Synthesis of Functionalized Chiral (Racemic) Cyclobutanones

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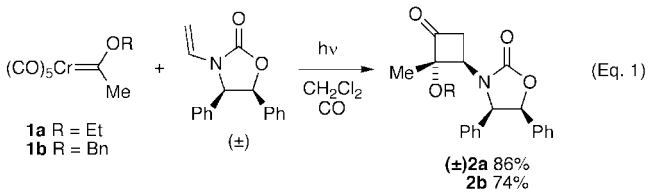
Chiral (racemic) cyclobutanones, produced by the photochemical reaction between chiral ene carbamates and chromium alkoxycarbene complexes, were functionalized in several ways. Enolization/O-alkylation produced enol ethers and esters that underwent facile ring opening to produce electron-rich dienes. Epoxidation of the silyl enol ether followed by epoxide opening produced α-(silyloxy)cyclobutanones. α-Bromination (NBS) of the cyclobutanones followed by Baeyer−Villiger oxidation led to α-bromobutyrolactones that could be converted to butenolides. By using α-stannyl ene carbamates as substrates for the photochemical cycloaddition, *β*-stannyl cyclobutanones were produced.

Introduction

Cyclobutanones are important synthetic intermediates because of their high intrinsic reactivity toward ring expansion, ring contraction, and ring cleavage.[1] They are typically synthesized by the [2 + 2] cycloaddition of ketenes with electron-rich alkenes,[2] in a process that is both regio- and stereoselective.[3] Asymmetric ketene−olefin cycloadditions to produce cyclobutanones from ketene iminium salts,[4] alkoxyketenes,[5] and enol ethers[6] have also been developed.

Research in these laboratories has centered on the development of photochemical reactions of chromium carbene complexes for use in organic synthesis.[7] An efficient route to cyclobutanones by the photolysis of chromium alkoxycarbene complexes in the presence of chiral ene carbamates[8] along with its conversion to butenolides[9] has been developed (eq 1). Below are



(Eq. 1)

described studies undertaken to increase the degree of functionalization of these chiral cyclobutanones. Note, in this study, all reactions were run on chiral, racemic material.

Results and Discussion

Initial studies centered on reaction chemistry at the α-position of cyclobutanones **2**. Attempted C-alkylation utilizing sodium hydride and methyl iodide resulted in recovery of substantial amounts of free oxazolidinone as the only identifiable product. This implies that elimination of oxazolidinone to form the cyclobutenone, which subsequently decomposed, had occurred. Generation of the enolate using LDA at −78 °C followed by treatment with methyl iodide and warming to room temperature also resulted in extensive decomposition, in this case giving traces of cyclobutanone **2** as the sole identifiable product.

In contrast, trapping of this lithium enolate with silyl chlorides was efficient, producing silyl enol ethers **3a** and **3b**. Upon standing at room temperature, **3a** and **3b** underwent facile conrotatory ring opening[10] to give dienes **4a** and **4b**. Trapping the enolate of **2a** with acetic anhydride or methyl chloroformate led directly to dienes **4c** and **4d**. Upon standing in $CDCl_3$, **4a** rearranged to what appears to be α-silyl ketone **5**, in what is likely to be an acid-catalyzed rearrangement[11] facilitated by the stability of the vinylogous amide formed in the process. This rearrangement is accompanied by substantial changes in the spectra, including the appearance of an infrared absorption at 1715 cm^{-1} corresponding to the conjugated carbonyl group, a dramatic downfield shift in the ^1H NMR spectrum for the vinyl proton α to the oxazoline (from *δ* 6.94 to 8.17), upfield shift of the methyl group, from *δ* 1.55 in **4a** to *δ* 1.20 in **5**, and the appearance of two signals (*δ* 0.00 and 0.02) for the diastereotopic silyl methyl groups on the new chiral center (Scheme 1).

Attempted α-functionalization of silyl enol ether **3a** met with limited success. Attempted Mukaiyama aldol

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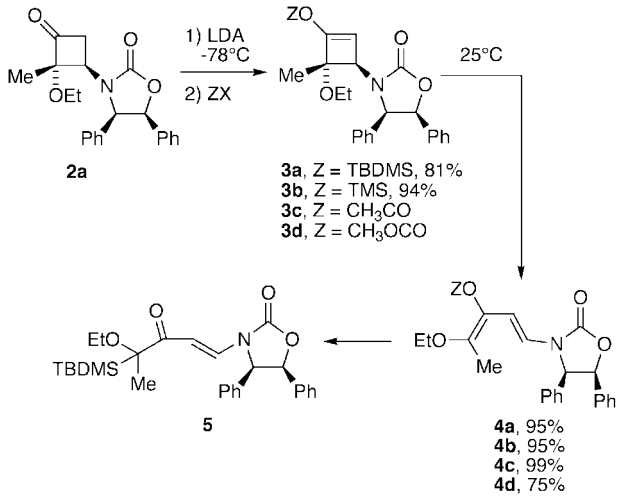
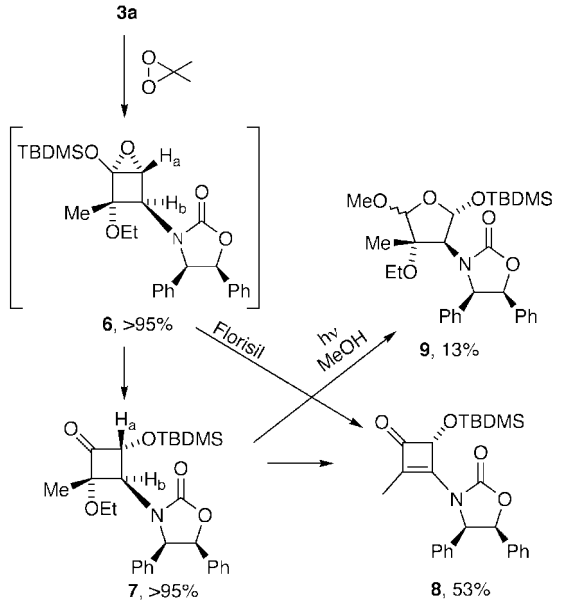
Scheme 1



