Pergamon

Tetrahedron 54 (1998) 2669–2682

TETRAHEDRON

Diastereoselective Manipulations of Bicyclo[*m*.1.0]alkane Derivatives. 5. α'–Alkylations of Bicyclo[*m*.1.0]alkan–2–ones

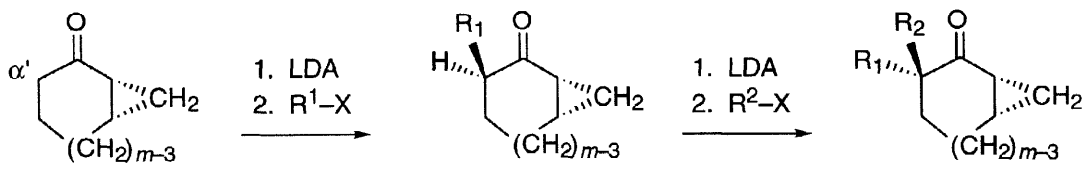
Eugene A. Mash*, James A. Baron, Timothy M. Gregg, and Sandeep K. Nimkar

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721–0041 USA

Received 15 October 1997; accepted 7 January 1998

Abstract: α'–Alkylations of bicyclo[*m*.1.0]alkan–2–ones were shown to proceed with high diastereoselectivity under conditions which favor kinetic control of the product distribution. Product yields for active electrophiles were good to very good. In sequential α'–alkylations with different electrophiles, reversal of the order of alkylation switches the configuration of the newly formed quaternary center.

Bicyclo[*m*.1.0]alkan–2–ones **1** possessing cis ring fusion for $m = 3–14$ or trans ring fusion for $m = 7–14$ are available in either enantiomeric form via diastereoselective cyclopropanation of certain 2–cycloalken–1–one ketals.[1] We have undertaken studies of the conformations[2] and reactivities[3] of these compounds in anticipation of their expanded use as intermediates in natural products synthesis.[4] We recently reported that nucleophilic additions of bicyclo[*m*.1.0]alkan–2–ones exhibit high diastereoselectivity when $m \geq 6$.[3a] This selectivity was attributed to a highly conserved local conformation for the α,β-cyclopropyl ketone functional group array in which approach to one face of the carbonyl is blocked by the transannular atoms of the larger ring. Also pertinent to future use in construction of natural products is α'–deprotonation and alkylation of such α,β-cyclopropyl ketones.[5] In principle, a new quaternary center might be established at C–3 by means of sequential alkylations with stereocontrol based on the chirality of the fused cyclopropane ring and the order of use of electrophiles. Presented herein are results of a study of alkylation of enolates derived from several α,β–cyclopropyl ketones **1**.[6]



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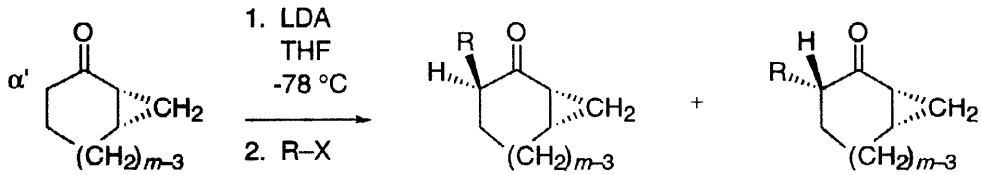
*emash@synthesis.chem.arizona.edu

0040-4020/98/$19.00
PII: S0040-4020(98)00036-2

Bicyclic ketones **2-6** were employed in this study (Table 1). Ketones **2-4** were racemic and were prepared by published procedures.[7] Ketones **5** and **6** were enantiomerically enriched (>90% ee) and were prepared as previously described.[3a]

Treatment of bicyclo[3.1.0]hexan–2–one (**2**) with lithium diisopropylamide (LDA) in THF solution at -78 °C, followed by addition of 5 equivalents of α–bromotoluene, produced a single monobenzylated product in 70% yield. Comparable yields were obtained using as little as 1.3 equivalents of α–bromotoluene, but use of excess alkylating reagent speeded completion of the reaction.[8] The product was assigned structure **7a** by comparison of the ^{1}H NMR chemical shifts of the geminal endo and exo cyclopropane protons with the chemical shifts of the corresponding protons of **2** and several α',α'-dialkylated ketones (*vide infra*).

Table 1. α'-Alkylations of Enolates Derived from Bicyclo[*m*.1.0]alkan–2–ones **2-6**.



Ketone	*m*	R-X	Products	Yield, %[a]	Diastereomer Ratio[b]
2[c]	3	$C_6H_5CH_2Br$	**7a**	70	>20:1
3[c]	4	$C_6H_5CH_2Br$	**8a,8b**	70	8:1
		CH_2=$CHCH_2Br$	**9a,9b**	73	7:1
		CH_3I	**10a,10b**	68	10:1
		$CH_3(CH_2)_6I$	**11a,11b**	18	4:1
4[c]	5	$C_6H_5CH_2Br$	**12a**	75	>20:1
		CH_2=$CHCH_2Br$	**13a**	78	>20:1
		CH_3I	**14a**	80	>20:1
5	6	$C_6H_5CH_2Br$	**15a**	73	>20:1
		CH_2=$CHCH_2Br$	**16a**	71	>20:1
		CH_3I	**17a**	81	>20:1
		$CH_3(CH_2)_8I$	**18a**	29	>20:1
6	12	$C_6H_5CH_2Br$	**19a,19b**	31,26[d]	1.2:1[e]

[a]Yield of monoalkylated products. [b]Determined by NMR spectroscopy; limit of detection 20:1. [c]Racemic ketone used. [d]Products **19a** and **19b** separated by chromatography. [e]Ratio of less polar to more polar product.

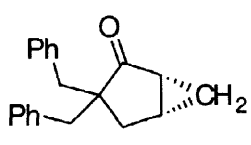
Bicyclo[4.1.0]heptan–2–one (**3**) was similarly deprotonated and alkylated using α–bromotoluene, 3-bromopropene, iodomethane, and 1–iodoheptane as electrophiles.[8] Yields of monoalkylated products were good except for 1–iodoheptane, where a substantial amount of **3** remained even after prolonged reaction times. Additionally, small amounts (>10%) of doubly alkylated products were obtained. Major and minor monoalkylated product diastereomers were detected by ^{13}C NMR and GC/MS analyses.[9,10] Product diastereomers were not separable by preparative column chromatography. In the case of benzylation, the initially formed major diastereomer was assigned structure **8a** by comparison of the ^{1}H NMR chemical shift of the geminal endo and exo cyclopropane protons with the chemical shifts of the corresponding protons of **3** and several α',α'-dialkylated ketones (*vide infra*). Structures **9a-11a** were assigned by analogy with **8a**.

