow oil (1.75 g, 81%; the ester was used without further purification): IR (film) 2969, 1740, 1151 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.11 (s, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz,

3H), 1.40−1.70 (m, 2H), 1.86 (dt, J = 12.9, 4.0 Hz, 1H), 2.54 (sept, J = 6.9 Hz, 1H), 2.74 (dt, J = 4.2, 13.1 Hz, 1H), 5.23 (d, J = 10.7 Hz, 1H), 5.27 (d, J = 17.4 Hz, 1H), 5.85 (dd, J = 17.4, 10.7 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 19.01, 19.10, 26.57, 29.63, 30.38, 33.66, 34.90, 35.86, 82.27, 115.94, 121.84, 137.38, 142.86, 175.27.

Acid 10a. (Method i). KHMDS (9.5 mL, 0.5M in toluene, 4.2 mmol) was added to a solution of ester **8a** (0.64 g, 2.4 mmol) in ether (100 mL) at −78 °C followed by TIPSOTf (1.7 mL, 4.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into sat. $NaHCO_3$ and the crude product isolated by extractive workup. A mixture of the crude material in methanol (30 mL), THF (10 mL), water (10 mL) and K_2CO_3 (1 g) was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo and poured into saturated NaCl solution and the crude product isolated by extractive workup. Purification by flash chromatography over silica gel with 25/75 ethyl acetate/hexane gave acid **10a** as yellow oil (0.40 g, 63%): IR (film) 2930, 1707 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 6H), 1.70 (pent, J = 6.1 Hz, 2H), 2.19 (m, 2H), 2.42 (d, J = 7.5 Hz, 2H), 2.43 (t, J = 6.1 Hz, 2H), 5.88 (t, J = 7.5 Hz, 1H), 6.23 (t, J = 4.3 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 22.19, 24.68, 27.12, 28.37, 37.79, 42.83, 124.28, 125.88, 132.10, 134.82, 184.33; MS (*m*/*z*) 27, 41, 77, 91, 105, 185, 272, 274; HRMS Calcd for $C_{12}H_{17}BrO_2$ 272.04119, found 272.04120.

Acid 10c. (Method ii). KHMDS (2.5 mL, 0.5 M in toluene, 1.25 mmol) was added to a solution of ester **8c** (0.27 g, 1.04 mmol) in ether (30 mL) at −78 °C. After 5 min, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After 1 h, the mixture was poured into 1 N HCl and the crude product isolated by extractive workup. The crude material was dissolved in ca. twice its volume of NEt_3 and the mixture purified by flash chromatography over silica gel with ether followed by 1/99 AcOH/ether to give acid **10c** as yellow oil (0.20 g, 74%): IR (film) 2980 (m) 1698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.33 (d, J = 7.7 Hz, 2H), 2.44(m, 2H), 2.56 (m, 2H), 5.47 (t, J = 7.2 Hz, 1H), 6.19 (t, J = 3.0 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 24.67, 25.79, 30.43, 39.63, 42.85, 116.68, 124.07, 137.27, 145.19, 184.72; MS (*m*/*z*) 262, 173, 91, 77, 65, 41. Anal. Calcd for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 50.81; H, 5.73.

Ester 11a. *t*-BuLi (10.00 mL, 1.7 M in pentane, 17.00 mmol) was added to a solution of (*E*)-1-propenyl bromide (0.73 mL, 1.03 g, 8.57 mmol) in THF (50 mL) at −78 °C. After 15 min, a solution of enone **7a** (0.5 g, 2.86 mmol) in THF (20 mL) was added. The ice bath was removed, the reaction mixture allowed to warm to 0 °C, and propionic anhydride (1.83 mL, 1.86 g, 14.27 mmol) added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into saturated $NaHCO_3$ solution and the crude product isolated by extractive workup. The crude material was rapidly purified by flash chromatography over neutral alumina with 20/80 ethyl acetate/hexane to give ester **11a** as yellow oil (0.66 g, 85%): IR (film) 2941, 1736, 1184 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (t, J = 7.5 Hz, 3H), 1.65 (m, 2H), 1.75 (dd, J = 6.3, 1.4 Hz, 3H), 2.00 (m, 2H), 2.20 (m, 1H), 2.30 (m, 2H), 2.56 (dt, J = 4.4, 12.5 Hz, 1H), 5.50 (dq, J = 15.4, 1.4 Hz, 1H), 5.70 (dq, J = 15.4, 6.3 Hz, 1H), 6.20 (dd, J = 5.3, 2.8 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 9.13, 17.86, 19.49, 27.44, 28.58, 32.88, 82.53, 124.19, 127.60, 130.85, 133.37, 172.77.

