Articles

Asymmetric Induction in Mn(III)-Based Oxidative Free-Radical Cyclizations of Phenylmenthyl Acetoacetates and 2,5-Dimethylpyrrolidine Acetoacetamides

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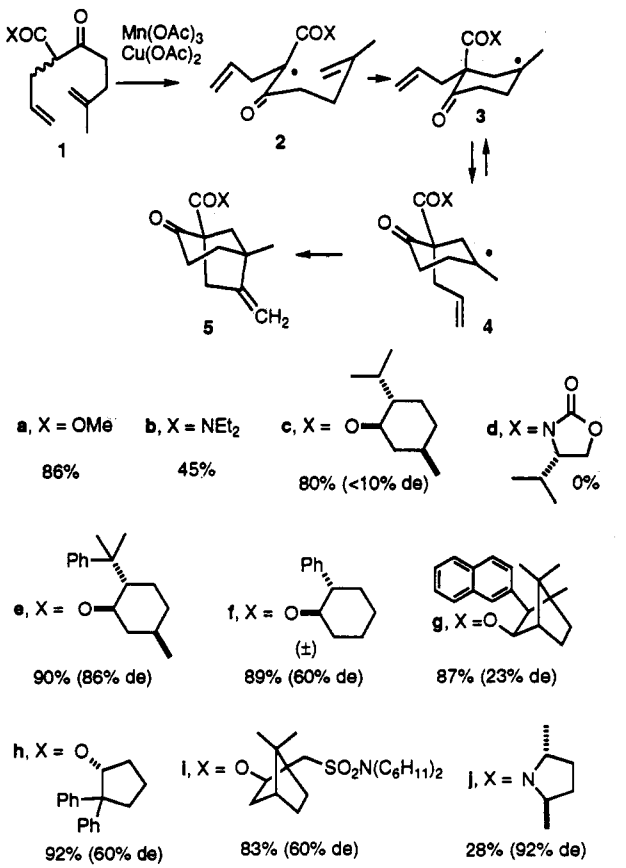
Mn(III)-based oxidative free-radical cyclization of phenylmenthyl ester **1e** afforded 90% of **13** with 86% de. Cyclization of **31b** provided 56% of (+)-podocarpic acid precursor **32e** with 82% de. The direction of de was opposite in these two cases. Oxidative cyclization of α-methyl β-keto ester **44b** gave a 1:1.6 mixture of **46b** and **47b** while α-propyl β-keto ester **44d** produced a >10:1 mixture of **46d** and **47d** indicating that the extent and direction of de is dependent on the size of the α-substituent. The reaction proceeds through transition states **12** and **56** with large α-substituents and through transition states **19** and **57** with small α-substituents. The de depends on the double-bond substitution pattern as shown by the decreased de with **37b** and **37d**, and selectivity in the 5-*exo* cyclization of **64b**, **65b**, **70b**, and **71b** is low.

We have recently developed Mn(III)-based oxidative free-radical mono, tandem, and triple cyclizations into a general route for the preparation of bicyclo[3.2.1]octan-2-one **5a** and a wide variety of other polycyclic systems.[1] Since these cyclizations proceed through achiral radical **2a** and produce chiral methyl ester **5a**, we were interested in modifications using chiral auxiliaries that would permit these cyclizations to be carried out with asymmetric induction. Initial studies using menthyl ester **1c** were discouraging[2] and keto imide **1d**, obtained from Evans' chiral oxazolidinone,[3] does not undergo oxidative cyclization on treatment with Mn(III) and Cu(II) in acetic acid.[2]

We recently reported that β-keto sulfoxide **6** can be used as a substrate for Mn(III)-based oxidative free-radical cyclization and that the sulfoxide chiral center completely controlled the stereochemistry of the cyclization, which afforded 44% of a single stereoisomer shown to be **10** by X-ray structure determination.[2] Cyclization of the conformer of radical **7** shown, with the S=O and C=O groups in the extended W conformation to minimize the dipole moment, should give **10** with ≈100% de since the face with a lone pair is much less hindered than the face with a phenyl group. The sulfoxide can be removed from **10** to give scalemic bicyclo[3.2.1]octanone **11** that shows the expected positive cotton effect.[4] Beckwith has shown that analogous intermolecular additions to radicals derived from β-sulfoxide esters also occur with high de.[5] Unfortunately, β-keto sulfoxide **6** was harder to prepare than β-keto ester **1**, and the yield of **10** (44%) was much lower than the yield of **5a** (86%).



Porter, Giese, and Curran have recently shown that high levels of diastereoselectivity can be obtained in the addition

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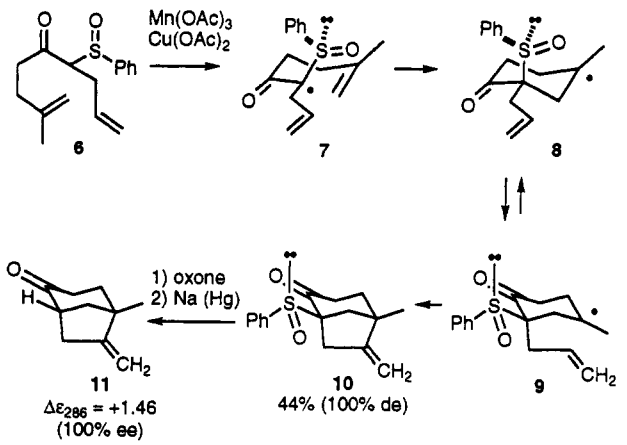

of chiral amide-substituted radicals to alkenes.[6] Although earlier indications were that ester-based chiral auxiliaries gave poor control in radical reactions,[7] Hamon[8] and Fang and Tsai[9] observed high levels of diastereoselectivity in reactions of 8-phenylmenthyl ester substituted radicals. We therefore decided to investigate the oxidative free-radical cyclization of a variety of ester and amide derivatives of **1** to ascertain whether chiral auxiliaries could be developed that give both high yield and high de in these cyclizations.[10] While this work was in progress, Zoretic and Caspar reported that the oxidative cyclization to give a methyleneindanone that we described[1c] can be carried out with 50% de using a β-keto imide containing Oppolzer's D-camphor sultam as the chiral auxiliary.[11]

Results and Discussion

Preparation of Chiral β-Keto Esters and Amides. Chiral β-keto esters were prepared by two general procedures. The exchange reaction with the previously described methyl and ethyl esters,[1d,e] the appropriate chiral alcohol, and 0.3 equiv of DMAP in anhydrous toluene at reflux for 3–5 d as described by Taber[12] provided esters **1e–1i**, **37b**, **37d**, **40Zb**, **58b**, **58c**, **59b**, and **59c** in 85–98% yield. Esters **37c**, **40Eb**, **44b–d**, **45b–d**, **64b**, **65b**, **70b**, and **71b** were prepared by alkylation of the corresponding β-keto ester dianion in 48–91% yield as described by Huckin and Weiler.[13] (−)-Phenylmenthyl acetoacetate, methyl acetoacetate (**29b**), and allyl acetoacetate were prepared from the methyl or ethyl ester by the DMAP-catalyzed exchange reaction.[12] Amide **1j** was prepared in 74% yield by heating a 1:1 mixture of **1a** and (2*R*,5*R*)-2,5-dimethylpyrrolidine[14] neat at 110 °C for 4 d.

Asymmetric Induction in the Formation of Bicyclo[3.2.1]octan-2-one 5. Oxidative cyclization of a 0.1 M solution of **1e–1i** in AcOH with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ as previously described[1d] provided **5e** (90% yield, 86% de), **5f** (89% yield, 60% de), **5g** (87% yield, 23% de), **5h** (92% yield, 60% de), and **5i** (83% yield, 60% de) as determined by analysis of the ^1H and ^{13}C NMR spectra. These results establish that bulky esters do not decrease the yield of the cyclization and that synthetically useful de was obtained with the 8-phenylmenthyl ester **1e**.

Oxidative cyclization of 2,5-dimethylpyrrolidine amide **1j** as described above for 40 h afforded **5j** (28% yield, 92% de). Since only traces of the minor diastereomer of **5j** are formed, an authentic sample of both diastereomers was prepared from **5a** to permit quantitation of the de by NMR spectral analysis. Hydrolysis of **5a** with 20% aqueous NaOH (25 °C, 20 h) provided the racemic β-keto acid. Reaction of the acid with oxalyl chloride in ether at reflux afforded the acid chloride that was heated with (2*R*,5*R*)-2,5-dimethylpyrrolidine[14] in toluene at 80 °C for 30 min to give **5j** as a 1:1 mixture of diastereomers (58% from **5a**).

Although the diastereoselectivity in the cyclization of pyrrolidine amide **1j** was slightly better than with phenylmenthyl ester **1e**, the yield was much lower. Oxidative cyclization of diethylamide **1b** afforded only 45% of **5b**, suggesting that the low yield of **5j** is inherent to the oxidative cyclization of β-keto amides.

The predominant stereoisomers of **5e** and **5j** were shown to be **13** and **17**, respectively, by chemical interconversion, correlation of (−)-ketone **14** with the (+)-isomer **11** obtained from β-keto sulfoxide **10** and X-ray structure determination of **5j**. Saponification of 8-phenylmenthyl ester **5e** (86% de) could not be carried out analogously to that of the methyl ester **5a**. With the more hindered ester, base catalyzed retro-Dieckmann reaction[15] by attack at the ketone carbonyl group was the major process. β-Keto acid **15** was therefore prepared from **5e** in two steps. LAH reduction afforded 86% of the diol as a 1.2:1 mixture of alcohol epimers and 97% of (−)-8-phenylmenthol, which can be recycled. Oxidation of the diol with PDC[16] in DMF (25 °C, 18 h) provided 90% of (−)-β-keto acid **15**, which is quite stable because decarboxylation must proceed through a strained enol.[17] Decarboxylation of **15** was effected by flash vacuum pyrolysis at 450 °C to give 89% of ketone **14**. The CD spectrum established that **14**, $\Delta\epsilon_{286} = -1.25$, has the opposite configuration to ketone **11**, $\Delta\epsilon_{286} = +1.46$, obtained from β-keto sulfoxide **10**. The difference in magnitude is consistent with 86% ee for **13**, if the ee is ~100% for **11**.

The stereochemistry of the major diastereomer of **5j** was established as **17** by preparation of an authentic sample of **17** from (−)-β-keto acid **15**, which was obtained from **1e**. Conversion of **15** to the acid chloride and reaction of the acid chloride with (2*R*,5*R*)-2,5-dimethylpyrrolidine as described above for the racemic acid afforded **17** (88% yield, 86% de). The major stereoisomer was identical to the major diastereomer obtained from the cyclization of **1j**. (−)-β-Keto acid **15** was converted analogously to **5h** as a 12:1 mixture of isomers in which the major isomer was the same as from cyclization of **1h**.

Although the structures of **13** and **17** were secure based on the CD data for **14** and correlation with **11**, the synthesis of *O*-methylpodocarpic acid described below raised ques-

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(9) Chen, M.-Y.; Fang, J.-M.; Tsai, Y.-M.; Yeh, R.-L. *J. Chem. Soc., Chem. Commun.* **1991**, 1603.
(10) For a preliminary report of a portion of this work see: Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921.
(11) Zoretic, P. A.; Weng, X.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637.
(12) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.
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(14) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.
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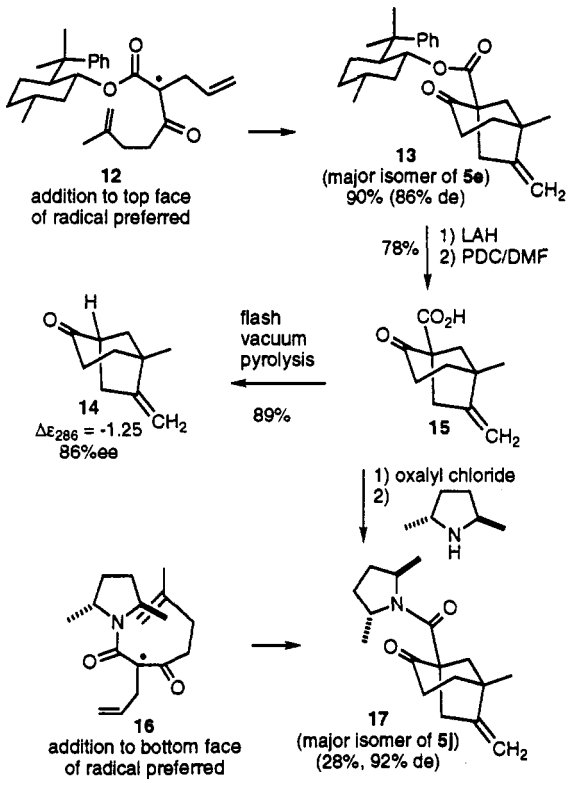
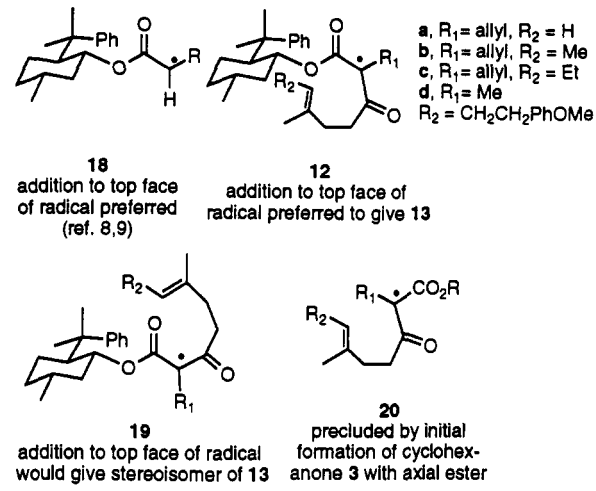
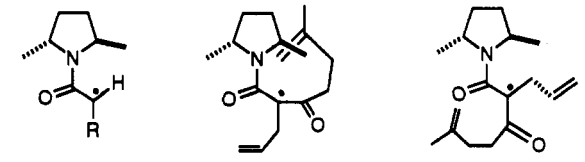




tions about the structure assignment. We therefore carried out an X-ray crystal structure determination on the major diastereomer **17** that confirmed the structure assigned.[18] The conformation of the 2,5-dimethylpyrrolidine amide moiety of **17** is identical to that in previously reported crystal structures.[19]

