Tremorgenic Indole Alkaloids. 9. Asymmetric Construction of an Advanced F–G–H-Ring Lactone Precursor for the Synthesis of Penitrem D

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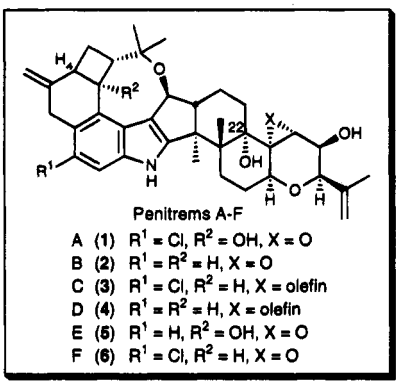
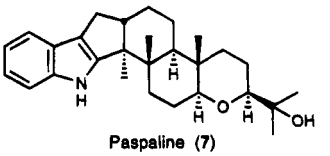
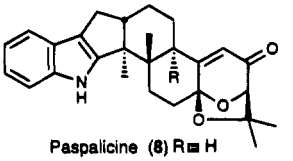
Lactone (+)-**12** is envisioned as the precursor to the F–G–H rings of penitrem D (**4**) in our ongoing synthetic venture. The efficient, stereocontrolled introduction of the vicinal quaternary methyl groups present the major challenge in the construction of this subunit. Our first route to (±)-**12** was marked by low overall yield (<2%) and the instability of several key intermediates; these deficiencies were rectified in a second-generation approach that produced optically active material (18 steps from **19a**, 2.1% overall). The successful strategies exploited enolate generation via either conjugate additions to α,β-enones or the Evans oxy-Cope rearrangement as key regiochemical control elements.

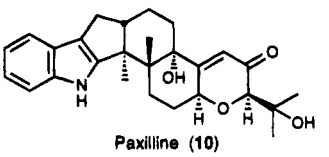
In 1968, Wilson and co-workers isolated the first in a series of fungal metabolites now known as penitrems A–F (**1**–**6**).[1] Common structural features and biological profiles[2] soon linked the penitrems with the indole diterpenes paspaline (**7**),[3] paspalicine (**8**),[3] paspalinine (**9**),[4] and paxilline (**10**).[5,6] Our long-standing interest in the latter family has led to the first total syntheses of paspaline,[7] paspalicine,[8] and paspalinine.[8]

Central to each of these natural products is an indole moiety fused to a *trans,anti-trans*-5,6,6-tricarbocyclic framework which incorporates vicinal quaternary methyl groups and terminates in a functionalized pyran ring. The unique nonacyclic structure of penitrem D (**4**),









elucidated by Steyn et al.[9,10] primarily via NMR tech-

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(1) The penitrems were initially termed the tremortins. See: Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77.

(2) In addition to their tremorgenic properties, recent studies have established that the penitrems strongly inhibit smooth-muscle maxi-K channels and can serve as potent insect antifeedants; see, respectively: Knaus, H.-G.; McManus, O. W.; Lee, S. H.; Schmalhofer, W. A.; Garcia-Calvo, M.; Helms, L. M. H.; Sanchez, M.; Giangiacomo, K.; Garcia, M. L.; Reuben, J. P.; Smith, A. B., III; Kaczorowski, G. J. *Biochemistry* **1994**, *33*, 5819. Dowd, P. F.; Cole, R. J.; Vesonder, R. F. *J. Antibiot.* **1988**, *41*, 1868.

(3) Fehr, T.; Acklin, W. *Helv. Chim. Acta* **1966**, *49*, 1907.

(4) (a) Gallagher, R. T.; Finer, J.; Clardy, J.; Leutweiler, A.; Weibel, F.; Acklin, W.; Arigoni, D. *Tetrahedron Lett.* **1980**, *21*, 235. (b) Cole, R. J.; Dorner, J. W.; Lamsden, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicolson, S. S.; Bedell, D. M. *J. Agric. Food Chem.* **1977**, *25*, 1197. (c) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069.

(5) Cole, R. J.; Kirksey, J. W.; Wells, J. M. *Can. J. Microbiol.* **1974**, *20*, 1159.

(6) Additional tremorgenic indole diterpenes include the related janthitrems and lolitrems; see: (a) Gallagher, R. T.; Latch, G. C. M.; Keogh, R. K. *Appl. Environ. Microbiol.* **1980**, *39*, 272. (b) Lauren, D. S.; Gallagher, R. T. *J. Chromatogr.* **1982**, *284*, 150. (c) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 697. (d) di Menra, M. E.; Mantle, P. G. *Res. Vet. Sci.* **1978**, *24*, 347. (e) Gallagher, R. T.; White, E. P.; Mortimer, P. H. *N. Z. Vet. J.* **1981**, *29*, 189.

(7) (a) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769. (b) Smith, A. B., III; Mewshaw, R.; Taylor, M. A. *J. Org. Chem.* **1989**, *54*, 3449. (c) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2787. (d) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2791. (e) Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761.

(8) (a) Smith, A. B. III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (b) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Sunazuka, T.; Nolan, E. G., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 1438.

(9) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289. De Jesus, A. E.; Hull, W. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1982**, 837. De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847. De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1857. De Jesus, A. E.; Gorst-Allman, C. P.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1863.

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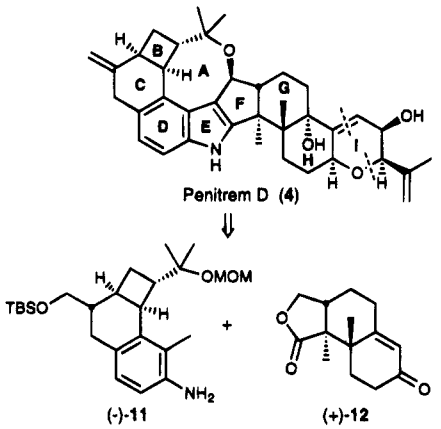
niques, embodies highly substituted indole and cyclobutane units, an eight-membered cyclic ether (oxocene), and 11 stereocenters. Herein we describe two approaches to the construction of an F–G–H-ring lactone (**12**) designed to serve as a key building block for penitrem D. Stereocontrolled introduction of the vicinal quaternary methyls presented a challenging obstacle, as exemplified in many syntheses of aphidicolin[11] and our first paspaline route.[12] The successful strategies (vide infra) exploited the generation of enolates either via conjugate additions to α,β-enones or via the Evans oxy-Cope rearrangement as key regiochemical control elements.

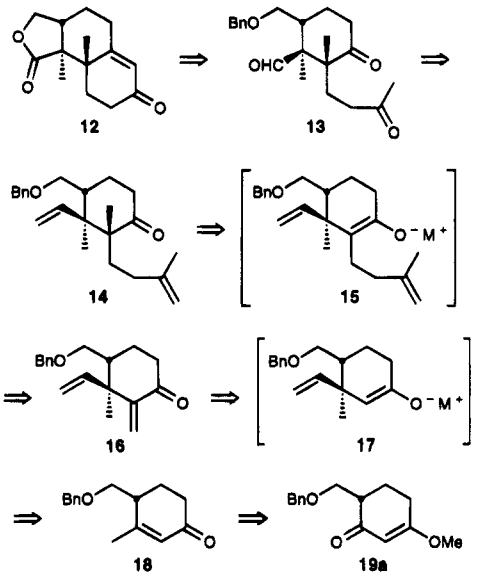
Synthetic Analysis. As outlined previously,[13] our synthetic analysis of penitrem D (**4**) requires union of aniline **11**, the western hemisphere precursor, with lactone **12**, the eastern hemisphere (Scheme 1). Toward this end, we have disclosed both a highly efficient synthesis of aniline (−)-**11** (13 steps, 12% yield)[13] and an effective construction of 2-substituted indoles which exploits coupling of *o*-toluidine derivatives with appropriate esters or lactones.[14]

Scheme 1



Analysis of subunit **12** began with hydrolysis of the lactone ring and retroaldol cleavage of the olefin, generating diketo aldehyde **13** (Scheme 2). Selective oxidation of the aldehyde to the ester should control the regiochemistry of closure to the requisite cyclohexenone ring. Transformation into bisolefin **14** would mask the appended carbonyls, permitting disconnection of the C(31) quaternary methyl group, and leading in turn to enolate **15**, available via 1,4-addition of a methallyl anion to exo methylene ketone **16**. The stereochemical outcome of the latter sequence would obviously be critical (vide infra).

Scheme 2



Enone **16** was expected to arise from enolate **17**, available via stereoselective 1,4-addition of a vinylmetallic species to enone **18**. Finally, **18** would derive from Stork–Danheiser alkylation[15] of dihydroresorcinol methyl ether followed by an alkylative 1,3-carbonyl transposition with methyllithium. We envisioned that resolution of **19a** would ultimately lead to both aniline **11** and lactone **12** in scalemic form,[16] but racemic material was employed for initial experiements. A key element of our strategic planning was the use of conjugate additions to establish the regiochemistry of enolates **15** and **17**.[17]

Construction of Exomethylene Ketone 16. As our point of departure, dihydroresorcinol methyl ether (**20**) was subjected to Stork–Danheiser alkylation[19] with BOMCl (Scheme 3). Treatment of the resultant vinylogous ester (±)-**19a** with MeLi followed by workup with aqueous acid then furnished enone (+)-**18**. Copper-catalyzed addition of vinylmagnesium bromide to **18** (5 mol% CuI, DMS[18] or TMEDA, THF[19]) occurred anti to the 4-[(benzyloxy)methyl] substituent, as anticipated;[20] enolate trapping with TMSCl and Et_3N then gave silyl enol ether (±)-**21** (86–97% yield) which was used without purification. Regeneration of the enolate (MeLi, THF, 0 °C) and alkylation with Eschenmoser's salt ($Me_2NCH_2^+ I^-$, THF, −78 °C)[21] afforded the β-dimethylamino ketone (±)-**22** as a mixture of epimers. The modest nucleophilicity of the enolate generated in the copper-catalyzed Grignard reaction precluded direct capture with the Eschenmoser reagent. Conversion of **22** to the exometh-

(11) (a) Trost, B. M.; Nagetoshi, Y.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1328. (b) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330. McMurry, J. E.; Andrus, A.; Ksanders, G. M.; Musser, J. H.; Johnson, M. A. *Tetrahedron, Suppl. 9* **1981**, *37*, 319. (c) Corey, E. J.; Tius, M.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (d) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446. Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001. (e) Bettolo, R. M.; Tagliatesta, P.; Lupi, A.; Bravetti, D. *Helv. Chim. Acta* **1983**, *66*, 1922. (f) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142.

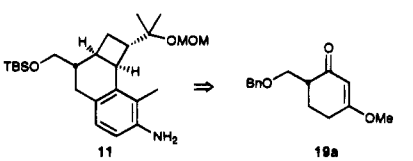
(12) (a) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769. (b) Smith, A. B., III; Mewshaw, R.; Taylor, M. A. *J. Org. Chem.* **1989**, *54*, 3449.

(13) (a) Haseltine, J. N.; Visnick M.; Smith, A. B., III. *J. Org. Chem.* **1988**, *53*, 6160. (b) Smith, A. B., III; Haseltine J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431.

(14) (a) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757. (b) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron, Symposia in Print* **1986**, *42*, 2957.

(15) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(16) Retrosynthesis of **11** from **19a**:



(17) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945. Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

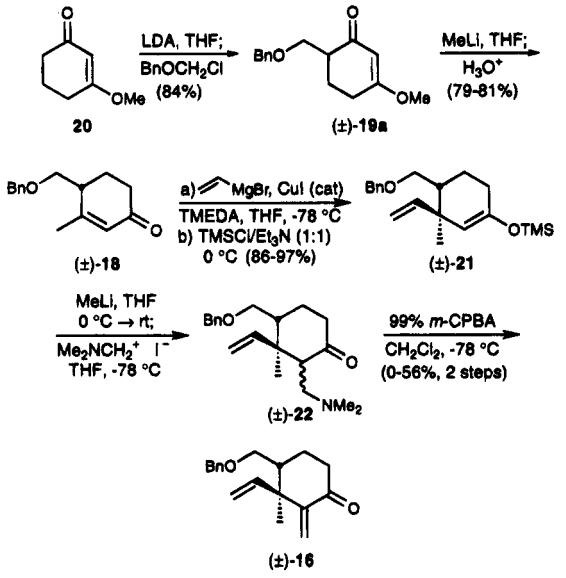
(18) Taber, D. F.; Korsmeyer, R. W. *J. Org. Chem.* **1978**, *43*, 4925.

