Enantioselective Synthesis of (−)-Trichodiene

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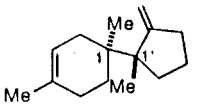
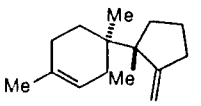
An enantioselective synthesis of trichodiene 1 has been accomplished. The key bond between the vicinal quaternary centers is formed by way of an Ireland–Claisen rearrangement of the ketene silyl acetal **24**. The rearrangement occurs with complete facial selectivity and excellent diastereoselectivity to give an advanced intermediate that is directly converted to *ent*-trichodiene, (−)-**1**.

The sesquiterpene trichodiene, (+)-**1**,[1] is the biogenetic precursor to the trichothecene mycotoxins, *e.g.*, verrucarol (**2a**), anguidine (**2b**), and deoxynivalenol (**2c**),[2] which are fungal metabolites possessing diverse biological activity.[3] The key role of **1** in the biosynthesis of the trichothecenes and the synthetic challenge posed by the presence of two contiguous asymmetric quaternary centers in the molecule[4] have prompted several groups to synthesize racemic trichodiene.[5] We report here the development of a chiral route to *ent*-trichodiene, (−)-**1**, the unnatural antipode of this hydrocarbon, via an Ireland ester–enolate Claisen rearrangement,[6] for which we define the facial preference and diastereoselectivity. The methodology that has been developed sets the stage for a highly convergent enantioselective synthesis of the trichothecenes **2** themselves.

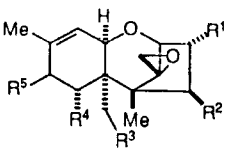
The present approach to **1** relied on studies toward trichodiene previously explored by our group.[5c,7] One of these investigations established that (*Z*)-ketene silyl acetal **3** is formed through chelation-controlled deprotonation and subsequent silylation of the corresponding ester and that the [3,3]-sigmatropic rearrangement of **3** occurs preferentially through a chairlike transition state; the resulting product has the correct *relative* stereochemical disposition about the vicinal quaternary centers for elaboration to trichodiene (Scheme I).[5c] In a companion study it was shown that the Claisen rearrangement of certain conformationally rigid cyclohexyl derivatives takes place *exclusively* from the equatorial face (eq 1) to give intermediates with vicinal quaternary centers.[7] This facial



(+)-**1**

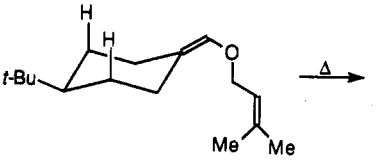


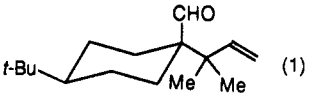
(−)-**1**



	R_1	R^2	R^3	R^4	R_5
2a	H	OH	OH	H	H
2b	OH	OAc	OAc	H	H
2c	OH	H	OH	OH	=O

selectivity appears to be the result of interaction between the substituents at the terminus of the allyl moiety and





(1)

the axial hydrogen atoms at C(3) and C(5) of the ring.

The retrosynthetic analysis outlined in Figure 1 summarizes a strategy that combines diastereoselective formation of a (*Z*)-ketene silyl acetal from a chiral ester with subsequent rearrangement having specific facial selectivity to enable a chiral synthesis of trichodiene (**1**). The linchpin of this synthetic sequence is ester **4**, in which the group G is an effective chelator of metal ions to ensure chelation control in the deprotonation step leading to the (*Z*)-ketene silyl acetal;[5c] thermal rearrangement of this intermediate via a preferred chairlike transition state would produce an advanced intermediate to trichodiene. The carboxylate portion of ester **4** was envisioned to arise from the known β-keto ester **6**.[8]

The proposed approach was first assessed on racemic substrates. Thus, reduction of **6** gave the three diastereomeric hydroxy esters **7a–c** in a ratio of 35:45:20 (eq 2). The relative stereochemistries of the three diastereomers were assigned based on the observed coupling constants,

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(1) (a) Machida, Y.; Nozoe, S. *Tetrahedron* **1972**, *28*, 5105–5111. (b) Nozoe, S.; Machida, Y. *Tetrahedron Lett.* **1970**, 2671–2674.

(2) For lead references see, Zamir, L. O.; Devor, K. A.; Nikolakakis; Nadeau, Y.; Sauriol, F. *Tetrahedron Lett.* **1992**, *33*, 5181–5184; Heskethy, A. R.; Gledhill, L.; Marsh, D. C.; Bycroft, B. W.; Dewick, P. M.; Gilbert, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1184–1186.

(3) Joffe, A. Z. *Fusarium Species: Their Biology and Toxicology*; John Wiley & Sons, Inc.: New York, 1986.

(4) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460.

(5) (a) Tanaka, M.; Sakai, K. *Tetrahedron Lett.* **1991**, *32*, 5581–5584. (b) Harding, K. E.; Clement, K. S.; Tseng, C.-Y. *J. Org. Chem.* **1990**, *55*, 4403–4410. (c) Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *30*, 4193–4196. (d) Snowden, R. L.; Brauchli, R.; Sonnay, P. *Helv. Chim. Acta* **1989**, *72*, 570–593. (e) Pearson, A. J.; O'Brien, M. K. *J. Org. Chem.* **1989**, *54*, 4663–4673. (f) Pearson, A. J.; O'Brien, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1445–1447. (g) VanMiddlesworth, F. L. *J. Org. Chem.* **1986**, *51*, 5019–5021. (h) Kraus, G. A.; Thomas, P. J. *Ibid.* **1986**, *51*, 503–505. (i) Gilbert, J. C.; Kelly, T. A. *Ibid.* **1986**, *51*, 4485–4488. (j) Gilbert, J. C.; Wiechman, B. E. *Ibid.* **1986**, *51*, 258–260. (k) Harding, K. E.; Clement, K. S. *ibid.* **1984**, *49*, 3870–3871. (l) Schlessinger, R. H.; Schultz, J. A. *Ibid.* **1983**, *48*, 402–408. (m) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427–428. (n) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077–4085.

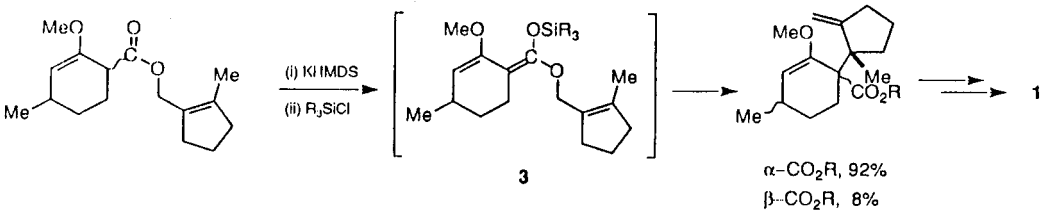
(6) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

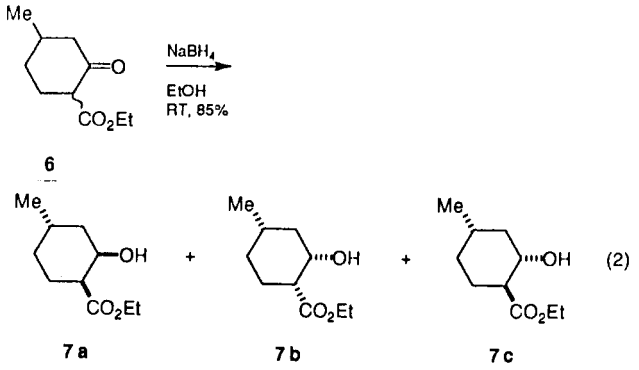
(7) Rojas, H. M. A. Thesis, University of Texas at Austin, 1983.

(8) Djerassi, C.; Burakevich, J.; Chamberlin, J. W.; Elad, D.; Toda, T.; Stork, G. *J. Am. Chem. Soc.* **1964**, *86*, 465–471.

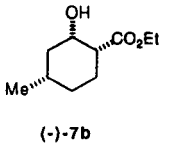
0022-3263/93/1958-6255$04.00/0

Scheme I





$J_{H\text{-}H}$, in the ^1H NMR spectra of these compounds.[9] The β-hydroxyallyl ester**9** was prepared from **7b** (Scheme II)



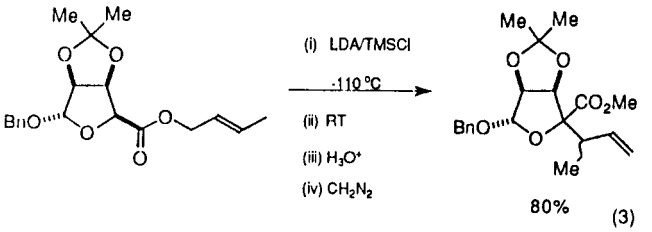
(-)-7b

to examine the potential of creating vicinal quaternary centers by the Claisen rearrangement of alkoxide enolates;- although the dianionic modification of the Claisen rearrangement of acyclic β-hydroxy allyl esters is known,[10] its applicability in a system like **9** was unexplored. Formation of the alkoxide enolate **9a**, thermal rearrangement, and transesterification afforded a product of rearrangement (40% yield), tentatively assigned the stereochemistry shown in **10**, together with the β-elimination product**11** (10% yield) and a mixture of **9** and its C(1) epimer (32% yield). The fact that only a *single* diastereomer arising from the rearrangement was seen in the ^1H NMR spectrum implied that complete facial selectivity attends the rearrangement of **9a**.

Si facial selectivity was expected for the rearrangement, based on analogy to the stereochemical outcome depicted in eq 1[7] and the assumption that the preferred conformation for the rearrangement would have the methyl and alkoxide functions of**9a** equatorial. Rigorous proof of the selectivity was provided by an X-ray crystallographic analysis of the 3,5-dinitrobenzoate ester (DNB) derived from **10** (Scheme II). The stereochemical assignments in **10** show that the dianionic version of the Claisen rearrangement of an appropriate analog of **9** might allow formation of the C(1)–C(1′) carbon–carbon bond of **1** to afford a product having both the relative *and* the absolute stereochemistry of (+)-trichodiene.

Unfortunately, extension of this methodology to the preparation of an advanced intermediate for synthesis of trichodiene failed. Indeed, the alkoxide enolate **13a** derived from **13**, itself prepared from acid **7b** and the known allyl alcohol **5**,[11] did not rearrange even under conditions of reflux in THF (Scheme III); rather, the only isolable product was the ester **15** derived from β-elimination of **13**. This undesired result presumably reflects increased steric hindrance in the transition state for rearrangement of **13a** as compared to that for **9a**.