Hamon[8] and Fang and Tsai[9] proposed that the diastereoselectivity in additions to α-substituted phenylmenthyl ester radicals results from addition to the less hindered top face in conformer **18**. Assuming that this geometry of the phenylmenthyl ester holds in the cyclization of β-keto ester radicals, four conformers must be considered because there are two conformers about each of the bonds between the radical-bearing carbon and the carbonyl groups. The two conformers shown in **20** with the ester syn to the ketone can be excluded since studies with alkyl substituents on the tether have established that the cyclization yields cyclohexyl radical **3**, with an axial ester group, as the initial intermediate. Conformers **12a** and **19a**, with the ester anti to the ketone, would both yield cyclohexanone **3**, with an axial ester group, as the initial intermediate. The formation of **13** with 86% de suggests that the double bond adds to the top face of the radical in conformer **12a**. Cyclization of the radical through conformer **19a** can be excluded since addition should occur from the top face to give the diastereomer of **13**. The preference for cyclization in conformer **12a** may result from minimization of the dipole moment with the carbonyl groups in the extended W conformation.

Porter, Giese, and Curran proposed that the diastereoselectivity in additions to α-substituted dimethylpyrrolidine amide radicals results from addition to the less hindered bottom face in conformer **21**.[6] The formation of **17** with 92% de could result from addition to the less hindered bottom face of radical conformer **16**. This conformer may be preferred since the carbonyl groups are in the W conformation that minimizes the dipole moment. However, there is severe steric interaction between the pyrrolidine ring and the alkenyl side chain in the transition state, so that alternate conformers need to be considered. Addition to the top face of conformer **22**, which is less hindered than **16**, would also yield **17**. Examination of models suggests that the top face of **22** may be less hindered since the β-methyl that is syn to the amide carbonyl group will interact more strongly with the approaching alkenyl side chain than the α-methyl that is anti to the carbonyl group. The α-methyl group may also force the allyl group to adopt the α-conformation further favoring attack from the top face.



The formation of **5e** in 90% yield with 86% de established that 8-phenylmenthyl esters are excellent chiral auxiliaries for asymmetric oxidative free-radical cyclizations. We decided to examine the scope and limitation of 8-phenylmenthol as a chiral auxiliary in oxidative free-radical cyclization.

Total Synthesis of (+)- and (−)-*O*-Methylpodocarpic Acid (33i and 32i). In 1985, we reported a synthesis of (±)-*O*-methylpodocarpic acid using a tandem oxidative free-radical cyclization as the key step to form two rings with the complete control of relative stereochemistry.[1a] Oxidation of alcohol **23** with PCC[20] in CH_2Cl_2 provided 82% of aldehyde **24**. Horner–Emmons Wittig reaction[21] of aldehyde **24** with triethyl 2-phosphonopropionate gave 91% of a 4.7:1 mixture of **25** and the *Z*-isomer, which were separated by chromatography. DIBAL reduction of the

(18) X-ray data, analyses, and experimental details are available from the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(19) (a) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (b) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.

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

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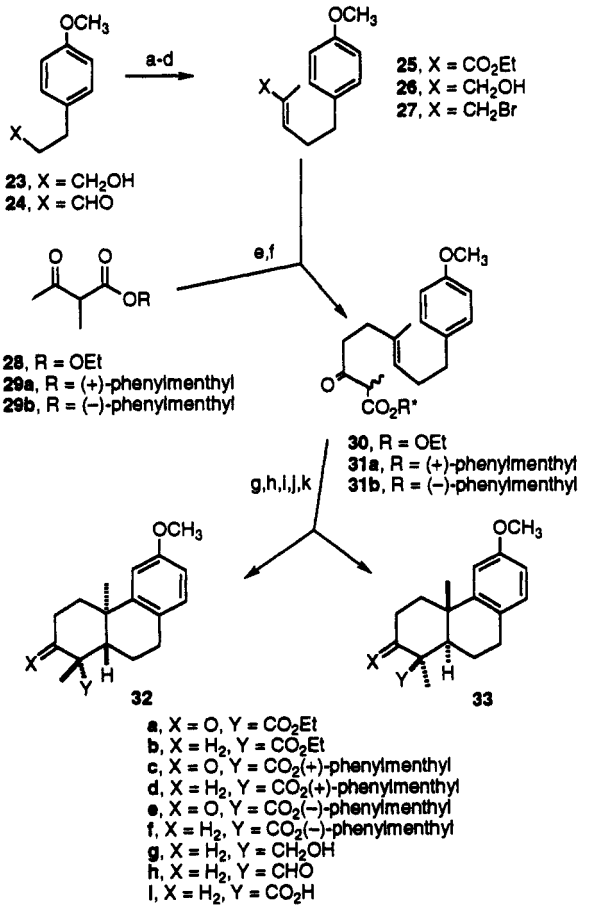
Scheme I



[a] Key: (a) PCC, CH_2Cl_2 (82%); (b) $(EtO)_2POCHMeCO_2Et$, NaH, THF (91%, 4.7:1 *E*-*Z*); (c) DIBAL, CH_2Cl_2; (d) PBr_3, THF (71% from **25**); (e) (+)- or (-)-phenylmenthol, DMAP, toluene (90%); (f) THF, 2 equiv of LDA, **28** or **29**, 2 equiv of DMPU, **27** (85%); (g) $Mn(OAc)_3{\cdot}2H_2O$, MeOH, 0 °C (56%); (h) Zn, HCl, ether (65%); (i) LAH, THF (98%); (j) Swern oxidation; (k) $NaClO_2$, *t*-BuOH (80% from **32g** or **33g**).

E-ester **25** in toluene overnight at rt afforded alcohol **26**.[22] Reaction of **26** with PBr_3[23] at 0 °C for 0.5 h in THF gave bromide **27** in 71% yield from **25**. Alkylation of the dianion of **28** with **27** afforded 85% of β-keto ester **30**.Oxidative cyclization of **30** (0.2 M) in acetic acid with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ at 15–20 °C for 1 h gave 50% of a racemic mixture of tricyclic keto esters **32a** and **33a** with complete control of relative stereochemistry.[1a,b,d] Clemmensen reduction[24] afforded 60% of racemic ethyl *O*-methylpodocarpate (**32b** and **33b**), which was spectroscopically identical with an authentic sample of **33b** prepared from the commercially available methyl ester by saponification and treatment of the ester with diazoethane. This synthetic strategy has since been adapted to the synthesis of (±)-triptoquinones B and C.[25]

Although (±)-*O*-methylpodocarpic acid has been synthesized numerous times,[26a] (+)-*O*-methylpodocarpic acid (**33i**) has been synthesized only twice[26b,c] by long routes in low overall yield. We therefore chose to carry out an asymmetric synthesis of (+)-*O*-methylpodocarpic acid (**33i**) using the optimal chiral auxiliary, 8-phenylmenthol, with the expectation that cyclization of **31** would provide mainly one of the eight possible stereoisomers. An examination of transition-state model **12a** for the cyclization of **1e** indicated that cyclization of (-)-phenylmenthyl ester **31b** would give unnatural (-)-*O*-methylpodocarpic acid (**32i**), if the transition state for the cyclization of **31** is analogous to that for the cyclization of **1e**. We therefore prepared (+)-phenylmenthyl ester **31a**.

DMAP-catalyzed transesterification[12] of **28** with (+)-phenylmenthol[27] in toluene at reflux for 3 d afforded 90% of β-keto ester **29a**. Alkylation of the dianion of **29a** with **27** gave β-keto ester **31a** in 85% yield. Treatment of **31a** with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ at 15 °C for 1 h in AcOH as previously described[1a] provided 50% of a 7:1 mixture of tricyclic diastereomers. The selectivity increased as the reaction temperature decreased; cyclization of **31a** with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ at 0 °C for 8 h in MeOH provided a 10:1 mixture of diastereomers (82% de), which were separated by flash chromatography to give 50% of the major diastereomer and 6% of the minor isomer.

Modified Clemmensen[28] reduction of the major diastereomer with zinc powder in ether saturated with HCl gave 65% of the reduction product. To our surprise, LAH reduction of the ester in THF at reflux overnight provided 98% of (-)-*O*-methylpodocarpinol (**32g**), $[\alpha]_D = -67°$, and 96% of recovered (+)-8-phenylmenthol. The optical rotation of **32g** is the same magnitude, but opposite sign,[29] as natural (+)-*O*-methylpodocarpinol (**33g**). Therefore, the unexpected diastereomer **32c** was formed as the major product in the oxidative free-radical cyclization of **31a** and Clemmensen reduction gave **32d**.

Natural (+)-*O*-methylpodocarpic acid was prepared using (-)-8-phenylmenthol as the chiral auxiliary. Following the above synthetic route we obtained (+)-*O*-methylpodocarpinol (**33g**) which was identical to an authentic sample prepared by LAH reduction of methyl (+)-*O*-methylpodocarpate in all respects. Swern oxidation of **33g** yielded *O*-methylpodocarpinal (**33h**), which was oxidized with $NaClO_2$[30] in NaH_2PO_4 buffer at 25 °C for 3 d to give (80% from **33g**) (+)-*O*-methylpodocarpic acid (**33i**) which was identical with a natural sample in all respects.

We were delighted to find that the oxidative free-radical cyclization of **31** also proceeded with synthetically useful asymmetric induction, but were disconcerted to find that the direction of induction was opposite to that obtained with **1e**. We initially considered whether the absolute stereochemistry of **13**, the major diastereomer from **1e**, or (+)-*O*-methylpodocarpic acid was misassigned. We confirmed the structure of **13** by the X-ray structure deter-

(22) Use of LAH led to some 1,4-reduction. Exclusive 1,2-reduction was observed with DIBAL.

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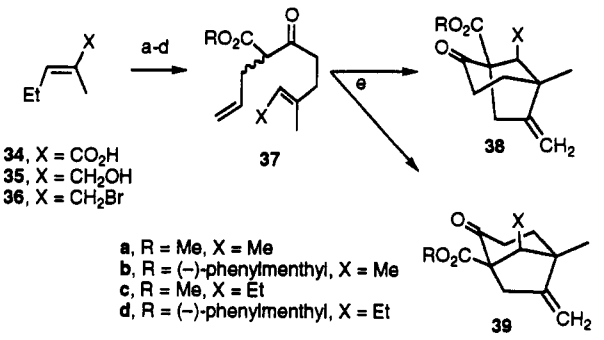
Scheme II



[a] Key: (a) DIBAL, CH_2Cl_2 (60%); (b) PBr_3, THF (61%); (c) 2 equiv of LDA, methyl allylacetoacetate, THF, 2 equiv of DMPU (61%); (d) (-)-phenylmenthol, DMAP, toluene (87%); (e) 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, AcOH (91%).

mination of 17, prepared from (2*R*,5*R*)-2,5-dimethylpyrrolidine,[14] and the absolute stereochemistry of **33i** has been determined by anomalous dispersion.[31] Therefore, the differences in the direction of asymmetric induction is real and must result from structural differences in the two radicals.

Apparently, the radical from **1e** cyclizes through transition state **12a** while the radical from **31b** cyclizes through transition state **19d**. The only difference between the two radicals is the addition of an alkyl substituent R_2 on the double bond **31b** and a smaller R_1 substituent in **31b** (Me) than in **1e** (allyl). We set out to design experiments to determine whether these changes were responsible for the switch in the direction of asymmetric induction.

