Reaction of a Polycyclic Diketone with Lithiated Methoxyallene: Synthesis of New Functionalized Cage Compounds

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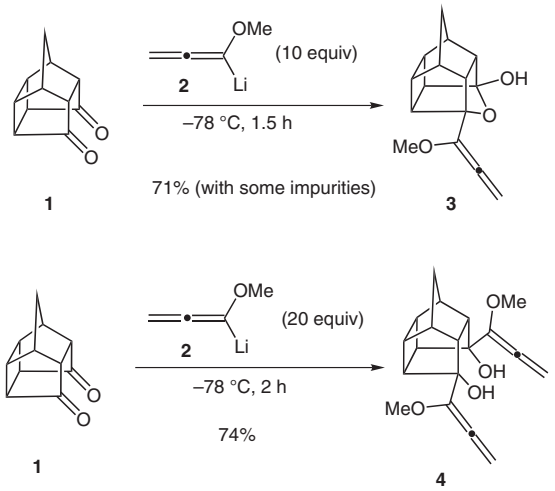
Received 7 May 2008

Abstract: Syntheses of several new functionalized cage compounds are described. The key steps of the reaction sequence are addition of lithiated methoxyallene **2** to cage diketone **1**, preparation of dehydrated intermediate **5**, and its ozonolysis leading to diester **7**. Alternatively, **5** could be hydrolyzed to provide cage compound **6** with a bisenone subunit. Via diol **9** chiral crown ether **11** could be prepared in low yield. A first stereoselective epoxidation of chalcone **12** with *tert*-butyl hydroperoxide in the presence of **11** gave the epoxide **13** in reasonable yield, but with a low level of enantioselectivity.

Key words: methoxyallene, cage molecules, crown ether, ozonolysis, epoxidation.

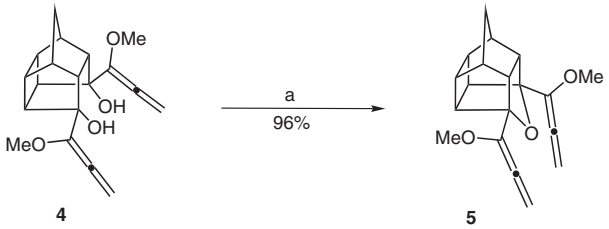
We and others explored alkoxyallenes[1] as interesting key intermediates for the syntheses of different types of heterocycles. Compounds such as 1,2-oxazines,[2,3] dihydrofuranones,[4] dihydropyrroles,[5] pyrrolidinones,[6] pyridines,[7] imidazoles,[8] pyrroloisoindolones,[9] and bisbenzannulated spiroketals[10] have been prepared. Stereoselective synthesis of heterocycles via lithiated alkoxyallenes makes these C-3 building blocks particularly attractive.[1,11] Most of these reactions of lithiated alkoxyallenes were performed with monofunctionalized electrophiles. Only a few special examples are known where the lithiated allenyl species react with electrophiles bearing more than one electrophilic center, for example, bisnitrones,[3c,12] bisimines,[5c] or diketones.[13] In this communication we describe the addition of lithiated methoxyallene **2** to pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**1**) as an interesting biselectrophile[14] and the elaboration of the resulting addition product to various functionalized cage compounds, including a chiral crown ether. A number of cage-annulated macrocycles based on diketone **1** are interesting targets due to their potential for enantioselective recognition of chiral ammonium salts[15] as well as their ability as host compounds for transport processes.[16,17]

Diketone **1** is easily available in a two-step sequence from cyclopentadiene and *para*-benzoquinone.[18] In a first attempt **1** was treated with ten equivalents of lithiated methoxyallene **2**, generated in situ from methoxyallene and *n*-BuLi in THF (Scheme 1). Instead of the expected double addition product **4**, the monosubstituted compound **3** was formed in 71% yield as main product contaminated with unknown impurities. Compound **4** was only detected in trace amounts. Gratifyingly, when the reaction was performed with a larger excess (20 equiv) of **2** at –78 °C bisallenylated C_S-symmetrical product **4** was obtained in 74% yield.[19] The first addition of lithiated methoxyallene to **1** provides the lithium salt of **3** and by this internal protection as lithiated hemiketal the second addition is fairly difficult. Only application of a larger excess of the nucleophile allows the efficient trapping of the small quantities of free ketone in equilibrium with lithiated **3**.



