Single-Step Synthesis of Cyclooctadienone Derivatives by Reaction of Alkenylcyclobutenones with Alkenyllithiums: Enhanced Reactivity of 8π Cyclization by Acetylating the Intermediary Lithium Tetraenolate

Toshiyuki Hamura, Nobuyuki Kawano, Shinsuke Tsuji, Takashi Matsumoto, and Keisuke Suzuki*
Department of Chemistry, Tokyo Institute of Technology and CREST, Japan Science and Technology Corporation (JST),
O-okayama, Meguro-ku, Tokyo 152-8551

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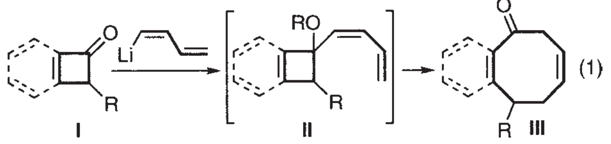
Various functionalized cyclooctadienones are accessible in high yields by the reaction of alkenylcyclobutenones with alkenyllithiums.

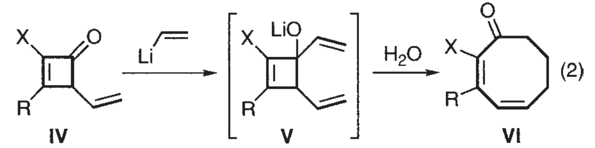
We recently reported an approach to eight-membered carbocycles via ring expansion of dienylbenzocyclobutene or dienylcyclobutene derivatives (eq 1),[1,2] which could be formally categorized as [4 + 4] processes.

Reported herein is an alternative synthetic access to cyclooctadienone derivatives,[3] which could be viewed as a [4 + 2 + 2] process[4] as shown in eq 2. The process relies on the ability of dichlorocyclobutenone derivatives **1** to accept two alkenyl anions, *same* or *different*, and subsequent consecutive electrocyclic ring opening and ring closure.

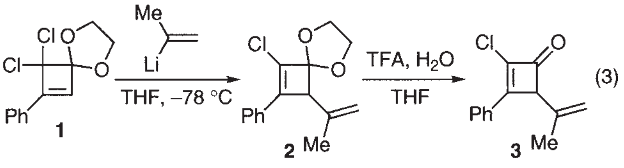
[4+4] approach – previous work



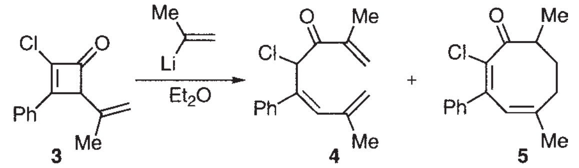
[4+2+2] approach – this work



Thus, the S_N2' reaction of dichloride **1**[5] by 2-propenyllithium gave the alkenylated acetal **2**, which was hydrolyzed to furnish ketone **3**,[6] ready for accepting the second alkenyl group.



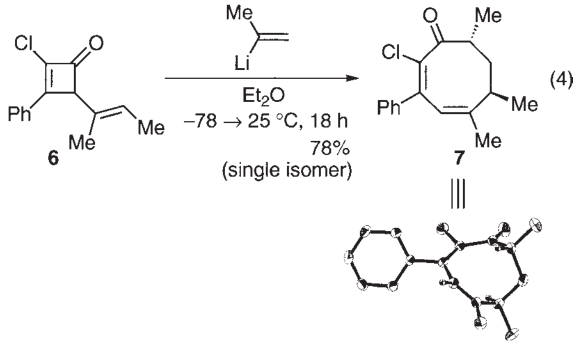
Upon treatment with 2-propenyllithium, generated from $CH_2{=}C(CH_3)Br$ and $t\text{-}C_4H_9Li$, (1.3 mol. amt. and 2.6 mol. amt. to **3**, respectively, in Et_2O, −78 °C), ketone **3** was quickly consumed, and direct warming of the resulting lithium alkoxide, gratifyingly, yielded the ring-enlarged product **5** in 82% yield (Scheme 1, entry 1). By contrast, when the above reaction was immediately quenched with H_2O at −78 °C (entry 2), the only product was the ring-opened ketone **4** in 84% yield. These results gave us a mechanistic insight that the process is comprised of two consecutive electrocyclic reactions, (1) ring opening of the dialkenylcyclobutene, and (2) subsequent closure of the resulting tetraene, among which the former step is facile, being already complete at −78 °C.



