Effect of β-Substituents on the Regioselectivity of the Diazomethane Ring Expansion of α-Methyl-α-methoxycyclobutanones to Cyclopentanones

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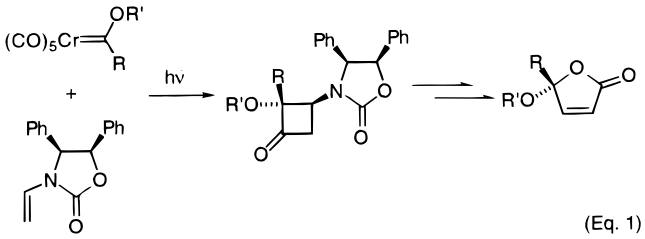
The ring expansion of 22 differently β-substituted α-methyl-α-methoxycyclobutanones by diazomethane was studied. Migration of the less-substituted α-carbon was favored with the single exception of a very sterically hindered β-benzyloxy β-substituent.

Introduction

Cyclobutanones are useful synthetic intermediates, undergoing a variety of functionalization and ring-expansion processes.[1] They are usually synthesized by the 2 + 2 cycloaddition reaction of ketenes (generated from acid chlorides) with alkenes.[2] We have developed a route to functionalized, optically active cyclobutanones (eq 1)[3] and have utilized them as key intermediates in the synthesis of the carbocyclic nucleoside analogues (−)-cyclobut-A and (±)-3′-*epi*-cyclobut-A[4] and, via a Baeyer−Villiger ring expansion, the butenolides (+)-tetrahydrocerulenin[5] and (+)-cerulenin[6] as well as a template for the synthesis of optically active 4′,4′-disubstituted nucleoside analogues.[7]

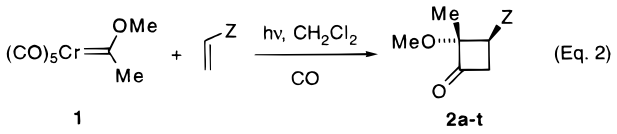


Cyclobutanones also undergo a variety of carbocyclic ring expansions to give cyclopentanones.[8] Among these, diazomethane methodology is the most extensively used.[9] With unsymmetrical cyclobutanones, diazomethane ring expansions tend to favor migration of the less-substituted α-carbon and disfavor migration of α-positions bearing electronegative halogen groups. However, other factors including steric effects, ring strain, steric hindrance to the approach of the diazomethane, and conformation in the intermediate betaine all can influence the regioselectivity of migration, making predictions difficult.

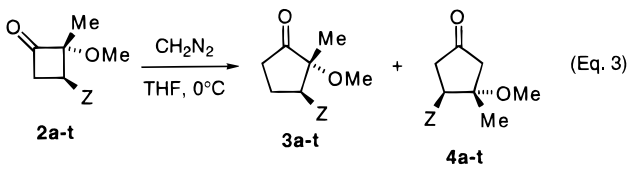
In the course of studies directed toward the synthesis of five-membered carbocyclic nucleoside analogues via diazomethane ring expansion of 2,2,3-trisubstituted cyclobutanones, an unexpected influence of the β-substituent on the regioselectivity of expansion was noted. Below are detailed the results of studies addressing this question.

Results and Discussion

The requisite cyclobutanones were synthesized in fair to good yield by the photolysis of alkoxycarbene complex **1** with a range of alkenes (eq 2, Table 1). As expected,



the reaction was quite stereoselective, giving almost exclusively the cyclobutanone having the α-methyl group syn to the β-substituent. Because electron-deficient alkenes undergo reaction with ketenes poorly, electron-withdrawing β-substituted cyclobutanones **2g**, **2h**, and **2k** were generated by acetylation or triflation of **2f** and by oxidation of **2j**. With this broad range of substituted cyclobutanones in hand, ring expansion studies were initiated (eq 3).



Freshly prepared diazomethane[10] was bubbled through a solution of the cyclobutanone in THF at 0 °C. After 0.5−1 h at 0 °C, the reaction mixture was warmed to

(1) For reviews, see: (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *27*, 797. (b) Lee-Ruff, E. New Synthetic Pathways from Cyclobutanones. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: Greenwich, CT, 1991; Vol. 1.

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(8) For reviews, see: (a) Wovkulich, P. M. Skeletal Reorganizations: Chain Extension and Ring Expansion. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 1, pp 843−861. (b) Reference 9.

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(10) Diazomethane was prepared from Diazald according to Aldrich Technical Information Bulletin No. AL-180.

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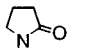
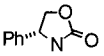
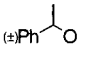
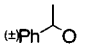
Table 1. Preparation of Cyclobutanones 2a−t

Compound	Z	Yield, %[a]
2a	n-C_4H_9	55
2b	$TMSCH_2$	78
2c	$-(CH_2)-_3$	84[b]
2d	$-CH=CH-CH_2-$	80[c]
2e	Ph	61
2f	p-HOPh	51
2g	p-AcOPh	51[d]
2h	p-TfOPh	---[e]
2i	p-MeOPh	59
2j	PhS	58
2k	PhSO	77[f]
2l		66[g]
2m		53
2n	EtO	65
2o	$-CH_2CH_2CH_2O-$	80[h]
2p	t-BuO	51
2q	$PhCH_2O$	82
2r		68[i]
2s	2,4,6-$(iPr)_3PhCH_2O$	72
2t	(±)-2,4,6-$(iPr)_3$PhCHO CH_3	67[j]

[a] Yields are for isolated, purified material. [b] The bicyclic ketone from cyclopentene. [c] The bicyclic ketone from cyclopentadiene. [d] Prepared by treating **2f** with acetic anhydride. [e] Prepared by treating **2f** with triflic anhydride. [f] Prepared by oxidation of **2j** with oxone. [g] Obtained as an 85:15 mixture of syn/anti isomers. [h] The bicyclic ketone from dihydropyran. [i] Obtained as an inseparable 1:1 mixture of diastereoisomers with the relative stereochemistry of the cyclobutanone as shown. [j] Obtained as an 86:14 mixture of diastereoisomers.

