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DOUBLY DIASTEREOSELECTIVE NUCLEOPHILIC ADDITIONS TO A BICYCLIC β,γ-UNSATURATED KETONE POSSESSING A CONFORMATIONALLY MOBILE DOUBLE BOND†

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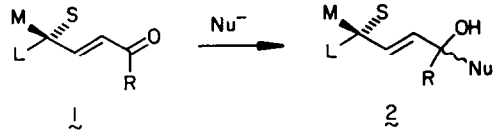
Abstract: (7R*)-7-Methyl-7-vinylbicyclo[3.2.0]hept-2-en-6-one was condensed with several chiral cyclopentenyllithium reagents for the purpose of assaying the diastereoselectivity of this coupling. Due to ring strain, the alkoxides that are formed spontaneously undergo anionic oxy-Cope rearrangement. The initial diastereoselectivity is thereby incorporated into additional stereogenic centers. The mechanistic details of the two steps are discussed. Although the resultant diastereoselectivity is low, it is shown that polycyclic networks with as many as nine asymmetric carbons can be cleanly elaborated in very few steps.

Organic chemists are well acquainted with Cram's rule,[1] Felkin's rule,[2] and other theoretical treatments[3] relevant to the realization of relative asymmetric induction in nucleophilic 1,2-additions to a carbonyl group. These examples have invariably involved substrates where the carbonyl carbon is specifically positioned immediately adjacent to a chiral center. An attempt to achieve Cram-like stereocontrol in a system where the two sites are separated by an intervening double bond as in 1 resulted in greatly reduced or negligible diastereoselection.[4]



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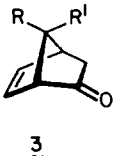

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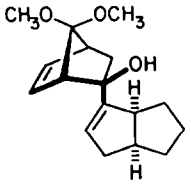

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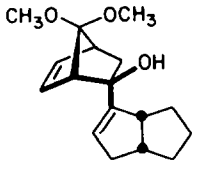

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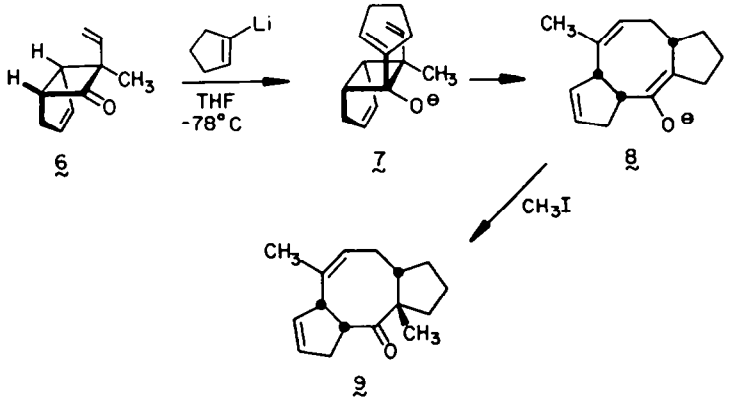
Recently, we reported that norbornenone 3 (R = R' = OCH_3), so constructed that nucleophilic attack at C=O is totally impeded from the exo surface,[5] can become highly diastereoselective toward certain cyclopentenylcerium reagents.[6] Comparable behavior is observed when other apical substituents (R, R' ≠ OCH_3) are present.[7] The 16:1 ratio of 4 to 5, realized in tetrahydrofuran solution at -78°C, is illustrative and points up the fact that kinetic resolution would be eminently feasible if one of the reagents were in homochiral condition.

†This paper is dedicated to Professor Hans Wynberg on the occasion of his 65th birthday and retirement as Professor of Organic Chemistry from the University of Groningen. As a man of great scientific vision and enormous enthusiasm, Hans has been a prime force in the fundamental development of several important areas, perhaps most notably that of asymmetric induction. We wish him well in the years ahead.

The transition state model tentatively advanced to account in consistent fashion for the wide-ranging diastereoselectivity ratios determined for **3** is intimately linked to the Bürgi-Dunitz trajectory model[8] and the conformational rigidity of the norbornenone framework. The spatial relationship of the β,γ-double bond and the carbonyl carbon in **3** is defined with virtual inflexibility. As a consequence, the approaching organometallic must cope with non-mollifiable steric barriers as bonding into the carbonyl group is initiated, particularly if molecular stacking is relevant.[6,7]

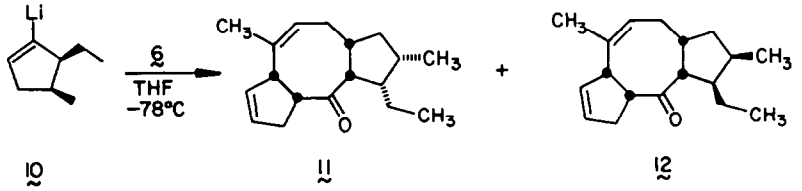
One test of this hypothesis resides in the examination of ketones where the β,γ-double bond is conformationally mobile and does not share with **3** a highly restricted topography. The purpose of this paper is to describe results derived from the examination of (7*R**)-7-methyl-7-vinylbicyclo-[3.2.0]hept-2-en-6-one (**6**).[9] This readily available bicyclic compound[10] exhibits a strong kinetic bias for nucleophilic capture from its exo surface. Addition of cyclopentenyllithium to **6** has previously been shown to eventuate in spontaneous oxyanionic Cope rearrangement within **7**.[11] The substantive relief of ring strain leads stereospecifically to enolate anion **8**, which can be methylated to provide **9**, a functionalized all-cis-dicyclopenta[a,d]cyclooctane related to the ophiobolins, ceroplastols, and fusicoccins.



6 **7** **8** **9**

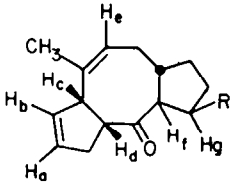
Results

The cyclopentenyllithium reagents utilized herein were made available by the action of tert-butyllithium on the vinyl bromides, which in turn were prepared by Shapiro degradation of the ketone tosylhydrazones followed by quenching with cyanogen bromide as previously described.[7,12] Addition of 1.5 equiv of **10** to **6** in tetrahydrofuran solution at -78°C led to a 1.65:1 mixture of **11** and **12** which were readily separated by silica gel chromatography. Although the 300 MHz ^{1}H NMR spectra of these ketones in $CDCl_3$ are distinctively different (Table I), no clear-cut stereochemical differentiation could be made between these diastereomers. Recourse to X-ray crystallographic analysis of **11** confirmed the anticipated all-cis stereochemistry of the four ring juncture sites and established the anti relationship of the sp^3-bound methyl and ethyl groups to these tertiary hydrogens (Figure 1, Table II).



