Diastereoselective Manipulations of Bicyclo[*m*.1.0]alkane Derivatives. 6. Stereocontrolled Synthesis of Tricyclo[*m*.*n*.0.0]alkenones

Eugene A. Mash* and James A. Baron

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721-0041

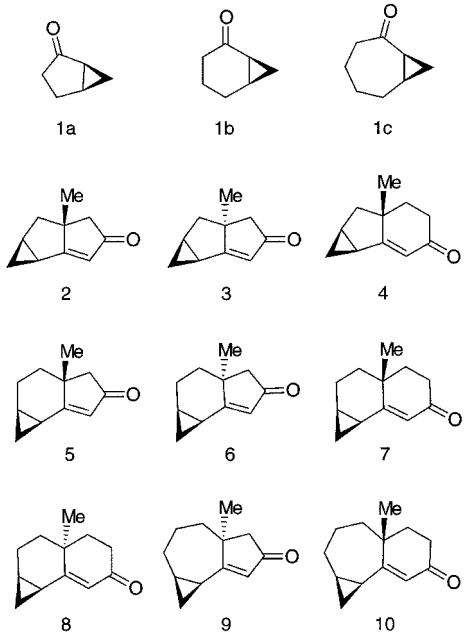
Received April 29, 1999

Enolates derived from bicyclo[*m*.1.0]alkan-2-ones possessing 5-, 6-, and 7-membered rings were sequentially alkylated with iodomethane and with precursors to 2-oxopropyl or 3-oxobutyl substituents. High diastereoselectivities were observed. Product yields for more active electrophiles were generally good to very good and were fair for less active electrophiles. Following unmasking of the 2-oxopropyl or 3-oxobutyl substituents, ring closure and dehydration under basic conditions provided the corresponding tricyclic γ,δ-cyclopropyl-α,β-enones. Reversal of the order of alkylation switched the configuration of the angular methyl substituent relative to the stereogenic cyclopropane in the tricyclo[*m*.*n*.0.0]alkenone product.

Introduction

Development of reactions for the stereocontrolled synthesis of fused carbocyclic rings is important since many natural products contain such structures. The Robinson annulation and related reactions of 1,4- and 1,5-diones have been especially useful in synthesis.[1] Variants of these reactions that afford absolute stereocontrol have been described.[2] Recently, we demonstrated that sequential alkylations of enolates derived from bicyclo[*m*.1.0]-alkan-2-ones **1a**−**c** with different electrophiles afforded 3,3-dialkylbicyclo[*m*.1.0]alkan-2-ones in a stereocontrolled manner.[3] Stereocontrol was attributed to steric impedance to approach of the electrophile due to the cyclopropane methylene. Stereochemistry at C-3 was determined by the stereochemistry of the bridgehead atoms and the order in which the electrophiles were employed. These results suggested the use of this chemistry to build fused ring systems by employing electrophiles that, when unmasked, would cyclize onto the carbonyl of the bicyclo[*m*.1.0]alkan-2-one. Herein, we demonstrate the utility of this process by preparation of tricyclic γ,δ-cyclopropyl-α,β-enones **2**−**10**.

Sequential α′-Alkylations of Bicyclo[*m*.1.0]alkan-2-ones 1a−c. Results of sequential α′-alkylations of ketones **1a**−**c** are given in Table 1.[4] Deprotonation of **1a** with LDA and addition of iodomethane produced bicyclic ketone **11** in an unoptimized 27% yield. This low yield can in part be attributed to the volatility of this product. Formation of dimers by aldol condensation may also have been a factor.[5] Alkylation of **1a** with 2-methyl-3-bromopropene gave **12** in 58% yield. Both alkylations gave



products with >20:1 diastereoselection.[6] Stereochemistry was assigned in accord with our previous observations and assignments.[3]

Deprotonation of **1b** with LDA and alkylation with iodomethane and with 2-methyl-3-bromopropene gave **13** in 68% yield and **14** in 90% yield, respectively. Use of 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate[7] as the electrophile gave **15** in unsatisfactory yields when LDA was used as the base since elimination to give isoprene was the predominant reaction. Modest, but better, yields of **15** were obtained when NaH was employed as the base

(1) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3−31. (b) Gawley, R. E. *Synthesis* **1976**, 777−794.

(2) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (c) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238−2244. (d) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273−274. (e) Nerinckx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265−276.

(3) Mash, E. A.; Baron, J. A.; Gregg, T. M.; Nimkar, S. K. *Tetrahedron* **1998**, *54*, 2669−2682.

(4) Ketones **1a**−**c** employed in this study were racemic and were prepared by published procedures; see: Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3449−3452.

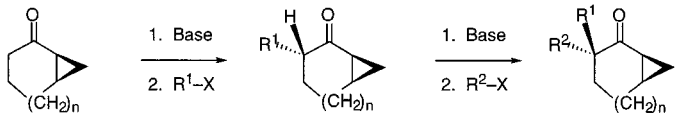
(5) This process has previously been observed during attempted methylation of the enolate derived from 3-(phenyl)methylbicyclo[3.1.0]-hexan-2-one; see ref 3, footnote 13.

(6) Diastereomer ratios were determined by integration of signals in the ^{13}C NMR; limit of detection ca. 20:1. For previous use of ^{13}C NMR in determining diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183−2186.

(7) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152−7157.