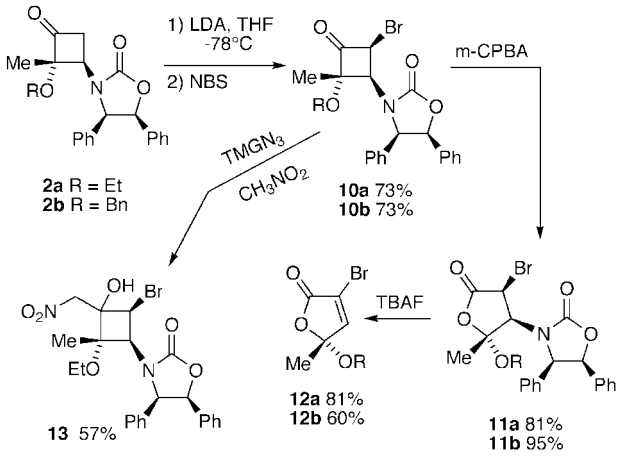
Scheme 2



coupling to benzaldehyde[12] (BF_3·OEt_2, −78 °C) resulted in rapid ring opening to **4a** rather than coupling. Attempted fluoride-mediated alkylation[13] with benzaldehyde or methyl iodide led only to recovery of starting material, **4a**, and cyclobutanone **2a**. Attempted acetoxylation with lead tetraacetate[14] again led to ring opening to **4a** and hydrolysis to **2a**. Epoxidation of **3a** with dimethyldioxirane[15] gave the epoxide **6** ($J_{ab} \approx 0$ Hz, trans), which spontaneously rearranged to the α-(silyloxy)cyclobutanone **7** ($J_{ab} \approx 2$ Hz, trans) (Scheme 2).

Attempted purification of both **6** and **7** using chromatography on Florisil resulted in elimination of ethanol to give cyclobutenone **8**. Photolysis of crude **7** in the presence of methanol[16] gave a complex mixture of regioisomeric and epimeric tetrahydrofurans (four OMe signals in the ^{1}H NMR spectrum), which were relatively

Scheme 3



unstable to silica gel, Florisil, and neutral alumina chromatgraphy, and only a low yield of regioisomer **9** could be isolated. This ring expansion of cyclobutanones to tetrahydrofurans is usually quite regioselective,[16] but the similarity of substitution at the two α-positions in **7** resulted in a nonselective process.

Treatment of cyclobutanone **2** with LDA followed by *N*-bromosuccinimide produced α-bromocyclobutanones **10** (Scheme 3). The large vicinal coupling ($J_{ab} = 8.1$ Hz) between the ring protons indicated a cis relationship, which contrasts with the stereochemistry of epoxidation and may have resulted from epimerization of the initially formed product.[1] Attempted α-alkylation using $Me_2Cu(CN)Li_2$ resulted in reduction back to **2**, while treatment with zinc and allyl bromide in DMSO resulted in no reaction. Cyclobutanones **10** underwent regio- and stereospecific Baeyer−Villiger oxidation to give α-bromo lactones **11** and bromobutenolides **12** after treatment with tetrabutylammonium fluoride (Scheme 3).[9a]

Attempts to displace the α-bromo group with azide (tetramethylguanidinium azide)[17] in nitromethane instead resulted in a nitroaldol reaction at the cyclobutanone carbonyl group to give **13**. In acetonitrile solvent, no reaction occurred. Bromobutenolide **12b** was unreactive toward palladium-catalyzed carbonylation [$(Ph_3P)_4$-Pd, CO, Et_3N, MeOH] and alkylation by $Me_2Cu(CN)Li$·BF_3, while Me_2CuLi simply resulted in replacement of the α-bromo group by hydrogen.

Introduction of functionality at the 3-position of chiral cyclobutanones was next addressed. Photolysis of chromium carbene complexes **1a**−**d** with stannyl ene carbamates **14** (synthesized by treatment of the parent ene carbamate in eq 1 with lithium tetramethylpiperidide in the presence of trialkyltin chlorides[18]) produced 3-stannylated cyclobutanones **15** in good yields and as single diastereoisomers (Scheme 4) (stereochemistry unassigned). Attempted Baeyer−Villiger ring expansion (*m*-CPBA/Na_2HPO_4; CF_3CO_3H;[19] TMSOOTMS/BF_3·OEt;[20]

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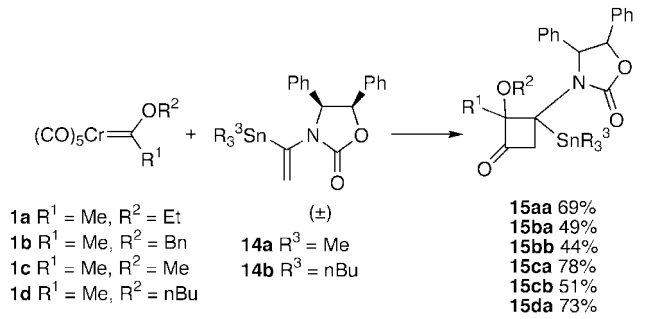
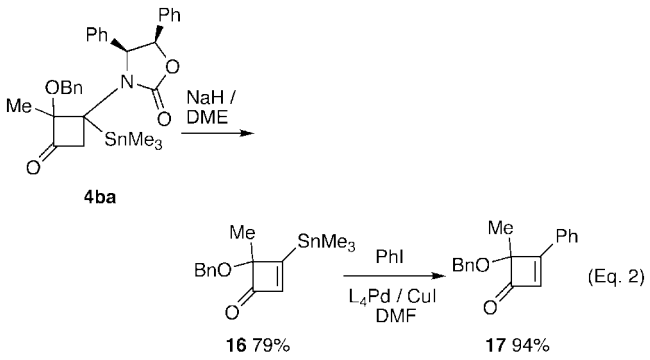
Scheme 4



$PhCHO/O_2/Cu(II)$[21]) resulted in production of some of the desired lactones, but incomplete conversion and competitive reactions at tin prevented the isolation of pure material.