10 **11** **12**

Table I. Select Proton Chemical Shift Data (δ, 300 MHz, $CDCl_3$ solution).



Compd	H_a	H_b	H_c	H_d	H_e	H_f	H_g	CH_3
11	5.59	5.90	4.20(d)	3.71(q)	5.34(t)	3.19(t)	2.67(m)	1.50
12	5.64	5.77	4.14(d)	3.82(dq)	5.28(t)	a	2.69(dq)	1.59
14	5.58	5.88	4.18(d)	3.67(q)	5.40(dd)	3.09(t)	2.72(m)	1.50
15	5.58	5.83	4.20(d)	3.78(dq)	5.78	a	2.59(dd)	1.55
17	5.58	5.84	4.15(d)	3.64(m)	5.32(t)	3.15(t)	2.55-2.75(m)	1.51
18	5.52	5.80	4.16(d)	3.65(q)	5.27(t)	a	2.65(dd)	1.44
22	5.56	5.86	4.21(d)	3.65(q)	5.34(t)	a	2.75(d)	1.47
23	5.56	5.81	4.16(d)	3.66(m)	5.41(t)	a	2.78[b]	1.51
24	5.55	5.86	4.28(d)	3.80(q)	5.42[b]	a	2.83[b]	1.42
27	5.56	5.73	4.15(d)	3.69(dq)	5.29[b]	a	2.73[b]	1.48
28	5.52	5.73	4.12(d)	3.77(dq)	5.42[b]	a	2.60[b]	1.51
32	5.53	5.84	4.18(d)	3.44(dd)	5.37(d)	a	2.28(dd)	1.46
33	5.60	5.78	4.16(d)	3.72(ddd)	5.43(t)	a	2.48(dd)	1.58
34	5.65	5.76	4.09(d)	3.75(dt)	5.23(t)	a	2.35(dd)	1.59

[a]Signal overlapping and chemical shift not clearly visible. [b]Multiplicity unclear because of overlapping peaks.

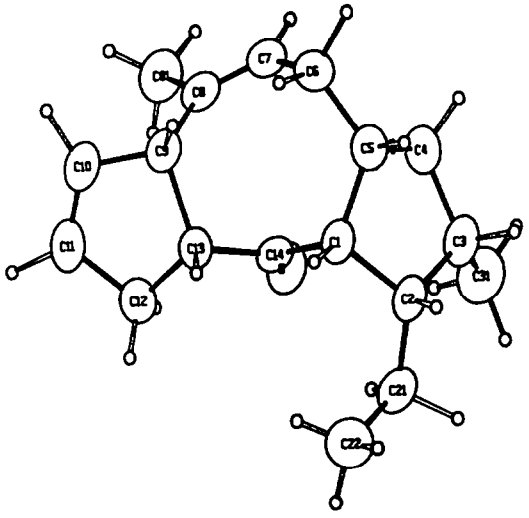
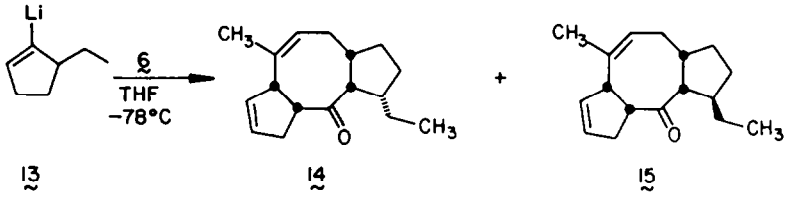
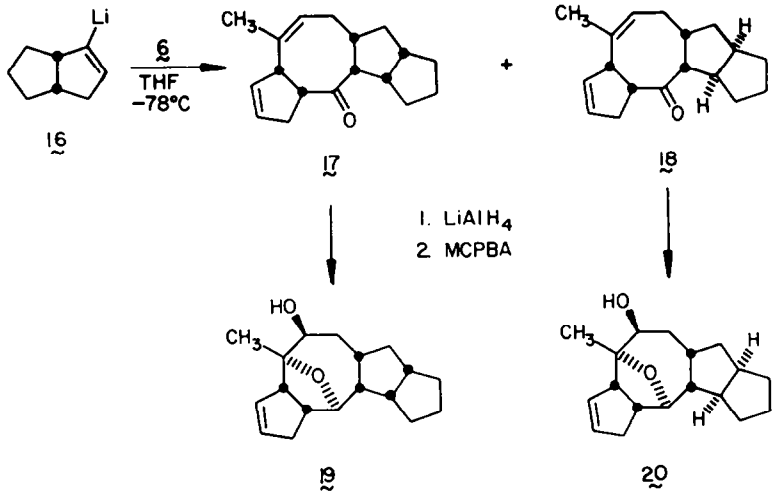


Figure 1. Diagram for **11** as derived by X-ray crystal structure analysis (courtesy of Y.-L. Hsu, The Ohio State University).

When the 4-methyl group was deleted as in **13**, coupling to **6** proceeded preferentially along the same course to give **14** and **15**, although with diminished diastereoselectivity (1.06:1). In this case, the individual assignments to the tricyclic ketones are based upon comparison of the individual ^{1}H NMR spectra (Table I).



The capacity of this methodology for the rapid construction of intricate polycyclic networks with good stereocontrol is illustrated for the bicyclo[3.3.0]octenyllithium reagent **16**. Condensation with **6** under identical conditions afforded **17** and **18** in 88% yield and a diastereomeric ratio of 1.43:1. Once chromatographic separation had been achieved, **17** and **18** were individually



reduced with very high stereoselectivity to their α-alcohols with lithium aluminum hydride. Individual treatment with m-chloroperbenzoic acid gave **19** and **20**. Available in only three steps from **6**, these products contain nine configurationally defined stereogenic centers, seven of which are clustered on the central cyclooctane ring. Figure 2 is a three-dimensional view of the beautifully crystalline **20** as established by X-ray methods (Table II).

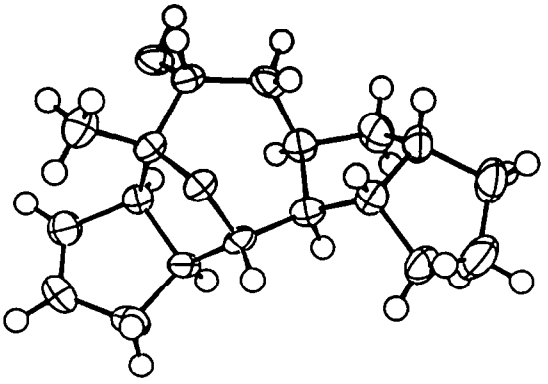


Figure 2. Diagram for **20** as derived by X-ray crystal structure analysis. (courtesy of J. Troup and P. Swepton, Molecular Structure Corporation).