α'-Alkylations of bicyclo[5.1.0]octan–2–one (**4**) and bicyclo[6.1.0]nonan–2–one (**5**) using α–bromotoluene, 3-bromopropene, and iodomethane as electrophiles gave only monoalkylated products in good yields. Alkylation of **5** using 1-iodononane gave a monoalkylated product in poor yield. Minor diastereomers were not detected. Structures **12a–18a** were tentatively assigned to the products based on the expected approach of the electrophile to the less hindered exo face of the enolate.[11]

α'–Alkylation of **6** using α–bromotoluene as the electrophile gave recovered **6** and, in fair yield, a 1.2:1 mixture of chromatographically separable products **19a** and **19b**. Structures could not be assigned to these diastereomeric products.[12]

Following studies of monoalkylation, our attention turned to studies of sequential alkylation (Table 2). Treatment of bicyclo[3.1.0]hexan–2–one derivative **7a** with LDA, followed by addition of iodomethane, produced a single methylated product in 32% yield, along with considerable amounts (ca. 35%) of a dimer.[13] The result of this alkylation was disappointing, and so alternative alkylation procedures were investigated. It was found that treatment of **7a** with NaH and iodomethane in THF solution at reflux produced the methylated product in 63% yield with no apparent loss of diastereoselectivity. Structure **20a** was assigned to this product by comparison of the ^{1}H NMR chemical shift of the geminal endo and exo cyclopropane protons with the chemical shifts of the corresponding protons of **2**, **7a**, and α',α'-dibenzylated ketone **21**, prepared by benzylation of **7a** (Table 2 and *vide infra*).

α'–Allylation of bicyclo[4.1.0]heptan–2–one derivative **8a** also exhibited high diastereoselectivity. An improvement in yield was again observed when NaH was employed as the base in THF solution at reflux. Structure **22a** was assigned to the product by comparison of the ^{1}H NMR chemical shift of the geminal endo and exo cyclopropane protons with the chemical shifts of the corresponding protons of **3**, **8a**, **9a**, and α',α'-dibenzylated ketone **23**, which was isolated as a minor product from benzylation of **3** (*vide infra*). α'-Benzylation of **9a** was somewhat less diastereoselective, producing in 74% yield an 11:1 mixture of products that were inseparable by preparative column chromatography. Structure **24a** was assigned to the major diastereomer and structure **24b** (identical with **22a**) was assigned to the minor diastereomer.



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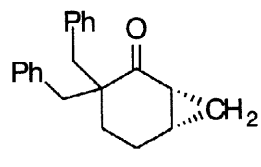

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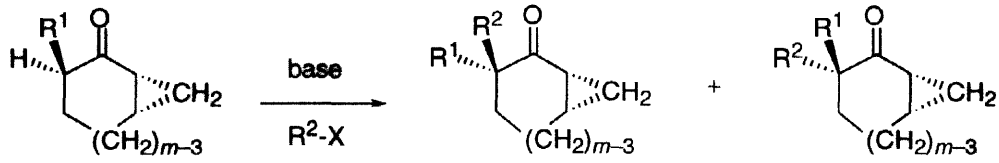
Table 2. α'–Alkylations of Enolates Derived from 3-Alkylbicyclo[*m*.1.0]alkan-2-ones.



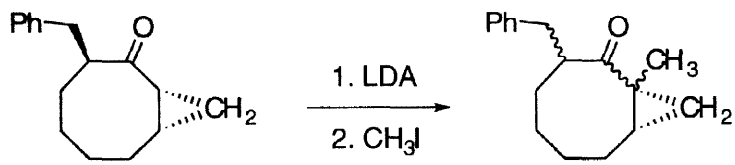
a **b**

Ketone	*m*	R^1	Base	R^2-X	Products	Yield, %	Diastereomer Ratio[a]
7a	3	$CH_2C_6H_5$	LDA	CH_3I	**20a**	32	>20:1
			NaH	CH_3I	**20a**	63	>20:1
			NaH	$C_6H_5CH_2Br$	**21**	43	na
8a	4	$CH_2C_6H_5$	LDA	CH_2=$CHCH_2Br$	**22a**	54	>20:1
			NaH	CH_2=$CHCH_2Br$	**22a**	80	>20:1
9a	4	CH_2=$CHCH_2$	LDA	$C_6H_5CH_2Br$	**24a,24b**	74	11:1
12a	5	$CH_2C_6H_5$	LDA	CH_3I	**25a**	44	>20:1
14a	5	CH_3	LDA	$C_6H_5CH_2Br$	**26a**	46	>20:1

[a]Determined by NMR spectroscopy; limit of detection 20:1.

α'-Alkylations of bicyclo[5.1.0]octan-2-one derivatives **12a** and **14a** were both highly diastereoselective. Yields have not been optimized. Structures **25a** and **26a**, which are diastereomeric, were tentatively assigned to the products from α'-methylation of **12a** and α'-benzylation of **14a**, respectively, based on the expected approach of the electrophile to the less hindered exo face of the enolate.[11]

Bicyclo[6.1.0]nonan-2-one derivative **15a** resisted α'-alkylation with iodomethane when LDA was used as the base. After two days at -22 °C, an α-methylated product **27** of unknown stereochemistry was isolated in ca. 5% yield along with recovered **15a**. This result may be attributable to low kinetic acidity of the remaining α' proton.[14]

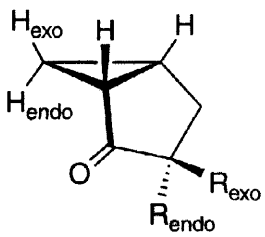


15a **27**

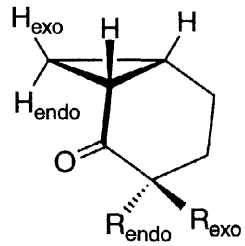
Trans geometries are prescribed for enolates derived from ketones **2-5**, **7a**, **8a**, **9a**, **12a**, and **14a** due to ring size limitations. These enolates, which are contained in common rings, have little conformational freedom.

From considerations of steric impedance, electrophilic attack under kinetic control was expected to occur anti to the methylene carbon of the cyclopropane ring.[11] The high levels of diastereoselection observed were consistent with this expectation. Equilibration studies with **8a**, **10a**, and **14a** established that these alkylation reactions were kinetically controlled.[15,16] Further evidence that the reactions had followed the anticipated course was provided by assignments of structure to the benzylated products derived from bicyclo[3.1.0]hexan-2-one (**2**) and bicyclo[4.1.0]heptan-2-one (**3**). Structure assignments were based on the chemical shifts of the geminal endo and exo protons attached to the methylene carbon of the cyclopropane ring (Table 3). For compounds **20a** and **21**, significant upfield shifts of the signals from the endo protons were observed. These shifts were attributed to anisotropic shielding due to the proximity of a phenyl ring. For compounds **22a** and **23**, upfield shifts of the signals from the endo protons were also observed. The magnitudes of these shifts were smaller, as would be expected for the somewhat less rigid bicyclo[4.1.0]heptan-2-one ring system. There were not sufficient chemical shift differences for assignments of structure to **12a-14a**, **25a**, and **26a**. Structures for these compounds and for **15a-18a** were tentatively assigned based on the expected approach of the electrophile to the less hindered enolate face.[11]

Table 3. Chemical Shifts of Endo and Exo Cyclopropane Protons of Benzylated Derivatives of **2** and **3**.



