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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]

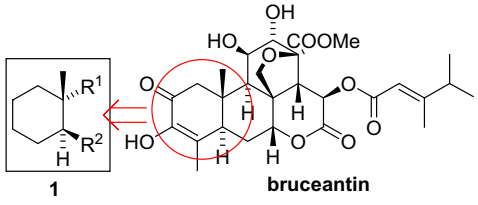
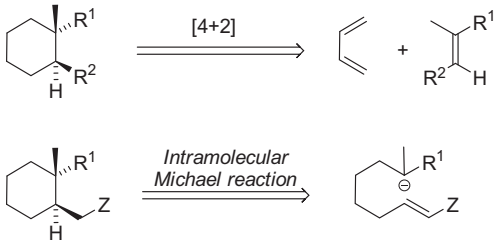


Figure 1. Structures of **1** and bruceantin.



Scheme 1.

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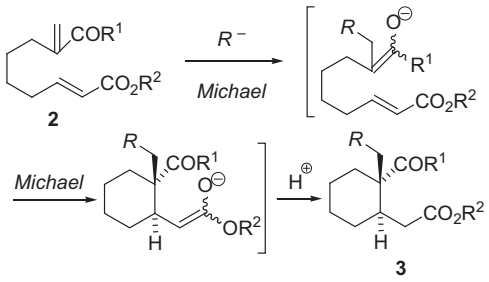
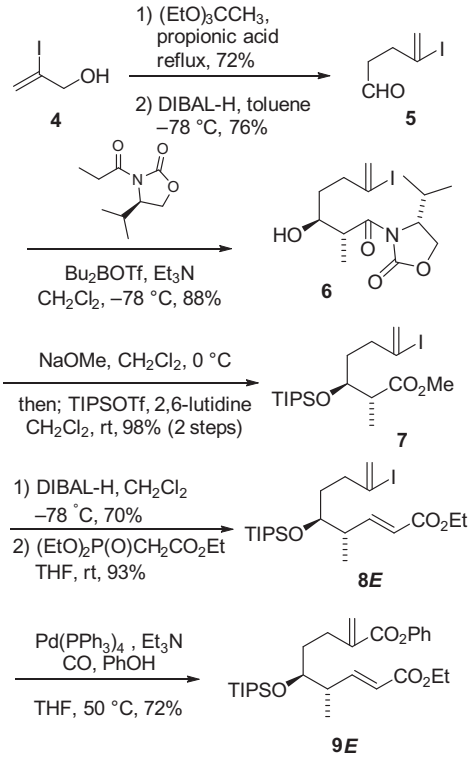


Scheme 2.

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).

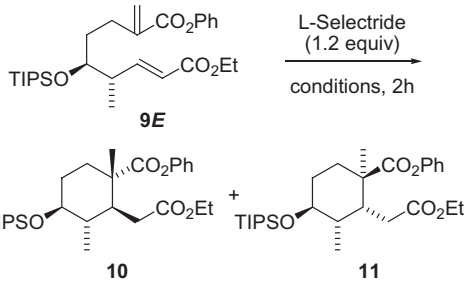
We selected compound ***9E*** (Scheme 3) as a substrate to examine the Michael reduction/intramolecular Michael reaction cascade because expected products prepared by the reaction of compound ***9E*** could be used for the enantioselective total synthesis of bruceantin. Moreover, the reaction of compound ***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.

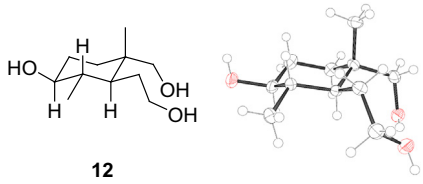


Figure 2.

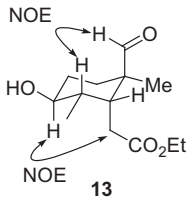


Figure 3.