Progressive contraction of the non-functionalized ring in **16** is recognized to have a deleterious effect on diastereocontrol when **3** is involved.[6,7] In the present situation, some dropoff is also encountered. However, no widely varying response materializes, probably because partitioning between the transition states leading to **17** and **18** is already relatively closely balanced. At the experimental level, bicyclo[3.2.0]heptenyllithium **21** furnished in 80% yield the pair of tricyclic ketones **22** (46%) and **23** (34%) alongside 9% of a third substance tentatively identified as **24**. Since the relative stereochemistry of **23** was ascertained beyond doubt by crystal structure analysis (Figure 3, Table II), the three-dimensional topology of **22** can be assumed as established with reasonable confidence. Its ^{1}H NMR spectral features (Table I) provide additional corroboration.

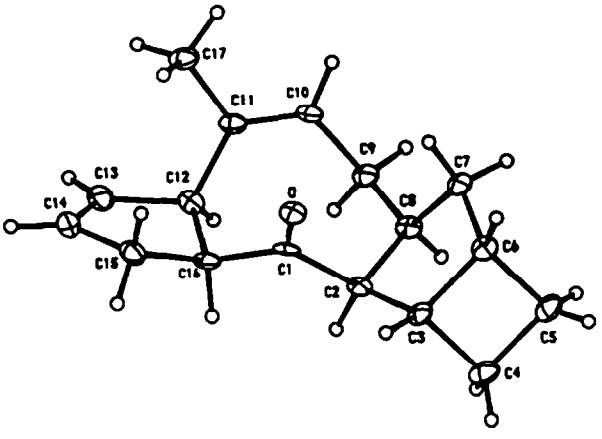
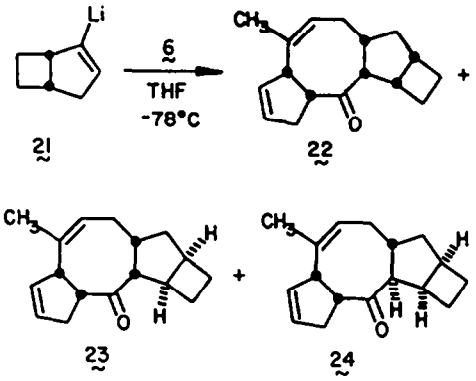


Figure 3. Three-dimensional structure of **23** as determined by X-ray analysis (courtesy of G. Williams and A. Syed, Enraf-Nonius Corporation, and J. C. Gallucci, The Ohio State University).

Our conclusion that **24** is derived from the same stereochemical series as minor diastereomer **23** rests on two points, one spectral and one mechanistic. The general features seen in the ^{1}H NMR spectrum of **24** most closely resemble those exhibited by **23**. Unfortunately, all attempts to induce epimerization in **23** either returned unchanged starting material or induced decomposition (more forcing conditions). From the mechanistic standpoint, kinetic protonation of **25**, the enolate

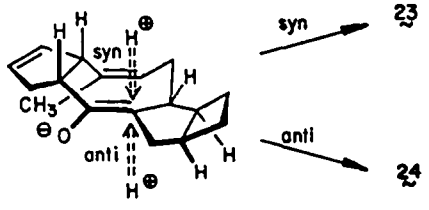
Table II. Crystallographic Data.

	11	20	23	32	33
formula	$C_{18}H_{26}O$	$C_{18}H_{26}O_2$	$C_{17}H_{22}O$	$C_{17}H_{22}O$	$C_{17}H_{22}O$
form wt, amu	258.41	274.40	242.36	242.36	242.36
space group	$P2_{1/C}$	$P2_12_12_1$(#19)	$P\bar{1}$	$P2_{1/C}$	$P\bar{1}$
a, Å	10.189(5)	8.429(0)	9.572(4)	10.180(2)	9.787(1)
b, Å	8.203(3)	16.908(1)	13.658(11)	14.222(2)	6.312(1)
c, Å	18.233(3)	10.802(1)	5.353(9)	10.111(1)	11.105(1)
α, deg			97.67(9)	90.000(0)	93.061(10)
β, deg	93.37(3)		96.31(11)	108.117(1)	79.069(10)
γ, deg			70.22(6)	90.000(0)	100.130(10)
vol, $Å^3$	1521	1539	651	1391	663
Z	4	4	2	4	2
ρ_c, g/cm^3	1.128	1.18	1.24	1.157	1.213
final R	0.043	0.047	0.056	0.070	0.058



21 22 23 24

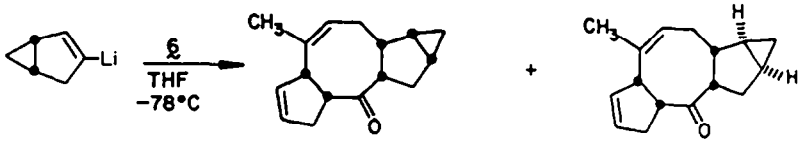
anion precursor to **23** can be seen to experience a reasonable level of steric impedance to syn protonation. Consequently, delivery of a proton from the anti direction becomes kinetically competitive. Our examination of Dreiding models revealed that the steric congestion just



25 **23** **24**

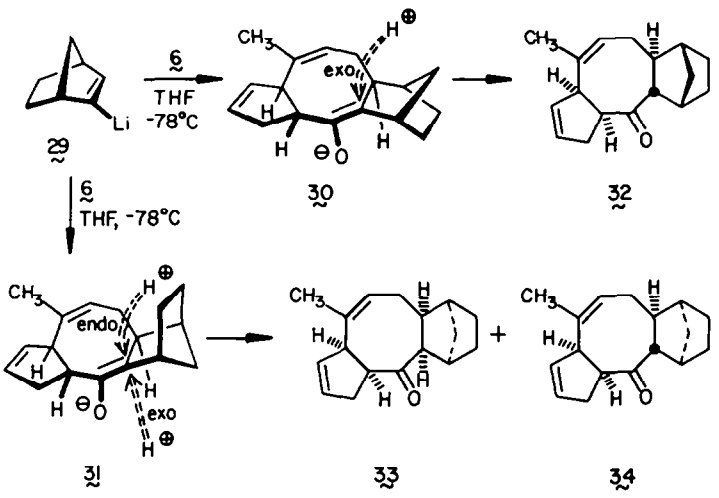
referred to is abated in the bicyclo[3.3.0]octyl and bicyclo[3.1.0]hexyl analogues of **25**. However, steric blockade is heightened when the eastern sector becomes norbornyl. This latter phenomenon is specifically addressed below. The diastereomer ratio **22**/(**23** plus **24**) was determined to be 1.35:1.