Table 2. Ring Expansion of Cyclobutanones 2a−t

Cyclobutanone	Z	Yield, %[a]	Ratio 3/4[b]
2a	n-C_4H_9	61	59/41
2b	$TMSCH_2$	67	59/41
2c	$-(CH_2)-_3$	72	91/9
2d	$-CH=CH-CH_2-$	68	91/9
2e	Ph	79	72/28
2f	p-HOPh	76	71/29
2g	p-AcOPh	---	66/34
2h	p-TfOPh	---	77/33
2i	p-MeOPh	52	80/20
2j	PhS	92	80/20
2k	PhSO	67	92/8
2l		89	97/3
2m		84	100/0
2n	EtO	70	67/33
2o	$-CH_2CH_2CH_2O-$	81	95/5
2p	t-BuO	---	62/38
2q	$PhCH_2O$	84	72/28
2r		[c]	~70/30
2s	2,4,6-$(iPr)_3PhCH_2O$	46	68/32
2t	(±)-2,4,6-$(iPr)_3$PhCHO CH_3	76	30/70

[a] Yields are for isolated pure *mixtures* of regioisomers. [b] Ratios are for crude reaction mixtures, determined by ^1H NMR spectroscopy and GLC analysis. [c] Obtained as a mixture of four diastereoisomers.

room temperature then concentrated under vacuum once the yellow color had dissipated. The product distribution of the crude reaction mixture was determined by ^1H NMR spectroscopy (300 MHz), comparing the peak intensities for the α-methyl group, the α-methoxy group, or both. The ratios were confirmed by GLC analysis. The crude material was then purified (for chemical yield) by flash chromatography or evaporative distillation. When possible, the regioisomers were separated and fully characterized. The results are reported in Table 2.

Since the α-substitution pattern in cyclobutanones **2a**−**t** is identical, any differences in regioselectivity in the ring expansion must be due to the influence of the β-substituent. Published studies[9] indicate that migration of the less-substituted α-position is favored and that electronegative groups suppress migration. Both of these factors should strongly favor formation of regioisomer **3**. Although this is indeed the major regioisomer observed in the diazomethane ring expansion of cyclobutanones **2**, the observed ratios of **3** to **4** vary from 100/0 to 1/2 depending on the β-substituent, an effect not previously addressed systematically.

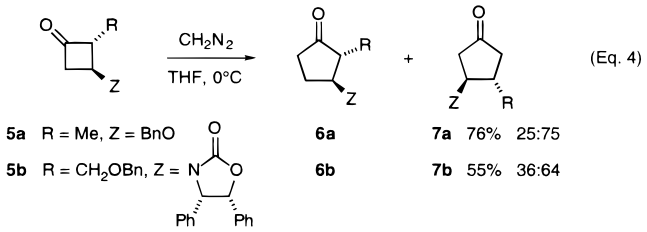
Although β-substitution clearly influences the regioselectivity of ring expansion, the root cause of this influence is unclear from the experimental evidence, since no clear correlation to either steric or electronic factors is evident. Of the range of substituents examined, alkyl groups in the β-position (**2a**,**b**) result in the least regioselectivity, ~3:2 in favor of regioisomer **3**. Since, with the exception of **2t**, regioisomer **3** is strongly favored, this implies that β-alkyl substitution results in an *increased* preference for migration of the more substituted α-carbon, which also bears an electronegative methoxy group. Fused bicyclic systems, from cyclic olefins (**2c**,**d**,**o**), strongly favor (~10:1) formation of regioisomer **3**.

Electronic factors seem to be of little importance in directing the insertion process. Both electron-rich (**2e**,**f**,**i**) and electron-poor substituents (**2g**,**h**) favor regioisomer **3**, although the range is fairly broad (~2:1 to ~12:1). Amide (**2l**) and oxazolidinone substituents (**2m**) give almost exclusively regioisomer **3**, while alkoxy groups (**2n**−**s**) also favor formation of **3** but to a lesser degree.

Steric factors play little role in the regioselectivity of the ring expansion. Ethoxy (**2n**), *tert*-butoxy (**2p**), benzyloxy (**2q**), α-phenethyloxy (**2r**), and even the very bulky 2,4,6-triisopropylbenzyloxy (**2s**) all give roughly the same regioselectivity in the ring expansion, favoring **3** over **4** by a factor of ~2. The striking exception to this is the last entry, **2t**, which bears an alkoxy group having α-branching (as in the case with **2p** and **2r**) as well as the very hindered aryl group found in **2s**. In this unique case, the regioselectivity is reversed, favoring regioisomer

4 by a factor of 2. The enol ether of this same sterically hindered alcohol [1-(triisopropylphenyl)ethanol] undergoes highly diastereoselective 2 + 2 cycloaddition with dichloroketenes,[11] a fact rationalized by the lowest energy conformation of the enol ether. How it reverses the regioselectivity of the ring expansion of **2t** to **3t** and **4t** is less obvious.

That the α-alkoxy group in cyclobutanones **2a**−**t** is the major determinant of the regioselective outcome of the diazomethane ring expansion is seen from the results shown in eq 4. Cyclobutanones **5a** and **5b**, lacking the α-methoxy group present in cyclobutanones **2** (SmI_2 reduction),[4] undergo diazomethane ring expansion favoring migration of the *more* substituted α-carbon. *β*-Substituents play a subsidiary but sometimes significant role in directing diazomethane ring expansions of cyclobutanones.