(19) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27.

(20) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(21) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

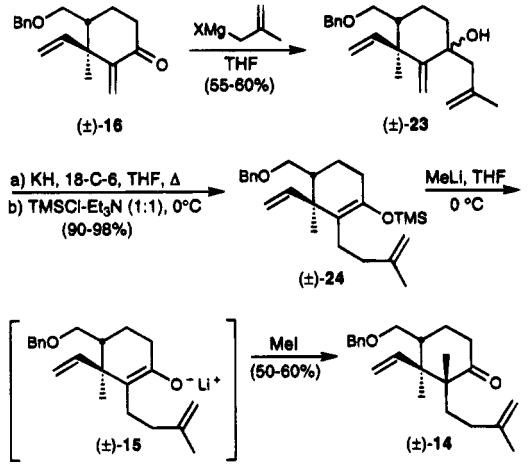
Scheme 3



ylene ketone (±)-**16** could be achieved in low yield by quaternization of the amine and treatment with DBU. Oxidation (99% *m*-CPBA, CH_2Cl_2, −78 °C) followed by Cope elimination did provide the desired enone in up to 56% yield, but the variable quality of both commercial and freshly prepared Eschenmoser's salt rendered this sequence extremely capricious. Moreover, neat **16** proved to be unstable, apparently undergoing Diels-Alder dimerization.[22] Purification could be achieved by direct adsorbtion of the cold (−78 °C) reaction mixture onto a silica column, elution with Et_2O/petroleum ether/Et_3N (25:4:1), and concentration at 0 °C.

Stereocontrolled Installation of the Vicinal Quaternary Methyl Groups. Attempted conjugate addition of an allyl cuprate to enone **16** afforded mainly the alcohols (±)-**23** (Scheme 4); as noted by Lipshutz,[23] allylic cuprates are in equilibrium with the parent lithium

Scheme 4

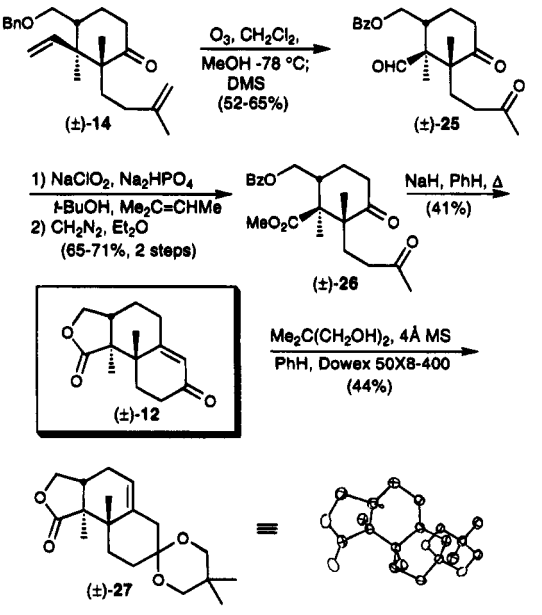


species which react in 1,2 fashion. We recognized, however, that **23** could also furnish the 1,4-adduct (±)-**24** via [3,3]-sigmatropic Evans oxy-Cope rearrangement (Scheme 4).[24] To this end, the Grignard reagent derived from methallyl chloride (Mg^0, THF, 65 °C or Riecke magnesium, THF, 0 °C) was added to **16** at −78 °C, followed by oxy-Cope rearrangement (washed KH, THF, catalytic 18-crown-6, 60 °C). It would have been desirable, once again, to employ the resultant enolate in the next step, but the observed propensity of the potassium enolate to alkylate on oxygen necessitated trapping in situ as a silyl ether. Generation of the lithium enolate (MeLi, THF, 0 °C) and treatment with methyl iodide then produced the requisite trans-diaxial vicinal quaternary methyl groups in ketone (±)-**14** (42−56% yield), accompanied by varying amounts of O-alkylated and α′-dialkylated side products. Only traces of the epimer of **14** were detected. Both steric and stereoelectronic effects were expected to favor the formation of **14** in the key alkylation step.[25] The relative stereochemistry of **14** was later verified by X-ray analysis of the more advanced intermediate **27**.

Elaboration of the F−G−H-Ring Lactone 12. The latent carbonyl moieties in ketone **21** could not be unmasked by ozonolysis (CH_2Cl_2/MeOH, 1:6, −78 °C; DMS) without competitive benzylic oxidation (Scheme 5); fortunately, prolonged exposure to ozone resulted in complete conversion to the benzoate ester (±)-**25** (52−56%). Sodium chlorite oxidation of the aldehyde moiety and diazomethane esterification then afforded (±)-**26** in 65−71% overall yield for the three steps. We had planned to induce closure of ring H by treating diketone **26** with NaH in hot benzene, thereby completing this alternative Robinson annulation sequence. In the event, this process unexpectedlly furnished the desired lactone (±)-**12**, as hydroxide generated in situ presumably effected benzoate hydrolysis leading to cyclization. The yield, only 40−42%, was deemed acceptable in view of the scope and operational simplicity of this transformation. Protection as the ketal with 2,2-dimethyl-1,3-propanediol provided (±)-**27** which proved suitable for single-crystal X-ray analysis.

The synthesis afforded racemic lactone **12** in 11 steps

Scheme 5

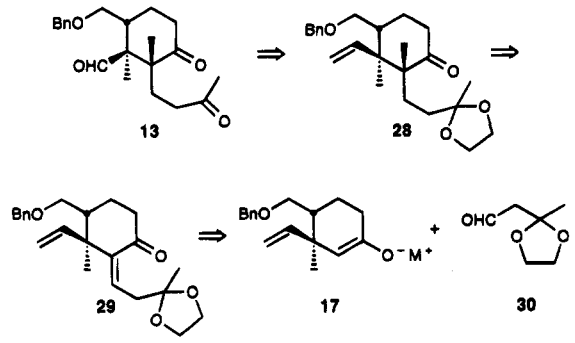


(22) Romann, E.; Frey, A. J.; Stacker, P. A.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1900.
(23) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *Am. Chem. Soc.* **1990**, *112*, 4404.
(24) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. Steigerwald, M. L.; Gaddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994.
(25) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, 1972; pp 586−595.

from **20**. Although the scheme embodied some very desirable features, not the least of which was the stereocontrolled introduction of the vicinal methyl groups, we recognized that the low overall yield (ca. 0.4–2%) would present an obstacle to the construction of penitrem D. Several steps also suffered from a lack of consistency upon scale-up, and the instability of exomethylene ketone **16** and aldehyde **25** was problematic. These considerations led us to devise an improved route to **12**.

Design of the Second-Generation Approach. In refining our synthetic plan, we sought to retain the successful strategy for incorporation of the methyl groups while circumventing the problems associated with enone **16**. Accordingly, we envisioned that the aldehyde and methyl ketone moieties of **13** could be differentially masked in **28** (Scheme 6). Retrosynthetic removal of the α-methyl group and introduction of an exocyclic double bond then generates enone **29**. In the synthetic direction, 1,4-reduction followed by alkylation with MeI was expected to install the second quarternary center with the requisite stereochemistry, as before. Moreover, we anticipated that the steric encumbrance of **29** would inhibit the Diels–Alder dimerization which complicated the isolation of **16**. Enone **29** in turn would derive from enolate **17**, an intermediate in the first approach, and aldehyde **30**. To ensure dehydration of the intermediate aldol, we planned to employ the lithium enolate; aldol magnesium alkoxides generally do not eliminate.[26] We also elected to address the requirement for optically active starting material at this juncture.

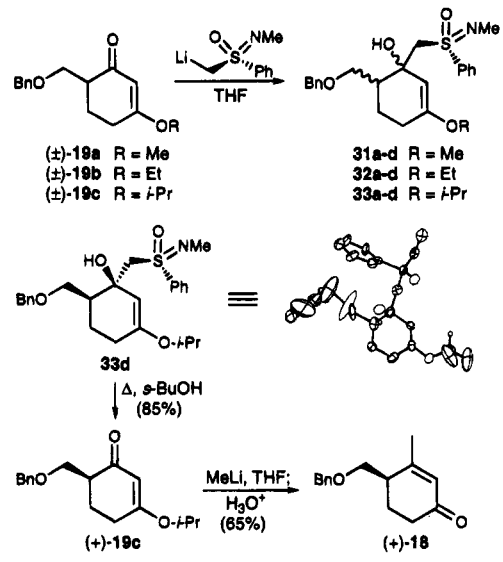
Scheme 6



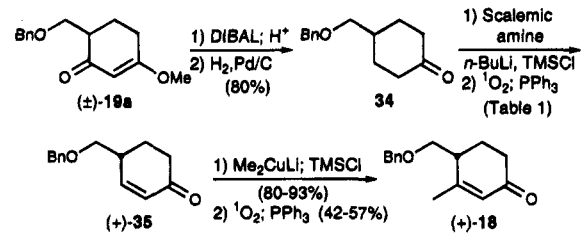
Synthesis of Enantiomerically Enriched Starting Material. Initially, we explored the resolution of **19a** via the Johnson sulfoximine procedure[27] (Scheme 7). Addition of the lithium salt of *(S)-N,S*-dimethyl-*S*-phenylsulfoximine to (±)-**19a** afforded, not unexpectedly, a mixture of all four possible diastereomers of **31**; on a large scale the products were quite difficult to separate. Attempts to improve the separation by changing the R group from methyl to ethyl [(±)-**19b**] or isopropyl [(±)-**19c**] were unsuccessful. Importantly, X-ray analysis of **33d** did reveal the *S* configuration of the dextrorotatory enone (+)-**18**.

We then turned to a two-step asymmetric induction tactic: enantioselective deprotonation of the achiral ketone **34** with a scalemic lithium amide base,[28,29] followed by oxidation of the derived enol silyl ether (Scheme 8). Ketone **34** is readily available in two steps from (±)-**19a** (DIBAL, acidic workup; H_2, Pd/C). As outlined in Table 1, we investigated several amide bases; the Whitesell reagent (−)-**39**[29a] proved to be superior in terms of yield and asymmetric induction. The enantiomeric purity of (+)-**35** (ca. 80–84% ee) was determined via polarimetry.[30] The intermediate silyl enol ethers could be oxidized to enone (+)-**35** either via the Saegusa protocol [$Pd(OAc)_2$, MeCN][31] or with singlet oxygen and PPh_3.[32] The requisite β-methyl derivative (+)-**18** was then generated by cuprate addition and a second silyl enol ether oxidation (Scheme 8).

Scheme 7



Scheme 8



Aldol Approach to Lactone 12. In initial experiments, the lithium enolate derived from racemic silyl enol ether **21** was added to known ketal aldehyde **30**[33] (THF, −78 → 0 °C) (Scheme 9). The resultant enone underwent Tsuda–Saegusa conjugate reduction (DIBAL, catalytic

(26) House, H. O.; Crumrie, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(27) (a) Johnson, C. R.; Stark, C. J. *J. Org. Chem.* **1982**, *47*, 1193. (b) Johnson, C. R. *Aldrichim. Acta* **1985**, *18*, 1, and references cited therein.

(28) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543.

(29) (a) Whitesell, J. K.; Felmen, S. W. *J. Org. Chem.* **1980**, *45*, 755. Also see: (b) Hogeveen, H.; Zwart, L. *Tetrahedron Lett.* **1982**, *23*, 105. (c) Cousins, R. P. C.; Simpkins, N. S. *Tetrahedron Lett.* **1989**, *30*, 7241. (d) Cain C. M.; Cousins, R. P. C.; Coumbarides, G. *Tetrahedron* **1990**, *46*, 523.

