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Stereoselective construction of the ABC-ring system of fusidane triterpenes via intermolecular/transannular Michael reaction cascade

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ABSTRACT

A stereoselective construction of the ABC-ring system of fusidane triterpenes via intermolecular/transannular Michael reaction cascade is described. The substrate, a ten-membered carbocyclic ketone, has been successfully prepared by the Cr-mediated intramolecular alkenylation of the corresponding acyclic compound. The array of functionalities in the product stereoselectively obtained by the cascade reaction is useful for further structural modifications directed toward the total synthesis of fusidane and other triterpenes, and designed molecules intended for studying structure–activity relationships.

Fusidane triterpenes are a relatively small family of naturally occurring steroidal antibiotics.[1] To the best of our knowledge, helvolic acid (Fig. 1) was the first reported fusidane triterpene, which was isolated from *Aspergillus fumigatus* in the early 1940s.[2] Helvolic acid was the subject of structural investigation for a considerable period;[3] Okuda and co-workers finally established the molecular structure.[4] Recent biological evaluation of helvolic acid revealed that it shows antibiotic activities against *Escherichia coli*, *Bacillus subtilis*, and *Micrococcus lysodeikticus* with MICs of 14.49, 87.92, and 10.99 μM, respectively,[5] but exhibits synergistic effects with erythromycin, penicillin, and tetracycline on multi-drug resistant *Staphylococcus aureus*.[6]

Fusidic acid (Fig. 1), isolated from *Fusidium coccineum*[7a,b] as well as other fungal sources,[7c,d,8] is the most important member of fusidane family as fusidic acid shows potent effects against staphylococci, including the methicillin-resistant *Staphylococcus aureus* (MRSA), while exhibiting low toxicity and allergic reactions. Moreover, it has little cross-resistance with other clinically used antibiotics.[9] Furthermore, the global challenge of antimicrobial resistance has made fusidic acid a renewed antibiotic candidate; to date, phase 2 clinical trials have finished and the supporting results proceed to phase 3 studies.[10]

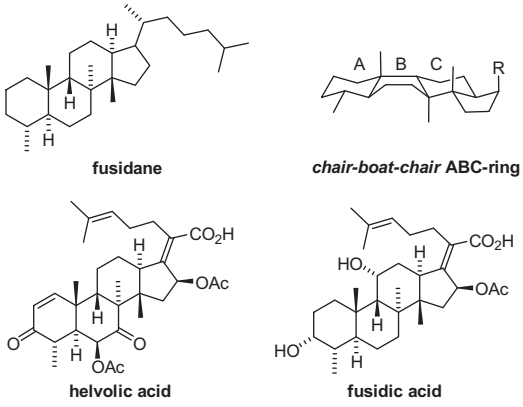

Figure 1. Structures of fusidine, helvolic acid, fusidic acid, and *chair-boat-chair* ABC-ring.

Synthetic studies on fusidic acid have been reported owing to the promising biological activities described above,[11] however, only one formal total synthesis of fusidic acid[12] and no synthetic studies of helvolic acid have been reported. We report herein a stereoselective intermolecular/transannular Michael reaction cascade to construct the ABC-ring system of fusidane triterpenes.

Fusidane triterpenes comprise a unique chair-boat-chair ABC tricyclic ring system in their structures (Fig. 1), which differs from

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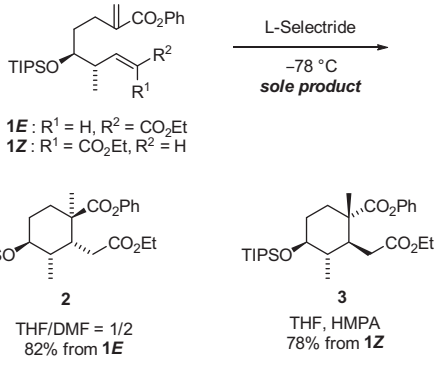
those found in common steroidal terpenes. Although a number of synthetic strategies have been reported, transannular processes are particularly effective to construct such polycyclic ring systems.[13] For example, transannular Diels–Alder reactions can generate a high degree of structural complexity with high chemo-, regio-, and diastereoselectivites (which are difficult to achieve by inter- or intramolecular processes) as the result of conformational restrictions, as well as entropic activation derived from the close proximity in the macrocyclic environment.[14]