Experimental Section

Materials. The following compounds were prepared according to literature methods: [(methoxy)(methyl)carbene]pentacarbonylchromium (0) **(1)**,[12] 2-methoxy-2-methyl-3-phenylcyclobutan-1-one **(2e)**,[13] 7-methoxy-7-methylbicyclo[3.2.0]hept-2-en-6-one **(2d)**,[13] 3-ethoxy-2-methoxy-2-methylcyclobutan-1-one **(2n)**,[13] 8-methoxy-8-methyl-2-oxabicyclo[4.2.0]octan-7-one **(2o)**,[13] diazomethane,[10] and 2-methoxy-2-methyl-3-(2-oxo-1-pyrrolidinyl)cyclobutan-1-one **(2l)**.[13]

General Procedures. The 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectra were recorded in $CDCl_3$, and chemical shifts are given in ppm relative to $CHCl_3$. Purification of compounds was achieved by column chromatographic techniques using Merck silica gel (230−400 mesh) as the stationary phase or vacuum distillation (Kugelrohr).

GLC analyses were conducted on an HP5 25 M × 0.125 mm i.d. column. GLC conditions: initial temperature 100 °C (8 psi head pressure), ramp at 10 °C/min, final temperature 250 °C for 10 min.

HPLC separations were conducted on a Microsorb (5 μM particle size) 25 cm × 21.4 mm i.d. column. HPLC conditions for the separation of **3i**/**4i**: 10% EtOAc/Hex at 10 mL/min flow rate. For the separation of **3s/4s**: 5% EtOAc/Hex at 8 mL/min flow rate.

General Procedure for the Photochemical [2 + 2] Reaction for the Formation of Cyclobutanones. A solution of the carbene complex and olefin in degassed CH_2Cl_2 in a Pyrex pressure tube was saturated with CO (80 psi, three cycles) and then photolyzed under 80 psi of CO at 35 °C for 4−20 h. Photolysis reactions were carried out by placing the tube at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled Pyrex immersion well. A Conrad-Hanovia 7830-C power supply was used. After the reaction was complete, the crude mixture was concentrated in vacuo and the slurry triturated with methanol (4−6 mL). The precipitated chromium hexacarbonyl was removed by filtration through Celite and then the filtrate concentrated in vacuo. Syn/anti ratios were obtained by ^{1}H NMR (300 MHz) and confirmed by GLC analysis. The product was purified by either silica gel chromatography or vacuum distillation (Kugelrohr).

2-Methoxy-2-methyl-3-butylcyclobutan-1-one (2a). From 315 mg (1.25 mmol) of [(methoxy)(methyl)carbene]pentacarbonylchromium (0) **(1)** and 1.6 mL (12.59 mmol) of 1-hexene in 12 mL of CH_2Cl_2 was obtained after vacuum distillation (Kugelrohr, 110 °C/0.7 mmHg), 118 mg (55%) of **2a** as an oil: ^{1}H NMR δ 3.35 (s, 3H), 2.84 (dd, J = 13.3, 20.4 Hz, 1H), 2.50 (m, 2H), 1.75−1.61 (m, 1H), 1.48−1.25 (m, 5H), 1.29 (s, 3H), 0.91 (br s, 3H); ^{13}C NMR δ 209, 93, 52, 45, 34, 31, 30, 22, 15, 14; IR (neat) ν 1779 cm^{-1}; MS (FAB) 171 (M + H); HRMS (FAB) calcd for $C_{10}H_{18}O_2$ 171.1385, found 171.1382.

2-Methoxy-2-methyl-3-trimethylsilylmethylenecyclobutan-1-one (2b). From 330 mg (1.31 mmol) of **1** and 2.1 mL (13.19 mmol) of allyl trimethylsilane in 12 mL of CH_2Cl_2 was obtained after vacuum distillation (Kugelrohr, 65 °C/0.7 mmHg), 205 mg (78%, 91/9 syn/anti) of **2b** as an oil. *syn*-**2b**: ^{1}H NMR δ 3.33 (s, 3H), 2.83 (dd, J = 9.2, 16.4 Hz), 2.58−2.32 (m, 2H), 1.25 (s, 3H), 0.93 (dd, J = 3.6, 14.4 Hz, 1H), 0.61 (dd, J = 11.7, 14.8 Hz, 1H), 0.00 (s, 9H); ^{13}C NMR δ 209, 94, 52, 47, 30, 17, 15, −1; IR (neat) ν 1769 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.80; H, 9.99.

7-Methoxy-7-methylbicyclo[3.2.0]heptan-6-one (2c). From 310 mg (1.23 mmol) of **1** and 1.1 mL (12.39 mmol) of cyclopentene in 12 mL of CH_2Cl_2 was obtained after vacuum distillation (Kugelrohr, 100 °C/0.7 mmHg), 160 mg (84%) of **2c** as an oil: ^{1}H NMR δ 3.80 (t, J = 8.2 Hz, 1H), 3.32 (s, 3H), 2.72 (t, J = 8.5 Hz, 1H), 2.11−2.01 (m, 1H), 1.93−1.62 (m, 3H), 1.59−1.31 (m, 2H), 1.14 (s, 3H); ^{13}C NMR δ 214, 97, 62, 52, 43, 29, 28, 26, 11; IR (neat) ν 1779 cm^{-1}; MS (FAB) 155 (M + H); HRMS (FAB) calcd for $C_9H_{14}O_2$ 155.1072, found 155.1069.

2-Methoxy-2-methyl-3-*p*-hydroxyphenylcyclobutan-1-one (2f). From 830 mg (3.31 mmol) of **1** and 600 mg (4.97 mmol) of *p*-hydroxy styrene in 25 mL of CH_2Cl_2 was obtained after chromatography (20% EtOAc/Hex), 346 mg (51%) of **2f** as a solid: ^{1}H NMR δ 7.10 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.87 (br s, 1H), 3.84 (t, J = 10.4 Hz, 1H), 3.50 (s, 3H, OCH_3), 3.14 (dd, J = 10.2, 17.4 Hz, 1H), 3.00 (dd, J = 10.2, 17.3 Hz, 1H), 1.03 (s, 3H); ^{13}C NMR δ 209, 154, 129.2, 129.0, 115, 95 (C_2), 53, 42, 38, 16; IR (film) ν 3357, 1774 cm^{-1}; MS (FAB) 207 (M + H); HRMS (FAB) calcd for $C_{12}H_{14}O_3$ 207.1021, found 207.1015.

