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Synthesis of Methylenebicyclo[3.2.1]octanol by a Sm(II)-Induced 1,2-Rearrangement Reaction with Ring Expansion of Methylenebicyclo[4.2.0]octanone

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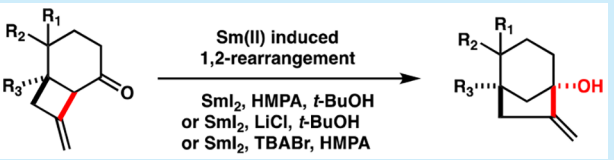
Supporting Information

ABSTRACT: Direct conversion of methylenebicyclo[4.2.0]-octanone to methylenebicyclo[3.2.1]octanol by a Sm(II)-induced 1,2-rearrangement with ring expansion of the methylene-cyclobutane is described. Three conditions were optimized to allow the adaptation of this approach to various substrates. A rearrangement mechanism is proposed involving the generation of a ketyl radical and cyclopentanation by ketyl−olefin cyclization, followed by radical fragmentation and subsequent protonation.



Bicyclo[3.2.1]octane is a common framework found in biologically important natural products such as gibberellins and kauranoids.[1] Some of these compounds have common characteristic functional groups in the bicyclic system. For example, the C/D ring system of gibberellins A_1, A_3, and steviol is functionalized bicyclo[3.2.1]octanol **1**, with a methylene group in the cyclopentane and a hydroxyl group at the bridgehead carbon (Figure 1).[2] Many methods for the synthesis of bicyclo[3.2.1]octane have recently been developed,[1,3] and excellent stereoselective syntheses of those diterpenoids have been reported.[2a,4]

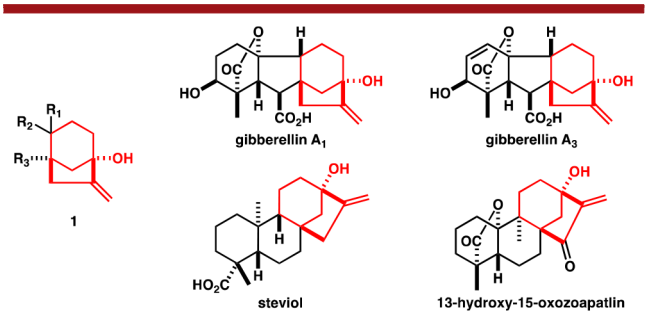
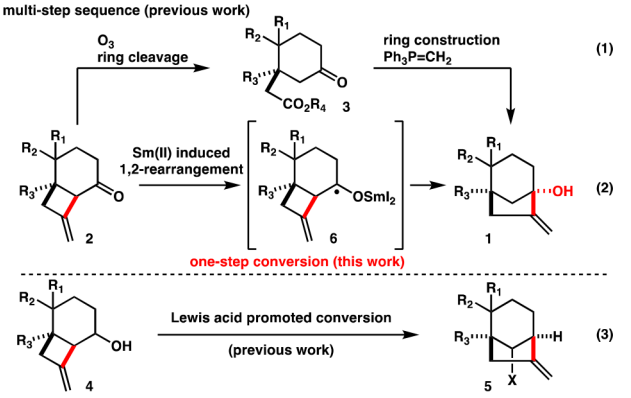


Figure 1. Structures of methylenebicyclo[3.2.1]octanol and related natural products.

The conversion of bicyclo[4.2.0]octanone **2** to bicyclo-[3.2.1]octanol **1** is an effective approach for synthesizing the functionalized C/D ring system of gibberellins and kauranoids (Scheme 1). The bicyclo[4.2.0]octanone **2** is easily obtained by [2 + 2] photocycloaddition of allene to cyclohexenone. However, this conversion requires a multistep sequence (eq 1).[6] Treatment of ketone **2** with Lewis acid affords products with other ring systems rather than **1**.[7] One-step conversion of **4** to the bicyclo[3.2.1]octane system is possible by Wagner−

