Synlett H. Yamaga, K. Tanino Letter

Synthesis of Substituted Cyclopentenol Derivatives via Intramolecular Addition Reaction of Vinylcopper Species

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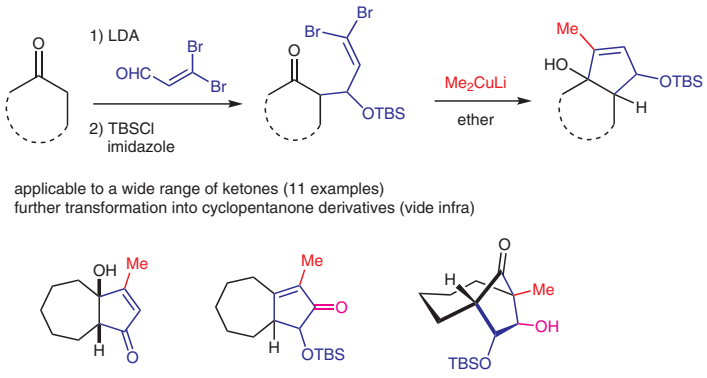

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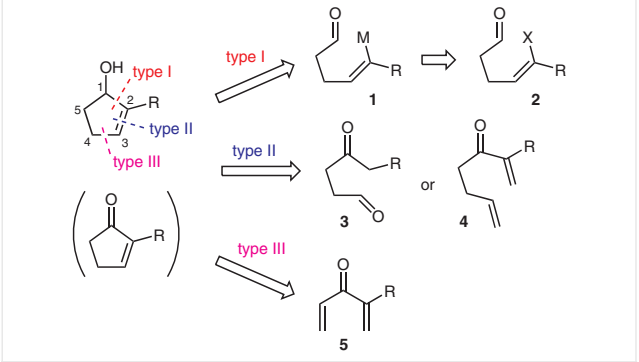
Abstract A new method for the synthesis of substituted cyclopentenes is developed, based on an intramolecular 1,2-addition reaction of vinylcopper species generated from 1,1-dibromoalkene derivatives. The substrates are prepared from ketones through the aldol reaction with 3,3-dibromoacrolein followed by silylation of the hydroxyl group. Treatment of the substrate with excess Me_2CuLi results in the formation of 3-methyl-2-cyclopenten-1-ol derivatives with good yields.

Key words annulation reactions, ketones, 1,1-dibromoalkenes, Gilman reagents, cyclopentenes



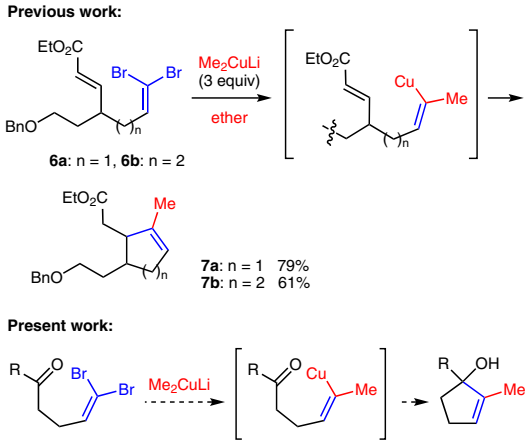
Scheme 1 Retrosynthetic analysis of cyclopentene derivatives

Several polycyclic natural products possess a 2-cyclopenten-1-one or 2-cyclopenten-1-ol substructure.[1] While several methods for obtaining these cyclopentene derivatives have been reported,[2] three types of approach are very important from a retrosynthetic point of view, as depicted in Scheme 1. Thus, the five-membered ring can be constructed by the formation of the C1–C2 single bond (type I), the C2–C3 double bond (type II), or the C3-C4 single bond (type III).