2-Methoxy-2-methyl-3-*p*-acetoxyphenylcyclobutan-1-one (2g). To a solution of 100 mg (0.45 mmol) of **2f** in 5 mL of tetrahydrofuran was added 150 μL (1.06 mmol) of triethylamine, 50 μL (0.53 mmol) of acetic anhydride, and a few crystals of DMAP, and the resulting solution was stirred at room temperature for 16 h. The reaction was diluted with 5 mL of brine and then extracted into Et_2O (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. After chromatography (20% EtOAc/Hex), 62 mg (51%) of **2g** was obtained as an oil: ^{1}H NMR δ 7.22 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 3.90 (t, J = 10.3 Hz, 1H), 3.50 (s, 3H), 3.16 (dd, J = 10.4, 17.3 Hz, 1H), 3.01 (dd, J = 10.2, 17.3 Hz, 1H), 2.31 (s, 3H), 1.04 (s, 3H); ^{13}C NMR δ 208, 168, 149, 134, 128, 121, 95, 53, 42, 38, 21, 16; IR (neat) ν 1774, 1754 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.35.

2-Methoxy-2-methyl-3-*p*-trifluoromethanesulfonylcyclobutan-1-one (2h). To a solution of 108 mg (0.52 mmol) of **2f** in 5 mL of tetrahydrofuran was added 180 μL (1.30 mmol) of triethylamine, 132 μL (0.78 mmol) of trifluoromethane sulfonic anhydride, and a few crystals of DMAP, and the resulting solution was stirred at room temperature for 16 h. The reaction was diluted with 5 mL of brine and then extracted into Et_2O (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. After chromatography (20% EtOAc/Hex), **2h** was obtained as an oil: ^{1}H NMR δ 7.27 (br s, 5H), 3.90 (t, J = 10.2 Hz, 1H), 3.50 (s, 3H), 3.13 (dd, J = 10.4, 17.4 H, 1H), 3.01 (dd, J = 10.1,

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17.4 Hz, 1H), 0.99 (s, 3H); ^{13}C NMR δ 207, 148, 138, 129, 121, 116, 95, 53, 42, 38, 16; IR (neat) ν 1784 cm^{-1}.

2-Methoxy-2-methyl-3-*p*-methoxyphenylcyclobutan-1-one (2i). From 610 mg (2.43 mmol) of **1** and 393 mg (2.92 mmol) of *p*-methoxystyrene in 25 mL of CH_2Cl_2 was obtained after chromatography (20% EtOAc/Hex), 320 mg (59%, 96/4 syn/anti) of **2i** as a white solid. *syn*-**2i:** mp 33−35 °C; ^{1}H NMR δ 7.14 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.85 (t, J = 10.5 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 3.15 (dd, J = 10.4, 17.3 Hz, 1H), 2.99 (dd, J = 10.3, 17.3 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR δ 208, 158, 129, 128, 114, 95, 55, 52, 42, 38, 16; IR (film) ν 1779 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.74; H, 7.30.

3-Phenylthio-2-methoxy-2-methylcyclobutan-1-one (2j). From 620 mg (2.47 mmol) of **1** and 0.36 mL (2.72 mmol) of phenyl vinyl sulfide in 25 mL of CH_2Cl_2 was obtained after chromatography (20% EtOAc/Hex), 316 mg (58%) of **2j** as a pale yellow oil: ^{1}H NMR δ 7.44−7.18 (m, 5H), 4.00 (t, J = 9.8 Hz, 1H), 3.40 (s, 3H), 3.24 (dd, J = 10, 18 Hz, 1H), 2.85 (dd, J = 9.5, 18 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR δ 206, 136, 129, 128, 126, 96, 52, 47, 39, 16; IR (neat) ν 1784 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35. Found: C, 64.94, H, 6.20.

3-Sulfoxyphenyl-2-methoxy-2-methylcyclobutan-1-one (2k). Following the procedure of Quallich and Lackey,[14] to a solution of 86 mg (0.30 mmol) of **2j** in 2 mL of acetone was added a solution of 290 mg (0.46 mmol) of oxone in 1.5 mL of water and the cloudy slurry stirred at room temperature for 1 h. The reaction was diluted with 4 mL of 10% aqueous $NaHSO_3$ and then extracted into CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo, affording 72 mg (77%) of **2k** (>95% purity): ^{1}H NMR δ 7.96−7.89 (m, 2H), 7.74−7.57 (m, 3H), 3.85 (t, J = 9.7 Hz, 1H), 3.50 (dd, J = 9.7, 17.7 Hz, 1H), 3.40 (s, 3H), 2.98 (dd, J = 9.8, 17.8 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR δ 201, 140, 134, 129, 127, 96, 57, 52, 43, 14; IR (neat) ν 1789 cm^{-1}.

2-Methoxy-2-methyl-3-((*S*)-4-phenyl-2-oxazolidinyl)cyclobutan-1-one (2m). From 320 mg (1.27 mmol) of **1** and 363 mg (1.91 mmol) of 3-vinyl-(*S*)-4-phenyl-2-oxazolidinone[15] in 14 mL of CH_2Cl_2 was obtained after chromatography (40% EtOAc/Hex) 187 mg (53%) of **2m** as a white solid: $[\alpha]_D$ +31 (*c* 1.6, $CHCl_3$); mp 130−132 °C; ^{1}H NMR δ 7.48−7.39 (m, 3H), 7.36−7.29 (m, 2H), 4.87 (dd, J = 5.4, 8.7 Hz, 1H), 4.70 (t, J = 8.7 Hz, 1H), 4.25 (dd J = 5.5, 8.8 Hz, 1H), 4.18 (t, J = 10 Hz, 1H), 3.47 (dd, J = 9.1, 18 Hz, 1H), 3.14 (s, 3H), 2.71 (dd, J = 10.2, 18 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR δ 206, 157, 138, 129.4, 129.3, 126, 96, 70, 61, 52, 48, 42, 14; IR (film) ν 1794, 1723 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{17}NO_4$ 276.1235, found 276.1229.