(30) The optical rotation of the (+)-**18** from this procedure was compared with that of (+)-**18** obtained from the Johnson protocol shown in Scheme 7. The enantiomeric purity of the intermediate sulfoximine adduct was shown to be ≥99% by an NMR experiment using two optically acitve Eu(II) shift reagents. The optical rotation of (+)-**35** was also compared with the value (−)-**35** {$[\alpha]^{25}_D$ −129.3° (*c* 1.8, MeOH)}, prepared in nine steps from the Diels–Alder adduct of butadiene and acrylate pantolactone ester (Personal communication: Stork, G., Columbia University).

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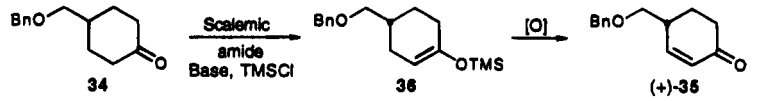
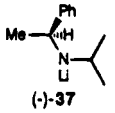
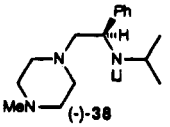
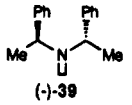
(33) (a) Uno, H.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1984**, *40*, 4741. (b) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N.; King, P. F.; Lyding, J. M.; Tsang, W. G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569. (c) Sharma, A. D.; Sethi, A. S.; Bedi, A. L.; Aggarwal, R. C. *Indian J. Chem.* **1980**, *19B*, 811.

Table 1. Preparation of Enone (+)-35 via Asymmetric Deprotonation of Ketone 34

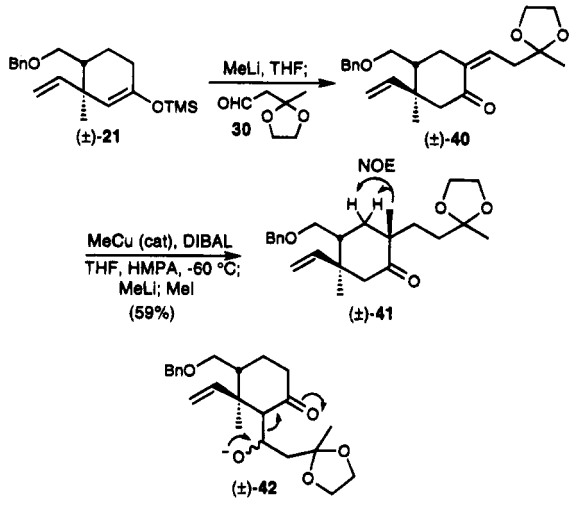


Amine Base	Additive	Temperature (°C)	Yield of 36 (%)	Oxidant[a]	ee of 35 (%)
 (-)-37	None	-78 -120	83 20	A A	62 70
 (-)-38	HMPA	-78 -105 -120	44 44 NR	A A	58 70 –
 (-)-39	None None	-78 -78	96 96	A B	84 84

[a] A: $Pd(OAc)_2$, MeCN (54% yield); B: $^1O_2$, PPh_3 (56-61% yield).

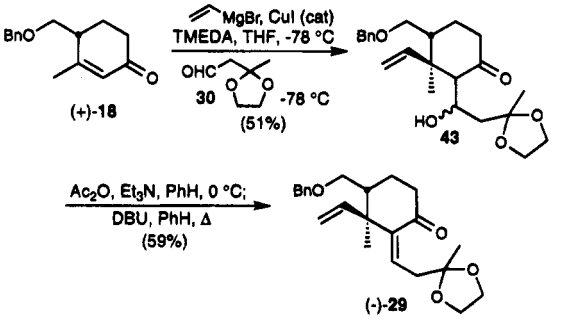
CuMe, THF–HMPA, −78 °C),[34] generating an aluminum enolate which could be methylated via an ate complex (MeLi, then MeI; ca. 75% yield from **21**). To our surprise, difference NOE analysis revealed that the product ketone was (±)-**41**, derived from enone (±)-**40**, rather than the requisite **28**. The formation of **40** clearly involves enolate equilibration, with **30** as the most likely proton source; this result may reflect the relative stabilities of the enolates as well as steric congestion in alkoxide **42** which may favor retroaldol fragmentation.

Scheme 9



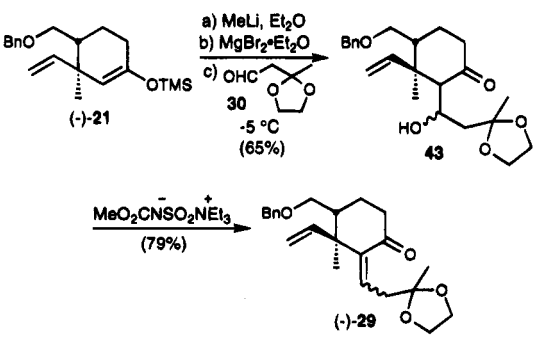
In an attempt to circumvent this isomerization, we explored aldol trapping of the magnesium enolate, generated via conjugate addition of the vinyl group to (+)-**18**.[26] Indeed, copper-catalyzed Grignard reaction followed by enolate capture with aldehyde **30** at −78 °C did afford the desired aldol **43** as a mixture of diastereomers (Scheme 10). Elimination to enone (−)-**29** was then effected by acylation (acetic anhydride, Et_3N, benzene, 0 °C) and exposure to catalytic DBU (benzene, reflux). The overall yield for the 1,4-addition, aldol, acylation, and elimination processes was 30%. This sequence generated a single geometric isomer of **29**; the *Z* configuration was assigned via NOE difference experiments. The use of acetic or triflic anhydride in the acylation step led to considerable decomposition.

Scheme 10



In preparative experiments it proved more convenient to regenerate the enolate from silyl enol ether (−)-**21** (MeLi, Et_2O, 0 °C); addition of $MgBr_2 \cdot Et_2O$ and **30** then afforded aldol **43** (Scheme 11). Elimination with the Burgess reagent, found to be superior on large scale, gave (−)-**29** as 3:1 *Z/E* mixture.

Scheme 11

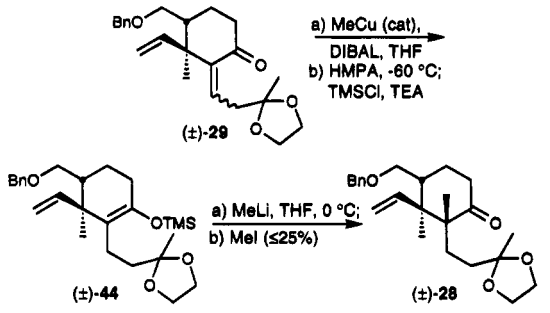


The Tsuda–Saegusa reduction/alkylation protocol, employed successfully with enone (±)-**40** (Scheme 9), effected clean 1,4-reduction of (±)-**29**; unfortunately, the alkyla-

(34) (a) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537. (b) Tsuda, T.; Kawamoto, T.; Kumamoto, Y.; Saegusa, T. *Synth. Commun.* **1986**, *16*, 639. (c) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439.
(35) Petrier, C.; Luche, J.-L. *Tetrahedron Lett.* **1987**, *28*, 2351.

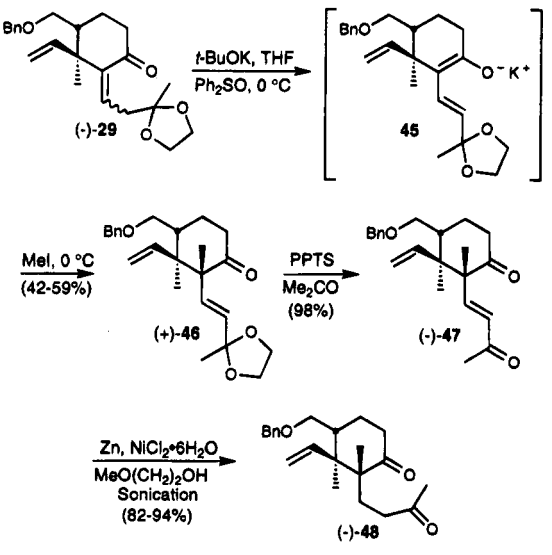
tion step failed. We next investigated conjugate reduction (catalytic MeCu, DIBAL; THF/HMPA, −60 °C) followed by enolate trapping (TMSCl, Et_3N, 1:1) (Scheme 12). The lithium enolate, regenerated without purification of (±)-**44** (MeLi, THF, 0 °C), was then alkylated with MeI as in the first-generation lactone synthesis, but the yield of (±)-**28** was low (≤25%).

Scheme 12



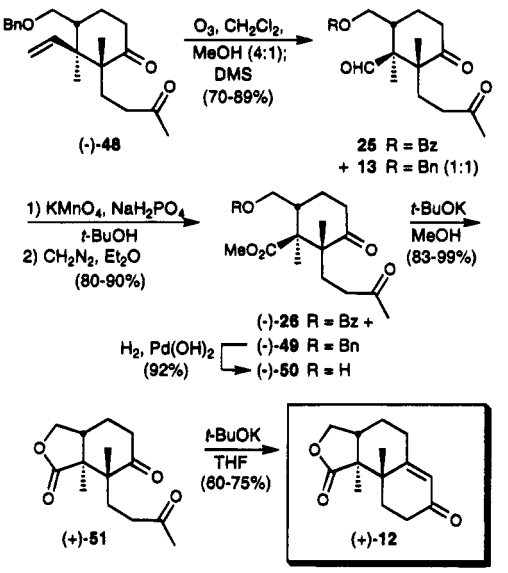
In search of more efficient reduction/alkylation methodology, we generated the extended enolate **45** by treatment of enone (−)-**29** with KO-*t*-Bu in THF/Ph_2SO at 0 °C (Scheme 13). Alkylation (MeI, 0 °C) provided trans olefin (+)-**46** (J = 16.2 Hz) in 42−59% yield, together with 15% recovered starting material. The use of Ph_2SO as cosolvent favors C-alkylation; however, attempts to further suppress O-alkylation (ca. 30%) by employing lithium bases or trapping with TMSCl were unsuccessful. Deketalization of **46** (PPTS, aqueous acetone) and chemoselective reduction of (−)-**47** (Zn, $NiCl_2 \cdot 6H_2O$, 2-methoxyethanol, sonication)[35] afforded the desired dione (−)-**48** in high yield.

Scheme 13



Completion of the Second-Generation Synthesis. The exhaustive ozonolysis employed in our earlier approach caused extensive decomposition with olefin **48**. Accordingly, the reaction was terminated when TLC analysis showed complete disappearance of starting material, providing a 1:1 mixture (NMR) of benzoate **25** and benzyl ether **13** in 70−89% yield (Scheme 14). On a large scale the inclusion of pyridine[36] provided a cleaner

Scheme 14



reaction but did not completely suppress benzylic oxidation. Olefin cleavage and esterification ($KMnO_4$, NaH_2PO_4, *t*-BuOH; CH_2N_2, Et_2O; 80−90%) gave the corresponding carbomethoxy benzoate (−)-**26** and benzyl ether (−)-**49**; hydrogenation (H_2, catalytic Pd/C) of the mixture transformed (−)-**49** to primary alcohol (−)-**50** in 92% yield. As the earlier cyclization/lactonization protocol performed poorly with these substrates, the mixture of diones (−)-**26** and (−)-**50** was treated instead with KO-*t*-Bu (MeOH, reflux), affording the lactone (+)-**51** in 80% yield. Final cyclization with KO-*t*-Bu in THF at reflux gave enone (+)-**12**, spectroscopically indistinguishable from the racemate prepared by the first-generation route.

Summary. The second-generation strategy proved amenable to the large-scale preparation of optically active lactone (+)-**12** in 18 steps from **19a** and 2.1% average overall yield, offering enhanced efficiency vis-à-vis the initial approach and avoiding unstable intermediates. The coupling of (+)-**12** with aniline (−)-**11** for the synthesis of penitrem D (**4**) is currently under investigation; these studies will be reported in due course.