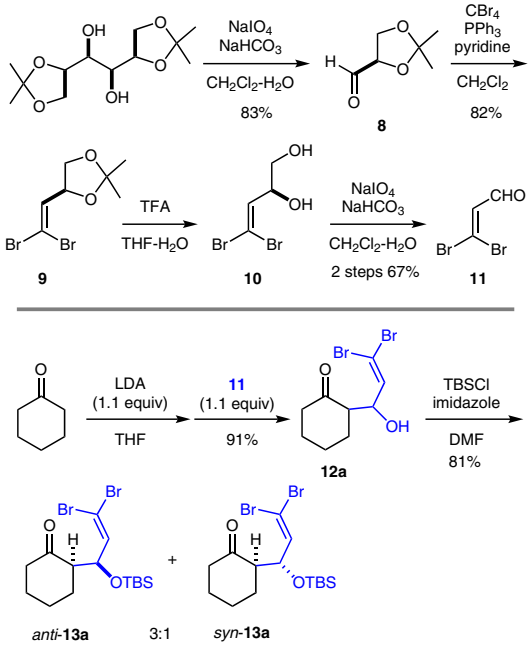
As for type II cyclization, intramolecular aldol condensation of the 1,4-dicarbonyl compound[2b] **3** and ring-closing metathesis of the 1,6-diene[3] **4** are frequently employed. On the other hand, the Nazarov cyclization reaction of ketone[4] **5** is the representative method of the type III approach. Regarding type I cyclization, the intramolecular addition reaction of carbonyl compound **1**, which includes a vinyl metal moiety, has been investigated widely. While a vinylsilane ($M=SiR_3$) can serve as the nucleophile in the presence of a Lewis acid,[5] generation of a vinyl anion species from the corresponding vinyl halide **2** seems more versatile. For example, the reaction with *n*-butyllithium gives a vinyl lithium,[6] and a Gilman reagent undergoes a halogen–metal exchange reaction with vinyl iodide.[7] The intramolecular Nozaki–Hiyama–Kishi coupling reaction is also applicable to the type I cyclization reaction.[8] One drawback of these intramolecular addition reactions, however, is that substrate **2** should include the vinyl halide moiety with a Z-configuration.

In 2006, we reported the cyclization reaction of 1,1-dibromoalkene derivatives with an α,β-unsaturated ester moiety (Scheme 2).[9a] Under the influence of Me_2CuLi, 1,1-dibromoalkenes **6** were converted into (*Z*)-vinylcopper species, which in turn underwent an intramolecular conjugate addition reaction, giving rise to substituted cycloalkene derivatives **7**. The utility of the 'alkylative in situ generation of (*Z*)-vinylcopper species' led us to explore the intramolecular addition reactions of ketone derivatives. The substrate was synthesized as shown in Scheme 3.

Cyclohexanone was subjected to aldol reaction with 3,3-dibromoacrolein[10] (**11**), which was prepared via Wittig reaction of glyceraldehyde acetonide[11] (**8**) followed by oxidative cleavage of diol **10**, and the hydroxy group was protect-



Scheme 2 Intramolecular addition reactions of in-situ generated vinylcopper species.



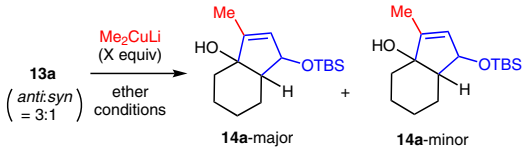
Scheme 3 Preparation of the cyclization precursor

ed to provide ketone **13a**. The product was obtained as a 3:1 mixture of *anti* and *syn* isomers, and the mixture was subjected to the cyclization reactions (Table 1).

The reaction was initially performed at –78 °C by treating ketone **13a** with 3 equivalents of Me_2CuLi in ether (Table 1, entry 1), in a similar manner to that in the previous work. Disappointedly, the cyclopentene derivative **14a** was obtained in only 6% yield, while the use of 5 equivalents of the Gilman reagent led to an increased yield (19%) of the desired compound (Table 1, entry 2). It is known that organocopper reagents usually show low reactivity with saturated ketones, contrasting with that in conjugate addition with α,β-unsaturated ketones. Indeed, when the reaction mixture was warmed from –78 °C to 0 °C, the cyclization product was obtained in high yield (Table 1, entry 3). Again, the use of a large excess of the Gilman reagent afforded better results (Table 1, entry 4). In entries 3 and 4, the cyclization product was obtained as a mixture of mainly two isomers along with a small amount of one isomer.