Scheme 1 Synthesis of methoxyallene adducts **3** and **4**

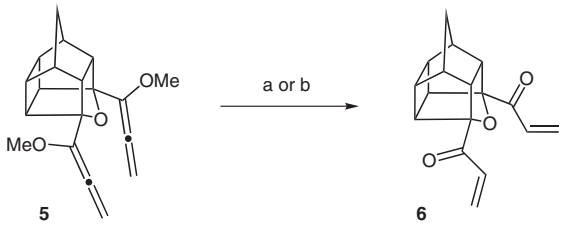
The subsequent dehydration of diol **4** was first examined under standard conditions as described by Marchand and co-workers for other cage diols.[16] Treatment of **4** with *p*-toluenesulfonic acid in refluxed benzene only led to decomposition of the acid labile compound **4**. Mesylation of **4** in the presence of triethylamine as base was more successful. The expected polycyclic ether **5** was directly obtained under these reaction conditions in excellent yield (Equation 1).[20]



Equation 1 Dehydration of **4**. *Reagents and conditions*: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; r.t., 2.5 h.

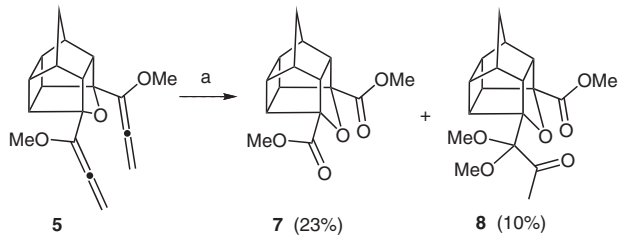
SYNLETT 2008, No. 13, pp 2046–2050
Advanced online publication: 15.07.2008
DOI: 10.1055/s-2008-1077975; Art ID: G16208ST

When bisallenyl ether **5** was allowed to stand with $MgSO_4$ in dichloromethane at room temperature (drying of the extracts after aqueous workup) it was converted into bisenone **6** (Equation 2). The same hydrolyzed product **6** was obtained when **5** was treated under acidic reaction conditions[21] (e.g., 5% aq H_2SO_4, 0 °C, 48% yield). α,β-Unsaturated carbonyl compounds are synthetically very useful building blocks.[22] Therefore, compound **6** may serve as useful intermediate for further transformations such as Michael addition, Baylis–Hillman or metathesis reaction preparing new functionalized cage molecules.



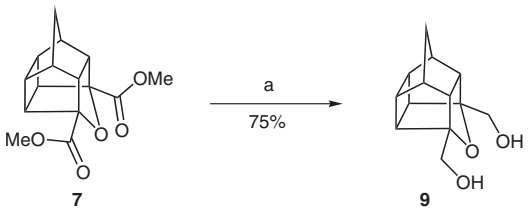
Equation 2 Formation of α,β-unsaturated bisenone **6**. *Reagents and conditions*: a) $MgSO_4$, r.t., quant.; b) 5% aq H_2SO_4, 0 °C, 48%.

The ozonolysis of bisallenyl ether **5** at –78 °C gave a mixture of diester **7**[23] (23% yield) with methyl ketone **8** (10% yield, Equation 3).[24] At present we have to state that all attempts to increase the yield of diester **7** by changing the reaction conditions (e.g., different solvents and reaction times, workup with and without of Ph_3P or Me_2S) did not lead to an improvement. The formation of **7** is in accordance to known ozonolyses of alkoxy-substituted allenes.[5c,25,26]



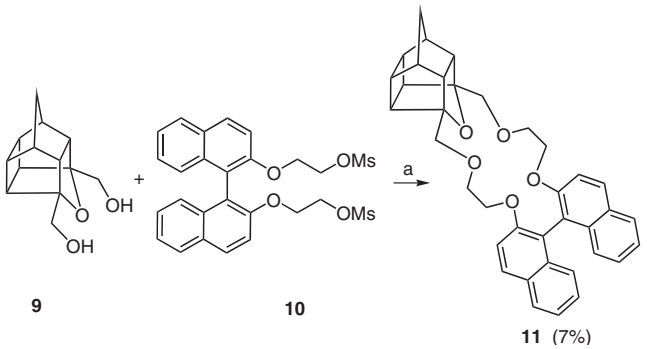
Equation 3 Ozonolysis of **5**. *Reagents and conditions*: a) O_3, MeOH, CH_2Cl_2, –78 °C, 20 min.

Diester **7** served as starting material for the preparation of a chiral crown ether which should be tested as ligand in a stereoselective reaction, for example, an epoxidation reaction.[27] Reduction of **7** by treatment with lithium aluminum hydride smoothly afforded the expected diol **9** in 75% yield (Equation 4).