Scheme 1. Conversion of Bicyclo[4.2.0]octane to Bicyclo[3.2.1]octane



Meerwein rearrangement or related reactions, but these approaches do not provide the required hydroxyl group at the bridgehead carbon in the product **5** (eq 3).[8] A very efficient skeletal transformation of bicyclo[4.2.0]octanone **2** to bicyclo-[3.2.1]octanol **1** could be realized by 1,2-rearrangement of the methylene carbon to the carbonyl group in **2**, accompanied by ring expansion of the cyclobutane in one step (eq 2). Kakiuchi et al. reported a radical ring-opening reaction of the cyclobutane at the carbonyl α-position of bicyclo[4.2.0]-octanones with SmI_2.[9] SmI_2 is an effective reagent for generating ketyl radicals as key intermediates for a variety of reactions involving carbonyl groups.[10] Therefore, the use of SmI_2 should be effective for generating ketyl radical **6**, thereby initiating 1,2-rearrangement with ring expansion of the

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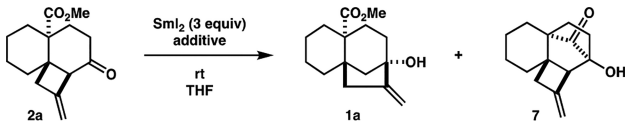
cyclobutane. Herein we report a Sm(II)-induced novel 1,2-rearrangement for the one-step conversion of bicyclo[4.2.0]-octanone **2** to methylenebicyclo[3.2.1]octanol **1**.

Our initial investigation of the 1,2-rearrangement involved dropwise addition of a solution of SmI_2 (3 equiv) in THF to a solution of **2a** or **2b** in THF.[11] The reaction of **2a** did not go to completion in the absence of additives and afforded undesired coupling product **7** (Table 1, entry 1). However, the addition of

Table 1. Optimization of the Reaction Conditions for 2a

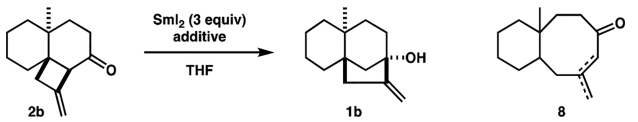


entry	additive (equiv)	time	yield (%)[a] 1	7
1[b]	none	24 h	0	41
2[b]	HMPA (12)	20 h	63	12
3[b]	HMPA (12), *t*-BuOH (1)	30 min	90	4
4[c]	LiCl (6), *t*-BuOH (1)	15 min	trace	72

[a]Isolated yield. [b]A solution of SmI_2 in THF was added dropwise to a stirred solution of the substrate and additives in THF. [c]A solution of the substrate and additives in THF was added dropwise to a stirred solution of SmI_2 in THF.

HMPA was effective in preventing the formation of **7** (entry 2), and subsequent addition of *t*-BuOH accelerated the reaction and gave the desired rearrangement product **1a** in good yield (entry 3). In contrast, the addition of LiCl afforded **7** (entry 4). The reaction of substrate **2b** in the absence of additives did not proceed (Table 2, entry 1). The addition of HMPA and *t*-

Table 2. Optimization of the Reaction Conditions for 2b



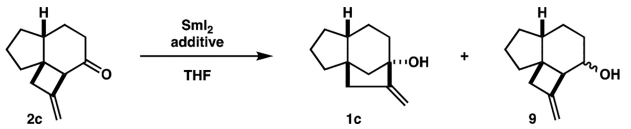
entry	additive (equiv)	temp	time	yield (%) of **1b**[a]
1[b]	none	rt	12 h	NR
2[b]	HMPA (12), *t*-BuOH (1)	rt	20 min	36
3[c]	HMPA (12), *t*-BuOH (1)	rt	20 min	61
4[c]	LiCl (6), *t*-BuOH (1)	reflux	20 min	91

[a]Isolated yield. [b]A solution of SmI_2 in THF was added dropwise to a stirred solution of the substrate and additives in THF. [c]A solution of the substrate and additives in THF was added dropwise to a stirred solution of SmI_2 in THF.