(36) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

(37) Materials and Methods. All reactions were carried out under argon with dry, freshly distilled solvents, vacuum-flamed glassware, and magnetic stirring, unless otherwise stated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone, benzene and toluene were distilled from sodium, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Triethylamine, diisopropylethylamine, and pyridine were distilled from calcium hydride and stored over KOH. Dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves. *n*-Butyllithium and (cyclohexylmethyl)lithium were standardized by titration with diphenylacetic acid. All reactions were monitored by thin layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents and E. Merck silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Proton NMR spectra were recorded on either a Bruker AM-500 or WH-250 spectrometer; carbon-13 NMR spectra were recorded on a Bruker WH-250 or WH-500 instrument. Chemical shifts are reported in δ values relative to tetramethylsilane. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter in the solvent indicated. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Labs, Madison, NJ.

Experimental Section[37]

4-[(Benzyloxy)methyl]-3-methyl-2-cyclohexen-1-one [(±)-18]. Methyllithium (1.10 M in Et_2O, 205 mL, 226 mmol) was diluted with tetrahydrofuran (205 mL), the solution was cooled to −42 °C, and vinylogous ester (±)-**19a**[17b] (29.50 g, 119.0 mmol) dissolved in tetrahydrofuran (100 mL) was added. The reaction mixture was then allowed to warm to 0 °C over 45 min, quenched with 1 N HCl (226 mmol), and after 1 h extracted with ether (3 × 500 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (15% ethyl acetate/hexanes) afforded **18** (21.57 g, 79% yield) as a colorless liquid: IR ($CHCl_3$) 3000 (m), 2940 (br, m), 2860 (m), 1670 (s), 1630 (w), 1500 (w), 1450 (m), 1440 (w), 1380 (m), 1360 (m), 1330 (w), 1250 (s), 1100 (br, s), 1030 (w), 860 (m), 700 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5 H), 5.86 (s, 1 H), 4.50 (ABq, J = 12.0, 27.4 Hz, 2 H), 3.56 (d, J = 5.7 Hz, 2 H), 2.52 (apparent q, J = 5.4 Hz, 1 H), 2.45−2.39 (m, 1 H), 2.29−2.23 (m, 1 H), 2.12−2.01 (m, 2 H), 1.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 162.4, 138.0, 128.5, 128.2, 127.8, 127.6, 73.2, 70.4, 40.3, 34.6, 25.7, 23.0; high-resolution mass spectrum (CI, NH_3) m/z 231.1385 [(M + H)$^+$, calcd for $C_{15}H_{19}O_2$ 231.1396].

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.98; H, 7.77.

Vinyl Enol Silane (±)-21. Method 1. At −78 °C a suspension of copper(I) iodide (829 mg, 4.35 mmol) in dry dimethyl sulfide (30 mL) was treated with vinylmagnesium bromide (1 M in THF, 43.13 mL, 43.130 mmol). The black reaction mixture was stirred for 10 min at −78 °C prior to addition of a solution of enone of (±)-**18** (4.93 g, 21.4 mmol) in ether (30 mL). After 15 min a mixture of TMSCl and triethylamine (1:1 v/v, 11 mL, 43 mmol of TMSCl) was introduced and the temperature adjusted to 0 °C. The mixture was stirred for 30 min further and then poured into cold NH_4OH buffered with NH_4Cl to pH 8 and extracted with ether (2 × 100 mL). The ether solutions were washed with the cold buffered solution, dried over $MgSO_4$, filtered, and concentrated. Filtration through a pad of activity II alumina then furnished **21** (5.26 g, 74% yield) as a colorless liquid.

Method 2. At room temperature a slurry of CuI (290.4 mg, 5 mol %) in THF (40 mL) was treated with TMEDA (13.7 mL, 3 equiv) and stirred until homogeneous. The solution was cooled to −78 °C, vinylmagnesium bromide (1.0 M in THF, 60 mL, 2 equiv) was added dropwise, and the mixture was then stirred for an additional 10 min. A solution of enone (±)-**18** (6.87 g, 29.8 mmol) in THF (40 mL) was added dropwise via a cannula, and the solution was again allowed to stir for 10 min further. A mixture of freshly distilled TMSCl and Et_3N (1:1 v/v, 23 mL) was centrifuged under Ar, the superatant was transferred into the reaction mixture, and after 5 min the −78 °C bath was replaced with an ice−water bath. The mixture was stirred until TLC analysis showed complete reaction (usually after 1−3 h), and then partitioned between EtOAc (200 mL) and aquous NH_4OH buffered to pH 8 (200 mL). The organic layer was washed with pH 8 NH_4OH (200 mL), and the combined aqueous phases were extracted with EtOAc (3 × 200 mL). The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography [60−80 mesh silica gel treated with 5% (wt/wt) H_2O, 10% EtOAc/hexanes] afforded **21** (8.52 g, 86% yield) as a pale yellow oil: IR ($CHCl_3$) 2900 (br, s), 1450 (m), 1410 (w), 1365 (s), 1250 (s), 1185 (s), 1100 (br, s), 1030 (w), 1000 (w), 940 (w), 910 (s), 890 (s), 840 (s), 690 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5 H), 5.82 (dd, J = 10.1, 17.7 Hz, 1 H), 5.00 (d, J = 1.0 Hz, 1 H), 4.97 (dd, J = 1.3, 4.9 Hz, 1 H), 4.55 (d, J = 0.9 Hz, 1 H), 4.48 (ABq, J_{AB} = 12.0, 36.7 Hz, 2 H), 3.57 (dd, J = 4.0, 9.1 Hz, 1 H), 3.24 (apparent t, J = 9.2 Hz, 1 H), 2.12−2.06 (m, 1 H), 2.05−1.95 (m, 2 H), 1.76−1.71 (m, 1 H), 1.63−1.56 (m, 1 H), 0.96 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 148.2, 138.6, 128.3, 127.5, 127.4, 112.9, 111.7, 73.1, 70.8, 42.1, 40.2, 29.0, 22.2, 21.2, 0.2; high-resolution mass spectrum (CI, NH_3) m/z 331.2117 [M + H$^+$, calcd for $C_{20}H_{30}SiO_2$ 331.2092].

***(N,N*-Dimethylamino)methyl Ketones (±)-22. Method 1.** A solution of silyl enol ether (±)-**21** (3.11 g, 9.44 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C, and MeLi (1.28 M in Et_2O, 8.09 mL, 10.4 mmol) was added. The mixture was stirred for 30 min at room temperature, recooled to 0 °C, and transferred via a cannula into a suspension of *N,N*-dimethylmethyleneammonium iodide (Eschenmoser's salt, 93.5 g, 18.8 mmol) in tetrahydrofuran (20 mL) stirred at −78 °C. After 3 h at ambient temperature, the reaction was quenched with brine (10 mL), and water was added to dissolve the salts. The aqueous phase was basified to pH 10 with sodium carbonate and extracted with ether (4 × 50 mL), and the extracts were combined with the original organic layer and concentrated. The residue was taken up in cold (0 °C) pentane and extracted with cold 5 N HCl (2 × 100 mL). The combined acidic solutions were washed with cold pentane, carefully basified to pH 10−11 with 10 N NaOH, concentrated to ca. one-half volume, and extracted with dichloromethane (7 × 100 mL). The combined extracts were then dried over Na_2SO_4, filtered, and concentrated, affording **22** (1.89 g, 64%) as an oil: IR ($CHCl_3$) 2980, 2870, 1710 (s), 1455, 1368, 1230, 1078, 1000, 918, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 5.79 (dd, J = 10, 17 Hz, 1 H), 5.20 (d, J = 10 Hz, 1 H), 4.96 (d, J = 17 Hz, 1 H), 4.44 (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 21 Hz, 2 H), 3.54 (dd, J = 3, 8 Hz, 1 H), 3.12 (t, J = 9 Hz, 1 H), 2.91 (dd, J = 8, 11 Hz, 1 H), 2.55 (m, 4 H), 2.12 (s, 6 H), 2.30−1.60 (m, 3 H), 0.62 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 316.2226 [(M + H)$^+$, calcd for $C_{20}H_{30}NO_2$ 316.2277].

Method 2. A solution of silyl enol ether (±)-**21** (3.38 g, 10.2 mmol) in tetrahydrofuran (35 mL) was cooled, and MeLi (0.95 M in Et_2O, 12 mL, 11.4 mmol) was added. The mixture was stirred for 30 min at room temperature, recooled to 0 °C, and transferred via a cannula into a suspension of (Eschenmoser's salt, 3.79 g, 20.5 mmol, purified by Soxhlet extraction with THF overnight) in tetrahydrofuran (30 mL) at −78 °C. After 3 h at ambient temperature, the reaction was quenched with brine (10 mL) and water was added to dissolve the salts. The aqueous phase was basified to pH 10 with sodium carbonate and extracted with ether (4 × 50 mL). The extracts were combined with the original organic layer and concentrated, providing crude **22** (4.8 g) as an oil. This material was used without purification in the next step.

Methylene Cyclohexanone (±)-16. At 0 °C, a solution of **22** (293 mg, 0.930 mmol) in dichloromethane (2 mL) was treated with 99% *m*-chloroperbenzoic acid (317 mg, 1.86 mmol); 99% *m*-CPBA was prepared by extraction of an ethereal solution of commerical reagent with three portions of pH 7.4 phosphate buffer, followed by concentration *in vacuo* and storage in the refrigerator. The reaction mixture was stirred for 20 min at room temperature and then filtered through 6 g of silica gel (75% EtOAc, 20% hexanes, 5% NEt_3). Concentration at 0−5 °C and flash chromatography (15% EtOAc/hexanes) provided **16** (32−97% yields) as an unstable oil which was dissolved in benzene and stored in the freezer: IR ($CHCl_3$) 3015, 2995, 2980, 1690, 1610, 1455, 1368, 1248, 1090, 910 (s), 698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45−7.22 (m, 5 H), 5.90 (d, J = 2 Hz, 1 H), 5.83 (dd, J = 10, 17 Hz, 1 H), 5.22 (d, J = 2 Hz, 1 H), 5.16 (dd, J = 1, 10 Hz, 1 H), 4.97 (dd, J = 1, 17 Hz, 1 H), 4.50 (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 20 Hz, 2 H), 3.63 (dd, J = 3, 7 Hz, 1 H), 3.34 (t, J = 7 Hz, 1 H), 2.60−1.84 (m, 5 H), 1.13 (s, 3 H).

Methallylvinylcarbinols (±)-23. Method 1. A solution of methallyl chloride (1.22 mL, 12.5 mmol) in tetrahydrofuran (5 mL) was added over ca. 30 min to a suspension of flame-dried magnesium metal turnings (455 mg, 18.81 mmol) in tetrahydrofuran (5 mL) at 60 °C. The Grignard solution darkened while heating at reflux for an additional 20 min. The mixture was then cooled to −42 °C, a solution of enone (±)-**16** (1.13 g, 4.18 mmol) in tetrahydrofuran (5 mL) was added dropwise, and after 5 min the cooling bath was removed and the reaction stirred at room temperature for 1.5 h. The mixture was decanted into ice-cold 0.1 N HCl (50 mL) and extracted with ether (3 × 50), and the combined extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) afforded **23** (1.00 g, 74% yield) as a colorless oil: IR ($CHCl_3$) 3580, 3540, 3010, 2930, 2870, 1635 (w), 1455, 1365, 1225, 1095,

1070, 1060, 920 (s), 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 5.77 (dd, J = 9, 17 Hz, 1 H), 5.33 (d, J = 2 Hz, 1 H), 5.27–4.69 (m, 5 H), 4.44 (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 23 Hz, 2 H), 3.46 (dd, J = 3, 9 Hz, 1 H), 3.16 (t, J = 9 Hz, 1 H), 2.45 (ABq, J_{AB} = 13 Hz, $\Delta\nu_{AB}$ = 19 Hz, 2 H), 2.17–1.40 (m, 5 H), 1.81 (s, 3 H), 1.08 (s, 3 H).

