Single Step Synthesis of Cyclooctadienone Derivatives by Reaction of Cyclobutenones with Dienyllithium

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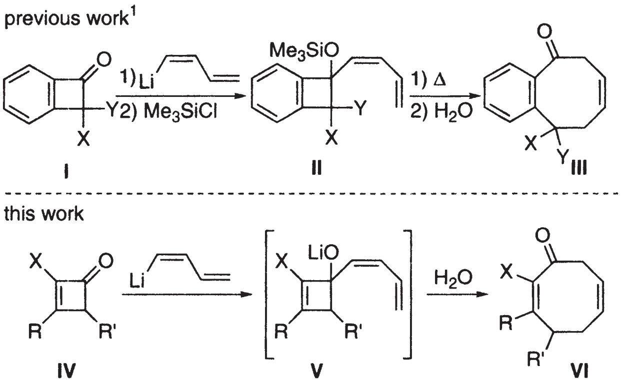
Various functionalized cyclooctadienones are accessible in high yields by the reaction of cyclobutenones with dienyllithium.

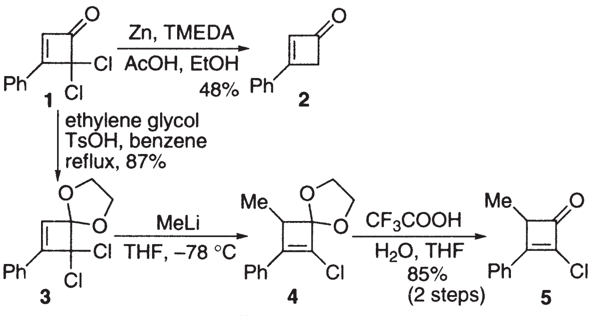
We recently reported an approach to benzocyclooctenone **III** via the thermal ring expansion of dienylbenzocyclobutenol derivative **II**, prepared by the dienylation–silylation of benzocyclobutenone **I** (Scheme 1).[1,2]

By analogy, we became interested in the corresponding reactions of the simpler, "non-benzo" series of compounds, which is reported in this communication. Particularly notable in the latter series was that the rearrangement proceeded quite easily in one pot, i.e. without isolation and derivation of intermediates (cf. **II**). Thus, the alkoxide **V**, formed by the reaction of **IV** with dienyllithium, directly underwent the ring enlargement, providing a facile access to cyclooctadienone **VI**.[4]



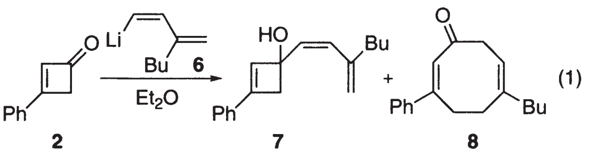
Scheme 1.

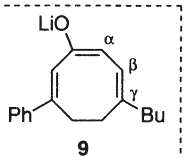
Ketone **2** was prepared from **1** by known methods (Scheme 2).[5] Chloroketone **5** was obtained via the selective S_N2' reaction of the acetal **3** with MeLi as reported previously,[6] and subsequent acid hydrolysis.



Scheme 2.

Eq 1 shows the preliminary experiments on cyclobutenone **2**. Upon treatment of **2** with dienyllithium **6**[7] (1.3 equiv) in $\mathrm{Et_2O}$ at −78 °C, the starting material **2** was quickly consumed. Immediate quenching with $\mathrm{H_2O}$ gave a mixture of alcohol **7** and cyclooctadienone **8** (entry 1), suggesting that the ring expansion could be executed in one pot, simply by warming the reaction. Indeed, we were pleased to find that when the identical reaction was gradually warmed to room temperature, the ring-enlarged product **8** was obtained as a sole product in 89% yield (entry 2).[8] The formation of **8** implies that the intermediary enolate **9** underwent protonation selectively at the α position.