Where vinyllithium **26** was concerned, only **27** and **28** were isolated (94% combined yield) in a ratio of 1.36:1. The constancy in diastereoselectivity seen for **16**, **21**, and **26** is noteworthy.



26 **27** **28**

At this point, attention was given to 2-norbornenyllithium (**29**). Because the two surfaces of this nucleophilic reagent hold the greatest steric similarity of those presently investigated, a near-equitable distribution of tetracyclic ketonic products was anticipated. Once 1,2-addition and oxy-Cope rearrangement occur to provide enolate anion **30**, exo protonation to deliver the trans-fused product **32** should be overwhelmingly favored due to obvious steric accessibility. One consequence of this kinetic control is trans-locking of the eight-membered ring. On the other hand, the diastereomerically related enolate **31** is subject to different steric demands. The site immediately adjacent to the enolate carbon now projects the unwieldy substituent in the endo direction. Exo protonation delivers the all-cis product **33** where the endo surface of the norbornane ring engages in serious nonbonded interactions with the cyclooctenone ring. To the extent that the transition state for exo proton transfer reflects this steric congestion, endo protonation leading to **34** will compete.



In point of fact, condensation of **29** with **6** under the usual conditions followed by chromatography led to the isolation of **32** (35%), **33** (15%), and **34** (23%). Ketones **32** and **33** were immediately subjected to X-ray analysis (Table II) and their three-dimensional structures are displayed in Figures 4 and 5, respectively. The crystallinity of **34** proved less good and its epimeric relationship to **33** was deduced solely on the basis of ^{1}H NMR spectral comparisons (Table I). Accordingly, the diastereoselectivity observed during initial 1,2-addition to the carbonyl group in **6** is 1.09:1. As before, efforts to effect epimerization in the series **32-34** were unsuccessful owing to decomposition of these materials in the presence of standard acids and bases.

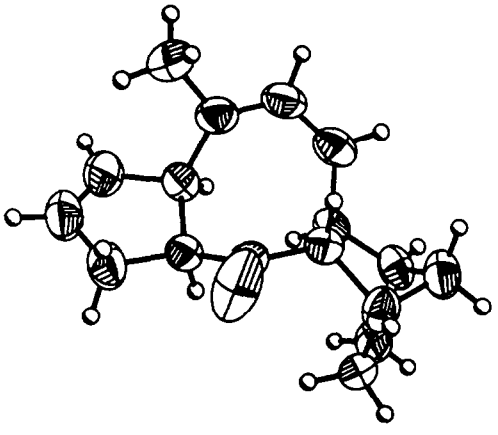
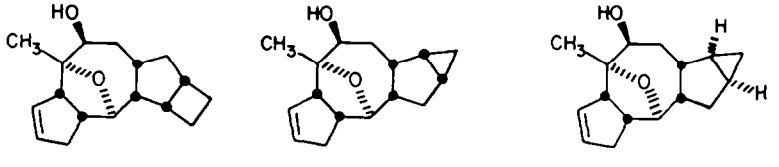


Figure 4. Three-dimensional structure of **32** as determined by X-ray analysis (courtesy of N. D. Jones, J. K. Swartzendruber, and J. B. Deeter, Eli Lilly Company).

The hydride reductions of **22**, **27**, and **28** proceed stereospecifically via attack from the β-face of the carbonyl group. Subsequent treatment of these α-alcohols with *m*-chloroperbenzoic acid



35 36 37

eventuated in the clean production of the pentacyclic tetrahydrofurans **35–37**. Thus, the diastereoselectivity realized in the initial 1,2-carbonyl addition can readily be parlayed into the controlled elaboration of numerous additional chiral centers.

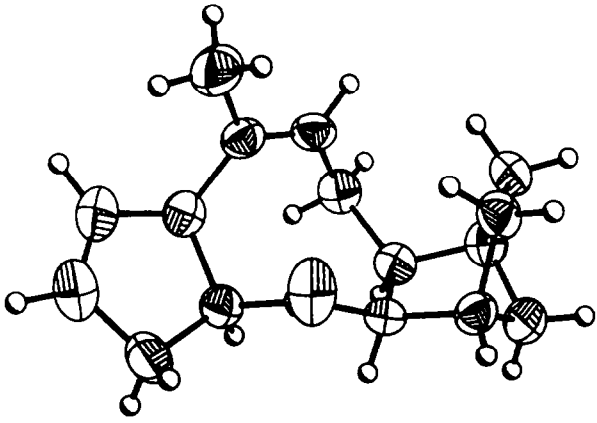
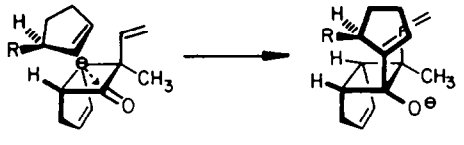


Figure 5. Structure of **33** showing its relative stereochemistry as determined by X-ray analysis (courtesy of N. D. Jones, J. K. Swartzendruber, and J. B. Deeter, Eli Lilly Company).

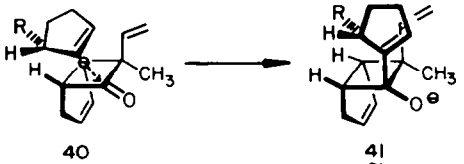
Discusssion

While it is not possible at present to calculate reaction trajectories in systems as complicated as those involving **6**,[13] existing approximations do allow a reasonable reaction profile to be developed.[14] Thus, it is generally assumed for reasons extensively detailed elsewhere[3,8,13,14] that nucleophilic attack on the π system of a carbonyl group customarily occurs from above or below and slightly to the rear of the carbon atom. The question is simplified where **6** is concerned since the concave surface of its carbonyl is sterically blockaded to an extent adequate to prevent nucleophilic capture from that direction. On this basis, the modest diastereoselectivity uncovered above very likely owes its origins to a substantive decrease in the level of nonbonded interactions generated between the enantiotopic faces of the approaching cyclopentenyllithium reagent and the convex surface of the ketone.