Effect of the Double-Bond Substituents on Asymmetric Induction. We have shown that cyclization of **37a** gave predominantly the racemic mixture of **38a** and **39a** in which the methyl group on the one-carbon bridge occupies the axial position.[1d] Oxidative cyclization of **37b**, prepared from transesterification of **37a** with (-)-8-phenylmenthol, provided 91% of a 2.5:1 mixture of **38b** and **39b**. Replacement of the alkene hydrogen of **1e** with the methyl group of **37b** markedly perturbs the extent of asymmetric induction.We examined the oxidative cyclization of **37d**, since the ethyl group is closer in size to the alkyl group of **31b**. DIBAL reduction of 2-methyl-2(*E*)-pentenoic acid (**34**) gave 60% of alcohol **35**,which was converted to the allylic bromide **36** with PBr_3 in 61% yield. Alkylation of the dianion of methyl allylacetoacetate with **36** gave 61% of **37c**, which was converted to **37d** in 91% yield by DMAP-catalyzed transesterification.[12] Oxidative cyclization of **37d** afforded 90% of a 1.8:1 mixture of **38d** and **39d**. The selectivity drops from 12:1 with a hydrogen substituent to 2.5:1 with a methyl group and to 1.8:1 with a larger ethyl group.

The structures of **38b**, **38d**, **39b**, and **39d** were assigned by comparison of the ^1H and ^{13}C NMR spectra with those of **13** and the minor diastereomer. There is a very strong correlation between the spectra of **38b** and **38d** on the one hand and **39b** and **39d** on the other hand. The data for the major products **13**, **38b**, and **38d** are similar as are the data for the three minor products. For instance, the downfield allylic methylene hydrogen absorbs at δ 2.39–2.30 in the major products **38b** and **38d** and at δ 2.53–2.52 in the minor products **39b** and **39d**. This hydrogen absorbs at δ 2.43 in **13** and at δ 2.68 in the minor diastereomer.

(31) Clark, G. R.; Waters, T. N. *J. Chem. Soc. C* **1970**, 887.

Mechanistic considerations support this assignment. Increasing the size of the X group from H in **1e** to Me in **37b** and Et in **37d** should result in a monotonic change in the level of asymmetric induction. Since the selectivity decreases from 12:1 to 2.5:1 and 1.8:1, respectively, the major products probably have the same stereochemistry.

The major products **13**, **38b** and **38d** are formed from transition state **12a–c** in which the carbonyl groups are in the extended W conformation to minimize the dipole moment, and the double bond approaches from the top face. However, as the size of the R_2 group increases, the steric interaction between the R_2 group and the bulky phenylmenthyl ester becomes more significant and the extent of asymmetric induction decreases. Therefore, the phenylethyl substituent on the double bond of **31b** is partially responsible for the different direction of asymmetric induction from that observed with **1e**.

Effect of the α-Substituent on the Direction of Asymmetric Induction. Determination of the effect of an α-methyl vs an α-allyl group on the diastereoselectivity of the cyclization is not straightforward, since reaction must occur cleanly with both substrates and lead to products whose absolute stereochemistry can be determined. Replacement of the allyl group with a methyl group in starting material **1e** is not practical since this will lead to a tertiary radical that cannot undergo a tandem cyclization and will be oxidized to give a complex mixture of products. Similarly, we cannot put an allyl group on the podocarpic acid precursor **31**, since this could give either bicyclo[3.2.1]octanes or allyl analogues of podocarpic acid. Finally, we would not be able to assign the absolute stereochemistry easily to the products of these reactions.

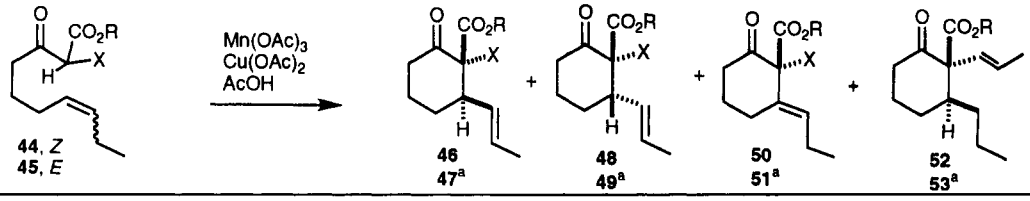
We therefore decided to compare the reactions of the α-methyl acetoacetates **44b** and **45b** with those of the α-propyl acetoacetates **44d** and **45d**. We made the assumption that the allyl and propyl groups would have similar steric effects and chose these two reactions since they should lead to **46** and **47** as the major products. The problem of stereochemical assignment was straightforward since the α-unsubstituted acetoacetates **40Zb** and **40Eb** would give **41b** and **42b**, which can be correlated both with 3-propylcyclohexanone, whose stereochemistry can be assigned by analogy to other 3-alkylcyclohexanones, and with **46** and **47** by alkylation of the enolate from the less hindered face.

Oxidative cyclization of methyl ester **40Za** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in AcOH gave a racemic mixture of **41a** and **42a** in 75% yield.[1a,e] Oxidative cyclization of (-)-phenylmenthyl ester **40Zb** afforded 69% of a 12:1 mixture (85% de) of **41b** and **42b**. The stereochemistry of the major product **41b** was established by conversion of the 12:1 mixture to (*S*)-3-propylcyclohexanone (**43**). Hydrogenation of the mixture over Pd/C in CH_2Cl_2 at 25 °C, followed by hydrolysis[32] with NaCl and H_2O in DMSO at reflux for 20 h, gave **43**, $[\alpha]_D = -15°$, in 59% yield. The absolute stereochemistry of (-)-3-propylcyclohexanone is not known. However, the *R* configuration of 3-methyl-, 3-ethyl-, and 3-butylcyclohexanone is dextrorotary.[32a,33] Therefore, **43** was assigned the *S* configuration and the stereochemistry of the major cyclization product was assigned as **41b**. The CD spectrum

(32) (a) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (b) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.

(33) (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (b) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710.

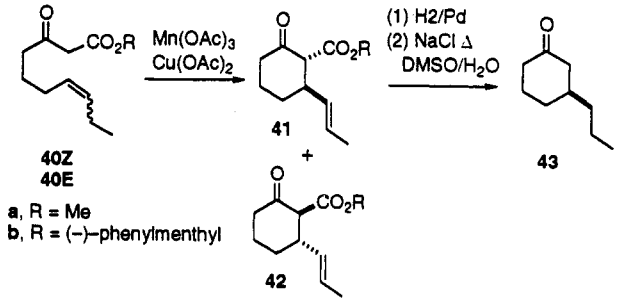
Table I. Oxidative Free-Radical Cyclization of 44 and 45



substituents	yield, % (ratio of products[b])			
44a, X = Me, R = Et	77	4	19	
44b, X = Me, R = (−)-phenylmenthyl	70 (1:1.6)	15 (1:1.6)[c]	15 (1.1.5)[c]	
44c, X = Pr, R = Me	66	13	5	16
44d, X = Pr, R = (−)-phenylmenthyl	56 (>10:1)	22 (>10:1)[c]	7 (>10:1)[c]	15 (>10:1)[c]
45a, X = Me, R = Et	68	16	16	
45b, X = Me, R = (−)-phenylmenthyl	66 (1:2.5)	16 (1:2)[c]	18 (1:1.25)[c]	
45c, X = Pr, R = Me	53	30	5	12
45d, X = Pr, R = (−)-phenylmenthyl	46 (>10:1)	39 (>10:1)[c]	5 (>10:1)[c]	10 (>10:1)[c]

[a] Diastereomer with opposite stereochemistry at all cyclohexane stereocenters. [b] The numbers refer to the upper and lower structures, respectively. [c] Tentative assignment of stereochemistry by analogy to **46** and **47**.

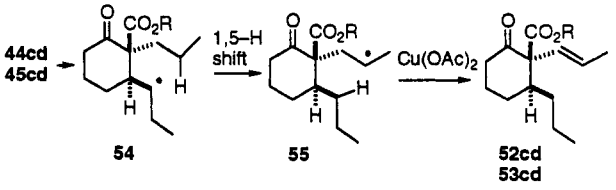
of **43** shows a negative Cotton effect, $\Delta\epsilon_{297} = -0.19$, which confirms the stereochemical assignment. Oxidative cyclization of **40Eb** provided 70% of a 1.1:1 mixture of **41b** and **42b**.



The origin of the high diastereoselectivity with **40Zb** and the low selectivity with **40Eb** is not obvious. We know that the alkene reacts with the manganese enolate in the rate-determining step to form a cyclic radical.[1c,f] Because the ester can equilibrate after cyclization, we know much less about the stereochemistry of these reactions than of the cyclizations of α-substituted acetoacetates that proceed through Mn-free free radicals.[1c,d,f] We do not know the geometry of the enolate, the conformation of the ester, whether the manganese chelates, or whether the alkene adopts an axial or equatorial conformation in the transition state. On the basis of previous studies of the cyclization of **44a** and **45a**,[1d-f] we would expect that **40Zb** would cyclize almost exclusively through 6-*exo* transition states with the double bond equatorial, while **40Eb** would show only a slight preference for transition states with the double bond equatorial. Since the orientation of the double bond in the transition state controls the stereochemistry of the product, this could explain the low de with **40Eb**.

Oxidative cyclization of **44a** and **45a** produced the three products indicated in Table I.[1a,e,f] Oxidative cyclization of (−)-phenylmenthyl esters **44b** and **45b** provided a mixture of six products as indicated in Table I. The absolute stereochemistry of the major products **46b** and **47b** was established by methylation of the 12:1 mixture of **41b** and **42b** giving a 20:1 mixture of **46b** and **47b**. As expected,[34] methylation occurs exclusively from the less hindered bottom face of **41b** leading to **46b**. The stereochemistry of **48b**, **49b**, **50b**, and **51b** was tentatively assigned by analogy to **46b** and **47b**. Replacement of the hydrogen of **40Zb** with the methyl group of **44b** reverses the diastereoselectivity from 12:1 to 1:1.6, while replacement of the hydrogen of **40Eb** with a methyl group changes the diastereoselectivity from 1.1:1 to 1:2.5. These observations support kinetic results that indicated that the cyclizations of α-unsubstituted and α-substituted β-keto esters proceed through different mechanisms.[1c]

Oxidative cyclization of α-propyl methyl esters **44c** and **45c** gave four products in the yields indicated in Table I. The formation of **52c** was not anticipated. The stereochemistry of **52c** was established by hydrogenation of **46c** and **52c** to the same compound, methyl *trans*-1,2-dipropyl-6-oxocyclohexanecarboxylate. The most likely mechanism for the formation of **52c** involves formation of the expected cyclic radical **54**, a 1,5-hydrogen shift to give **55**, and oxidation of **55** by Cu(II) to give **52c**. The 1,5-shift must be rapid,[35] since oxidation of radicals by Cu(II) usually occurs with a rate constant of $\approx 10^6$ s^{-1} M^{-1}.[36] The formation of **52** by oxidation of **55** is surprising since we have usually observed a preference for the formation of the less substituted alkene in the Cu(II) oxidation of secondary radicals.[37]



Oxidative cyclization of α-propyl (−)-phenylmenthyl esters **44d** and **45d** gave a mixture of the eight products indicated in Table I. The absolute stereochemistry of the major products **46d** and **47d** was established by propylation of the 12:1 mixture of **41b** and **42b** giving 34% of **46d**. Replacement of the methyl group of **44b** with the propyl

(34) Paquette, L. A.; Wiedeman, P. E. *Tetrahedron Lett.* **1985**, *26*, 1603.

(35) The second-order rate constant for oxidation of the 5-phenylhexyl radical by Cu(II) in acetic acid is 700 times larger than the first-order rate constant for the 1,5-hydrogen shift to give the benzylic radical: Kochi, J. K.; Gilliom, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 5251. On the basis of these data, the oxidation of **54** by 0.1 M Cu(II) should be 70 times faster than the 1,5-hydrogen shift to give **55**. Presumably, oxidation of **54** is slow because the radical center is sterically hindered and 1,5-hydrogen shift is accelerated since the two diequatorial side chains are fixed in close proximity.

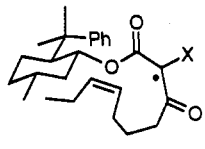
(36) Kochi, J. K. *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 11.

(37) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 1965.

group of **44d** reverses the diastereoselectivity from 1:1.6 to >10:1, while replacement of the methyl group of **45b** with the propyl group of **45d** reverses the diastereoselectivity from 1:2.5 to >10:1.

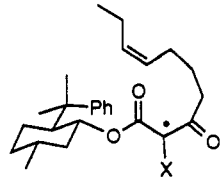
These results indicate that replacement of the α-allyl group of **1e** with the methyl group of **31** should change the direction of the diastereoselectivity since allyl and propyl groups should have similar effects. Both the substituent on the double bond and the nature of the α-substituent perturb the diastereoselectivity. While neither alone is able to account for the high but opposite selectivity, taken together they do account fully for the observed differences between **1e** and **31b**.

6-*exo*-Cyclization of **44** and **45** proceeds through transition states **56** and **57**. With X = propyl, the cyclization proceeds through **56**, which is analogous to **12**, with high selectivity to give **46d**. With X = methyl, the cyclization proceeds through **57**, which is analogous to **19**, with modest selectivity to give mainly **47b**. Analysis of models suggests that both transition states **56** and **57** are similar in energy when X = methyl. With a larger X group, i.e., propyl or allyl, steric interactions between the X group and the chiral auxiliary in transition state **57** make transition state **56** the preferred pathway. This also explains the selective cyclization of **1e** through transition state **12a** and the cyclization of **31b** through transition state **19d**.