Method 2. A suspension of Mg(0) (1.4 g, 57 mmol) in THF (150 mL) was treated dropwise with 1,2-dibromoethane (5.5 mL, 63 mmol), and the mixture was heated at reflux for 1.5 h. The solvent was distilled away and the resultant solid dried at 150 °C in vacuo for 1 h. KI (9.28 g, 56 mmol) and THF (150 mL) were added followed by solid K(0) (4.28 g, 109 mmol), and the mixture was heated at reflux for 5 h and cooled to room temperature. Following the introduction of methallyl chloride (2.6 mL, 26 mmol) dissolved in THF (10 mL), the mixture was stirred for 2.5 h further and cooled to −78 °C. A solution of enone (±)-**16** (4.4 g, 16 mmol) in THF (40 mL) was added via a cannula over 30 min and the mixture stirred for 1.5 h at -78 °C. The reaction mixture was quenched with MeOH (50 mL), filtered through a plug of silica, and concentrated. Flash chromatography (10% EtOAc/hexanes) afforded **23** (2.94 g, 55% yield) as a colorless oil.

Rearranged Enol Silane (±)-24. A suspension of oil-free potassium hydride (440 mg, 3.70 mmol) in tetrahydrofuran (24 mL) was treated with 18-crown-6 (814 mg, 3.08 mmol) and a solution of dienol (±)-**23** (1.0 g, 3.08 mmol) in tetrahydrofuran (16 mL). The reaction mixture was heated at 55–60 °C for 2 h and then cooled to 0 °C, and a mixture of trimethylsilyl chloride and triethylamine (1:1 v/v, 1.6 mL, 6.2 mmol of TMSCI) was added. After 10 min the reaction mixture was poured into cold saturated aqueous sodium bicarbonate and extracted with ether (2×). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated, furnishing crude **24** (1.16 g, 95% yield) as a yellow oil: IR ($CHCl_3$) 3080, 3005, 2960, 2920, 2865, 1665, 1455, 1365, 1255, 1187, 1075, 910, 842 (s), 693 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H), 5.62 (dd, J = 11, 17 Hz, 1 H), 5.10 (d, J = 11 Hz, 1 H), 4.96 (d, J = 17 Hz, 1 H), 4.64 (br s, 2 H), 4.47 (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 22 Hz, 2 H), 3.50 (m, 1 H), 3.16 (t, J = 9 Hz, 1 H), 2.30–1.50 (m, 9 H), 1.70 (s, 3 H), 0.95 (s, 3 H), 0.20 (s, 9 H).

α-Methylcyclohexanone (±)-14. At ambient temperature a solution of silyl enol ether (±)-**24** (770 mg, 1.86 mmol) in tetrahydrofuran (8 mL) was treated with MeLi (2.23 M in Et_2O, 1.00 mL, 2.23 mmol). After 30 min the mixture was cooled to 0 °C and methyl iodide (1.0 mL, 16.0 mmol) was added by passing through a plug of activity II alumina. The mixture was then stirred for 2.5 h further, poured into water, and extracted with ether (3×). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (7% EtOAc/hexanes) furnished **14** (377 mg, 47% yield) as a colorless oil: IR ($CHCl_3$) 3010, 2930, 1710 (s), 1365, 1228, 1090, 1073, 925, 695, 510 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.46–7.24 (m, 5 H), 5.86 (dd, J = 10, 16 Hz, 1 H), 5.22 (dd, J = 2, 10 Hz, 1 H), 4.99 (dd, J = 2, 16 Hz, 1 H), 4.68 (br s, 2 H), 4.44 (ABq, J_{AB} = 11 Hz, $\Delta\nu_{AB}$ = 19 Hz, 2 H), 3.51 (dd, J = 3, 10 Hz, 1 H), 3.12 (t, J = 10 Hz, 1 H), 2.74 (dt, J = 6, 12 Hz, 1 H), 2.54–2.15 (m, 3 H), 2.08–1.52 (m, 4 H), 1.75 (s, 3 H), 1.23 (s, 3 H), 1.12 (dt, J = 3, 12 Hz, 1 H), 0.79 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 341.2441 [$(M + H)^+$, calcd for $C_{23}H_{33}O_2$ 341.2481].

Diketo Aldehyde (±)-25. A solution of dienone (±)-**14** (351 mg, 1.03 mmol) in methanol (6 mL) and dichloromethane (1 mL) was cooled to −78 °C and treated with ozone for 40 min whereupon a blue color persisted, at which time argon was bubbled through the reaction to remove the excess ozone. Dimethyl sulfide (30 mL, 410 mmol) was then added and the mixture stirred at room temperature overnight. Concentration and flash chromatography (40 → 60% EtOAc/hexanes) afforded **25** (218 mg, 59% yield) as a white crystalline solid: IR ($CHCl_3$) 3015, 1720 (s), 1272, 1005, 908 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 8.06–7.96 (m, 2 H), 7.62–7.32 (m, 3 H), 4.23 (dd, J = 6, 10 Hz, 1 H), 4.08 (dd, J = 6, 10 Hz, 1 H), 3.29 (m, 1 H), 2.81 (dt, J = 6, 12 Hz, 1 H), 2.60 (m, 1 H), 2.40–2.06 (m, 4 H), 2.14 (s, 3 H), 1.73 (m, 1 H), 1.38 (s, 3 H), 1.36–1.18 (m, 1 H), 1.06 (s, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 359.1841 [$(M + H)^+$, calcd for $C_{21}H_{27}O_5$ 359.1858].

Methyl Ester (±)-26. Aldehyde (±)-**25** (218 mg, 0.609 mmol) was dissolved in 2-methyl-2-propanol (11.9 mL) and 2-methyl-2-butene (2.8 mL) at room temperature, and a solution of sodium chlorite (475 mg, 5.23 mmol) and sodium dihydrogen phosphate (475 mg, 3.95 mmol) in water (4.7 mL) was then added. The mixture was stirred for 3 h further and then concentrated. The residue was taken up in water (13 mL), and the solution was washed with hexanes (ca. 3 mL), acidified to pH 3 with 0.1 N HCl, and extracted with ether/dichloromethane mixture (3:1, 6 × 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to ca. half of the original volume. The acid was then esterified with excess ethereal diazomethane. Concentration and flash chromatography (30% EtOAc/hexanes) gave **26** (168 mg, 71% yield) as a colorless solid: mp 134–135 °C; IR ($CHCl_3$) 3000 (br, m), 2980 (m), 1720 (br, s), 1450 (m), 1440 (m), 1380 (m), 1360 (m), 1320 (m), 1280 (s), 1240 (br, s), 1150 (br, m), 1120 (s), 1040 (w), 1000 (w), 960 (w), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J = 1.4, 7.1 Hz, 2 H), 7.54 (dd, J = 7.5, 13.7 Hz, 1 H) 7.42 (dd, J = 7.9, 13.8 Hz, 2 H), 4.13 (m, 2 H), 3.63 (s, 3 H), 3.27–3.21 (m, 1 H), 2.74 (dt, J = 7.2, 13.9 Hz, 1 H), 2.57 (ddd, J = 4.0, 12.4, 16.5 Hz, 1 H), 2.26–2.15 (m, 4 H), 2.11 (s, 3 H), 1.64 (dq, J = 5.1, 13.4 Hz, 1 H), 1.31 (ddd, J = 3.5, 12.0, 14.7 Hz, 1 H), 1.25 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 208.4, 172.9, 166.3, 133.1, 129.8, 129.6, 128.4, 66.3, 54.5, 52.5, 52.0, 39.4, 37.5, 36.2, 29.8, 25.6, 25.5, 19.5, 12.7.

Tricyclic Enone Lactone (±)-12. A solution of diketone (±)-**26** (168 mg, 0.433 mmol) in benzene (15 mL) was treated with 97% sodium hydride (52 mg, 2.17 mmol) and heated at reflux for 12 h. The mixture was cooled, diluted with ether (15 mL), and washed with saturated aqueous ammonium chloride (30 mL). The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (35% EtOAc/hexanes) provided **12** (42 mg, 41% yield) as a white solid: mp 166–167 °C; IR ($CHCl_3$) 3000 (s), 2980 (s), 2920 (m), 2900 (w), 1780 (s), 1670 (s), 1620 (m), 1490 (w), 1450 (m), 1430 (m), 1380 (m), 1350 (m), 1260 (s), 1240 (s), 1220 (m), 1100 (s), 1050 (br, s), 1005 (s), 990 (s), 920 (b, w), 870 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, J = 2.0 Hz, 1 H), 4.28 (dd, J = 7.4, 8.7 Hz, 1 H), 3.97 (dd, J = 8.8, 11.3 Hz, 1 H), 2.92–2.89 (m, 1 H), 2.51–2.34 (complex m, 5 H), 2.20 (dt, J = 5.1, 14.9 Hz, 1 H), 1.77–1.73 (m, 1 H), 1.61 (dq, J = 5.1, 12.8 Hz, 1 H), 1.35 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 178.2, 165.4, 128.5, 68.9, 47.3, 41.8, 39.4, 33.7, 31.8, 28.6, 20.6, 18.5, 13.5; high-resolution mass spectrum (CI, NH_3) m/z 235.1316 [$(M + H)^+$, calcd for $C_{14}H_{19}O_3$ 235.1334].

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.54; H, 7.95.

Dioxane (±)-27. A solution of enone (±)-**12** (55 mg, 0.235 mmol) in benzene (5 mL) and 2,2-dimethyl-1,3-propanediol (34 mg, 0.34 mmol) was heated at reflux for 2.5 h. Upon cooling, the reaction mixture was diluted with ether (5 mL) and washed with saturated aqueous sodium bicarbonate (10 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded **27** (33 mg, 44% yield) as a colorless crystalline solid: mp 200–205 °C; IR ($CHCl_3$) 2960, 1770, 1460, 1450, 1388, 1352, 1235, 1150, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (br s, 1 H), 4.33 (t, J = 9 Hz, 1 H), 4.01 (dd, J = 9, 11 Hz, 1 H), 3.68–3.39 (m, 4 H), 2.74 (m, 1 H), 2.62 (dd, J = 3, 14 Hz, 1 H), 2.34 (m, 2 H), 2.05 (m, 2 H), 1.98–1.72 (m, 2 H), 1.57 (dt, J = 3, 11 Hz, 1 H), 1.26 (s, 3 H), 1.11 (s, 3 H), 1.05 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 178.2, 165.4, 128.5, 68.9, 47.3, 41.8, 39.4, 33.7, 31.8, 28.6, 20.6, 18.5, 13.5; high-resolution mass spectrum (CI, NH_3) m/z 321.2096 [$(M + H)^+$, calcd for $C_{19}H_{29}O_4$ 321.2066].

Sulfoximine Adducts of (±)-19a-c. A solution of *(S)-N,S*-dimethyl-*S*-phenylsulfoximine (0.68–18 mmol) in THF (1.5–30 mL) was cooled to 0 °C, and *n*-BuLi (2.5 M in hexanes, 1.1

equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and cooled to −78 °C, and the vinylogous ester (±)-**19a,b**, or **c**[17] (0.88 equiv) in THF (1−10 mL) added. The mixture was stirred for 30 min and poured into saturated NH_4Cl solution (5−50 mL). The aqueous layer was extracted with ether (3×) and the combined extracts were washed brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting mixture consisted of all four diastereomers of the sulfoximine adducts **31**, **32**, or **33** which were prone to decompose on silica.

To obtain the crystal structure of **33d**, the above procedure was followed using *(S)-N,S*-dimethyl-*S*-phenylsulfoximine (344 mg, 2.03 mmol) in THF (3 mL), *n*-BuLi (1.24 M in hexanes, 1.8 mL, 2.23 mmol), and (±)-**19c** (507.3 mg, 1.85 mmol) to afford upon flash chromatography (30% EtOAc/hexanes) **33d** (144.3 mg, 18% yield) as a white crystalline solid: mp 98−99.5 °C (Et_2O); ^1H NMR (250 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2 H), 7.67−7.50 (m, 4 H), 7.37−7.23 (m, 4 H), 6.28 (br s, 1 H), 4.55 (s, 1 H), 4.52 (ABq, J_{AB} = 19.0, 27.0 Hz, 2 H), 4.08−3.88 (m, 2 H), 3.50 (apparent t, J = 8.5, Hz, 1 H), 3.48 (ABq, J_{AB} = 13.5, 67.5 Hz, 2 H), 2.67 (s, 3 H), 2.14−1.83 (m, 2 H), 1.80−1.62 (m, 1 H), 1.43−1.22 (m, 1 H), 1.17 (d, J = 6.0 Hz, 3 H), 1.08 (d, J = 6.0 Hz, 3 H), 0.90 (apparent t, J = 8.5, Hz, 1 H).