An alternate route to effect the rearrangement was based on the work of Ireland's report that ketene silyl acetals could be produced from ester enolates having β-alkoxy leaving groups (eq 3).[12] Thus, it was felt that prior



protection of the hydroxy group in **13** would enable formation of the intermediate ketene silyl acetal for the [3,3]-sigmatropic rearrangement.[13] An important criterion for the protecting group was that it not inhibit the chelation needed to ensure formation of the (*Z*)-ketene acetal.[5c] This excluded protection of the alcohol as the silyl ether because it is known that the oxygen atom of such a group is a poor chelator of metal ions when compared to alkyl ethers.[14] Therefore, a methyl ether seemed appropriate from the point of view of ease of installation and removal of the protecting group.[15]

To prepare the appropriate carboxylate portion and to set the stage for a chiral synthesis of **1**, the β-keto ester **6** was reduced with bakers' yeast under fermenting conditions to give (−)-**7b**, as the only product, in 40% yield but in only 45 ± 2% enantioselectivity (ee).[16] Reductions of related β-keto esters with bakers' yeast under a variety of conditions are reported in the literature, and product ee's up to 98% have been observed.[17] Given that the enantioselectivity in the yeast reduction of acyclic β-keto esters is influenced by the steric bulk at the site of reduction,[18] it is likely that the low ee seen in the reduction

(9) For a detailed discussion of the structural assignments of **7a** and **7c** see: Selliah, R. D. Ph. D. Dissertation, The University of Texas at Austin, 1992.

(10) (a) Kurth, M. J.; Yu, C.-M. *Tetrahedron Lett.* **1984**, *25*, 5003–5006. (b) Fujisawa, T.; Tajima, K.; Ito, M.; Sato, T. *Chem. Lett.* **1984**, 1169–1172.

(11) Harding, K. E.; Clement, K. S.; Gilbert, J. C.; Wiechman, B. E. *J. Org. Chem.* **1984**, *49*, 2049–2050.

(12) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285.

(13) Attempts to trap dianion **13a** by addition of (trimethylsilyl)-trifluoromethane sulfonate or of diisopropylsilyl bis(trifluoromethanesulfonate) afforded *rac*-**15** as the only isolable product, in yields of 65 and 75%, respectively.

(14) (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1986**, *27*, 281–284. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480–5482. (c) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697–703.

(15) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 15–17.

(16) Enantiomeric purity was determined by ^1H NMR analysis of (−)-**7b** in the presence of (+)-Eu(hfc)$_3$ shift reagent. Resolution of the methyl triplet of the ester was sufficient for the desired analysis.

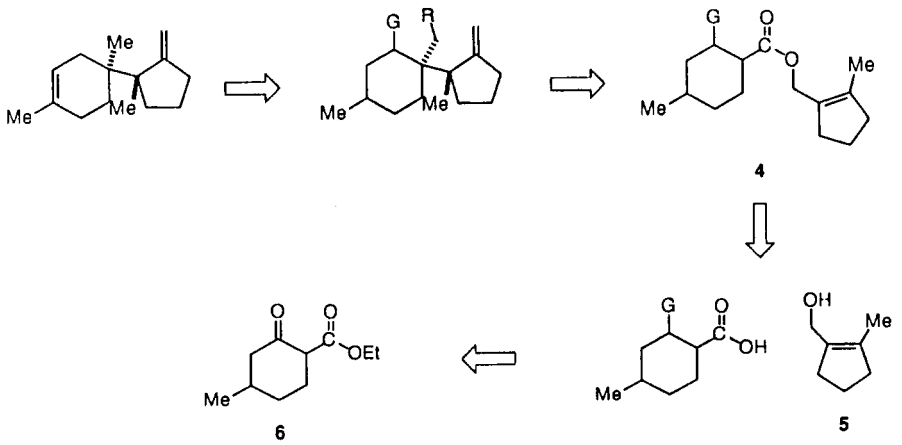
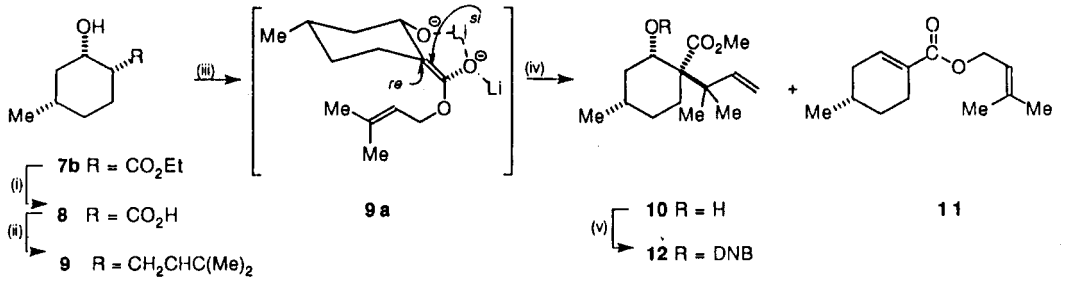


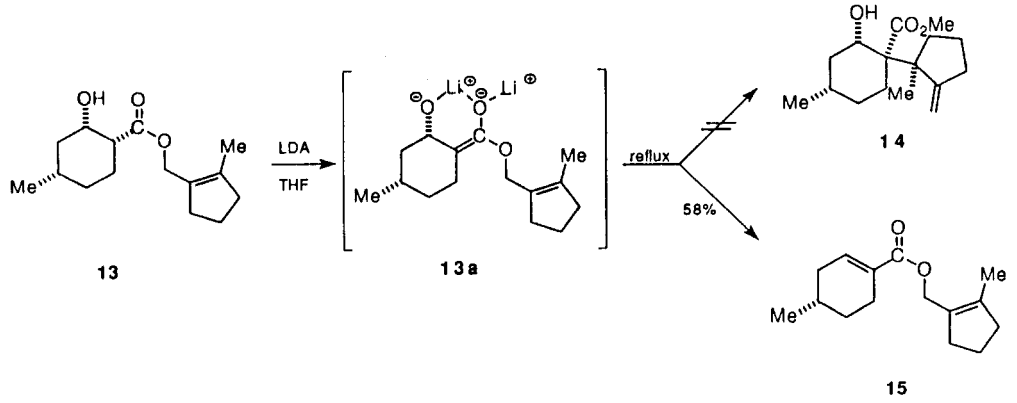
Figure 1. Retrosynthetic analysis for preparation of trichodiene (1).

Scheme II[a]

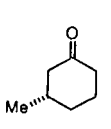


[a] Reagents: (i) (a) 2.5 N LiOH, H_2O; (b) H_3O^+, 99%; (ii) DCC, DMAP, prenyl alcohol (2.0 equiv), CH_2Cl_2, 60%; (iii) 2.2 equiv of LDA, THF; (iv) (a) rt, 60 h; (b) H_3O^+; (c) CH_2N_2, 40%; (v) 3,5-DNBCl, pyridine, 93%.

Scheme III



of **6** reflects such steric factors. The absolute configurations of the chiral centers in (−)-**7b** were determined to be 1*R*, 2*S*, and 4*S* by hydrolysis and decarboxylation of the ester to the known (−)-(*S*)-3-methylcyclohexanone (**16**).[19] This stereochemical outcome is similar to that observed with the yeast reduction of related systems.[17]



(-)-16

Methylation of (−)-**7b** (Scheme IV) required *in situ* trapping of the alkoxide, since attempts to produce the desired ether **17** by sequential formation of the alkoxide followed by alkylation led to substantial β-elimination. The product was contaminated with some 8% of its C(1) epimer, **18**, as determined by ^1H NMR spectroscopy. Hydrolysis of the mixture of **17** and **18** according to the procedure of Seebach *et al.*[20] afforded the acid **19** as a single compound after recrystallization.

For the purpose of model studies, **19** was first esterified with prenyl alcohol (Scheme IV), following a procedure described by Turner *et al.*[21] to form ester **20** without epimerization, as shown by its ^1H NMR spectrum.[22] The next task was to subject **20** to the conditions prescribed by Ireland *et al.*[12] for the formation and rearrangement

(17) (a) Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459–2467. (b) Herrandón, B.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690–714. (c) Fráter, G.; Günther, W.; Müller, U. *Helv. Chim. Acta* **1989**, *72*, 1846–1851.

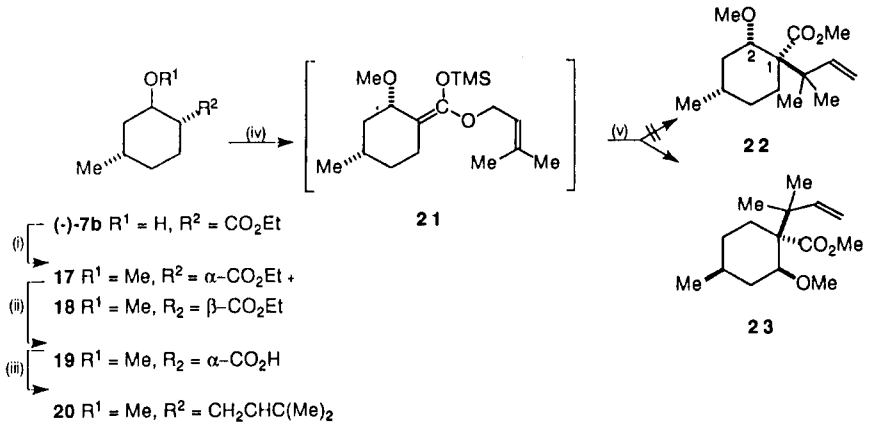
(18) Hudlicky, T.; Tsunoda, T.; Gadamasetti, K. G.; Murry, J. A.; Keck, G. E. *J. Org. Chem.* **1991**, *56*, 3619–3623.

(19) Thurkauf, A.; Hillery, P.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **1987**, *52*, 5466–5467.

(20) Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F. *Helv. Chim. Acta*, **1984**, *67*, 1843–1853.

(21) Chandrasekaren, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727–731.

Scheme IV[a]



[a] Reagents: (i) CH_3I, KH, THF, −20 °C, 95%; (ii) 4 N HCl, reflux, 88%; (iii) MsCl, TEA, CH_2Cl_2, then DMAP, prenyl alcohol, 95%; (iv) LDA, TMSCl, TEA, THF, −110 °C; (v) (a) rt, 12 h, (b) H_3O^+; (c) CH_2N_2.

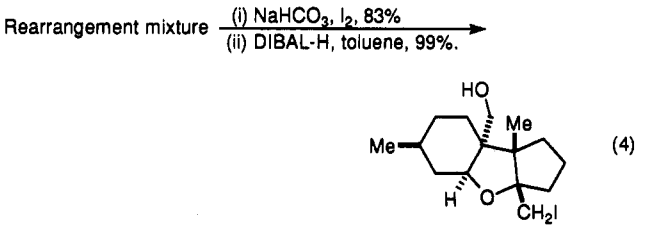
of the intermediate ketene silyl acetal. Their use of HMPA as a co-solvent had to be avoided in order to optimize chelation control for the formation of the enolate, since HMPA would compete for the metal ion involved in the intramolecular complex. Although omission of HMPA might have affected the rate and regioselectivity of silylation of the enolate and even fostered elimination, this was not to be the case. Indeed, Ireland–Claisen rearrangement of **20** afforded a gratifying 76% yield of a rearranged ester as a *single* diastereomer (NMR spectroscopy), which was initially assigned as **22** (Scheme IV), the product of *si* facial selectivity. The β-elimination product was not detectable by ^1H NMR spectroscopy, under conditions such that as little as 5% of it would have been seen.

