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Rh(I)-catalyzed hydroacylation/cycloisomerization cascade: synthesis of (±)-epiglobulol

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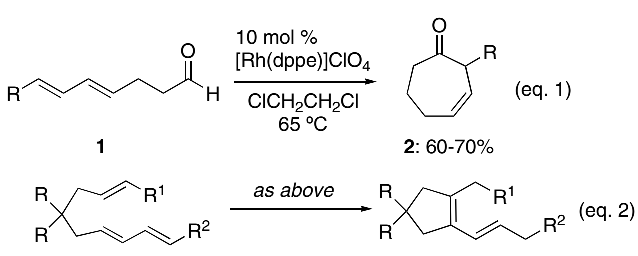
Abstract—A novel Rh(I)-catalyzed cascade reaction was developed by combination of a hydroacylation of 4,6-dienal and a cycloisomerization of the resultant triene, giving the bicyclo[5.3.0]decenone derivative **8b** in a stereoselective manner. It was found that the Thorpe–Ingold effect played an important role in the second cycloisomerization step of this cascade cyclization. From the cascade cyclization product, (±)-epiglobulol could be synthesized.

We have recently reported the first examples of Rh(I)-catalyzed intramolecular hydroacylation of 4,6-dienals **1** by which various cycloheptenones **2** were obtained in good yields (Scheme 1, Eq. 1).[1,2] During our ongoing investigation of this hydroacylation, we also found that an unusual cycloisomerization reaction between 1,3-dienes and tethered alkenes proceeded smoothly, giving cyclopentene derivatives **4** in good yields (Scheme 1, Eq. 2).[3,4]

These reactions proceeded using the same cationic Rh catalyst under almost the same reaction conditions. In addition, these two cyclizations are completely atom economical processes,[5] in which the molecular formula of the product is the same as that of the substrate. We therefore planned to develop a new cascade reaction by a combination of these reactions. The development of cascade reactions is important in synthetic organic chemistry because these reactions enable several carbon–carbon bonds to be formed in one sequence without isolating intermediates, changing the reaction conditions, or adding reagents.[6] Our initial plan is shown in Scheme 2.



Scheme 1.

If 4,6-dienal **5** having a 1,3-diene moiety is treated with Rh complex, cycloheptenone **6** would be initially formed via hydroacylation, and then cycloisomerization of 1,3-diene with olefin of the resultant product **6** would occur to produce a bicyclo[5.3.0]decenone **7** by a one-pot reaction. Herein, we report a novel Rh(I)-catalyzed cascade reaction and its application to the synthesis of (±)-epiglobulol.

Initially, cyclization of the simple substrate **5a** was attempted using 10 mol % of $[Rh(dppe)]ClO_4$ in dichloroethane at 65 °C. As a result, the desired cascade reaction product **7a** was not produced but cycloheptenone **6a** was obtained in 66% yield (Table 1, run 1).

When the cyclic compound **6a** was subjected again to a higher temperature condition using the same catalyst and solvent, none of the desired products was obtained and a complex mixture was produced. These results indicate that it is difficult for the second cycloisomerization step in the cascade reaction of **5a** to proceed. In order to

Keywords: Rhodium; Hydroacylation; Cycloisomerization; Cascade reaction; Epiglobulol; Apoaromadendrone.
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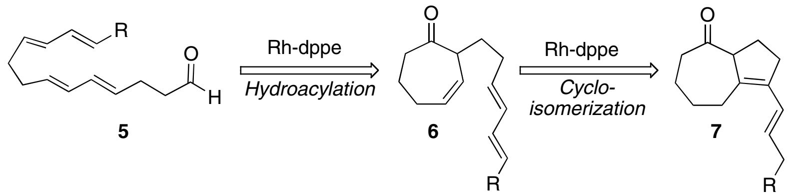
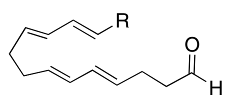
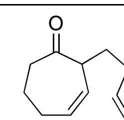
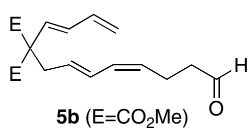
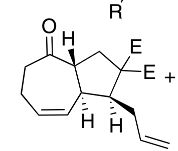
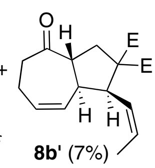
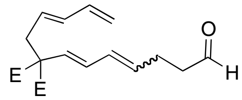
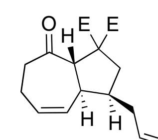
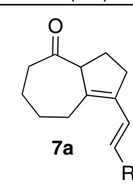