(+)-4-[(Benzyloxy)methyl]-3-methyl-2-cyclohexen-1-one [(+)-18] from Crystalline 40d. A solution of **33d** (58.6 mg, 0.132 mmol) in *s*-BuOH (20 mL) was degassed by bubbling Ar through for ca. 10 min and then heated at reflux for 1.5 h. The solvent was removed in vacuo and the residue purified by flash chromatography (50% Et_2O/hexanes) to provide (+)-**19c**[17] (30.8 mg, 85% yield) as a colorless oil: $[\alpha]^{25}_D$ +52.9° (*c* 0.62, acetone).

Methyllithium (1.17 M in Et_2O, 211 μL, 0.247 mmol) was diluted with tetrahydrofuran (0.5 mL), the solution was cooled to −42 °C, and vinylogous ester (+)-**19a** (30.8 mg, 0.112 mmol) dissolved in tetrahydrofuran (0.5 mL) was added. The reaction mixture was then allowed to warm to 0 °C over 45 min, quenched with 1 N HCl (50 mL) and ice (50 g), and after 1 h extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% Et_2O/hexanes) afforded (+)-**18** (16.7 mg, 65% yield) as a colorless liquid identical to the racemic material: $[\alpha]^{25}_D$ +80.8° (*c* 0.33, $CHCl_3$).

4-[(Benzyloxy)methyl]cyclohexanone (34). A solution of vinylogous ester (±)-**19a** (190 g, 0.771 mol) in CH_2Cl_2 (1.900 L) was treated with DIBAL (1 M in hexanes, 0.887 L, 0.887 mol) dropwise over 50 min, maintaining the internal temperature below 10 °C. The reaction mixture was stirred at room temperature for 2 h and then quenched by slow dropwise addition of 2 N HCl (1.800 L) which induced a gentle reflux. The mixture was stirred for 1 h further and extracted with CH_2Cl_2 (3 × 1.8 L), and the combined extracts were washed with H_2O and saturated aqueous $NaHCO_3$, dried, filtered, and concentrated. The crude enone (±)-**35** (172.3 g, 100% yield) was used without purification in the next reaction.

To a mixture of (±)-**35** (172.3 g) in MeOH (1.70 L) under argon was added 5% Pd/C (10.0g) in *i*-PrOH (100 mL). The reaction mixture was placed under a hydrogen atmosphere and hydrogenated at atmospheric pressure for 2 h; the reaction was monitored by TLC and ^1H NMR. After filtration through Celite, concentration and flash chromatography (25% EtOAc/hexanes), distillation afforded **34** (134.6 g, 80% yield from **19a**) as a colorless oil: bp 133−135 °C/0.5−1 mmHg; IR ($CHCl_3$) 3000 (m), 2925 (s), 2860 (s), 1710 (s), 1450 (m), 1360 (m), 1225 (m), 1170 (m), 1025 (s), 1000 (s), 970 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.40 (m, 5 H), 4.55 (s, 2 H), 3.35 (d, J = 7 Hz, 2 H), 2.25−2.50 (m, 4 H), 2.00−2.25 (m, 3 H), 1.35−1.55 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 138.3, 128.3, 127.6, 127.5, 74.1, 73.1, 40.4, 36.5, 29.5; high-resolution mass spectrum (CI, NH_3) m/z 236.1635 [$(M + NH_4)^+$, calcd for $C_{14}H_{18}O_2$ 236.1650].

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.33. Found: C, 77.14; H, 8.21.

(+)-4-[(Benzyloxy)methyl]-2-cyclohexen-1-one [(+)-35]. A solution of homochiral amine (−)-**39** (36.4 g, 162 mmol) in THF (500 mL) was cooled to −78 °C, *n*-BuLi (2.5 M in hexane, 60 mL, 150 mmol) was added dropwise over 10 min, and the violet solution was stirred for 30 min further. Following the introduction of TMSCl (78.7 mL, 620 mmol) dropwise over 10 min, the solution became colorless. After an additional 10 min, a solution of ketone **34** (27.1 g, 124 mmol) in THF (30 mL) was added dropwise over 30 min. The mixture was stirred for 10 min and then treated with Et_3N (173 mL, 1.24 mol) at −78 °C followed by saturated aqueous $NaHCO_3$ (150 mL) below −20 °C. After extraction with hexanes (3 × 150 mL), the combined organic solutions were washed with 3 N citric acid (1 × 200 mL), 1 N citric acid (2 × 130 mL), 0.6 N citric acid (7 × 130 mL, or until all of amine **39** is removed as determined by thin layer chromatography and ninhydrin stain), saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. Distillation through a short path Widmer column gave silyl enol ether **36** (34.5 g, 96% yield) as a colorless oil: bp 135−140 °C/0.5−1 mmHg; $[\alpha]^{25}_{Hg365}$ +103° (*c* 2.09, benzene); IR ($CHCl_3$) 3005 (m), 2960, (w), 2920 (s), 2860 (s), 1670 (s), 1450 (w), 1365 (m), 1250 (s), 1180 (s), 1110 (m), 880 (s), 840 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.30−1.50 (m, 1 H), 1.70−2.00 (m, 3 H), 2.00−2.20 (m, 3 H), 3.30−3.45 (m, 2 H), 4.50 (s, 3 H), 4.80−4.85 (m, 1 H), 7.25−7.35 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 138.7, 128.3, 127.5, 127.4, 103.0, 74.8, 73.0, 33.8, 29.1, 27.1, 26.1, 0.3; high-resolution mass spectrum (CI, NH_3) m/z 291.1721 [$(M + H)^+$, calcd for $C_{17}H_{26}O_2Si$ 291.1730].

The amine (−)-**39** was recovered by neutralization of the acidic aqueous layer with 25% NaOH and extraction with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Distillation through a short path Widmer column afforded (−)-**39** (34.6 g, 95% recovery) as a colorless oil: bp 98−100 °C/0.5 mmHg; $[\alpha]^{25}_D$ −171° (*c* 2.04, $CHCl_3$), 100% ee.

At −78 °C oxygen was bubbled through a solution of silyl enol ether **36** (347.8 g, 1.197 mol) and rose bengal (725 mg) in THF (2 L) with irradiation by a 1000 W Hg lamp through a 2% aqueous $K_2Cr_2O_7$ filter solution. The reaction was monitored by TLC. After 8 h, triphenylphosphine (329.8 g, 1.257 mol) was added at −78 °C, and the resultant mixture was allowed to warm to room temperature overnight. MeOH (150 mL) was then added and the mixture concentrated. The residue was taken up in Et_2O/EtOAc (1:1, 3 L) and undissolved material were filtered off. Following concentration and flash chromatography (12.5% EtOAc/hexanes), distillation afforded (+)-**35** (158.0 g, 61% yield) as a colorless oil: bp 140−145 °C/0.5−1 mmHg; $[\alpha]^{25}_D$ +103.7° (*c* 1.89, MeOH), 80% ee); UV (EtOH) λ_{max} 211.2 (ε 16 000); IR ($CHCl_3$) 3000 (s), 2860 (s), 1680 (s), 1450 (m), 1390 (m), 1360 (m), 1230 (m), 1110 (s), 835 (m), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.10−7.30 (m, 5 H), 6.80 (br d, J = 10 Hz, 1 H), 6.40 (dd, J = 10, 3 Hz, 1 H), 4.40 (s, 2 H), 3.30−3.40 (m, 2 H), 2.55−2.65 (m, 1 H), 2.15−2.45 (m, 2 H), 1.90−2.05 (m, 1 H), 1.60−1.75 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 151.5, 137.9, 130.0, 128.4, 127.7, 127.5, 73.2, 72.4, 36.9, 36.6, 25.8; high-resolution mass spectrum (CI, NH_3) m/z 217.1231 [$(M + H)^+$, calcd for $C_{14}H_{17}O_2$ 217.1228].

(+)-4-[(Benzyloxy)methyl]-3-methyl-2-cyclohexen-1-one [(+)-18]. A suspension of CuI (23.1 g, 121 mmol) in Et_2O (240 mL) was cooled to 0 °C. MeLi (1.4 M in Et_2O, 173 mL, 242 mmol) was added dropwise over 20 min, and the resultant dark greenish-yellow, clear solution was stirred 0.5 h further. A solution of enone (+)-**35** (17.5 g, 80.9 mmol) in Et_2O (50 mL) was then introduced dropwise over 15 min and the mixture stirred for an additional 1 h, affording a greenish-yellow suspension. Following the dropwise addition of TMSCl (15.3 mL, 121 mmol) over 15 min, the mixture was stirred for 1.5 h at 0 °C and treated with Et_3N (33.6 mL, 241 mmol) dropwise over 5 min. Cold water (500 mL) was then added, maintaining the temperature of the mixture below 10 °C, and the orange precipitates were removed by filtration through Celite. The filtrate was washed with 1 N citric acid, water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) furnished the silyl enol ether (19.7 g, 80% yield) as a colorless oil: bp 150 °C/1 mmHg; ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 0.83 (d, J = 7 Hz, 0.5 H) and 0.98 (d, J = 7 Hz, 2.5 H),

1.35–1.60 (m, 2 H), 1.88–2.13 (m, 4 H), 3.27–3.43 (m, 1.15 H) and 3.48–3.52 (m, 0.85 H) 4.45 (d, J = 11 Hz, 1 H), 4.53 (d, J = 11 Hz, 1 H), 4.66–4.70 (m, 0.8 H) and 4.83–4.87 (m, 0.2 H), 7.20–7.35 (m, 5 H).

Via the procedure described above for (+)-**35**, the silyl enol ether (309 g, 1.01 mol) afforded (+)-**18** (117.6 g, 50%) with *spectral data identical to* (±)-**18**: *bp* 140–145 °C/0.5–1 *mmHg*; $[\alpha]^{25}_D$ +65.8° (*c* 1.98, $CHCl_3$), 81% ee.

Methylated Keto Dioxolane (±)-41. A solution of silyl enol ether (±)-**21** (2.05, g 7.45 mmol) in THF (24 mL) was cooled to 0 °C, and MeLi (1.4 M in Et_2O, 4.4 mL) was added. The mixture was stirred at room temperature for 10 min, cooled to −78 °C, and treated dropwise with a solution of aldehyde **30** (1.02 g, 7.85 mmol) in THF (4 mL). After removal of the cold bath, the reaction mixture was stirred for 0.5 h and then quenched with saturated aqueous NH_4Cl (35 mL). The aqueous layer was extracted with EtOAc (3 × 35 mL), and the combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10–20% EtOAc/hexanes) gave enone (±)-**40** (574 mg, 25% yield) as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.24 (m, 5 H), 6.72 (tt, J = 2, 8 Hz, 1 H), 5.79 (dd, J = 10, 17 Hz, 1 H), 5.04 (d, J = 11 Hz, 1 H), 4.97 (d, J = 17 Hz, 1 H), 4.50 (dd, J = 12, 18 Hz, 2 H), 4.02–3.99 (m, 4 H), 3.64 (dd, J = 4, 9 Hz, 1 H), 3.34 (t, J = 8 Hz, 1 H), 2.60–1.30 (m, 5 H), 2.12–1.96 (m, 1 H), 1.37 (s, 3 H), 1.02 (s, 3 H).