For bonding to **6** to occur with a minimal amount of <u>differential</u> steric encumbrance, the vinyl group must be oriented away from the area directly above the cyclobutanone surface. This state of affairs is reflected in transition state models **38** and **40**, where restraint on the rotational orientation of the cyclopentenyllithium reagent is not at all intended. What is clear from the data is that the lessened steric bias arising from the conformational mobility of the vinyl group (compare **3** where this is not possible) and the greater reactivity of cyclobutanones relative to 5-norbornen-2-ones combine to compromise the difference in energy between these diastereotopic



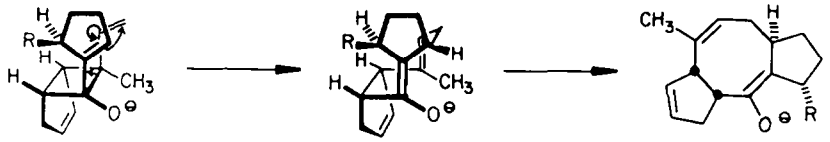
38 **39**



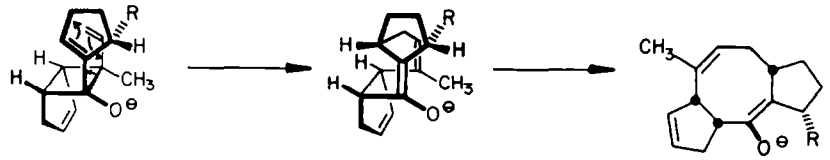
40 **41**

transition states, thus lowering the ratios of **39** to **41**. The bias unquestionably lies in favor of **39**, this evidence lending credence to the stacking model originally proposed.[6,7]

A second important consideration leads to insights into the transition state energetics of the ensuing anionic oxy-Cope rearrangement. Irrespective of the specific conformations that are adopted immediately following bonding to the carbonyl, some realignment of the relative spatial orientation of the π bonds needs to be implemented prior to expansion of the four-membered ring. The two plausible structural arrangements, both boat-shaped, are illustrated in **42** and **45**. Electronic reorganization via **42** is coerced to proceed via **43**, formally a trans,trans-1,5-cycloocta-



42 **43** **44**



45 **46** **47**

diene. This reaction course is certain to be more energy-demanding than the cis,cis option given by **46**. Its operation can be discounted since the relative stereochemistry of the three stereogenic centers that become fixed about the eight-membered ring (see **44**) does not conform to that established by X-ray crystallography. On the other hand, passage via cisoid **46** to **47** accords fully with the experimental observations.

It should be clear that some progress has been made in the design and application of doubly diastereoselective nucleophilic additions to β,γ-unsaturated ketones.[15] Although applications to kinetic resolutions[16] and to natural products synthesis[17] have been made, much remains to be accomplished. We hope to be in a position to report in more detail on this area of stereocontrol at a later date.

Experimental Section

Condensation Involving 5-Ethylcyclopentenyllithium. To a magnetically stirred solution of 1-bromo-5-ethylcyclopentene[7] (426 mg, 2.43 mmol) in 15 mL of dry tetrahydrofuran at -78°C under argon was added tert-butyllithium (4.86 mmol) during 5 min. The mixture was stirred at this temperature for 15 min, allowed to warm slightly for 5 min, and recooled to -78°C. Ketone **6** (237 mg, 1.60 mmol) in 6 mL of the same solvent was introduced during 5–10 min, stirred for 1 h, and treated while at -78°C with 1–2 mL of saturated sodium bicarbonate solution. The products were extracted into ether (3 × 35 mL) and the combined ethereal phases were washed with brine (35 mL), dried, and concentrated. Medium pressure liquid chromatography (MPLC) of the residue on silica gel (elution with 2% ethyl acetate in petroleum ether) gave 154 mg (40%) of pure **14** and 146 mg (37%) of pure **15** (ratio 1.06:1).

For **14**: white solid, mp 93–94°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1 H), 5.58 (m, 1 H), 5.40 (dd, *J* = 7, 9 Hz, 1 H), 4.18 (d, *J* = 9 Hz, 1 H), 3.67 (q, *J* = 9 Hz, 1 H), 3.09 (t, *J* = 6 Hz, 1 H), 2.78 (m, 2 H), 2.12 (m, 3 H), 1.89 (m, 1 H), 1.81 (m, 1 H), 1.65 (m, 3 H), 1.50 (s, 3 H), 1.28 (m, 2 H), 0.76 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.03, 139.60, 132.06, 130.51, 123.25, 61.70, 58.56, 47.92, 46.19, 43.13, 33.28, 30.43, 28.20, 27.04, 24.04, 23.48, 14.01; MS *m/z* (M^+) calcd 244.1827, obsd 244.1816.

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.01, H, 9.91.

For **15**: white solid, mp 49–50°C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.83 (m, 1 H), 5.58 (m, 1 H), 5.38 (m, 1 H), 4.20 (d, *J* = 10 Hz, 1 H), 3.78 (m, 1 H), 2.78 (m, 2 H), 2.59 (dd, *J* = 5, 9 Hz, 1 H),

2.43-2.21 (m, 3 H), 2.14 (m, 1 H), 1.93 (m, 1 H), 1.55 (m, 1 H), 1.55 (s, 3 H), 1.44 (m, 1 H), 1.25 (m, 2 H), 1.07 (m, 1 H), 0.82 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.00, 140.63, 131.46, 130.02, 122.34, 61.94, 57.69, 48.02, 43.53, 41.43, 35.56, 31.76, 30.79, 30.11, 28.69, 22.94, 12.93; MS m/z (M^+) calcd 244.1827, obsd 244.1827.

Condensation Involving cis-4-Methyl-5-ethylcyclopentenyllithium. The bromide (567 mg, 3.0 mmol) was converted in the predescribed manner with tert-butyllithium (6.0 mmol) into the lithium derivative. Condensation with **6** (296 mg, 2.0 mmol) in a total volume of 18 mL of dry tetrahydrofuran as before afforded after MPLC (silica gel, elution with 2% ethyl acetate in petroleum ether) 216 mg (42%) of **11** and 130 mg (25%) of **12** (ratio 1.65:1).

For **11**: white solid, mp 70-72°C; IR ($CDCl_3$, cm^{-1}) 1705; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1 H), 5.59 (m, 1 H), 5.34 (m, 1 H), 4.20 (d, J = 9 Hz, 1 H), 3.71 (q, J = 9 Hz, 1 H), 3.19 (t, J = 6 Hz, 1 H), 2.77 (m, 2 H), 2.21-2.00 (m, 5 H), 1.73 (m, 1 H), 1.50 (s, 3 H), 1.31 (m, 3 H), 1.03 (d, J = 7 Hz, 3 H), 0.70 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.17, 139.36, 131.72, 130.25, 122.99, 61.06, 59.43, 48.55, 45.98, 41.32, 37.95, 33.30, 28.04, 23.15, 19.50, 16.34, 14.03 (one signal not apparent); MS m/z (M^+) calcd 258.1984, obsd 258.1990.