56

addition to top face preferred to give **46**, **48**, **50** and **52**. (favored by X = propyl, allyl)



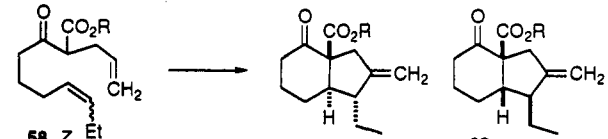
57

addition to top face preferred to give **47**, **49**, **51** and **53**. (favored by X = Me)

Ihara has reported that the same stereoisomer predominates from either methylation of mono(phenylmenthyl) α-ethylmalonate (5:1) or ethylation of mono(phenylmenthyl) α-methylmalonate (4:1).[38] He explained this unexpected result by postulating the alkylation of an enolate conformation analogous to **56** with a large, ethyl α-substituent and the alkylation of a conformation analogous to **57** with a small, methyl α-substituent. The similarity between our results and Ihara's provide further support for Giese, Curran, and Porter's observation that the control of stereochemistry in additions to enol radicals is usually similar to that observed in additions to enolates.[6]

The data in Table I indicate that more **48** and **49** were formed with phenylmenthyl esters than with methyl esters. Examination of transition-state models[1d-f] suggested that increasing the size of the ester group will increase the steric interactions between the axial ester and the cis equatorial double bond in the transition states leading to **46** and **47**. There are no steric interactions between the trans diaxial ester and double bond in the transition states leading to **48** and **49**. More **48** and **49** was formed from α-propyl β-keto esters than from α-methyl β-keto esters.

Table II. Oxidative Free-Radical Cyclization of 58 and 59



58, *Z*
59, *E*

60
61[a]

62
63[a]

substituents	yield, % (ratio of products[b])	
58a, R = Me	65	3
58b, R = (−)-phenylmenthyl	67 (12:1)[c]	5 (>12:1)[c]
58c, R = (±)-phenylcyclohexyl	60 (4:1)[d]	16 (3:1)[d]
59a, R = Me	45	20
59b, R = (−)-phenylmenthyl	47 (6.7:1)[c]	23 (10:1)[c]
59c, R = (±)-phenylcyclohexyl	45 (1:1.2)[d]	18 (3.8:1)[d]

[a] Diastereomer with opposite stereochemistry at all ring stereocenters. [b] The numbers refer to the upper and lower structures, respectively. [c] Tentative assignment of stereochemistry by analogy to **46** and **47**. [d] Racemic products, stereochemistry of major isomer unknown.

In order to ascertain that α-allyl and α-propyl groups have the same effect on the diastereoselectivity we examined the oxidative cyclization of (−)-phenylmenthyl and phenylcyclohexyl α-allyl β-keto esters **58bc** and **59bc** as shown in Table II. The formation of only two of the four possible isomers whose ratio depends on the double bond stereochemistry has been discussed previously for **58a** and **59a**.[1d,f] Cyclization of **58b** and **59b** proceeds with high de analogous to that observed with α-propyl β-keto esters **44d** and **45d** suggesting that the propyl group and the allyl group have similar effects on the stereoselectivity. The absolute stereochemistries of the major isomers cannot be determined unambiguously and are tentatively assigned as **60b** and **62b** by analogy to **46d**. The phenylcyclohexyl esters **58c** and **59c** react with 10–60% de, indicating that the phenylmenthyl ester is a much better chiral auxiliary in this case as well as **1**.

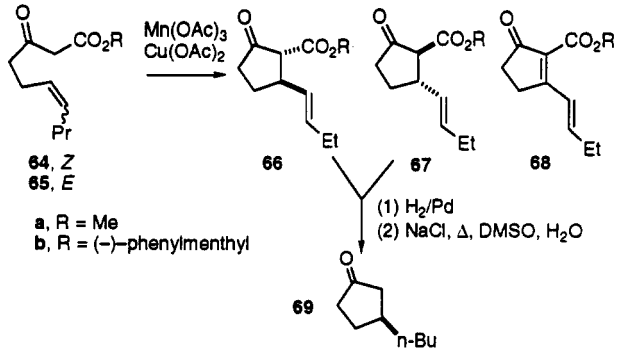
The structures of **60–63** were assigned based on the absorption of the downfield allylic methylene hydrogen at δ 2.47–2.80 in the *trans*-fused isomers **60** and **61** and at δ 2.95–3.30 in the *cis*-fused isomers **62** and **63**. The ratio of products was most easily determined by integrating the absorptions of the alkene methylene carbon at δ 106.3–107.6. This also permits assignment of relative stereochemistry since the *trans*-fused methyl ester **60a** absorbs at δ 107.2 while the *cis*-fused methyl ester **62a** absorbs at δ 106.0.

Diastereoselectivity in 5-*Exo*-Cyclization. Oxidative cyclization of **64b** provided 24% of a 2.5:1 mixture of **66b** and **67b** and 7% of dienone **68b**, while cyclization of **65b** gave 25% of a 1.5:1 mixture of **66b** and **67b** and 8% of dienone **68b**. These yields are analogous to those that are obtained with methyl esters **64a** and **65a** since the products **66** and **67** are oxidized further to give polymer and dienone **68**.[1a,c,e] The stereochemistry of **66b** and **67b** was established by hydrogenation of the 2.5:1 mixture over Pd/C and hydrolysis[32] of the ester with NaCl and H_2O in DMSO at reflux to give 75% of partially resolved (*S*)-3-butylcyclopentanone (**69**), $[\alpha]_D$ = −68°. The optical rotation of (*R*)-(−)-3-butylcyclopentanone of unknown purity has been reported to be +107°.[32a] The optical rotation of (*S*)-(−)-3-butylcyclopentanone of 46% and 73% optical purity (determined by preparation of a chiral ketal) has been reported to be −58.6° and −99.3°, respectively.[39]

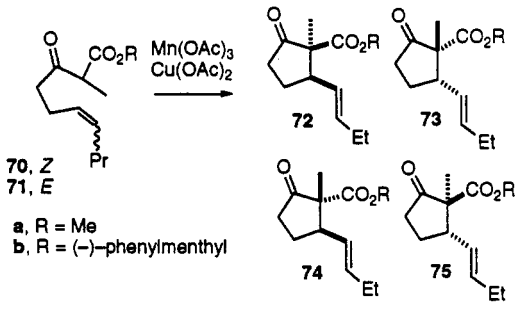
(38) (a) Ihara, M.; Tahakashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413. (b) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525. (c) Ihara, M.; Tankguchi, N.; Suzuki, S.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, 976.

(39) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349.

Our sample of **69** should be 43% optically pure since it was prepared from a 2.5:1 mixture of diastereomers.



Oxidative cyclization of *Z*-isomer **70b** provided 85% of a 2.5:1:2:2.8 mixture of **72b–75b**, respectively. Cyclization of *E*-isomer **71b** afforded 78% of a 1.9:1.6:1:1.1 mixture of **72b–75b**, respectively. Although these reactions proceed in high yield, their synthetic utility is limited since mixtures of *cis*- and *trans*-isomers are formed with only 5–43% asymmetric induction.



The structures of **72b–75b** were established by methylation of the enolates of the 2.5:1 mixture of **66b** and **67b** giving a 5:2:2.5:1 mixture of **72b–75b**, respectively. Methylation of cyclopentanes **66b** and **67b** was not stereospecific giving a 2:1 mixture of *trans*-isomers (**72b** and **73b**) and *cis*-isomers (**74b** and **75b**), despite the fact that alkylation of closely related compounds has been reported to be stereospecific.[40] Since the lack of stereocontrol in the alkylation was not expected, it was confirmed by methylation of racemic methyl ester **66a** which gave 81% of a 2:1 mixture of racemic **72a** and racemic **74a**. Since a 2.5:1 mixture of **66b** and **67b** was used for the methylation, **72b** must be the major product and **75b** must be the minor product. This permits assignment of all four diastereomers since **73** and **74** have very different NMR spectra. The ring methine hydrogen is deshielded by the cis ester group and absorbs at δ 2.9–3.3 in **74a**, **74b**, and **75b**. This absorption is below δ 2.70 in **72a**, **72b**, and **73b**. The quaternary methyl carbon absorbs at δ 18.2, 18.4, and 17.3 in **72a**, **72b**, and **73b** and is shielded by the cis propenyl group to δ 13.8, 13.5, and 13.7 in **74a**, **74b**, and **75b**.

Conclusion. Mn(III)-based oxidative free-radical cyclization of phenylmenthyl ester **1e** afforded 90% of **13** with 86% de. Cyclization of **31b** provided 56% of (+)-podocarpic acid precursor **32e** with 82% de. The direction of de was opposite in these two cases. Oxidative cyclization of α-methyl β-keto ester **44b** gave a 1:1.6 mixture of **46b** and **47b** while α-propyl β-keto ester **44d** afforded a >10:1 mixture of **46d** and **47d** indicating that the extent and direction of de is dependent on the size of the α-substituent. The reaction proceeds through transition states **12** and **56** with large α-substituents and through transition states **19** and **57** with small α-substituents. The de depends on the double bond substitution pattern as shown by the decreased de with **37b** and **37d**, and selectivity in the 5-*exo* cyclization of **64b**, **65b**, **70b**, and **71b** is low.

Experimental Section

NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants in Hz. Absorptions are for all the diastereomers unless otherwise indicated. IR spectra are recorded in cm^{-1}. Combustion analyses were performed by Spang Microanalytical Laboratory or Baron Consulting Co. All alkylations and oxidative cyclizations were run under N_2.

$Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, (−)-8-phenylmenthol, (±)-*trans*-2-phenylcyclohexanol, and (−)-10-dicyclohexylsulfamoyl-D-isoborneol were purchased from Aldrich. We thank Prof. Douglass Taber, University of Delaware, for a gift of the alcohol precursor to **1g**, and Prof. Scott Denmark, University of Illinois at Urbana–Champaign, for the alcohol precursor to **37h**. (+)-8-Phenylmenthol was prepared by the literature procedure.[27]

General Procedure for Ester Exchange.[12] A flame-dried 50-mL round-bottomed flask equipped with a reflux condenser and a nitrogen purge was flushed with N_2 and charged with alcohol (1 equiv), 4-(dimethylamino)pyridine (DMAP, 0.3 equiv), and β-keto ester (1 equiv) in anhydrous toluene (10 mL/mmol). The mixture was stirred under reflux for 3–5 days, cooled to rt, and concentrated under reduced pressure. Flash chromatography of the crude mixture on silica gel (20:1 hexane–EtOAc) gave esters **1e** (630 mg, 98%), **1f** (201 mg, 93%), **1g** (216 mg, 91%), **1h** (100 mg, 96%), **1i** (540 mg, 94%), **29b** (2.50 g, 90%), **37b** (1.550 g, 87%), **37d** (842 mg, 86%), **40Zb** (720 mg, 90%), **58b** (1.333 g, 98%), **58c** (414 mg, 97%), **59b** (218 mg, 86%), **59c** (309 mg, 85%), (−)-phenylmenthyl acetoacetate (2.39 g, 89%), and (−)-phenylmenthyl α-allylacetoacetate (400 mg, 90%) as a mixture of diastereomers (a and b).

The data for **1e** (a:b = 2.5:1): ^1H NMR 7.31–7.26 (m, 4), 7.20–7.15 (m, 1), 5.70–5.52 (m, 1), 5.02 (m, 2), 4.82 (m, 1), 4.72 (br s, 1), 4.67 (br s, 1, b), 4.61 (br s, 1, a), 2.96 (dd, 1, J = 6.2, 8.2, b), 2.63 (dd, 1, J = 6.8, 7.8, a), 2.72–2.00 (m, 7), 1.90–0.90 (m, 7), 1.73 (s, 3, b), 1.70 (s, 3, a), 1.31 (s, 3, b), 1.29 (s, 3, a), 1.21 (s, 3, b), 1.19 (s, 3, a), 0.85 (d, 3, J = 6.6); ^{13}C NMR 204.4 (a), 204.3 (b), 169.0 (b), 167.9 (a), 152.0 (a), 151.3 (b), 144.3 (b), 144.1 (a), 134.6 (a), 134.4 (b), 128.0 (a), 127.9 (b), 125.4 (b), 125.3 (a), 125.2 (b), 125.0 (a), 117.3 (a), 117.2 (b), 110.2, 76.0 (b), 75.2 (a), 57.7 (b), 57.5 (a), 50.2 (a), 50.0 (b), 41.5 (b), 41.12 (a), 41.07 (a), 40.9 (b), 39.8 (b), 39.5 (a), 34.48 (a), 34.44 (b), 32.16 (b), 31.8 (a), 31.3 (b), 31.2 (a), 30.9 (b), 30.8 (a), 29.1 (a), 27.2 (b), 26.7 (a), 26.4 (b), 26.3 (a), 25.9 (b), 23.5 (b), 22.7, 21.7 (a); IR (neat) 3095, 2960, 2930, 2880, 1745, 1720, 1650, 1605, 1450, 1180, 765, 700; $[\alpha]_D$ 24.5° (*c* 0.153, CH_2Cl_2). Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 79.07; H, 9.48.