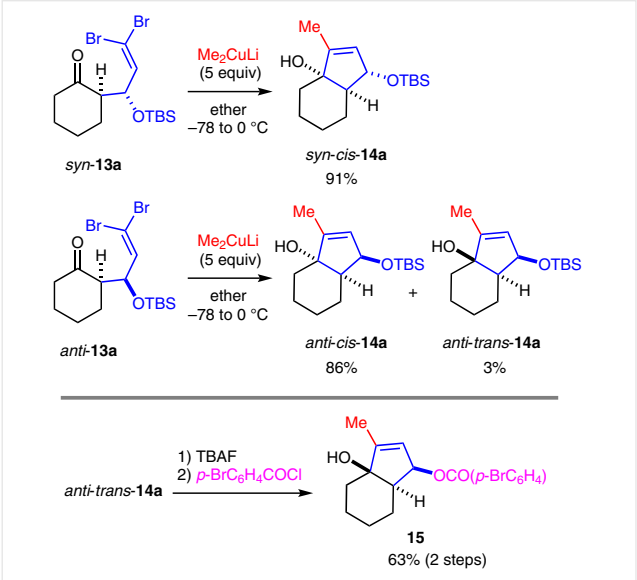
To clarify the stereochemistry of the cyclization reaction, the mixture of ketones *anti*-**13a** and *syn*-**13a** was purified repeatedly. Although complete separation could not be achieved, each pure isomer was reacted with Me_2CuLi under similar conditions to those for Table 1, entry 4 (Scheme 4).

Table 1 Optimization of the Reaction Conditions of Cyclization



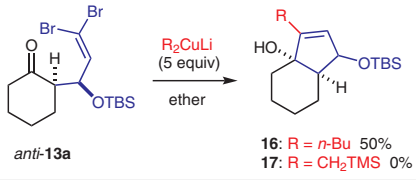
Entry	X	Conditions	**14a** major (%)[c]	**14a** minor (%)[c]
1	3	–78 °C, 20 min[a]	6	–
2	5	–78 °C, 20 min[a]	19	–
3	3	–78 °C then 0 °C, 10 min[b]	80	7
4	5	–78 °C then 0 °C, 10 min[b]	86	4

[a] To a solution of Me_2CuLi in ether was added ketone **13a** at –78 °C. After 20 min, the reaction was quenched with an aqueous NH_4Cl solution.
[b] After addition of **13a** to the solution of Me_2CuLi at –78 °C, the mixture was stirred at 0 °C for 10 min before quenching.
[c] Yields determined by ^1H NMR analysis of the crude product mixture using pyrazine as an internal standard.

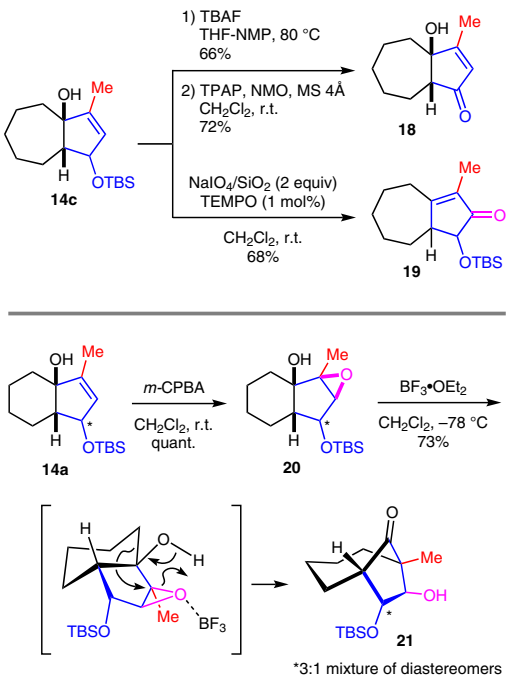


Scheme 4 Stereochemistry of the cyclization reactions of **13a**

Thus, bicyclic compound *syn-cis*-**14a** was obtained as the sole product from *syn*-**13a**, and *anti*-**13a** afforded *anti-cis*-**14a**, along with a small amount of *anti-trans*-**14a**. The minor isomer *anti-trans*-**14a** was converted into *p*-bromobenzoate **15**, whose structure was confirmed by X-ray crystallographic analysis. On the other hand, it was difficult to determine the stereochemistry of *syn-cis*-**14a** and *anti-cis*-**14a**, and the crystalline derivatives of ketone **21** in Scheme 6 gave crucial information about the configuration of the parent compounds **14a** (see Supporting Information). Notably, intramolecular cyclization reactions of substituted cyclohexanones usually prefer the formation of the *cis* isomer of the 5-6-fused products. Small amounts of the *trans*-fused compound *anti-trans*-**14a** were formed due to the steric repulsion between the silyloxy group and the cyclohexane ring in the transition state, leading to *anti-cis*-**14a**.