Entry		4	5
1	−78 → 25 °C, 12 h	—	82%
2	−78 °C, 5 min	84%	—

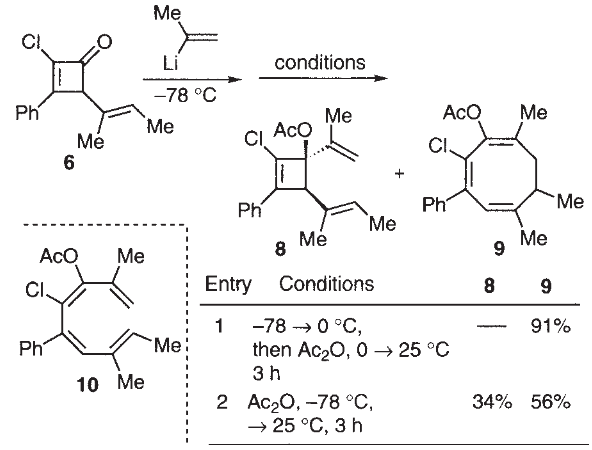
Scheme 1.

The procedure was applicable also to cyclobutenone **6** with a 2-buten-2-yl group. Treatment of **6** with 2-propenyllithium at −78 °C followed by gradual warming to 25 °C brought about a slow, but smooth conversion to ketone **7** in 78% yield. It is notable that ketone **7** was formed as a single isomer having a *trans* relationship of two methyl groups as evidenced by X-ray analysis.[7]



We found that, furthermore, the formation of the eight-membered rings was facilitated by *acetylating* the intermediary lithium tetraenolates. Thus, ketone **6** was treated with 2-propenyllithium at −78 °C, and the temperature raised to 0 °C. At this stage, Ac_2O was added, the temperature further raised to 25 °C, where only 3 h (cf. eq 4) was required to obtain the cyclooctatriene **9** as the sole product in 91% yield (Scheme 2).

Relevant to the origin of this enhanced reactivity by acetylation, the following data are noted. (1) If the reaction was quenched after the addition of Ac_2O at 0 °C, the main product was tetraene **10**, which was gradually converted to cyclooctatriene **9**. (2) If Ac_2O was added at −78 °C, the overall process proceeded more slowly, giving cyclooctatriene **9** in 56% yield along with cyclobutene **8** in 34% yield (entry 2). (3) Compound **8** was stable at room temperature, and was composed solely of the *trans* isomer

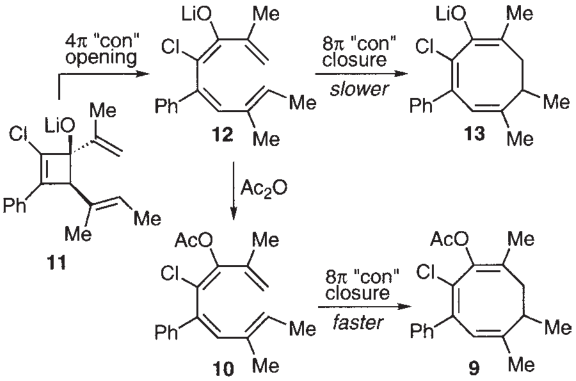


Entry	Conditions	8	9
1	−78 → 0 °C, then Ac_2O, 0 → 25 °C 3 h	—	91%
2	Ac_2O, −78 °C, → 25 °C, 3 h	34%	56%

Scheme 2.

with respect to two alkenyl groups, as shown by NOE study.