Pyrrolidine amide 1j was prepared as a 1:1 mixture of diastereomers (a:b) by the above exchange procedure using (2*R*,5*R*)-2,5-dimethylpyrrolidine[14] without solvent or 4-DMAP in 74% yield (471 mg): ^1H NMR 5.72 (m, 1), 5.11 (br d, 1, J = 17.0), 5.03 (br d, 1, J = 10.3), 4.70 (br s, 1), 4.65 (br s, 1, a or b), 4.62 (br s, 1, a or b), 4.26 (m, 1), 4.14 (m, 1, a or b), 4.02 (m, 1, a or b), 3.58 (dd, 1, J = 6.8, 8.1, a or b), 3.53 (dd, 1, J = 6.8, 8.1, a or b), 2.79–2.58 (m, 4), 2.30–2.10 (m, 4), 1.72 (br s, 3, a or b), 1.71 (br s, 3, a or b), 1.66–1.54 (m, 2), 1.26 (d, 3, J = 6.4, a or b), 1.17 (d, 3, J = 6.4, a or b), 1.16 (d, 3, J = 6.4, a or b), 1.15 (d, 3, J = 6.4, a or b); ^{13}C NMR 205.9, 205.8, 168.0, 166.5, 144.3 (a and b), 135.0, 134.3, 117.5, 117.2, 110.04, 109.96, 59.5, 58.1, 53.9, 53.7, 53.6, 53.3, 38.6, 37.2, 34.6, 33.0, 31.02, 30.83, 30.76, 30.70, 29.1, 28.8, 22.7, 22.6, 22.4, 22.3, 18.7, 18.5; IR (neat) 3080, 2970, 2930, 2880, 1725, 1635, 1410; $[\alpha]_D$ −4.6° (*c* 0.430, CH_2Cl_2). Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81. Found: C, 73.68; H, 9.92.

General Procedure for Alkylation of β-Keto Ester Dianions. To 2.0 equiv of LDA (0.3 M in THF) was added 1.0

(40) (a) Tanimori, S.; Ohashi, T.; Nakayama, M. *Biosci. Biotech. Biochem.* **1992**, *56*, 351. (b) Sakurai, K.; Kitahara, T.; Mori, K. *Tetrahedron* **1990**, *46*, 761. (c) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1989**, *30*, 4999.

equiv of keto ester (1.0 M in THF) dropwise at 0 °C. The solution was stirred for 0.5 h, and 2.0 equiv of DMPU followed by 1.0 equiv of alkyl bromide were added. The mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of water, acidified with 0.1 M HCl, and extracted with three portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alkylation product. Flash chromatography of the crude mixture on silica gel (20:1 hexane–EtOAc) gave esters **37c** (480 mg, 61%), **40Zb** (361 mg, 91%), **44b** (420 mg, 56%), **44c** (230 mg, 48%), **44d** (149 mg, 81%), **45b** (307 mg, 75%), **45c** (239 mg, 50%), **45d** (225 mg, 73%), **64b** (790 mg, 66%), **65b** (298 mg, 75%), **70b** (301 mg, 73%), and **71b** (181 mg, 72%).

General Procedure for Oxidative Cyclization. The β-keto ester (1 equiv) was added to a stirred solution of $Mn(OAc)_3 \cdot 2H_2O$ (2 equiv) and $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in degassed glacial acetic acid (10 mL/mmol). The reaction mixture was stirred under N_2 at rt for 16–34 h until the brown color of $Mn(OAc)_3$ was gone. The solution was diluted with water, and the resulting solution was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave 97–100% of crude product which was purified by flash chromatography on silica gel (10:1 hexane–EtOAc). The ratio of isomers was determined by analysis of ^1H and ^{13}C NMR spectral data of both crude and purified products.

Oxidative cyclization of 1e (513 mg, 1.25 mmol) as described above gave 459 mg (90%) of a 12:1 inseparable mixture of the two diastereomers of **5e** (**13**, a, major, b, minor): ^1H NMR (partial data for b) 7.32–7.22 (m, 4), 7.16–7.08 (m, 1), 4.98 (br s, 1, b), 4.93 (br s, 1, b), 4.92 (br s, 2, a), 4.88 (ddd, 1, J = 4.2, 11.2, 11.2, a), 2.68 (br d, 1, J = 18.1, b), 2.43 (br d, 1, J = 18.1, a), 2.37 (ddd, 1, J = 8.2, 11.8, 16.3, a), 2.26 (ddd, 1, J = 1.3, 6.3, 16.3, a), 2.14 (br d, 1, J = 18.1, a), 2.08–2.02 (m, 3, a), 1.78 (dd, 1, J = 3.3, 12.2, a), 1.68 (ddd, 1, J = 6.3, 11.8, 12.5, a), 1.65–1.45 (m, 4, a), 1.54 (br d, 1, J = 12.2, a), 1.35–0.90 (m, 2, a), 1.33 (s, 3, a), 1.31 (s, 3, b), 1.17 (s, 3, a), 1.16 (s, 3, a), 1.14 (s, 3, b), 0.87 (d, 3, J = 6.5, a); ^{13}C NMR 207.4 (a), 170.6 (a), 153.9 (a), 152.0 (a), 127.9 (a), 125.6 (a), 125.0 (a), 105.9 (a), 105.8 (b), 75.9 (a), 62.1 (b), 62.0 (a), 49.8 (b), 49.7 (a), 46.0 (a), 43.8 (a), 41.5 (a), 40.3 (b), 40.0 (a), 39.7 (a), 39.1 (a), 35.5 (a), 34.6 (a), 31.3 (a), 28.4 (a), 26.7 (a), 24.9 (a), 22.7 (a), 21.8 (a); IR (neat) 3080, 3030, 2970, 2930, 2880, 1740, 1720, 1660, 1605, 1460, 1450, 1260, 1240, 1200, 760, 730, 700; $[\alpha]_D$ −46.7° (c 0.320, CH_2Cl_2). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.81; H, 8.69.

Oxidative cyclization of 1j (55 mg, 0.2 mmol) as described above gave 15.6 mg (28%) of a 24:1 inseparable mixture of diastereomers of **5j** (**17**, major): mp 90–92 °C; ^1H NMR (**17**) 5.05 (t, 1, J = 2.7), 4.98 (t, 1, J = 2.7), 4.22 (m, 1), 3.72 (m, 1), 2.95 (br s, 2), 2.55 (ddd, 1, J = 8.5, 12.2, 15.2), 2.40 (dd, 1, J = 3.5, 12.5), 2.35 (ddd, 1, J = 1.5, 6.2, 15.2), 2.20–2.05 (m, 2), 1.97 (br d, 1, J = 12.5), 1.74 (ddd, 1, J = 6.2, 12.2, 12.5), 1.68 (dddd, 1, J = 1.5, 3.5, 8.5, 12.5), 1.56–1.45 (m, 2), 1.28 (d, 3, J = 6.4), 1.25 (s, 3), 1.12 (d, 3, J = 6.4); ^{13}C NMR (**17**) 209.3, 169.2, 154.5, 105.7, 62.5, 54.5, 53.5, 49.4, 43.5, 42.6, 41.1, 36.4, 30.9, 28.9, 22.72, 22.6, 18.9; IR (neat) 3070, 2960, 2920, 2860, 1715, 1610, 1400; $[\alpha]_D$ −33.5° (c 0.350, CH_2Cl_2). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.24; H, 9.24.

Preparation of (±)-β-Keto Acid 15. A solution of methyl ester **5a** (50 mg, 0.24 mmol) and 1 mL of 20% NaOH solution was stirred at rt for 20 h. The crude mixture was washed with 1 mL of hexane twice and acidified with 3 mL of cold 10% HCl solution at 0 °C. The mixture was extracted with 5 × 10 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to give 46.0 mg (99%) of (±)-**15** which is 95% pure: ^1H NMR 10.89 (br s, 1), 5.09 (br t, 1, J = 2.0), 5.04 (dd, 1, J = 2.1, 3.0), 3.13 (br dt, 1, J = 17.8, 2.4), 2.81 (dq, 1, J = 17.8, 2.0), 2.56 (dddd, 1, J = 1.1, 8.5, 11.9, 16.4), 2.44 (ddd, 1, J = 1.7, 6.4, 16.4), 2.27 (dd, 1, J = 3.3, 12.2), 2.05 (dd, 1, J = 2.1, 12.2), 1.83 (ddd, 1, J = 6.4, 11.9, 12.5), 1.72 (dddd, 1, J = 1.7, 3.3, 8.5, 12.5), 1.28 (s, 3); ^{13}C NMR 210.1, 175.9, 153.1, 106.5, 60.6, 47.7, 44.2, 40.7, 40.4, 35.8, 22.6; IR (neat) 3500–2700 (br), 1740–1690 (br).

Preparation of (−)-β-Keto Acid 15. A solution of ester **5e** (412.2 mg, 1.00 mmol) and $LiAlH_4$ (100 mg, 2.63 mmol) in 5 mL of anhydrous ether was heated at reflux for 1 h and cooled to rt. Saturated NaCl solution (5 mL) and then 10 mL of 1 M HCl were added slowly. The solution was extracted with ether (3 × 30 mL). The combined ether layers were dried (Na_2SO_4) and concentrated to give 423.0 mg of crude diol. Flash chromatography on silica gel (3:1 EtOAc–hexane then 3:1 EtOAc–CH_2Cl_2) gave 225.0 mg (97%) of (−)-8-phenylmenthol, followed by 155.5 mg (86%) of a 1.2:1 mixture of equatorial (a) and axial alcohols (b): mp 92.0–94.0 °C; ^1H NMR 4.86 (br s, 1, a), 4.81 (br s, 1, b), 4.76 (t, 1, J = 2.5, b), 4.73 (t, 1, J = 2.5, a), 3.89 (m, 1), 3.79 (d, 1, J = 10.5, b), 3.75 (d, 1, J = 10.6, a), 3.59 (br d, 1, J = 10.6), 3.03 (br s, 2), 2.71 (dq, 1, J = 17.1, 2.1), 2.14 (br d, 1, J = 17.4), 2.10–2.05 (m, 1), 1.85–1.15 (m, 6), 1.11 (s, 3, b), 1.09 (s, 3, a); ^{13}C NMR 157.2 (a), 156.1 (b), 103.8 (b), 103.4 (a), 75.6 (a), 73.9 (b), 71.9 (b), 71.2 (a), 47.2 (a), 46.4 (a), 46.3 (b), 45.0 (b), 43.8 (a), 42.0 (b), 39.9 (b), 39.2 (a), 36.5 (b), 35.9 (a), 30.0 (a), 28.9 (b), 23.9 (b), 23.4 (a); IR (neat) 3400–3100 (br), 3070, 2950, 2920, 2860, 1655, 1450, 1370, 1005, 870; $[\alpha]_D$ −26.1° (c 0.330, CH_2Cl_2). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.34; H, 9.92.

To 70 mg (0.385 mmol) of diol was added 1.1 g of PDC[16] (2.93 mmol) and 2.5 mL of DMF. The mixture was stirred at rt for 18 h and filtered through silica gel twice. The silica gel was rinsed with ether. The solvent was removed to give 74.3 mg of crude (−)-**15**. Flash chromatography on silica gel (2:1 EtOAc–hexane) gave 67.0 mg (90%) of (−)-**15**: mp 96–98 °C; $[\alpha]_D$ −72.1° (c 0.363, CH_2Cl_2). The other data are identical to those of (±)-**15**.

Preparation of (±)-5j. Crude (±)-**15** in 1 mL of anhydrous ether was treated with oxalyl chloride (87 mg, 0.69 mmol), and the mixture was heated at reflux for 2 h and evaporated under reduced pressure to give the crude acid chloride. (2*R*,5*R*)-2,5-Dimethylpyrrolidine (69 mg, 0.70 mmol) and 1 mL of toluene were added, and the mixture was warmed to 60–80 °C for 0.5 h. The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 20 mL of water. The organic layer was dried ($NaSO_4$) and concentrated in vacuo to give 68.0 mg of crude (±)-**5j**. Flash chromatography on silica gel (1:1 hexane–EtOAc) gave 38.3 mg (58%, from **5a**) of a 1:1 mixture of **17** and the diastereomer: mp 88–92 °C; IR (neat) 1715, 1610; $[\alpha]_D$ 27.5° (c 0.335, CH_2Cl_2).

The data for the diastereomer of **17** were determined from the mixture: ^1H NMR 5.06 (t, 1, J = 2.4), 4.99 (t, 1, J = 2.4), 4.32 (m, 1), 3.98 (m, 1), 3.18 (br d, 1, J = 17.1), 2.88 (br d, 1, J = 12.1), 2.60–2.30 (m, 3), 2.20–2.10 (m, 3), 1.85–1.45 (m, 4), 1.24 (s, 3), 1.21 (d, 3, J = 6.4), 1.07 (d, 3, J = 6.4); ^{13}C NMR 209.0, 169.2, 154.2, 105.5, 63.7, 54.8, 53.0, 50.4, 43.7, 40.9, 40.7, 36.7, 31.5, 28.4, 22.69, 22.4, 18.7.