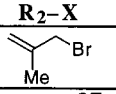
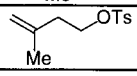
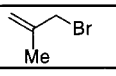
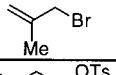
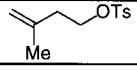
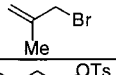
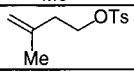
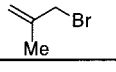
10.1021/jo990720s CCC: $18.00
Published on Web 09/10/1999

Table 1. Sequential Alkylations of Bicyclo[*m*.1.0]alkan-2-ones 1a−c



1a n = 0
1b n = 1
1c n = 2

11-16 **17-24**

	First Alkylation					Second Alkylation				
Ketone	**Base**	**R_1–X**	**Product**	**Yield, %**	**DR[a]**	**Base**	**R_2–X**	**Product**	**Yield, %**	**DR[a]**
1a	LDA	MeI	**11**	27	>20:1	NaH		**17**	56	>20:1
						NaH		**18**	38	>20:1
1a	LDA		**12**	58	>20:1	NaH	MeI	**19**	70	>20:1
1b	LDA	MeI	**13**[b]	68	10:1	NaH		**20**	78	>20:1
						NaH		**21**	75	>20:1
1b	LDA		**14**	90	4:1	NaH	MeI	**22**	88	>20:1
1b	NaH		**15**	34	2:1	NaH	MeI	**23**	93	>20:1
1c	LDA		**16**	61	>20:1	LDA	MeI	**24**	35	>20:1

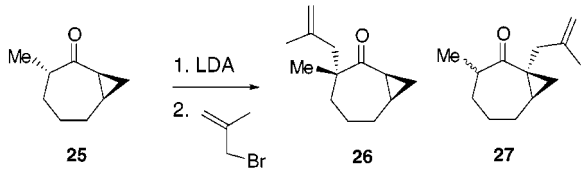
[a] Diastereomer ratio determined by ^{13}C NMR analysis. [b] Preparation of this ketone was previously reported (see ref 5).

in refluxing THF. Mixtures of diastereomers were obtained for these alkylations. This fact was previously attributed to the ease of epimerization of the stereogenic center at C-3 in this ring system.[3]

Deprotonation of **1c** with LDA and alkylation with 2-methyl-3-bromopropene produced **16** in 61% yield. Here again, diastereoselectivity was high (>20:1), and stereochemistry was assigned in accord with previous work.[3] Deprotonation of **1c** with LDA and alkylation with iodomethane was previously reported.[3]

For alkylations of ketones **11**−**15**, the use of NaH in refluxing THF gave superior product yields. Alkylation of **11** with 2-methyl-3-bromopropene and with 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate gave **17** in 56% yield and **18** in 38% yield, respectively. Alkylation of **12** with iodomethane gave **19** in 70% yield. Alkylation of **13** with 2-methyl-3-bromopropene and with 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate gave **20** in 78% yield and **21** in 75% yield, respectively. Alkylation of **14** and **15** with iodomethane gave **22** in 88% yield and **23** in 93% yield, respectively. In all cases, the observed diastereoselectivity was high (>20:1) and stereochemistry was assigned to the products in accord with previous work.[3]

Attempted alkylations of ketones **16** and **25**[3] using NaH as the base in refluxing THF were unsatisfactory since substantial cyclopropane ring fragmentation occurred. Alkylation of **16** using LDA as the base and iodomethane as the electrophile gave **24** in 35% yield with high diastereoselectivity. However, attempted alkylation of **25** with 2-methyl-3-bromopropene under similar conditions produced variable mixtures of **26** and **27**. Although the inherent acidity of the proton at C-1 should be greater than that of the proton at C-3 due to hybridization of the C-1 cyclopropane carbon, there had been no indication that alkylation at C-1 could occur for the bicyclo[5.1.0]octan-2-one system in any of our previous work.[8] It had been assumed that strain associated with the formation of a delocalized enolate involving an endomethylene cyclopropane was prohibitive.[9] However, at least one example of a bicyclo[5.1.0]oct-1-ene is known.[10]



25 **26** **27**

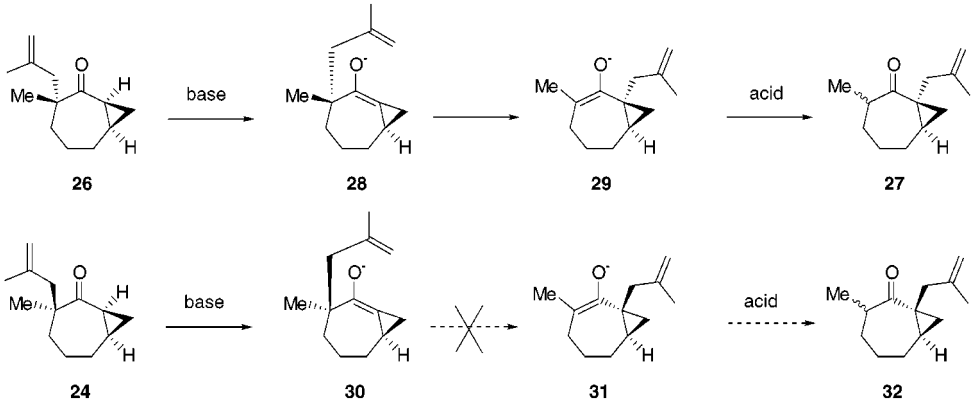
We then surmised that following the expected alkylation at C-3, deprotonation of **26** by the enolate of **25** could have reversibly generated the bridgehead enolate **28**. This enolate is well set up to undergo an oxy-Cope rearrangement[11] to produce **27** via enolate **29**. In keeping with this mechanistic proposal are the following observations: (1) considerable staring material was invariably recovered from this reaction; (2) no similar product was observed during synthesis of **24** from **16** since rearrangement of enolate **30** would lead to a highly strained transfused bicyclic enolate **31**; and (3) NMR spectra for **27** show evidence for a mixture of epimers at C-3 (Scheme 1).

