A New Alkoxyallene-Based [3+2] Approach to the Synthesis of Highly Substituted Cyclopentenones

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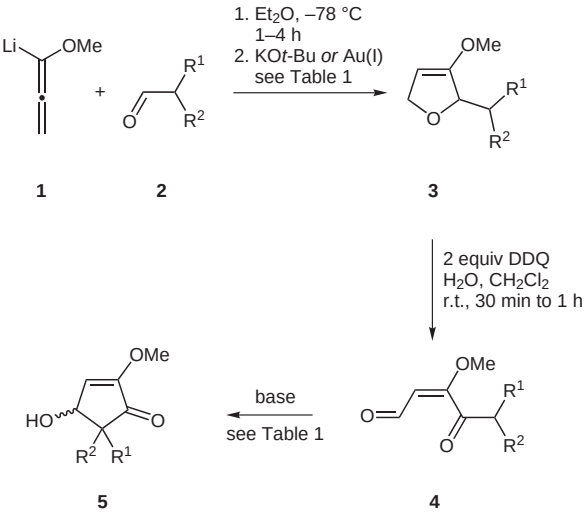
Received 30 November 2007

Abstract: Lithiated methoxyallene **1** and aldehydes **2** provided after base- or gold-catalyzed cyclization dihydrofurans **3** which were oxidatively cleaved giving α,β-unsaturated γ-ketoaldehydes **4** as key intermediates. These smoothly underwent intramolecular aldol addition to furnish highly substituted cyclopentene derivatives **5** in good yields. Due to their dense pattern of functional groups compounds **5** are versatile intermediates, suitable for subsequent elaborations. This was demonstrated by transformation of **5e** into enol phosphate **8** and of **5c** into tetracyclic nitrone cycloadduct **13**.

Key words: allenes, gold catalysis, aldol reactions, cyclopentenones, cycloadditions

Recently, we have demonstrated the versatility of α,β-unsaturated γ-ketoaldehydes **4** as useful building blocks for the synthesis of different heterocycles[1] as well as heterocyclic natural products and their analogues.[2] In this report we expand this methodology to the synthesis of highly functionalized carbocycles.[3] The cyclopentenone ring structure is present in a wide array of natural products and interesting drug targets such as prostaglandins,[4] pentenomycins,[5] and methylenomycins.[6] Methods to generate the cyclopentenone core include intramolecular aldol and Wittig-type reactions, Pauson–Khand reactions, Nazarov cyclizations, and several other reactions.[7] Here we would like to report an efficient synthesis of densely substituted cyclopentenone derivatives **5** starting from lithiated methoxyallene **1** and aldehydes **2** bearing an α-C–H moiety with dihydrofurans **3** and ketoaldehydes **4** as crucial intermediates (Scheme 1).

Addition of lithiated methoxyallene **1** towards aldehydes **2a**–**e** quantitatively furnishes the expected allenyl alcohols (purity generally >95% by ^{1}H NMR).[1,8] These intermediates are subjected to a 5-*endo*-*trig* cyclization to dihydrofurans **3a**–**c** without further purification in the presence of KO*t*-Bu (1 equiv, 60 °C in DMSO). This method, developed by Brandsma and Arens,[9] utilizes rather harsh reaction conditions and therefore sensitive substrates may provide considerably lower yields. Alternative Lewis acid promoted cyclizations are also known. The efficacy of Ag(I)-catalyzed cyclizations of α-allenyl alcohols or amines was also found to be substrate sensitive.[1,10,11] Fortunately, a strongly improved protocol for 5-*endo*-*trig* cyclization of α-allenyl alcohols has recently been developed in our group.[11] The method utilizes AuCl (5 mol%), pyridine (15 mol%) in CH_2Cl_2 (the catalytic system originally reported by Krause for 6-*endo* cyclization of β-allenyl alcohols to dihydropyrans)[12] and proved to be superior to all aforementioned reagent systems. All reactions investigated were completed very rapidly and products were formed with high yields and perfect selectivity even in the case of sensitive substrates.[11] The corresponding dihydrofurans **3a**–**e** were obtained in good to excellent yields using either KO*t*-Bu- (method A) or AuCl-mediated (method B) cyclizations (Table 1).