	R_{exo}	R_{endo}
2	H	H
7a	CH_2Ph	H
20a	CH_3	CH_2Ph
21	CH_2Ph	CH_2Ph



	R_{exo}	R_{endo}
3	H	H
8a	CH_2Ph	H
9a	$CH_2CH{=}CH_2$	H
22a	$CH_2CH{=}CH_2$	CH_2Ph
23	CH_2Ph	CH_2Ph
24a	CH_2Ph	$CH_2CH{=}CH_2$

	Chemical Shift, PPM	
Ketone	**Endo Proton**	**Exo Proton**
2	0.95	1.22
7a	0.96	1.17
20a	-0.15	0.85
21	-0.47	0.62

	Chemical Shift, PPM	
Ketone	**Endo Proton**	**Exo Proton**
3	1.23	1.09
8a	1.05	1.21
9a	1.08	1.19
22a	0.32	0.66
23	0.24	0.62
24a	1.16	0.96

Stereocontrolled alkylations of ketones **2-6** should facilitate syntheses of fused bicycles via subsequent ring annulation reactions. This methodology, which is presently under development in our laboratory, should be applicable to stereocontrolled syntheses of many natural products.

EXPERIMENTAL

All reactions were performed in flame-dried glassware under argon. Reaction mixtures were stirred magnetically. Hygroscopic liquids were transferred via syringe or cannula. Diethyl ether ("ether") and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from CaH_2. Diisopropylamine was distilled from and stored over CaH_2. Ketones **2**, **3**, and **4** were racemic and were prepared by literature procedures.[7] Ketones **5** and **6** were enantiomerically enriched and were prepared as previously described.[3a] Analytical thin-layer chromatography was performed on Merck glass-backed pre-coated 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 mm Hg. NMR spectra were recorded in $CDCl_3$ solution unless otherwise noted. Proton NMR spectra were recorded at 200 MHz or 250 MHz using tetramethylsilane (0 ppm) as an internal standard. Carbon–13 NMR spectra were recorded at 50.3 MHz or 62.9 MHz using the center line of the $CDCl_3$ triplet (77.0 ppm) as an internal standard. GC/MS analyses were performed using one of two temperature programmed methods on a 0.25 mm X 30.0 m Hewlett-Packard HP–5 column (crosslinked 5% PhMe silicone, 0.25 μm film thickness) using He as the carrier, 1.0 mL/min; method A: injection port temp 250 °C, detector temp 280 °C, initial column temp 100 °C, final column temp 230 °C, ramp 20 °C/min; method B: as in method A except final column temp 180 °C, ramp 10 °C/min. The mass detector operated in electron impact mode at 70 eV. Diastereomer ratios were determined by ^1H and ^{13}C NMR analyses or by isolation. High resolution mass spectral analyses were obtained by the Nebraska Center for Mass Spectrometry, Lincoln, Nebraska, or 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.

General Alkylation Procedure. To a solution of lithium diisopropylamide (LDA, 1–1.2 equiv) in THF (1 mL/mmol) under argon at -78 °C was added a solution of bicyclic ketone (1 equiv) in THF (1.5 mL/mmol) via cannula. The cannula was rinsed with THF. After 15–45 min, alkylating agent (1–8 equiv) was added slowly via syringe. The reaction flask was kept at -78 °C for several hours, then capped and stored at -22 °C. Progress of the reaction was monitored by thin–layer chromatography. When judged to be over, the reaction was quenched by addition of saturated NH_4Cl solution (4 mL/mmol) and the mixture diluted with water and extracted with CH_2Cl_2 or ether. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated. Column chromatography gave purified product(s).

(1*R,3*S**,5*S**)–3–(Phenyl)methylbicyclo[3.1.0]hexan–2–one (7a).** From LDA (2.08 mmol), ketone **2** (200 mg, 2.08 mmol), and α–bromotoluene (1.78 g, 10.4 mmol) was obtained 270 mg (1.45 mmol, 70%) of **7a** as a white solid, mp 40–41 °C, R_f 0.51 (40% EtOAc/hexanes), after flash column chromatography (200 mL of silica

eluted with 10% EtOAc/hexanes). IR (neat) cm^{-1} 1721, 1604, 1505, 1468, 1307, 1190, 1042; ^1H NMR δ 0.91–1.02 (1, m), 1.09–1.25 (1, m), 1.75–2.44 (6, m), 3.06–3.27 (1, m), 7.06–7.32 (5, m); ^{13}C NMR δ 14.5, 19.9, 27.4, 29.9, 35.5, 42.2, 126.0, 128.3, 128.7, 139.9, 214.6; GC/MS (method B, R_t = 10.65 min) *m/z* (relative intensity) 188 (0.5), 187 (7), 186 (48), 145 (27), 117 (15), 115 (16), 104 (22), 103 (13), 95 (40), 91 (100), 78 (12), 77 (16); HRMS (EI^+) calcd for $C_{13}H_{14}O$ (M^+) 186.1044, found 186.1039.

(1*R,3*S**,6*S**)–3–(Phenyl)methylbicyclo[4.1.0]heptan–2–one (8a), (1*R**,3*R**,6*S**)–3–(Phenyl)methylbicyclo[4.1.0]heptan–2–one (8b), and (1*R**,6*S**)–3,3–Di(phenyl)methylbicyclo[4.1.0]heptan–2–one (23).** From LDA (2.00 mmol), ketone **3** (200 mg, 1.82 mmol), and α–bromotoluene (2.33 g, 13.6 mmol) was obtained 253 mg (1.26 mmol, 70%) of an 8:1 mixture of diastereomers **8a/8b** as a pale yellow oil, R_f 0.54 (40% EtOAc/hexanes), and 43 mg (0.15 mmol, 8%) of **23** as a white solid, mp 110-114 °C, R_f 0.64, after flash column chromatography (200 mL of silica eluted with 10% EtOAc/hexanes).

Spectral data for **23**: IR (neat) cm^{-1} 1686, 1620, 1587, 1507, 1467, 1368, 1288, 1229, 1182, 944; ^1H NMR δ 0.21 (1, dm, *J* = 10.0 Hz), 0.62 (1, ddd, *J* = 10.0, 7.82, 5.37 Hz), 1.31-1.53 (3, m), 1.68-1.88 (3, m), 2.16 (1, d, *J* = 12.9 Hz), 2.73 (1, d, *J* = 13.1 Hz), 3.00 (1, d, *J* = 13.1 Hz), 3.40 (1, d, *J* = 12.9 Hz), 6.96-7.36 (10, m); ^{13}C NMR δ 7.7, 16.8, 18.0, 21.6, 26.2, 42.7, 44.1, 50.0, 126.3, 126.6, 127.9, 128.1, 130.7, 130.9, 137.0, 137.8, 208.5; GC/MS (method A, R_t = 14.83 min) *m/z* (relative intensity): 207 (0.4), 200 (16), 199 (100), 129 (11), 117 (16), 115 (18), 91 (89), 65 (12); HRMS (EI^+) calcd for $C_{21}H_{22}O$ (M^+) 290.1671, found 290.1668.