A suspension of CuI (20.2 mg) in THF (5 mL) was cooled to 0 °C and treated with MeLi (1.4 M in Et_2O, 100 μL). The temperature was then lowered to −60 °C and HMPA (520 μL) added, followed by DIBAL (1.0 M in hexanes, 2.2 mL). After 30 min a solution of enone (±)-**40** (52.3 mg, 0.141 mmol) in THF (1 mL) was introduced dropwise, and the mixture was stirred for 40 min further. Following the addition of MeLi (1.4 M in Et_2O, 1.7 mL), the reaction was stirred for 15 min and methyl iodide (1.5 mL, 24 mmol) was introduced through activity II alumina. After an additional 45 min, the reaction was quenched with 1 N HCl (2 mL), the layers were separated, and the organic phase was washed with a saturated solution of Roscelle's salt. The combined aqueous layers were extracted with EtOAc (3 × 10 mL), and the combined solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) gave **41** (48.8 mg, 59% yield) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5 H), 5.83 (dd, J = 11, 17 Hz, 1 H), 5.05 (d, J = 10 Hz, 1 H), 4.96 (d, J = 16 Hz, 1 H), 4.47 (dd, J = 11, 18 Hz, 2 H), 3.97–3.91 (m, 4 H), 3.57 (dd, J = 3, 9 Hz, 1 H), 3.13 (t, J = 9 Hz, 1 H), 2.48–1.55 (m, 8 H), 1.62 (s, 3 H), 1.40–1.25 (m, 1 H), 1.33 (s, 3 H), 0.86 (s, 3 H).

Dioxolane Ketols 43. Method 1. A suspension of CuI (57 mg, 3.6 mmol) in THF (5 mL) was treated with TMEDA (540 mL) at room temperature and cooled to -78 °C. Addition of vinylmagnesium bromide (1.0 M in THF, 6.0 mL) resulted in a black solution. After 15 min a solution of enone (+)-**18** in THF (6 mL) was added dropwise over 20 min, and the resultant mixture was stirred for 10 min further. Following the dropwise addition of a solution of aldehyde **30** (1.29 g, 9.9 mmol) in THF (10 mL) over 10 min, the reaction mixture was stirred for 2 h and quenched with saturated aqueous NH_4Cl (20 mL) at −78 °C. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (30% EtOAc/hexanes) gave a mixture of diastereomeric aldols **43** (589 g, 51% yield) as a pale yellow oil.

Method 2. Following the procedure described above for (±)-**21**, reaction of enone (+)-**18** (5.0 g, 21.7 mmol) in THF (25 mL), CuI (0.413 g, 2.17 mmol) and TMEDA (10.8 mL, 71.6 mmol) in THF (70 mL), vinylmagnesium bromide (39.1 mL, 39.1 mmol), and trimethylsilyl chloride/triethylamine (20.0 mL, 1:1 v/v) afforded (−)-**21** (6.5 g, 90% yield) as a pale yellow oil: $[\alpha]^{25}_D$ −30.9 (*c* 1.08, $CHCl_3$).

A solution of silyl enol ether (−)-**21** (28.0 g, 84.8 mmol) in Et_2O (200 mL) was treated with MeLi (1.4 M in Et_2O, 72.7 mL, 102 mmol) at room temperature and stirred 1 h further. TLC analysis then indicated complete disappearance of starting material. The reaction mixture was transferred via a cannula into a solution of $MgBr_2 \cdot Et_2O$ (28.4 g, 110 mmol) in Et_2O (200 mL). After an additional 30 min, the reaction was cooled to −5 °C, and neat aldehyde **30** (17.6 g, 136 mmol) was added dropwise. The thick, pasty mixture was stirred at −5 °C for 10 min and quenched with 10% HCl (200 mL), and the organic layer was washed with brine, quickly dried over $MgSO_4$, filtered, and concentrated. Prolonged drying with $MgSO_4$ resulted in loss of product. Flash chromatography (20% EtOAc/hexanes) furnished a mixture of diastereomers **43** (21.4 g, 65% yield) as a pale yellow oil which was used without purification.

Enones (−)-*(Z)*-29 and (−)-*(E)*-29. Method 1. At room temperature a solution of crude aldols **43** (mixture of diastereomers, 51.0 mg, 13.2 mmol) in pyridine (1 mL) was treated with Ac_2O (1 mL) and DMAP (ca. 2 mg, 0.017 mmol) and stirred overnight. The mixture was then cooled to 0 °C and quenched with H_2O (3 mL) and 1 N HCl (3 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to provide a mixture of acetates (55.0 mg, 97% yield). The crude acetate (28.0 mg, 0.065 mmol) was dissolved in toluene (1 mL) and treated with DBU (15 μL, 0.018 mmol) at 0 °C. The reaction mixture was warmed to room temperature for 1 h, and additional DBU (10 μL) was added. After 2 h the temperature was raised to 50 °C, and DBU (10 μL) was again added after 1 h. Upon stirring overnight at 50 °C, the resultant mixture was evaporated. Preparative thin layer chromatography (0.5-mm silica gel plate; 33% EtOAc/hexanes) afforded (−)-*(Z)*-**29** (14.7 mg, 61% yield).

Method 2. A solution of crude aldols **43** (mixture of diastereomers, 16.5 g, 42.5 mmol) in anhydrous benzene (90 mL) was treated with freshly prepared Burgess reagent (15.2 g, 63.8 mmol) and heated at reflux for 1 h. The mixture was then cooled, diluted with EtOAc (90 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded the separable isomers (3:1) (−)-*(Z)*-**29** and (−)-*(E)*-**29** (12.0 g, 79% yield) as colorless oils.

(−)-*(Z)*-**29**: $[\alpha]^{25}_D$ −27.0 (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3000 (br, m), 2890 (m), 1690 (s), 1630 (br, w), 1450 (w), 1380 (m), 1300 (w), 1220 (br, w), 1100 (s), 1050 (s), 950 (w), 920 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5 H), 5.78 (dd, J = 10.7, 17.6 Hz, 1 H), 5.64 (apparent t, J = 7.4 Hz, 1H), 5.14 (dd, J = 0.6, 10.7 Hz, 1 H), 4.96 (d, J = 17.4 Hz, 1 H), 4.48 (ABq, J_{AB} = 11.9, 45.1 Hz, 2 H), 3.92–3.84 (m, 4 H), 3.59 (dd, J = 4.0, 9.3 Hz, 1 H), 3.31 (apparent t, J = 9.2 Hz, 1 H), 2.66–2.57 (m, 2 H), 2.47–2.33 (m, 2 H), 2.22–2.15 (m, 1 H), 2.07–2.01 (m, 1 H), 1.91–1.84 (m, 1 H), 1.26 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 146.2, 145.0, 138.3, 129.4, 128.4, 127.6, 127.5, 115.0, 109.6, 73.2, 70.4, 64.7, 48.5, 44.2, 40.7, 37.9, 24.2, 23.9, 20.2; high-resolution mass spectrum (CI, NH_3) m/z 371.2233 [$(M + H)^+$, calcd for $C_{23}H_{30}O_4$ 371.2222].

(−)-*(E)*-**29**: $[\alpha]^{25}_D$ −3.40 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3000 (br, s), 2890 (s), 1680 (s), 1600 (m), 1450 (w), 1415 (w), 1380 (m), 1220 (br, m), 1100 (br, s), 1060 (s), 1040 (m), 950 (w), 920 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5 H), 6.84 (apparent t, J = 7.5 Hz, 1 H), 5.84 (dd, J = 10.7, 17.6 Hz, 1 H), 5.17 (dd, J = 0.9, 10.7 Hz, 1 H), 5.03 (dd, J = 0.6, 17.6 Hz, 1 H), 4.45 (ABq, J_{AB} = 12.0, 37.2 Hz, 2 H), 3.95–3.89 (m, 4 H), 3.57 (dd, J = 2.8, 9.0 Hz, 1 H), 3.23 (apparent t, J = 8.7 Hz, 1 H), 2.71 (dd, J = 7.6, 16.3 Hz, 1 H), 2.59–2.50 (m, 2 H), 2.43–2.37 (m, 1 H), 2.20–2.16 (m, 1 H), 1.83–1.77 (m, 2 H), 1.30 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 145.2, 143.0, 138.8, 138.4, 128.4,127.6, 127.5, 113.4, 109.2, 73.2, 70.2, 64.8, 44.8, 44.0, 39.0, 38.1, 24.4, 21.6, 18.7; high-resolution mass spectrum (CI, NH_3) m/z 371.2168 [$(M + H)^+$, calcd for $C_{23}H_{30}O_4$ 371.2222].

Methylated Keto Dioxolane (±)-28. A suspension of CuI (21.3 mg) in THF (15 mL) was cooled to 0 °C and treated with MeLi (1.4 M in Et_2O, 115 μL). The temperature was then lowered to −60 °C and HMPA (500 μL) added, followed by DIBAL (1.0 M in hexanes, 1.7 mL). After 30 min a solution of enone (±)-**29** (214.0 mg, 0.578 mmol) in THF (6 mL) was introduced dropwise, and the mixture was stirred for 40 min further. A mixture of TMSCl and triethylamine (1:1 v/v, 5 mL,

20 mmol of TMSCl) was introduced and the temperature adjusted to 0 °C. The mixture was stirred for 30 min further and then poured into cold NH_4OH buffered to pH 8 and extracted with ethyl acetate (3 × 25 mL). The combined organic solutions were washed with the cold buffered NH_4OH solution, dried over $MgSO_4$, filtered, and concentrated. Filtration through a pad of activity II alumina then furnished (±)-**44** (66.7 mg, 40% yield) as a colorless liquid.

At ambient temperature a solution of silyl enol ether (±)-**44** (39.5 mg, 0.089 mmol) in tetrahydrofuran (1 mL) was treated with MeLi (0.96 M in Et_2O, 105 μL), the reaction was stirred for 15 min, and methyl iodide (500 μL, 8 mmol) was introduced through activity II alumina. After an additional 45 min, the reaction was quenched with 1 N HCl (1 mL), the layers were separated, and the organic phase was washed with a saturated solution of Roscelle's salt. The combined aqueous layers were extracted with EtOAc (3 × 5 mL), and the combined solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. ^1H NMR (250 MHz, $CDCl_3$) of the crude reaction product indicated that approximately 25% of (±)-**28** was present.

α-Methylcyclohexanone (+)-46. A mixture of enones (−)-*(Z)*- and (−)-*(E)*-**29** (3:1, 8.0 g, 21.6 mmol) was dissolved in THF (180 mL) at room temperature, and diphenyl sulfoxide (4.8 g, 23.8 mmol) was added. After several minutes potassium *tert*-butoxide (2.7 g, 23.8 mmol) was introduced in one portion, and the resultant dark solution was stirred for 10 min further and cooled to 0 °C. Following dropwise addition of methyl iodide (3.98 g, 28.1 mmol), the reaction mixture was stirred at 0 °C for 3 h, gradually warmed to room temperature, stirred at ambient temperature for 30 min, cooled to 0 °C, and quenched with saturated aqueous NH_4Cl (200 mL). After extraction with EtOAc (3 × 200 mL) the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) gave (+)-**46** (4.90 g, 59% yield) as a colorless oil: $[\alpha]^{25}_D$ +24.4 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 2980 (br, s), 2890 (s), 1705 (s), 1450 (w), 1370 (m), 1360 (w), 1210 (br, s), 1090 (br, s), 1040 (s), 980 (w), 920 (w), 860 (w)cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 6.15 (d, *J* = 16.2 Hz, 1 H), 5.74 (dd, *J* = 11.0, 17.6 Hz, 1 H), 5.21 (d, *J* = 16.2 Hz, 1 H), 5.13 (dd, *J* = 1.0, 11.0 Hz, 1 H), 4.83 (dd, *J* = 1.0, 17.6 Hz, 1 H), 4.45 (ABq, J_{AB} = 11.9, 35.7 Hz, 2 H), 3.93–3.89 (m, 3 H), 3.82–3.79 (m, 1 H), 3.53 (dd, *J* = 2.7, 8.9 Hz, 1 H), 3.13 (apparent t, *J* = 8.8 Hz, 1 H), 2.71 (dt, *J* = 7.0, 13.9 Hz, 1 H), 2.43–2.30 (complex m, 3 H), 1.69 (dq, *J* = 5.3, 12.9 Hz, 1 H), 1.42 (s, 3 H), 1.25 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 140.7, 138.2, 131.1, 129.9, 128.4, 127.6, 127.5, 115.4, 107.6, 73.3, 72.7, 64.5, 64.1, 48.4, 39.8, 36.8, 26.4, 25.3, 18.4, 14.9; high-resolution mass spectrum (CI, NH_3) *m/z* 385.2379 [$(M + H)^+$, calcd for $C_{24}H_{32}O_4$ 3385.2379].