Attempted alkylation of **25** with 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate gave only isoprene. How-

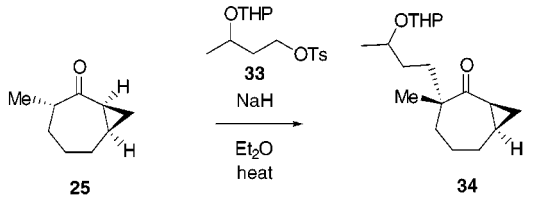
(8) However, alkylation at C-1 during attempted methylation of 3-(phenyl)methylbicyclo[6.1.0]nonan-2-one has been noted; see ref 3, footnote 14.

(9) Bredt, J. *Liebigs Ann. Chem.* **1924**, *437*, 1−13.
(10) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 464−473.
(11) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609−626.

Scheme 1



ever, alkylation of **25** with 3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butanol 4-methylbenzenesulfonate (**33**) using NaH as the base gave ketone **34** in an unoptimized yield of 35%. Thus, an alternative to the troublesome 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate was demonstrated.



Unmasking of the 2-Oxopropyl and 3-Oxobutyl Substituents and Cyclization. Cleavage of the 2-methyl-2-propenyl and 3-methyl-3-butenyl appendages to give the necessary 2-oxopropyl and 3-oxobutyl substituents was best effected using ruthenium tetroxide and sodium periodate.[12] Reaction times were short, and yields of diketones **35**−**43** were good to excellent (Table 2). Treatment of THP ether **34** (last entry in Table 2) with *p*-toluenesulfonic acid in aqueous methanol removed the protecting group, and oxidation of the resulting alcohol with pyridinium dichromate in dichloromethane afforded dione **44** in 70% yield.

Cyclizations of diones **38**−**44** were effected by treatment with KOH in ethanol at reflux. Yields of the product tricyclo[*m*.*n*.0.0]alkenones **5**−**10** and **45** were good to excellent (Table 2). Attempted cyclizations of diones **35**−**37** under these conditions resulted in mixtures of products. Analysis by NMR indicated that substantial cyclopropane ring fragmentation had occurred. However, cyclizations of **35**−**37** to tricyclo[*m*.*n*.0.0]alkenones **2**−**4** were achieved in high yields without side reactions by using sodium *tert*-butoxide in *tert*-butyl alcohol at room temperature.

Conclusion

Bicyclo[*m*.1.0]alkan-2-ones **1a**−**c** and related compounds are available in either enantiomeric form via diastereoselective cyclopropanation of certain 2-cycloalken-1-one ketals.[13] We have undertaken studies of the conformations[14] and reactivities[15] of these ketones in anticipation of their expanded use as intermediates in natural product synthesis.[16] Following our demonstration that quaternary stereogenic centers could be established with absolute stereocontrol at C-3 by sequential α′-deprotonations of bicyclo[*m*.1.0]alkan-2-ones and alkylations with different electrophiles,[3] we recognized the potential of this process for stereocontrolled construction of fused carbocyclic rings. We have demonstrated the versatility of this synthesis by preparation of tricyclic γ,δ-cyclopropyl-α,β-enones **2**−**10**, which should serve as useful templates for stereocontrolled syntheses of a variety of natural products.

Experimental Section

All reactions were performed in flame-dried glassware under argon. Reaction mixtures were stirred magnetically. Hygroscopic liquids were transferred via syringe or cannula. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from CaH_2. Diisopropylamine was distilled from and stored over CaH_2. Ketones **1a**−**c** were racemic and were prepared by literature procedures.[4] Analytical thin-layer chromatography was performed on Merck glass-backed precoated plates (0.25 mm, silica gel 60, F-254). Visualization of spots was effected by treatment of the plate with a 2.5% solution of anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid followed by charring on a hot plate. Flash column chromatography was performed on Merck silica gel 60 (230−400 mesh). Gravity-driven column chromatography was performed on Merck silica gel 60 (70−230 mesh). Solutions were concentrated using a rotary evaporator at 30−150 mmHg. NMR spectra were recorded in $CDCl_3$ solution unless otherwise noted. Proton NMR spectra were recorded at 200 or 250 MHz using tetramethylsilane (0 ppm) as an internal standard. Carbon-13 NMR spectra were recorded at 50.3 or 62.9 MHz using the center line of the $CDCl_3$ triplet (77.0 ppm) as an internal standard. Diastereomer ratios were determined by ^1H and ^{13}C NMR analyses or by isolation. Unless otherwise indicated, all of the major product diastereomers were judged to be greater than 95% pure on the basis of ^1H and ^{13}C NMR analysis. High-resolution mass spectral

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; and Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