BuOH was effective for producing **1b**, but the major product was a derivative of bicyclo[6.4.0]dodecane **8** formed by cleavage of the fusion bond in the cyclobutane (entry 2). Dropwise addition of **2b**, HMPA, and *t*-BuOH in THF to a solution of SmI_2 in THF improved the yield of **1b** (entry 3). The addition of LiCl instead of HMPA dramatically increased the yield of **1b**, and reproducibility was increased under reflux conditions (entry 4).

Quite different results were obtained using substrate **2c**, in which the angular position is unsubstituted and corresponds to the gibberellin C/D ring (Table 3). Under the conditions optimized for **2a** and **2b** (Table 1 entry 3 and Table 2 entry 4), no desired rearrangement product **1c** was obtained, and HMPA/*t*-BuOH mainly caused cleavage of the cyclobutane to

Table 3. Optimization of the Reaction Conditions for 2c



entry	SmI_2 (equiv)	additive (equiv)	temp	time (h)	yield (%), ratio[a] **1c**:**9**
1	3	HMPA (12) *t*-BuOH (1)	rt	0.5	ND
2	3	LiCl (6) *t*-BuOH (1)	rt	0.5	98, >1:25
3	3	LiCl (6)	rt	0.5	97, 1:25
4	4	TBACl (8)	reflux	3	98, >1:25
5	4	TBABr (8)	reflux	12	93, 1:1
6	4	TBABr (8) HMPA (16)	reflux	0.5	88, 11:1

[a]The ratio **1c**:**9** was determined from the ^1H NMR spectrum of the mixture because the compounds were difficult to separate.

form a complex mixture containing bicyclo[6.3.0]undecanes, similar to the formation of **8** from **2b** (Table 3, entry 1). Furthermore, the use of LiCl/*t*-BuOH afforded only reduced product **9** (entry 2). Removal of the proton source was vital to suppress reduction, and the reaction using only dried LiCl as an additive gave a small amount of **1c** (entry 3). It is difficult to remove all moisture from the lithium salt, and thus we tried using ammonium salt. Tetrabutylammonium chloride (TBACl) is insoluble in THF and yielded poor results (entry 4); however, use of tetrabutylammonium bromide (TBABr), which is soluble in THF, to form $SmBr_2$ in situ, provided **1c** and reduced product **9** (entry 5).[12] Furthermore, when HMPA was added to enhance the reduction,[13] the reaction proceeded rapidly and the yield of **1c** was satisfactory (entry 6), but the reaction gave almost exclusively **9** upon further addition of *t*-BuOH. Entry 6 shows the optimum conditions for substrates lacking a substituent at the angular position.

Next, the 1,2-rearrangement reaction with ring expansion of bicyclo[4.2.0]octanones **2d**–**r** was examined under the three optimized conditions (Scheme 2). Bicyclo[4.2.0]octanones **2d**–**f** with an ester carbonyl group at the angular position were rearranged to the corresponding bicyclo[3.2.1]octanols **1d**–**f** in high yield using SmI_2/HMPA/*t*-BuOH (condition A). Reaction of **2d**–**f** with SmI_2/LiCl/*t*-BuOH (condition B) afforded the products of coupling between two carbonyl groups such as **7**. Reaction condition A was optimal even for **2g**, which has an oxygen functional group at the angular position and gave **1g** in satisfactory yield. For substrates **2h**–**l**, which have a methyl or methylene group at the angular position, condition B gave results comparable to that obtained with the reaction of **2b**. The reactions of **2j** and **2k** under condition B did not require *t*-BuOH because the hydroxyl group acted as an internal proton source. The use of SmI_2/TBABr/HMPA (condition C) also gave good results for **2k**. Condition C was superior for substrates **2m**–**o**, in which R_2 and R_3 are not connected by a tether, and for substrates **2p**–**r**, which lack a substituent at angular position R_1. These substrates gave only alcohols produced by reduction of the carbonyl group under condition A. Condition B provided the target products, but the major products were the corresponding reduced alcohols. Therefore, by selecting the most appropriate of the three conditions, it was possible to conduct the desired 1,2-rearrangement reaction with