A puzzling observation arose from the ^1H NMR spectrum of the rearrangement product: the signal for C(2)-H appeared as a broad multiplet, implying an equatorial or pseudoequatorial orientation for this proton. It should be in an axial position if the same facial selectivity as seen in the rearrangement of **9a** had prevailed with **21**. Such an axial orientation of C(2)-H is apparent in the solid structure of **12** *and* in the ^1H NMR spectrum of **10**, in which the signal for this proton appears as a doublet-of-doublets with coupling constants of 11.4 ($J_{ax\text{-}ax}$) and 4.1 ($J_{eq\text{-}ax}$) Hz. The NMR data for the product derived from **20** are thus more consistent with the stereochemistry expected from *re* facial selectivity, which would provide **23** instead of **22** (Scheme IV).

Despite the uncertainty regarding the facial selectivity, the formation of only a single diastereomer from the silylation and rearrangement of **20** was a key observation. It proved that thermal isomerization of ketene silyl acetal **21** occurs with complete facial selectivity and strongly implies that a single diastereomer of **21** is produced as well. Confirmation of the latter point was available from the ^1H NMR spectrum of **21**, in which only one singlet for methoxy and one doublet for the C-4 methyl protons were detected. It is highly unlikely that a minor amount (>4–5%) of another diastereomer would have all its signals obscured by the resonances of the major diastereomer. Although this result did not define the geometry of the ketene acetal, precedent[5c] dictates that chelation control directs the enolization of the ester and fosters eventual formation of (*Z*)-ketene silyl acetal **21**.

The successful Ireland–Claisen rearrangement of **20** prompted application of this synthetic concept to the creation of the trichodiene skeleton. The requisite precursor for the rearrangement is ester **24** (Scheme V), which was prepared from the optically active carboxylic acid **19** and alcohol **5** with the methodology outlined for the synthesis of **20**. Ireland–Claisen reaction of **24** by the protocol used with **20** afforded a mixture of two diastereomeric products in the ratio of 92:8 and initially assigned as **26** and **27**, respectively. The observed ratio reflects dominance of the chairlike pathway for the [3,3] sigmatropic rearrangement and correlates well with those reported by Gilbert *et al.* for the rearrangement of related systems.[23]

As was noted for the rearrangement product from **20**, a disturbing feature in the ^1H NMR spectrum of the product mixture was that the C(2)-H resonance was a broad multiplet. There was no direct method for analyzing these compounds to confirm whether the distortion was due to a conformational effect or was the result of a facial selectivity different from that observed with **9a**. This question was answered, however, by conversion of the major diastereomer to a solid iodo ether, which was found to have structure **28** by X-ray crystallography.



(4)

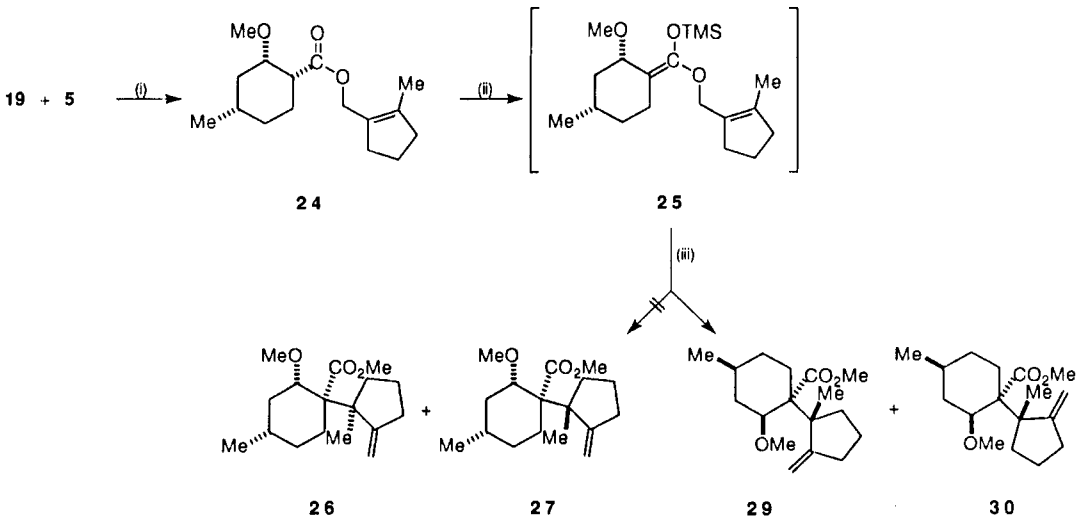
Consequently, the ketene silyl acetal **25** rearranges with *re* rather than *si* facial selectivity to give **29** and **30** (Scheme V). Moreover, the characterization of **28** confirms that **29** has the same *relative* stereochemistry as **1** at its vicinal quaternary centers, the result of a chairlike rearrangement of the (*Z*)-ketene silyl acetal **25** (Figure 2). Finally, on the reasonable assumption that the same *re* selectivity applies to the rearrangement of **21**, the correct structural assignment for its product is indeed **23**.

The structural assignments derived from **28** explain the appearance of C(2)-H as a broad multiplet in the ^1H NMR spectra of **23**, **29**, and **30**. The steric demand of the bulky

(22) The lack of epimerization is mainly of academic interest in the present instance, since the stereochemistry at C(1) is ultimately lost upon formation of the ketene silyl acetal.

(23) For a discussion of the chair/boat selectivity in related rearrangements see refs 5c and 5j.

Scheme V[a]



[a] Reagents: (i) MsCl, TEA, DMAP, CH_2Cl_2, 80%; (ii) LDA, TMSCl, TEA, THF, −110 °C; (iii) (a) reflux, 12 h; (b) H_3O^+; (c) CH_2N_2, Et_2O, 75%.

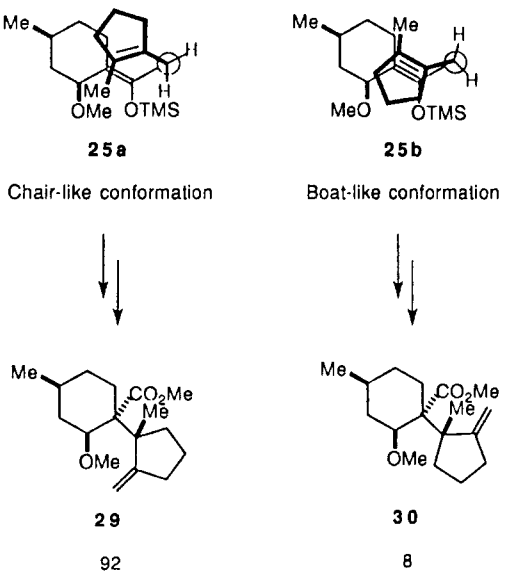
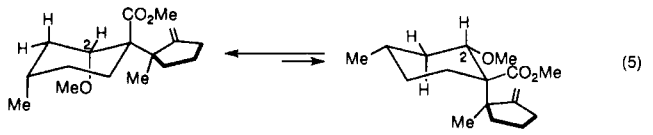


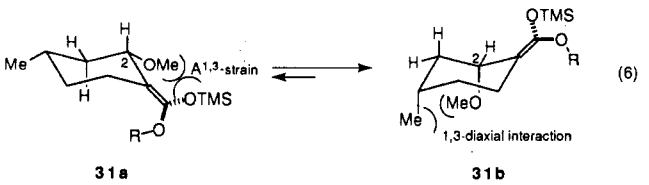
Figure 2. Reactive conformations for rearrangement of ketene silyl acetal **25**.

methylcyclopentyl group in **29**, for example, may be compared to a *tert*-butyl group (*A*-value for Bu^t = 5.7 kcal/mol[24]). Hence, this substituent would be expected to occupy an equatorial position in a chair conformation, as seen in **29a** (eq 5). This in turn would compel the other



three substituents to be axially oriented, even though an unfavorable 1,3-diaxial interaction between methoxy and methyl (a destabilization of about 1.9 kcal/mol[25]) is present in such a conformation. This interaction, together with that for an ester group (*A*-value of 1.1 kcal/mol),[24] is insufficient to counterbalance the large destabilization caused by the axial orientation of the methylcyclopentyl group in **29b**. Therefore, the appearance of C(2)-H as a broad multiplet is consistent with its being equatorially oriented in the conformation that has the bulky group equatorial as well.[26] This conclusion is borne out in the solid state, wherein the cyclohexane ring of **28** adopts a chair conformation in which the C(7)–C(8) bond is equatorial; hence, the C(1)–O(2) bond is axial and, in turn, C(1)-H, which corresponds to C(2)-H in **29**, is equatorial.

The complete reversal of facial selectivity in the isomerization of the ketene silyl acetals **21** and **25** as compared to that of the alkoxide enolate **9a** is remarkable. The *si* selectivity observed for the latter substrate is in complete accord with the proclivity of Claisen rearrangement of conformationally rigid cyclohexyl systems to occur from the equatorial face (eq 1),[7] and a rationale for departure from this in the acetals **21** and **25** is necessary. The most obvious explanation involves recognition of the fundamental structural differences in the two types of substrates. Namely, the strong chelation of Li^+ ions by the alkoxide and enolate moieties of **9a** promotes conformational rigidity in this intermediate and defines an equatorial disposition of the methyl and alkoxide groups; *si* selectivity of rearrangement is then expected. In contrast, **21** and **25**, collectively represented as **31** (eq 6),

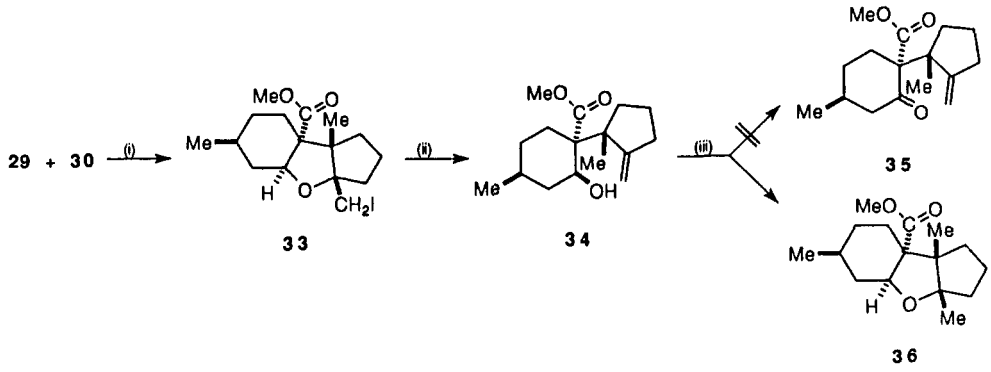


should be more mobile geometrically and presumably would allow access to **31b**, from which rearrangement could still occur from an equatorial face, *but* with *re* selectivity.

The interconversion of **31a** and **31b** should have an energy of activation of less than 10 kcal/mol.[27] Because this value is below the expected activation energy for the

(24) Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: New York, 1978; pp 153–154.
(25) Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765–780.
(26) MM2 calculations support the assumption that a chairlike conformation of **25a** is preferred to either a boatlike or twist-boat conformation.
(27) Gerig, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 1065–1066

Scheme VI[a]



[a] Reagents: (i) I_2, $NaHCO_3$, CH_3CN, 78%; (ii) Zn, EtOH, reflux 95%; (iii) Swern oxidation.