Spectral data for **8a/8b**: IR (neat) cm^{-1} 2932, 1691, 1450, 1345, 1215, 758, 715; ^1H NMR (mixture of diastereomers) δ 0.85–2.50 (10, m), 3.10–3.26 (1, m), 7.08–7.33 (5, m); ^{13}C NMR δ major diastereomer 8.0, 16.5, 20.9, 21.1, 25.7, 36.6, 48.5, 126.0, 128.21, 129.2, 139.7, 210.1; minor diastereomer 15.2, 19.1, 20.5, 25.4, 26.5, 35.8, 45.9, 126.0, 128.3, 129.1, 139.9, 211.0; GC/MS (method A) *m/z* (relative intensity) major diastereomer (R_t = 7.89 min) 201 (15), 200 (100), 145 (19), 144 (11), 131 (16), 129 (15), 118 (22), 117 (55), 115 (19), 109 (35), 104 (11), 92 (10), 91 (87), 81 (13); minor diastereomer (R_t = 7.76 min) 201 (13) 200 (89), 171 (11), 145 (16), 131 (16), 129 (15), 118 (25), 117 (61), 115 (21), 109 (42), 105 (13), 104 (13), 91 (100), 81 (17); HRMS (EI^+) calcd for $C_{14}H_{16}O$ (M^+) 200.1201, found 200.1195.

(1*R,3*S**,6*S**)–3–(2-Propenyl)bicyclo[4.1.0]heptan–2–one (9a) and (1*R**,3*R**,6*S**)–3–(2-Propenyl)bicyclo[4.1.0]heptan–2–one (9b).** From LDA (2.18 mmol), ketone **3** (200 mg, 1.82 mmol), and 3-bromopropene (1.10 g, 9.09 mmol) was obtained 199 mg (1.32 mmol, 73%) of a 7:1 mixture of diastereomers **9a/9b** as a pale yellow oil, R_f 0.53 (40% EtOAc/hexanes), after flash column chromatography (200 mL of silica eluted with 10% EtOAc/hexanes). IR (neat) cm^{-1} 1684, 1437, 1350, 993; ^1H NMR (mixture of diastereomers) δ 0.92–2.57 (11, m), 4.95–5.09 (2, m), 5.58–5.86 (1, m); ^{13}C NMR δ major diastereomer 14.8, 18.9, 20.4, 25.2, 26.7, 34.2, 43.4, 116.4, 136.1, 210.7; minor diastereomer 7.9, 16.3, 21.0, 25.5, 26.7, 35.0, 46.0, 116.7, 135.5, 209.4; GC/MS (method B) *m/z* (relative intensity) major diastereomer (R_t = 6.08 min) 151 (5), 150 (42), 117 (20), 109 (21), 108 (21), 107 (36), 106 (11), 96 (29), 95 (56), 94 (31), 93 (41), 92 (12), 91 (29), 84 (26), 83 (11), 82 (62), 81 (100), 79 (81); minor diastereomer (R_t = 5.98 min) 151 (0.5), 150 (54), 149 (14), 135 (29), 122 (12), 121 (29), 117 (18), 109 (39), 108 (24), 107 (38), 106 (12), 96 (27), 95 (57), 94 (34), 93 (40), 92 (12), 91 (28), 84 (25), 83 (14), 82 (63), 81 (100).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.40. Found: C, 80.18; H, 9.63.

(1*R,3*R**,6*S**)–3–Methylbicyclo[4.1.0]heptan–2–one (10a) and (1*R**,3*S**,6*S**)–3–Methylbicyclo[4.1.0]–heptan–2–one (10b).**[6a] From LDA (2.72 mmol), ketone **3** (300 mg, 2.72 mmol), and iodomethane (1.93 g, 13.6 mmol) was obtained 230 mg (1.85 mmol, 68%) of a 10:1 mixture of diastereomers **10a/10b** as a colorless oil, R_f 0.52 (40% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 2944, 2876, 1703, 1450, 1382, 1357, 1221, 1092, 980; ^1H NMR δ mixture of diastereomers 0.95–2.36 (9, m), 1.03 (3, d, J = 7.0 Hz); ^{13}C NMR δ major diastereomer 14.8, 15.6, 18.9, 20.2, 24.7, 30.5, 38.4, 211.6; minor diastereomer 7.6, 15.8, 18.9, 21.0, 24.3, 24.6, 41.7, 211.6; GC/MS (method B) *m/z* (relative intensity) major diastereomer (R_t = 4.04 min) 125 (46), 124 (50), 109 (19), 95 (16), 69 (17), 68 (22), 67 (26), 55 (43), 54 (100); minor diastereomer (R_t = 3.95 min) 124 (80), 109 (27), 96 (12), 95 (21), 94 (41), 83 (13), 82 (72), 81 (95), 80 (17), 78 (17), 67 (33), 55 (53), 54 (100).

(1*R,3*S**,6*S**)–3-Heptylbicyclo[4.1.0]heptan-2-one (11a) and (1*R**,3*R**,6*S**)–3-Heptylbicyclo[4.1.0]-heptan-2-one (11b).** From LDA (2.18 mmol), ketone **3** (200 mg, 1.82 mmol), and 1-iodoheptane (2.06 g, 9.11 mmol) was obtained 69 mg (0.33 mmol, 18%) of a 4:1 mixture of **11a** and **11b** as a pale yellow oil, R_f 0.52 (30% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 1699, 1467, 1368, 1215, 1096, 1036, 924; ^1H NMR δ 0.87 (3, t, J = 7.1 Hz), 0.92-1.21 (3, m), 1.26 (12, br s), 1.46-2.05 (8, m); ^{13}C NMR δ major diastereomer 8.1, 14.0, 14.1, 18.3, 20.2, 22.6, 25.0, 26.6, 27.1, 29.2, 29.6, 31.8, 44.3, 211.8; minor diastereomer 8.1, 14.0, 14.1, 16.8, 21.2, 21.8, 25.8, 26.6, 27.1, 30.0, 31.0, 31.5, 46.8, 210.7; GC/MS (method B) *m/z* (relative intensity) mixture of diastereomers (R_t = 7.38 min) 210 (0.02), 209 (0.2), 208 (0.8), 124 (1), 123 (11), 111 (8), 110 (100), 109 (7), 95 (34); HRMS (EI^+) calcd for $C_{14}H_{24}O$ (M^+) 208.1827, found 208.1829.