Acid 13a. (Method iii). KHMDS (11.43 mL, 0.5 M in toluene, 5.72 mmol) was added to a solution of ester **11a** (0.60 g, 2.20 mmol) in ether (50 mL) at −78 °C followed by TIPSOTf (2.30 mL, 8.56 mmol). The reaction mixture was stirred for 15 min at −78 °C and then AcOH (1 mL) added. The mixture was allowed to warm to room temperature, stirred for 30 min, and then poured into saturated $NaHCO_3$ and the crude product isolated by extractive workup. The crude material was dissolved in dry THF (50 mL) and treated with Bu_4NF (10 mL, 1 M in THF, 10 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature, stirred for 2 h, and then was poured into 1 N HCl and the crude product isolated by extractive workup. The crude material was dissolved in ca. twice its volume of NEt_3 and the mixture purified by flash chromatography over silica gel with ether followed by 1/99 AcOH/ether to give *anti*-acid **13a** as yellow oil (0.44 g, 73%): IR (film) 2934 (m) 1705 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.03 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.70(m, 2H), 2.19 (q, J = 5.9 Hz, 2H), 2.33 (m, 1H), 2.46 (t, J = 5.7 Hz, 2H), 2.76 (m, 1H), 5.62 (d, J = 10.1 Hz, 1H), 6.23 (t, J = 4.4 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 15.30, 19.29, 22.27, 27.34, 28.35, 35.31, 45.93, 124.10, 132.30, 133.01, 133.14, 182.93; MS (*m*/*z*) 27, 41, 55, 65, 77, 91, 119, 199, 272. Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 52.97; H, 6.45.

Bromo Lactone.[26] Br_2 (0.029 mL, 0.56 mmol) was added to a solution of acid **13a** (0.14 g, 0.51 mmol) and pyridine (0.083 mL, 0.081 g, 1.03 mmol) in CH_2Cl_2 (15 mL) at −78 °C. After 10 min, the reaction mixture was allowed to warm to room temperature and then was poured into saturated $Na_2S_2O_3$ solution and the crude product isolated by extractive workup with CH_2Cl_2. The crude material was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give the lactone as white solid, mp: 145 °C (0.14 g, 78%): IR (film) 1730, 1240, 973 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.18 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 7.5 Hz, 3H), 1.6−2.0 (m, 2H), 2.0−2.3 (m, 3H), 2.5−2.6 (m, 2H), 2.8 (m, 1H), 4.69 (d, J = 12.3 Hz, 1H), 6.51 (dd, J = 2.8, 5.9 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 13.46, 17.67, 17.74, 27.64, 32.48, 32.86, 40.78, 55.94, 83.75, 123.79, 138.71, 173.32; MS (*m*/*z*) 352, 232, 177, 151, 105, 91, 69, 56, 41, 28. Anal. Calcd for $C_{12}H_{16}Br_2O_2$: C, 40.94; H, 4.58. Found: C, 41.12; H, 4.60. The X-ray data for the bromo lactone have been deposited with the Cambridge Crystallographic Database.[26]

Alcohol 15c. To a suspension of Mg (200 mg, 8.3 mmol) in THF (20 mL) was added (*E*)-1-propenyl bromide (1.0 mL, 1.41 g, 8.3 mmol). The resulting mixture was stirred for 5 h at room temperature and then cooled to −78 °C and (*R*)-carvone (**14**) (0.83 g, 5.5 mmol) added. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The resulting mixture was poured into saturated NH_4Cl and the crude product isolated by extractive workup. The crude material was purified by flash chromatography over silica gel with 20/80 ethyl acetate/hexane to give alcohol **15c** as colorless oil (0.86 g, 81%): IR (film) 3365, 2963, 1642 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.70 (m, 7H), 1.80−2.00 (m, 2H), 2.00−2.18 (m, 1H), 2.20−2.35 (m, 1H), 4.69 (s, 2H), 5.51 (m, 3H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 17.45, 17.80, 20.71, 31.25, 38.85, 42.76, 75.70, 109.00, 124.67, 125.37, 135.49, 136.32, 149.03; MS (*m*/*z*) 192, 174, 159, 145, 134, 123, 109, 91, 69, 55, 39.

Ester 16c. *O*-Benzyl lactic acid chloride[42] (0.18 g, 0.9 mmol) and NEt_3 (0.17 mL, 1.2 mmol) were added to a solution of alcohol **15b** (100 mg, 0.6 mmol) and DMAP (89 mg, 0.7 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 24 h at room temperature and then poured into saturated $NaHCO_3$ and the crude product isolated by extractive workup. The crude material was purified by flash chromatography over a short column of alumina with 20/80 ethyl acetate/hexane to give ester **16c** as colorless oil (0.17 g, 81%), major isomer: IR (film) 2923, 1747, 1142 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (d, J = 6.9 Hz, 3H) 1.62 (s, 3H), 1.72 (s, 3H), 1.74 (m, 1H), 2.08 (m, 3H), 2.33 (m, 2H), 4.01 (q, J = 6.9 Hz, 1H) 4.47 (m, 1H), 4.72 (s, 2H), 4.73 (d, J = 11.5 Hz, 1H), 5.19 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.9 Hz, 1H), 5.70 (s, 1H), 6.02 (dd, J = 10.9, 17.2 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 17.87, 18.90, 20.74, 30.67, 36.96, 38.75, 72.01, 74.50, 86.77, 109.51, 115.52, 126.70, 127.83, 128.03, 128.46, 132.17, 137.86, 138.56, 148.24, 171.52

Acid 18a. (Method i). Ester **16a** (248 mg, 1.00 mmol) gave after purification by flash chromatography over silica gel with 25/75 ethyl acetate/hexane acid **18a** as yellow oil (144 mg, 58%): IR (film) 3582 (m), 1772, 1220 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.74 (s, 3H), 1.78 (s, 3H), 1.85−2.25 (m, 4H), 2.4 (m, 2H), 2.68 (d, J = 14.2 Hz, 1H), 4.73 (s, 2H), 5.38

(42) Auge, C.; David, S.; Gautheron, C.; Malleron, A.; Cavaye, B. *New. J. Chem.* **1988**, *12*, 733−744.