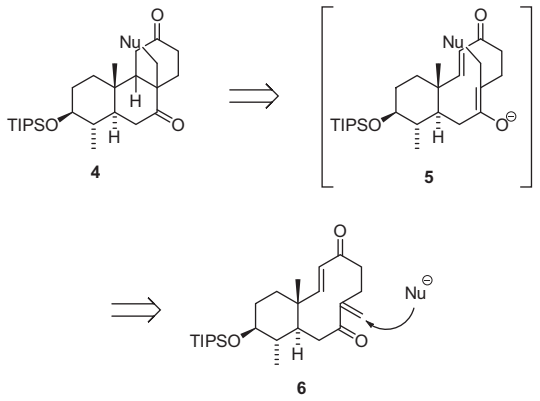
The transannular Diels–Alder reaction was considered for the synthesis of the unique chair-boat-chair ABC tricyclic ring system in fusidane triterpenes based on the literature precedent.[15] Conversely, to the best of our knowledge, construction of the chair-boat-chair tricyclic ring system via the transannular Michael reaction has never been reported. The array of functional groups in the products obtained via the transannular Michael reaction is different from those in the products synthesized by the transannular Diels–Alder reaction. Thus, the product obtained by the intermolecular/transannular Michael reaction[16,17c] cascade could be a unique synthetic intermediate for the total synthesis of not only fusidane triterpenes, but also other terpenes in general. We have been investigating transannular approaches to the synthesis of polycyclic ring systems,[17] and to this end we report the challenging intermolecular/transannular Michael reaction cascade which affords the unique tricyclic ring system.

We have recently developed a highly stereoselective Michael reduction/intramolecular Michael reaction cascade of compound **1*E*** and **1*Z*** using L-Selectride which affords compounds **2** and **3**, respectively (Scheme 1).[18] The three contiguous stereogenic centers in compound **3** (which includes an all-carbon quaternary stereogenic center) correspond to those in the A-ring moiety of fusidane triterpenes. Our investigation therefore focused on the analogous intermolecular/transannular Michael reaction cascade, which is shown as a retrosynthetic analysis in Scheme 2.

The less-hindered α-methylene of compound **6**, which would be prepared from compound **3**, is expected to be more reactive toward a nucleophile when compared with the internal enone. Hence, the enolate **5** would be preferentially formed by the Michael reaction of compound **6**, which would undergo the transannular Michael reaction to afford the tricyclic product **4**. The stereoselectivity of the transannular Michael reaction would depend on the difference of the stability of transition states derived from the enolate **5** when the reaction is kinetically controlled. The conformation of enolate **5** changes by some factors such as solvent and additives. Therefore, the stereoselectivity of the reaction would be difficult to predict, but the conformation of enolate **5** is restricted by the ten-membered ring; thereby, the reaction could be stereoselective. This assumption prompted us to investigate the preparation of the macrocyclic ketone **6** to examine the cascade reaction.



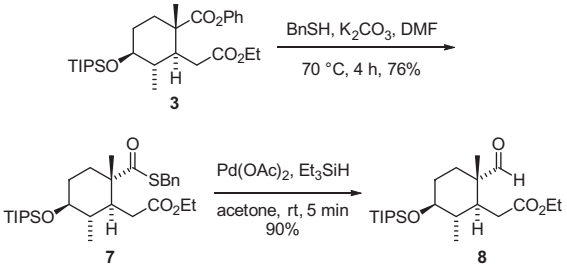
Scheme 1. Highly stereoselective Michael reduction/intramolecular Michael reaction cascade.



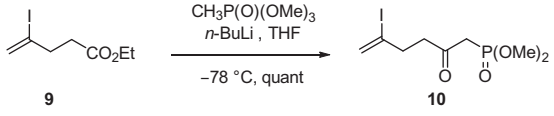
Scheme 2. Planned intermolecular/transannular Michael reaction cascade.

The preparation of compound **6** was challenging due to the presence of the ten-membered carbocyclic ring, which are difficult to synthesize owing to transannular strain, though the four sp^2-hybridized carbons in the ten-membered carbocyclic ring would relieve the strain in compound **6**. We employed the intramolecular Cr-mediated alkenylation[19] to construct the ten-membered carbocyclic ring because the Cr-mediated reaction is a powerful carbon-carbon bond-forming reaction that proceeds under mild conditions, and moreover, it is compatible with many functional and protecting groups. However, to the best of our knowledge, no examples of the formation of a non-bridged ten-membered carbocyclic ring by the Cr-mediated alkenylation have been reported thus far.[20]

The transformation of compound **3** to the substrate for the Cr-mediated reaction was examined. The Horner–Wadsworth–Emmons (HWE) reaction of the aldehyde **8** (Scheme 3) with the keto phosphonate **10** (Scheme 4) was intended as the method of carbon-carbon bond elongation. Preparation of the aldehyde **8** commenced with the ester exchange reaction of compound **3**. The reaction was performed with benzyl thiol and potassium carbonate, which caused the selective ester exchange of the more reactive phenyl ester to afford the benzyl thioester, which was then converted to the aldehyde **8** by Fukuyama reduction.[21]



Scheme 3. Preparation of **8**.