[3,3]-sigmatropic rearrangement of simple ketene silyl acetals, which are reported to be in the range 15–20 kcal/mol,[28] the Curtin–Hammett principle[29] applies to the system. To account for the stereochemical outcome of the rearrangement, the activation barrier for isomerization by way of **31a**, which would provide *si* facial selectivity, must be greater than that for **31b**, the source of *re* selectivity. We believe that torsional strain is the primary factor that destabilizes the transition state for rearrangement through conformer **31a** relative to that for **31b**. Specifically, during the rearrangement of **31a** from the more accessible *si* face, the developing carboxylate group becomes eclipsed with the equatorial OMe group, thus maximizing torsional strain.[30] Although a value for this strain cannot be readily estimated, the observed results would require that it be in the range of at least 1–2 kcal/mol.[31]

A second scenario provides a simpler, but, in the end, less probable way to explain the observed facial selectivity. This analysis starts with the relatively unlikely assumption that the barrier to interconversion of **31** is greater than that for Claisen rearrangement of the two conformers. This circumstance would dictate that the observed products would reflect the ground-state population of the ketene acetal conformers.[29] Superficial analysis of the conformational equilibrium for **31** (eq 6) would appear to favor **31a**, which has the methyl (Me) and methoxy (OMe) groups both equatorial and would lead to *si* selectivity. However, consideration of other possible intramolecular interactions makes it clear that the energy difference between the two chairlike conformations of the molecule may in fact favor **31b**. The assessment relies on computational studies of methylenecyclohexanes, **32**, in which conformer **32b** is found to be favored by 2.0 kcal/mol (eq 7).[32] The source of this preference is the $A^{1,3}$-strain in **32a**, which was shown to be 5.6–6.7 kcal/mol, as compared to the destabilization due to 1,3-diaxial interaction in **32b**, which is reported to be 2.6 kcal/mol. Extrapolation of these findings to ketene

32a 32b (7)

silyl acetals **31** (eq 6) implies that significant $A^{1,3}$-strain should be present in the conformer **31a**, due to the interaction of the OTMS group with the equatorial OMe group. The exact magnitude for this interaction cannot be inferred from the $A^{1,3}$-strain found in **32a** because of the difference in substituents in the two systems, but it seems reasonable that it would be greater than the approximately 1 kcal/mol of destabilization estimated[33] to be associated with the 1,3-diaxial interaction between the Me and OMe groups in conformer **31b**.

In summary, we believe that a rationale for the difference in the facial selectivity seen with the alkoxide enolate and the ketene silyl acetals is found in the greater conformational mobility of the latter substrates and torsional factors associated with their rearrangement. Equatorial approach of the allyl moiety to the cyclohexane ring prevails in both types of intermediates. Finally, an important ramification of the *re* facial selectivity is that the trichodiene produced by the isomerization of **24**, the *absolute* configuration of which is defined by (−)-**7b**, will be the unnatural antipode, *ent*-trichodiene, ((−)-**1**).

The transformations required to complete the synthesis were all centered on the cyclohexane ring of the advanced intermediate **29** and involved creation of a double bond between C(3) and C(4), removal of the oxygen atom at C(2), and reduction of the ester function to a methyl group. Deprotection of the methyl ether was the first task, and this was accomplished efficiently by subjecting **29** to the iodocyclization/reductive cleavage route shown in Scheme VI. The hydroxyolefin **34** was isolated as the only product of this sequence, as determined by ^1H NMR spectroscopy.

Attempted oxidation of **34** under the standard Swern reaction conditions[34] failed to produce the keto ester **35**; instead, the cyclization product **36** was isolated in high yield (Scheme VI). Since **36** was known to be the product of acid-catalyzed cyclization of **29**,[35] this result was initially ascribed to the acidic nature of the reaction medium.

(28) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733–5734.

(29) For a review of conformational effects on reactivity and the role of the Curtin–Hammett principle in such situations, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

(30) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205–2208.

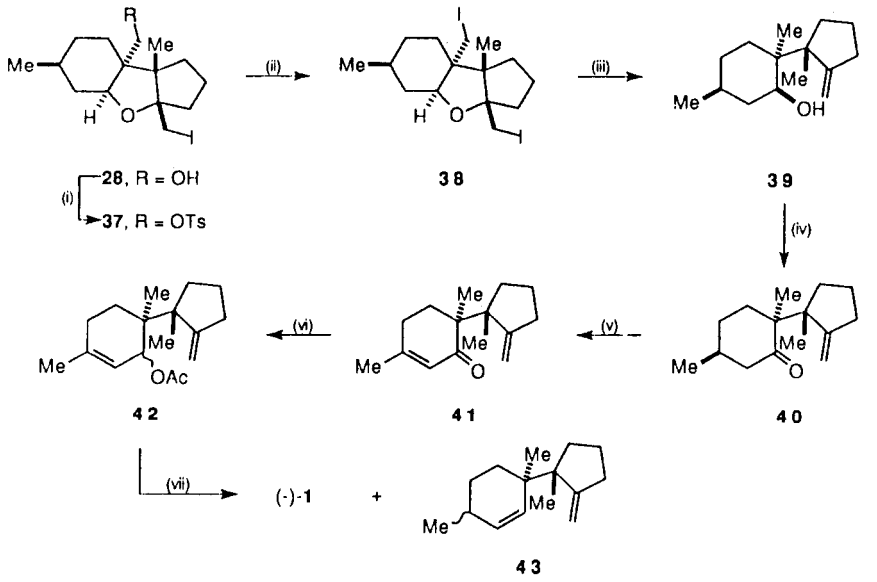
(31) It is recognized that development of the transition state for equatorial rearrangement of this conformation will potentially involve unfavorable steric hindrance caused by the axial OMe group; the axial Me group itself is unlikely to be a destabilizing factor for this transition state since it is remote from the site of reaction. However, examination of the chairlike transition state for the equatorial rearrangement, with the aid of Dreiding models, indicates that this interaction would not be particularly severe.

(32) Castello, A.; Jaime, C.; Marquet, J.; Moreno-Mañas, M. *Tetrahedron* **1985**, *41*, 3791–3802.

(33) The 1,3-diaxial interaction between OMe and Me in methylenecyclohexane was estimated based on the reported decrease in Me–Me 1,3-diaxial interaction in going from cyclohexane (3.7 kcal/mol[25]) to methylenecyclohexane (2.6 kcal/mol[32]). The Me–OMe 1,3-diaxial interaction in cyclohexane is reported to be 1.9 kcal/mol.[25]

(34) Mancuso, A. J.; Swern, D. *Synthesis*, **1981**, 165–185.

Scheme VII[a]

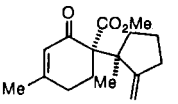


[a] Reagents: (i) TsCl, pyr, rt, 95%; (ii) NaI, DME, DMPU, 85 °C, 76%; (iii) Zn, THF, pyr, EtOH, reflux; (iv) oxalyl chloride, DMSO, TEA, CH_2Cl_2, 88%; (v) LDA, THF, PhSeCl, −78 °C, then H_2O_2, CH_2Cl_2, pyr, 45% (70% based on recovered 37); (vi) (a) DIBAL-H, toluene, 0 °C, (b) Ac_2O, pyr, rt, 63% (two steps); (vii) Li, $EtNH_2$, THF, −78 °C, 86% (combined yield).

Modified Swern conditions were later discovered under which **34** could be oxidized to **35** efficiently, an indication that the formation of **36** was *not* due to the acidity of the medium. Rather, the unexpected stability of **34** to the normal conditions for the Swern oxidation results in formation of **36** upon workup of the reaction mixture.[36]

The difficulties encountered with the oxidation of **34** led to development of a different approach for the conversion of iodo ester **33** to trichodiene. Thus, the ester group in **33** was reduced to the alcohol **28** (eq 4), which was transformed to diiodo compound **38** via the tosylate **37** (Scheme VII). Refluxing a slurry of **38** and Zn in a solvent system composed of 95% EtOH, THF, and pyridine[37,38] simultaneously reduced the C(2)-(iodomethyl) group and reversed iodoetherification to give hydroxyolefin **39** as the only isolable product. The crude product was immediately oxidized according to standard Swern protocol[34] to afford ketone **40**. This ketone was in turn converted to the enone **41** (Scheme VII) according to the procedure of Reich *et al.*[39]

The final step of the synthesis was excision of the enone oxygen to give (−)-**1**. In a previous synthesis of trichodiene, Gilbert and Kelly have reported that such a transformation could be effected in good yield in the closely related system **44** via the reduction of the tosylhydrazone.[5c,40,41] For the present case, the requisite tosylhydrazone derivative of **41** could not be prepared even under forcing conditions, a result that implicates the ester function in **44** as playing



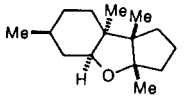
44

a role in the formation of the tosylhydrazone. An alternate route to the desired reduction of **41** to (−)-**1** was available, however, by way of the metal-promoted reduction of allylic acetates.[42] Toward this end, **41** was first reduced with DIBAL-H, and the resulting crude allylic alcohol was immediately acetylated to afford a diastereomeric mixture of two acetates **42**. Reduction of the acetates **42** with Li in ethylamine gave an 86% yield of a 2:1 mixture of trichodiene and the thermodynamically less stable double-bond isomer **43** (Scheme VII). The failure of the reaction to occur with the high regioselectivity engendered in the literature precedents is apparently the result of kinetic protonation of the intermediate allyl anion, which experiences severe steric hindrance at the secondary carbon site.[43] Pure trichodiene was readily separated from this mixture by chromatography on $AgNO_3$-impregnated silica gel.[5e] The product had α^{23}_D −10.0° (c = 0.2, $CHCl_3$) which translates to 47% ee, given the literature value[1] of +21° for the specific rotation of natural trichodiene (**1a**); its spectral data were identical to those of an authentic sample of natural trichodiene. The sign of the rotation for the synthetic material confirms that the Ireland ester–enolate Claisen rearrangement of **22** gives a product having the

(35) A sample of **29** in $CDCl_3$ was found to cyclize to **36** when allowed to stand overnight.

(36) A detailed analysis of this observation will be reported in due course: Gilbert, J. C.; Selliah, R. Manuscript in preparation.

(37) When the reductive cleavage of this compound was carried out in 95% EtOH some 30% of the undesired cyclized product **i** was also formed. Incorporation of pyridine into the solvent system prevented this side reaction. It is likely that Zn^{2+} promotes some aggregation which facilitates the formation of **i**. Pyridine has been used in other instances to sequester Zn^{2+} ions.[38]



i

(38) See, for example: Denis, J. M.; Girad, C.; Conia, J. M. *Synthesis* **1972**, 549–551.

(39) Reich, H. J.; Renga, J. M.; Reich, I. C. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

(40) In light of the fact that reductions of this nature are known to proceed with migration of the double bond,[41] our earlier report[5c] appears to be in error with regard to the selectivity of the reduction.