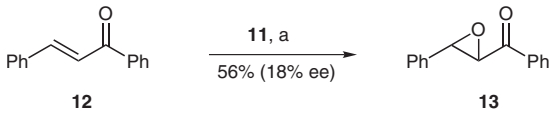
Equation 4 Reduction of diester **7**. *Reagents and conditions*: a) $LiAlH_4$, 0 °C to r.t.

The known bismesylated BINOL derivative **10**[28] served as chiral moiety in the crown ether synthesis. The reaction of diol **9** with **10** was performed in the presence of sodium hydride as base under reflux conditions which gave the crown ether **11** in low yield; 12% of **10** could be re-isolated (Equation 5). So far, no attempts to optimize this double substitution reaction have been made;[29] the low yield is probably due to a high degree of oligomerization (intermolecular reaction instead of ring closure). The structure of **11** was clearly confirmed by NMR spectroscopy, MS (EI method) and HRMS.[30]



Equation 5 Formation of the chiral crown ether **11**. *Reagents and conditions*: a) NaH, THF, reflux, 84 h.

Finally, we tested chiral crown ether **11** in an epoxidation reaction employing a typical protocol as described by Bakó et al.[27a] The reaction of chalcone **12** with *tert*-butyl hydroperoxide was carried out in a two-phase system (toluene–aq NaOH solution) in the presence of 5 mol% of **11** (Equation 6). The expected epoxide **13** was obtained in 56% yield, but with a low enantioselectivity of only 18% ee.



Equation 6 Epoxidation of **12** using chiral crown ether **11**. *Reagents and conditions*: a) *t*-BuOOH, 20% aq NaOH, toluene, 5 °C to r.t., 15 h.

In summary, we prepared a series of new functionalized cage compounds including chiral macrocycle **11**. The key steps are addition of lithiated alkoxyallene to the diketone **1** and ozonolysis of bisallenyl-substituted intermediate **5** forming diester **7**. Although the low stereoselectivity in the epoxidation induced by **11** certainly needs improvements, further options are the application of chiral crown ethers such as **11** as a host in the recognition of guest molecules.[31] Functionalized cage compounds such as **5**, **6**, and **7** may also be of interest for other applications.

Acknowledgment

Support of this work by the Fonds der Chemischen Industrie and the Bayer Schering Pharma AG is most gratefully acknowledged. We

thank Prof. A. P. Marchand for the donation of a fair amount of diketone **1**.

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(19) **Bisallenyl Adduct 4**
Methoxyallene (4.20 g, 60.0 mmol) was dissolved in dry THF (35 mL) and treated with *n*-BuLi (16.0 mL, 40.0 mmol, 2.5 M in hexanes) at –40 °C under argon atmosphere. After 5 min the solution of **2** was cooled to –78 °C and diketone **1** (0.522 g, 3.00 mmol, dissolved in 5 mL of THF) was added within 5 min. The reaction mixture was stirred for 2 h at –78 °C and quenched with sat. aq NH_4Cl solution (25 mL). Warmup to r.t. was followed by extraction with Et_2O (3 × 30 mL) and drying (Na_2SO_4). Purification of the crude product by recrystallization (hexane–Et_2O) provided **4** (0.678 g, 74%) as a beige-colored solid, mp 148–150 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03, 1.54 (AB system, J_{AB} = 10.5 Hz, 2 H, CH_2), 2.25–2.46, 2.61–2.73 (2 m, 4 H each, 8 CH), 3.43 (s, 6 H, OMe), 5.46 (s, 2 H, OH), 5.48 (s, 4 H, =CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 196.6 (s, C=*C*=CH_2), 137.5 (s, =C=*C*OMe), 91.8 (t, =C=*C*H_2), 79.1 (s, C-3, C-5), 56.6 (q, OMe), 47.8, 44.8, 40.7, 33.8 (4 d, CH), 41.4 (t, CH_2). IR (KBr): 3630–3150 (OH), 3020–2820 (=CH, CH), 1930 (C=C=C), 1650 (C=C) cm^{-1}. MS (EI, 80 eV): *m/z* (%) = 314 (6) [M]$^+$, 281 (44), 161 (46), 147 (66), 115 (70), 103 (34), 69 (65), 55 (100), 43 (38). HRMS (80 eV): *m/z* calcd for $C_{19}H_{22}O_4$: 314.1518; found: 314.1543. Anal. Calcd for $C_{19}H_{22}O_4$ (314.4): C, 72.59; H, 7.05. Found: C, 71.81; H, 6.97.