β-Stannylcyclobutenones are known to undergo facile palladium-catalyzed cross-coupling with aryl halides.[22] Given the facile elimination of the β-oxazolidinone group from butyrolactones[9] (e.g., **11** → **12**, Scheme 3) by tetrabutylammonium fluoride, cyclobutanone **15ba** was subjected to similar conditions in an attempt to generate the β-stannylcyclobutenone. The use of fluoride resulted in destannylation products, and the procedure was inefficient. However, treatment with sodium hydride in DME gave the desired cyclobutenone **16** in fair yield. Treatment of **1b** with iodobenzene and the palladium(0)/copper(I) catalyst system[23] resulted in efficient coupling. This chemistry should provide a general route to chiral 3-substituted cyclobutenones.



Experimental Section

General Methods. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ unless otherwise specified, and all chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm for ^1H, 77 ppm for ^{13}C). Tetrahydrofuran (THF) and ether were freshly distilled from sodium/benzophenone. Dichloromethane was dried by distillation from calcium hydride. Lithium diisopropylamide (LDA) was prepared by addition of an *n*-BuLi solution in hexanes to an equimolar amount of diisopropylamine at 0 °C in THF. Photolyses were carried out using a Conrad−Hanovia lamp at either 55 or 0 °C, as indicated under carbon monoxide (60 psi). Carbene complexes **1a**−**d** were synthesized by literature procedures,[8] as were cyclobutenones **2a** and **2b**.[9c,d]

***tert*-Butyldimethylsilyl Enol Ether 3a.** To a stirred solution of LDA (0.22 mmol) in THF (2 mL) at −78 °C was added dropwise a solution of TBDMSCl (39 mg, 0.26 mmol) in THF (1 mL), followed after 10 min by a solution of cyclobutanone **2a** (75 mg, 0.21 mmol) in THF (2 mL). Stirring was continued at −78 °C for a further 15 min, and the mixture was then allowed to warm to room temperature over 20 min. The solvent was immediately removed under reduced pressure (bath temperature 25 °C or less). After removal of traces of THF in vacuo, the residue was taken into CH_2Cl_2/hexanes (1:1) and filtered through a short column of Florisil. Evaporation gave silyl enol ether **3a** (77 mg, 78%) as a colorless solid. An analytical sample was obtained by dissolving in CH_2Cl_2 and rapidly precipitating with hexanes: mp 97−99 °C; IR (thin film) ν 2931, 1747, 1634 cm^{-1}; ^1H NMR δ 7.11−7.05 (m, 6H), 6.99−6.96 (m, 2H), 6.83−6.79 (m, 2H), 5.81 (d, J = 7.6 Hz, 1 H), 4.88 (d, J = 7.6 Hz, 1H), 4.45 (d, J = 1.2 Hz, 1H), 3.89 (d, J = 1.2 Hz, 1H), 3.65 (m, 2H), 1.48 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 157.8, 156.3, 136.5, 134.0, 128.2, 127.9, 127.7, 126.9, 126.1, 100.5, 86.8, 80.2, 64.5, 59.8, 55.2, 25.4, 18.1, 16.65, 15.8, −4.9, −5.0. Anal. Calcd for $C_{28}H_{37}NO_4Si$: C, 70.11; H, 7.77; N, 2.92. Found: C, 70.10; H, 7.73; N, 3.14.

Trimethylsilyl Enol Ether 3b. To a stirred solution of diisopropylamine (71 μL) in THF (3 mL) under Ar at 0 °C was added *n*-BuLi (271 μL, 1.67 M in hexanes) and the mixture cooled to −78 °C. A solution of TMSCl (75 μL) was then added dropwise, followed after 10 min by a solution of the cyclobutanone **2a** (172 mg) in THF (2 mL). Stirring was continued at −78 °C for a further 15 min, and the mixture was then allowed to warm to room temperature over 20 min and immediately evaporated using a water bath at room temperature. After removal of traces of THF *in vacuo*, the residue was taken into dry CH_2Cl_2 and filtered through Celite. Evaporation afforded essentially pure silyl enol ether **3b** (200 mg, 94%) as a colorless solid: mp 88−90 °C; IR (thin film) ν 1728, 1630 cm^{-1}; ^1H NMR δ 7.11−7.05 (m, 6H), 6.99−6.96 (m, 2H), 6.83−6.80 (m, 2H), 5.81 (d, J = 7.3 Hz, 1H), 4.88 (d, J = 7.3 Hz, 1H), 4.45 (d, J = 0.6 Hz, 1H), 3.92 (d, J = 0.6 Hz, 1H), 3.63 (m, 2H), 1.48 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.15 (s, 9H). This compound underwent ring opening and hydrolysis during attempted acquisition of ^{13}C NMR data.

Silyloxy Diene 4a. A sample of the silyl enol ether **3a** (60 mg, 0.13 mmol) was allowed to stand for 24 h in $CDCl_3$ containing a trace of triethylamine, after which time the ^1H NMR spectrum indicated complete conversion into diene **4a**. Evaporation gave a pale yellow oil (60 mg, 100%). Due to its instability, this compound could not be further purified: IR (thin film) ν 1746, 1636 cm^{-1}; ^1H NMR δ 7.10−7.06 (m, 6H), 6.99−6.97 (m, 2H), 6.94 (d, J = 14.0 Hz, 1H), 6.85−6.82 (m, 2H), 5.91 (d, J = 8.3 Hz, 1H), 5.37 (d, J = 14.0 Hz, 1H), 5.25 (d, J = 8.3 Hz, 1H), 3.70 (q, J = 7.0 Hz, 2H), 1.55 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 0.96 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR 155.1, 136.3, 133.9, 133.5, 132.0, 128.2, 128.1, 128.0, 127.9, 127.1, 126.2, 120.5, 109.1, 80.0, 64.0, 63.3, 26.0, 18.5, 15.4, 13.12, −4.1, −4.2; HRMS (M + H) calcd for $C_{28}H_{38}NO_4Si$ m/z 480.2570, found m/z 480.2567.