The X-ray crystallographic analysis of **11** is described in the Supplementary Material.

For **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1 H), 5.64 (m, 1 H), 5.28 (m, 1 H), 4.14 (d, J = 10 Hz, 1 H), 3.82 (dq, J = 5, 11 Hz, 1 H), 2.90 (m, 1 H), 2.79 (m, 1 H), 2.69 (m, 1 H), 2.44 (m, 2 H), 2.38 (m, 1 H), 2.15 (m, 1 H), 2.07 (m, 1 H), 1.66 (m, 1 H), 1.59 (s, 3 H), 1.36 (m, 1 H), 1.17 (m, 2 H), 0.81 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.05, 141.83, 130.62, 129.80, 121.06, 60.10, 54.24, 49.73, 45.60, 39.54, 36.89, 36.77, 33.21, 29.22, 23.59, 22.54, 14.47, 12.90; MS m/z (M^+) calcd 258.1984, obsd 258.1981.

Condensation Involving cis-1-Bicyclo[3.3.0]oct-1-enyllithium. Reaction of the bromide (580 mg, 3.04 mmol) with tert-butyllithium (6.08 mmol) and subsequently **6** (296 mg, 2.0 mmol) in 18 mL of dry tetrahydrofuran in identical fashion left an oil, MPLC of which (silica gel, elution with 2% ethyl acetate in petroleum ether) furnished 264 mg (52%) of **17** and 185 mg (36%) of **18** (ratio 1.43:1).

For **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.58 (m, 1 H), 5.32 (m, 1 H), 4.15 (d, J = 9 Hz, 1 H), 3.64 (q, J = 9 Hz, 1 H), 3.15 (t, J = 7 Hz, 1 H), 2.79 (m, 1 H), 2.68 (m, 1 H), 2.58 (m, 1 H), 2.38 (m, 2 H), 2.19 (tq, J = 2, 9 Hz, 1 H), 2.08 (m, 1 H), 1.92 (m, 1 H), 1.65 (m, 2 H), 1.51 (s, 3 H), 1.58-1.28 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.71, 139.44, 131.49, 130.07, 122.77, 59.50, 58.95, 47.82, 47.15, 44.83, 44.47, 35.57, 33.76, 32.29, 29.30, 28.98, 26.70, 23.04; MS m/z (M^+) calcd 256.1827, obsd 256.1826.

For **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.52 (m, 1 H), 5.27 (m, 1 H), 4.16 (d, J = 10 Hz, 1 H), 3.65 (q, J = 9 Hz, 1 H), 2.83 (m, 1 H), 2.73 (m, 1 H), 2.65 (m, 1 H), 2.58-2.27 (m, 3 H), 2.19 (m, 1 H), 2.08 (m, 1 H), 1.82 (m, 2 H), 1.64 (m, 1 H), 1.53 (m, 1 H), 1.44 (s, 3 H), 1.25 (m, 1 H), 1.12 (dq, J = 2, 6 Hz, 1 H), 0.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.22, 139.55, 131.61, 130.05, 122.90, 63.72, 59.53, 47.12, 46.37, 42.03, 39.64, 36.17, 35.07, 34.44, 33.71, 27.99, 27.33, 22.78; MS m/z (M^+) calcd 256.1827, obsd 256.1827.

Reduction-Epoxidation of 17. To a cold (0°C), magnetically stirred slurry of lithium aluminum hydride (38 mg, 1.0 mmol) in 15 mL of anhydrous ether was added **17** (216 mg, 0.844 mmol) dissolved in 1 mL of ether. The reaction mixture was stirred for 1 h and the excess hydride was decomposed by the slow addition of water. The product was extracted into ether (3 x 35 mL) and the combined ethereal phases were washed with brine (35 mL), dried, and concentrated. MPLC on silica gel of the residue (elution with 10% ethyl acetate in petroleum ether) afforded 172 mg (80%) of the alcohol; ^{1}H NMR (300 MHz, C_6D_6) δ 5.60 (m, 1 H), 5.53 (m, 2 H), 3.90 (d, J = 12 Hz, 1 H), 3.66 (d, J = 9 Hz, 1 H), 2.89 (m, 1 H), 2.63 (m, 1H), 2.56-2.31 (m, 3 H), 2.29-2.14 (m, 3 H), 2.13-1.90 (m, 3 H), 1.64 (s, 3 H), 1.65-1.35 (m, 5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.18, 132.69, 132.21, 126.71, 74.08, 54.53, 50.04, 49.27, 49.15, 45.87, 44.39, 38.22, 37.29, 33.39, 30.19, 29.20, 27.60, 23.29.

To m-chloroperbenzoic acid (MCPBA, 139 mg of 82.5% purity, 0.664 mol) and sodium bicarbonate (101 mg, 1.2 mmol) in 3 mL of dry dichloromethane at 0°C was added dropwise during 2 min a solution of the α-alcohol (172 mg, 0.664 mol) in 1 mL of the same solvent. The reaction mixture was stirred at 0°C for 1 h, diluted with water, and extracted with dichloromethane (3 x 5 mL). The organic phases were combined, dried, and concentrated. The residue was purified by MPLC (silica gel, elution with 25% ethyl acetate in petroleum ether) to give **19** in 54% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1 H), 5.52 (m, 1 H), 3.96 (d, J = 3 Hz, 1 H), 3.73 (m, 1 H), 3.35 (m, 1 H), 2.67 (m, 2 H), 2.48 (m, 1 H), 2.38-2.16 (m, 4 H), 1.90 (m, 2 H), 1.81 (m, 1 H), 1.77-1.63 (m, 3 H), 1.57-1.37 (m, 4 H), 1.27 (s, 3 H), 1.25 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.63, 130.12, 91.07, 87.58, 74.89, 53.87, 50.04, 49.63, 49.06, 43.39, 42.65, 41.20, 38.79, 34.73, 30.97, 28.71, 28.14, 23.20; MS m/z (M^+) calcd 274.1933, obsd 274.1932.

Reduction-Epoxidation of 18. Analogous reduction of **18** (160 mg, 0.625 mmol) with lithium aluminum hydride (25 mg, 0.650 mmol) in anhydrous ether (15 mL) followed by standard workup and chromatography (SiO_2, 10% ethyl acetate in petroleum ether) furnished 128 mg (79%) of the α-alcohol; ^{1}H NMR (300 MHz, C_6D_6) δ 5.81 (m, 1 H), 5.51 (m, 1 H), 5.40 (m, 1 H), 3.85 (d, J = 12 Hz, 1 H), 3.69 (d, J = 9 Hz, 1 H), 2.88 (m, 1 H), 2.60 (m, 2 H), 2.45-2.21 (m, 4 H), 2.13 (m, 1 H), 2.00 (m, 1 H), 1.88-1.73 (m, 3 H), 1.63 (s, 3 H), 1.57 (m, 1 H), 1.48 (m, 1 H), 1.38 (m, 1 H), 1.28-1.11 (m, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 141.60, 132.96, 132.11, 126.64, 77.74, 57.58, 53.39, 50.09, 45.85, 42.07, 41.51, 40.29, 36.47, 35.38, 34.69, 29.96, 27.03, 24.24; MS m/z (M^+) calcd 258.1984, obsd 258.1987.