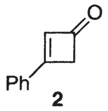
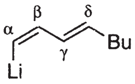
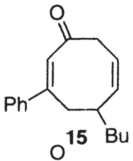
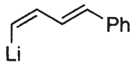
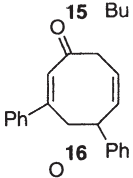
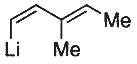
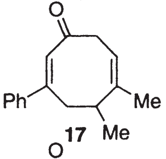
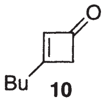
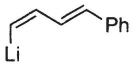
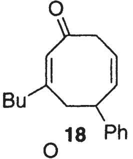
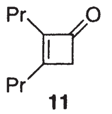
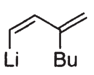
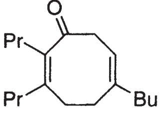


Entry		7	8
1	−78 °C	42%	22%
2	−78 °C → r.t.	—	89%

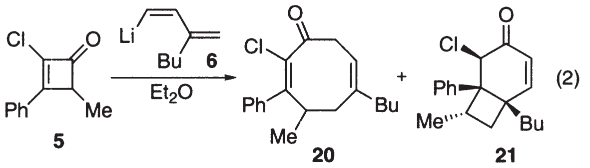
The application of this protocol to other substrate combinations is summarized in Table 1.[10] Upon treatment of **2** with δ-substituted dienyllithiums **12** and **13** at −78 °C followed by warming to room temperature, the ring expansion smoothly occurred to give ketones **15** and **16** in high yield, respectively (entries 1 and 2). Likewise, the procedure was applied to dienyllithium **14** with γ, δ-dimethyl groups, which was treated with **2** (−78 °C → room temperature) to give ketone **17** in 81% yield. Clean ring expansion was also achieved for the cyclobutenones **10** and **11**, having a butyl group or two propyl groups on the four-membered ring (entries 4 and 5).[11]

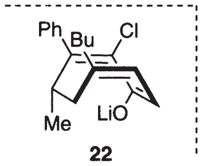
Also examined were reactions of the chlorinated cyclobutenone **5** (eq 2). When **5** was treated with dienyllithium **6** in $\mathrm{Et_2O}$ at −78 °C followed by warming to room temperature, cyclooctadienone **20** was obtained in 77% yield (entry 1). Bicyclic compound **21** was obtained as a side product,[12] which was possibly formed by the 6π electrocyclization of the intermediary enolate **22**.[13] This side reaction, though interesting in its own right, was suppressed by keeping the reaction temperature at 0 °C, and cyclooctadienone **20** was obtained in 89% yield (eq 2, entry 2).

Table 1.[a]

Entry	Cyclobutene	Dienyllithium	Product[b]	Yield/%
1	 **2**	 **12**	 **15**	80
2		 **13**	 **16**	95
3		 **14**	 **17**	81
4	 **10**	 **13**	 **18**	85
5	 **11**	 **6**	 **19**	82

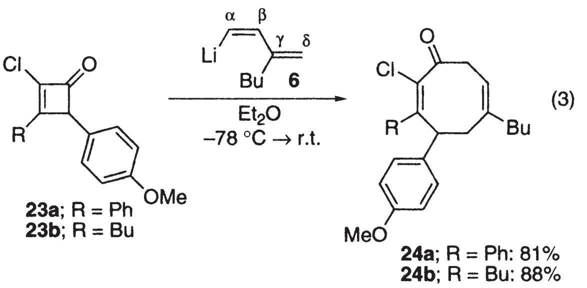
[a] −78 °C → room temperature in Et_2O. [b] All new compounds were fully characterized by spectroscopic means and combustion analysis.





Entry		20	21
1	−78 °C → r.t. 15 min	77%	18%
2	−78 → 0 °C 1 h	89%	5%

Similarly, chlorocyclobutenones **23a** and **23b**[14] reacted with dienyllithium **6**, where the addition and ring expansion sequence again proceeded smoothly to give ketones **24a** and **24b** in high yield, respectively (eq 3). In contrast to the case in eq 2, no four-membered ring compounds were obtained.



23a; R = Ph
23b; R = Bu

24a; R = Ph: 81%
24b; R = Bu: 88%

In summary, the present [4 + 4] approach to the cyclooctadienone derivatives starting from cyclobutenes and dienes would find utility in natural product synthesis, and further studies are currently underway in our laboratories.