Scheme 2.

Table 1.[a]

Run	Substrate	Conditions	Products
1[b]	 **5a** (R=$PhCH_2CH_2$)	65 °C, 24 h	 **6a** (66%)
2[c]	 **5b** (E=CO_2Me)	65 °C, 24 h	 +  **8b** (19%) **8b'** (7%)
3	**5b**	Reflux, 9 h	**8b** (44%)
4[d]	 **5c** (E=CO_2Me, *E/Z*=1.4/1)	Reflux, 26 h	 **8c** (0%)

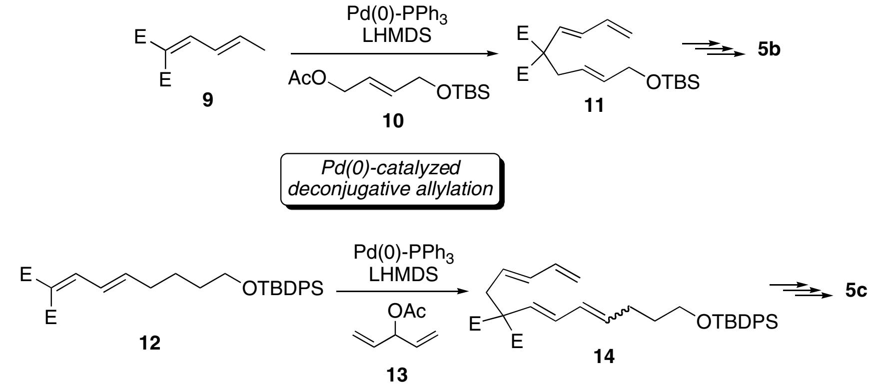
[a] All reactions were carried out in the presence of $[Rh(dppe)]ClO_4$ (10 mol %) in $ClCH_2CH_2Cl$.
[b] The cascade reaction product **7a** (R = $PhCH_2CH_2$) was not obtained.
[c] **5b** and its olefinic isomers were recovered in 13% yield.
[d] **5c** and its olefinic isomers were recovered in 44% yield.