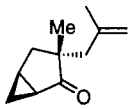
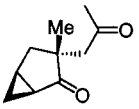
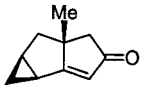
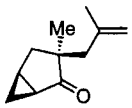
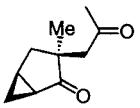
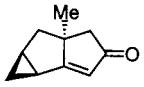
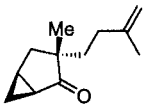
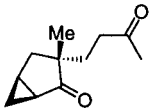
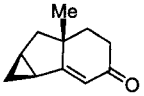
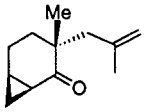
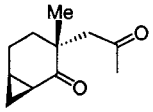
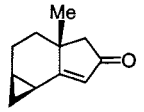
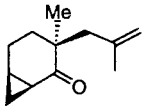
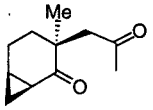
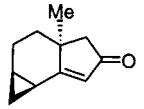
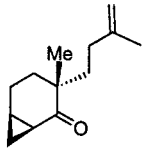
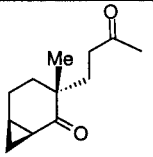
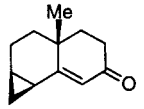
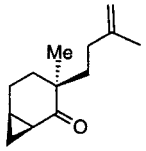
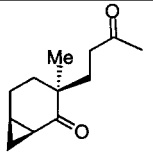
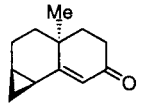
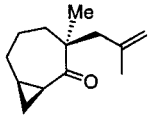
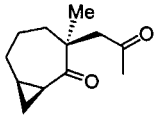
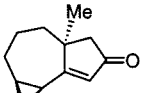
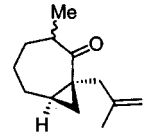
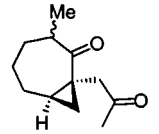
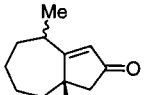
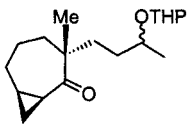
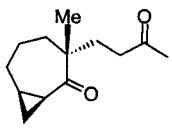
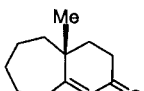
(13) (a) Mash, E. A.; Math, S. K.; Arterburn, J. B. *J. Org. Chem.* **1989**, *54*, 4951−4953. (b) Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250−253. (c) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679−692. (d) Yeh, S.-M.; Huang, L.-H.; Luh, T.-Y. *J. Org. Chem.* **1996**, *61*, 3906−3908.

(14) (a) Mash, E. A.; Gregg, T. M.; Stahl, M. T.; Walters, W. P. *J. Org. Chem.* **1996**, *61*, 2738−2742. (b) Mash, E. A.; Gregg, T. M.; Stahl, M. T. *J. Org. Chem.* **1997**, *62*, 3715−3721.

(15) (a) Mash, E. A.; Gregg, T. M.; Kaczynski, M. A. *J. Org. Chem.* **1996**, *61*, 2743−2752. (b) Mash, E. A.; Gregg, T. M.; Baron, J. A. *J. Org. Chem.* **1997**, *62*, 8513−8521. (c) Mash, E. A.; Nimkar, K. S.; Baron, J. A. *Tetrahedron* **1997**, *53*, 9043−9056.

(16) (a) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721−2724. (b) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1987**, *52*, 3000−3003. (c) Mash, E. A. *J. Org. Chem.* **1987**, *52*, 4142−4143. (d) Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron* **1989**, *45*, 4945−4950. (e) Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic M. R. *J. Org. Chem.* **1996**, *61*, 118−124. (f) Cossy, J.; BouzBouz, S. *Tetrahedron Lett.* **1996**, *37*, 5091−5094.

Table 2. Unmasking of the 2-Oxopropyl and 3-Oxobutyl Substituents and Cyclization To Give Tricyclo[*m.n*.0.0]alkenones 2−10 and 45

Alkene Cleavage[a]			Cyclization		
Starting Alkene	Dione Product	Yield, %	Conditions	Tricyclic Product	Yield, %
 **17**	 **35**	66	*t*–BuONa *t*–BuOH rt	 **2**	88
 **19**	 **36**	90	*t*–BuONa *t*–BuOH rt	 **3**	81
 **18**	 **37**	88	*t*–BuONa *t*–BuOH rt	 **4**	95
 **20**	 **38**	88	KOH EtOH reflux	 **5**	77
 **22**	 **39**	89	KOH EtOH reflux	 **6**	88
 **21**	 **40**	92	KOH EtOH reflux	 **7**	83
 **23**	 **41**	93	KOH EtOH reflux	 **8**	85
 **24**	 **42**	76	KOH EtOH reflux	 **9**	75
 **27**	 **43**	60	KOH EtOH reflux	 **45**	73
 **34**	 **44**	70[b]	KOH EtOH reflux	 **10**	87

[a] Reagents and conditions: $RuCl_3$ (cat.), $NaIO_4$, CCl_4, CH_3CN, H_2O, room temperature, 10−30 min. [b] Reagents and conditions: (a) TsOH, aqueous MeOH; (b) PDC, CH_2Cl_2.

analyses were obtained by the Mass Spectrometry Facility in the Department of Chemistry at the University of Arizona. Elemental analyses were carried out by Desert Analytics, Tucson, AZ.