Preparation of 5j from (−)-**15** gave a 12:1 mixture of **17** and the diastereomer: mp 89–90 °C; $[\alpha]_D$ −25.2° (c 0.485, CH_2Cl_2).

(−)-Ketone 14. Flash-vacuum thermolysis (pot, 120 °C; oven, 450 °C; 1.5 Torr; trapped in liquid N_2) of (−)-acid **15** (29.1 mg, 0.15 mmol) gave 22.7 mg of crude **14**. Flash chromatography on silica gel (CH_2Cl_2) gave 20.0 mg (89%) of (−)-**14**. The ^1H and ^{13}C NMR and IR spectra are identical to those previously described for (+)-**11**:[2] CD ϵ_{290} −1.2 (c 0.075 g/dm^3, CH_2Cl_2); $[\alpha]_D$ −90.8° (c 0.420, CH_2Cl_2).

3-(4-Methoxyphenyl)propanal (24). To a suspension of PCC[20] (10.5 g, 45 mmol) in CH_2Cl_2 (75 mL) was added 3-(4-methoxyphenyl)propanol (**23**) (5.1 g, 30.4 mmol). The mixture was stirred at rt for 1.5 h. Ether was then added to the reaction mixture. The ether layer was decanted. The residue was washed with ether. The combined ether layers were evaporated to afford 4.8 g of crude **24**. Flash chromatography of the crude product (8:1 EtOAc–hexane) on silica gel gave 4.1 g (82%) of aldehyde **24**: ^1H NMR 9.78 (br s, 1), 7.09 (br d, 2, J = 8.8), 6.82 (br d, 2, J = 8.8), 3.76 (s, 3), 2.88 (br t, 2, J = 7.5), 2.72 (br t, 2, J = 7.5); ^{13}C NMR 201.6, 158.0, 132.2, 129.1, 113.8, 55.1, 45.4, 27.1; IR (neat) 1724.

Ethyl 2-Methyl-5-(4-methoxyphenyl)-2-pentenoate (25). NaH (1.21 g, 60% suspension in mineral oil, 30.3 mmol, washed with hexane) was covered with THF (20 mL), and triethyl 2-phosphonopropionate (6.56 g, 27 mmol) was added dropwise. The mixture was stirred at rt for 1 h. Aldehyde **24** (4.03 g, 24.6 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 1 h. Water (150 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to afford 6.33 g of crude **25**. Flash

chromatography on silica gel (5:1 EtOAc–hexane) gave 0.956 g (16%) of *Z*-isomer followed by 4.55 g (75%) of **25**.

The data for the *Z*-isomer: ^{1}H NMR 7.11 (d, 2, J = 8.4), 6.82 (d, 2, J = 8.4), 5.94 (tq, 1, J = 7.0, 1.4), 4.19 (q, 2, J = 7.1), 3.78 (s, 3), 2.71 (m, 4), 1.88 (d, 3, J = 1.4), 1.29 (t, 3, J = 7.1); ^{13}C NMR 168.0, 157.8, 141.6, 133.6, 129.3, 127.7, 113.7, 60.1, 55.2, 34.6, 31.4, 20.6, 14.3; IR (neat) 1700, 1510.

The data for **25**: ^{1}H 7.10 (d, 2, J = 8.5), 6.83 (d, 2, J = 8.5), 6.80 (tq, 1, J = 7.4, 1.6), 4.18 (q, 2, J = 7.1), 3.78 (s, 3), 2.69 (dd, 2, J = 7.4, 8.1), 2.45 (ddd, 2, J = 7.4, 8.1, 7.4), 1.78 (br s, 3), 1.28 (t, 3, J = 7.1); ^{13}C NMR 168.1, 157.9, 140.9, 133.3, 129.2, 128.3, 113.8, 60.3, 55.2, 33.8, 30.8, 14.2, 12.3; IR (neat) 1702, 1507. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.68; H, 8.08.

5-(4-Methoxyphenyl)-2-methyl-2(*E*)-penten-1-ol (26). To a solution of **25** (3.12 g, 12.56 mmol) in toluene (30 mL) was added DIBAL (27.6 mL, 1.0 M in CH_2CL_2, 27.6 mmol) dropwise at 0 °C. The mixture was stirred at rt overnight, and MeOH (15 mL) was added slowly. The mixture was poured into 0.1 M HCl (150 mL) and extracted with CH_2Cl_2 (4 × 60 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford 2.52 g (97%) of alcohol **26** which was used without purification: ^{1}H NMR 7.09 (d, 2, J = 8.9), 6.81 (d, 2, J = 8.9), 5.43 (qt, 1, J = 1.3, 7.0), 3.95 (br s, 2), 3.75 (br s, 3), 2.59 (dd, 2, J = 7.3, 8.3), 2.31 (ddd, 2, J = 7.3, 8.1, 7.0), 2.04 (br s, 1), 1.59 (br s, 3); ^{13}C NMR 157.6, 135.3, 134.0, 129.2, 125.0, 113.6, 68.5, 55.1, 34.7, 29.6, 13.5; IR (neat) 3500–3100.

1-Bromo-5-(4-methoxyphenyl)-2-methyl-2-pentene (27). To alcohol **26** (2.475 g, 12 mmol) in THF (60 mL) was added PBr_3[23] (1.14 mL, 12 mmol) dropwise at 0 °C. The solution was stirred for 0.5 h. The mixture was poured into water (100 mL) and extracted with ether (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford 2.84 g of bromide. Flash chromatography (8:1 hexane–EtOAc) gave 2.3 g (71% from **25**) of pure bromide **27**: ^{1}H NMR 7.08 (d, 2, J = 8.5), 6.81 (d, 2, J = 8.5), 5.62 (br t, 1, J = 7.2), 3.94 (br s, 2), 3.77 (s, 3), 2.60 (dd, 2, J = 7.4, 8.0), 2.30 (ddd, 2, J = 7.2, 7.4, 8.0), 1.68 (br s, 3); ^{13}C NMR 157.7, 133.5, 132.5, 130.3, 129.2, 113.6, 55.1, 41.5, 34.2, 30.3, 14.5; IR (neat) 2933, 2834, 1611, 1512, 1247, 1177, 1037, 826, 607.

Preparation of 31b. Alkylation of the dianion of **29b** with **27** by the general procedure described above gave 440 mg (85%) of ester **31b** (a (keto):b (keto):c (enol) = 4:2:1): ^{1}H NMR 7.28 (m, 4), 7.14 (m, 1), 7.09 (d, 2, J = 8.7, a), 7.08 (d, 2, J = 8.7, b), 6.83 (d, 2, J = 8.7, a), 6.82 (d, 2, J = 8.7, b), 5.18 (qt, 1, J = 1.2, 6.9, a), 5.12 (qt, 1, J = 1.2, 7.1, b), 4.84 (ddd, 1, J = 4.4, 10.8, 10.8, a), 4.83 (ddd, 1, J = 4.3, 10.8, 10.8, b), 3.79 (s, 3, a), 3.78 (s, 3, c), 3.77 (s, 3, b), 2.98 (q, 1, J = 7.2, a), 2.91 (q, 1, J = 7.3, b), 2.56–1.45 (m, 16), 1.55 (s, 3, b), 1.51 (s, 3, a), 1.31 (s, 3, b), 1.29 (s, 3, a), 1.22 (s, 3, b), 1.19 (s, 3, a), 1.10 (d, 3, J = 7.2, b), 1.08 (d, 3, J = 7.0, a), 0.87 (d, 3, J = 6.5, b), 0.86 (s, 3, J = 6.5, a); ^{13}C NMR 205.9 (a), 170.2 (b), 169.3 (a), 157.70 (a), 157.68 (b), 152.0 (a), 151.2 (b), 134.22 (b), 134.18 (a), 134.0 (a), 129.3 (a, b, and c), 127.93 (b), 127.85 (a), 125.4 (b), 125.3 (a), 125.2 (c), 125.0 (a), 124.2 (a), 113.6 (a, b, and c), 75.7 (b), 74.9 (c), 74.8 (a), 55.2 (a, b, and c), 52.9 (c), 52.6 (b), 52.1 (a), 50.2 (a), 50.1 (b), 41.4 (b), 41.22 (a), 41.15 (c), 40.5 (b), 40.2 (a), 39.8 (b), 39.5 (a), 35.0 (a), 34.5 (a), 34.4 (b), 33.1 (b), 33.0 (a), 31.24 (b), 31.19 (a), 30.1 (a), 29.2 (a), 29.1 (b), 26.4 (b), 26.3 (a), 23.51 (b), 23.48 (c), 23.37 (a), 21.7 (a), 16.0 (a), 12.6 (b), 12.3 (a), 12.2 (c); IR (neat) 2953, 1738, 1714, 1612, 1512, 1456, 1245, 1179, 1037, 766, 701; $[\alpha]_D$ 8.5° (*c* 0.680, CH_2Cl_2).

The data for **31a** are identical except $[\alpha]_D$ −8.3° (*c* 1.00, CH_2Cl_2).

Oxidative Cyclization of 31b. To a stirred solution of $Mn(OAc)_3 \cdot 2H_2O$ (54 mg, 0.2 mmol) in MeOH (1.5 mL) was added ester **31b** (52 mg, 0.1 mmol). The reaction was stirred at 0 °C for 8 h and quenched by addition of water. The resulting solution was extracted with 3 × 10 mL of CH_2Cl_2. The combined organic extracts were washed with saturated NaCl and dried ($MgSO_4$). Removal of the solvent in vacuo gave 53.1 mg of a crude 10:1 mixture of **33e** and **32e**. Purification by flash chromatography (10:1 hexane–EtOAc) gave 3.1 mg (6%) of ester **32e** (90% pure by ^{1}H and ^{13}C NMR) followed by 25.7 mg (50%) of pure ester **33e**.

The data for **32e**: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 7.01 (d, 1, J = 8.3), 6.81 (d, 1, J = 2.7), 6.71 (dd, 1, J = 2.7, 8.3), 4.91 (dt, 1, J = 4.2, 10.3), 3.78 (s, 3), 3.09 (dt, 1, J = 6.0, 16.4), 2.94 (br dd, 1, J = 5.0, 16.0), 2.77 (ddd, 1, J = 6.6, 11.8, 16.7), 2.55 (m, 2), 2.33–0.70 (m, 12), 1.49 (s, 3), 1.41 (s, 3), 1.27 (s, 3), 1.23 (s, 3), 0.85 (d, 3, J = 6.4); ^{13}C NMR 207.4, 171.9, 157.8, 150.0, 147.2, 130.1, 128.1, 128.0, 127.3, 125.8, 111.6, 111.0, 76.3, 57.8, 55.3, 55.0, 50.5, 41.2, 40.4, 39.4, 38.3, 37.8, 34.2, 31.6, 31.3, 31.0, 27.6, 23.9, 22.5, 21.8, 21.3, 21.2.

The data for **33e**: mp 68.0–69.0 °C; ^{1}H NMR 7.30 (m, 4), 7.18 (m, 1), 7.01 (d, 1, J = 8.3), 6.81 (d, 1, J = 2.5), 6.71 (dd, 1, J = 2.5, 8.3), 4.95 (dt, 1, J = 4.4, 10.6), 3.77 (s, 3), 3.09 (dt, 1, J = 6.1, 16.4), 2.92 (br dd, 1, J = 4.2, 12.5), 2.73 (ddd, 1, J = 6.8, 12.1, 16.8), 2.52 (m, 2), 2.02 (m, 4), 1.72 (m, 2), 1.52–0.70 (m, 6), 1.41 (s, 3), 1.36 (s, 3), 1.34 (s, 3), 1.25 (s, 3), 0.82 (d, 3, J = 6.4); ^{13}C NMR 208.0, 173.2, 157.9, 150.5, 147.5, 130.1, 128.1, 127.0, 125.7, 125.4, 111.7, 110.9, 77.2, 58.1, 55.3, 53.8, 49.8, 41.7, 40.2, 38.8, 38.2, 37.5, 34.3, 31.3, 30.9, 29.9, 27.5, 24.6, 23.7, 21.79, 21.77, 20.8; IR (KBr) 2955, 2924, 2866, 1719, 1700, 1609, 1505, 1497, 1457, 1264, 1237, 1191, 1091, 766, 701; $[\alpha]_D$ 30.5° (*c* 0.43, CH_2Cl_2). Anal. Calcd for $C_{34}H_{44}O_4$: C, 79.03; H, 8.58. Found: C, 78.85; H, 8.55.

A similar cyclization of ester **31a** gave a 10:1 mixture of **32c** and **33c**. The data for **32c** are identical to those of the enantiomer **33e** except $[\alpha]_D$ −29° (*c* 0.308, CH_2Cl_2).