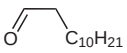
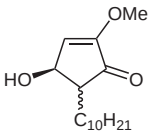
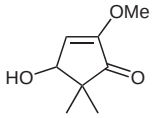
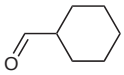
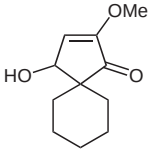
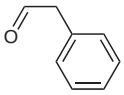
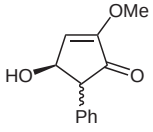
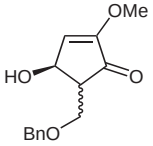


Scheme 1 Synthesis of cyclopentenone derivatives **5**

Oxidative ring-opening reaction of dihydrofurans **3** with DDQ in wet CH_2Cl_2 selectively affords *E*-isomers of α,β-unsaturated γ-ketoaldehydes **4** in good yields.[1,2] The ketoaldehydes **4a**–**e** derived from aldehydes **2a**–**e** with α-C–H units (Table 1, entries 1–5) smoothly undergo intramolecular aldol addition either in the presence of MeONa in MeOH (method C) or of saturated aqueous Na_2CO_3 solution in THF (method D) to generate highly substituted cyclopentenones **5a**–**e** in good yields (Table 1).[13] In the case of aldehydes **4a**,**d**,**e**, the intramolecular aldol reaction proceeds with high diastereoselectivity, preferentially giving in all cases the more stable 4,5-*trans* configured cyclopentenones **5a**,**d**,**e**. This is clearly the result of a thermodynamically controlled reaction, since treatment of pure *trans*-**5e** or *cis*-**5e** with saturated aqueous Na_2CO_3 solution in THF resulted in both cases in the formation of the mixture of diastereomers.[14]

SYNLETT 2008, No. 5, pp 0769–0773
Advanced online publication: 10.03.2008
DOI: 10.1055/s-2008-1042895; Art ID: Y01907ST

Table 1 Addition of Lithiated Methoxyallene **1** to Aldehydes **2** Followed by Cyclization to Dihydrofurans **3**, Oxidative Ring Opening to **4** and Intramolecular Aldol Addition to Cyclopentenones **5**

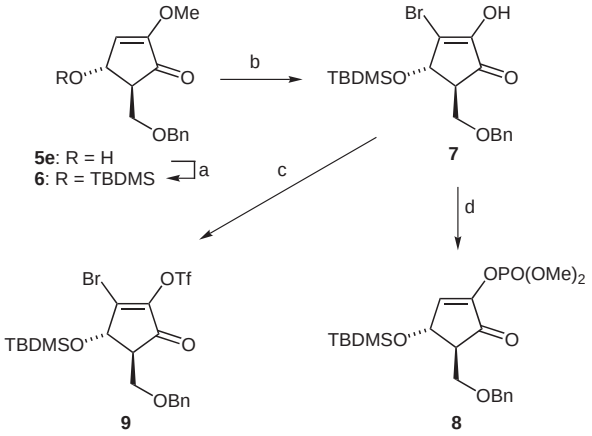
Entry	Aldehyde	Cyclization conditions[a]	Yield of **3** (%)	Yield of **4** (%)[b]	Aldol conditions[a]	Yield of **5** (%)	Product
1	 **2a**	**A**	55	68	**C**	77	 *trans*/*cis* = 94:6 **5a**
2	 **2b**	**A**	47	76	**C**	83	 **5b**
3	 **2c**	**A**	91	93	**C**	76	 **5c**
4	 **2d**	**B**	76	–[c]	–[c]	76	 *trans*/*cis* = 94:6 **5d**
5	 **2e**	**B**	77	67	**D**	78	 *trans*/*cis* = 92:8 **5e**

[a] Conditions **A**: KO*t*-Bu (1 equiv), DMSO, 60 °C, 1–2 h. Conditions **B**: AuCl (0.05 equiv), pyridine (0.15 equiv), CH_2Cl_2, r.t., 0.5–5 h. Conditions **C**: MeONa (0.1 equiv), MeOH, r.t., 2–15 h. Conditions **D**: sat. aq Na_2CO_3 solution, THF (1:3), r.t., 2 d.
[b] Conditions: DDQ (2 equiv), H_2O, CH_2Cl_2 (1:20), r.t., 30 min to 1 h.
[c] Ketoaldehyde **4d** spontaneously undergoes intramolecular aldol reaction during flash chromatography on silica gel.