Acetoxy Diene 4c. LDA (0.22 mmol) was prepared at 0 °C and cooled to −78 °C, and a solution of the cyclobutanone **2a** (85 mg) in THF (2 mL) was then added dropwise. After the mixture was stirred for 10 min at −78 °C, acetic anhydride (32 μL, 0.34 mmol) was added all at once. Stirring was continued at −78 °C for a further 10 min before the mixture was allowed to warm to room temperature over 45 min. The mixture was then evaporated and the residue taken into dichloromethane and filtered through Celite. Evaporation of the filtrate gave essentially pure acetoxy diene **4c** as a pale yellow oil (90 mg, 99%). Crystallization from ethyl acetate/hexanes gave colorless needles: mp 123−125 °C; IR (thin film) ν 1761 cm^{-1}; ^1H NMR δ 7.06−7.12 (m, 6H), 6.94−6.97 (m, 2H), 6.81−6.84 (m, 2H), 6.76 (d, J = 14.1 Hz, 1H), 5.89 (d, J = 8.2 Hz, 1H), 5.29 (d, J = 14.1 Hz, 1H), 5.25 (d, J = 8.2 Hz, 1H), 3.70 (q, J = 7.1 Hz, 2H), 2.21 (s, 3H), 1.60 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 168.7, 155.0, 141.2, 133.6, 133.3, 128.9, 128.5, 128.3, 128.2, 127.9, 127.0, 126.2, 120.0, 115.3, 80.1, 64.0,

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63.8, 20.5, 15.2, 12.5; HRMS calcd for $C_{24}H_{25}NO_5$ *m/z* 407.1733, found *m/z* 407.1728.

Carbonate Diene 4d. To a solution of LDA (0.20 mmol) in THF (2 mL) at −78 °C was added dropwise a solution of cyclobutanone **2a** (73 mg, 0.20 mmol) in THF (2 mL). After the mixture was stirred for 10 min at this temperature, methyl chloroformate (23 μL, 0.20 mmol) was added. Stirring was continued at −78 °C for a further 10 min before the mixture was allowed to warm to room temperature over 40 min. The mixture was then evaporated and the residue taken into dichloromethane and filtered through Celite. Evaporation of the filtrate and crystallization from ethyl acetate/hexanes gave the diene **4d** (177 mg, 75%) as colorless needles: mp 138−140 °C; IR (thin film) ν 1781, 1629 cm^{-1}; ^{1}H NMR δ 7.07−7.10 (m, 6H), 6.95−6.98 (m, 2H), 6.86 (d, J = 14.2, Hz, 1H), 6.83−6.85 (m, 2H), 5.89 (d, J = 8.2 Hz, 1H), 5.31 (d, J = 14.2 Hz, 1H), 5.25 (d, J = 8.2 Hz, 1H), 3.74 (q, J = 7.0 Hz, 1H), 1.61 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 155.1, 153.9, 141.7, 133.6, 133.3, 129.9, 128.4, 128.3, 128.2, 127.9, 127.0, 126.2, 120.0, 105.2, 80.2, 64.0, 63.9, 55.2, 15.3, 12.7. Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 67.98; H, 5.94; N, 3.25.

Enone 5. A solution of silyl enol ether **3a** (60 mg, 0.13 mmol) was allowed to stand in $CDCl_3$ at room temperature for 24 h. The solvent was evaporated and the residue subjected to flash chromatography on SiO_2, eluting with EtOAc/hexanes (1:4) to give impure enone **5**. Crystallization from EtOAc/hexanes gave **5** (25 mg, 54%) as colorless needles: mp 115−116 °C; IR ν 1750, 1719 cm^{-1}; ^{1}H NMR δ 8.17 (d, J = 14.3, 1H), 7.13−7.09 (m, 6H), 6.99−6.95 (m, 2H), 6.84−6.81 (m, 2H), 5.99 (d, J = 8.1 Hz, 1H), 5.73 (d, J = 14.3 Hz, 1H), 5.35 (d, J = 8.1 Hz), 3.14 (m, 1H), 3.05 (m, 1H), 1.25 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H), 0.70 (s, 9H), 0.02 (s, 3h), 0.00 (s, 3H). Anal. Calcd for $C_{28}H_{37}NO_4Si$: C, 70.11; H, 7.77; N, 2.92. Found: C, 68.03; H, 7.63; N, 2.95.

Epoxidation of 3a. A stirred solution of silyl enol ether **3a** (93 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) under Ar was cooled to −78 °C, and a solution of dimethyldioxirane (70 mL, ca. 0.1 M in acetone[24]) was added over 5 min. After the addition was complete, the solution was allowed to warm to 0 °C, and stirring was continued at this temperature for 6 h. The mixture was then evaporated to give crude epoxide **6** (96 mg, 100%) as a colorless oil that solidified to a foam upon drying in vacuo: IR (thin film) ν 1752 cm^{-1}; ^{1}H NMR δ 7.15−6.80 (m, 10H), 5.84 (d, J = 7.8 Hz, 1H), 4.99 (d, J = 7.8 Hz, 1H), 3.82 (s, 1H), 3.63 (m, 1H), 3.53 (s, 1H), 3.51 (m, 1H), 1.50 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 157.8, 134.9, 133.7, 128.7, 128.2, 127.9, 127.8, 127.1, 126.1, 89.3, 88.0, 80.3, 66.1, 60.2, 59.9, 58.6, 25.4, 15.7, 15.6, 14.8, −4.1, −4.3; HRMS (M + H) Calcd for $C_{28}H_{38}NO_5Si$ *m/z* 496.2519, found *m/z* 496.2498.