(1*R,3*S**,7*S**)–3–(Phenyl)methylbicyclo[5.1.0]octan–2–one (12a).** From LDA (1.01 mmol), ketone **4** (120 mg, 0.97 mmol), and α–bromotoluene (198 mg, 1.14 mmol) was obtained 155 mg (0.72 mmol, 75%) of **12a** as a colorless oil, R_f 0.53 (40% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 10% EtOAc/hexanes). IR (neat) cm^{-1} 3080, 3059, 3023, 2922, 2850, 1672, 1600, 1580, 1494, 1450, 1380; ^1H NMR δ 0.80–2.05 (10, m), 2.45–2.72 (2, m), 2.95–3.20 (1, m), 7.05–7.33 (5, m); ^{13}C NMR δ 12.4, 19.2, 23.9, 26.7, 29.3, 30.2, 36.9, 49.1, 125.9, 128.2, 129.1, 140.6, 211.9; GC/MS (method B, R_t = 8.37 min) *m/z* (relative intensity) 215 (4), 214 (24), 131 (31), 130 (100), 129 (22), 118 (30), 127 (26), 115 (17), 105 (12), 104 (23), 95 (16), 92 (11), 91 (93), 81 (11); HRMS (EI^+) calcd for $C_{15}H_{18}O$ (M^+) 214.1358, found 214.1351.

(1*R,3*S**,7*S**)–3–(2-Propenyl)bicyclo[5.1.0]octan–2–one (13a).** From LDA (1.01 mmol), ketone **4** (118 mg, 0.95 mmol), and 3-bromopropene (138 mg, 1.14 mmol) was obtained 121 mg (0.74 mmol, 78%) of **13a** as a colorless oil, R_f 0.41 (30% EtOAc/hexanes), after flash column chromatography (60 mL of silica eluted with 8% EtOAc/hexanes). IR (neat) cm^{-1} 2926, 1668, 1264; ^1H NMR δ 0.86–1.08 (2, m), 1.25–1.32 (1, m), 1.44–1.52 (2, m), 1.59–1.72 (2, m), 1.9–2.05 (3, m), 2.36–2.52 (3, m), 4.96–5.03 (2, m), and 5.65–5.74 (1, m); ^{13}C NMR δ 12.2, 19.0, 23.8, 26.7, 29.5, 30.0, 35.1, 47.0, 116.0, 136.7, 211.8; HRMS (EI^+) calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1199.

(1*R,3*R**,7*S**)–3–Methylbicyclo[5.1.0]octan–2–one (14a).** From LDA (1.01 mmol), ketone **4** (118 mg, 0.95 mmol), and iodomethane (162 mg, 1.14 mmol) was obtained 105 mg (0.76 mmol, 80%) of **14a** as a colorless oil, R_f 0.47 (30% EtOAc/hexanes), after flash column chromatography (200 mL of silica eluted with 10% EtOAc/hexanes). IR (neat) cm^{-1} 2972, 2928, 2852, 1666; ^1H NMR δ 0.82–2.13 (10, m), 1.04 (3, d, J = 6.6 Hz), 2.39–2.59 (1, m); ^{13}C NMR δ 11.9, 16.5, 19.0, 23.7, 26.7, 29.8, 32.1, 41.7, 212.7; GC/MS (method B, R_t = 5.13 min) *m/z* (relative intensity) 139 (2), 138 (23), 96 (10), 95 (26), 94 (51), 83 (28), 82 (36), 81 (62), 79 (20), 68 (25), 67 (50), 55 (100), 54 (37), 53 (17).

(1*R*,3*S*,8*S*)–3–(Phenyl)methylbicyclo[6.1.0]nonan–2–one (15a). From LDA (1.1 mmol), ketone **5** (131 mg, 0.95 mmol), and α–bromotoluene (195 mg, 1.1 mmol) was obtained 158 mg (0.69 mmol, 73%) of **15a** as colorless crystals, mp 50–54 °C, R_f 0.34 (10% EtOAc/hexanes), after gravity–driven column chromatography (200 mL of silica eluted with 10% EtOAc/hexanes). $[\alpha]^{23}_D$ +2.63° (*c* 7.83, $CHCl_3$); IR (neat) cm^{-1} 3024, 2999, 2925, 2852, 1689, 1493, 1450, 1389, 1376; ^1H NMR δ 0.69–0.98 (2, m), 0.94–1.14 (2, m), 1.21–1.43 (2, m), 1.55–1.78 (1, m), 1.71–1.90 (3, m), 2.03 (1, dm, J = 14.4 Hz), 2.20–2.31 (1, m), 2.55–2.70 (1, m), 2.81 (1, dd, J = 13.7, 8.0 Hz), 3.05 (1, dd, J = 13.7, 7.4 Hz), 7.13–7.32 (5, m); ^{13}C NMR δ 9.4, 22.7, 23.5, 25.7, 28.2, 29.9, 33.2, 38.6, 57.1, 126.2, 128.4, 128.7, 139.1, 213.0.

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.21; H, 8.69.

(1*R*,3*S*,8*S*)–3–(2-Propenyl)bicyclo[6.1.0]nonan–2–one (16a). From LDA (1.2 mmol), ketone **5** (156 mg, 1.1 mmol), and 3-bromopropene (150 mg, 1.2 mmol) was obtained 144 mg (0.81 mmol, 71%) of **16a** as a colorless oil, R_f 0.39 (10% EtOAc/hexanes), after gravity–driven column chromatography (200 mL of silica eluted with 3–10% Et_2O/hexanes). $[\alpha]^{23}_D$ -15.0° (*c* 5.09, $CHCl_3$); IR (neat) cm^{-1} 3074, 2999, 2923, 2853, 1690, 1638, 1450, 1389, 1376; ^1H NMR δ 0.67–0.86 (2, m), 0.96–1.16 (2, m), 1.19–1.43 (2, m), 1.55–1.97 (4, m), 2.04 (1, dm, J = 14.9 Hz), 2.11–2.22 (1, m), 2.23–2.55 (3, m), 5.02 (1, d, J = 9.4 Hz), 5.07 (1, d, J = 16.3 Hz), 5.73 (1, ddt, J = 16.3, 9.4, 6.6 Hz); ^{13}C NMR δ 9.2, 22.6, 23.1, 25.8, 28.2, 30.0, 33.5, 36.9, 55.4, 116.5, 135.5, 213.3; MS (EI^+) *m/z* (relative intensity) 179 (10), 178 (74), 177 (9), 163 (47), 150 (48), 149 (41), 137 (53), 136 (32), 135 (53), 134 (14), 131 (13), 124 (33), 123 (40), 122 (16), 121 (34), 120 (18), 119 (37), 118 (21), 117 (20), 111 (24), 110 (56), 109 (100), 108 (21), 107 (29), 106 (13), 105 (13), 98 (40); HRMS (EI^+) calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1357.