Exposure of the α-alcohol (128 mg, 0.495 mmol) to MCPBA (104 mg of 82.5%, 0.495 mmol) and sodium bicarbonate (84 mg, 1.0 mmol) in 4 mL of dry dichloromethane gave 69 mg (51%) of **20** as a white solid, mp 144-145°C, following chromatography (SiO_2, 25% ethyl acetate in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 1 H), 5.51 (m, 1 H), 3.92 (br s, 1 H), 3.79 (m, 1 H), 3.50 (m, 1 H), 2.67 (m, 2 H), 2.47-2.23 (m, 4 H), 1.98 (m, 1 H), 1.90 (m, 1 H), 1.77-1.58 (m, 4 H), 1.58-1.40 (m, 3 H), 1.33 (m, 2 H), 1.26 (s, 3 H), 1.20 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.40, 130.07, 91.89, 87.23, 75.69, 56.40, 53.49, 49.71, 49.38, 41.83, 41.62, 39.39, 36.08, 35.33, 33.46, 32.77, 25.63, 23.93; MS m/z (M^+) calcd 274.1933, obsd 274.1945.

The X-ray analysis sample of **20** was obtained by recrystallization from ether. The data, which are reported in the Supplementary Material, reveal the crystal to be enantiomerically homogeneous. The $[\alpha]_D^{20}$ of these crystals in CH_2Cl_2 was -2.53.

Condensation Involving cis-1-Bicyclo[3.2.0]heptenyllithium. Reaction of the bromide (519 mg, 3.0 mmol) with tert-butyllithium (6.0 mmol) and subsequently **6** (296 mg, 2.0 mmol) in 18 mL of dry tetrahydrofuran as previously described afforded after MPLC (silica gel, elution with 2% ethyl acetate in petroleum ether) a total of 388 mg (80%) of **22**, **23**, and **24** (order of elution).

For **22**: 223 mg (46%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.56 (m, 1 H), 5.34 (m, 1 H), 4.21 (d, J = 10 Hz, 1 H), 3.65 (q, J = 9 Hz, 1 H), 2.94-2.68 (m, 6 H), 2.27 (m, 1 H), 2.14 (m, 3 H), 1.63 (dt, J = 7, 15 Hz, 1 H), 1.47 (s, 3 H), 1.43 (m, 2 H), 1.25 (dd, J = 5, 12 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.29, 139.60, 131.53, 129.91, 122.76, 62.93, 60.28, 45.78, 42.34, 39.83, 37.84, 35.58, 33.59, 27.26, 24.47, 23.32, 22.78; MS m/z (M^+) calcd 242.1671, obsd 242.1670.

For **23**: 131 mg (34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.56 (m, 1 H), 5.41 (m, 1 H), 4.16 (d, J = 10 Hz, 1 H), 3.66 (q, J = 8 Hz, 1 H), 2.83 (m, 5 H), 2.62 (m, 1 H), 2.33-2.06 (m, 4 H), 1.93 (m, 2 H), 1.82-1.63 (m, 2 H), 1.51 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.65, 139.58, 131.33, 129.89, 122.79, 61.04, 55.18, 48.50, 42.59, 40.91, 40.02, 37.42, 33.60, 30.62, 25.93, 22.50, 21.88; MS m/z (M^+) calcd 242.1671, obsd 242.1669.

The X-ray crystallographic analysis of **23** is described in the Supplementary Material.

For **24**: 34 mg (9%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.55 (m, 1 H), 5.42 (m, 1 H), 4.28 (d, J = 10 Hz, 1 H), 3.80 (q, J = 9 Hz, 1 H), 3.47 (m, 1 H), 2.99 (m, 2 H), 2.85 (m, 2 H), 2.37 (m, 1 H), 2.28-2.12 (m, 2 H), 2.00 (m, 1 H), 1.94 (dd, J = 7, 13 Hz, 1 H), 1.85-1.58 (m, 3 H), 1.42 (s, 3 H), 1.28 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.29, 139.02, 131.29, 130.05, 124.57, 60.90, 57.94, 49.06, 43.24, 42.57, 39.05, 38.32, 31.93, 31.60, 24.84, 21.46, 19.95; MS m/z (M^+) calcd 242.1671, obsd 242.1669.

Condensation Involving cis-1-Bicyclo[3.1.0]hexenyllithium. Reaction of the bromide (477 mg, 3.0 mmol) with tert-butyllithium (6.0 mmol) and subsequently **6** (296 mg, 2.0 mmol) in 18 mL of dry tetrahydrofuran provided after MPLC (SiO_2, elution with 3% ethyl acetate in petroleum ether) a total of 427 mg (94%) of **27** and **28** in a ratio of 1.36:1.

For **27**: 231 mg (51%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 5.56 (m, 1 H), 5.29 (m, 1 H), 4.15 (d, J = 10 Hz, 1 H), 3.69 (m, 1 H), 2.93 (m, 1 H), 2.76 (m, 2 H), 2.21 (m, 2 H), 1.97 (m, 1 H), 1.83 (m, 2 H)), 1.48 (s, 3 H), 1.22 (m, 1 H), 1.07 (m, 1 H), 0.37 (m, 1 H), 0.10 (q, J = 5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.82, 139.45, 131.20, 129.67, 122.90, 54.16, 53.09, 49.32, 39.89, 33.76, 33.10, 28.61, 25.43, 22.57, 14.71, 8.10; MS m/z (M^+) calcd 228.1514, obsd 228.1517.

For **28**: 196 mg (43%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 5.52 (m, 1 H), 5.42 (m, 1 H), 4.12 (d, J = 11 Hz, 1 H), 3.77 (dq, J = 6, 11 Hz, 1 H), 2.89 (m, 3 H), 2.68 (m, 1 H), 2.32 (m, 2 H), 2.20 (d, J = 13 Hz, 1 H), 1.73 (m, 1 H), 1.51 (s, 3 H), 1.05 (m, 2 H), 0.39 (dd, J = 4, 10 Hz, 1 H), 0.17 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.81, 138.72, 130.53, 129.50, 123.52, 55.34, 53.55, 48.28, 41.61, 36.74, 30.29, 29.41, 22.23, 22.04, 14.07, 7.33; MS m/z (M^+) calcd 228.1514, obsd 228.1526.

