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Highly stereoselective Michael reduction/intramolecular Michael reaction cascade to synthesize *trans*-stereodiad comprising an all-carbon quaternary stereogenic center

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ABSTRACT

A highly stereoselective Michael reduction/intramolecular Michael reaction cascade is described. The cascade is initiated by the regioselective Michael reduction of an α-methylidene ester with L-Selectride. This is followed by the highly stereoselective intramolecular Michael reaction which efficiently constructs a six-membered carbocyclic ring with formation of the *trans*-stereodiad, composed of an all-carbon quaternary center and a tertiary stereogenic center. The stereoselectivity is perfectly controlled by the choice of alkene geometry in the Michael acceptor.

Many bioactive terpenoids contain a six-membered carbocyclic ring including a *trans*-stereodiad composed of an all-carbon quaternary center and a tertiary stereogenic center. For example, such a six-membered carbocyclic ring can be found as a partial structure **1** in bruceantin (Fig. 1),[1] an antitumor terpenoid.

One of the effective construction methods of a six-membered carbocyclic ring which includes a stereodiad, is [4+2] cycloaddition (Scheme 1). However, to enhance the reaction, the use of reactive dienes and trisubstituted dienophiles under heating or Lewis acidic conditions is necessary; this is because [4+2] cycloaddition, which generates an all-carbon quaternary stereogenic center is usually slow.[2]

An alternative method for the construction of such a six-membered carbocyclic ring is the intramolecular Michael reaction (Scheme 1).[3] An intramolecular Michael reaction is generally fast, proceeds below room temperature, and effectively generates an all-carbon quaternary stereogenic center. Hence, the development of the intramolecular Michael reaction is important for the construction of such a six-membered carbocyclic ring.

We were interested in the Michael reduction/Michael reaction cascade, which initiates with the intermolecular Michael reduction of an α-methylidene ester **2** (Scheme 2), because the aforementioned reaction cascade of compound **2** would effectively generate a six-membered carbocyclic ring with the formation of the stereodiad, composed of an all-carbon quaternary and tertiary stereogenic centers. However, the use of α-methylidene ester has not been reported previously, though Michael reduction/Michael reaction cascades of α,β-unsaturated esters have been reported.[3,4]

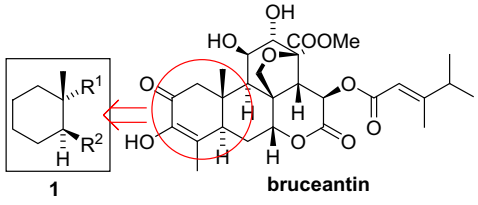
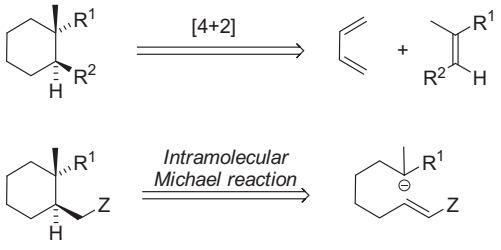


Figure 1. Structures of **1** and bruceantin.



Scheme 1.

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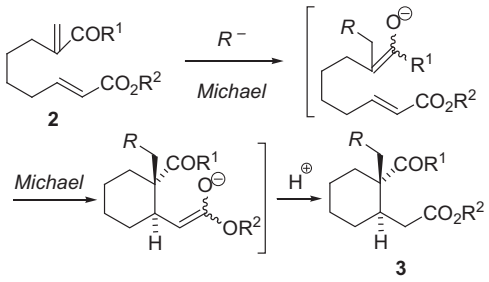
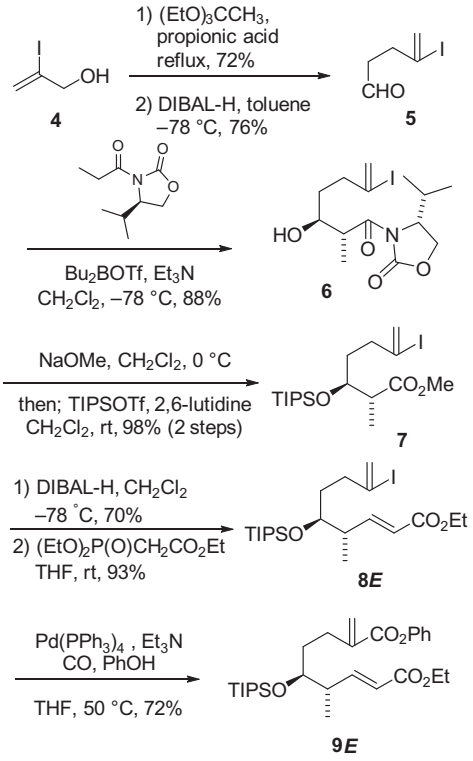


Scheme 2.