(1*S,3*S**,5*R**)-3-Methylbicyclo[3.1.0]hexan-2-one (11).** To a solution of diisopropylamine (765 mg, 5.92 mmol) in THF at 0 °C under argon was added butyllithium (3.42 mL of a 1.6 M solution, 5.5 mmol) via syringe. This solution was stirred for 15 min and then cooled to −78 °C, and a solution of **1a**[4] (438 mg, 4.56 mmol) in THF (3 mL) was added via cannula. The cannula was rinsed with THF (1 × 3 mL). After 15 min, iodomethane (3.23 g, 22.8 mmol) was added slowly via syringe. The reaction was capped and stored at −22 °C for 18 h. The mixture was quenched by addition of saturated NH_4Cl solution (8 mL) and water (20 mL). The mixture was extracted with CH_2Cl_2 (4 × 30 mL), the organic extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a yellow oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (250 mL) eluted with 10% EtOAc/hexanes to give 136 mg (1.23 mmol, 27%) of **11** as a clear, colorless oil, R_f 0.39 (40% EtOAc/hexanes).

(1*S,3*R**,5*R**)-*3*-(2-Methyl-2-propenyl)bicyclo[3.1.0]-hexan-2-one (12).** By a similar method, deprotonation of 303 mg (3.15 mmol) of **1a** with LDA (1.7 equiv) and alkylation with 3-bromo-2-methylpropene (2.24 g, 15.8 mmol) over 4.5 h at −22 °C gave 275 mg (1.83 mmol, 58%) of **12** as a clear, colorless oil, R_f 0.45 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-*3*-(2-Methyl-2-propenyl)bicyclo[4.1.0]-heptan-2-one (14a) and (1*S**,3*S**,6*R**)-*3*-(2-Methyl-2-propenyl)bicyclo[4.1.0]heptan-2-one (14b).** By a similar method, deprotonation of 500 mg (4.54 mmol) of **1b**[4] with LDA (1.2 equiv) and alkylation with 3-bromo-2-methylpropene (3.06 g, 22.7 mmol) over 4.5 h at −22 °C gave 675 mg (4.11 mmol, 90%) of a chromatographically inseparable 4:1 mixture of **14a** and **14b**, R_f 0.49 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-*3*-(3-Methyl-3-butenyl)bicyclo[4.1.0]-heptan-2-one (15a) and (1*S**,3*S**,6*R**)-*3*-(3-Methyl-3-butenyl)bicyclo[4.1.0]heptan-2-one (15b).** A solution of **1b** (1.00 g, 9.08 mmol), 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate[7] (2.62 g, 10.9 mmol), and NaH (653 mg, 27.2 mmol) in THF (30 mL) was heated at reflux for 5 h and then cooled to room temperature. Water (50 mL) was cautiously added, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a clear, colorless oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (400 mL) eluted with 5 → 10% EtOAc/hexanes to afford 543 mg (3.05 mmol, 34%) of a chromatographically inseparable 2.4:1 mixture of **15a** and **15b**, R_f 0.60 (40% EtOAc/hexanes).

(1*S,3*R**,7*R**)-3-(2-Methyl-2-propenyl)bicyclo[5.1.0]-octan-2-one (16).** By a method similar to that described for the preparation of **11**, deprotonation of 200 mg (1.61 mmol) of **1c**[4] with LDA (1.1 equiv) and alkylation with 3-bromo-2-methylpropene (652 mg, 4.83 mmol) over 17 h at −22 °C gave 175 mg (0.98 mmol, 61%) of **16** as a clear, colorless oil, R_f 0.63 (40% EtOAc/hexanes).

(1*S,3*S**,5*R**)-3-(2-Methyl-2-propenyl)-3-methylbicyclo-[3.1.0]hexan-2-one (17).** A solution of **11** (140 mg, 1.46 mmol), 3-bromo-2-methylpropene (591 mg, 4.38 mmol), and NaH (105 mg, 4.38 mmol) in THF (8 mL) was heated at reflux for 10 h and then cooled to room temperature. Water (2 mL) was cautiously added, and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a yellow oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (200 mL) eluted with 10% EtOAc/hexanes to afford 133 mg (0.81 mmol, 56%) of **17** as a clear, colorless oil, R_f 0.57 (40% EtOAc/hexanes).

(1*S,3*R**,5*R**)-3-(3-Methyl-3-butenyl)-3-methylbicyclo-[3.1.0]hexan-2-one (18).** A solution of **11** (300 mg, 2.72 mmol), 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate (1.31 g, 5.44 mmol), and NaH (195 mg, 8.16 mmol) in THF (10 mL) was heated at reflux for 4 h. Over this time, additional 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate (1.31 g, 5.44 mmol) and NaH (195 mg, 8.16 mmol) were added. The mixture was cooled to room temperature, water (10 mL) was cautiously added, and the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a yellow oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (200 mL) eluted with 5% EtOAc/hexanes to give 182 mg (1.02 mmol, 38%) of **18** as a clear, colorless oil, R_f 0.60 (40% EtOAc/hexanes).

(1*S,3*S**,5*R**)-3-(2-Methyl-2-propenyl)-3-methylbicyclo-[3.1.0]hexan-2-one (19).** By a method similar to that described for the preparation of **17**, deprotonation of 232 mg (1.54 mmol) of **12** with NaH (3 equiv) and alkylation with iodomethane (657 mg, 4.63 mmol) over 2 h gave 177 mg (1.07 mmol, 70%) of **19** as a clear, colorless oil, R_f 0.24 (10% EtOAc/hexanes).