Deketalized Diene Diketone (-)-47. A solution of ketal (+)-**46** (7.00 g, 18.2 mmol) and H_2O (10 mL) in acetone (400 mL) was treated with pyridinium *p*-toluenesulfonate (1.4 g, 5.5 mmol) and stirred at ambient temperature for 24 h. After concentration, the residue was dissolved in EtOAc (400 mL), and the solution was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded (−)-**47** (6.00 g, 98% yield) as a colorless solid: $[\alpha]^{25}_D$ −74 (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 3000 (br, m), 1710 (s), 1680 (s), 1630 (m), 1460 (m), 1420 (w), 1380 (m), 1365 (s), 1260 (br, s), 1100 (br, s), 1005 (m), 985 (m), 925 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5 H), 7.14 (d, *J* = 16.8 Hz, 1 H), 5.86 (d, *J* = 16.8 Hz, 1 H), 5.71 (dd, *J* = 11.0, 17.6 Hz, 1 H), 5.14 (d, *J* = 11.0 Hz, 1 H), 4.82 (d, *J* = 17.6 Hz, 1 H), 4.40 (ABq, J_{AB} = 11.9, 32.4 Hz, 2 H), 3.50 (dd, *J* = 2.6, 8.8 Hz, 1 H), 3.12 (apparent t, *J* = 8.8 Hz, 1 H), 2.70 (dt, *J* = 7.8, 14.9 Hz, 1 H), 2.45–2.26 (m, 3 H), 2.23 (s, 3 H), 1.68 (dq, *J* = 5.1, 13.2 Hz, 1 H), 1.28 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 198.2, 146.7, 139.7, 138.0, 131.8, 128.2, 127.5, 127.4, 116.2, 73.2, 72.1, 56.6, 48.6, 39.5, 36.6, 26.6, 26.1, 18.2, 14.9.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.48; H, 8.53.

Dihydro Diketone (−)-48. A solution of diene diketone (−)-**47** (5.00 g, 14.7 mmol) in 2-methoxyethanol (135 mL) was treated with Zn dust (8.5 g, 130 mmol) at ambient temperature. A solution of $NiCl_2 \cdot 6H_2O$ (3.50 g, 14.7 mmol) in H_2O (20 mL), buffered to pH 7.0 with several drops of NH_4Cl buffer (95% H_2O, 1% NH_4Cl, 4% NH_4OH), was then added in one portion, and the resultant slurry was sonicated for 3 h and stirred for 24 h further at room temperature. The mixture was filtered through Celite, and the filtrate was diluted with EtOAc (100 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded (−)-**48** (4.50 g, 90% yield) as a colorless solid: $[\alpha]^{25}_D$ −14 (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 2920 (br, s), 1710 (s), 1450 (m), 1420 (m), 1360 (m), 1300 (br, w), 1150 (m), 1130 (w), 1090 (m), 1070 (m), 1020 (m), 1000 (m), 900 (br, m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5 H), 5.80 (dd, *J* = 11.0, 17.6 Hz, 1 H), 5.21 (dd, *J* = 0.8, 10.9 Hz, 1 H), 4.99 (dd, *J* = 0.8, 17.5 Hz, 1 H), 4.41 (ABq, J_{AB}= 11.8, 35.6 Hz, 2 H), 3.49 (dd, *J* = 2.7, 8.9 Hz, 1 H), 3.11 (apparent t, *J* = 8.9 Hz, 1 H), 2.68 (dt, *J* = 7.1, 13.8 Hz, 1 H), 2.58 (ddd, *J* = 4.2, 11.1, 16.4 Hz, 1 H), 2.46–2.40 (m, 1 H), 2.39–2.33 (m, 1 H), 2.22–2.12 (complex m, 2 H), 2.11 (s, 3 H), 1.98 (ddd, *J* = 4.2, 11.1, 13.5 Hz, 1 H), 1.61 (dq, *J* = 5.0, 13.8 Hz, 1 H), 1.30 (ddd, *J* = 5.3, 11.3, 13.5 Hz, 1 H), 1.16 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 209.3, 140.8, 138.3, 129.6, 128.4, 127.6, 116.2, 73.3, 72.7, 52.9, 49.0, 40.0, 39.6, 37.2, 29.9, 27.3, 24.4, 18.1, 13.0.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.30; H, 8.83.

Benzyl and Benzoyl Aldehydes 13 and 25. Ozone was rapidly bubbled into a solution of diketo olefin (−)-**48** (2.7 g, 7.9 mmol) in CH_3OH/CH_2Cl_2 (4:1, 450 mL) at −78 °C until TLC analysis indicated the complete disappearance of starting material (ca. 20 min). The mixture was then flushed with argon at -78 °C for 30 min, treated with dimethyl sulfide (90 mL), gradually warmed to room temperature, and stirred overnight. Concentration gave a mixture of **13** and **25** (2.4 g, 86% crude yield) as a pale yellow oil which was used immediately without purification.

Methyl Esters 26 and 49. At room temperature a solution of the crude aldehydes **13** and **25** (2.40 g, 6.98 mmol) in *t*-BuOH (55 mL) was treated with 5% NaH_2PO_4 buffer solution (28 mL). The rapidly stirred mixture was treated with 1 M aqueous $KMnO_4$ (10 mL, 10 mmol) dropwise over 1.5 h. TLC analysis then indicated complete consumption of starting material. After addition of saturated aqueous Na_2SO_3 until the purple color disappeared and a brown precipitate formed and 1 N HCl until the pH reached 1–2 (pH paper), the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated, furnishing the corresponding crude acids as a white solid. This material was dissolved in CH_2Cl_2/Et_2O (1:1, 22 mL) and treated with ethereal diazomethane at room temperature. Flash chromatography (25% EtOAc/hexanes) then furnished the benzoyl methyl ester (−)-**26** (2.1 g, 82% yield) and benzylated methyl ester (−)-**49** (0.3 g, 10% yield).

(−)-**49**: colorless oil; $[\alpha]^{25}_D$ −6.0 (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3020 (s), 2980 (s), 2890 (m), 1720 (br, s), 1450 (m), 1440 (m), 1390 (w), 1370 (m), 1250 (br, s), 1130 (br, m), 1110 (s), 1090 (s), 1000 (w), 970 (w), 910 (w), 700 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5 H), 4.42 (s, 2 H), 3.56 (s, 3 H), 3.25–3.19 (m, 2 H), 3.03 (dt, *J* = 5.2, 12.3 Hz, 1 H), 2.66 (dt, *J* = 7.3, 13.8 Hz, 1 H), 2.52 (ddd, *J* = 4.1, 11.4, 16.5 Hz, 1 H), 2.23–2.10 (complex m, 4 H), 2.09 (s, 3 H), 1.49 (dq, *J* = 5.0, 13.2 Hz, 1 H), 1.27–1.23 (m, 1 H), 1.22 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 208.4, 173.2, 138.0, 128.3, 128.0, 127.6, 73.2, 72.2, 54.3, 52.4, 51.6, 39.3, 38.2, 36.3, 29.7, 25.8, 25.6, 19.5, 12.6; high-resolution mass spectrum (CI, NH_3) *m/z* 371.2197 [$(M + H)^+$, calcd for $C_{22}H_{30}O_5$ 375.2171].

Benzoate methyl ester (−)-**26** was spectroscopically indistinguishable from the racemic material characterized previously: $[\alpha]^{25}_D$ −2.7 (*c* 1.66, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 68.10; H, 7.25.

Hydroxy Ester (−)-50. Benzyl ether (−)-**49** (1.60 g, 4.28 mmol) was dissolved in 95% EtOH (60 mL), Pearlman's catalyst [$Pd(OH)_2$, 0.45 g] was added, and the reaction vessel

was repeatedly evacuated and flushed with argon and then with hydrogen. The mixture was stirred at room temperature under a hydrogen atmosphere for 24 h, the excess hydrogen was purged by passing argon gas through the solution, filtering through Celite, and rinsing with Et_2O. Concentration and flash chromatography (Et_2O) afforded (−)-**50** (1.10 g, 92% yield) as a colorless oil: $[\alpha]^{25}_D$ −1.1 (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 3400 (br, m), 3020 (s), 2960 (s), 1720 (s), 1440 (w), 1390 (w), 1360 (m), 1250 (br, s), 1150 (m), 1170 (m), 1110 (m), 1090 (m), 1070 (w), 1010 (w), 970 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3 H), 3.45−3.39 (m, 2 H), 2.92−2.86 (m, 1 H), 2.66 (dt, J = 7.7, 14.2 Hz, 1 H), 2.54 (ddd, J = 4.2, 11.2, 16.3 Hz, 1 H), 2.23−2.11 (complex m, 4 H), 1.93−1.87 (m, 1 H), 2.09 (s, 3 H), 1.93−1.87 (m, 1 H), 1.46 (dq, J = 5.5, 14.0 Hz, 1 H), 1.28−1.23 (m, 1 H), 1.21 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 208.7, 173.9, 64.7, 54.3, 52.4, 51.9, 40.7, 39.3, 36.3, 29.8, 25.5, 25.4, 19.4, 12.3; high resolution mass spectrum (CI, NH_3) m/z 302.1967 [$(M + NH_4)^+$, calcd for $C_{15}H_{24}O_5$ 302.1973].

Diketo Lactone (+)-51. A solution of benzoate (−)-**26** (0.30 g, 0.77 mmol) and alcohol (−)-**50** (1.10 g, 3.87 mmol) in anhydrous MeOH (85 mL) was treated with solid potassium *tert*-butoxide (0.052 g, 0.46 mmol), heated at reflux for 3 h, and cooled to room temperature. After dilution with CH_2Cl_2 (85 mL), the mixture was washed with 1 N HCl and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (Et_2O) afforded (+)-**51** (1.00 g, 86% yield) as a colorless solid: mp 114−115 °C; $[\alpha]^{25}_D$ +35 (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 3000 (br, s), 1785 (s), 1715 (s), 1490 (w), 1440 (br, w), 1380 (w), 1350 (m), 1300 (w), 1220 (br, w), 1170 (m), 1100 (m), 1060 (m), 1000 (m), 970 (w), 950 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, J = 7.3, 8.8 Hz, 1 H), 3.96 (dd, J = 8.8, 11.3 Hz, 1 H), 3.16−3.09 (m, 1 H), 2.73 (ddd, J = 4.7, 10.7, 17.2 Hz, 1 H), 2.54−2.47 (m, 2 H), 2.32 (ddd, J = 1.7, 5.6, 15.8 Hz, 1 H), 2.15−2.03 (m, 2 H), 2.11 (s, 3 H), 1.91−1.83 (m, 1 H), 1.72 (dq, J = 5.7, 12.9 Hz, 1 H), 1.23 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 208.3, 176.9, 68.0, 52.9, 49.0, 39.8, 39.1, 36.7, 29.8, 24.6, 19.9, 17.5, 12.5.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.59; H, 8.10.

Tricyclic Enone Lactone (+)-12. A solution of diketo lactone (+)-**51** (1.00 g, 3.97 mmol) in THF (190 mL) was treated with solid potassium *tert*-butoxide (0.19 g, 1.7 mmol), heated at reflux for 6 h, and cooled to room temperature. After dilution with CH_2Cl_2 (190 mL), the mixture was washed with 1 N HCl and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% $CHCl_3/Et_2O$) gave (+)-**12** (0.69 g, 75% yield) as a pale yellow solid, sepctroscopically indistinguishable from the racemic material described above: $[\alpha]^{25}_D$ +160 (*c* 0.8, $CHCl_3$).

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Supporting Information Available: Copies of ^1H NMR spectra of **12**, **14**, **16**, **18**, **21**−**27**, **29*Z*,*E***, **33d**, **34**−**36**, **40**, **41**, and **46**−**51** and ^{13}C NMR spectra of **12**, **18**, **21**, **26**, **27**, **29*Z*,*E***, **34**−**36**, and **46**−51 (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions. Atomic coordinates, bond lengths and angles, thermal parameters and structure factors for compounds **27** and **33d** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

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