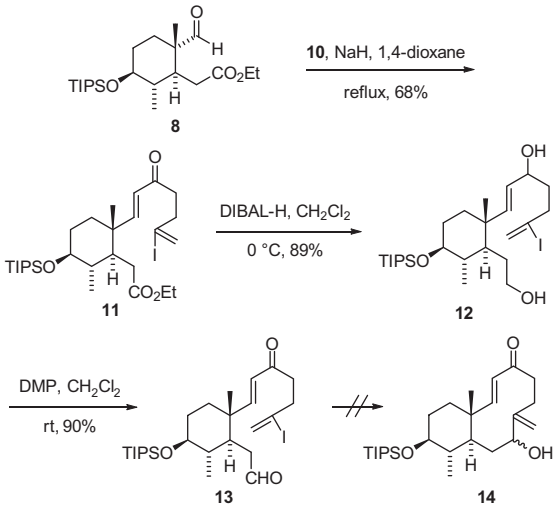


Scheme 4. Preparation of **10**.

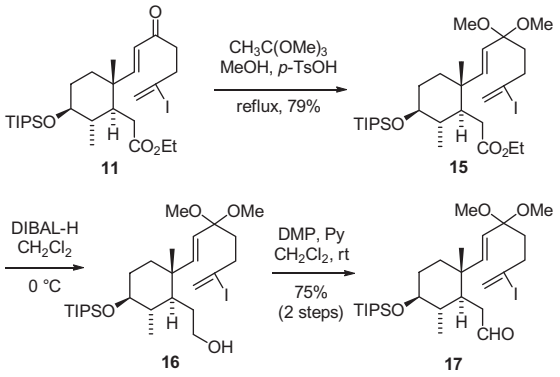
The HWE reaction of the aldehyde **8** with the keto phosphonate **10** (prepared by reaction of the known compound **9**[22] with lithiated dimethyl methylphosphonate, Scheme 4), successfully afforded the enone **11** (Scheme 5). Compound **11** was reduced with DIBAL-H to afford the diol **12**, which was oxidized with Dess–Martin periodinane (DMP) to afford the keto-aldehyde **13**. The intramolecular Cr-mediated cyclization of compound **13** was attempted because the enone was hindered owing to the adjacent all-carbon quaternary stereogenic center; however, only the 6-*endo*-trig cyclization was observed.

Consequently, compound **11** was converted to its dimethyl acetal **15** (Scheme 6), followed by reduction with DIBAL-H to afford the alcohol **16**. Finally, Dess–Martin oxidation of the alcohol **16** afforded the aldehyde **17**, the substrate for the Cr-mediated reaction.

The intramolecular Cr-mediated reaction of compound **17** was carried out in DMSO at 50 °C to afford a mixture of the products **18** (36%) and **14** (16%) (Table 1, entry 1). Conversely, the same reaction in a THF/DMF mixture afforded only **14** (entry 2, 70%). The reason for the different results derived from different solvents is not clear at this stage and further investigation is now underway, but the concomitant removal of the acetal is beneficial to reducing the synthetic steps because the subsequent oxidation afforded the desired bis-enone. Thus, Dess–Martin oxidation of compound **14** afforded the bis-enone **6** (Scheme 7), the substrate for the intramolecular Cr-mediated reaction.

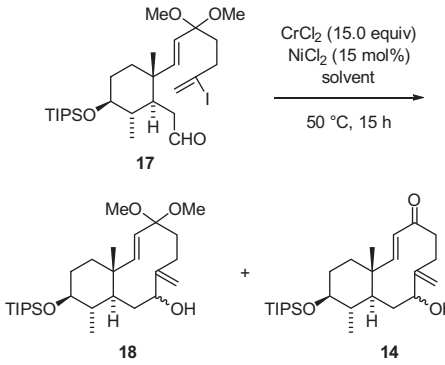


Scheme 5. Attempted preparation of **14**.



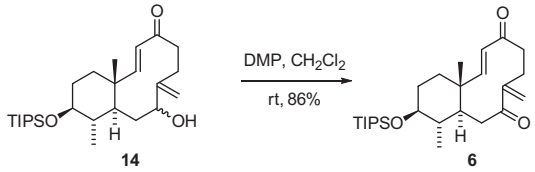
Scheme 6. Preparation of **17**.