(1*S,3*S**,6*R**)-3-(2-Methyl-2-propenyl)-3-methylbicyclo-[4.1.0]heptan-2-one (20).** By a method similar to that described for the preparation of **11**, deprotonation of 350 mg (2.82 mmol) of **13**[3] with LDA (1.3 equiv) and alkylation with 3-bromo-2-methylpropene (1.90 g, 14.1 mmol) over 2 d at −22 °C gave 391 mg (2.19 mmol, 78%) of **20** as a clear, colorless oil, R_f 0.51 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-3-(3-Methyl-3-butenyl)-3-methylbicyclo-[4.1.0]heptan-2-one (21).** By a method similar to that described for the preparation of **17**, deprotonation of 500 mg (4.03 mmol) of **13** with NaH (3 equiv) and alkylation with 3-methyl-3-buten-1-ol 4-methylbenzenesulfonate (1.36 g, 5.64 mmol) over 6 h gave 578 mg (3.00 mmol, 75%) of **21** as a clear, colorless oil, R_f 0.62 (40% EtOAc/hexanes).

(1*S,3*S**,6*R**)-3-(2-Methyl-2-propenyl)-3-methylbicyclo-[4.1.0]heptan-2-one (22).** By a method similar to that described for the preparation of **17**, deprotonation of 1.50 g (9.13 mmol) of **14** with NaH (3 equiv) and alkylation with iodomethane (6.48 g, 45.7 mmol) over 3.5 h gave 1.43 g (8.0 mmol, 88%) of **22** as a clear, colorless oil, R_f 0.52 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-*3*-(3-Methyl-3-butenyl)-3-methylbicyclo-[4.1.0]heptan-2-one (23).** By a method similar to that described for the preparation of **17**, deprotonation of 380 mg (2.13 mmol) of **15** with NaH (3.75 equiv) and alkylation with iodomethane (1.13 g, 7.98 mmol) over 35 min gave 381 mg (1.98 mmol, 93%) of **23** as a clear, colorless oil, R_f 0.62 (40% EtOAc/hexanes).

(1*S,3*S**,7*R**)-3-(2-Methyl-2-propenyl)-3-methylbicyclo-[5.1.0]octan-2-one (24).** By a method similar to that described for the preparation of **11**, deprotonation of 290 mg (1.63 mmol) of **16** with LDA (3 equiv) and alkylation with iodomethane (712 mg, 5.1 mmol) over 3 d at −22 °C gave 110 mg (0.57 mmol, 35%) of **24** as a clear, colorless oil, R_f 0.60 (40% EtOAc/hexanes).

(1*S,3*S**,7*R**)-1-(2-Methyl-2-propenyl)-3-methylbicyclo-[5.1.0]octan-2-one (27).** To a solution of diisopropylamine (336 mg, 2.60 mmol) in THF at 0 °C under argon was added butyllithium (1.6 mL of a 1.6 M solution, 2.4 mmol) via syringe. This solution was stirred for 15 min and then was cooled to −78 °C. A solution of **25**[3] (300 mg, 2.17 mmol) in THF (3 mL) was added via cannula, and the cannula was rinsed with THF (1 × 3 mL). After 30 min, 3-bromo-2-methylpropene (879 mg, 6.51 mmol) was added slowly via syringe. The reaction was capped and stored at −22 °C for 48 h. The mixture was quenched by addition of saturated NH_4Cl solution (8 mL) and water (15 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The extracts were dried ($MgSO_4$) and filtered, and volatiles were removed under vacuum to give a yellow oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (200 mL) eluted with 5% EtOAc/hexanes to give 192 mg (0.99 mmol, 46%) of **27** as a clear, colorless oil, R_f 0.68 (40% EtOAc/hexanes). Additionally, 114 mg (0.82 mmol, 38%) of **25** was recovered.

3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-1-butanol 4-Methylbenzenesulfonate (33).[17] A stirred solution of 1,3-butanediol (6.92 g, 76.8 mmol) in pyridine (16.5 mL) was cooled to 0 °C, and *p*-toluenesulfonyl chloride (7.33 g, 38.4 mmol) was added in one portion. After 2 d at 0 °C, the reaction mixture was poured into water (50 mL) and extracted with ether (4 × 100 mL). The extracts were combined, washed with 10% aqueous HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and filtered, and volatiles were removed to give an oil (8.32 g). This oil was dissolved in CH_2Cl_2 (75 mL), and dihydropyran (3.23 g, 38.4 mmol) and pyridinium *p*-toluenesulfonate (200 mg) were added. After 24 h, the reaction mixture was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and filtered, and volatiles were removed to give an oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (400 mL) eluted with 10 → 20% EtOAc/hexanes to give 8.84 g (25.7 mmol, 67%) of **33** as a clear, colorless oil, R_f 0.41 (40% EtOAc/hexanes).

(1*S,3*R**,7*R**)-3-Methyl-3-[3-[(tetrahydro-2*H*-pyranyl)-oxy]butyl]bicyclo[5.1.0]octan-2-one (34).** A solution of **25** (100 mg, 0.72 mmol), **33** (300 mg, 0.87 mmol), and NaH (70 mg, 2.88 mmol) in THF (10 mL) was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, water (25 mL) was cautiously added, and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a yellow oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (200 mL) eluted with 6% EtOAc/hexanes to give 73 mg (0.25 mmol, 35%) of **34** as a clear, colorless oil, R_f 0.61 (40% EtOAc/hexanes).