α-[(*tert*-Butyldimethylsilyl)oxy]cyclobutanone 7. A sample of crude epoxide **6** (45 mg, 0.09 mmol) was allowed to stand in $CDCl_3$ at room temperature for 72 h. Evaporation gave crude **7** (45 mg, 100%) as a colorless glass: IR (thin film) ν 1797, 1754 cm^{-1}; ^{1}H NMR δ 7.15−6.80 (m, 10H), 5.91 (d, J = 8.5 Hz, 1H), 5.18 (d, J = 8.5 Hz, 1H), 4.88 (d, J = 2.2 Hz, 1H), 3.96 (d, J = 2.2 Hz, 1H), 3.22 (m, 1H), 2.97 (m, 1H), 1.53 (s, 3H), 0.91 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 205.3, 157.2, 134.5, 133.7, 128.9, 128.6, 128.1, 128.0, 126.0, 125.8, 87.0, 79.8, 72.4, 67.6, 59.3, 25.5, 18.3, 15.3, −4.7, −5.0; HRMS (M + H) calcd for $C_{28}H_{38}NO_5Si$ *m/z* 496.2519, found *m/z* 496.2525.

Cyclobutenone 8. The crude α-(silyloxy)cyclobutanone **7** (27 mg, 0.05 mmol) was eluted through a column of Florisil with EtOAc/hexanes (1:4) to give cyclobutenone **8** (13 mg, 53%) as the sole product. Florisil chromatography of epoxide **6** gave an identical product: IR (thin film) ν 1768, 1647 cm^{-1}; ^{1}H NMR δ 7.12−6.89 (m, 10H), 5.98 (d, J = 8.0 Hz, 1H), 5.78 (d, J = 8.0 Hz, 1H), 4.91 (s, 1H), 2.43 (s, 3H), 0.81 (s, 9H), 0.1 (s, 3H), −0.07 (s, 3H); ^{13}C NMR δ 201.9, 185.5, 162.7, 134.3, 133.4, 128.4, 128.3, 128.0, 127.9, 127.1, 126.0, 83.7, 81.4, 63.4, 25.6, 18.2, 14.0, −4.7, −5.0; MS (FAB) 450 (M + 1, 17), 203 (29), 180 (100); HRMS (M + H) calcd for $C_{26}H_{32}NO_4Si$ *m/z* 450.2100 found *m/z* 450.2092.

Photolytic Ring Expansion of 7. The cyclobutanone **7** (35 mg, 0.07 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL) in a small test tube under argon, and dry methanol (15 drops) was added. The tube was immediately sealed with a rubber septum and degassed by the freeze−pump−thaw method (four cycles), photolyzed at 0 °C for 20 h, and then evaporated. Chromatography of the residue on SiO_2 eluting with EtOAc/hexanes (1:4) led to isolation of furan **9** (5 mg, 13%) as a colorless oil: IR (thin film) ν 1753 cm^{-1}; ^{1}H NMR δ 7.13−6.79 (m, 10H), 5.79 (d, J = 6.9 Hz, 1H), 5.67 (s, 1H), 5.00 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 5.2 Hz, 1H), 3.91 (d, J = 5.2 Hz, 1H), 3.73−3.60 (m, 2H), 2.84 (s, 3H), 1.46 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H); HRMS (M + H) calcd for $C_{29}H_{42}NO_6Si$ *m/z* 528.2278, found *m/z* 528.2279.

Bromocyclobutanone 10a. To a stirred solution of LDA (1.39 mmol) in THF (25 mL) at −78 °C was added dropwise a solution of cyclobutanone **2a** (597 mg, 1.39 mmol) in THF (10 mL), followed after 15 min by addition, all at once, of *N*-bromosuccinimide (273 mg, 1.536 mmol). The mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature over 40 min. The mixture was then evaporated and the residue taken into dichloromethane and filtered through a short column of Florisil. Evaporation of the filtrate gave essentially pure bromocyclobutanone **10a** (515 mg, 73%) as colorless crystals from ethyl acetate/hexanes: mp 135−136 °C dec; IR (thin film) ν 1801, 1751 cm^{-1}; ^{1}H NMR δ 7.16−7.11 (m, 6H), 6.99−6.90 (m, 4H), 5.92 (d, J = 8.1 Hz, 1H), 5.53 (d, J = 8.5 Hz, 1H), 5.25 (d, J = 8.1 Hz, 1H), 4.32 (d, J = 8.5 Hz, 1H), 3.22 (m, 2H), 1.59 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 201.2, 157.4, 133.8, 133.5, 129.0, 128.5, 128.2, 128.1, 128.0, 125.9, 93.6, 79.8, 67.5, 61.0, 59.3, 42.8, 16.2, 15.1. Anal. Calcd for $C_{22}H_{22}BrNO_4$: C, 59.47; H, 4.99; N, 3.15. Found: C, 59.59; H, 5.18; N, 2.89.

4-(Benzyloxy)-4-methyl-2-bromocyclobutanone 10b. LDA (0.785 mmol) was prepared in THF (20 mL) at 0 °C and cooled to −78 °C. A solution of the cyclobutanone (335 mg, 0.785 mmol) in THF (10 mL) was then added dropwise. Stirring was continued at −78 °C for 15 min after the addition was complete, *N*-bromosuccinimide (140 mg, 0.785 mmol) was then added all at once, and the mixture was allowed to warm to room temperature over 1 h and then evaporated. The residue was taken into dichloromethane and filtered through a plug of Florisil. Evaporation of the filtrate gave bromocyclobutanone **10b** (289 mg, 0.571 mmol, 73%) as a pale yellow oil that solidified to a foam *in vacuo*: ^{1}H NMR δ 1.67 (s, 3H), 4.24 (d, J = 10.6 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 4.39 (d, J = 8.4 Hz, 1H), 5.26 (d, J = 8.1 Hz, 1H), 5.65 (d, J = 8.4 Hz, 1H), 5.95 (d, J = 8.1 Hz, 1H), 6.95−7.40 (m, 15H).