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

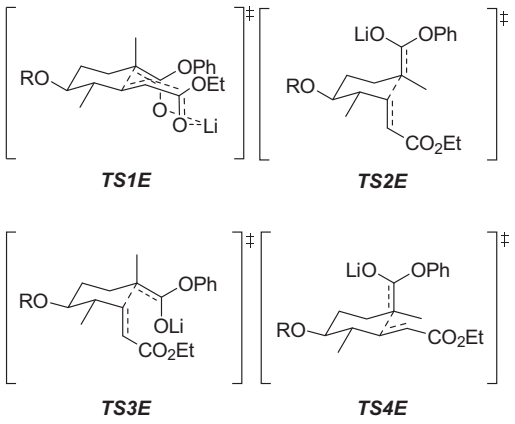


Figure 4.

THF resulted in a low stereoselectivity (entry 7), but, interestingly, the reaction in a mixed solvent (THF/DMF = 1:2) afforded **11** as the sole product (entry 8). In all the reactions in Table 1, only *trans*-isomers were formed. The results in Table 1 indicate that reactions of ***9E*** in the relatively low-polar solvent (entries 1–5) afford compound **10** as the major product, and reactions in the polar solvent (entries 6–8) afford compound **11** as the major product.

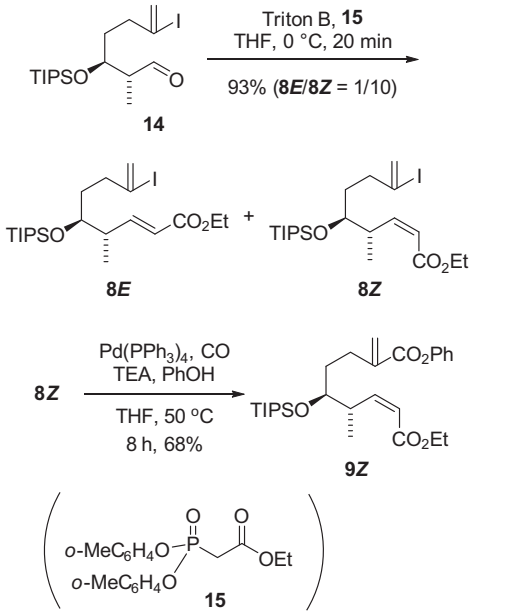
Chamberlin reported that enolates which were generated by the Michael reduction of α-methylene ketones with L-Selectride were trapped as their *Z*-silyl enol ethers;[10] hence, the enolate formed by the Michael reduction of α-methylene esters with L-Selectride could have an *E*-configuration. Considering the stereoselective enolate formation by the Michael reduction, the stereoselectivity of the intramolecular Michael reaction could be explained by the proposed transition state models in Figure 4. Thus, in the less-polar solvent, the enolate generated by the initial Michael reduction could form a chelate with another α,β-unsaturated ester to stabilize ***TS1E***. This would be an energetically favored, fused system composed of a chair six-membered ring and a boat-chair eight-membered ring to afford compound **10**. On the other hand, the reaction in the polar solvent could proceed via a non-chelated ***TS2E*** owing to the solvation to afford compound **11** because the steric repulsion between two large groups (enolate and ethyloxycarbonylmethyl) is minimum in ***TS2E***. Other two possible transition state models, ***TS3E*** and ***TS4E*** are energetically unfavorable because the unstable chelate is formed in ***TS3E*** and the steric repulsion between two large groups (enolate and ethyloxycarbonylmethyl) is relatively large in both models The models in Figure 4 also explain the *trans*-stereoselectivity of the reaction.

As the reaction conditions for the stereoselective formation of compound **11** were optimized, the stereoselective formation of compound **10** was then examined. We envisioned that when the substrate with a *Z*-enoate is used for the reaction, ***TS2E*** in Figure 4 would be energetically unfavorable owing to the $A^{(1,3)}$-strain.

Consequently, compound ***9Z*** (Scheme 4) was prepared to examine the Michael reduction/intramolecular Michael reaction cascade. The HWE reaction of Ando's phosphonate **15**[11] with aldehyde **14**, which was obtained by the DIBAL-H reduction of compound **7** (Scheme 3), stereoselectively afforded ***8Z***, which successfully underwent the Pd-catalyzed carbonylation to afford ***9Z***.