Scheme 5 Cyclization reaction with other Gilman reagents



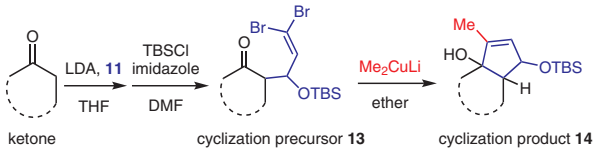
Scheme 6 Transformation of cyclopentene products into cyclopentenone derivatives

Next, the present method for cyclopentenol synthesis was applied to various kinds of ketones (Table 2). Aldol reaction of ketones with 3,3-dibromoacrolein (**11**) afforded the adducts, which were converted into the corresponding TBS ethers with good overall yields. The substrates, which were obtained as a mixture of diastereomers, were added to the ethereal solution of Me_2CuLi (5 equivalents) at –78 °C, and the mixture was warmed to 0 °C, unless otherwise noted. The desired bicyclic compounds **14b**, **14c**, **14d**, and **14e** were obtained with good overall yield from five-, seven-, eight-, and twelve-membered ketones (Table 2, entries 1–4). Substituted cyclohexanones, namely, 1,4-cyclohexanone monoethylene acetal, 2-norbornanone, and menthone, were also converted into the desired cyclopentenols **14f**, **14g**, and **14h** with good yields, respectively (Table 2, entries 5–7). The method described here was also applicable to acetophenone, and the monocyclic compound **14i** was obtained as a single diastereomer, in which the phenyl group and the silyloxy group were directed to the opposite side (Table 2, entry 8). The intramolecular addition reaction of the vinylcopper species occurred even with a sterically demanding ketone, and the products **14j** and **14k** possessing a neopentyl alcohol moiety were synthesized from pinacolone and epiandrosterone benzyl ether (Table 2, entries 9, 10). The use of other Gilman reagents in the cyclization reaction was briefly examined (Scheme 5). The desired product **16** was obtained in moderate yield by the reaction of ketone *anti*-**13a** with $^nBu_2CuLi$, although the reaction with $(TMSCH_2)_2CuLi$ resulted in the formation of a complex mixture.

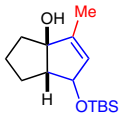
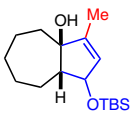
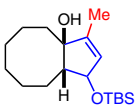
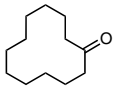
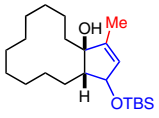
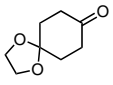
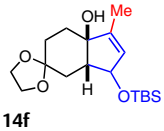
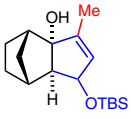
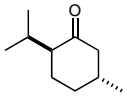
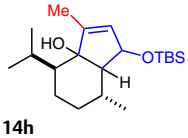
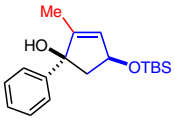
Finally, the synthetic utility of the cyclopentenol derivatives was briefly investigated (Scheme 6). Removal of the silyl group of **14c**, which was derived from cycloheptanone, followed by the tetrapropylammonium perruthenate (TPAP) oxidation gave enone **18**. On the other hand, enone **19** was obtained by the oxidation of **14c** with a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and sodium periodate on silica gel via transposition of the allylic alcohol moiety.[12] The allylic alcohol moiety could also be utilized to transform the bicyclic skeleton. Thus, bicyclo[4.3.0]nonane derivative **14a** was oxidized to epoxide **20**, which was reacted with boron trifluoride etherate to obtain ketone **21** with a bicyclo[4.2.1]nonane skeleton.