(1*S,3*R**,5*R**)-3-Methyl-3-(2-oxopropyl)bicyclo[3.1.0]-hexan-2-one (35).** To a biphasic solution of **17** (133 mg, 0.81 mmol) and $NaIO_4$ (728 mg, 3.40 mmol) in a 2:2:3 mixture of $CH_3CN/CCl_4/H_2O$ (7 mL) was added 10−15 mg of $RuCl_3$. The reaction mixture was stirred for 15 min in a water bath at room temperature. Water (10 mL) and CH_2Cl_2 (10 mL) were then added, and the layers were separated. The water layer was extracted with CH_2Cl_2 (4 × 15 mL), the organic phases were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to give a brown oil. This oil was subjected to flash column chromatography on 230−400 mesh silica gel (100 mL) eluted with 30% EtOAc/hexanes to give 88 mg (0.53 mmol, 66%) of **35** as a clear, colorless oil, R_f 0.34 (40% EtOAc/hexanes).

(1*S,3*S**,5*R**)-3-Methyl-3-(2-oxopropyl)bicyclo[3.1.0]-hexan-2-one (36).** By a similar method, 189 mg (1.15 mmol) of **19** gave 172 mg (1.04 mmol, 90%) of **36** as a clear, colorless oil, R_f 0.34 (40% EtOAc/hexanes).

(1*S,3*R**,5*R**)-3-Methyl-3-(3-oxobutyl)bicyclo[3.1.0]-heptan-2-one (37).** By a similar method, 168 mg (0.94 mmol) of **18** gave 149 mg (0.83 mmol, 88%) of **37** as a clear, colorless oil, R_f 0.29 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-3-Methyl-3-(2-oxopropyl)bicyclo[4.1.0]-heptan-2-one (38).** By a similar method, 400 mg (2.24 mmol) of **20** gave 357 mg (1.98 mmol, 88%) of **38** as a clear, colorless oil, R_f 0.36 (40% EtOAc/hexanes).

(1*S,3*S**,6*R**)-3-Methyl-3-(2-oxopropyl)bicyclo[4.1.0]-heptan-2-one (39).** By a similar method, 300 mg (1.68 mmol) of **22** gave 270 mg (1.50 mmol, 89%) of **39** as a clear, colorless oil, R_f 0.35 (40% EtOAc/hexanes).

(1*S,3*R**,6*R**)-3-Methyl-3-(3-oxobutyl)bicyclo[4.1.0]-heptan-2-one (40).** By a similar method, 320 mg (1.66 mmol) of **21** gave 297 mg (1.53 mmol, 92%) of **40** as a clear, colorless oil, R_f 0.31 (40% EtOAc/hexanes).

(1*S,3*S**,6*R**)-3-Methyl-3-(3-oxobutyl)bicyclo[4.1.0]-heptan-2-one (41).** By a similar method, 381 mg (1.98 mmol) of **23** gave 356 mg (1.83 mmol, 93%) of **41** as a clear, colorless oil, R_f 0.35 (40% EtOAc/hexanes).

(1*S,3*S**,7*R**)-3-Methyl-3-(2-oxopropyl)bicyclo[5.1.0]-octan-2-one (42).** By a similar method, 107 mg (0.56 mmol) of **24** gave 82 mg (0.42 mmol, 75%) of **42** as a clear, colorless oil, R_f 0.46 (40% EtOAc/hexanes).

(1*S,3*S**,7*R**)-3-Methyl-1-(2-oxopropyl)bicyclo[5.1.0]-octan-2-one (43).** By a similar method, 220 mg (1.14 mmol) of **27** gave 133 mg (0.68 mmol, 60%) of **43** as a clear, colorless oil, R_f 0.36 (40% EtOAc/hexanes).

(1*S,3*R**,7*R**)-3-Methyl-3-(3-oxobutyl)bicyclo[5.1.0]-octan-2-one (44).** THP ether **34** (153 mg, 0.52 mmol) was taken up in 5% aqueous methanol (20 mL), and a catalytic amount of *p*-toluenesulfonic acid was added. After 4 h, saturated aqueous $NaHCO_3$ (20 mL) and H_2O (10 mL) were added. The mixture was extracted with CH_2Cl_2 (5 × 40 mL), the extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to leave an oil. This oil was dissolved in CH_2Cl_2 (20 mL), and PDC (255 mg, 0.67 mmol) was added. After being stirred for 8 h, additional PDC (255 mg, 0.67 mmol) was added and stirring was continued overnight. The reaction mixture was then filtered through Celite, and volatiles were removed under vacuum. The residual oil was subjected to chromatography on 230−400 mesh silica gel (50 mL) eluted with 15% EtOAc/hexanes to give 76 mg (0.36 mmol, 70%) of **44** as a clear, colorless oil, R_f 0.50 (40% EtOAc/hexanes).

(2*S,3*R**,6*R**)-5-Methyl-$\Delta^{1,8}$-tricyclo[3.3.0.0^{2,3}]nonen-7-one (2).** Metallic sodium (approximately 20 mg) was added to dry *t*-BuOH (20 mL). Diketone **35** (88 mg, 0.52 mmol) was taken up in a 3 mL aliquot of this solution. After 10 min, the reaction mixture was poured into water (10 mL), and the mixture was extracted with hexanes (5 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum to afford 69 mg (0.46 mmol, 88%) of **2** as a pale yellow oil that was homogeneous by TLC, R_f 0.42 (40% EtOAc/hexanes), and was not further purified.