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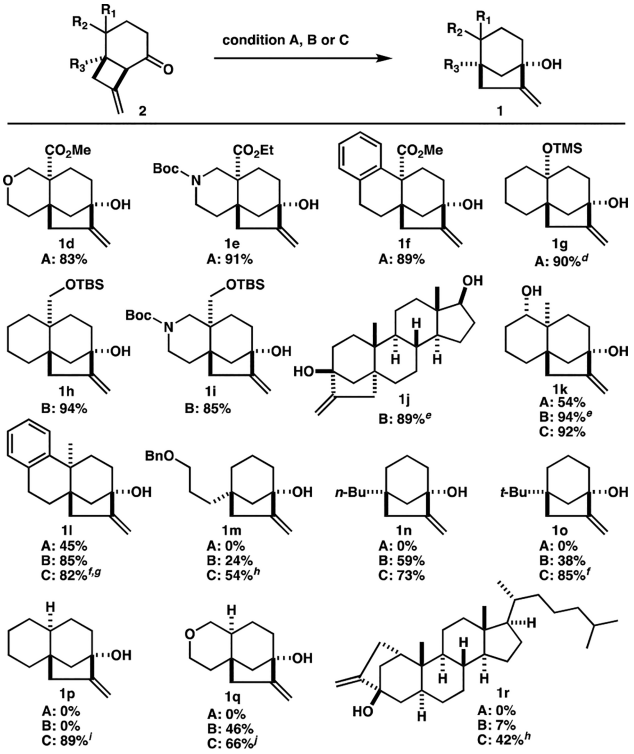
Scheme 2. Scope of the 1,2-Rearrangement with Ring Expansion Strategy[a,b,c]

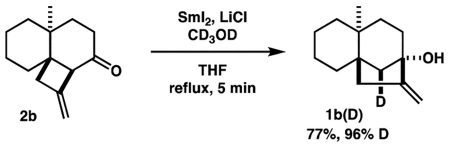


[a]Substrates **2** were prepared by [2 + 2] photocycloaddition of the corresponding cyclohexenones and allene. [b]Reaction conditions: A: SmI_2 in THF (0.1 M, 3 equiv), HMPA (12 equiv), *t*-BuOH (1 equiv) for 30 min at rt; B: SmI_2 in THF (0.1 M, 3 equiv), LiCl (6 equiv), *t*-BuOH (1 equiv) for 30 min under reflux; C: SmI_2 in THF (0.1 M, 4 equiv), TBABr (8 equiv), HMPA (16 equiv) for 30 min under reflux. [c]Yield of isolated product. [d]The reaction was carried out for 45 min under reflux. [e]The reaction was conducted without *t*-BuOH. [f]Reaction time was 3 h. [g]Starting material **2l** was recovered in 12% yield. [h]Reaction time was 1 h. [i]Reaction time was 2 h. [j]Reaction time was 12 h and starting material **2q** was recovered in 21% yield.

ring expansion for various types of substrates, and bicyclo[3.2.1]octanols were obtained in excellent yield.

We conducted a deuteration experiment to analyze the reaction mechanism (Scheme 3). CD_3OD was used as a proton

Scheme 3. Deuteration Experiment Using 2a



source instead of *t*-BuOH in the rearrangement of **2b** under condition B, and the product **1b(D)** was labeled stereoselectively with deuterium with a high labeling ratio at the carbon originating from the carbonyl α-carbon fused with the cyclobutane in **2b**. On the other hand, rearrangement of **2k** under condition B at room temperature (Scheme 2) provided trace amounts of unknown colorless crystals together with product **1k** as a white solid. Surprisingly, X-ray crystallographic analysis of the crystals revealed that the compound was the rather unusual tetracyclo[7.2.1.0.^{1,6}0^{10,12}]dodecane **10** containing a cyclopropane (Figure 2).