Condensation Involving 2-Norbornenyllithium. Reaction of the bromide (199 mg, 1.15 mmol) with tert-butyllithium (2.45 mmol) and then **6** (148 mg, 1.0 mmol) in 14 mL of dry tetrahydrofuran furnished after MPLC (SiO_2, 1.75% ethyl acetate in petroleum ether) a total of 178 mg (74%) of **32**, **33**, and **34**.

For **32**: 85 mg (35%) of colorless solid, mp 99.5-100°C (from petroleum ether); IR (KBr, cm^{-1}) 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.53, (m, 1 H), 5.37 (d, J = 9 Hz, 1 H), 4.18 (d, J = 10 Hz, 1 H), 3.44 (dd, J = 7, 17 Hz, 1 H), 2.80 (m, 1 H), 2.75-2.62 (m, 2 H), 2.48 (m, 1 H), 2.36 (m, 1 H), 2.28 (dq, J = 2, 9 Hz, 1 H), 2.08 (d, J = 2 Hz, 1 H), 1.69 (m, 1 H), 1.54 (m, 1 H), 1.46 (s, 3 H), 1.44 (m, 1 H), 1.34 (d, J = 10 Hz, 1 H), 1.30-1.04 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.89, 138.56, 131.28, 130.55, 124.88, 61.07, 60.53, 48.89, 43.26, 42.60, 40.45, 36.60, 32.73, 32.42, 31.29, 24.45, 22.02; MS m/z (M^+) calcd 242.1671, obsd 242.1673.

The X-ray crystallographic analysis of **32** is detailed in the Supplementary Material.

For **33**: 37 mg (15%), colorless crystals; IR (neat, cm^{-1}) 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 5.60 (m, 1 H), 5.43 (t, J = 9 Hz, 1 H), 4.16 (d, J = 11 Hz, 1 H), 3.72 (ddd, J = 4, 10, 11 Hz, 1 H), 2.97-2.67 (m, 3 H), 2.48 (dd, J = 2, 12 Hz, 1 H), 2.38 (m, 2 H), 2.26 (br s, 1 H), 2.11 (dd, J = 7, 14 Hz, 1 H), 1.62 (m, 2 H), 1.58 (s, 3 H), 1.48-1.17 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.16, 141.36, 130.93, 129.41, 123.80, 59.51, 50.12, 49.15, 45.49, 39.13, 39.01, 38.93, 36.16, 28.88, 26.15, 22.28, 22.17; MS m/z (M^+) calcd 242.1671, obsd 242.1683.

The X-ray crystallographic analysis of **33** is detailed in the Supplementary Material.

For **34**: 56 mg (23%) of an oil; IR (neat, cm^{-1}) 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 5.65 (m, 1 H), 5.23 (dd, J = 6, 11 Hz, 1 H), 4.09 (d, J = 9 Hz, 1 H), 3.75 (dt J = 3, 9 Hz, 1 H), 2.83 (m, 1 H), 2.74 (m, 2 H), 2.43 (m, 1 H), 2.35 (dd, J = 2, 10 Hz, 1 H), 2.22 (m, 2 H), 2.04 (br s, 1 H), 1.59 (s, 3 H), 1.46 (m, 2 H), 1.38-1.20 (m, 2 H), 1.10-0.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.60, 140.81, 130.60, 129.57, 122.24, 62.07, 51.22, 50.20, 44.55, 43.76, 37.83, 37.14, 36.32, 31.69, 31.60, 27.07, 22.23; MS m/z (M^+) calcd 242.1671, obsd 242.1656.

Reduction-Epoxidation of 22. Treatment of 191 mg (0.748 mmol) of **22** sequentially with $LiAlH_4$ and MCPBA in an identical manner to that described above furnished 152 mg (85%) of colorless crystalline **35**; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1 H), 5.51 (m, 1 H), 3.83 (m, 2 H), 3.41 (m, 1 H), 3.18 (br s, 1 H), 2.86 (m, 2 H), 2.72 (m, 2 H), 2.60 (m, 1 H), 2.28 (m, 2 H), 2.12-1.93 (m, 4 H), 1.86 (d, J = 8 Hz, 1 H), 1.44 (m, 2 H), 1.35 (dd, J = 6, 12 Hz, 1 H), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.46, 129.89, 95.26, 88.11, 74.49, 58.20, 53.21, 50.74, 48.03, 42.50, 38.41, 37.54, 37.51, 33.66, 25.61, 23.91, 23.20; MS m/z (M^+) calcd 260.1776, obsd 260.1790.

Reduction-Epoxidation of 27. Treatment of 212 mg (0.926 mmol) of **27** sequentially with $LiAlH_4$ and MCPBA exactly as described earlier produced 122 mg (74%) of colorless crystalline **36**; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1 H), 5.57 (m, 1 H), 3.90 (br s, 3 H), 3.66 (m, 1 H), 2.62 (m, 2 H), 2.29 (m, 2 H), 2.00 (m, 1 H), 1.93 (m, 1 H), 1.58 (m, 3 H), 1.25 (s, 3 H), 1.17 (m, 1 H), 0.88 (m, 1 H), 0.31 (m, 1 H), 0.16 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.70, 130.49, 87.97, 86.87, 77.84, 54.26, 48.90, 43.71, 40.72, 37.82, 34.49, 30.42, 25.21, 24.17, 14.54, 7.94; MS m/z (M^+) calcd 246.1620, obsd 246.1627.

Reduction-Epoxidation of 28. Treatment of 173 mg (0.759 mmol) of **28** sequentially with $LiAlH_4$ and MCPBA as described above produced 122 mg (90%) of colorless crystalline **37**; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1 H), 5.50 (m, 1 H), 4.11 (dd, J = 4, 11 Hz, 1 H), 3.72 (br s, 1 H), 3.03 (m, 1 H), 2.85 (m, 1 H), 2.64 (m, 2 H), 2.31 (m, 4 H), 2.08-1.87 (m, 2 H), 1.65 (d, J = 12 Hz, 1 H), 1.30 (s, 3 H), 1.16 (m, 2 H), 1.02 (m, 1 H), 0.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.61, 129.77, 93.88, 87.36, 74.40, 53.81, 49.31, 47.76, 42.56, 39.37, 37.71, 35.87, 24.04, 22.80, 14.71, 10.65; MS m/z (M^+) calcd 246.1620, obsd 246.1627.

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