The Michael reduction of compound **2** was expected to preferentially take place at the less-hindered, reactive methylene terminal of the α,β-unsaturated ester in order to generate an enolate, which would undergo an intramolecular Michael reaction to afford compound **3** after workup (Scheme 2).

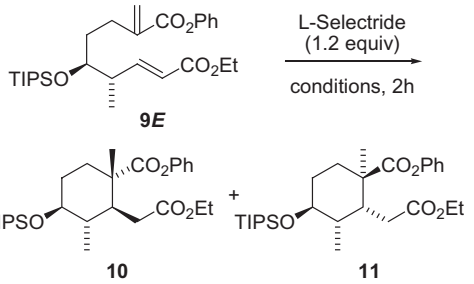
We selected compound ***9E*** (Scheme 3) as a substrate to examine the Michael reduction/intramolecular Michael reaction cascade because expected products prepared by the reaction of compound ***9E*** could be used for the enantioselective total synthesis of bruceantin. Moreover, the reaction of compound ***9E*** was thought to be useful for understanding the stereoselective cascade reaction because the intramolecular Michael reaction of the enolate generated by the Michael reduction of ***9E*** would proceed via a six-membered transition state in which the two substituents, the methyl and the TIPS-oxy groups would be equatorial.

Compound ***9E*** was prepared from the known compound **4**.[5] The Johnson–Claisen rearrangement of **2** with triethylortho acetate and subsequent DIBAL-H reduction afforded aldehyde **5**. The Evans aldol reaction[6–8] of **5** successfully afforded compound **6**, which was converted to methyl ester **7** by reaction with sodium methoxide and subsequent TIPS ether formation. DIBAL-H reduction of **7**, subsequent Horner–Wadsworth–Emmons (HWE) reaction, and a Pd-catalyzed carbonylation afforded compound ***9E***.



Scheme 3.

Table 1



Entry	Solvent	Temp (°C)	Yield[a] (%)		Ratio
			10	**11**	**10**:**11**
1	Toluene	−78	31	31	1:1
2	Toluene	0	40	27	1.5:1
3	CH_2Cl_2	−78	30	25	1.2:1
4	Et_2O	−78	22	10	2.2:1
5	Et_2O[b]	−78	29	12	2.4:1
6	THF	−78	20	50	1:2.5
7	THF[c]	−78	26	31	1:1.2
8	**THF/DMF = 1/2**	**−78**	**0**	**82**	**0:1**

[a] Isolated yield.
[b] $LiClO_4$ (2.0 equiv) was added.
[c] HMPA (2.0 equiv) was added.

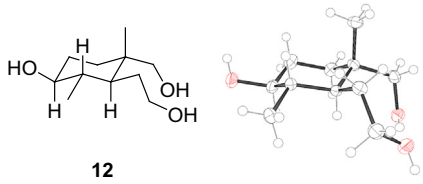


Figure 2.

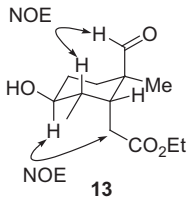


Figure 3.

The Michael reduction/intramolecular Michael reaction cascade of ***9E*** was examined (Table 1). The reaction of ***9E*** with K-Selectride resulted in low conversion, but the reaction with L-Selectride in toluene at −78 °C afforded compounds **10** and **11** in 62% yield with a 1:1 ratio (entry 1). The structure of **10** was determined by X-ray crystallographic analysis of its derivative **12** (Fig. 2),[9] and the structure of **11** was determined by the NOESY analysis of the derivative **13** (Fig. 3). The reaction of ***9E*** in toluene at 0 °C increased the ratio of **10** with respect to **11** (entry 2, **10**:**11** = 1.5:1).

The reaction in CH_2Cl_2 (entry 3) gave almost the same results as those in toluene and the reaction in Et_2O slightly increased the ratio of **10** (entry 4). The use of $LiClO_4$ as an additive increased the combined yield of products and the ratio of **10** (entry 5). The reaction in THF, a more polar solvent, afforded products in 70% combined yield with an increased ratio of **11** (entry 6, **10**:**11** = 1:2.5). The use of 10.0 equiv of HMPA as an additive in the reaction in