It is worth to mention that the overall sequence does not require any purification of intermediates **3** and **4**, which in fact tend to be rather unstable upon exposure to silica gel. In the case of cyclopentenones **5c** and **5e** we were able to obtain comparable overall yields (65% vs. 64% in the case of **5c**) or even higher yields (55% vs. 40% in the case of **5e**) when no purification was performed. A further simplification of our protocol represents a one-pot transformation of crude primary allene adducts into ketoaldehydes **4**. Upon completion of the AuCl-catalyzed 5-*endo*-*trig* cyclization of α-allenyl alcohols, just H_2O and DDQ were added to the reaction mixture and after usual workup[15] the resulting α,β-unsaturated γ-ketoaldehydes **4** were isolated.

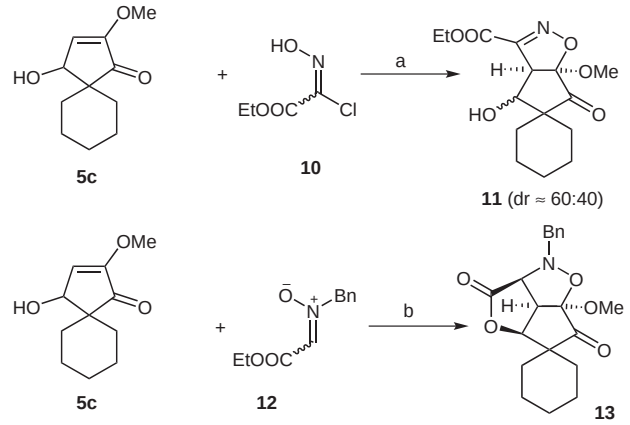
We were then interested in selective transformations of the enol ether moiety of the cyclopentenones prepared. This, however, proved to be an arduous task as different attempts failed. After protection of the hydroxyl group of **5e** and chromatographic separation of diastereomers, we finally succeeded to convert compound **6** into 3-bromo-2-hydroxycyclopent-2-enone **7** using NBS in MeCN and H_2O (Scheme 2).[16] This opened us access to enol phosphate **8**[17] and bromo triflate **9** in moderate yields.[18] These intermediates may be suitable for cross-coupling reactions.

Next, we wanted to demonstrate the potential of our highly substituted cyclopentenones as precursors of unusual amino acid derivatives. This goal should be achieved by 1,3-dipolar cycloaddition[19] of nitrone **12** (Scheme 3). The thermal intermolecular cycloaddition of cyclopentenone **5c** and nitrone **12** did not yield any product, whereas the more reactive nitrile oxide, generated in situ from the corresponding chloroxime **10**, provided at least 28% of the expected cycloadduct **11** (60:40 mixture of two diaste-



Scheme 2 Synthesis of enol phosphate **8** and of bromo triflate **9**. *Reagents and conditions*: a) TBDMSCl, imidazole, CH_2Cl_2, r.t., 12 h, 80%; b) NBS, MeCN, H_2O, r.t., 18 h, 75%; c) 1. *n*-BuLi, Et_2O, –78 °C; 2. Tf_2O, –78 °C, 1 h, 38%; d) $P(OMe)_3$, CH_2Cl_2, r.t., 2 d, 42%.

reomers). The low reactivity of cyclopentenone **5c** is probably due to the fact that electron-donating and electron-withdrawing substituents are geminally attached to double bond.[20] It is well known that nitrone cycloadditions can be strongly accelerated in the presence of Lewis acids.[21] Tamura et al. reported that treatment of α-methoxycarbonyl-substituted nitrones with allyl alcohols in the presence of Ti(O*i*-Pr)$_4$ resulted in tandem transesterification, *E*/*Z*-isomerization and an intramolecular cycloaddition to provide polycyclic compounds in a stereocontrolled manner.[22] Gratifyingly, the Ti(O*i*-Pr)$_4$-promoted cycloaddition of nitrone **12** to cyclopentenone **5c**, gave a single tetracyclic product **13** in 75% yield.[23] This interestingly functionalized cycloadduct offers many options for further synthetic endeavors.