(1*R*,3*R*,8*S*)–3–Methylbicyclo[6.1.0]nonan–2–one (17a). From LDA (1.5 mmol), ketone **5** (172 mg, 1.3 mmol), and iodomethane (368 mg, 2.6 mmol) was obtained 154 mg (1.0 mmol, 81%) of **17a** as a colorless oil, R_f 0.37 (10% EtOAc/hexanes), after gravity–driven column chromatography (200 mL of silica eluted with 3–10% Et_2O/hexanes). $[\alpha]^{23}_D$ -8.9° (*c* 6.1, $CHCl_3$); IR (neat) cm^{-1} 3430 (br), 3000, 2961, 2921, 2853, 1690, 1445, 1389, 1375; ^1H NMR δ 0.64–0.84 (2, m), 0.95–1.14 (2, m), 1.19–1.42 (2, m), 1.22 (3, d, J = 7.0 Hz), 1.57–1.70 (1, m), 1.72–1.96 (3, m), 1.98–2.10 (1, m), 2.18–2.29 (1, m), 2.33–2.50 (1, m); ^{13}C NMR δ 9.0, 17.6, 22.3, 22.6, 26.3, 28.2, 30.0, 35.9, 50.2, 214.6; MS (EI^+) *m/z* (relative intensity) ; MS (EI^+) *m/z* (relative intensity) 153 (15), 152 (65), 137 (15), 134 (29), 123 (19), 119 (15), 111 (16), 110 (36), 109 (33), 108 (44), 98 (16), 97 (40), 96 (43), 95 (50), 94 (17), 93 (27), 92 (15), 84 (26), 83 (25), 82 (40), 81 (72), 80 (23), 79 (25), 77 (15), 69 (30), 68 (60), 67 (70), 56 (19), 55 (100), 54 (75), 53 (34); HRMS (EI^+) calcd for $C_{10}H_{16}O$ (M^+) 152.1201, found 152.1196.

(1*R*,3*R*,8*S*)–3–Nonylbicyclo[6.1.0]nonan–2–one (18a). From LDA (1.1 mmol), ketone **5** (124 mg, 0.89 mmol), and 1–iodononane (250 mg, 0.98 mmol) was obtained 69 mg (0.26 mmol, 29%) of **18a** as a colorless oil, R_f 0.50 (10% EtOAc/hexanes), after gravity–driven column chromatography (200 mL of silica eluted with 3–10% Et_2O/hexanes). $[\alpha]^{24}_D$ -5.4° (*c* 2.70, $CHCl_3$); IR (neat) cm^{-1} 3000, 2953, 2919, 2848, 1681, 1469, 1437, 1394, 1377; ^1H NMR δ 0.65–0.84 (2, m), 0.87 (3, t, *J* = 6.6 Hz), 0.97–1.18 (2, m), 1.18–1.40 (16, m), 1.42–1.94 (6, m), 2.20 (1, dm, *J* = 14.4 Hz), 2.12–2.36 (2, m); ^{13}C NMR δ 9.1, 14.0, 22.6, 22.7, 26.2, 27.7, 28.3, 29.2, 29.4, 29.5, 29.6, 30.2, 31.8, 32.9, 34.3, 56.2, 214.1; MS (EI^+) *m/z* (relative intensity) 265 (16), 264 (55), 179 (8), 152 (8), 151 (8), 138 (45), 137 (11), 123 (9), 121 (12), 120 (100), 110 (16), 109 (17), 97 (13), 96 (22); HRMS (EI^+) calcd for $C_{18}H_{32}O$ (M^+) 264.2453, found 264.2453.

(1*S*,3*S*,12*S*)–3–(Phenyl)methylbicyclo[10.1.0]tridecan–2–one (19a) and (1*S*,3*R*,12*S*)–3–(Phenyl)methylbicyclo[10.1.0]tridecan–2–one (19b). From LDA (0.53 mmol), ketone **6** (86 mg, 0.44 mmol), and α–bromotoluene (83 mg, 0.49 mmol) was obtained 35 mg (40%) of recovered starting material **6**; 39 mg (0.14 mmol, 31%) of a less polar α–benzylated product, R_f 0.47 (10% EtOAc/hexanes), mp 79–80 °C; and 27 mg (0.96 mmol, 26%) of a more polar α–benzylated product, R_f 0.38, mp 110–111 °C after gravity–driven column chromatography (160 mL of silica eluted with 4–10% Et_2O/hexanes).

Spectral data for less polar diastereomer: $[\alpha]^{24}_D$ +41.8° (*c* 1.94, $CHCl_3$); IR (neat) cm^{-1} 3057, 3022, 3007, 2917, 2855, 1679, 1492, 1463, 1451, 1437, 1404, 1347; ^1H NMR δ 0.55–0.78 (2, m), 1.20–1.86 (17, m), 1.97 (1, ddt, *J* = 14.4, 9.2, 2.4 Hz), 2.60 (1, dd, *J* = 13.5, 7.3 Hz), 2.92 (1, dd, *J* = 13.5, 7.6 Hz), 3.11–3.25 (1, m), 7.12–7.31 (5, m); ^{13}C NMR δ 18.7, 24.1, 25.1, 26.1, 26.6, 27.1, 27.8, 29.9, 30.2, 32.5, 37.1, 54.7, 125.9, 128.2, 128.9, 140.4, 214.0.

Spectral data for more polar diastereomer: $[\alpha]^{24}_D$ +34.9° (*c* 1.36, $CHCl_3$); IR (neat) cm^{-1} 3054, 3000, 2912, 2851, 1674, 1492, 1463, 1455, 1435, 1403, 1355; ^1H NMR δ 0.72–0.90 (2, m), 1.19–1.70 (15, m), 1.88–2.08 (3, m), 2.55–2.69 (1, m), 2.84 (1, dd, *J* = 13.7, 7.7 Hz), 3.03 (1, dd, *J* = 13.7, 7.7 Hz), 7.13–7.30 (5, m); ^{13}C NMR δ 19.3, 22.4, 23.5, 26.4, 26.5, 26.6, 27.3, 28.0, 28.4, 30.0, 32.8, 39.0, 58.1, 126.3, 128.4, 128.9, 139.0, 213.1; MS (EI^+) *m/z* (relative intensity) 285 (23), 284 (100), 193 (8), 159 (21), 146 (17), 131 (11), 117 (23), 104 (19), 91 (60); HRMS (EI^+) calcd for $C_{20}H_{28}O$ (M^+) 284.2140, found 284.2139.

(1*R,3*R**,5*S**)–3–Methyl–3–(phenyl)methylbicyclo[3.1.0]hexan–2–one (20a).** From LDA (1.22 mmol), ketone **7a** (208 mg, 1.11 mmol), and iodomethane (788 mg, 5.55 mmol) was obtained 70 mg (0.35 mmol, 32%) of **20a** as a colorless oil, R_f 0.49 (30% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 10-20% Et_2O/hexanes). IR (neat) cm^{-1} 1728, 1610, 1493, 1376, 1307, 1197; ^1H NMR δ -0.20–-0.10 (1, m), 0.78–0.92 (1, m), 1.16 (3, s), 1.67–1.92 (3, m), 2.05 (1, d, J=13.2 Hz), 2.43 (1, d, 13.3 Hz), 2.86 (1, d, J=13.3 Hz), 7.01–7.32 (5, m); ^{13}C NMR δ 12.1, 17.1, 27.8, 28.9, 34.9, 43.4, 50.8, 126.5, 128.1, 130.3, 138.2, 218.2; MS (EI^+) *m/z* (relative intensity) 200 (17), 185 (12), 159 (6), 145 (7), 129 (7), 117 (17), 109 (11), 91 (100); HRMS (EI^+) calcd for $C_{14}H_{16}O$ (M^+) 200.1201, found 200.1199.