(20) **Compound 5**
To a solution of **4** (0.205 g, 0.655 mmol) in CH_2Cl_2 (13 mL) mesyl chloride (0.082 g, 0.723 mmol, dissolved in 2 mL of CH_2Cl_2) and Et_3N (0.658 g, 6.55 mmol) were added at 0 °C. The solution was warmed up to r.t. and stirred for additional

2.5 h. Then, sat. aq NH_4Cl solution (5 mL) was added and the phases were separated. The organic phase was successively washed with H_2O (3 × 5 mL) and brine (1 × 5 mL) and dried (Na_2SO_4). Purification of the crude product by chromatography on alumina (hexane–EtOAc, 4:1) provided **5** (0.186 g, 96%) as an orange resin. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.55, 1.92 (AB system, J_{AB} = 10.5 Hz, 2 H, CH_2), 2.43, 2.65, 2.86, 2.93 (4 br s, 2 H each, 8 CH), 3.46 (s, 6 H, OMe), 5.51 (s, 4 H, $=CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 198.7 (s, C=*C*=CH_2), 132.0 (s, =C=*C*OMe), 91.1 (t, =C=*C*H_2), 95.1 (s, C-3, C-5), 56.4 (q, OMe), 57.3, 47.4, 44.3, 41.0 (4 d, CH), 43.3 (t, CH_2). IR (neat): 3010–2860 (CH), 1930 (C=C=C) cm^{-1}. MS (EI, 80 eV): *m/z* (%) = 296 (100) $[M]^+$, 281 (29) $[M - CH_3]^+$, 265 (12) $[M - OMe]^+$, 227 (15), 145 (18), 115 (15). HRMS (80 eV): *m/z* calcd for $C_{19}H_{20}O_3$: 296.1412; found: 296.1442.

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(23) The diester **7** was recently obtained by a one-pot reaction of **1** with dimethoxycarbene in moist toluene in 19% yield, see: Romański, J.; Mlostoń, G.; Heimgartner, H. *Helv. Chim. Acta* **2007**, *90*, 1279.

(24) **Ozonolysis of Bisallenyl-Substituted Compound 5**
To a solution of **5** (0.37 g, 1.25 mmol) in MeOH (30 mL) argon was bubbled for 5 min with cooling to –78 °C. Then, the solution was treated with ozone until the solution remained blue for 20 min, followed by oxygen for 5 min. The reaction mixture was allowed to warm to r.t. within 1 h and the solvent was evaporated in vacuo. Purification of the crude product by chromatography (alumina, hexane–EtOAc, 4:1, 1:1 to 0:1) afforded diester **7** (0.080 g, 23%) as colorless crystals and methyl ketone **8** (0.033 g, 10%) as a pale yellow oil.
Diester **7**: mp 134–136 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.66, 2.04 (AB system, J_{AB} = 11 Hz, 2 H, CH_2), 2.60–2.88, 3.00–3.15 (2 m, 4 H each, 8 CH), 3.80 (s, 6 H, CO_2Me). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 43.2 (t, CH_2), 42.1, 45.2, 49.2, 58.6 (4 d, CH), 52.2 (q, OMe), 94.7 (s, C-3, C-5), 170.7 (s, *C*O_2Me). IR (KBr): 2990–2840 (CH), 1720 (C=O) cm^{-1}. MS (EI, 80 eV): *m/z* (%) = 276 (2) $[M]^+$, 245 (4) $[M - OMe]^+$, 218 (15), 217 (100) $[M - CO_2Me]^+$. HRMS (80 eV): *m/z* calcd for $C_{15}H_{16}O_5$: 276.0998; found: 276.0978.
Methyl ketone **8**: ^1H NMR (250 MHz, $CDCl_3$): δ = 1.52, 1.89 (AB system, J_{AB} = 11 Hz, 2 H, CH_2), 2.27 (s, 3 H, Me), 2.32 (m_c, 1 H, CH), 2.62–2.67, 2.71–2.76 (2 m, 2 H, 1 H, 3 CH), 2.77–2.81, 2.84–2.88, 2.94–2.99, 3.08–3.13 (4 m, 1 H each, CH), 3.27, 3.32 (2 s, 3 H each, OMe), 3.73 (s, 3 H, CO_2Me). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.2 (q, Me), 43.1 (t, CH_2), 41.6, 42.1, 44.7, 45.6, 46.0, 49.0, 55.9, 58.9 (8 d, CH), 51.4, 51.7, 52.0 (3 q, OMe), 94.2, 98.7, 102.8 [3 s, *C*$(OMe)_2$, C-3, C-5], 171.5 (s, *C*O_2Me), 205.9 (s, *C*OMe). MS (FAB$^+$, 80 eV): *m/z* (%) = 357 (4) $[M + Na]^+$, 335 (3) $[MH]^+$, 304 (18), 303 (85), 291 (100) $[M - MeCO]^+$, 154 (17), 137 (25), 136 (19), 105 (21), 81 (26), 69 (34), 55 (49), 43 (47).