7a

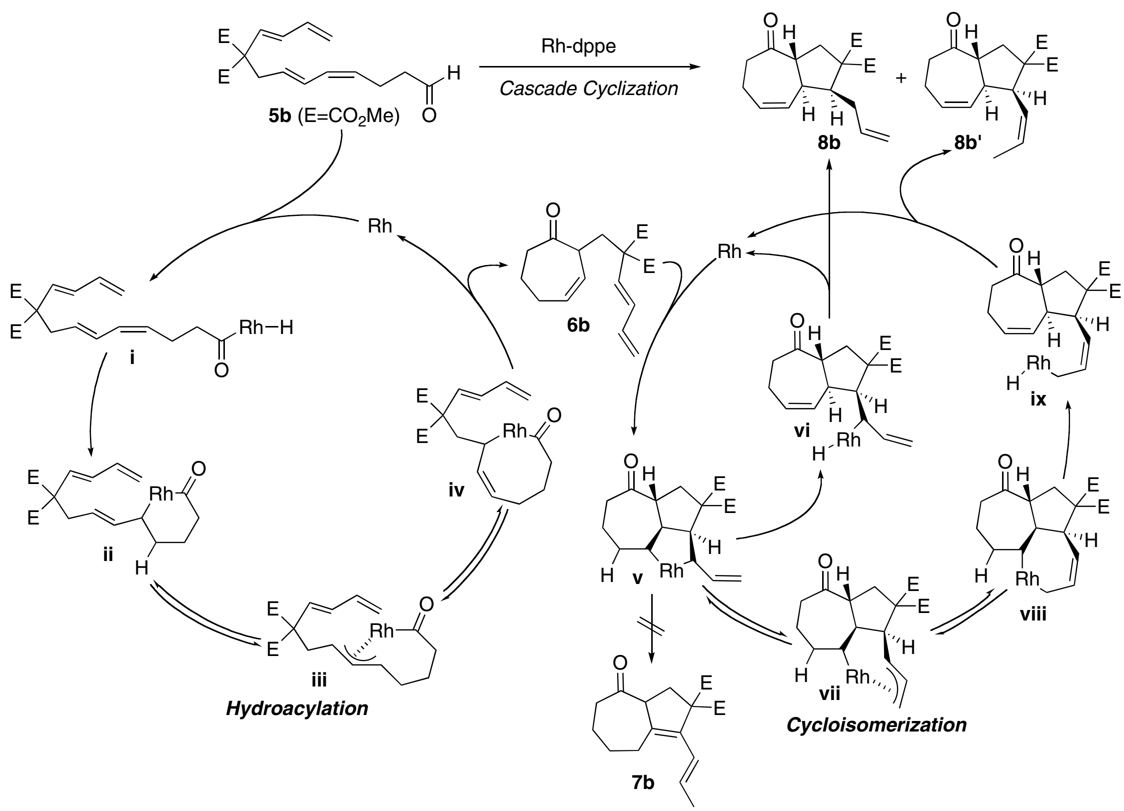
promote the second cycloisomerization step, substrates **5b** and **5c**, which have a quaternary carbon center in a tether,[7] were examined. Although these substrates have a 1,3-diene moiety next to a quaternary carbon center, they could be easily prepared by Pd(0)-catalyzed deconjugated allylation of alkenylidenemalonates developed by our group (Scheme 3).[8]

When compound **5b** was treated with 10 mol % of $[Rh(dppe)]ClO_4$ in dichloroethane at 65 °C for 24 h, we were very pleased to find that bicyclic compounds **8b** and **8b′** were obtained in 19% and 7% yields, respectively (Table 1, run 2).[9] Interestingly, the cyclization of **5b** under reflux conditions gave **8b** in 44% yield as a sole product. (Table 1, run 3). On the other hand, the reaction of **5c** under similar conditions did not proceed, and the starting material and its olefinic isomers were recovered in 44% yield (Table 1, run 4).

A possible mechanism for the formation of **8b** and **8b′** from **5b** using a Rh complex is shown in Scheme 4. A C–H bond of an aldehyde moiety of **5b** is oxidatively added to a Rh complex followed by insertion of a C=C bond of a diene moiety into the Rh–H bond to give 6-membered rhodacycle intermediate **ii**, which would be in a state of equilibrium with π-allyl intermediate **iii** and 8-membered rhodacycle intermediate **iv**. Reductive elimination from **iv** gives cycloheptenone **6b** along with regeneration of Rh complex. Then stereoselective oxidative cyclization of cycloheptenone **6b** with a Rh catalyst would produce rhodacycle intermediate **v**. β-Hydrogen elimination from **v** followed by reductive elimination from the resultant rhodium hydride complex **vi** would give bicyclic compound **8b**. On the other hand, rhodacycle intermediate **v** would be in equilibrium with rhodacycle intermediates **vii** and **viii**. β-Hydrogen elimination from **viii** followed by reductive elimination from the resultant rhodium hydride complex **ix** would give bicyclic compound **8b′**. Interestingly, bicyclic compounds **8b** and **8b′** were obtained by a one-pot reaction, and the initially expected product **7b** (Scheme 4) was not obtained because β-hydrogen on the 7-membered ring



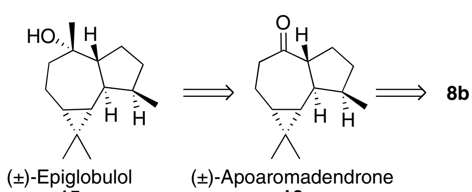
Scheme 3.