Scheme 3 1,3-Dipolar cycloadditions of cyclopentenone **5c**. *Reagents and conditions*: a) Et_3N, Et_2O, r.t., 17 h, 28%; b) Ti(O*i*-Pr)$_4$ (1 equiv), CH_2Cl_2, r.t., 2 d, 75%.

In conclusion, we have reported a simple and efficient synthesis of highly substituted cyclopentenones starting from lithiated methoxyallene as C3 building block and aldehydes with α-C–H moiety as C2 unit.[24] Easy access, unique substitution pattern, and structural variability predestine them as interesting substrates for diversity oriented synthesis.

Acknowledgment

The authors thank the Deutsche Forschungsgemeinschaft, the Alexander von Humboldt Stiftung (research fellowship for B.D.), the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG for generous support. We are very grateful to Dr. Malte Brasholz for preliminary experiments on intramolecular aldol additions and help during preparation of this manuscript.

References and Notes

(1) Flögel, O.; Reissig, H.-U. *Eur. J. Org. Chem.* **2004**, 2797.
(2) Brasholz, M.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2007**, *46*, 1634; *Angew. Chem.* **2007**, *119*, 1659.
(3) Related ketoaldehydes have recently been utilized for the total synthesis of the cyclopentenone core of Litseaverticillols: (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5465; *Angew. Chem.* **2003**, *115*, 5623. (b) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett.* **2004**, *6*, 2039.
(4) Noyori, R.; Suzuki, M. *Science* **1994**, *259*, 44.
(5) (a) Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506. (b) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233.
(6) (a) Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *J. Antibiot.* **1974**, *27*, 386. (b) Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *J. Antibiot.* **1974**, *27*, 393.
(7) For recent reviews on routes to cyclopentenones, see: (a) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (b) Gibson, S. E.; Mainolfi, N. *Angew. Chem. Int. Ed.* **2005**, *44*, 3022; *Angew. Chem.* **2005**, *117*, 3082. (c) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873.
(8) (a) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179. (b) Magnus, P.; Albaugh-Robertson, P. *J. Chem. Soc., Chem. Commun.* **1984**, 804. (c) Zimmer, R.; Reissig, H.-U. In *Modern Allene Chemistry*, Vol. 1; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**, Chap. 8, 425–492. (d) Hormuth, S.; Reissig, H.-U. *Synlett* **1991**, 179. (e) Hormuth, S.; Reissig, H.-U. *J. Org. Chem.* **1994**, *59*, 67.
(9) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.
(10) (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743. (b) Okala Amombo, M.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871. (c) Flögel, O.; Okala Amombo, M.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem. Eur. J.* **2003**, *9*, 1405. (d) Kaden, S.; Brockmann, M.; Reissig, H.-U. *Helv. Chim. Acta* **2005**, *88*, 1826. (e) Kaden, S.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4763. (f) Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383.
(11) Brasholz, M.; Reissig, H.-U. *Synlett* **2007**, 1294.
(12) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.
(13) **Typical Procedure for the Intramolecular Aldol Reaction: Preparation of Compound 5c**
The mixture of ketoaldehyde **4c** (1.61 g, 8.20 mmol) and MeONa (44 mg, 0.82 mmol) in dry MeOH (15 mL) was stirred at r.t. overnight. The reaction was quenched with sat. aq NH_4Cl solution, extracted with Et_2O, and dried (Na_2SO_4). After evaporation of solvents the resulting crude product was purified by flash chromatography [silica gel, EtOAc–hexane (1:2)] yielding 1.23 g (76%) of a brownish syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32–1.80 (m, 10 H,