(41) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299–2301 and references cited therein.

(42) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501–1509 and references cited therein.

absolute configuration of *ent* trichodiene. Furthermore, a 47% ee for the trichodiene thus prepared demands complete transfer of chirality from (−)-**7b**, which was shown to be 45 ± 2% ee, as noted earlier.

In conclusion the present work outlines the first chemical synthesis of an optically active trichodiene. The presently revealed facial selectivity of the Ireland–Claisen rearrangement that is the key step of this synthetic sequence would enable the preparation of the natural antipode of trichodiene in optically pure form if the β-hydroxy ester (+)-**7b** were used as the starting material. The latter compound can be readily prepared by the chemical reduction of the known, chiral β-ketoester **6**[8] derived from (*R*)-3-methylcyclohexanone.

The methodology described herein for the preparation of trichodiene has been successfully applied to the synthesis of optically active *ent* trichothecenes. The details will be reported in due course.[44]

Experimental Section

Melting and boiling points were are uncorrected. High-pressure liquid chromatography was performed with two linked 2-ft × 1/4-in. columns packed with LC Porasil (type A) silica gel. Unless otherwise noted, chromatography of product mixtures was effected by flash column chromatography over silica gel, according to the procedure described by Still *et al.*[45] Title compounds were judged to be >95% pure by ^{1}H NMR spectroscopy. Unless otherwise noted, NMR spectra were obtained on samples in $CDCl_3$ and IR spectra on thin films. Chloroform that had been passed through a short pad of activated basic alumina was used as solvent for optical rotations.

All anhydrous reactions were performed under an inert atmosphere of dry N_2 or Ar. All reaction vessels, syringes, and hypodermic needles used in these reactions were dried in an oven at 120 °C for at least 12 h and cooled under an atmosphere of N_2 or in a desiccator. Solvents were dried by distillation, under an atmosphere of N_2, using the drying agents, sodium benzophenone ketyl, for tetrahydrofuran (THF), or CaH_2, for dichloromethane (CH_2Cl_2), triethylamine (TEA), diisopropylamine, *N,N'*-dimethylpropyleneurea (DMPU), and dimethyl sulfoxide (DMSO); THF and CH_2Cl_2 were used immediately after distillation, whereas the other solvents could be stored over 4Å molecular sieves. Skelly-B was stirred over concd sulfuric acid for at least 24 h and then over sodium carbonate for 24 h, after which it was filtered and distilled. All other reagents and solvents were purified, as necessary, according to standard procedures.[46] Alkyllithiums were titrated by the method of Suffert.[47] Unless noted otherwise, concentration of solutions was accomplished by rotary evaporation at water aspirator pressures.

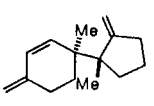
Ethyl (1*R,2*S**,4*S**)-2-Hydroxy-4-methylcyclohexanecarboxylate (7b).** To a solution of **6**[8] (5.6 g, 0.03 mol) in absolute ethyl alcohol (225 mL) was added $NaBH_4$ (2.3 g, 0.04 mol). The resulting mixture was stirred at room temperature for 2 h and then quenched by careful addition of 10 mL of 10% aqueous HCl. Solvent was removed under reduced pressure, and the residue was dissolved in 200 mL of ether and washed sequentially with H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried ($MgSO_4$) and concentrated to obtain 5.3 g of a colorless liquid, GLC analysis of which showed the presence of three diastereomers in the ratio of 35:45:20. The components were separated by HPLC (30% EtOAc/Skelly B), and **7b**, the compound of intermediate polarity, was obtained as a colorless liquid with a sweatlike odor (2.13 g, 38% yield): bp 45–50 °C (Kugelrohr distillation, 0.05 Torr); IR 3450 (broad), 1740 (s) cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 3.85 (m, 2H, 3.55 (dt, *J* = 10.7, 4.5 Hz, 1H), 3.46 (d, *J* = 9.2 Hz, 1H), 2.72 (q, *J* = 4.1 Hz, 1H), 2.05 (dq, *J* = 13.8, 3.5 Hz, 1H), 1.85 (m, 1H), 1.52 (q, *J* = 11.3, 11.6, 12.5 Hz, 1H), 1.22 (m, 1H), 1.19–1.08 (m, 2H), 0.95 (m, 1H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz) δ 174.52, 70.81, 60.35, 45.32, 40.53, 31.46, 30.57, 26.68, 21.94, 14.16; HRMS (CI, CH_4) *m/z* calcd for $C_{10}H_{19}O_3$ (M + H)$^+$ 187.1334, found 187.1327.

(−)-Ethyl (1*R*,2*S*,4*S*)-2-Hydroxy-4-methylcyclohexanecarboxylate [(−)-7b]. A procedure similar to that described by Fráter *et al.*[17c] was used. A 2-L Erlenmeyer flask, equipped for magnetic stirring, was charged with dry, active bakers' yeast (50 g, Red Star, Universal Foods Corp.) and deionized water (500 mL), and the mixture was stirred vigorously to effect a homogeneous suspension. Sugar (75 g) was added, and the mixture was stirred for 30 min. At this time **6** (5.0 g, 27 mmol) was introduced to the rapidly foaming mixture, and stirring was continued for 48 h at 23 °C. Products were isolated by extracting the aqueous reaction mixture with hexanes. The combined organic extracts were washed with brine until formation of an emulsion ceased (*ca.* 6–8 washes) and then dried ($MgSO_4$). Removal of solvent gave a reddish brown liquid which was chromatographed (20% EtOAc/Skelly-B) to give unreacted β-keto ester **6** (2.63 g, R_f 0.56, 52% yield) and β-hydroxy ester (−)-**7b** (2.40 g, R_f 0.32) as a pale yellow liquid. Kugelrohr distillation of this oil (bp 45–50 °C, 0.05 Torr) gave (−)-**7b** (2.0 g, 40% yield) as a colorless liquid. Spectral data were identical with those reported for racemic **7b**: α^{23}_D −18.3° (*c* = 1.0), corresponding to an ee of 45 ± 2.[16]

(1*R,2*S**,4*S**)-2-Hydroxy-4-methyl-1-cyclohexanecarboxylic Acid (8).** A mixture of 2.5 N aqueous LiOH (100 mL) and **7b** (3.0 g, 16 mmol) in 100 mL of THF was stirred at room temperature for 24 h. The reaction mixture was then cooled to 0 °C, acidified to pH 2 with 6 N HCl, and subsequently warmed to RT and saturated with solid NaCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$). Filtration and solvent removal gave a yellow liquid which was distilled to provide8 (2.5 g, 99% yield) as a clear, colorless viscous oil: bp 100–110 °C (Kugelrohr distillation, 0.05 Torr); IR 3200 (broad), 1720 (s) cm^{-1}; ^{1}H NMR δ 3.82 (m, 1H), 2.94 (m, 1H), 2.29 (m, 1H), 1.89 (m, 1H), 1.55–1.40 (m, 3H), 1.31 (m, 1H), 1.05 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR δ 177.79, 70.73, 44.81, 40.37, 31.39, 30.32, 26.34, 21.87; HRMS (CI, CH_4) *m/z* calcd for $C_8H_{14}O_3$ (M$^+$) 158.0943, found 158.0946.

3-Methyl-2-butenyl (1*R,2*S**,4*S**)-2-Hydroxy-4-methylcyclohexanecarboxylate (9).** A dry 100-mL round-bottom flask was charged with **8** (0.68 g, 4.3 mmol), 3-methyl-2-buten-1-ol (0.80 g, 10 mmol), DMAP (0.12 g, 1.0 mmol), and dry CH_2Cl_2 (30 mL). The mixture was stirred and cooled to 0 °C under an inert atmosphere. A solution of dicyclohexyl carbodiimide (DCC, 1.02 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was added to the mixture slowly via cannula over a period of 5 min. The resulting mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature, and stirred at that temperature for 18 h. The precipitate formed was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 mL of Skelly-B and filtered to remove solids, and the filtrate was then washed with 10% HCl, 10 mL of water, and brine and dried ($MgSO_4$). Removal of solvent left a viscous oil which was chromatographed to afford **9** (0.57 g, 60% yield) as a clear liquid: R_f 0.34 (30% EtOAc/Skelly-B); IR 3540 (m), 1735 (s) cm^{-1}; ^{1}H NMR δ 5.33 (m, 1H), 4.62 (d, *J* = 7.2 Hz, 2H), 3.65 (m, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 2.87 (m, 1H), 2.23 (m, 1H), 1.91 (m, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.56-1.25 (m, 4H), 0.92 (d, *J* = 6.2 Hz), 0.85 (m, 1H); ^{13}C NMR δ 174.62, 139.46, 118.21, 70.78, 61.31, 45.16, 40.47, 31.45, 30.51, 26.75, 25.69, 22.00, 10.02; HRMS (CI,CH_4) *m/z* calcd for $C_{13}H_{22}O_3$ (M$^+$) 226.1568, found 226.1577.

(43) Pearson *et al.* have reported that reduction of the diene ii with Na/NH_3 gave 1 and 41 in a ratio variously reported as 5:1[5f] and 9:1,[5e] both of which differ from the 2:1 ratio observed in the reduction of the acetates **40**. This discrepancy may reflect differences in the nature of ion pairing of the intermediate allyl anion formed in the two cases.



ii

(44) Gilbert, J. C.; Selliah, R. D. *Tetrahedron*, in press.

(45) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(46) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: New York, 1980.

(47) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–510.

Methyl (1S*,2S*,4S*)-2-Hydroxy-1-(2-methyl-3-butenyl)-4-methylcyclohexanecarboxylate (10). A solution of lithium diisopropylamide (LDA, 2.50 mmol) in dry THF (10 mL) was prepared and cooled to −78 °C under an Ar atmosphere. The allyl ester **9** (0.23 g, 1.0 mmol) in THF (2.0 mL) was added to the cold solution. The resulting mixture was stirred at −78 °C for 0.5 h and then allowed to warm to room temperature and stirred at that temperature for a period of 60 h. A positive pressure of Ar was maintained throughout this time. The solution was then cooled to 0 °C and quenched by treatment with 10 mL of 10% HCl solution. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, which had been acidified to pH 2, and then dried ($MgSO_4$). The ethereal solution was filtered, concentrated to about 10 mL, and treated with excess ethereal CH_2N_2. Workup of this mixture, in the manner outlined before, and concentration gave a yellow oil, which was subjected to flash chromatography (10% EtOAc/Skelly-B) to afford three components. The fastest moving component (R_f = 0.44), was found to be **11** (40 mg, 10% yield). The compound with intermediate mobility (R_f = 0.36) was **10** (97 mg, 40% yield), which was obtained as a colorless oil: IR 3550 (s), 3080 (w), 1735 (s), 1630 (w) cm^{-1}; ^1H NMR δ 6.11 (d, J = 17.4, 10.9 Hz, 1H), 4.95 (m, 2H), 3.72 (s, 3H), 3.60 (m, 2H), 2.12 (ddd, J = 13.6, 3.2, 3.2, 1H), 1.87 (m, 1H), 1.55 (m, 1H), 1.38 (m, 1H), 1.26–1.02 (m, 2H), 1.18, 1.12 (2 × s, 2 × 3H), 0.85 (d, J = 6.3 Hz, 3H), 0.66 (dq, J = 12.0, 2.9 Hz, 1H); ^{13}C NMR δ 176.24, 145.45, 112.32, 74.52, 51.20, 43.46, 41.15, 32.50, 31.81, 29.46, 25.01, 24.20, 21.65; HRMS (EI) m/z calcd for $C_{14}H_{24}O_3$ (M^+) 240.1725, found 240.1712.