Scheme 4.

could be easily eliminated compared with that on the 5-membered ring.

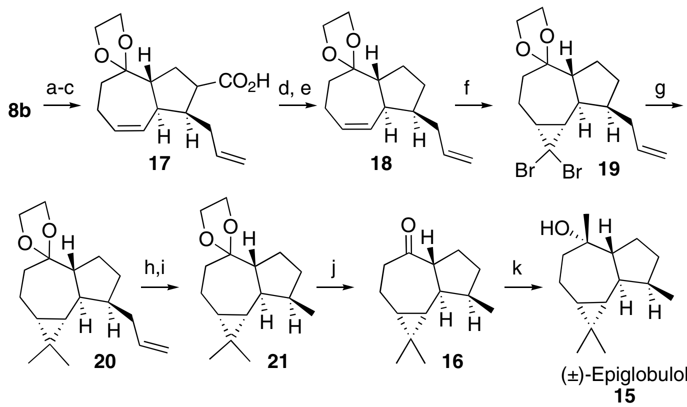
Since the structure of the cascade reaction product **8b** has been found in a variety of natural products such as hydroazulenes, we planned to synthesize (±)-epiglobulol[10] from **8b** via (±)-apoaromadendrone (Scheme 5).



Scheme 5.

Ketalization of **8b**[11] and then hydrolysis of esters followed by decarboxylation afforded mono carboxylic acid **17**, which was converted into **18** using Barton reaction[12] in 65% yield (Scheme 6).

The regioselective dibromocyclopropanation of internal olefin in **18** gave **19** in 71% yield (conversion yield).[13] Two methyl groups were introduced on the cyclopropane ring by treatment of **19** with a copper reagent to afford **20** in 99% yield. An allyl moiety of cyclic compound **20** was converted to a methyl group by ozonolysis of olefin in **20** and then decarbonylation using a Wilkinson complex in



Scheme 6. Reagents and conditions: (a) TMSOTf, $TMSO(CH_2)_2OTMS$, CH_2Cl_2, −78 °C, quant.; (b) NaI, $NaHCO_3$, DMF, 150 °C; (c) $LiOH{\cdot}H_2O$, $MeOH–H_2O$, 50 °C, 2 steps 99%; (d) $(EtO)_2P(O)Cl$, Et_3N, MS 4A, THF, rt; (e) 2-mercaptopyridine N-oxide sodium salt, ^{t}BuSH, toluene, reflux, 2 steps 65%; (f) $BnEt_3NCl$, $CHBr_3$, 50% NaOH aq, CH_2Cl_2, 0 °C, 71% (conversion yield); (g) Me_3CuLi_2, Et_2O, then MeI, rt, 99%; (h) O_3, CH_2Cl_2, −78 °C. then PPh_3, rt; (i) $RhCl(PPh_3)_3$, PhCN, 140 °C, 2 steps 66%; (j) $FeCl_3{\cdot}SiO_2$, acetone, rt, 67% and (k) MeLi, Et_2O, −78 °C, 84%.

66% yield. Deprotection of ketal **21** afforded (±)-apoaromadendrone (**16**), whose spectral data were completely identical with those reported in the literature.[10b] Finally, (±)-apoaromadendrone (**16**) was converted into (±)-epiglobulol (**15**) by treatment with MeLi in Et_2O according to the literature method (Scheme 6).[10b]

In summary, we have succeeded in developing a new cascade reaction by a combination of Rh(I)-catalyzed hydroacylation of 4,6-dienal and cycloisomerization of 1,3-diene with alkene in a tether. By using this cascade reaction, the synthesis of (±)-epiglobulol was accomplished. The present cascade cyclization is a completely atom economical reaction and a unique method for construction of hydroazulene skeleton. Further studies along this line are in progress.

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