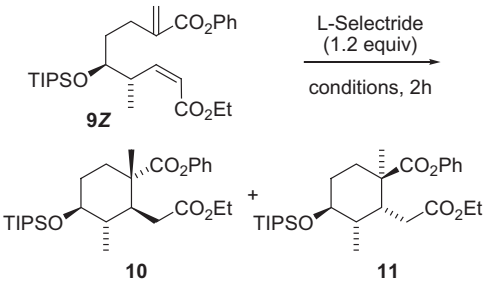
Having prepared ***9Z***, we examined the Michael reduction/intramolecular Michael reaction cascade of ***9Z*** (Table 2). No desired products were formed in toluene, CH_2Cl_2, Et_2O at −78 °C, and the product derived from the first Michael reduction was obtained (entries 1–4). The reaction in THF afforded compound **10** as the sole product but the yield was low (entry 5). The reaction in a mixed solvent (THF/DMF = 1:2) reduced the yield (22%, entry 6), but the same reaction at 0 °C afforded compound **10** in 61% yield without forming other isomers (entry 7). The reaction in DMF did not improve the yield (24%, entry 8). Finally, the reaction in THF using 10.0 equiv of HMPA as an additive afforded compound **10** in 78% yield as the sole isomer (entry 9). The reaction of ***9Z*** with K-Selectride was also attempted (entries 10–12), but the yield was low even though compound **10** was formed as the sole product.

The reaction of compound ***9Z*** should proceed via the six-membered transition state, which has the equatorial methyl and TIPSoxy groups. Among four possible transition state models of



Scheme 4.

Table 2



Entry	Solvent	Temp (°C)	Yield[a] (%)		Ratio
			10	**11**	**10:11**
1[b]	Toluene	−78	0	0	—
2[b]	CH_2Cl_2	−78	0	0	—
3[b]	Et_2O	−78	0	0	—
4[b]	Et_2O[c]	−78	0	0	—
5	THF	−78	45	0	1:0
6	THF/DMF = 1:2	−78	22	0	1:0
7	THF/DMF = 1:2	0	61	0	1:0
8	DMF	0	24	0	1:0
9	**THF**[d]	**−78**	**78**	**0**	**1:0**
10[e]	THF	−78	38	0	1:0
11[e]	THF/DMF = 1:2	−78	48	0	1:0
12[e]	THF	−78	20	0	1:0

[a] Isolated yield.
[b] $LiClO_4$ (2.0 equiv) was added.
[c] HMPA (2.0 equiv) was added.
[d] HMPA (10.0 equiv) was added.
[e] K-Selectride was used.

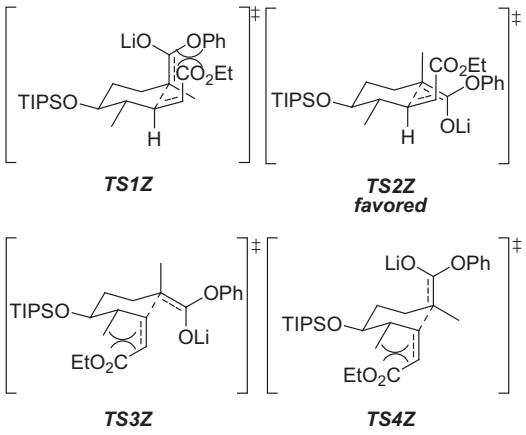


Figure 5.

TS1Z–4Z in Figure 5, ***TS1Z***, ***3Z***, and ***4Z*** are energetically unfavorable owing to the $A^{(1,3)}$-strain and 1,3-diaxial interaction. Consequently, the reaction would proceed via the least strained ***TS2***, but the relatively strained nature of ***TS2*** could lead to slow cyclization, resulting in the formation of the acyclic by-product (entries 1–4).

In summary, we found that the highly stereoselective Michael reduction/intramolecular Michael reaction cascade which is initiated by the Michael reduction of an α-methylidene ester with L-Selectride. The cascade efficiently synthesizes 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. A natural product synthesis utilizing the herein reported highly stereoselective construction method is now underway and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (full characterization of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.110.

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