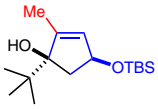
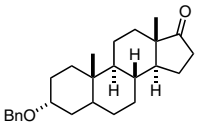
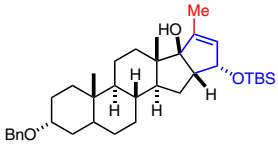
In conclusion, a new method for the synthesis of substituted cyclopentenes was developed based on an intramolecular 1,2-addition reaction of vinylcopper species.[13] The substrates were prepared from various kinds of ketones through the aldol reaction with 3,3-dibromoacrolein followed by protection of the hydroxyl group as a TBS ether. Treatment of the substrate with an excess amount of Me_2CuLi resulted in formation of 3-methyl-2-cyclopenten-1-ol derivatives in good yields. The bicyclic skeleton of the products derived from cyclic ketones shows promise for application in the total synthesis of sesquiterpenoid natural products.

Table 2 Transformation of Various Ketones into Cyclopentene Derivatives **14**



ketone cyclization precursor **13** cyclization product **14**

Entry	Ketone	Yield of **13** (%)[a]	dr of **13**[d]	Cyclization product[b]	Yield of **14** (%)[c]	dr of **14**[d]
1		97	1.5:1	 **14b**	79	2:1
2[e]		84	1:1	 **14c**	77	1.2:1
3[e]		84	1.1:1	 **14d**	85	1:1
4		86	1:1	 **14e**	65	2.5:1
5		67	2:1	 **14f**	99	2:1
6		97	2:1	 **14g**	71	1.7:1
7		86	>10:1	 **14h**	93	>10:1
8		83	–	 **14i**	76	>100:1

Entry	Ketone	Yield of **13** (%)[a]	dr of **13**[d]	Cyclization product[b]	Yield of **14** (%)[c]	dr of **14**[d]
9		57	–	 **14j**	75	3:1
10		86 (68% after recystallization)	–	 **14k**	71	–

[a] Isolated yield of cyclization precursor from the corresponding ketone.
[b] Reaction conditions: To a solution of Me_2CuLi in ether was added cyclization precursor **13** at –78 °C, and the mixture was stirred at 0 °C for 10 min before quenching with an aqueous NH_4Cl solution.
[c] Isolated yield after purification.
[d] Determined by ^1H NMR spectroscopy of the crude product, relative stereochemistry not assigned.
[e] Cyclization precursor **13** was added at –20 °C, and the mixture was stirred at –20 °C for 20 min before quenching with an aqueous NH_4Cl solution.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611366.

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(12) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008**, *10*, 4715.
(13) **General Procedure (Table 2, Entry 1)**
To a cooled (–78 °C) suspension of CuI (609 mg, 3.20 mmol) in ether (6.4 mL) was added dropwise a 1.17 M ethereal solution of MeLi (5.47 mL, 6.40 mmol). The mixture was warmed up to 0 °C and stirred for 10 min. The resulting clear solution was cooled to –78 °C, and a 1.5:1 diastereomeric mixture of ketone **13b** (264 mg, 0.640 mmol) in ether (6.4 mL) was added. The mixture was warmed up to 0 °C immediately and stirred for 10 min at the temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was filtered through a short pad of Celite, and the aqueous layer was extracted with ether. Concentration in vacuo and purification by silica gel column chromatography afforded a 2:1 diastereomeric mixture of cyclopentenol **14b** (136 mg, 0.50 mmol, 79%) as a yellow oil. ^1H NMR (500 MHz $CDCl_3$): δ = 5.36 (0.5 H, s), 5.33 (1 H, s), 4.86 (1 H, dt, *J* = 7.4, 1.7 Hz), 4.14 (0.5 H, d, *J* = 1.1 Hz), 2.41 (1 H, td, *J* = 8.3, 4.6 Hz), 2.16 (0.5 H, t, *J* = 4.6 Hz), 2.03 (1 H, dt, *J* = 10.7, 3.6 Hz), 1.90–1.80 (3 H, m), 1.74 (1 H, t, *J* = 1.4 Hz), 1.72 (3 H, dd, *J* = 4.9, 3.7 Hz), 1.70–1.47 (3 H, m), 0.88 (13.5 H, m), 0.07 (3 H, t, *J* = 3.2 Hz), 0.05 (6 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.23, 144.46, 131.3, 129.61, 95.6, 93.69, 81.98, 74.89, 61.04, 54.82, 38.28, 36.55, 31.63, 26.52, 26.40, 25.98, 25.93, 25.63, 25.46, 18.33, 11.95, 11.54, –4.50, –4.58, –4.74, –4.91.