Data for 3-methyl-2-butenyl (4S*)-4-methyl-1-cyclohexenecarboxylate (**11**): R_f 0.5; IR 1715 (s), 1670 (w), 1650 (w); ^1H NMR δ 6.94 (m, 1H), 5.34 (m, 1H), 4.62 (d, J = 7.1 Hz, 2H), 2.49–2.12 (m, 3H), 1.82–1.58 (m, 3H), 1.75 (s, 3H), 1.71 (s, 3H), 1.20 (m, 1H), 0.95 (d, J = 6.45 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.61, 139.08, 138.50, 130.15, 118.96, 61.18, 34.14, 30.34, 27.57, 25.76, 24.18, 21.43, 18.03; HRMS (EI) m / z calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1459.

The slowest moving component (R_f 0.2, 20% EtOAc/Skelly-B) to elute was a 1:1 mixture of **9** and its C-1 epimer (74 mg, 32% yield of mixture).

Methyl (1S*,2S*,4S*)-2-(3,5-Dinitrobenzoyloxy)-1-(2-methyl-3-butenyl)-4-methyl-1-cyclohexanecarboxylate (12). A mixture of **10** (97 mg, 0.40 mmol), freshly purified 3,5-dinitrobenzoyl chloride (0.20 g, 1.0 mmol), and pyridine (2.0 mL) was stirred at room temperature for 48 h. The reaction mixture was diluted with 50 mL of ether and washed sequentially with 10% HCl, water, sat. $NaHCO_3$ and brine and dried ($MgSO_4$). Filtration and solvent removal gave a yellow oil, which was purified by passage through a short column of silica gel (30% EtOAc/Skelly-B) to yield **12** (0.161 g, 93% yield) as a white powder. Crystallization of this material from a 1:1 mixture of 95% EtOH/CH_2Cl_2 afforded pale yellow cubic crystals: mp 111.0–112.5 °C; ^1H NMR δ 9.23 (s, 3H), 5.90 (dd, J = 17.3, 10.8 Hz, 1H), 5.14 (dd, J = 11.4,4.1 Hz, 1H), 4.81 (m, 2H), 3.90 (s, 3H), 2.37 (m, 1H), 1.95 (m, 1H), 1.65 (m, 2H), 1.42 (m, 2H), 1.09 (s, 6H), 0.90 (d, J = 6.2 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR δ 172.84, 161.43, 148.71, 144.77, 134.58, 129.69, 122.25, 111.93, 77.25, 56.87, 51.41, 41.64, 38.27, 31.90, 31.25, 30.57, 24.66, 24.07, 21.48; HRMS (EI) m/z calcd. for $C_{22}H_{26}N_2O_8$ (M^+) 434.1689, found 434.1686.

(2-Methyl-1-cyclopentenyl)methyl (1R*,2S*,4S*)-2-Hydroxy-4-methyl-1-cyclohexanecarboxylate (13). Esterification of **8** (2.66 g, 16 mmol) with 2-methyl-1-cyclopentenemethanol (**5**, 2.26 g, 20 mmol),[11] following the procedure described for preparation of **9**, provided **13** as a pale yellow oil after chromatography. Distillation of this oil afforded 1.73 g (43% yield) of pure **13** as a colorless liquid: R_f = 0.36 (30% EtOAc/Skelly-B); bp 110–120 °C (Kugelrohr distillation, 0.1 Torr); IR 3440 (s), 1720 (s) cm^{-1}; ^1H NMR δ 4.67 (s, 2H), 3.62 (m, 1H), 3.48 (d, J = 10.4 Hz, 1H), 2.87 (m, 1H), 2.34 (m, 4H), 2.20 (m, 1H), 1.76 (m, 3H), 1.70 (s, 3H), 1.40 (m,4H), 0.91 (d, J = 6.2 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR δ 174.66, 138.95, 129.34, 70.79, 60.99, 45.20, 40.51, 38.63, 34.55, 31.45, 30.55, 26.76, 22.01, 21.49, 13.92; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1713.

Rearrangement of Dianion Derived from 13. Ester **13** (0.25 g, 1.0 mmol) was converted to **13a** as a solution in THF (12.0 mL), utilizing the same procedure as that for forming **9a**. This solution was heated at the reflux temperature in THF for 12 h. Workup and chromatography of the reaction mixture, according to the method outlined for the rearrangement of **9**, gave **15** (0.135 g, 58% yield) as a colorless oil. A mixture of **13** and its C-1 epimer (47 mg) was also eluted from the chromatography column.

Data for (2-methyl-1-cyclopentenyl)methyl 4(S*)-methyl-1-cyclohexenecarboxylate (**15**): R_f = 0.56 (30% EtOAc/Skelly-B); IR 1710 (s), 1645 (w) cm^{-1}; ^1H NMR δ 6.93 (m, 1H), 4.67 (s, 2H), 2.35 (m, 8H), 1.76 (m, 5H), 1.70 (s, 3H), 1.22 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 167.60, 139.04, 137.94, 130.18, 130.02, 60.87, 38.72, 34.53, 34.14, 30.35, 27.56, 24.17, 21.43, 13.91; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{22}O_2$ (M^+) 234.1619, found 234.1616.

Ethyl (1R,2S,4S)-2-Methoxy-4-methylcyclohexanecarboxylate (17). In a dry 100-mL round-bottom flask was placed KH (35% suspension in mineral oil, 2.40 g, 21.0 mmol) under an inert atmosphere. The oil was removed by washing with hexanes, and the oil-free KH was suspended in dry THF (30 mL) and cooled to −20 °C. To this suspension was added CH_3I (20.5 g, 145 mmol) and, after 5.0 min, a solution of the hydroxy ester (−)-**7b** (2.50 g, 13 mmol) in THF (5.0 mL); the resulting mixture was maintained at −20 °C for 2.0 h. The reaction was quenched by careful addition of 5.0 mL of a saturated NH_4Cl solution. The resulting slurry was allowed to warm to room temperature and transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to give a yellow liquid. When subjected to chromatography (10% EtOAc/Skelly-B, R_f 0.40) the concentrate yielded 2.47 g of a colorless liquid as mixture of **17** and its C-1 epimer **18** (8% of mixture), which were not separable by chromatographic methods (95% combined yield): ^1H NMR δ (for **17**) 4.18 (m, 2H), 3.39 (s, 3H), 3.35 (m, 1H), 3.00 (m, 1H), 1.98 (m, 1H), 1.72 (m , 2H), 1.46 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H), 0.97 (d, J = 6.3 Hz, 3H).

(−)-(2R,2S,4S)-2-Methoxy-4-methylcyclohexanecarboxylic Acid (19). A mixture of **15** (2.0 g, 10.0 mmol) and 4 N aqueous HCl (37 mL) was heated at gentle reflux for 6.0 h under a inert atmosphere. The mixture was then rapidly cooled in an ice–salt bath, and the cold reaction mixture was extracted with CH_2Cl_2. The organic extracts were combined and dried ($MgSO_4$), filtered, and concentrated to afford a colorless viscous liquid as a mixture of **19** and its C-1 epimer (1.5 g, 88% combined yield, 92:8 ratio). Pure **19** was obtained as fine white needles by crystallization, at −20 °C, from an ethereal solution of the crude mixture: mp 49.5–51.0 °C; α^{23}_D −25.2° (c = 4.1); IR (CCl_4) 3100 (broad, m), 1738 (m), 1686 (s) cm^{-1}; ^1H NMR δ 10.65 (broad, 1H), 3.51 (s, 3H), 3.50 (m, 1H), 2.92 (m, 1H), 2.37 (ddd, J = 13.7, 3.2 Hz, 1H), 2.01 (m, 1H), 1.41 (m, 3H), 1.08 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 174.40, 79.81, 56.42, 42.54, 36.17, 30.96, 29.86, 25.59, 21.81; HRMS (CI, CH_4) m/z calcd for $C_9H_{17}O_3$ $(M+H)^+$ 173.1177, found 173.1179.

(−)-(3-Methyl-2-butenyl) (1R,2S,4S)-2-Methoxy-4-methylcyclohexanecarboxylate (20). A solution of **19** (0.52 g, 3.0 mmol) in dry CH_2Cl_2 (7.0 mL) was placed in a dry 25-mL round-bottom flask and cooled to 0 °C under an inert atmosphere. To this was added TEA (0.61 g, 6.0 mmol), and the mixture was stirred for 10 min, at which time freshly distilled methanesulfonyl chloride (MsCl, 0.34 g, 3.0 mmol) was added dropwise via a syringe. The resulting mixture was stirred for 1 h, and then a solution of 3-methyl-2-buten-1-ol (0.48 g, 6.0 mmol) and DMAP (70 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL) was added. This mixture was stirred for 1.0 h at 0 °C and then allowed to warm to room temperature and stirred at that temperature for 16 h. The reaction mixture was diluted with 100 mL of ether and washed sequentially with 10% HCl, water, saturated $NaHCO_3$, and brine. The ethereal solution was dried ($MgSO_4$), filtered and concentrated to give a pale yellow oil, which upon chromatographic purification gave **20** (0.68 g, 95% yield) as a colorless oil: R_f 0.46 (20% EtOAc/Skelly-B); α^{23}_D −32° (c = 1.5); IR 1725 (s) cm^{-1}; ^1H NMR δ 5.33 (m, 1H), 4.57 (d, J = 7.1 Hz, 2H), 3.37 (s, 3H), 3.34 (m, 1H), 3.00 (q, J = 4.3 Hz, 1H), 1.95 (m, 1H), 1.74 (m, 2H), 1.74 (s, 3H), 1.70 (s, 3H), 1.44 (m, 4H), 0.98 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 173.18, 138.44, 118.87, 79.70, 60.87, 56.28, 42.53, 35.06, 30.72, 29.47, 25.90, 25.68, 21.86, 17.98; HRMS (CI, CH_4) m/z calcd for $C_{14}H_{24}O_3$ (M^+) 240.1725, found 240.1728.

Procedure for the Ireland–Claisen Rearrangement of β-Methoxy Allyl Esters. Formation of (+)-Methyl (1R,2S,4S)-1-(2-Methyl-3-butenyl)-2-methoxy-4-methylcy-

clohexanecarboxylate (23). Preparation of the Ketene Silyl Acetal Intermediate 21. The procedure used is a modified version of that published by Ireland *et al.*[12] and was carried out under strictly anhydrous conditions. A solution of LDA (2.2 mmol) in THF (4.0 mL) was prepared and cooled to −110 °C under an inert atmosphere. To this was added via cannula the supernatant centrifugate of a solution of TMSCl/TEA/THF (3.0 mL of 2.0:0.5:3.7 volume ratio) which had been precooled to −78 °C. The resulting mixture was stirred for 2 min, and then a solution of **20** (0.24 g, 1.0 mmol) in THF (1.0 mL), precooled to −78 °C, was added dropwise via cannula over a period of 1 min. This mixture was maintained at −110 °C for 10 min and then gradually allowed to warm to 0 °C.