(2*S,3*R**,6*S**)-5-Methyl-$\Delta^{1,8}$-tricyclo[3.3.0.0^{2,3}]nonen-7-one (3).** Metallic sodium (approximately 10 mg) was added to dry *t*-BuOH (10 mL). Diketone **36** (159 mg, 0.95 mmol) was then taken up in a 5 mL aliquot of this solution. The reaction mixture was stirred for 8 h at room temperature, during which time aliquots of the *t*-BuONa/*t*-BuOH solution (3 × 1 mL) were added. The reaction mixture was then poured into water (20 mL), and the mixture was extracted with hexanes (5 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum. The residual yellow oil was subjected to chromatography on 230−400 mesh silica gel (150 mL) eluted with 20% EtOAc/hexanes to give 115 mg (0.78 mmol, 81%) of **3** as a clear, colorless oil, R_f 0.47 (40% EtOAc/hexanes).

(6*S,8*R**,9*S**)-6-Methyl-$\Delta^{1,2}$-tricyclo[4.3.0.0^{8,9}]decen-3-one (4).** By a method similar to that described for the preparation of **3**, 131 mg (0.73 mmol) of diketone **37** gave 112 mg (0.69 mmol, 95%) of **4** as a clear, colorless oil, R_f 0.29 (40% EtOAc/hexanes).

(2*S,3*R**,6*R**)-6-Methyl-$\Delta^{1,9}$-tricyclo[4.3.0.0^{2,3}]decen-8-one (5).** A solution of diketone **38** (133 mg, 0.74 mmol) and KOH (12 pellets) in absolute EtOH (10 mL) was heated for 1 h at reflux under argon. The reaction mixture was cooled to room temperature, H_2O (50 mL) was added, and the mixture was extracted with hexanes (8 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered, and volatiles were removed under vacuum. The residual yellow oil was subjected to chromatography on 230−400 mesh silica gel (200 mL) eluted with 20% EtOAc/hexanes to give 92 mg (0.56 mmol, 77%) of **5** as a clear, colorless oil, R_f 0.30 (40% EtOAc/hexanes).

(2*S,3*R**,6*S**)-6-Methyl-$\Delta^{1,9}$-tricyclo[4.3.0.0^{2,3}]decene-8-one (6).** By a method similar to that described for the preparation of **5**, 270 mg (1.50 mmol) of diketone **39** gave 204 mg (1.26 mmol, 84%) of **6** as a colorless solid, mp 45−48 °C, R_f 0.38 (40% EtOAc/hexanes).

(2*S,3*R**,6*R**)-6-Methyl-$\Delta^{1,10}$-tricyclo[4.4.0.0^{2,3}]undecen-9-one (7).** By a method similar to that described for the preparation of **5**, 280 mg (1.44 mmol) of diketone **40** gave 209 mg (1.19 mmol, 83%) of **7** as a clear, colorless oil, R_f 0.43 (40% EtOAc/hexanes).

(17) While racemic **33** is apparently unknown, the 3*R* and 3*S* enantiomers have been described; see: (a) Mori, K.; Watanabe, H. *Tetrahedron* **1984**, *40*, 299−303. (b) Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221−3225. (c) Mori, K. *Tetrahedron* **1981**, *37*, 1341−1342.

(2*S,3*R**,6*S**)-6-Methyl-$\Delta^{1,10}$-tricyclo[4.4.0.0^{2,3}]undecen-9-one (8).** By a method similar to that described for the preparation of **5**, 354 mg (1.82 mmol) of diketone **41** gave 271 mg (1.54 mmol, 85%) of **8** as a clear, colorless oil, R_f 0.41 (40% EtOAc/hexanes).

(2*S,3*R**,7*S**)-7-Methyl-$\Delta^{1,10}$-tricyclo[5.3.0.0^{2,3}]undecen-9-one (9).** By a method similar to that described for the preparation of **5**, 76 mg (0.39 mmol) of diketone **42** gave 52 mg (0.30 mmol, 75%) of **9** as a clear, colorless oil, R_f 0.37 (40% EtOAc/hexanes).

(2*S,3*R**,7*R**)-7-Methyl-$\Delta^{1,11}$-tricyclo[5.4.0.0^{2,3}]dodecen-10-one (10).** By a method similar to that described for the preparation of **5**, 75 mg (0.36 mmol) of diketone **44** gave 59 mg (0.31 mmol, 87%) of **10** as an oil,, R_f 0.50 (40% EtOAc/hexanes).

(1*S,2*R**,6*S**)-12-Methyl-$\Delta^{7,8}$-tricyclo[5.3.0.0^{1,2}]undecen-9-one (45).** By a method similar to that described for the preparation of **5**, 120 mg (0.62 mmol) of diketone **43** gave 79 mg (0.45 mmol, 73%) of **45** as a clear, colorless oil, R_f 0.38 (40% EtOAc/hexanes).

Acknowledgment. Partial support of this work by Research Corp. and by the University of Arizona through the Office of the Vice President for Research and the Materials Characterization Program is gratefully acknowledged.

Supporting Information Available: Product characterization data and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990720S