4-Ethoxy-4-methyl 2-Bromo Lactone 11a. To a stirred solution of bromocyclobutanone **10a** (38 mg, 0.08 mmol) in dry dichloromethane (2 mL) was added Na_2HPO_4 (36 mg, 0.15 mmol) followed by *m*-CPBA (26 mg, 0.25 mmol). The mixture was stirred at room temperature for 4 h. A 10% solution of $Na_2S_2O_3$ was added and the biphasic mixture stirred vigorously for 1 h. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were washed with saturated $NaHCO_3$, dried, and evaporated to give a colorless solid. Recrystallization from EtOAc/hexanes gave colorless needles of bromo lactone **11a** (43 mg, 81%): mp 106−107 °C dec; IR (thin film) ν 1786, 1753 cm^{-1}; ^{1}H NMR δ 7.17−6.89 (m, 10H), 5.96 (d, J = 8.3 Hz, 1H), 5.64 (d, J = 9.4 Hz, 1H), 5.17 (d, J = 8.3 Hz, 1H), 4.12 (d, J = 9.4 Hz, 1H), 3.29 (q, J = 7.0 Hz, 2H), 1.73 (s, 3H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 167.6, 157.1, 133.8, 133.5, 129.0, 128.5, 128.2, 128.1, 128.0, 125.8, 109.8, 80.2, 68.8, 68.6, 59.1, 36.9, 19.7, 14.7. Anal. Calcd for $C_{22}H_{22}BrNO_5$: C, 57.40; H, 4.82; N, 3.04. Found: C, 57.20; H, 4.86; N, 2.86.

4-(Benzyloxy)-4-methyl-2-bromo Lactone 11b. The bromocyclobutanone **10b** (196 mg, 0.387 mmol) was dissolved in dry dichloromethane (15 mL), and Na_2HPO_4 (165 mg, 1.161 mmol) was added, followed (portionwise) by *m*-CPBA (120 mg,

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0.697 mmol). The mixture was stirred at room temperature for 3 h. A 10% solution of $Na_2S_2O_4$ was added and the resulting biphasic mixture stirred vigorously for 20 min. The organic layer was separated and the aqueous layer reextracted with dichloromethane. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried, and evaporated to give bromo lactone **11b** (193 mg, 95%) as a colorless solid: ^{1}H NMR δ 1.85 (s, 3H), 4.24 (d, J = 8.6 Hz, 1H), 4.36 (s, 2H), 5.18 (d, J = 8.3 Hz, 1H), 5.58 (d, J = 8.6 Hz, 1H), 5.96 (d, J = 8.3 Hz, 1H), 6.89−7.24 (m, 15H).

4-Ethoxy-4-methyl-2-bromobutenolide 12a. To a stirred solution of bromolactone **11a** (222 mg, 0.482 mmol) in dry THF (5 mL) at 0 °C was added TBAF (482 μL, 1.0 M in THF). Stirring was continued for 10 min, and the mixture was poured into water and extracted twice with dichloromethane. The combined organic layers were dried and evaporated to give a pink oil. Flash chromatography (EtOAc/hexanes 3:1) gave the bromobutenolide **12a** as a colorless, somewhat volatile, oil (86 mg, 81%): IR (thin film) ν 1777, 1615 cm^{-1}; ^{1}H NMR δ 7.25 (s, 1H), 3.52 (m, 1H), 3.43 (m, 1H), 1.68 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 165.5, 151.3, 115.9, 108.5, 60.1, 24.1, 15.0; HRMS (M + H) calcd for $C_7H_{10}BrO_3$ m/z 222.9793, found m/z 222.9790.

4-(Benzyloxy)-4-methyl-2-bromobutenolide 12b. To a stirred solution of bromolactone **11b** (486 mg, 0.930 mmol) in dry THF (5 mL) at 0 °C was added TBAF (930 μL, 1.0 M in THF). Stirring was continued for 10 min, and the mixture was poured into saturated NH_4Cl and stirred vigorously. This mixture was extracted twice with ether. The combined organic layers were dried and evaporated to give a pale yellow oil. Flash chromatography (ethyl acetate/hexanes 3:1) gave the bromobutenolide **12b** (157 mg, 60%) as a colorless oil that solidified on standing: mp 66−68 °C; IR (thin film) ν 2930, 1774, 1631 cm^{-1}; ^{1}H NMR δ 1.75 (s, 3H), 4.39 (d, J = 11.3 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 7.21 (s, 1H), 7.27−7.38 (m, 5H); ^{13}C NMR δ 24.0, 66.4, 108.4, 116.0, 127.9, 127.9, 128.2, 128.6, 136.5, 151.3, 165.4.

Nitroaldol Addition Product 13. To a solution of the bromocyclobutanone **10a** (46 mg, 0.10 mmol) in dry nitromethane (2 mL) was added tetramethylguanidinium azide[24] (48 mg, 0.41 mmol) and the mixture stirred under Ar at room temperature for 20 h. Evaporation and flash chromatography of the residue on SiO_2 eluting with EtOAc/hexanes (2:5) gave the aldol addition product **13** (30 mg, 57%) as a white solid: IR (thin film) ν 3450, 2976, 1718 cm^{-1}; ^{1}H NMR δ 7.15−6.92 (m, 10H), 5.95 (d, J = 8.1 Hz, 1H), 5.06 (d, J = 8.1 Hz, 1H), 4.70 (d, J = 9.7 Hz, 1H), 4.58 (d, J = 12.8 Hz, 1H), 4.51 (d, J = 12.8 Hz, 1H), 4.07 (d, J = 9.7 Hz, 1H), 3.98 (s, 1H), 3.28 (m, 1H), 3.10 (m, 1H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 157.1, 134.4, 133.8, 128.9, 128.3, 128.2, 128.2, 128.0, 125.7, 81.4, 79.8, 77.0, 74.2, 67.7, 67.4, 59.9, 42.3, 15.3, 14.6. Anal. Calcd for $C_{23}H_{25}BrN_2O_6$: C, 54.66; H, 4.99; N, 5.54. Found: C, 54.80; H, 5.13; N, 5.51.