$5 \times CH_2$), 1.90 (s_{br}, 1 H, OH), 3.76 (s, 3 H, OCH_3), 4.60 (d_{br}, J = 3.2 Hz, 1 H, 4-H), 6.22 (d, J = 3.2 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 22.7, 25.0, 27.7, 34.1 (5 t, $5 \times CH_2$), 50.6 (s, C-5), 57.1 (q, OCH_3), 74.1 (d, C-4), 123.6 (d, C-3), 156.5 (s, C-2), 205.1 (s, C-1) ppm. IR (film): ν = 3430 (OH), 3010–2855 (=CH, CH), 1710 (C=O), 1635 (C=C) cm^{-1}. MS (EI, 80 eV): *m/z* (%) = 196 (64) [M^+], 179 (7) [M^+ – OH], 71 (100) [$C_5H_{11}^+$]. HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{17}O_3^+$ [M + H]$^+$ 197.1178; found: 197.1157.

(14) The organocatalytic approach using L-proline as catalyst for aldol reaction resulted only in moderate yields (12–34%) of cyclopentenones **5a**. Moreover, in most cases a significant amount of starting ketoaldehyde **4a** was recovered: Dugovič, B.; Reissig, H.-U. *unpublished results*.

(15) **Typical Procedure for the One-Pot Transformation: Preparation of Compound 4c**
Methoxyallene (6.90 mL, 5.80 g, 82.6 mmol) was dissolved in Et_2O (150 mL) at –40 °C under an atmosphere of Ar. *n*-BuLi (30.4 mL, 2.5 M in hexane, 75.9 mmol) was added, the mixture was stirred for 1 h and then cooled to –78 °C. A solution of cyclohexanecarbaldehyde (**2c**, 4.00 mL, 3.70 g, 33.0 mmol) in Et_2O (50 mL) was slowly added and the mixture was stirred at –78 °C for 1.5 h. Then, H_2O (50 mL) was added and the mixture was warmed up to r.t. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and after evaporation the allenyl alcohol was obtained as a yellow oil (6.13 g, quant.). The crude product was dissolved in dry CH_2Cl_2 (300 mL). Pyridine (0.40 mL, 0.39 g, 4.95 mmol) and AuCl (0.38 g, 1.65 mmol) were added with vigorous stirring under an atmosphere of Ar at r.t. After 1 h TLC showed complete consumption of allenyl alcohol. Water (15.0 mL) and DDQ (15.0 g, 66.0 mmol) were added and stirring was continued for 1 h. The mixture was poured into sat. aq $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried (Na_2SO_4) and the solvent was removed to provide 6.75 g of crude ketoaldehyde **4c**. Purification by flash chromatography on silica gel (CH_2Cl_2) provided 5.51 g (85%) of pure **4c**.
Mp 41–45 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.19–1.27, 1.28–1.40, 1.68–1.71, 1.78–1.87 (4 m, 10 H, $5 \times CH_2$), 2.90–2.95 (m, 1 H, 1′-H), 3.79 (s, 3 H, OCH_3), 5.53 (d, J = 7.3 Hz, 1 H, 2-H), 9.76 (d, J = 7.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 25.7, 27.7 (3 t, $3 \times CH_2$), 46.7 (d, C-1′), 56.4 (q, OCH_3), 108.4 (d, C-2), 169.5 (s, C-3), 191.0 (d, C-1), 201.3 (s, C-4) ppm. IR (KBr): ν = 3070–2850 (=CH, CH), 1705, 1660 (C=O), 1595 (C=C) cm^{-1}. MS (EI, 80 eV): *m/z* (%) = 196 (35) [M^+], 83 (72) [$C_6H_{11}^+$], 55 (100) [$C_3H_3O^+$]. Anal. calcd for $C_{11}H_{16}O_3$ (196.2): C, 67.32; H, 8.22. Found: C, 67.22; H, 8.11.

(16) (a) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113. (b) Flögel, O.; Reissig, H.-U. *Synlett* **2003**, 405.