(−)-Phenylmenthyl (+)-*O*-Methylpodocarpate (33f). To ester **33e** (52 mg, 0.1 mmol) in 8 mL of ether (saturated with HCl gas) at 0 °C was added active Zn powder (1.05 g).[24] The solution was stirred at 0 °C for 4 h and then warmed to rt for 1 h and quenched by addition of water. The resulting solution was extracted with ether (3 × 10 mL). The combined ether layers were dried ($MgSO_4$), and solvent was removed in vacuo to give 51.7 mg of crude product. Flash chromatography on silica gel (12:1 hexane–EtOAc) gave 32.7 mg (65%) of pure ester **33f** followed by 9.0 mg (17%) of recovered ester **33e**: ^{1}H NMR 7.28 (m, 4), 7.18 (m, 1), 6.98 (d, 1, J = 8.3), 6.82 (d, 1, J = 2.7), 6.68 (dd, 1, J = 2.7, 8.3), 4.95 (dt, 1, J = 4.4, 10.7), 3.77 (s, 3), 2.87 (br dd, 1, J = 4.9, 16.4), 2.71 (ddd, 1, J = 16.4, 12.3, 6.3), 2.27 (br dd, 2, J = 16.0, 13.8), 2.15–1.85 (m, 5) 1.65–0.68 (m, 10), 1.41 (s, 3), 1.27 (s, 3), 1.20 (s, 3), 1.15 (s, 3), 0.79 (d, 3, J = 6.4); ^{13}C NMR 176.8, 157.7, 150.8, 149.6, 129.9, 128.0, 127.5, 125.8, 125.3, 111.2, 110.9, 75.8, 55.2, 52.7, 50.1, 44.4, 41.9, 40.4, 39.4, 38.7, 38.2, 34.4, 31.4, 31.3, 30.6, 28.7, 27.8, 24.5, 24.0, 21.8, 21.2, 20.1; IR (neat) 2960, 1725, 765, 700; $[\alpha]_D$ 39° (*c* 0.250, CH_2Cl_2).

Ester **32d** was prepared analogously from **32c**. The data are identical to those of the enantiomer **33f** except $[\alpha]_D$ −37° (*c* 0.300, CH_2Cl_2).

(+)-*O*-Methylpodocarpinol (33g). Ester **33f** (28 mg, 0.040 mmol) in THF (3 mL) was added to a flask charged with LAH (25 mg, 0.52 mmol). The solution was heated at reflux overnight and quenched by addition of 1 M HCl (5 mL) at 0 °C. The mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 31 mg of crude **33g**. Flash chromatography on silica gel (10:1 hexane–EtOAc) gave 12.6 mg (96%) of (−)-8-phenylmenthol followed by 15.0 mg (98%) of alcohol **33g**: mp 90.5–91.5 °C (lit.[29] 90–91.5 °C); ^{1}H NMR 6.94 (d, 1, J = 8.4), 6.80 (d, 1, J = 2.5), 6.66 (dd, 1, J = 8.3, 2.5), 3.85 (d, 1, J = 11.0), 3.76 (s, 3), 3.53 (d, 1, J = 11.0), 2.87 (br dd, 1, J = 6.8, 16.8), 2.75 (ddd, 1, J = 7.1, 11.2, 16.8), 2.27 (br d, 1, 12.7), 2.00–0.95 (m, 8), 1.18 (s, 3), 1.05 (s, 3); ^{13}C NMR 157.6, 150.9, 129.7, 127.0, 110.8, 110.2, 65.1, 55.2, 51.1, 38.9, 38.7, 37.9, 35.1, 30.1, 26.8, 25.6, 19.2, 18.9; IR (neat) 3420; $[\alpha]_D$ 66° (*c* 0.15, CH_2Cl_2) (lit.[29] $[\alpha]_D$ 67°, $CHCl_3$).

(−)-*O*-Methylpodocarpinol (**32g**) was prepared analogously from **32d**. The data are identical to those of the enantiomer **33g** except $[\alpha]_D$ −67° (*c* 0.15, CH_2Cl_2).

***O*-Methylpodocarpinal (33h).** To a solution of oxalyl chloride (6 mL, 0.069 mmol) in CH_2Cl_2 (0.3 mL) at −78 °C was added DMSO (11 mL, 0.15 mmol). The mixture was stirred for 20 min. Alcohol **33g** (14.0 mg, 0.051 mmol) in 0.2 mL of CH_2Cl_2 was added, and the reaction was stirred for 0.5 h. Et_3N (0.1 mL, 0.18 mmol) was added, and the reaction was warmed to rt for 20 min. Water (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give 13.4 mg of crude **33h** which was used without purification: ^{1}H NMR 9.82 (d, 1, J = 1.5), 6.98 (d, 1, J = 8.4), 6.80 (d, 1, J = 2.7), 6.68 (dd, 1, J = 2.7, 8.4), 3.77 (s, 3), 2.93 (ddd, 1, J = 6.2, 1.7, 16.6), 2.82 (ddd, 1, J = 6.7, 12.0, 16.3), 2.21 (m, 3), 2.00 (dddd, 1, J = 6.3, 11.7, 12.9, 13.0), 1.70 (m, 3),

1.41 (dt, 1, J = 4.2, 13.2), 1.11 (m, 1), 1.10 (s, 3), 1.06 (s, 3); ^{13}C NMR 205.6, 157.8, 148.8, 129.9, 126.8, 111.3, 110.6, 55.2, 51.9, 48.6, 38.4, 38.3, 33.8, 30.4, 24.2, 24.0, 19.2, 18.9.

(+)-*O*-Methylpodocarpic Acid (33i). To a stirred mixture of **33h** (13.4 mg, 0.05 mmol) and 2-methyl-2-butene (0.15 mL) in t-BuOH (0.3 mL) was added a solution of $NaClO_2$[30] (7 mg) and $NaH_2PO_4 \cdot 2H_2O$ (5.5 mg) in water (0.17 mL). The reaction was stirred for 3 days at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with water (2 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 17.0 mg of crude acid. Flash chromatography on silica gel (3:1 hexane–EtOAc) gave 11.8 mg (80% from **33g**) of pure **33i**: mp 157.0–158.0 °C (lit.[29] mp 158 °C); ^{1}H NMR 6.96 (d, 1, J = 8.4), 6.79 (d, 1, J = 2.6), 6.66 (dd, 1, J = 8.4, 2.6), 3.76 (s, 3), 2.85 (br dd, 1, J = 5.1, 16.4), 2.72 (ddd, 1, J = 5.9, 12.3, 16.4), 2.20 (m, 3), 2.06 (dd, 1, J = 5.7, 12.3), 1.99 (ddd, 1, J = 4.3, 12.1, 13.5), 1.65 (m, 1), 1.55 (dd, 1, J = 1.8, 12.1), 1.40 (dt, 1, J = 4.0, 13.3), 1.33 (s, 3), 1.12 (s, 3), 1.09 (m, 1); ^{13}C NMR 184.1, 157.6, 149.2, 129.8, 127.6, 111.2, 111.0, 55.2, 52.8, 43.9, 39.3, 38.8, 37.3, 31.1, 28.7, 23.1, 21.0, 19.9; IR (KBr) 2957, 2935, 1697; $[\alpha]_D$ 131.9° (c 0.410, CH_2Cl_2) (lit.[29] $[\alpha]_D$ 132°, $CHCl_3$).

Oxidation of 40Zb (640 mg, 1.71 mmol) as described above gave 470 mg (69%) of a 12:1 mixture of **41b** and **42b**: IR (neat) 3087, 3055, 2951, 1741, 1715, 1600, 1496, 1456, 1390, 1363, 1335, 1303, 1227, 1187, 1148, 1122, 1094, 1049, 1031, 1008, 964, 766, 737, 701; $[\alpha]_D$ -18.4° (c 1.16, CH_2Cl_2). Anal. Calcd for $C_{26}H_{36}O_3$: C, 78.75; H, 9.15. Found: C, 78.65; H, 9.01.

Oxidation of 40Eb (215 mg, 0.54 mmol) as described above gave 151 mg (70%) of a 1.1:1 mixture of **41b** and **42b**. The data for **41b** and **42b** were determined from comparison of the two mixtures: ^{1}H NMR (**41b**) 7.25 (m, 4), 7.15 (m, 1), 5.43 (dq, 1, J = 15.3, 6.4), 5.16 (br dd, 1, J = 7.6, 15.3), 4.72 (ddd, 1, J = 4.4, 10.7, 10.7) 2.68–0.89 (m, 15), 2.52 (d, 1, J = 11.3), 1.57 (br d, 3, J = 6.4), 1.31 (s, 3), 1.23 (s, 3), 0.84 (d, 3, J = 6.4); (**42b**) 7.25 (m, 4), 7.15 (m, 1), 5.50 (dq, 1, J = 15.3, 6.5), 5.25 (br dd, 1, J = 7.5, 15.3), 4.76 (ddd, 1, J = 4.4, 10.7, 10.7), 2.73 (d, 1, J = 11.3), 2.68–0.89 (m, 15), 1.62 (br d, 3, J = 6.5), 1.33 (s, 3), 1.20 (s, 3), 0.86 (d, 3, J = 6.5); ^{13}C NMR (**41b**) 205.0, 168.5, 151.7, 131.7, 127.5, 126.4, 125.6, 124.6, 75.6, 62.4, 50.4, 45.2, 41.4, 40.8, 39.6, 34.5, 31.0, 30.6, 27.0, 26.6, 25.4, 24.6, 21.7, 17.5; (**42b**) 205.4, 168.4, 151.5, 132.4, 127.7, 126.6, 125.5, 124.8, 75.8, 63.0, 50.1, 43.9, 41.2, 41.0, 39.7, 34.6, 31.2, 30.4, 26.8, 26.4, 26.1, 24.7, 21.7, 17.8.

Hydrogenation of a 12:1 Mixture of β-Keto Esters 41b and 42b. A mixture of **41b** and **42b** (50 mg, 0.126 mmol) and 0.1 equiv of 10% Pd/activated carbon in CH_2Cl_2 was stirred under 1 atm of H_2 for 2 h at rt. The solution was filtered, and the solvent was removed under reduced pressure to give 48 mg (96%) of the saturated ester which was used without purification (mainly one isomer): ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 4.77 (ddd, 1, J = 4.4, 10.7, 10.7), 2.45 (d, 1, J = 11.3), 2.25–0.85 (m, 19), 1.30 (s, 3), 1.22 (s, 3), 0.87 (d, 3, J = 6.5), 0.83 (t, 3, J = 7.4); ^{13}C NMR 206.1, 169.4, 151.8, 127.6, 125.6, 124.7, 76.0, 63.0, 50.4, 41.3, 41.1, 41.0, 39.7, 36.3, 34.6, 31.2, 28.4, 27.0, 26.7, 25.4, 24.3, 21.7, 19.3, 14.0.

(*S*)-(−)-3-Propylcyclohexanone (43). A solution of the saturated ester (50 mg, 0.126 mmol), DMSO (1 mL), H_2O (0.06 mL), and NaCl (35 mg) was stirred at reflux for 20 h, cooled, diluted with 15 mL of water, and extracted with ether (2 × 15 mL).[32] The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to give 56 mg of crude product. Evaporative distillation (10 Torr, 60 °C) gave 10.4 mg (59% from **41b** and **42b**) of pure **43** with 85% ee: ^{1}H NMR 2.42 (ddddd, 1, J = 2.0, 2.0, 2.0, 2.0, 13.8), 2.34 (m, 1), 2.25 (dddd, 1, J = 1.3, 6.0, 12.1, 13.8), 2.05 (m, 1), 2.00 (ddd, 1, J = 1.3, 11.8, 13.8), 1.95–1.55 (m, 3), 1.34 (m, 5), 0.89 (t, 3, J = 7.0); ^{13}C NMR 212.2, 48.2, 41.5, 38.84, 38.81, 31.3, 25.3, 19.7, 14.1; IR (neat) 2957, 2928, 2871, 1714; CD ϵ_{297} −0.19 (c 3.55 g/dm^3, CH_2Cl_2); $[\alpha]_D$ −15° (c 0.19, CH_2Cl_2).

Oxidation of 44b (165 mg, 0.4 mmol) as described above gave 150 mg of a 4.6:7.2:1.0:1.6:1.0:1.5 crude mixture of **46b**, **47b**, **48b**, **49b**, **50b**, and **51b**.

Oxidation of 45b (180 mg, 0.44 mmol) as described above gave 170 mg of a crude 3.7:9.2:1.0:2.0:1.6:2.0 mixture of **46b**, **47b**, **48b**, **49b**, **50b**, and **51b**. Flash chromatography on silica gel (20:1 hexane–EtOAc) gave 77.0 mg (43%) of a 1:2.5 mixture of **46b** and **47b**, 17.6 mg (10%) of a 1:2 mixture (the absolute stereochemistry was not assigned) of **50b** and **51b**, followed by 21.6 mg (12%) of a 1:1.2 (the absolute stereochemistry was not assigned) mixture of **48b** and **49b**.

The data for **46b** and **47b**: IR (neat) 3088, 2955, 2869, 1731, 1713, 1456, 1373, 1311, 1245, 1213, 763, 734, 701; $[\alpha]_D$ -29.3° (c 1.92, CH_2Cl_2).