(t, J = 7.5 Hz, 1H), 5.63 (br s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 19.87, 20.78, 24.58, 24.81, 31.19, 31.39, 37.87, 41.83, 42.96, 109.10, 118.77, 126.23, 133.06, 138.58, 149.56, 184.78; MS (*m*/*z*) 248, 207, 133, 119, 88, 55; HRMS calcd for $C_{16}H_{24}O_2$ 248.17763, found 248.17845.

Acid 18b. (Method i). Ester **16b** (234 mg, 1.0 mmol) gave after purification by flash chromatography over silica gel with 25/75 ethyl acetate/hexane acid **18b** as yellow oil (152 mg, 65%).

(Method iv). ^{n}BuLi (0.8 mL, 1.6M in hexane, 1.28 mmol) was added to diisopropylamine (0.18 mL, 1.27 mmol) in THF (40 mL) at −78 °C. After 15 min, ester **16b** (0.2 g, 0.85 mmol) in THF (10 mL) was added. The resulting mixture was allowed to warm to 0 °C over 30 min then was poured into 1 N HCl solution and the crude product isolated by extractive workup. The crude material was dissolved in ca. twice its volume of NEt_3 and the mixture purified by flash chromatography over silica gel with ether followed by 1/99 AcOH/ether to give acid **18b** as yellow oil (0.18 g, 90%). The isomeric ratio of the product was determined by GC after amidation. IR (film) 3544 (m), 2910, 1762 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 3H), 1.74 (s, 3H), 1.78 (s, 3H), 1.90−2.40 (m, 5H), 2.45−2.65 (m, 2H), 2.68 (d, J = 14.2 Hz, 1H), 4.73 (s, 2H), 5.35 (t, J = 7.1 Hz, 1H), 5.61 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 16.64, 19.78, 20.78, 31.09, 31.37, 31.49, 40.00, 41.75, 109.13, 120.06, 126.31, 132.86, 138.12, 149.38, 183.29; MS (*m*/*z*) 234, 193, 161, 147, 119, 105, 93, 74, 55; HRMS calcd for $C_{15}H_{22}O_2$ 234.16198, found 234.16256.

Acid *Epi*-18b. (Method v). ^{n}BuLi (0.6 mL, 1.6 M in hexane, 0.96 mmol) was added to a solution of diisopropylamine (0.14 mL, 0.99 mmol) in THF (20 mL) at −78 °C, followed after 15 min by HMPA (10 mL). After 5 min, ester **16b** (0.15 g, 0.64 mmol) in THF (10 mL) was added, followed after 20 min by TMSCl (0.16 mL, 1.26 mmol). The reaction mixture was allowed to warm to −10 °C and then quenched with AcOH (0.1 mL, 1.7 mmol). Upon reaching rt, the reaction mixture was diluted with water and the crude product isolated by extractive workup. The crude material was purified as above to give acid *epi*-**18b** as a yellow oil (0.12 g, 80%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (d, J = 6.7 Hz, 3H), 1.73 (s, 3H), 1.77 (s, 3H), 1.90−2.40 (m, 5H), 2.40−2.60 (m, 2H), 2.65 (d, J = 14.2 Hz, 1H), 4.73 (s, 2H), 5.35 (t, J = 7.1 Hz, 1H), 5.61 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 16.41, 19.76, 20.75, 31.05, 31.36, 39.85, 41.73, 109.15, 120.03, 126.25, 132.89, 138.12, 149.40, 183.19.

Acid 18c. (Method vi). KHMDS (6.8 mL, 0.5 M in toluene, 3.4 mmol) was added to a solution of ester **16c** (580 mg, 1.71 mmol) in dry toluene (50 mL) at −78 °C. The resulting mixture was stirred for 1.5 h at −78 °C and then TMSCl (0.87 mL, 6.85 mmol) added. After 10 min, the ice bath was removed and the reaction mixture allowed to warm to room temperature. After 5 h, the resulting mixture was poured into saturated NH_4Cl solution and the crude product isolated by extractive workup. The crude material was dissolved in ca. twice its volume of NEt_3 and the mixture purified by flash chromatography over silica gel with ether followed by 1/99 AcOH/ether to give acid **18c** as yellow oil (0.49 g, 84%): IR (film) 3051 (m), 2908, 1702 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.79 (s, 3H), 1.87 (s, 3H), 2.00−2.40 (m 4H), 2.70−3.00 (m, 3H), 4.60 (s, 2H), 4.80 (s, 2H), 5.58 (t, J = 6.7 Hz, 1H), 5.71 (s, 1H), 7.41 (m, 5H), 11.03 (bs, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 19.92, 20.87, 21.68, 31.39, 31.42, 36.01, 41.77, 66.92, 80.71, 109.32, 116.61, 126.65, 127.81, 128.50, 133.03, 138.24, 139.22, 149.37, 179.90; MS (*m*/*z*) 340, 312, 249, 234, 205, 187, 163, 147, 133, 119, 105, 91, 79, 65, 43. Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found C, 77.30; H, 8.15.