For spectroscopic analysis, the crude ketene acetal **21** could be isolated at this temperature as a solution in C_6D_6 as follows. The THF was removed from the reaction mixture under high vacuum (oil pump), and the residue was immediately suspended in dry C_6D_6. This suspension was rapidly filtered directly into an NMR sample tube through a tight cotton pad and was analyzed immediately.

Partial ^{1}H NMR spectral data for **21** are: δ 5.45 (m, 1H), 4.30 (m, 2H), 3.58 (m, 1H), 3.25 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H).

Thermal Rearrangement of 21. For preparative purposes, the solution of **21** in THF was allowed to warm to room temperature and stirred at this temperature for 16 h. The reaction mixture was diluted with 25 mL of ether and stirred with 5.0 mL of 5% HCl for 10 min. The biphasic mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with 5% HCl solution and brine (acidified to pH 2) and dried ($MgSO_4$). Filtration and removal of solvent left the crude carboxylic acid as yellow oil. This was purified by flash chromatography (20% EtOAc/Skelly-B, R_f 0.38) and immediately esterified with an excess of ethereal CH_2N_2. Workup of this reaction mixture gave a pale yellow oil, which was purified by chromatography to afford **23** (0.19 g, 76% yield) as a colorless oil: R_f 0.58 (20% EtOAc/Skelly-B); α^{23}_D +17.8° (c = 3.2); IR 3080 (w), 1720 (s) cm^{-1}; ^{1}H NMR δ 6.11 (dd, J = 17.3, 10.9 Hz, 1H), 4.87 (m, 2H), 3.85 (m, 1H), 3.62 (s, 3H), 3.26 (s, 3H), 1.98–1.55 (m, 5H), 1.42 (m, 1H), 1.21 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H), 1.06, 1.05 (2 × s, 2 × 3H); ^{13}C NMR δ 174.33, 146.35, 110.41, 79.52, 56.52, 55.13, 50.67, 41.90, 29.51, 28.89, 25.79, 24.82, 22.62, 20.19, 19.93; HRMS (EI) m/z calcd for $C_{15}H_{26}O_3$ (M^+) 254.1881, found 254.1868.

(−)-(2-Methyl-1-cyclopentenyl)methyl (1*R*,2*S*,4*S*)-2-Methoxy-4-methylcyclohexanecarboxylate (24). Esterification of **19** (2.0 g, 12.0 mmol) with **5** (1.72 g, 15.0 mmol), according to the procedure outlined for the preparation of **20**, gave **24** (2.53 g, 80% yield) as a colorless liquid, after chromatography: R_f 0.56 (20% EtOAc/Skelly-B); α^{23}_D −11.0° (c = 1.2); IR 1720 (s) cm^{-1}; ^{1}H NMR δ 4.62 (s, 2H), 3.35 (s, 3H), 3.32 (m, 1H), 3.02 (q, J = 4.5 Hz, 1H), 2.36 (m, 4H), 1.94 (m, 1H), 1.82–1.38 (m, 8H), 1.68 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 173.29, 138.10, 129.98, 79.76, 60.56, 56.29, 42.60, 38.69, 35.17, 34.52, 30.77, 29.54, 25.95, 21.88, 21.58, 13.91; HRMS (CI) m/z calcd for $C_{16}H_{27}O_3$ (M + H)$^+$ 267.1960, found 267.1967.

Methyl (1*R*,2*S*,4*S*)-1-[1(R)-Methyl-2-methylenecyclopentenyl]-2-methoxy-4-methylcyclohexanecarboxylate (29) and Methyl (1*R*,2*S*,4*S*)-1-[1(*S*)-Methyl-2-methylenecyclopentenyl]-2-methoxy-4-methylcyclohexanecarboxylate (30). Ketene silyl acetal **25** derived from **24** (0.26 g, 1.0 mmol) was prepared according to part A of the general procedure outlined above. After the mixture had warmed to rt the reaction flask was fitted with a dry reflux condenser, and the mixture was refluxed for 12 h under an inert atmosphere. Quenching and workup followed the protocol for preparating **23**. The ethereal solution of the rearranged acids was concentrated to an approximate volume of 1.0 mL, and the concentrate was purified by chromatography on silica gel. The column fractions containing the carboxylic acid (R_f 0.37, 20% EtOAc/Skelly-B) were combined and concentrated to a volume of about 10 mL, and this solution was treated with excess ethereal CH_2N_2. Workup in the usual manner and chromatography (20% EtOAc/Skelly-B, R_f 0.52) of the crude gave **29** and **30** (0.21 g, 75% combined yield) as an inseparable 92:8 mixture: ^{1}H NMR (C_6D_6) δ (partial spectrum for major isomer) 5.02 (m, 1H), 4.72 (m, 1H), 4.03 (m, 1H), 3.33 (s, 3H), 2.98 (s, 3H), 1.32 (s, 3H), 0.98 (d, J = 7.2 Hz, 3H), minor isomer has peaks at δ 5.30 (m, 1H), 5.12 (m, 1H), 4.11 (m, 1H); ^{13}C NMR (major isomer only) δ 174.50, 159.99, 106.46, 78.94, 57.60, 55.37, 50.74, 50.00, 38.38, 36.88, 29.37, 29.15, 26.25, 25.73, 22.87, 20.62, 20.12.

(−)-(1*S*,3*S*,7*S*,8*R*,11*R*)-7,11-Dimethyl-3-(iodomethyl)-8-(methoxycarbonyl)-2-oxatricyclo[6.4.0.0^{3,7}]dodecane. The mixture of diastereomeric esters **29** and **30** (94 mg, 0.33 mmol) was dissolved in CH_3CN (3.0 mL) and cooled to 0°C under an inert atmosphere. To this were sequentially added $NaHCO_3$ (0.22 g, 2.65 mmol) and I_2 (0.18 g, 0.69 mmol), and the resulting mixture was stirred for 3.0 h at 0 °C. The reaction was quenched at the same temperature by sequential addition of 1.0-mL portions of water and saturated $NaHCO_3$, followed by solid $Na_2S_2O_3$ (0.5 g). The resulting slurry was extracted with ether, and the combined ether extracts were washed with water, 10% aqueous $Na_2S_2O_3$, water, and brine and then dried ($MgSO_4$). Solvent evaporation gave a yellow viscous oil, which was chromatographed to afford **31** (0.11 g, 83% yield) as colorless viscous oil: R_f 0.43 (15% EtOAc/Skelly-B); α^{23}_D −1.8° (c = 3.8); IR 1725 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.29 (m, 1H), 3.69 (s, 3H), 3.47, 3.21 (AB, J_{AB} = 9.9 Hz, 2H), 2.14 (m, 1H), 1.95–1.20 (m, 13H), 1.15 (s, 3H and d, 3H); ^{13}C NMR δ 174.07, 90.08, 74.00, 57.97, 56.01, 51.55, 42.04, 39.71, 30.61, 28.56, 25.13, 23.29, 21.74, 19.98, 17.36, 16.08; HRMS (EI) m/z calcd for $C_{16}H_{25}O_3I$ (M^+) 392.0848, found 392.0853.

(−)-(1*S*,3*S*,7*S*,8*S*,11*S*)-7,11-Dimethyl-8-(hydroxymethyl)-3-(iodomethyl)-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (28). The iodo ester from above (0.78 g, 2.0 mmol) was dissolved in dry toluene (25 mL) in a dry 100-mL round-bottom flask, and the solution was cooled to 0 °C under an inert atmosphere. To this was added DIBAL-H (6.0 mL, 1.0 *M* in toluene) dropwise over a period of 5 min, and the resulting mixture was stirred at 0 °C for 5 h. The reaction was quenched by carefully adding to it 20 mL of a saturated solution of sodium potassium tartrate, and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated to leave a pale yellow, waxy solid that was purified by chromatography to give **27** (0.71 g, 99% yield) as a white crystalline solid. Crystallization from 1:1 Et_2O/CH_2Cl_2 provided colorless plates: R_f 0.22 (30% EtOAc/Skelly-B); mp 134.5–137 °C; α^{23}_D −3.6 (c = 1.00); IR (CCl_4) 3450 (m, broad) cm^{-1}; ^{1}H NMR δ 3.75 (m, 1H), 3.62 (m, 2H), 3.57, 3.22 (AB, J_{AB} = 9.9 Hz, 2H, CH_2-I), 2.10 (m, 2H), 1.83 (m, 2H), 1.75–1.30 (m, 10H), 1.17 (d, J = 7.3 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR δ 89.84, 74.96, 62.22, 57.27, 48.73, 42.65, 38.22, 31.05, 26.80, 25.38, 23.43, 20.52, 19.16, 18.81, 17.51; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{26}O_2I$ (M + H)$^+$ 365.0977, found 365.0977.

(−)-(1*S*,3*S*,7*S*,8*S*,11*S*)-7,11-Dimethyl-3-(iodomethyl)-8-[[(*p*-toluenesulfonyl)oxy]methyl]-2-oxatricyclo[6.4.0.0^{3,7}]-dodecane (37). A mixture of alcohol **28** (0.60 g, 1.6 mmol) and *p*-toluenesulfonyl chloride (1.02 g, 3.28 mmol) in pyridine (10 mL) was stirred at room temperature for 48 h under an inert atmosphere. The pyridine was removed under reduced pressure, and the residue was dissolved in ether and washed sequentially with water, saturated $CuSO_4$, water, and brine. The ethereal solution was dried ($MgSO_4$), and solvent was removed to yield a pale yellow solid that was purified by chromatography to give **35** (0.81 g, 95% yield) as a white crystalline solid. Crystallization from a 1:1 mixture of ether/Skelly-B gave white needles: R_f 0.28 (30% Et_2O/Skelly-B); mp 139.0–141.5 °C; α^{23}_D −0.65° (c = 1.7); ^{1}H NMR (500 MHz) δ 7.75 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.07, 3.87 (*AB*, J_{AB} = 10.0 Hz, 2H), 3.60 (m, broad, 1H), 3.47, 3.16 (*AB*, J_{AB} = 10.0 Hz, 2H), 2.43 (s, 3H), 2.11 (m, 1H), 1.78 (m, 3H), 1.58 (m, 3H), 1.46 (m, 3H), 1.39 (m, 2H), 1.27 (m,1H), 1.10 (d, J = 7.3 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz) δ 144.94, 132.54, 129.88, 127.86, 90.23, 74.08, 69.38, 57.05, 47.56, 42.38, 37.95, 30.82, 26.30, 25.06, 23.28, 21.65, 20.43, 19.21, 18.19, 16.59; HRMS (CI, CH_4) m/z calcd for $C_{22}H_{32}O_4SI$ (M + H)$^+$ 519.1066, found 519.1061.