The data for **46b** were determined from the mixture: ^{1}H NMR 7.25 (m, 4), 7.15 (m, 1), 5.78 (br dd, 1, J = 15.2, 6.7), 5.45 (dq, 1, J = 15.2, 6.4), 4.90 (ddd, 1, J = 4.4, 10.7, 10.7), 2.70 (dt, 1, J = 6.5, 13.6), 2.46 (br d, 1, J = 13.6), 2.20–0.70 (m, 13), 1.68 (dd, 3, J = 1.0, 6.3), 1.28 (s, 3), 1.24 (s, 3), 1.21 (s, 3), 0.84 (d, 3, J = 6.4); ^{13}C NMR 207.3, 170.5, 150.1, 130.8, 127.9, 127.2, 125.6, 125.3, 76.1, 60.6, 53.7, 50.09, 41.6, 40.3, 40.0, 34.2, 31.30, 30.7, 29.0, 27.4, 25.6, 23.0, 21.68, 18.9, 17.9;

The data for **47b** were determined from the mixture: ^{1}H NMR 7.26 (m, 4), 7.14 (m, 1), 5.61 (br dd, 1, J = 8.1, 15.2), 5.46 (dq, 1, J = 15.2, 6.1), 4.85 (ddd, 1, J = 4.4, 10.7, 10.7), 2.83 (dt, 1, J = 6.5, 13.6), 2.40 (br d, 1, J = 13.6), 2.30–0.80 (m, 13), 1.68 (dd, 3, J = 1.0, 6.3), 1.25 (s, 3), 1.23 (s, 3), 1.21 (s, 3), 0.86 (d, 3, J = 6.4); ^{13}C NMR 207.5, 170.6, 150.0, 130.6, 128.0, 127.1, 125.6, 125.3, 76.2, 60.8, 53.5, 50.1, 42.0, 40.2, 40.0, 34.3, 31.26, 30.4, 28.4, 27.3, 25.6, 23.6, 21.70, 18.6, 17.9.

The data for **48b** and **49b**: IR (neat) 2954, 1732, 1705, 1456, 1257, 1223, 1143, 1113, 1091, 976, 911, 767, 733, 701; $[\alpha]_D$ -16.2° (c 0.54, CH_2Cl_2).

The data for **48b** were determined from the mixture: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 5.55 (ddq, 1, J =0.8, 15.0, 6.3), 5.21 (ddq, 1, J = 10.7, 15.0, 1.7), 4.90 (ddd, 1, J = 4.5, 10.7, 10.7), 2.98 (ddd, 1, J = 3.7, 8.3, 10.7), 2.45 (t, 2, J = 6.8), 2.13–0.80 (m, 12), 1.65 (dd, 3, J = 1.3, 6.3), 1.35 (s, 3), 1.22 (s, 3), 1.14 (s, 3), 0.86 (d, 3, J = 6.4); ^{13}C NMR 209.1, 172.2, 151.0, 128.4, 128.00, 127.94, 125.6, 125.2, 76.8, 61.1, 50.2, 47.3, 41.6, 40.2, 38.7, 34.5, 31.3, 29.4, 27.7, 27.2, 24.2, 23.4, 21.8, 18.0, 16.7.

The data for **49b** were determined from the mixture: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 5.48 (ddq, 1, J = 0.8, 15.0, 6.4), 5.16 (ddq, 1, J = 10.7, 15.0, 1.7), 4.85 (ddd, 1, J = 4.5, 10.7, 10.7), 2.94 (ddd, 1, J = 3.7, 8.3, 10.7), 2.40 (t, 2, J = 6.7), 2.13–0.80 (m, 12), 1.62 (dd, 3, J = 1.2, 6.4), 1.30 (s, 3), 1.25 (s, 3), 1.02 (s, 3), 0.85 (d, 3, J = 6.4); ^{13}C NMR 209.2, 172.3, 150.8, 128.8, 128.03, 127.90, 125.7, 125.1, 76.5, 61.4, 50.0, 47.3, 41.5, 40.1, 38.5, 34.5, 31.2, 28.4, 27.4, 27.2, 25.3, 23.6, 21.8, 17.9, 16.1.

The data for **50b** and **51b**: IR (neat) 3056, 2960, 2871, 1732, 1715, 1456, 1240, 1144, 1089, 765, 733, 701; $[\alpha]_D$ +17.7° (c 1.10, CH_2Cl_2).

The data for **50b** were determined from the mixture: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 5.35 (t, 1, J = 7.1), 4.96 (ddd, 1, J = 4.5, 10.7, 10.7), 2.64 (ddd, 1, J = 6.0, 10.9, 15.5), 2.42 (m, 1), 2.30–0.80 (m, 12), 2.10 (dq, 2, J = 7.3, 7.5), 1.39 (s, 3), 1.32 (s, 3), 1.23 (s, 3), 0.98 (t, 3, J = 7.5), 0.89 (d, 3, J = 6.4); ^{13}C NMR 205.7, 171.9, 150.3, 136.1, 128.5, 128.1, 125.40, 125.35, 76.6, 63.5, 50.23, 41.3, 39.7, 39.5, 34.3, 31.3, 30.7, 29.0, 26.34, 26.30, 23.7, 21.69, 21.1, 18.9, 14.1.

The data for **51b** were determined from the mixture: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 5.35 (t, 1, J = 7.1), 4.82 (ddd, 1, J = 4.5, 10.7, 10.7), 2.64 (ddd, 1, J = 6.0, 10.9, 15.5), 2.47 (m, 1), 2.30–0.80 (m, 12), 2.10 (dq, 2, J = 7.3, 7.5), 1.39 (s, 3), 1.30 (s, 3), 1.23 (s, 3), 0.98 (t, 3, J = 7.5), 0.85 (d, 3, J = 6.4); ^{13}C NMR 207.0, 171.9, 150.3, 136.1, 128.5, 128.0, 125.7, 125.31, 76.9, 63.5, 50.18, 41.0, 40.3, 39.7, 34.4, 31.3, 30.7, 27.5, 25.8, 23.4, 23.2, 21.72, 21.1, 18.9, 14.1.

Methylation of a 12:1 mixture of 41b and 42b (40 mg, 0.1 mmol, 1.1 equiv of NaH/ THF, 1.1 equiv of DMPU, 1.1 equiv of MeI at 0 °C for 1 h) gave 26 mg (63%) of a 20:1 mixture of **46b** and **47b**: $[\alpha]_D$ -1.3° (c 0.58, CH_2Cl_2).

Oxidation of 44d (28 mg, 0.06 mmol) as described above gave 27 mg of a 7.5:2:3:1 crude mixture of **46d**, **52d**, **48d**, and **50d**. Compounds **47d**, **49d**, **51d**, and **53d** were not observed in the oxidation of either **44d** or **45d** and are therefore present in <10% of the amount of **46d**, **48d**, **50d**, and **52d**.

Oxidation of 45d (97 mg, 0.22 mmol) gave 95 mg of a 9.5:2.0:8.0:1.0 crude mixture of **46d**, **52d**, **48d**, and **50d**. Flash chromatography of the crude mixture on silica gel (20:1 hexane–EtOAc) gave **46d** (21 mg, 22%), followed by a 1:1.5:1 mixture (12 mg, 12%) of **46d**, **52d**, and **50d**, and then by **48d** (17 mg, 18%).

The data for **48d**: ^{1}H NMR 7.28 (m, 4), 7.15 (m, 1), 5.55 (dq, 1, J = 15.1, 6.5), 5.22 (ddq, 1, J = 9.6, 15.1, 1.4), 4.89 (ddd, 1, J = 4.4, 10.7, 10.7), 3.15 (m, 1), 2.55–0.77 (m, 18), 1.65 (dd, 1, J =

6.5, 1.4), 1.32 (s, 3), 1.24 (s, 3), 0.861 (d, 3, J = 6.2), 0.860 (t, 3, J = 6.7); ^{13}C NMR 208.3, 171.2, 150.5, 128.4, 128.1, 128.0, 125.7, 125.3, 77.0, 64.1, 50.3, 46.7, 41.5, 40.5, 40.3, 34.5, 31.8, 31.4, 30.5, 28.8, 27.6, 23.4, 23.0, 21.8, 18.0, 16.6, 14.4; IR (neat) 2959, 1731, 1715, 765, 701; $[\alpha]_D$ -27.3° (c 0.50, CH_2Cl_2).

Partial spectral data for **52d** were determined from the mixture: ^{1}H NMR 5.65 (dq, 1, J = 16.0, 1.8), 1.78 (dd, 3, J = 1.6, 6.4); ^{13}C NMR 67.9, 47.8, 28.9, 26.8, 18.1, 16.2, 13.4.

Partial spectral data for **50d** were determined from the crude mixture: ^{1}H NMR 5.40 (t, 1, J = 7.0); ^{13}C NMR 134.0, 129.2.

Propylation of a 12:1 mixture of 41b and 42b (80 mg, 0.2 mmol, 10 equiv of 1-iodopropane, 3 equiv of K_2CO_3, 2 equiv of DMPU/ THF, reflux for 8 days) gave 29.5 mg (34%) of **46d**: ^{1}H NMR 7.25 (m, 4), 7.15 (m, 1), 5.77 (ddd, 1, J = 8.8, 15.3, 1.5), 5.48 (dq, 1. J = 15.3, 6.3), 4.90 (ddd, 1, J = 4.4, 10.7, 10.7), 2.68 (ddd, 1, J = 14.9, 12.9, 6.4), 2.50–0.89 (m, 18), 1.70 (dd, 3, J = 1.5, 6.3), 1.27 (s, 3), 1.23 (s, 3), 0.89 (t, 3, J = 7.1), 0.85 (d, 3, J = 6.3); ^{13}C NMR 207.2, 170.4, 150.3, 131.0, 128.0, 126.7, 125.7, 125.4, 76.5, 64.2, 50.3, 48.3, 41.8, 40.5, 40.3, 34.3, 33.8, 31.4, 30.8, 29.0, 27.5, 24.5, 22.8, 21.8, 18.0, 17.5, 14.7; IR (neat) 2959, 1732, 1711, 762, 700; $[\alpha]_D$ 6.3° (c 0.298, CH_2Cl_2). Anal. Calcd for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65. Found: C, 79.25; H, 9.34.

Oxidation of 58b (1.096 g, 2.5 mmol) as described above gave 745 mg (72%) of an inseparable 12:1:1 mixture of **60b**, **61b**, and **62b**: IR (neat) 3090, 3070, 3010, 2970, 2930, 2870, 1745, 1720, 1650, 1605, 1370, 1180, 760, 700; $[\alpha]_D$ 13.0° (c 0.364, CH_2Cl_2). Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23. Found: C, 79.82; H, 9.08.

Oxidation of 59b (90 mg, 0.20 mmol) as described above gave 63 mg (70%) of an inseparable 20:3:10:1 mixture of **60b**, **61b**, **62b**, and **63b**. The data for the four isomers were determined by comparison of the spectra of the two mixtures: ^{1}H NMR 7.22–7.15 (m, 5), 5.01 (br s, 1, **60b**), 4.98 (br s, 1, **62b**), 4.93 (br s, 1, **60b**), 4.85 (ddd, 1, J = 4.1, 10.6, 10.6), 4.81 (br s, 1, **62b**), 3.27 (br d, 1, J = 16.1, **62b**), 3.04–2.97 (m, 1), 2.75 (qd, 1, J = 2.7, 16.8, **60b**), 2.55 (br d, 1, J = 16.8, **a**), 2.55–2.42 (m, 1), 2.30 (qd, 1, J = 2.6, 16.1, **62b**), 2.25–2.15 (m, 1), 2.00–1.40 (m, 10), 1.30 (s, 3, **60b**), 1.28 (s, 3, **62b**), 1.23 (s, 3, **60b**) 0.89 (t, 3, J = 7.4, **60b**), 0.85 (d, 3, J = 6.4, **60b**); ^{13}C NMR 206.3 (**62b**), 205.7 (**60b**), 171.4 (**62b**), 170.0 (**60b**), 150.4 (**60b**), 150.2 (**62b**), 150.1 (**62b**) 150.0 (**60b**), 128.0, 125.7, 125.4, 107.6 (**60b**), 107.5 (**61b**), 106.7 (**62b**), 106.6 (**63b**), 76.5 (**62b**), 76.4 (**60b**), 65.5, 55.6 (**60b**), 50.14 (**62b**), 50.07 (**60b**), 49.8 (**61b**), 45.7 (**60b**), 44.3 (**62b**), 41.5 (**62b**), 41.4 (**60b**), 40.8 (**62b**), 40.31 (**60b**), 40.27 (**62b**), 40.24 (**61b**), 40.18 (**63b**), 40.0 (**60b**), 38.3 (**62b**), 38.2 (**61b**), 37.4 (**60b**), 34.3, 31.3, 31.0 (**60b**), 30.5 (**62b**), 30.4 (**61b**), 27.4 (**60b**), 27.3 (**62b**), 27.2 (**61b**), 27.1, 24.4, 24.0 (**60b**), 23.7 (**62b**), 23.6 (**62b**) 23.1 (**60b**), 22.9 (**62b**), 21.7 (**60b**), 10.1 (**60b**), 9.8 (**62b**).

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Supplementary Material Available: Complete experimental details for all reactions and compounds not presented in the Experimental Section and an ORTEP drawing of **17** (20 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.