α-Methylbenzyl Amide of Acid 18b. DPPA (0.37 mL, 0.47 g, 1.7 mmol) was added to a solution of acid **18b** (0.127 g, 0.51 mmol), NEt_3 (0.38 mL, 2.7 mmol), and (*S*)-α-methylbenzylamine (0.11 mL, 0.10 g, 0.85 mmol) in DMF at 0 °C. The resulting mixture was allowed warm to room temperature and stirred for 16 h. The reaction mixture was diluted with water and extracted with ether three times. The combined organic phases were washed with water, 1 N HCl solution, water, saturated $NaHCO_3$ solution, water, and saturated NaCl solution. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 50/50 ethyl acetate/hexane to give amide **18b′** as a white solid, mp: 113 °C (0.133 g, 74%): IR (film) 3291, 2969, 2087, 1645 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (d, J = 6.7 Hz, 3H), 1.45 (d, J = 6.9 Hz, 3H), 1.73 (s, 3H), 1.76 (s, 3H), 1.90−2.50 (m, 7H), 2.65 (d, J = 14.2 Hz, 1H), 4.72 (s, 2H), 5.12 (quintet, J = 8.1 Hz, 1H), 5.34 (t, J = 6.9 Hz, 1H), 5.64 (m, 2H), 7.29 (m, 5H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 17.60, 19.81, 20.78, 21.75, 31.09, 31.37, 32.41, 41.78, 41.96, 48.49, 109.19, 120.16, 120.81, 125.67, 126.33, 127.40, 128.74, 129.91, 132.81, 137.79, 143.28, 149.43, 174.92.

Ketone 23. ^{n}BuLi (19.6 mL, 1.6 M in hexane, 31.1 mmol) was added to a solution of diisopropylamine (4.4 mL, 31.1 mmol) in THF (100 mL) at −78 °C. After 20 min, cyclohex-2-ene-1-one (2 g, 20.8 mmol) in THF (20 mL) was added, followed after 5 min by isobutyraldehyde (3.76 mL, 2.99 g, 41.6 mmol). After 5 min, AcOH (3.6 mL, 62.4 mmol) was added. The resulting mixture was allowed to warm to room temperature and the crude product isolated by extractive workup. The crude material was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give the corresponding alcohol as colorless oil (2.09 g, 60%): IR (film) 3470 (broad), 1651 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.76 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 1.50−1.77 (m, 2H), 1.86−1.95 (m, 1H), 2.20−2.36 (m, 3H), 3.49 (dt, J = 3.2, 7.9 Hz, 1H), 3.92 (d, J = 3.0 Hz, 1H), 5.86 (dt, J = 2.0, 9.9 Hz, 1H), 6.87 (m, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 14.60, 19.99, 24.97, 25.67, 29.25, 49.52, 75.66, 129.76, 151.04, 204.25; MS (*m*/*z*) 168, 150, 96, 68, 43, 27. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.52.

TBSOTf (1.47 mL, 5.97 mmol) was added to a solution of the alcohol (0.67 g, 3.98 mmol) and 2,6-lutidine (0.7 mL, 7.96 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 10 min, the mixture was poured into saturated $NaHCO_3$ solution and the crude product isolated by extractive workup with CH_2Cl_2. The crude material was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give ketone **23** as colorless oil (1.18 g, 79%): IR (film) 1672 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.06 (s, 3H), 0.74 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H), 1.65 (m, J = 6.7 Hz, 1H), 1.82 (m, 1H), 2.20 (m, 1H), 2.42 (m, 1H), 4.17 (dd, J = 3.5, 7.4 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 6.92 (m, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ −4.47, −4.38, 18.13, 19.73, 20.46, 22.01, 25.97, 31.62, 54.04, 74.50, 130.22, 149.58, 199.00; MS (*m*/*z*) 282, 267, 225, 153, 129, 75, 59, 41. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 68.13; H, 10.46.

Enone 28. A solution of 6-hydroxy-2-cyclohexen-1-one[34] (1.4 g, 12.8 mmol), diisopropylethylamine (2.48 g, 19.1 mmol), and MEMCl (2.39 g, 19.1 mmol) in CH_2Cl_2 (50 mL) was allowed to stir for 16 h at room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution, extracted three times with CH_2Cl_2, washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography on Florisil using 60/40 hexanes/THF to give MEM ether **28** as a yellow oil (1.82 g, 65%). IR (film) 1683 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.0 (m, 1H), 2.2 (m, 1H), 2.5 (m, 2H), 3.3 (s, 3H), 3.5 (t, J = 4.3 Hz, 2H); 3.7 (q, J = 4.9 Hz, 2H), 4.1 (dd, J = 4.6 Hz, 12.2 Hz, 1H), 4.8 (m, 2H), 5.9 (d, J = 9.9 Hz, 1H), 6.8 (m, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 25.4, 29.7, 59.0, 67.2, 71.7, 76.3, 94.9, 128.6, 149.9, 197.7. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.81; H, 8.13.