Table 1
Intramolecular Cr-mediated alkenylation



Entry	Conditions	Yield[a] (%)	
		18	**14**
1	DMSO	36	16
2	THF/DMF = 1/1	0	70[b]

[a] Isolated yield.
[b] α/β = 1/20.



Scheme 7. Dess–Martin oxidation of **14**.

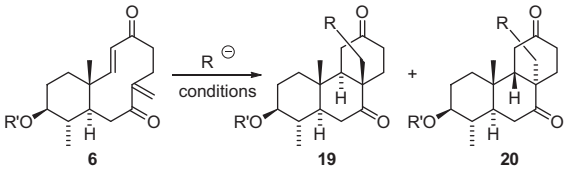
Having prepared compound **6**, the intermolecular/transannular Michael reaction cascade was investigated. Interestingly, the reaction of compound **6** with L-Selectride afforded no desired products and the products with the exomethylene were obtained under several reaction conditions. The results indicated that the first reaction took place at the inner enone in a 1,2-reduction manner and the preferential reaction of α-methylene ketone did not proceed. This unexpected result prompted us to investigate the reaction with other nucleophiles.

We examined the reaction of compound **6** with thiophenol because soft nucleophiles tend to undergo Michael addition and the introduced phenylthiomethyl group can be converted to a methyl group under the reductive conditions using Raney-Nickel (Table 2). Moreover, the reaction of thiophenol was expected to preferentially take place at the exomethylene because the reaction of thiophenol at the inner enone would suffer from the steric strain derived from the adjacent all-carbon quaternary center.

Indeed, the products **19** (9%) and **20** (30%) were obtained when potassium carbonate was used in methanol at 50 °C (entry 1). The same reaction at 0°C afforded the products **19** (8%) and **20** (54%) (entry 2), and the reaction with DBU afforded the products **19** (13%) and **20** (73%) (entry 3). The reaction with potassium thiophenoxide in methanol at 0 °C afforded only **20** but the yield was 41% (entry 4). The same reaction in THF at −78 °C improved the yield but was 43% (entry 5). Interestingly, the same reaction in the presence of 18-crown-6 afforded negligible products, even at room temperature (entry 6).

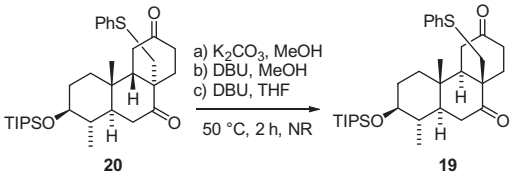
As the intermolecular/transannular Michael reaction cascade is reportedly initiated by an alkoxide,[16c] the reaction of compound **6** with alkoxides was examined. The reactions with *p*-methoxybenzyl alcohol afforded unidentified products, probably due to undesired

Table 2
Intermolecular/transannular Michael reaction cascade of **6** (R′ = TIPS)



Entry	Reagent (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	
					19	**20**
1	PhSH (3.0)/K_2CO_3 (5.0)	MeOH	50	2	9	30
2	PhSH (3.0)/K_2CO_3 (5.0)	MeOH	0	3	8	54
3	PhSH (3.0)/DBU (5.0)	MeOH	0	3	13	73
4	PhSK (2.0)	MeOH	0	1	0	41
5	PhSK (2.0)	THF	−78	1	0	43
6	PhSK (2.0)/18-C-6 (10.0)[b]	THF	rt	5	t[c]	t[c]
7	PMBOH (2.0)/^{n}BuLi (1.5)	THF	−78	4	0	0
8	PMBOH (2.0)/K_2CO_3 (5.0)	THF	−78	4	0	0
9	AllylOH/K_2CO_3 (5.0)	—	rt	3	0	0
10	*p*-MeOPhOH/KHMDS (1.5)	THF	−78	8	0	0
11	*p*-MeOPhOK (1.5)	THF	rt	8	0	0
12	*p*-MeOPhOK (1.5)	THF	50	8	0	0
13	*p*-MeOPhOK (1.5)	THF/DMF = 1/1	rt	8	0	0
14	*p*-MeOPhOK (1.5)	THF	rt	8	0	0

[a] Isolated yield.
[b] 18-C-6: 18-crown-6.
[c] t: trace amount.



Scheme 8. Attempted conversion of **20** to **19**.

side-reactions such as intramolecular Michael reactions owing to the relatively high basicity of the alkoxide (entries 7 and 8). The reaction with allyl alcohol resulted in the same results (entry 9). The reaction with the less basic *p*-methoxyphenoxide was attempted; no desired products were formed (entries 10–14).