(1*R,3*R**,5*S**)–3–Methyl–3–(phenyl)methylbicyclo[3.1.0]hexan–2–one (20a).** A solution of **7a** (104 mg, 0.56 mmol), iodomethane (397 mg, 2.80 mmol) and NaH (40 mg, 1.68 mmol) in THF (10 mL) was heated at reflux for 18 h, then cooled to room temperature (rt). Water (5 mL) was slowly added and the mixture was

extracted with CH_2Cl_2 (4 x 20 mL). The organic phases were combined, dried ($MgSO_4$), and volatiles removed under vacuum. Flash column chromatography (250 mL of silica cluted with 10% EtOAc/hexanes) afforded 71 mg (0.35 mmol, 63%) of **20a** as a colorless oil, R_f 0.57 (40% EtOAc/hexanes). Spectral data were as above.

(1*R,5*S**)–3,3–Di(phenyl)methylbicyclo[3.1.0]hexan–2–one (21).** A solution of **2** (200 mg, 2.08 mmol), α–bromotoluene (1.78 g, 10.40 mmol), and NaH (250 mg, 10.40 mmol) in THF (10 mL) was heated at reflux for 6 h, then cooled to rt. Water (10 mL) was slowly added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organic phases were combined, dried ($MgSO_4$), and volatiles removed under vacuum. Flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes) afforded 245 mg (0.89 mmol, 43%) of **21** as a white solid, mp 104-106 °C, R_f 0.63 (40% EtOAc/hexanes). IR (neat) cm^{-1} 1733, 1613, 1580, 1494, 1467, 1302, 1189, 1096, 765; ^1H NMR δ: -0.50– -0.41 (1, m), 0.54-0.70 (1, m), 1.26-1.40 (2, m), 1.86 (1, d, J = 13.2 Hz), 2.24-2.35 (1, m), 2.44 (1, d, J = 13.2 Hz), 2.67 (1, d, J = 12.8 Hz), 3.01 (1, d, J = 12.8), 3.10 (1, d, J = 13.2 Hz), 7.00-7.35 (10, m); ^{13}C NMR δ 11.7, 17.6, 29.3, 30.3, 42.9, 47.5, 56.6, 126.6, 128.1, 128.3, 130.5, 130.7, 136.9, 138.0, 218.3; MS (EI^+) *m/z* (relative intensity) 277 (2), 276 (6), 193 (4), 186 (16), 185 (100), 91 (48); HRMS (EI^+) calcd for $C_{20}H_{20}O$ (M^+) 276.1514, found 276.1505.

(1*R,3*S**,6*S**)–3–(Phenyl)methyl–3–(2-propenyl)bicyclo[4.1.0]heptan–2–one (22a).** From LDA (1.14 mmol), ketone **8a** (191 mg, 0.95 mmol), and 3-bromopropene (577 mg, 4.77 mmol) was obtained 123 mg (0.51 mmol, 54%) of **22a** as a colorless oil, R_f 0.55 (40% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 2926, 1684, 1456, 1450, 1351, 1339, 1221, 943; ^1H NMR δ 0.28–0.40 (1, m), 0.58–0.74 (1, m), 1.32–2.43 (9, m), 3.35 (1, d, J = 13.1 Hz), 5.05–5.20 (2, m), 5.83 (1, dddd, J = 12.4 Hz, J = 10.6 Hz, J = 7.8 Hz, J = 7.3 Hz), 7.10–7.32 (5, m); ^{13}C NMR δ 7.6, 16.2, 17.6, 22.6, 25.1, 41.6, 42.2, 49.8, 118.7, 126.2, 127.9, 130.4, 133.2, 138.1, 211.9; GC/MS (method A, R_t = 8.73 min) *m/z* (relative intensity) 241(7), 240 (34), 20 (14), 199 (97), 197 (17), 196 (18), 149 (20), 143 (25), 135 (11), 129 (28), 128 (17), 117 (25), 115 (24), 92 (11), 91 (100), 79 (18).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.63; H, 8.54.

(1*R,3*S**,6*S**)–3–(Phenyl)methyl–3–(2-propenyl)bicyclo[4.1.0]heptan–2–one (22a).** A solution of ketone **8a** (120 mg, 0.60 mmol), 3-bromopropene (363 mg, 3.0 mmol) and NaH (43.2 mg, 1.8 mmol) in THF (10 mL) was heated to reflux for 24 h, then cooled to rt. Water (5 mL) was slowly added and the water layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and volatiles removed under vacuum to give a yellow oil. Flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes) gave 115 mg (0.48 mmol, 80%) of **22a** as a colorless oil, R_f 0.58 (40% EtOAc/hexanes). Spectral data were as above.

(1*R,3*R**,6*S**)–3–(Phenyl)methyl–3–(2-propenyl)bicyclo[4.1.0]heptan–2–one (24a) and (1*R**,3*S**,6*S**)–3–(Phenyl)methyl–3–(2-propenyl)bicyclo[4.1.0]heptan–2–one (24b).** From LDA (1.32 mmol), ketone **9a** (165 mg, 1.10 mmol), and α–bromotoluene (940 mg, 5.49 mmol) was obtained 195 mg (0.81 mmol, 74%) of an 11:1 mixture of **24a** and **24b** as a colorless oil, R_f 0.57 (30% EtOAc/hexanes), after flash column chromatography (200 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 1672, 1468, 1443, 1357, 1339, 1215; ^1H NMR (for **24a**) δ 0.85–1.92 (9, m), 2.54–2.73 (1, m), 2.60 (1, d, J = 13.2 Hz), 2.93 (1, d, J =

13.5 Hz), 4.96 (1, d, J = 18.3 Hz), 5.03 (1, d, J = 10.6 Hz), 5.56 (1, dddd, J = 18.3 Hz, J = 10.6 Hz, J = 5.9 Hz, J = 5.5 Hz), 7.01–7.33 (5, m); ^{13}C NMR (for **24a**) δ 8.2, 16.4, 18.0, 22.2, 25.4, 41.9, 43.4, 48.8, 118.5, 126.5, 128.8, 130.6, 134.1, 136.9, 212.7; GC/MS (method A, R_t = 8.85 min) *m/z* (relative intensity) 241 (2), 240 (10), 199 (55), 149 (13), 143 (14), 135 (13), 129 (17), 115 (17), 91 (100), 79 (10).

(1*R,3*R**,7*S**)–3–Methyl–3–(phenyl)methylbicyclo[5.1.0]octan–2–one (25a).** From LDA (0.49 mmol), ketone **12a** (87 mg, 0.41 mmol), and iodomethane (291 mg, 2.05 mmol) was obtained 41 mg (0.18 mmol, 44%) of **25a** as a colorless oil, R_f 0.64 (30% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 1691, 1616, 1511, 1468, 1388, 1314, 1017; ^{1}H NMR δ 0.78–2.05 (12, m), 2.46–2.73 (2, m), 3.08 (1, dd J = 13.0 Hz, J = 5.2 Hz), 7.08–7.33 (5, m); ^{13}C NMR 21.1, 22.0, 24.4, 26.3, 28.0, 29.4, 33.8, 37.7, 48.0, 125.8, 128.2, 129.1, 140.8, 212.7; GC/MS (method A, R_t = 8.11 min) *m/z* (relative intensity) 228 (15), 144 (24), 131 (14), 130 (14), 129 (27), 119 (19), 117 (22), 115 (14), 109 (23), 104 (11), 95 (18), 94 (11), 92 (11), 91 (100), 81 (17).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.17; H, 8.83. Found: C, 84.50; H, 8.74.