Ester 29a. ^{n}BuLi (7.97 g, 18.8 mmol) was added to a solution of vinyltributyltin (5.95 g, 18.8 mmol) in THF (80 mL) at −78 °C. The reaction was allowed to stir at −78 °C for 15 min and then at room temperature for 1 h. The solution was then cooled to −78 °C and enone **28** (2.30 g, 12.5 mmol) in THF (30 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature. After 45 min the reaction mixture was cooled to −78 °C and isobutyric anhydride (2.97 g, 18.8 mmol) added. The mixture was stirred at −78 °C for 5 min, warmed to room temperature, and stirred for 2 h. The mixture was then poured into saturated $NaHCO_3$ solution and the crude

product isolated by extractive workup. The product was purified by flash chromatography on silica gel using 50/50 ether/hexanes to give ester **29a** as a yellow oil (2.42 g, 65%). IR (film) 1734 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.1 (d, J = 6.9 Hz, 6H), 2.0 (m, 4H), 2.5 (hept, J = 6.9 Hz, 1H), 3.4 (s, 3H), 3.5 (t, J = 4.5 Hz, 2H); 3.7 (m, 2H), 3.9 (dd, J = 2.7 Hz, 8.6 Hz, 1H,), 4.7 (d, J = 7.1 Hz, 1H), 4.8 (d, J = 7.1 Hz, 1H), 5.1 (d, J = 17.4 Hz, 1H), 5.2 (d, J = 10.5 Hz, 1H), 6.0 (m, 2H), 6.2 (dd, J = 17.6 Hz, 10.9 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 18.9, 19.1, 23.4, 23.5, 34.4, 59.1, 67.2, 71.7, 78.2, 80.8, 95.2, 115.9, 126.6, 131.6, 140.1, 176.0. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.36; H, 8.67.

Acid 31a. (Method vii). To a solution of LDA (0.64 mmol) in THF (10 mL) at −78 °C was added ester **29a** (0.076 g, 0.25 mmol) in THF (5 mL) via cannula. The reaction mixture was stirred at −78 °C for 30 min and then warmed to −10 °C and stirred an additional 30 min, after which it was quenched by addition of HOAc (0.38 g, 6.4 mmol). The reaction mixture was poured into 1 N HCl and the crude product isolated by extractive workup. The residue was purified by flash chromatography on silica gel using ether followed by 1/99 HOAc/ether acid **31a** as a colorless oil (0.053 g, 70%). IR (film) 1720, 1701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.2 (s, 6H), 1.7 (m, 1H), 1.9 (m, 1H), 2.1 (m, 1H), 2.3 (m, 3H), 3.4 (s, 3H), 3.5 (t, J = 4.9 Hz, 2H); 3.7 (m, 2H), 4.2 (m, 1H), 4.8 (d, J = 6.9 Hz, 1H), 5.4 (t, J = 7.2 Hz, 1H), 5.8 (m, 1H), 6.3 (d, J = 10.2 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 22.3, 24.7, 24.8, 28.2, 37.1, 42.6, 59.0, 66.8, 71.9, 74.4, 92.4, 122.2, 124.0, 130.3, 135.1, 183.4. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.57; H, 8.81.

***p*-Nitrobenzyl Amide of Acid 31b.** To a solution of acid **31b** (0.077 g, 0.27 mmol) in DMF (5 mL) at 0 °C were added NEt_3 (0.14 g, 1.35 mmol), diphenylphosphoryl azide (0.15 g, 0.56 mmol), and *p*-nitrobenzylamine hydrochloride (0.077 g, 0.41 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was then washed with water and extracted with ethyl acetate. The organic phase was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 20/80 ethyl acetate/hexanes to give the amide as a yellow oil (0.84 g, 74%, 8:1 mixture of diastereomers). IR (film) 1651, 1520, 1346 cm^{-1}; ^1H NMR (major isomer) (270 MHz, $CDCl_3$) δ 1.2 (d, J = 6.5 Hz, 3H), 1.7 (m, 1H), 1.9 (m, 1H), 2.1 (m, 1H), 2.3 (m, 3H), 2.5 (m, 1H), 3.4 (s, 3H), 3.5 (m, 2H); 3.7 (m, 2H), 4.2 (m, 1H), 4.5 (d, J = 6.1 Hz, 1H), 4.7 (dd, J = 17.2 Hz, 7.1 Hz, 2H), 5.4 (t, J = 7.5 Hz, 1H), 5.9 (m, 1H), 6.1 (t, J = 4.6 Hz, 1H), 6.3 (d, J = 10.5 Hz, 1H), 7.4 (d, J = 8.5 Hz, 2H), 8.2 (d, J = 8.7 Hz, 2H); ^{13}C NMR (major isomer) (67 MHz, $CDCl_3$) δ 17.8, 23.4, 28.3, 31.6, 41.6, 42.8, 59.0, 66.8, 71.9, 74.4, 92.5, 122.1, 123.9, 125.6, 128.3, 130.6, 134.4, 146.3, 147.2, 176.0. Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.07; H, 6.97; N, 6.71.