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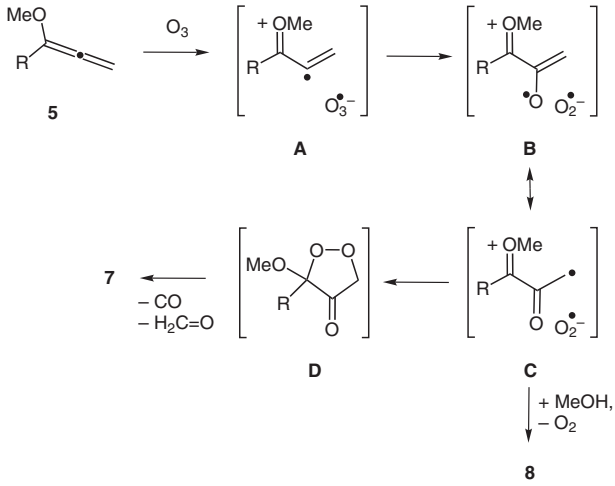
(26) (a) For a mechanistic discussion of the ozonolysis of allenes, see: Langler, R. F.; Raheja, R. K.; Schank, K.; Beck, H. *Helv. Chim. Acta* **2001**, *84*, 1943; and references therein. (b) The formation of diester **7** can be rationalized by single-electron transfers via intermediates **A** to **D**, whereas the formation of the methyl ketone **8** is more speculative. Therefore, a single-electron transfer to intermediate **C** by O_2^- and conversion of the carbonyl group into an acetal moiety by the solvent methanol may lead to this side product (Scheme 2).



Scheme 2

(27) For epoxidations using chiral crown ethers, see: (a) Bakó, P.; Bakó, T.; Mészáros, A.; Keglevich, G.; Szőllősy, A.; Bodor, S.; Makó, A.; Tőke, L. *Synlett* **2004**, 643. (b) Hori, K.; Tamura, M.; Tani, K.; Nishiwaki, N.; Ariga, M.; Tohda, Y. *Tetrahedron Lett.* **2006**, *47*, 3115; and references cited therein.

(28) Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996**, *61*, 3093.

(29) It should be noted that the yield of **11** may be enhanced by a template-directed reaction of **9** and **10** (e.g., by the use of a Cs salt). See also ref. 15.

(30) **Reaction of 9 and 10**
To a suspension of NaH (4 mg, 0.16 mmol) in THF (1 mL) were added a solution of **9** (18 mg, 0.08 mmol, dissolved in 5 mL of THF) and a solution of **10** (43 mg, 0.08 mmol, dissolved in 10 mL of THF) over a period of 30 min. The reaction mixture was refluxed for 84 h and after cooling to r.t. H_2O (10 mL) was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried with $MgSO_4$. Purification of the crude product by chromatography (SiO_2, hexane–EtOAc, 4:1, 1:1, then 1:3) gave product **11** (3 mg, 7%) as a pale yellow resin and starting material **10** (5 mg, 12%).
Product **11**: $[\alpha]_D$ = 6.7 (*c* 0.08, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83, 0.87 (2 d, *J* = 10 Hz, 1 H each, CH_2), 0.99–1.80 (m, 8 H, CH), 3.25–4.55 (m, 12 H, OCH_2), 7.05–7.35 (m, 6 H, Ar), 7.40 (d, *J* = 8 Hz, 2 H, Ar), 7.85 (d, *J* = 2 Hz, 2 H, Ar), 7.97 (d, *J* = 2 Hz, 2 H, Ar). MS (EI, 80 eV, 240 °C): *m/z* (%) = 558 (6) $[M]^+$, 356 (10), 327 (10), 284 (13), 269 (18), 268 (14), 239 (14), 129 (12), 123 (23), 113 (10), 111 (16), 109 (12), 105 (10), 99 (14), 97 (24), 96 (18), 91 (35), 85 (24), 83 (30), 82 (18), 74 (29), 72 (35), 55 (53), 44 (23), 43 (100) $[MeCO]^+$, 41 (47), 26 (43). HRMS (80 eV): *m/z* calcd for $C_{37}H_{34}O_5$: 558.24060; found: 558.24255.

(31) For chiral recognition of racemic primary amines by BINOL-containing crown ethers, see: (a) Kyba, E. P.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692. (b) Cram, D. J. *Science* **1974**, *183*, 803. (c) Yamamoto, K.; Yunioka, H.; Okamoto, Y.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1987**, 168. (d) Galán, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511; see also refs. 15 and 16.