3-*tert*-Butoxy-2-methoxy-2-methylcyclobutan-1-one (2p). From 270 mg (1.07 mmol) of **1** and 1.5 mL (10.79 mmol) of *tert*-butyl vinyl ether in 10 mL of CH_2Cl_2 was obtained after vacuum distillation (Kugelrohr, 125 °C/0.7 mmHg) 102 mg (51%) of **2p** as an oil: ^{1}H NMR δ 4.40 (t, J = 8.0 Hz, 1H), 3.39 (s, 3H), 2.91 (dd, J = 8.5, 18 Hz, 1H), 2.80 (dd, J = 7.7, 18 Hz, 1H), 1.38 (s, 3H), 1.24 (s, 9H); ^{13}C NMR δ 209, 95, 74, 63, 52, 48, 28, 14; IR (neat) ν 1779 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{18}O_3$ 187.1334, found 187.1327.

3-Benzyloxy-2-methoxy-2-methylcyclobutan-1-one (2q). From 570 mg (2.27 mmol) of **1** and 611 mg (4.55 mmol) of benzyl vinyl ether[16] in 25 mL of CH_2Cl_2 was obtained after chromatography (10% EtOAc/Hex), 414 mg (82%) of **2q** as an oil: ^{1}H NMR δ 7.42−7.29 (m, 5H), 4.66 (d, J = 12.1 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.35 (t, J = 7.6 Hz, 1H), 3.40 (s, 3H), 2.96 (dd, J = 8.1, 18 Hz, 1H), 2.88 (dd, J = 8, 18 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR δ 207, 137, 128, 127.9, 127.7, 95, 72, 70, 52, 46, 13; IR (neat) ν 1779 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}O_3$ 221.1177, found 221.1167.

3-α-Methylbenzyloxy-2-methoxy-2-methylcyclobutan-1-one (2r). From 284 mg (1.13 mmol) of **1** and 185 mg (1.25 mmol) of α-methylbenzyl vinyl ether[16] in 10 mL of CH_2Cl_2 was obtained after chromatography (20% EtOAc/Hex), 182 mg (68%) of **2r** as an inseparable 1:1 mixture of diasteroisomers: ^{1}H NMR δ 7.45−7.23 (m, 10H), 4.62−4.44 (m, 2H), 4.27−4.12 (m, 2H), 3.35 (s, 3H), 3.22 (s, 3H), 3.01−2.59 (m, 4H), 1.52 (s, 3H), 1.50 (d, J = 5.2 Hz, 6H), 1.41 (s, 3H).

3-(2,4,6-Triisopropylbenzyloxy)-2-methoxy-2-methylcyclobutan-1-one (2s). From 135 mg (0.54 mmol) of **1** and 168 mg (0.65 mmol) of 2,4,6-triisopropylbenzyl vinyl ether[16] in 10 mL of CH_2Cl_2 was obtained after chromatography (10% EtOAc/Hex) 134 mg (72%) of **2s** as an oil: ^{1}H NMR δ 7.05 (s, 2H), 4.72 (d, J = 10.6 Hz, 1H), 4.61 (d, J = 10.3 Hz, 1H), 4.38 (t, J = 8.0 Hz, 1H), 3.43 (s, 3H), 3.44−3.25 (m, 2H), 3.05 (dd, J = 8.1, 17.9 Hz, 1H), 2.97−2.87 (m, 2H, $CH(CH_3)_2$), 1.45 (s, 3H), 1.28 (m, 18H); ^{13}C NMR δ 207, 149, 148, 128, 121, 95, 71, 65, 52, 46, 34, 29, 25, 24, 13; IR (neat) ν 1784 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{34}O_3$ 345.2429, found 345.2439.

3-α-Methyl-(2,4,6-triisopropyl)benzyloxy-2-methoxy-2-methylcyclobutan-1-one (2t). From 180 mg (0.72 mmol) of **1** and 237 mg (0.86 mmol) of α-methyl-2,4,6-triisopropylbenzyl vinyl ether[16] in 10 mL of CH_2Cl_2 was obtained after chromatography (5% EtOAc/Hex) 173 mg (67%) of **2t** as an 86:14 mixture of diastereoisomers. Major: ^{1}H NMR δ 7.11−6.95 (br s, 2H), 5.19 (q, J = 7.0 Hz, 1H), 4.25 (t, J = 8.0 Hz, 1H), 3.97−3.82 (m, 1H), 3.36 (s, 3H), 3.30−3.19 (m, 1H), 2.96−2.85 (m, 2H, H_4), 2.80 (dd, J = 4.0, 8.7 Hz, 1H), 1.62 (d, J = 6.9 Hz, 3H), 1.50 (s, 3H), 1.26 (d, J = 6.9 Hz, 12H), 1.18 (d, J = 7.0 Hz, 6H); ^{13}C NMR δ 208, 147, 136, 132, 95, 73, 68, 53, 46, 34, 29, 25, 24, 14; IR (neat) ν 1779 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{36}O_3$ 359.2586, found 359.2584.

General Procedure for the Ring-Expansion Reactions of Cyclobutanones. Freshly prepared diazomethane was bubbled through a solution of cyclobutanone in 2−4 mL of tetrahydrofuran at 0 °C. The yellow solution remained at 0 °C for 30−60 min and then was slowly warmed to ambient temperature and concentrated in vacuo once the yellow color had dissipated. The ratio of cyclopentanones was obtained from the crude reaction mixtures by ^{1}H NMR spectroscopy and GLC analysis. Purification was achieved by either chromatography on silica gel or vacuum distillation (Kugelrohr).