Trimethylsilyl Ether 33.[34,36] ^{n}BuLi (15.7 g, 37 mmol) was slowly added to a solution of diisopropylamine (3.75 g, 37.1 mmol) in THF (50 mL) at −78 °C. The solution was stirred for 10 min, and then (*S*)-carvone (**32**) (5.0 g, 33.2 mmol) was added. The solution was stirred for 10 min, and then TMSCl (7.6 g, 70 mmol) added dropwise at −78 °C. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into cold $NaHCO_3$ solution and extracted three times with hexane. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford a the enol silane as a yellow oil (6.93 g, 94%): IR (film) 3065, 2952, 1675, 1251 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.2 (s, 9H), 1.70 (s, 3 H), 1.72 (s, 3H), 2.2 (m, 2H), 3.0 (m, 1 H), 4.7 (s, 1 H), 4.8 (m, 1 H), 5.5 (m, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.2, 17.4, 20.6, 28.7, 41.9, 105.8, 110.1, 123.1, 131.9, 148.4, 149.9; MS (*m*/*z*) 222, 207, 149, 133.

m-CPBA (9.17 g, 31.9 mmol) was added to a solution of the enol silane (5.88 g, 26.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C over 10 min. The solution was stirred for 1 h at 0 °C and then poured into saturated $Na_2S_2O_3$ solution. The organic phase was washed with saturated $NaHCO_3$ solution and saturated NaCl solution. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give silyl ether **33** (7:1 trans:cis) as yellow oil (4.69 g, 74%) (*trans* ether **33**): IR (film) 3481, 3070, 2944, 1729, 1673, 1243 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ *trans* isomer: 0.12 (s, 9H), 1,75 (s, 3H), 1.78 (s, 3H), 2.3−2.8 (m, 2H), 2.5 (m, 1H), 4.1 (d, J = 12.0 Hz, 1H), 4.83 (m, 2H), 6.65 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.45, 15.8, 19.9, 30.8, 51.1, 77.3, 113,1, 134.3, 143,7, 144.8, 199.6; MS (*m*/*z*) 238, 223, 182.

TBS Ether 34. HF (48%, 0.365 mL, 10.1 mmol) was added over 10 min to a mixture of *cis*- and *trans*-trimethylsiloxyketones **33** (2.00 g, 8.40 mmol) in CH_3CN (**20** mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and then concentrated in vacuo and the residue extracted three times with CH_2Cl_2. The combined organics were washed with saturated $NaHCO_3$ solution, saturated NaCl solution, and then dried over $MgSO_4$. Flash chromatography with 20/80 ethyl acetate/hexanes gave the corresponding alcohol (0.56 g, 40%) as a pale yellow oil. IR (film) 3453,3070, 2925, 1668 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ *trans* 1.8 (s, 6H), 2.4 (m, 2H), 2.7 (m, 2H), 3.8 (bs, 1H), 4.15 (d, J = 11.9 Hz, 1H), 4.9 (m, 1 H), 6.75 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.5, 18.8, 30.7, 51.1, 74.5, 113.6,133.1, 144.2, 145.7, 200.6; MS (*m*/*z*) 166, 161, 148, 137, 120, 109, 82, 77, 54, 41, 39.

Imidazole (0.104 g, 1.5 mmol) and TBDMSCl (0.108 g, 0.71 mmol) were added to a solution of the alcohol (0.100 g, 0.6 mmol) in dry DMF (1 mL). The reaction mixture was stirred at 50 °C for 10 h and then diluted with CH_2Cl_2 and filtered. The filtrate was washed once with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography with 5/95 ethyl acetate/hexane yielded TBS ether **34** (0.15 g, 92%) as a colorless liquid. IR (film) 3453,3070, 2925, 1677 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.19 (s, 3H), 0.86 (s, 9H), 1.74 (s, 3H), 1.76 (s, 3H), 2.4 (m, 2 H), 2.77 (ddd, J = 5.3, 11.7, 15.6 Hz, 1H), 4.12(d, J = 11.7 Hz, 1H), 4.85 (s, 2H), 6.64(m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.5, −3.5, 15.8, 18.7, 20.2, 25.7, 25.9, 30.5, 51.4, 113.6, 134.2, 143.4, 144.4, 200; MS (*m*/*z*) 265(M + 1), 223, 205, 193, 181, 165, 143, 129, 105, 75. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.32; H, 9.91.