(−)-(1*S*,3*S*,7*S*,8*R*,11*S*)-7,11-Dimethyl-3,8-bis(iodomethyl)-2-oxatricyclo[6.4.0.0^{3,7}]dodecane (38). A solution of NaI (1.94 g, 13.0 mmol) and **37** (0.81 g, 1.56 mmol) in a 1:1 mixture of DME/DMPU (20 mL) was heated to 85 °C and stirred under an inert atmosphere for 6.0 h. The mixture was cooled to room temperature, and the solvent was removed. The residue was dissolved in ether and washed with water, 10% $Na_2S_2O_3$, and water, followed by a final wash with brine. The ethereal solution

was dried ($MgSO_4$) and concentrated to afford a yellow solid that on chromatography gave **38** (0.56 g, 76% yield) as a white amorphous solid: R_f 0.46 (10% EtOAc/Skelly-B); mp 138.0–140.0 °C; α^{23}_D −29.2° (c = 2.4); ^{1}H NMR (500 MHz) δ 3.71 (m, 1H), 3.49, 3.20 (*AB*, J_{AB} = 10.7 Hz, 2H), 3.30, 3.19 (*AB*, J_{AB} = 9.9 Hz, 2H), 2.15 (m, 1H), 1.88 (m, 3H), 1.73–1.45 (m, broad, 9H), 1.15 (d, J = 7.3 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz) δ 90.82, 76.25, 57.38, 45.97, 42.35, 37.65, 30.37, 26.33, 25.28, 23.31, 23.03, 20.54, 17.48, 17.11, 8.85; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{25}OI_2$ $(M + H)^+$ 474.9994, found 474.9982.

(1*S*,2*S*,5*S*)-2,5-Dimethyl-2-[(1*R*)-1-methyl-2-methylenecyclopentyl]cyclohexan-1-ol (39). A mixture of **36** (0.10 g, 0.21 mmol), Zn dust (0.22 g, 3.38 mmol), and pyridine (1.0 mL) in 4:1 mixture (v/v) of THF:95% EtOH (10 mL) was heated at reflux for 20 h under an inert atmosphere. The reaction mixture was cooled and filtered through a short pad of activated basic alumina. The filter cake was washed with EtOAc, and the washings were combined with filtrate. Compound **37** was obtained as a viscous oil upon concentration of the filtrate and was used immediately in the oxidation step: ^{1}H NMR (C_6D_6) δ (partial) 5.02, 4.89 (m, 2H), 3.71 (m, 1H), 1.22 (d, J = 7.1 Hz, 3H), 1.09 (s, 3H, CH_3), 0.79 (s, 3H).

(−)-(2*S*,5*S*)-2,5-Dimethyl-2-[(1*R*)-1-methyl-2-methylenecyclopentyl]cyclohexan-1-one (40). A dry 5-mL round-bottom flask, equipped for magnetic stirring, was charged with dry CH_2Cl_2 (1.5 mL) and freshly distilled oxalyl chloride (0.04 g, 0.30 mmol) and cooled to −78 °C under an inert atmosphere. A solution of DMSO (0.05 mL, 0.58 mmol) in dry CH_2Cl_2 (0.50 mL) was added to the reaction flask dropwise via a syringe. After this mixture was stirred for 2 min, a solution of the crude **39** obtained above, in dry CH_2Cl_2 (0.5 mL), was added to it dropwise via cannula. The resulting cloudy solution was stirred for 15 min at −78 °C, at which time triethylamine (0.75 mL) was added. The white slushlike mixture was stirred for an additional 15 min at the same temperature and then allowed to warm to room temperature. The reaction was quenched with 1 mL of 1% HCl, and the mixture was extracted with ether. The organic layers were combined, washed with 1% HCl, water, and saturated $NaHCO_3$, and dried (K_2CO_3). Solvent removal gave a yellow liquid that upon chromatography yielded **40** (41 mg, 88% yield from **37**) as a clear colorless oil: R_f 0.30 (5% EtOAc/Skelly-B); α^{23}_D −68.2° (c = 2.2); IR 3045 (w), 1710 (s), 1640 (m) cm^{-1}; ^{1}H NMR δ 4.96, 4.84 (2 × m, 2 × 1H), 2.50 (dd, J = 13.3, 5.4, 1H), 2.31–2.01 (m, 5H), 1.94 (m, 2H), 1.72–1.33 (m, 5H), 1.20 (s, 3H), 1.16 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 216.50, 160.10, 106.95, 53.29, 49.37, 47.36, 38.33, 30.04, 29.47, 27.11, 25.07, 23.33, 20.71, 19.29; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1825.

(−)-(2*S*)-2,5-Dimethyl-2-[(1*R*)-1-methyl-2-methylenecyclopentyl]cyclohex-5-en-1-one (41). To a solution of LDA (0.28 mmol) in dry THF (3.0 mL) at −78 °C and under an inert atmosphere was added a solution of the ketone **40** (41 mg, 0.19 mmol) in THF (1.0 mL). After 0.5 h, a solution of phenylselenenyl chloride (40 mg, 0.20 mmol) in THF (0.5 mL) was added to the solution of enolate via cannula. The mixture was stirred for an additional 0.5 h at −78 °C and then quenched at the same temperature with 0.5 mL of a 1% HCl solution. The reaction mixture was allowed to warm to room temperature and then partitioned between ether and water. The organic layer was separated and dried ($MgSO_4$). Removal of solvent gave a yellow residue, which was dissolved in 5 mL of CH_2Cl_2 and treated with 2 mL of a 1:1 mixture of 30% H_2O_2 and water in the presence of 0.5 mL of pyridine. The mixture was stirred at room temperature for 45 min, after which the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined and dried ($MgSO_4$). Concentration gave a yellow oil that was chromatographed to afford **41** (18 mg, 72% yield based on recovered **40**) as a colorless liquid; unchanged ketone **40** (16 mg) was also eluted from the column: R_f 0.20 (5% EtOAc/Skelly-B); α^{23}_D −28.2° (c = 1.0); IR 3050 (w), 1665 (s), 1640 (shoulder, m) cm^{-1}; ^{1}H NMR δ 5.69 (s, 1H), 4.91, 4.81 (2 × m, 2 × 1H), 2.42–1.95 (m, 6H), 1.88 (s, 3H), 1.75 (m, 2H), 1.64 (m, 2H), 1.42 (m, 1H), 1.32 (s, 3H), 1.19 (s, 3H); ^{13}C NMR δ 204.12, 160.65, 158.90, 127.20, 106.17, 49.40, 48.46, 38.95, 38.40, 30.31, 28.36, 26.04, 23.71, 23.39, 17.41; HRMS (CI, CH_4) m/z calcd for $C_{15}H_{23}O$ $(M + H)^+$ 219.1748, found 219.1735.

(1*S*,2*R*)-2-Acetoxy-1,4-dimethyl-1-[(1*R*)-1-methyl-2-methylenecyclopentyl]cyclohex-3-ene and (1*S*,2*S*)-2-Acetoxy-1,4-dimethyl-1-[(1*R*)-1-methyl-2-methylenecyclopentyl]cyclohex-3-ene (42). To a solution of **41** (16 mg, 0.073 mmol) in dry toluene (3.0 mL) at 0 °C was added DIBAL-H (0.3 mL, 1.0 *M* in toluene). The resulting mixture was stirred at the same temperature for 0.5 h and then transferred to a refrigerator (0–5 °C) and kept unstirred for 12 h under an inert atmosphere. The reaction was quenched at 0 °C by careful addition of 30 μL of CH_3OH and allowed to warm to room temperature. The mixture was diluted with ether, and brine was added dropwise until precipitation occurred. A small amount of anhydrous K_2CO_3 was added to the mixture, which was then filtered through a pad of activated basic alumina into TEA (0.5 mL). The filter cake was washed with ether, and the washes were combined with the filtrate. The filtrate was dried (K_2CO_3) and concentrated to give a cloudy oil. This was immediately dissolved in 1 mL of pyridine and treated with 0.5 mL of acetic anhydride. This mixture was stirred for 48 h at room temperature under an inert atmosphere, diluted with ether, and then washed with saturated $CuSO_4$, water, brine and dried ($MgSO_4$). Concentration provided a yellow oil, which was chromatographed to afford **42** (12 mg, 63% yield from enone **41**) as a 6:1 mixture of diastereomers: ^{1}H NMR (for major isomer) δ 5.53 (m, 1H), 4.98, 4.68 (2 × m, 2 × 1H), 2.01 (s, 3H), 1.67 (s, 3H), 1.07 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (for major isomer) δ 170.49, 159.91, 139.21, 119.64, 107.68, 73.00, 49.85, 39.87, 38.51, 38.06, 28.16, 25.90, 23.28, 23.11, 21.76, 18.07; HRMS (CI, CH_4) m/z calcd for $C_{17}H_{21}O_2$ (M^+) 262.1945, found 262.1932.

(−)-Trichodiene [(−)-1]. Approximately 5.0 mL of $EtNH_2$, dried over KOH pellets, was distilled into a three-neck flask equipped with a dry ice cold finger and cooled to −78 °C. To this was added Li wire (15 mg, 2.2 mmol) as small pieces. When a blue color developed, the mixture of allyl acetates **42** (12 mg, 0.05 mmol) in THF (1.0 mL) was added to it, and the resulting solution was stirred for 15 min. The reaction was then quenched at −78 °C by addition of 0.5 mL of CH_3OH, diluted with ether, and allowed to warm to room temperature. The resulting mixture was decanted into a separatory funnel, washed with water, and dried ($MgSO_4$). Concentration gave a colorless liquid, which was purified by passage through a short column of silica gel with Skelly-B as the eluent (R_f 0.68). This afforded a 2:1 mixture of (−)-**1**, and its C-1 olefin isomer **43** (8.0 mg, 86% combined yield), as a colorless oil. The mixture was chromatographed on silver nitrate-impregnated silica gel (12.5 wt % $AgNO_3$) with Skelly-B as eluent to yield trichodiene (−)-**1** (4.0 mg) as a colorless oil: α^{23}_D −10.0° (c = 0.2); IR 3060 (w), 1640 (w) cm^{-1}; ^{1}H NMR δ 5.29 (m, 1H), 4.96, 4.73 (2 × m, 2 × 1H), 2.38–2.12 (m, 2H), 2.06–1.80 (m, 4H), 1.76–1.55 (m, 2H), 1.64 (s, 3H), 1.48–1.30 (m, 4H), 1.03 (s, 3H), 0.85 (s, 3H); HRMS (EI) m/z calcd for $C_{15}H_{24}$ (M^+) 204.1878, found 204.1881.

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Supplementary Material Available: ORTEP structures for compounds **12** and **28** and ^{1}H-NMR spectra of (−)-**1**, *rac*-**7b**, *rac*-**9**, *rac*-**10**, *rac*-**11**, *rac*-**13**, **23**, **27**, **29** and **30**, **31**, **37**, **38**, and **40–42** (19 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.