General Procedure for the Photoreaction of Chromium Carbene Complexes and α-Stannyl Ene Carbamates To Produce Cyclobutanones. The appropriate α-stannyl ene carbamate (1.0 equiv) and carbene complex (1.5−2.0 equiv) were dissolved in CH_2Cl_2 in an Ace pressure tube equipped with a pressure head. The mixture was subjected to freeze−pump−thaw cycles (3×), and then the pressure tube was charged to 80 psi CO (three cycles) and irradiated at 55 °C (16−48 h). At the end of the reaction, the mixture was filtered through Celite and the solvent removed under reduced pressure. The crude residue was dissolved in hexane/ethyl acetate (1:1) and allowed to air oxidize under six 20-W Vitalite lamps to remove chromium residues. Filtration of the resulting green suspension, removal of solvent under reduced pressure, and subsequent column chromatography on silica gel gave the desired product as indicated in the individual experiment.

Preparation of 15aa. α-Trimethylstannyl ene carbamate **14a** (0.72 g, 1.68 mol) and [(ethoxy)(methyl)carbene]pentacarbonylchromium(0) **1a** (0.61 g, 2.3 mmol) were dissolved in dichloromethane (9 mL) and irradiated according to the general procedure for 48 h. Workup and column chromatography (SiO_2/4:1 hexanes/ethyl acetate) gave 0.61 g (69%) of **15aa** as a white solid: mp 144 °C dec; ^{1}H NMR δ 6.81−7.12 (m, 10H), 5.83 (d, J = 7.5 Hz, 1H), 5.02 (d, J = 7.5 Hz, 1H), 3.56 (dq, J = 6.9, 3.3 Hz, 2H), 3.00 (d, J = 18.9 Hz, 1H), 2.88 (d, J = 18.9 Hz, 1H), 1.47 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR δ 207.3, 159.5, 136.0, 133.7, 128.7, 128.4, 128.1, 127.3, 127.2, 126.4, 98.6, 80.3, 77.4, 64.8, 61.1, 50.0, 15.7, 12.4, −4.2; IR ν 1738, 1780 cm^{-1}; HRMS (M + H) calcd for $C_{25}H_{32}NO_4{}^{120}Sn$ m/z 530.1363, found m/z 530.1349.

Preparation of Cyclobutanone 15ba. α-Trimethylstannyl ene carbamate **14a** (0.20 g, 0.47 mmol) and [(benzyloxy)(methyl)carbene]pentacarbonylchromium(0) **1b** (0.31 g, 0.94 mmol) were dissolved in dichloromethane (5 mL) and irradiated according to the general procedure for 16 h. Workup and column chromatography (SiO_2/4:1 hexanes/ethyl acetate) gave 0.14 g (49%) of **15ba** as a white solid: mp 143 °C dec; ^{1}H NMR δ 7.3 (m, 5H), 7.04−7.09 (m, 6H), 6.92−6.96 (m, 2H), 6.81−6.86 (m, 2H), 5.84 (d, J = 7.5 Hz, 1H), 5.04 (d, J = 7.5 Hz, 1H), 4.66 (s, 2H), 2.96 (s, 2H), 1.56 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 207.3, 159.7, 137.4, 136.0, 133.7, 128.8, 128.7, 128.5, 128.3, 128.1, 127.2, 126.4, 80.3, 77.2, 68.3, 64.9, 50.2, 12.9, −4.5; IR (NaCl, thin film) ν 1780, 1736 cm^{-1}; HRMS (M + H) calcd for $C_{30}H_{34}NO_4{}^{120}Sn$ m/z 592.1510, found m/z 592.1506; HRMS (M + H) calcd for $C_{3-}H_{34}NO_4{}^{118}Sn$ m/z 590.1459, found m/z 590.1454.

Preparation of Cyclobutanone 15bb. α-Tributylstannyl ene carbamate **14b** (0.18 g, 0.32 mmol) and [(benzyloxy)(methyl)carbene]pentacarbonylchromium(0) **1b** (0.16 g, 0.48 mmol) were dissolved in dichloromethane (2 mL) and irradiated according to the general procedure for 30 h. Workup and column chromatography (SiO_2/4:1 hexanes/ethyl acetate) gave 0.10 g (44%) of **15bb** as a white solid: mp 96−99 °C; ^{1}H NMR δ 7.26−7.32 (m, 5H), 6.81−7.07 (m, 10H), 5.83 (d, J = 7.8 Hz, 1h), 5.01 (d, J = 7.8 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.58 (d, J = 10.2 Hz, 1H), 3.10 (d, J = 18.9 Hz, 1H), 2.95 (d, J = 18.9 Hz, 1H), 1.53 (s, 3H), 0.76−1.34 (m, 27H); ^{13}C NMR δ 128.9, 128.7, 128.5, 128.2, 128.1, 127.3, 126.4, 80.3, 68.5, 64.8, 50.8, 29.3, 27.9, 13.9, 13.8, 12.8; IR ν 1742, 1778 cm^{-1}; HRMS (M + H) calcd for $C_{39}H_{52}NO_4{}^{120}Sn$ m/z 718.2918, found m/z 718.2924; HRMS (M + H) calcd for $C_{39}H_{52}NO_4{}^{118}Sn$ m/z 716.2912, found m/z 716.2886.

Preparation of Cyclobutanone 15ca. α-Trimethylstannyl ene carbamate **14a** (0.50 g, 1.42 mmol) and carbene complex **1c** (0.46 g, 1.85 mmol) in dichloromethane (8 mL) were irradiated according to the general procedure for 16 h. Workup and column chromatography (SiO_2/4:1 hexanes/ethyl acetate) gave 0.47 g (78%) of **15ca** as a white solid: mp 138−139 °C; ^{1}H NMR δ 6.82−7.05 (m, 10H), 5.84 (d, J = 7.8 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 3.38 (s, 3H), 2.93 (d, J = 19.2 Hz, 1H), 2.84 (d, J = 19.2 Hz, 1H), 1.50 (s, 3H), 0.20 (s, 9H); ^{13}C NMR δ 207.3, 159.7, 135.9, 133.7, 128.7, 128.3, 128.1, 127.3, 126.4, 98.5, 80.3, 64.9, 55.3, 49.8, 11.9, −4.7; IR (NaCl, film) ν 1780, 1740 cm^{-1}; HRMS (M + H) calcd for $C_{24}H_3NO_4{}^{120}Sn$ m/z 516.1197, found m/z 516.1199.