Butylcyclopentanones (3a/4a). From 110 mg (0.64 mmol) of **2a**, **3a/4a** as an inseparable 59:41 mixture of products, after vacuum distillation (Kugelrohr, 70 °C/0.7 mmHg), 72 mg (61%). The product ratio was determined by integration of the α-OCH_3 resonances in the ^{1}H NMR spectrum: **3a**, 3.26 (s); **4a**, 3.24 (s).

Trimethylsilylmethylenecyclopentanones (3b/4b). From 91 mg (0.45 mmol) of **2b**, **3b/4b** as an inseparable 59:41 mixture of products, after vacuum distillation (Kugelrohr, 80 °C/0.7 mmHg), 65 mg (67%). The product ratio was determined by integration of the α-CH_3 resonances in the ^{1}H NMR spectrum: **3b**, 1.05 (s); **4b**, 1.15 (s).

Bicyclo[3.3.0]heptanones (3c/4c). From 80 mg (0.51 mmol) of **2c**, **3c/4c** as a 91:9 mixture of products, after vacuum distillation (Kugelrohr, 110 °C/0.7 mmHg), 63 mg (72%). **3c:** ^{1}H NMR δ 3.15 (s, 3H), 2.85−2.65 (m, 2H), 2.41 (dd, J = 7.8, 17.9 Hz, 1H), 2.05−1.90 (m, 1H), 1.80−1.50 (m, 4H), 1.45−1.30 (m, 2H), 1.15 (s, 3H); ^{13}C NMR δ 213, 84, 52, 51, 42, 35, 33, 27, 25, 13; IR (neat) ν 1739 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1149.

Bicyclo[3.3.0]heptenones (3d/4d). From 58 mg (0.38 mmol) of **2d**, **3d/4d** as a 91:9 mixture of products, after vacuum distillation (Kugelrohr, 110 °C/0.7 mmHg), 43 mg (68%). **3d**: ^{1}H NMR δ 5.79−5.74 (m, 1H), 5.51−5.46 (m, 1H), 3.27 (d, 1H, J = 8.8 Hz), 3.15 (s, 3H), 2.80 (dd, J = 10.6, 19 Hz, 1H), 2.74−2.59 (m, 2H, H_5), 2.15 (d, 1H, J = 16.8 Hz), 1.83 (dd, J = 5.5, 19.1 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR δ 215, 133, 128, 82, 59, 51, 43, 40, 33, 13; IR (neat) ν 1738 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0998.

Phenylcyclopentanones (3e/4e). From 88 mg (0.46 mmol) of **2e**, **3e/4e** as an inseparable 72:28 mixture of products, after chromatography (10% EtOAc/Hex), 74 mg (79%). The product ratio was determined by integration of the α-OCH_3 and α-CH_3

(14) Quallich, G. J.; Lackey, J. W. *Tetrahedron Lett.* **1990**, *31*, 3685.

(15) For the synthesis of 3-vinyl-(*S*)-4-phenyl-2-oxazolidinone, see ref 5.

(16) For the synthesis of vinyl ethers, see: Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.

(17) Mr. Brian Brown is gratefully acknowledged for providing samples of **5a** and **5b**.

resonances in the ^{1}H NMR spectrum: **3e**, 3.40 (s), 0.90 (s); **4e**, 3.29 (s), 1.01 (s).

***p*-Hydroxyphenylcyclopentanones (3f/4f).** From 78 mg (0.38 mmol) of **2f**, **3f/4f** as an inseparable 71:29 mixture of products, after chromatography (30% EtOAc/Hex), 63 mg (76%). The product ratio was determined by integration of the α-OCH_3 and α-CH_3 resonances in the ^{1}H NMR spectrum: **3f**, 3.40 (s), 0.89 (s); **4f**, 3.27 (s), 1.00 (s).

***p*-Acetoxyphenylcyclopentanones (3g/4g).** From 45 mg (0.18 mmol) of **2g**, **3g/4g** as an inseparable 66:43 mixture of products. The product ratio was determined by integration of the α-OCH_3 and α-CH_3 resonances in the ^{1}H NMR spectrum: **3g**, 3.40 (s), 0.89 (s); **4g**, 3.29 (s), 1.01 (s).

***p*-Trifluoromethanesulfonylphenylcyclopentanones (3h/4h).** From 45 mg (0.13 mmol) of **2h**, **3h/4h** as an inseparable 77:23 mixture of products. The product ratio was determined by integration of the α-OCH_3 resonances in the ^{1}H NMR spectrum: **3h**, 3.39 (s); **4h**, 3.25 (s).

***p*-Methoxyphenylcyclopentanones (3i/4i).** From 67 mg (0.30 mmol) of **2i**, 37 mg (52%) of **3i/4i** as an 80:20 mixture of products which were separable by HPLC (10% EtOAc/Hex). **3i**: ^{1}H NMR δ 7.20 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.57−3.51 (m, 1H), 3.40 (s, 3H), 2.59−2.45 (m, 1H), 2.45−2.24 (m, 2H), 2.16−1.98 (m, 1H), 0.89 (s, 3H); ^{13}C NMR δ 218, 158, 131, 129, 113, 82, 55, 51, 45, 35, 22, 16; IR (neat) ν 1744 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H 7.74. Found: C, 71.51; H, 7.53. **4i**: ^{1}H NMR δ 7.10 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.60 (t, J = 7.7 Hz, 1H), 3.28 (s, 3H), 2.86 (dd, J = 8.6, 18.9 Hz, 1H), 2.56 (d, J = 18.7 Hz, 1H), 2.54 (d, J = 19.3 Hz, 1H), 2.41 (d, J = 18.2 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR δ 216, 158, 131, 129, 113, 83, 55, 50, 49, 48, 43, 19; IR (neat) ν 1744 cm^{-1}.

Phenylthiocyclopentanones (3j/4j). From 61 mg (0.27 mmol) of **2j**, **3j/4j** as an inseparable 80:20 mixture of products, after chromatography (20% EtOAc/Hex), 60 mg (92%). The product ratio was determined by integration of the α-OCH_3 and α-CH_3 resonances in the ^{1}H NMR spectrum: **3j**, 3.23 (s), 1.30 (s); **4j**, 3.27 (s), 1.49 (s).