Alcohol 35. n-BuLi (0.14 g, 0.35 mmol) was added to a solution of tetravinyltin (0.019 g, 0.083 mmol) in THF (5 mL) at −78 °C. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The mixture was then cooled to −78 °C and TBS ether **34** (0.100 g, 0.35 mmol) added. The cooling bath was removed and the reaction stirred at room temperature for 6 h. The reaction mixture was poured into saturated $NaHCO_3$ and isolated by extractive workup. The residue was purified by flash chromatography with 2/98 ethyl acetate/hexanes to give alcohol **35** (0.076 g, 70%) as a white solid, mp: 88−91 °C. IR (film) 3426 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 1.6 (s, 3H), 1.7 (s, 3H), 2.07 (m, 2H), 2.50 (ddd, J = 8.3, 10.2, 15.3 Hz, 1H), 3.04 (s, 1 H), 3.67 (d, J = 10.3 Hz, 1H), 4.83 (s, 2H), 5.24 (d, J = 10.1, 1H), 5.44 (d, J = 17.0 Hz, 1H), 5.56 (s, 1H), 5.62 (dd, J = 10.3, 17.1 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −3.6, −3.4, 18.5, 18.7, 22.1, 26.3, 30.0, 44.7, 76.0, 77.8, 113.3, 116.1, 124.5, 134.5, 143.1, 145.8; MS (*m*/*z*) 251,198, 159, 141, 131, 105, 95, 75. Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45. Found: C, 70.28; H, 10.35.

Isobutyrate Ester 36. TBAF (0.58 g, 0.64 mmol) was added to a solution of TBS ether **35** (0.100 g, 0.32 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred at room temperature for 30 min, and then concentrated in vacuo. The residue was dissolved in ether and washed with water. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography with 20/80 ethyl acetate/hexanes to furnish the corresponding diol **36** (0.056 g, 90%). IR (film) 3412, 1612, 1250 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.72 (s, 3 H), 2.0 (m, 3H), 2.59 (m, 2H), 3.56 (d, J = 8.7 Hz, 1H), 4.91 (s, 1 H), 4.93 (s, 1H), 5.33 (d, J = 10.5 Hz,1H), 5.46 (d, J = 17.1 Hz, 1H), 5.59 (m, 1H), 5.74 (dd, J = 10.5, 17.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) d; 18.7, 18.9, 30.1, 44.2, 73.3, 75.2,

114.2, 115.4, 125, 134.2, 142.05, 145.5; MS (*m*/*z*) 194, 176, 158, 138, 121, 110, 95, 77. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.12.

MEMCl (0.18 g, 1.35 mmol) and diisopropylethylamine (0.17 g, 1.35 mmol) were added to a solution of the diol (0.0150 g, 0.903 mmol) in CH_2Cl_2 (10 mL). After stirring for 16 h at room temperature, the solution was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over $MgSO_4$. The crude product was purified by flash chromatography over Florisil with 20/80 ethyl acetate/hexanes. Unreacted MEMCl was removed via Kugelrohr distillation (90−95 °C/ 0.3 mm/Hg). The MEM ether (0.153 g, 60% yield) was isolated as a pale yellow oil: IR (film) 3435, 2347, 1436, 1113 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.75 (s, 3H), 2.06 (m, 2H), 2.68 (ddd, 1 J = 5.2, 11.1, 15.7 Hz, 1H), 3.35 (s, 3H), 3.47 (t, J = 4.6 Hz, 2H), 3.65 (m, 3H), 4.69 (dd, J = 7.1, 17.8, 2H), 4.82 (s, 1H), 4.85 (s, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.44 (d, J = 17.0 Hz, 1H), 5.57 (bs, 1H), 5.73 (dd, J = 10.5, 17.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.6, 18.7, 20.2, 30.3, 44.1, 59, 67.7, 71.7, 81.9, 91.2, 96.3, 113.2, 116.0, 125, 143, 145.8 MS (*m*/*z*) 253, 176, 161, 147, 137, 123, 109, 89, 81, 59. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.27; H, 9.32.

To a solution of the MEM ether (0.050 g, 0.177 mmol) in THF (5 mL) at 0 °C was added vinylmagnesium bromide (0.046 g, 1 M in THF, 0.35 mmol). The ice bath was removed and the reaction was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and isobutyric anhydride (0.084 g, 0.53 mmol) added. After stirring at room temperature for 10 h, the reaction mixture was poured into saturated $NaHCO_3$ solution and isolated by extractive workup. The residue was purified by flash chromatography with 20/80 ethyl acetate/hexanes to give ester **36** (0.037 g, 60%). IR (film) 3435,2347, 1735,1113 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (d, J = 7.1 Hz, 6H), 1.2 (f, J = 1.4 Hz, 3H), 1.58 (s, 3H), 1.73 (s, 3), 2.12 (m, 2H), 2.59 (hept, J = 7.1 Hz, 1H), 3.0 (ddd, J = 5.5, 9.7, 17.4 Hz, 1H), 3.34 (s, 3H), 3.47 (m, 2H), 3.74 (m, 2H), 4.0 (d, J = 10.3 Hz, 1H), 4.61 (d, J = 6.9 Hz, 1H), 4.82 (m, 3H), 5.12 (d, J = 10.69 Hz, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.68 (bs, 1H), 5.75 (dd, J = 10.3, 17.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.9, 19.1, 19.3, 20.5, 28.8, 34.7, 44.1, 59.0, 67.5, 71.7, 76.6, 80.5, 82.7, 95.8, 112.4, 113.5, 125.2, 133.1, 140.3, 146.4, 175.0. MS (*m*/*z*) 375.2 (M + 23(Na)), 264, 189, 106. Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.28; H, 8.92.