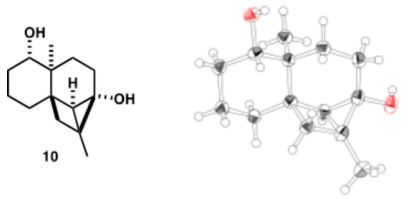
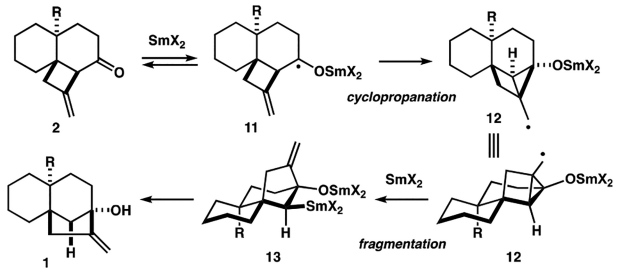


Figure 2. ORTEP drawing of **10**.

Based on these findings, we propose the following mechanism (Scheme 4). The ketyl radical **11** is generated by

Scheme 4. Proposed Mechanism



single-electron reduction of the carbonyl group in **2** with Sm(II), and a cyclopropane is formed by ketyl−olefin cyclization.[14] The resulting tetracyclic system **12** rearranges to the bicyclo[3.2.1] system **13** by fragmentation of the cyclopropane due to distortion, resulting in reformation of the exo-olefin.[15] At the same time, the generated radical is reduced by Sm(II), yielding Sm Grignard reagent **13**.[16] Finally, protonation of **13** completes the rearrangement with ring expansion, giving **1**. This mechanism is consistent with radical kinetic studies. The rate constants for the reduction of primary radicals, such as **12**, with SmI_2 are on the order of 10^5 to 10^6 s^{-1} and are 10^7 s^{-1} for the fragmentation of cyclopropylmethyl radicals similar to **12**.[17] For substrates with a bulky substituent at the angular position (R = Me or CO_2Me), cyclopropanation proceeds rapidly (e.g., **11** to **12**) because the ketyl radical carbon and the olefin carbon are in conformational proximity. In contrast, in the absence of a bulky substituent (R = H), cyclopropanation proceeds slowly because of the large distance between the reaction points. Therefore, in the latter case, the ketyl radical is protonated in the presence of *t*-BuOH to give the corresponding alcohol (such as **9**) under conditions A and B. The electron-withdrawing group at the angular position in substrates **2a,d−g** seems to prevent the radical formation by cleavage of the fusion bond in the cyclobutane, similar to the formation of **8** from **2b**. However, the cleavage is concomitant under condition A for substrates without an electron-withdrawing group. Coordination of sterically congested $(HMPA)_n$ to ketyl **11** (X = I) interferes slightly with cyclopropanation,[18] and less hindered $(THF)_n$ does not prevent cyclopropanation under condition B (X = Cl), although pinacol coupling is promoted for esters **2a,d−f**.[12d] Under condition C (X = Br), the cyclopropanation may proceed with a complex in which the coordination number of HMPA to $SmBr_2$ is smaller than SmI_2;[13] thus, the cleavage does not occur.

In conclusion, we developed a ring expansion rearrangement reaction for converting methylenebicyclo[4.2.0]octanones to methylenebicyclo[3.2.1]octanols using Sm(II), and optimized three conditions. This method is applicable to a wide range of [2 + 2] photocycloadducts of cyclohexenones and allene and

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provides a new and efficient pathway to the synthesis of gibberellins, kauranoids, and other natural products containing the bicyclo[3.2.1]octane framework with an oxygen functional group at the bridgehead carbon.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01604.

X-ray data for **10** (CIF)

Experimental procedures and spectral data for the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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