Sulfoxyphenylcyclopentanones (3k/4k). From 72 mg (0.30 mmol) of **2k**, 51 mg (67%) of **3k/4k** as a 92:8 mixture of products. **3k**: ^{1}H NMR δ 7.95−7.85 (m, 2H), 7.70−7.50 (m, 3H), 3.80−3.65 (m, 1H), 3.15 (s, 3H), 2.59−2.47 (m, 1H), 2.34−2.14 (m, 3H), 1.59 (s, 3H); ^{13}C NMR δ 212, 139, 134, 129, 128, 82, 66, 51, 33, 19, 15; IR (neat) ν 1748 cm^{-1}.

Pyrrolidinylcyclopentanones (3l/4l). From 76 mg (0.38 mmol) of **2l**, **3l/4l** as a 97:3 mixture of products, after chromatography (10% CH_3OH/Et_2O), 72 mg (89%). **3l:** ^{1}H NMR δ 4.50 (m, 1H), 3.46−3.36 (m, 1H), 3.31−3.20 (m, 1H), 3.25 (s, 3H), 2.49−2.33 (m, 5H), 2.10−1.91 (m, 3H), 1.14 (s, 3H); ^{13}C NMR δ 213, 175, 83, 56, 51, 46, 34, 31, 21, 18, 13; IR (neat) ν 1744 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.39; H, 7.92; N, 6.43.

2-Methoxy-2-methyl-3-((*S*)-4-phenyl-2-oxazolidinyl)cyclopentan-1-one (3m). From 98 mg (0.35 mmol) of **2m**, **3m** as a single product, after chromatography (40% EtOAc/Hex), 87 mg (84%) of **3m** as an oil: $[\alpha]_D$ +96 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 7.50−7.30 (m, 5H), 4.80 (t, J = 7.5 Hz, 1H), 4.65 (t, J = 8.6 Hz, 1H), 4.18 (dd, J = 7.1, 8.7 Hz, 1H), 3.72−3.65 (m, 1H), 3.10 (s, 3H), 2.54−2.36 (m, 1H), 2.34−2.13 (m, 2H), 1.94−1.78 (m, 1H), 1.20 (s, 3H); ^{13}C NMR δ 211, 158, 138, 129.6, 129.5, 127, 82, 70, 61, 58, 51, 34, 23, 13; IR (neat) ν 1749 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{19}NO_4$ 290.1395, found 290.1389.

Ethoxycyclopentanones (3n/4n). From 95 mg (0.60 mmol) of **2n**, **3n/4n** as an inseparable 67:33 mixture of products, after vacuum distillation (Kugelrohr, 75°/0.7 mmHg), 72 mg (70%). The product ratio was determined by integration of the α-OCH_3 resonances in the ^{1}H NMR spectrum: **3n**, 3.28 (s); **4n**, 3.20 (s).

Oxabicyclo[4.3.0]octanones (3o/4o). From 80 mg (0.47 mmol) of **2o**, **3o/4o** as a 95:5 mixture of products, after vacuum distillation (Kugelrohr, 75 °C/0.7 mmHg), 70 mg (81%). **3o**: ^{1}H NMR δ 3.95−3.90 (m, 1H), 3.57 (d, J = 3.1 Hz, 1H), 3.44−3.12 (m, 1H), 3.17 (s, 3H), 2.70−2.60 (m, 1H), 2.32 (s, 1H), 2.27 (d, J = 2.3 Hz, 1H), 1.85−1.60 (m, 3H), 1.40−1.32 (m, 1H), 1.18 (s, 3H); ^{13}C NMR δ 213, 82, 72, 67, 51, 36, 30, 23, 19, 10; IR (neat) ν 1744 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.74.

***tert*-Butoxycyclopentanones (3p/4p).** From 50 mg (0.27 mmol) of **2p**, **3p/4p** as a 62:38 mixture of products which were separable by chromatography (10% Et_2O/Hex). The product ratio was determined by integration of the α-OCH_3 and α-CH_3 resonances in the ^{1}H NMR. **3p:** ^{1}H NMR δ 3.99 (m, 1H), 3.29 (s, 3H), 2.43−2.12 (m, 3H), 1.81−1.69 (m, 1H), 1.20 (br s, 9H), 1.19 (s, 3H). **4p:** ^{1}H NMR δ 4.01 (d, J = 5.2 Hz, 1H), 3.21 (s, 3H), 2.67 (dd, J = 5.5, 18 Hz, 1H), 2.38 (d, J = 18 Hz, 1H), 2.27 (d, J = 17.7 Hz, 1H), 2.15 (d, J = 18.1 Hz, 1H), 1.34 (s, 3H), 1.19 (s, 9H).

Benzyloxycyclopentanones (3q/4q). From 83 mg (0.38 mmol) of **2q**, **3q/4q** as an inseparable 72:28 mixture of products, after chromatography (10% EtOAc/Hex), 74 mg (84%). The product ratio was determined by integration of the α-OCH_3 and α-CH_3 resonances in the ^{1}H NMR spectrum: **3q**, 3.40 (s), 1.29 (s); **4q**, 3.20 (s), 1.41 (s).

α-Methylbenzyloxycyclopentanones (3r/4r). From 68 mg (0.29 mmol) of the 1:1 mixture of **2r** was obtained an inseparable mixture of four products. The ratio of **3/4** was determined by treatment of 18 mg (0.07 mmol) of this mixture with 4 mg (0.08 mmol) of NaH (60% dispersion in mineral oil) in 1.4 mL of THF at room temperature for 2 h. The reaction was quenched with brine (5 mL) and then extracted using Et_2O (2 × 5 mL). The combined organic layers were washed with saturated NH_4Cl (10 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo, affording **3r** and the elimination product of **4r**. Before the elimination reaction, the ^{1}H NMR spectrum exhibited resonances for the α-OCH_3 groups as singlets at 3.24, 3.22, 3.10, and 3.08. After treatment with base, the peaks at 3.24 and 3.10 remain, while those at 3.22 and 3.08 have decreased, suggesting that the ratio of **3r/4r** was 70:30.