We examined the transformation of **20** to **19** via the retro-Michael process under several conditions used in Table 2 (Scheme 8). However, no isomerization was observed, indicating that the cascade process is kinetically controlled but not thermodynamically controlled.

The configuration of the products **19** (R = SPh) and **20** (R = SPh) was elucidated based on the NOESY spectra of their desilylated derivatives **21** and **22**; the selected NOE correlations are summarized in Figure 2.

The stereoselectivity of the intermolecular/transannular Michael reaction cascade depends on the transition states of the transannular Michael reaction because the results summarized in Scheme 8 indicates that the reaction is kinetically controlled. Although four transition states ***TS 1–4*** (Figure 3) are possible for the transannular Michael reaction, ***TS 2*** and ***TS 4*** are highly strained because the former includes the 1,3-diaxial interaction between the methyl and phenylthiomethyl groups, and in addition to that, the 1,3-diaxial interaction derived from the *cis*-fused decaline system, and the latter comprises two boat conformations.

Hence, the reaction was surmised to proceed via ***TS 1*** and ***TS 3*** that afford compounds **19** and **20**, respectively. ***TS 3*** would be energetically favored because the large 1,3-diaxial interaction in ***TS 1*** would render its energy level higher than that of ***TS 3***. However, ***TS 3*** includes the energetically unfavorable boat conformation. Hence, the difference of the stability between ***TS 1*** and ***TS 3*** would

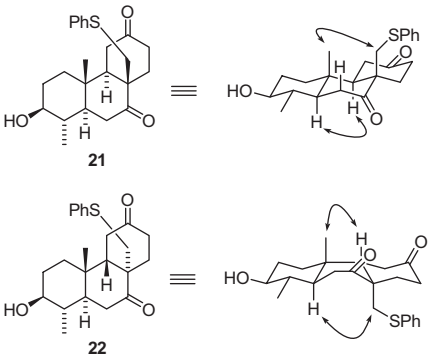


Figure 2. Selected NOE correlations observed in the NOESY spectra of **21** and **22**.

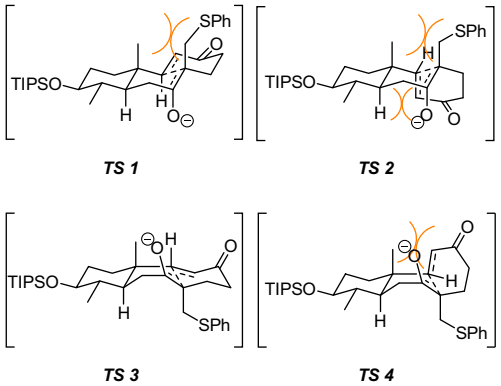
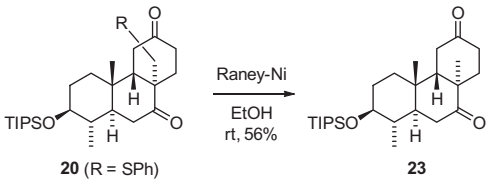


Figure 3. **TS 1**, **TS 2**, **TS 3**, and **TS 4**.



Scheme 9. Conversion of **20** (R = SPh) to **23**.

be not so large, resulting in the observed preferential formation of compound **20** with moderate stereoselectivity. It is interesting that compound **20** was formed as the single isomer in entries 4 and 5 though the yield should be improved. The reason for the high selectivity is now under investigation.

As compound **20** (R = SPh) was obtained in 73% yield, which is a reasonable yield for synthetic purpose, removal of the phenylthio group was examined. The phenylthio group in **20** (R = SPh) was expectedly removed using Raney-nickel in ethanol to afford compound **23** (56%, not optimized) (Scheme 9), which possesses the ABC-ring scaffold of fusidanes with correct stereogenic centers and appropriate functionalities for further transformations required for the total synthesis of fusidanes. The phenylthiomethyl group in **20** (R = SPh) would be converted to a formyl group via Pummerer rearrangement; thereby, an oxygen atom could be introduced at the same position. Therefore, **20** (R = SPh) could be a useful intermediate for other natural products, too.

In summary, we have developed an intermolecular/transannular Michael reaction cascade that could lead to a new stereoselective approach to the ABC-ring system in fusidane triterpenes. The substrate, a ten-membered carbocyclic ketone, has been successfully prepared by the Cr-mediated intramolecular alkenylation of the corresponding acyclic compound. The array of functionalities in the product obtained by the cascade reaction is useful for further structural modifications directed toward the total synthesis of fusidane and other triterpenes, and designed molecules intended for studying structure–activity relationships.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.071.

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