Diene (*Z*)-38. (Method i). Ester **36** (0.045 g, 0.12 mmol) gave the Claisen product as the TIPS ester. NBu_4F (0.144 g, 0.16 mmol) was added to a solution of the crude TIPS ester (0.040 g, 0.08 mmol) in THF (5 mL) at 0 °C. After 3 h the reaction mixture was concentrated in vacuo. The residue was dissolved in ether and washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield the corresponding acid **37**, which was used without further purification.

A stream of diazomethane, prepared from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (0.18 g, 1.22 mmol) and NaOH (0.58 g, 2N, 10.8 mL), was flushed with nitrogen gas into a solution of acid **37** (0.036 g, 0.102 mmol) in ether (10 mL). After the reaction was complete a drop of acetic acid was added. The solution was concentrated in vacuo and purified by flash chromatography with 10/90 ethyl acetate/hexane to give methyl ester **38** (0.026 g, 60% from ester **36**). IR (film) 2347, 1727, 1639,1113 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.15 (s, 3H), 1.69 (s, 3H), 1.95 (s, 3H), 2.14 (m, 1H), 2.54 (m, 4H), 3.38 (s, 3H), 3.45 (m, 2H), 3.63 (s, 3H), 3.75 (m, 2H), 4.1 (d, J = 4.2 Hz, 1H), 4.67 (d, J = 6.7 Hz, 1H), 4.74 (s, 2H), 4.76 (d, J = 6.7 Hz, 2H), 5.18 (t, J = 7.3 Hz, 1H), 5.54 (bs, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.3, 23.8, 24.7, 25.1, 27.4, 39.3, 42.7, 44.9, 51.7, 59.0, 66.9, 71.8, 80.5, 92.7, 111.3, 126.3, 127.8, 130.1,134.7,145.0, 177.9. MS (*m*/*z*)0.389.2 (M + 23(Na)), 260, 189, 176, 122, 106. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.69; H, 9.47.

Diene (*E*)-38. A solution of ester (Z)-**38** and a catalytic amount of Ph_2S_2 in $CDCl_3$ was irradiated using a sun lamp for 0.5 h to afford diene (*E*)-**38**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.19 (s, 3H), 1.70 (s, 3H), 1.75 (s, 3H), 2.10 (m, 1H), 2.59 (m, 4H), 3.39 (s, 3H), 3.56 (dd, J = 3.9, 4.9 Hz, 2H). 3.65 (s, 3H), 3.71 (m, 3H), 4.68 (m, 2H), 4.73 (s, 2H), 5.51 (t, J = 7.5 Hz, 1H), 5.58 (m, 1H).

Diene (*E*)-6b. ^{n}BuLi (2.1 mL, 1.6 M in hexane, 3.36 mmol) was added to a solution of acid **10b** (0.23 g, 0.76 mmol) in THF (30 mL) at −78 °C. After 30 min, AcOH (0.44 mL, 7.7 mmol) was added and the mixture allowed to warm to room temperature. The mixture was poured into water and the crude material isolated by extractive workup. The residue was dissolved in ca. twice its volume of NEt_3 and the mixture purified by flash chromatography over silica gel with ether followed by 1/99 AcOH/ether gave isomerically pure acid (*E*)-**6b** as colorless oil (0.13 g, 81%).

Alcohol 42. ^{n}BuLi (1.04 mL, 1.6 M in hexane, 1.66 mmol) was added to a solution of acid **10b** (100 mg, 0.33 mmol) in THF (30 mL) in hexane at −78 °C. After 30 min, isobutyraldehyde (0.18 mL, 0.14 g, 1.98 mmol) was added, followed after 30 min by AcOH. After warming to room temperature, the resulting mixture was poured into water and the crude material isolated by extractive workup. The product was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give acid alcohol **42** as clear oil (70 mg, 71%): IR ($CDCl_3$) 3412 (m), 2953 (m), 1691; ^1H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3H), 0.86, (d, J = 5.5 Hz, 3H), 0.98 (s, 3H), 0.99 (s, 3H), 1.78 (s, 3H), 1.19 (s, 3H), 1.44 (t, J = 6.5 Hz, 2H), 1.89 (m, 1H), 2.30 (m, 2H), 2.37 (d, J = 7.7, 2H), 4.12 (d, J = 5.7 Hz, 1H), 5.49 (t, J = 7.7 Hz, 1H), 5.54 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 17.28, 20.07, 23.24, 24.60, 24.82, 29.15, 29.34, 32.10, 32.54, 36.74, 38.38, 42.99, 77.05, 118.58, 135.70, 136.37, 136.41, 184.11; MS (*m*/*z*) 294, 276, 261, 233, 205, 189, 147, 133, 119, 105, 91, 55, 43, 28. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.15.

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Supporting Information Available: Experimental procedures for compounds **4b**, **6b**, **8c**, **10b**, **11b**, **13b**, **15b**, **16a**,**b**,**d**, amide of **18c**, **18d**, **20**, **22**, **24**, **26**, **29b**, **31b**; ^1H and ^{13}C NMR spectra data for all new compounds described in the Experimental Section; ORTEP of the amide of acid **18b** and of alcohol **35**; structure proof of esters **29a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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