(17) **Preparation of Compound 8**
The solution of **6** (329 mg, 0.91 mmol) in MeCN (12 mL) and H_2O (1 mL) was treated with NBS (161 mg, 0.91 mmol) at r.t. for 18 h. Water was added and the mixture was extracted with hexane, the combined extracts were dried (Na_2SO_4), and after evaporation the crude product was filtered through silica gel and washed with 2.5% *i*-PrOH in hexane to yield 292 mg (75%) of compound **7**. A solution of **7** (68 mg, 0.16 mmol) and $P(OMe)_3$ (56 μL, 59 mg, 0.48 mmol) in CH_2Cl_2 (1.5 mL) was stirred at r.t. for 2 d. The volatile components were removed in vacuo and the residue was purified by chromatography (silica gel, 1:3 EtOAc–hexane) to yield 31 mg (42%) of **8** as colorless oil.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.06, 0.10 [2 s, 2×3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 2.41–2.43 (m, 1 H, 5-H), 3.71 (dd, J = 9.4, 3.5 Hz, 1 H, CH_2O), 3.83 (d, J_{HP} = 11.9 Hz, 3 H, OCH_3), 3.85 (t, J = 9.4 Hz, 1 H, CH_2O), 3.88 (d, J_{HP} = 11.4 Hz, 3 H, OCH_3), 4.44, 4.52 (2 d, J = 12.0 Hz, 2×1 H, CH_2Ph), 4.96 (s_{br}, 1 H, 4-H), 7.06 (dt, J = 2.5, 1.2 Hz, 1 H, 3-H), 7.27–7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.7 [q, $Si(CH_3)_2$], 17.9 [s, $C(CH_3)_3$], 25.7 [q, $C(CH_3)_3$], 55.1 (d, C-5), 55.3 (2 qd, J_{CP} = 6.3 Hz, OCH_3), 65.9 (t, CH_2O), 68.9 (d, C-4), 73.3 (t, CH_2Ph), 127.7, 127.8, 128.3, 137.7 (3 d, s, Ph), 141.2 (dd, J_{CP} = 3.3 Hz, C-3), 148.3 (s, C-2), 197.5 (s, C-1) ppm. IR (film): ν = 2955–2855 (=CH, CH), 1735 (C=O), 1630 (C=C) cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{33}O_7NaPSi^+$ [M + Na]$^+$: 479.1631; found: 479.1631.

(18) **Preparation of Compound 9**
Under an atmosphere of Ar a solution of **7** (200 mg, 0.47 mmol) in Et_2O (5 mL) was successively treated at –78 °C with *n*-BuLi (2.5 M in hexane, 0.19 mL, 0.47 mmol) and Tf_2O (0.10 mL, 0.17 g, 0.62 mmol). After 1 h, the reaction was quenched by addition of sat. aq $NaHCO_3$ solution, H_2O was added and the mixture was extracted with Et_2O, the combined extracts were dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by chromatography on silica gel (3% EtOAc in hexane) to yield 100 mg (38%) of **9** as colorless oil.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.06, 0.19 [2 s, 2×3 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 2.64 (td, J = 3.3, 2.0 Hz, 1 H, 5-H), 3.69, 3.89 (2 dd, J = 9.6, 3.3 Hz, 2×1 H, CH_2O), 4.43, 4.54 (2 d, J = 12.1 Hz, 2×1 H, CH_2Ph), 4.96 (d, J = 2.0 Hz, 1 H, 4-H), 7.25–7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, –4.5 [2 q, $Si(CH_3)_2$], 18.0 [s, $C(CH_3)_3$], 25.6 [q, $C(CH_3)_3$], 56.4 (d, C-5), 65.2 (t, CH_2O), 72.4 (d, C-4), 73.5 (t, CH_2Ph), 127.9, 128.0, 128.5, 137.2 (3 d, s, Ph), 147.2, 150.9 (2 s, C-2, C-3), 191.3 (s, C-1) ppm, signal of CF_3 not detectable. IR (film): ν = 3090–2860 (=CH, CH), 1740 (C=O), 1635 (C=C) cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{27}BrF_3O_6SSi^+$ [M + H]$^+$: 559.0433; found: 559.0438.