Preparation of Cyclobutanone 15cb. α-Tributylstannyl ene carbamate **14b** (0.31 g, 0.54 mmol) and [(methoxy)(methyl)carbene]pentacarbonylchromium(0) **1c** were dissolved in dichloromethane (2 mL) and irradiated according to the general procedure for 22 h. Workup and column chromatography gave 0.18 g (51%) of **15cb** as a white solid: mp 118 °C; ^{1}H NMR δ 6.81−7.10 (m, 10H), 5.83 (d, J = 7.8 Hz, 1H), 5.01 (d, J = 7.8 Hz, 1H), 3.40 (s, 3H), 3.03 (d, J = 18.9 Hz, 1H), 2.90 (d, J = 18.9 Hz, 1H), 1.25−1.55 (m, 15H), 0.71−1.05 (m, 15H); ^{13}C NMR δ 207.4, 159.5, 136.2, 133.9, 128.6, 128.2, 128.1, 127.3, 126.3, 99.1, 80.2, 64.7, 55.9, 53.1, 50.5, 29.4, 27.9, 13.9, 13.6, 11.7; IR ν 1779, 1738 cm^{-1}; HRMS (M + H) calcd for $C_{33}H_{48}NO_4{}^{120}Sn$ m/z 642.2605, found m/z 642.2600.

Preparation of 15da. α-Trimethylstannyl ene carbamate **14ba** (0.16 g, 0.38 mmol) and [(*n*-butyloxy)(methyl)carbene]-pentacarbonylchromium(0) **1d** (0.16 g, 0.56 mmol) were dissolved in dichlormethane (4 mL) and irradiated according to the general procedure for 30 h. Workup and column chromatography (SiO_2/5.1 hexanes/ethyl acetate) gave 0.15 g (73%) of **15da** as a white solid: mp 135−136 °C; ^{1}H NMR δ 7.10−6.85 (m, 10H), 5.82 (d, J = 8.0 Hz, 1H), 5.00 (d, J = 8.0 Hz,

1H), 3.52 (t, J = 7.0 Hz, 2H), 3.01 (d, J = 18.5 Hz, 1H), 2.89 (d, J = 18.5 Hz, 1H), 1.52 (m, 2H), 1.49 (s, 3H), 1.38 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR δ 128.7, 128.4, 128.2, 127.3, 126.4, 80.4, 77.4, 65.7, 64.8, 50.3, 32.3, 19.4, 14.1, 12.5, −4.2; IR (NaCl, thin film) ν 1780, 1735 cm^{-1}; HRMS (M + H) calcd for $C_{27}H_{36}NO_4{}^{120}Sn$ m/z 558.1666, found m/z 558.1675; HRMS (M + H) calcd for $C_{27}H_{36}NO_4{}^{118}Sn$ m/z 556.1660, found m/z 556.1637.

Preparation of Cyclobutenone 16. Cyclobutanone **4ba** (0.08 g, 0.13 mmol) in THF (0.5 mL) at 0 °C was added to a suspension of NaH (0.007 g, 0.16 mmol) in THF (0.5 mL) also at 0 °C. Workup and chromatography (SiO_2/3:1 hexanes/ethyl acetate) gave 0.038 g (79%) of **16** as a white solid: ^{1}H NMR δ 7.25−7.31 (m, 5H), 6.81 (s, 1h), 4.45 (d, J = 10.8 Hz, 1H), 4.33 (d, J = 10.8 Hz, 1H), 1.51 (s, 3H), 0.38 (s, 9H); ^{13}C NMR δ 202.9, 195.3, 152.3, 138.2, 128.6, 127.8, 103.3, 67.9, 21.5, −9.1. This material was difficult to purify and was carried on to the next step without further characterization.

Palladium-Catalyzed Coupling of 16 with Iodobenzene. To iodobenzene (0.01 mL, 0.085 mmol) in DMF (0.5 mL) was added $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol, 20 mol %). The cyclobutenone **16** (0.03 g, 0.085 mmol) dissolved in DMF (0.5 mL) was added to the reaction and followed by the addition of CuI (0.002 g, 0.009 mmol). The reaction was stirred for 48 h. Distilled H_2O was added to the reaction and extracted with Et_2O (2×). The organic layers were combined and dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure followed by column chromatography (SiO_2/5:1 hexanes/ethyl acetate) gave 0.015 g (94%) of cyclobutenone **17** as an oil: ^{1}H NMR δ 7.46−7.75 (m, 5H), 7.2−7.3 (m, 5H), 6.55 (s, 1H), 4.51 (d, J = 10.5 Hz, 1H), 4.34 (d, J = 10.5 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR δ 195.3, 181.7, 137.8, 132.9, 132.0, 130.0, 129.5, 128.9, 128.5, 128.2, 128.0, 96.6, 67.8, 20.2; IR (NaCl, thin film) ν 3060, 2925, 1754, 1558, 1144 cm^{-1}; HRMS (M + H) calcd for $C_{18}H_{17}O_2$ m/z 265.1229, found m/z 265.1230.

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Supporting Information Available: ^{1}H NMR spectra for compounds **4a**,**c**, **5**−**9**, **12a**, **15aa**, **15ba**, **15bb**, **15cc**, **15cb**, **15da**, **16**, and **17** and ^{13}C NMR spectra for compounds **4a**,**c**, **6**−**8**, **12a**, **15aa**, **15ba**, **15bb**, **15cc**, **15cb**, and **17** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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