These results are consistent with a mechanistic proposal summarized in Scheme 3. There exists a seemingly opposite tendency in the relative reactivities of the alkoxide *vs* the acetate in the two electrocyclic processes: The initial ring opening of the four-membered ring is faster with the lithium alkoxide **11**, whereas the subsequent 8π ring closure of tetraene is faster with acetate **10** than the corresponding lithium alkoxide **12**.[8]

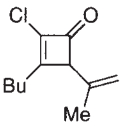
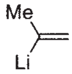
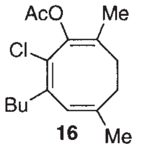
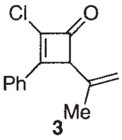
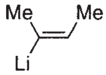
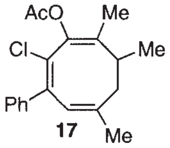
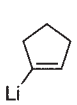
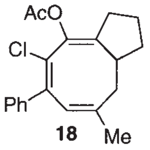
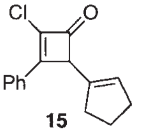
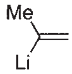
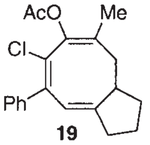


Scheme 3.

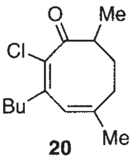
This finding was not only mechanistically interesting, but allowed us to establish a rapid, high-yielding synthetic protocol for constructing eight-membered ring compounds. Indeed, when cyclobutenone **14**, having a butyl group on the four-membered ring, was treated with 2-propenyllithium (−78 → 0 °C) followed by Ac_2O (0 → 25 °C), the ring expansion occurred to give eight-membered compound **16** in 83% yield (entry 1, Table 1). Under a similar set of conditions with acetylation, reaction of **3** with *cis*-2-butenyllithium and cyclopentenyllithium proceeded smoothly to give cyclooctatrienes **17** and **18** in 88% and 91% yield, respectively (entries 2 and 3). Alkenylcyclobutenone **15**, with a cyclic alkenyl moiety, was also a good substrate for the clean ring expansion (entry 4).

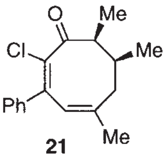
Compounds **16–19** were hydrolyzed by either of two procedures, (1) K_2CO_3, MeOH, 0 → 25 °C, 2–3 h (for **16** and **17**), or (2) 2 M NaOH, MeOH, 0 °C, 1 h (for **18** and **19**)[9] to give the corresponding ketones **20–23** in high yields, respectively. Compounds **21** and **22** were solely or mainly composed of the *cis* isomers with respect to the relation of *vicinal* dialkyl groups as evidenced by X-ray analysis.[10]

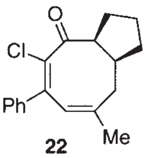
Table 1.[a]

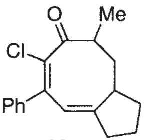
Entry	Cyclobutene	Vinyllithium	Time/h	Product[b]	Yield/%
1	 **14**		5	 **16**	88
2	 **3**		7	 **17**	88
3	**3**		5.5	 **18**	91
4	 **15**		6	 **19**	83

[a] −78 → 0 °C, then Ac_2O, 0 → 25 °C (*See text*), [b] All new compounds were fully characterized by spectroscopic means and combustion analysis.


20
92%


21
90%
(single isomer)


22
89%
(*cis*/*trans* = 9.8/1)


23
82%
(4.5 : 1)[10]

In summary, the present [4 + 2 + 2] approach to the cyclooctenone derivatives starting from cyclobutenes and dienes should 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. Hamura, S. Tsuji, T. Matsumoto, and K. Suzuki, *Chem Lett.*, **2002**, 750.
3 For the difficulty in forming eight-membered rings, and the strain inherent in such medium rings, 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). c) M. Zora, I. Koyuncu, and B. Yucel, *Tetrahedron Lett.*, **41**, 7111 (2000).
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, *Org. Synth.*, Coll. Vol. **VIII**, 82 (1993). 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 We thank Ms. Sachiyo Kubo, this department, for X-ray analysis. Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-192410. Copies of the data can be obtained free of charge on application to CCDC, 12 Unions Road, Cambridge, CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
8 For a related precedent, see: K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, and J. Uenishi, *J. Am. Chem. Soc.*, **104**, 5555 (1982).
9 Hydrolysis of compounds **18** and **19** with K_2CO_3 in MeOH gave lower yields of products.
10 The stereochemistry of **23** is currently under study, which will be reported in a full paper.