(19) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565; *Angew. Chem.* **1963**, *75*, 604.

(20) (a) We also tried [2+1] and [4+2] cycloadditions of cyclopentenone **5c** or its *tert*-butyldimethylsilyl ether with methyl diazoacetate and α-trifluoromethyl-α-nitrosoalkene, respectively, but in all cases no cycloadducts were formed. (b) For a recent study on 1,3-dipolar cycloadditions of captodative olefins see: Herrera, R.; Mendoza, J. A.; Morales, M. A.; Méndez, F.; Jiménez-Vázquez, H. A.; Delgado, F.; Tamariz, J. *Eur. J. Org. Chem.* **2007**, 2352.

(21) (a) Gothelf, K. V.; Kanemasa, S.; Jørgensen, K. A. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2001**, 211–326. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Dugovič, B.; Fišera, L.; Hametner, C. *Synlett* **2004**, 1569. (d) Dugovič, B.; Wiesenganger, T.; Fišera, L.; Hametner, C.; Prónayová, N. *Heterocycles* **2005**, *65*, 591. (e) Dugovič, B.; Fišera, L.; Cyrański, M. K.; Hametner, C.; Prónayová, N.; Obranec, M. *Helv. Chim. Acta* **2005**, *88*, 1432. (f) Dugovič, B.; Fišera, L.; Reissig, H.-U. *Eur. J. Org. Chem.* **2007**, 277.

(22) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009.

(23) **Preparation of Compound 13**
The reaction was carried out under an argon atmosphere. To a stirred solution of cyclopentenone **5c** (0.46 g, 2.35 mmol) and nitrone **12** (0.96 g, 4.63 mmol) in CH_2Cl_2 (10 mL) was added $Ti(O\textit{i}\text{-}Pr)_4$ (0.70 mL, 0.87 g, 2.35 mmol) at r.t., and stirring was continued at the same temperature until

cyclopentenone **5c** disappeared (monitored by TLC, 2 d). The reaction mixture was poured onto silica gel, which was then washed with EtOAc–hexane (1:3). After removal of solvents the crude product was recrystallized (EtOAc–hexane, 1:3) to provide 0.62 g (75%) of **13** as colorless solid. Mp 148–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36–1.54, 1.61–1.66, 1.73–1.81 (3 m, 4 H, 2 × 3 H, CH_2), 3.49 (s, 3 H, OCH_3), 4.00 (s_{br}, 1 H, 4-H), 4.25 (d, *J* = 13.3 Hz, 1 H, CH_2Ph), 4.30 (d, *J* = 7.7 Hz, 1 H, 3-H), 4.48 (d_{br}, *J* = 13.3 Hz, 1 H, CH_2Ph), 4.84 [d, *J* = 6.9 Hz, 1 H, CHOC(O)], 7.29 (d, *J* = 7.2 Hz, 1 H, Ph), 7.34 (t, *J* = 7.2 Hz, 2 H, Ph), 7.44 (d, *J* = 7.2 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.5, 25.0, 26.5, 30.9 (5 × t, CH_2), 52.8 (q, OCH_3), 54.1 (d, C-4), 57.4 [s, $C(CH_2)_2$], 67.3 (d_{br}, C-3), 79.7 [d, CHOC(O)] 127.7, 128.5, 128.8, 135.9 (3 × d, s, Ph), 172.4 [s_{br}, OC(O)], 206.2 (s, C=O) ppm; signals of C-5 and NCH_2Ph are not visible, according to HMBC C-5, δ ca. 110.2, NCH_2Ph, δ ca. 67.3 ppm. IR (KBr): ν = 3110–2840 (=CH, CH), 1790, 1750 (C=O) cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{24}NO_5^+$ $[M + H]^+$: 358.1655; found: 358.1687. Anal. calcd for $C_8H_{12}O_3$ (357.4): C, 67.21, H, 6.49; N, 3.92. Found: C, 67.03; H, 6.46; N, 3.95.

(24) For an interesting alternative approach to cyclopentene derivatives employing lithiated allenyl MOM ethers, see: Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398.