(1*R,3*S**,7*S**)–3–Methyl–3–(phenyl)methylbicyclo[5.1.0]octan–2–one (26a).** From LDA (1.50 mmol), ketone **14a** (148 mg, 1.07 mmol), and α–bromotoluene (915 mg, 5.35 mmol) was obtained 114 mg (0.50 mmol, 46%) of **26a** as a colorless oil, R_f 0.66 (40% EtOAc/hexanes), after flash column chromatography (250 mL of silica eluted with 5% EtOAc/hexanes). IR (neat) cm^{-1} 1684, 1604, 1511, 1455, 1381, 1091, 1005; ^{1}H NMR δ 0.82–1.10 (12, m), 2.40–2.65 (1, m), 2.57 (1, d, J = 14.5 Hz), 3.42 (1, d, J = 14.6 Hz), 7.08–7.42 (5, m); ^{13}C NMR 18.1, 19.1, 24.9, 26.9, 27.1, 33.2, 39.1, 41.0, 41.7, 126.4, 128.5, 129.8, 140.7, 213.3; MS (method A, R_t = 8.19 min) *m/z* (relative intensity) 229 (17), 228 (100), 213 (12), 199 (13), 186 (10), 185 (55), 172 (20), 171 (30), 157 (16), 145 (16), 143 (17), 131 (14), 130 (11), 129 (37), 128 (25), 109 (11), 91 (69).

1–Methyl–3–(phenyl)methylbicyclo[6.1.0]nonan–2–one (27). From LDA (0.48 mmol), ketone **15a** (91 mg, 0.40 mmol), and iodomethane (63 mg, 0.44 mmol) was obtained recovered starting material and 5 mg (0.02 mmol, 5%) of **27** as a colorless oil, R_f 0.40 (10% EtOAc/hexanes), after column chromatography (40 mL of silica eluted with 3% Et_2O/hexanes). ^{1}H NMR δ 0.78–0.90 (2, m), 1.00–1.15 (1, m), 1.20 (3, s), 1.39–1.70 (7, m), 2.19–2.32 (1, m), 2.55 (1, dd, J = 12.7, 5.3 Hz), 2.85-3.00 (1, m), 3.03 (1, dd, J = 12.7, 7.9 Hz), 7.09–7.30 (5, m).

Acknowledgment. Partial support of this research by Research Corporation, by the Elsa U. Pardee Foundation, and by the University of Arizona through the Materials Characterization Program is gratefully acknowledged.

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8. Use of 1.3 equivalents of α-bromotoluene gave **7a** in 48% yield and **8a** in 85% yield from **2** and **3**, respectively, after 24 hours at -22 °C.

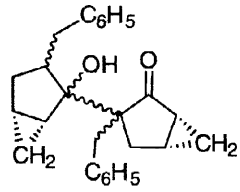
9. For previous use of ^{13}C NMR in determining diastereomer ratios, see Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183–2186.

10. Diastereomer ratios determined by ^{13}C NMR were in agreement with diastereomer ratios from GC/MS analyses.

11. Determined for enolates derived from bicyclic ketones by consideration of Dreiding models. The suitability of available molecular mechanics parameters to enolates derived from α,β–cyclopropyl ketones has not been established at this time.

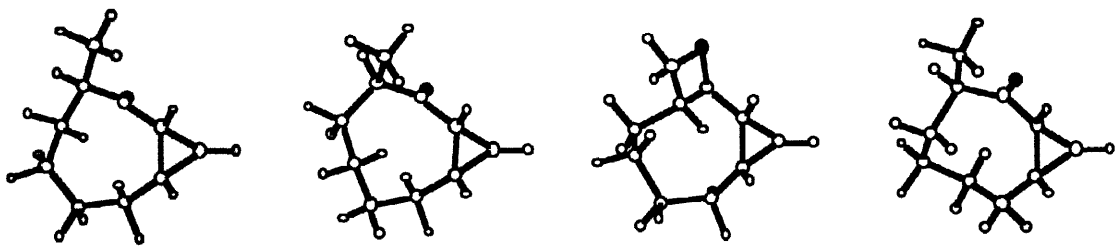
12. It is not presently known if stereocontrol was lost in the formation of the enolate, in the alkylation, or after alkylation by equilibration.

13. From IR, NMR, and MS data, the dimer, which was repeatably obtained, consists of one or more stereoisomers of ***i***.



i

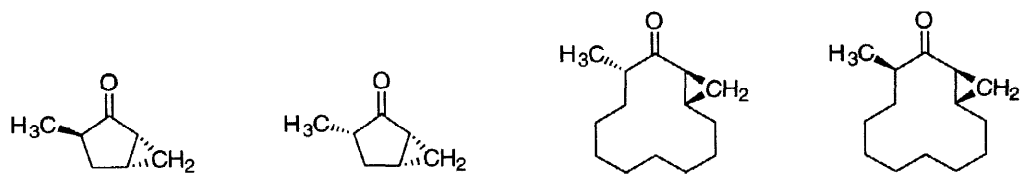
14. Conformational searching using a modified MM2* force field[2a] in BATCHMIN v4.0[17] found low energy conformers **17a**-1 through **17a**-4 (percentage of population at -78 °C given in parentheses). The O=C–Cα'–Hα' dihedral angles (also given) suggest that the α'-hydrogen would exhibit low kinetic acidity, especially at low temperatures.



17a-1 (>99%, 137°) **17a**-2 (<1%, 130°) **17a**-3 (<<1%, 11°) **17a**-4 (<<1%, 119°)

15. Equilibration (*t*–BuOK/*t*–BuOH, rt, 40 h) led to a 2:3 mixture of **10a** and **10b** and to a 3:2 mixture of **14a** and **14b**. Slow equilibration of **8a** and **8b** while standing in $CDCl_3$ was also noted.

16. Conformational searching using a modified MM2* force field[2a] in BATCHMIN v4.0[17] found ***ii*** (related to **7a**) to be more stable than ***iii*** (related to **7b**) by 11 kJ/mol, **10a** to be more stable than **10b** by 4 kJ/mol, **14a** to be more stable than **14b** by 1 kJ/mol, **17a** to be more stable than **17b** by 2 kJ/mol, and ***v*** (related to **19b**) to be more stable than ***iv*** (related to **19a**) by 4 kJ/mol.



ii ***iii*** ***iv*** ***v***

17. (a) *BATCHMIN, 4.0*; Columbia University: New York, 1993. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.