2,4,6-Triisopropylbenzyloxycyclopentanones (3s/4s). From 67 mg (0.19 mmol) of **2s**, 32 mg (46%) of **3s/4s** as a 68:32 mixture of products that were separable by HPLC (5% EtOAc/Hex). **3s**: ^{1}H NMR δ 7.03 (br s, 2H), 4.68 (d, J = 10.3 Hz, 1H), 4.60 (d, J = 10.2 Hz, 1H), 4.04 (t, J = 5.1 Hz, 1H), 3.34−3.21 (m, 2H), 3.30 (s, 3H), 2.94−2.83 (m, 1H), 2.44−2.24 (m, 3H), 2.08−1.95 (m, 1H), 1.28 (s, 3H), 1.27 (d, J = 6.6 Hz, 18H); ^{13}C NMR δ 214, 148, 128, 121, 83, 82, 64, 51, 34, 33, 29, 24.7, 24.5, 24.1, 23, 12; IR (neat) ν 1744 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{36}O_3$ 359.2586, found 359.2597. **4s**: ^{1}H NMR δ 7.03 (s, 2H), 4.62 (d, J = 10.3 Hz, 1H), 4.47 (d, J = 10.3 Hz, 1H), 4.02 (d, J = 5.1 Hz, 1H), 3.31−3.16 (m, 2H), 3.24 (s, 3H), 2.94−2.82 (m, 1H), 2.69 (dd, J = 5.2, 18.7 Hz, 1H), 2.50 (d, J = 18.6 Hz, 1H), 2.41 (d, J = 17.9 Hz, 1H), 2.27 (d, J = 17.9 Hz, 1H), 1.39 (s, 3H), 1.29−1.20 (m, 18 H); ^{13}C NMR δ 215, 149, 148, 128, 121, 83, 81, 64, 50, 46, 42, 34, 29, 24.7, 24.4, 24.1, 16; IR (neat) ν 1749 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{36}O_3$ 359.2586, found 359.2574.

α-Methyl-2,4,6-triisopropylbenzyloxycyclopentanones (3t/4t). From 54 mg (0.15 mmol) of **2t**, 43 mg (76%) of **3t/4t** as a 30:70 mixture of products that were separable by chromatography (5% EtOAc/Hex). **3t**: ^{1}H NMR δ 7.09−6.91 (m, 2H), 5.30 (q, J = 6.7 Hz, 1H), 4.00 (m, 1H), 3.98−3.87 (m, 1H), 3.33 (s, 3H), 3.33−3.17 (m, 1H), 2.93−2.79 (m, 1H), 2.40−1.97 (m, 3H), 1.77−1.62 (m, 1H), 1.55 (d, J = 6.6 Hz, 3H), 1.34−1.16 (m, 21H); ^{13}C NMR δ 215, 147, 133, 123, 120, 83, 79, 72, 52, 34.3, 34.2, 33, 25, 24.8, 24.5, 24.1, 22, 13; IR (neat) ν 1748 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{38}O_3$ 373.2742, found 373.2730. **4t**: ^{1}H NMR δ 7.07−6.98 (m, 2H), 5.15 (q, J = 6.3 Hz, 1H), 4.06 (m, 1H), 3.91−3.75 (m, 1H), 3.26 (s, 3H), 3.26−3.14 (m, 1H), 2.92−2.79 (m, 1H), 2.51 (dd, J = 6.2, 18.7 Hz, 1H), 2.41 (d, J = 18.3 Hz, 1H), 2.34 (d, J = 17.5 Hz, 1H), 2.16 (d, J = 18.7 Hz, 1H), 1.55 (d, J = 6.6 Hz, 3H), 1.47 (s, 3H), 1.33−1.14 (m, 18H); ^{13}C NMR δ 215, 147, 134, 123, 120, 83, 79, 73, 50, 47, 44, 34, 24.2, 24.1, 22, 17; IR (neat) ν 1748 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{38}O_3$ 373.2742, found 373.2745.

Methylbenzyloxycyclopentanones (6a/7a). From 41 mg (0.22 mmol) of **5a**,[17] **6a/7a** as an inseparable 24:76 mixture of products. The product ratio was determined by integration of the α-CH_3 resonances in the ^{1}H NMR spectrum (C_6D_6): **6a**, 1.02 (d, J = 7.3 Hz); **7a**, 0.68 (d, J = 6.9 Hz).

Benzyloxymethylenediphenyloxazolidinylcyclopentanones (6b/7b). From 35 mg (0.08 mmol) of **5b**,[17] **6b/7b** as an inseparable 36:64 mixture of products, after chromatography (40% EtOAc/Hex), 20 mg (55%). The product ratio was determined by integration of the $-CH_2OBn$- resonances in the ^1H NMR spectrum: **6b**, 3.75 (d, $J = 3.6$ Hz); **7b**, 3.60 (d, $J = 5.1$ Hz).

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Supporting Information Available: ^1H NMR spectra for compounds **2a**−**c**,**f**−**k**,**m**,**p**−**t**, **3a**/**4a**, **3b**/**4b**, **3c**,**d**, **3e/4e**, **3f**/**4f**, **3g**/**4g**, **3h**/**4h**, **3i**, **4i**, **3j**/**4j**, **3k**−**m**, **3n/4n**, **3o**, **3p**/**4p**, **3q**/**4q**, **3r**/**4r**, **3s**, **4s**, **3t**, **4t**, **6a**/**7a**, and **6b**/**7b** and ^{13}C NMR spectra for compounds **2a**−**c**,**f**−**k**,**m**,**p**,**q**,**s**,**t**, **3c**,**d**,**i**, **4i**, **3k**−**m**, **3o**, **3s**, **4s**, **3t**, and **4t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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