References and Notes

1 T. Hamura, S. Tsuji, T. Matsumoto, and K. Suzuki, *Chem. Lett.*, **2002**, 280.

2 T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, and K. Suzuki, *Synlett*, **1995**, 177; T. Hosoya, T. Hasegawa, Y. Kuriyama, and K. Suzuki, *Tetrahedron Lett.*, **36**, 3377 (1995); T. Hosoya, T. Hamura, Y. Kuriyama, M. Miyamoto, T. Matsumoto, and K. Suzuki, *Synlett*, **2000**, 520.

3 For a discussion of the difficulty in forming eight-membered rings, due to the inherent strain, see: a) G. Mehta and V. Singh, *Chem. Rev.*, **99**, 881 (1999). b) N. A. Petasis and M. A. Patane, *Tetrahedron*, **48**, 5757 (1992).

4 For related [4 + 2 + 2] approaches, see: a) L. A. Paquette and J. Tae, *Tetrahedron Lett.*, **38**, 3151 (1997). b) L. A. Paquette and T. M. Morwick, *J. Am. Chem. Soc.*, **119**, 1230 (1997).

5 a) R. L. Danheiser and H. Sard, *Tetrahedron Lett.*, **24**, 23 (1983). b) R. L. Danheiser and S. Savariar, *Tetrahedron Lett.*, **28**, 3299 (1987). c) R. L. Danheiser, S. Savariar, and D. D. Cha, "Organic Synthesis," Wiley, New York (1993), Collect. Vol. VIII, pp 82–86. d) A. Hassner and J. L. Dillon, Jr., *J. Org. Chem.*, **48**, 3382 (1983).

6 T. Hamura, M. Kakinuma, S. Tsuji, T. Matsumoto, and K. Suzuki, *Chem. Lett.*, **2002**, 748.

7 Dienyllithium was generated by halogen–lithium exchange of the corresponding dienyl bromide and *t*-BuLi. For the synthesis of dienyl bromides, see: J. Uenishi, R. Kawahama, O. Yonemitsu, and J. Tsuji, *J. Org. Chem.*, **63**, 8965 (1998).

8 A typical procedure: To a solution of *cis*-1-bromo-3-butylbuta-1,3-diene[9] (425 mg, 2.21 mmol) in Et_2O (4.0 mL) was added *t*-BuLi (1.64 M in pentane, 2.3 ml, 3.8 mmol) at −78 °C, and the reaction was further stirred for 1 h, to which was added ketone **2** (212 mg, 1.47 mmol) in Et_2O (3.0 mL). After warmed to room temperature over 2 h, and further stirred for 30 min, the reaction was quenched with water. The products were extracted with EtOAc (X3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 92/8) to give cyclooctadienone **8** (331 mg, 89%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, $J = 7.1$ Hz), 1.16–1.35 (m, 4H), 1.94 (t, 2H, $J = 7.6$ Hz), 2.44 (t, 2H, $J = 6.8$ Hz), 3.22 (t, 2H, $J = 6.8$ Hz), 3.45 (d, 2H, $J = 8.3$ Hz), 5.42 (t, 1H, $J = 8.3$ Hz), 6.27 (s, 1H), 7.35–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 30.4, 30.9, 31.0, 39.9, 44.0, 116.3, 126.7, 128.6, 128.8, 129.0, 142.0, 142.3, 153.0, 202.3; IR (neat) 3028, 2957, 2871, 1669, 1652, 1574, 1485, 1378, 1267, 1186, 1000, 968, 795 cm^{-1}; Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.76; H, 8.81.

9 *cis*-1-Bromo-3-butylbuta-1,3-diene was prepared by dibromo-olefination of 2-butylpropenal, and subsequent stereoselective reduction of the resulting 1,1-dibromo-1-alkene, see Ref. 7.

10 All new compounds were fully characterized by spectroscopic means and combustion analysis.

11 Cyclobutene **11** was prepared by the [2 + 2] cycloaddition of 4-octyne and dichloroketene, followed by reduction of two chlorine atom, see Ref. 5c.

12 The stereochemistry of **21** was determined by an NOE study.

13 For related reaction, see: K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, and J. Uenishi, *J. Am. Chem. Soc.*, **104**, 5555 (1982).

14 Cyclobutenones **23a** and **23b** were prepared by the S_N2' reaction of the corresponding dichlorocyclobutenone acetals with 4-methoxyphenyllithium, followed by acid hydrolysis (Ref. 6).