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An Efficient Method for Construction of the Angularly Fused 6,3,5-Tricyclic Skeleton of Mycorrhizin A and Its Analogues

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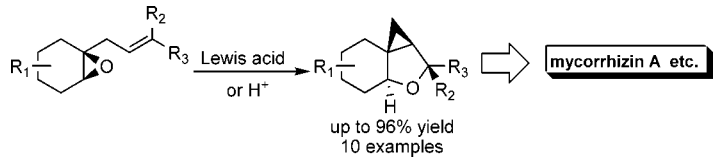
ABSTRACT



The angularly fused 6,3,5-tricyclic system is readily generated via a cascade cyclization under acid promotion. The reaction proceeds at room temperature with high stereochemical fidelity from the electrophilic center of the epoxide to the cyclopropane product. This methodology provides a potentially useful approach for the synthesis of mycorrhizin A and its analogues.

The antibiotic mycorrhizin A (**1a**, Figure 1), was first isolated and characterized by Wickberg and Trofast[1a] from a sterile mycelium of an endomycorrhizinal fungus in 1977. Several analogues of **1**, compounds **2**−**4**, have been obtained from other culture filtrates of the fungus.[1b−e] Biologically, these compounds possess varying degrees of antifungal and antibiotic activity.[1f] However, efforts directed toward the synthesis of the basic angularly fused 6,3,5-tricyclic skeleton have been limited to date.[2,3] Only two elegant strategies have been reported for such ring systems: an interesting synthetic approach was disclosed by Smith's group,[2] in which an intramolecular S_N2' reaction was utilized for construction of the cyclopropane ring, and Brown and co-workers reported that cycloaddition between diazomethane and an olefin, followed by extrusion of its nitrogen upon ultraviolet irradiation, led to the cyclopropane ring.[3] In connection with our current studies dealing with the synthesis of cyclopropane derivatives,[4] we describe herein a novel approach based on a cation−olefin cascade cyclization strategy for the construction of this tricyclic core system of mycorrhizin A and its analogues.

Cation-induced cyclization provides a valuable means of constructing a variety of natural products.[5] The reaction of an epoxy olefin with Lewis acids yields alcohols or ethers

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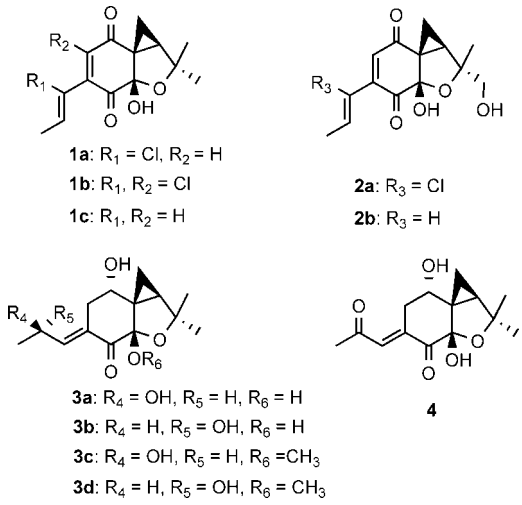
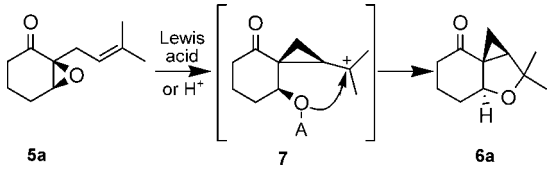


Figure 1. Some representative fungal metabolites incorporating a 6,3,5-tricyclic skeleton.

of the cyclopentane, cyclohexane, and cycloheptane series via an intramolecular nucleophilic attack of the double bond on the incipient carbocation. However, in the field of cation-induced cyclization, transformation of an epoxide to a

Scheme 1. Design of an Epoxide-Initiated Cascade Cyclization



cyclopropane is still rare,[6] and only a few examples of 3-exo cyclizations have been applied in the synthesis of natural products[6d,e] and with low yields. Hence, the synthetic potential of the corresponding epoxide-initiated 3-exo cyclizations warrants further investigation.

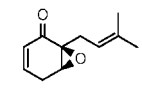
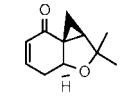
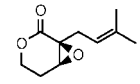
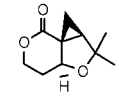
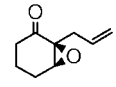
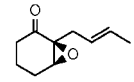
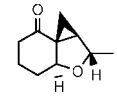
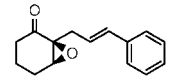
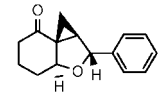
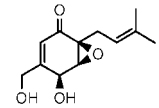
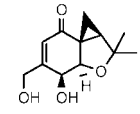
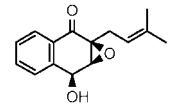
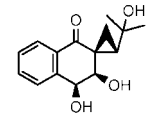
We envisioned that the method involves the intramolecular cyclization of a π-nucleophile with an epoxide adduct. This reaction proceeds via an initial attack of the double bond on the epoxide ring leading to a cyclopropylcarbinyl cation intermediate **7**, which could be trapped by the oxygen atom to provide the tricyclic product **6a** (Scheme 1). However, the cyclopropylcarbinyl cation may be considered to belong to a nonclassical or a delocalized cation[7] that is unstabilized without some substituents at appropriate positions; otherwise, ring-opening and rearrangment procedures would often occur.

Table 1. Optimization of Reaction Conditions

entry	acidic medium	equiv	T (°C)	time (min)	yield[a] (%)
1	$SnCl_4$	1.1	−20 to rt	60	44
2	BF_3•OEt_2	1.1	−20 to rt	60	70
3	BF_3•OEt_2	1.1	rt	3	98
4	BF_3•OEt_2	0.5	rt	3	45
5	$SnBr_4$	1.1	rt	15	34
6	$TiCl_4$	1.1	0 to rt	10	20
7	TMSOTf	1.1	0 to rt	10	25
8	$InCl_3$	2	rt	60	trace
9	$ZnCl_2$	2	rt	60	0
10	CF_3COOH	1.1	rt	60	20
11	CF_3SO_3H	1.1	rt	5	95
12	*p*-TsOH	1.1	rt	120	trace

[a] Yield of isolated product.

Table 2. Synthesis of the Angularly Fused Tricyclic Skeleton via Acid-Mediated Intramolecular Cascade Cyclization

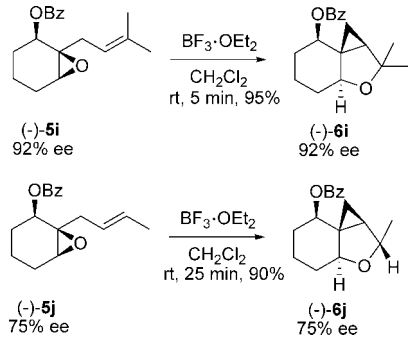
entry	substrate	product	time	yield (%)[d]
1 [a,b]	**5a**	**6a**	3 min	98 [a] / 95 [b]
2 [a]	 **5b**	 **6b**	3 min	95
3 [a]	 **5c**	 **6c**	10 min	84
4 [a,b]	 **5d**	 **6d**	5 h	95 [a] / 93 [b]
5 [a,b]	 **5e**	 **6e**	2 h	96 [a] / 94 [b]
6 [a]	 **5f**	 **6f**	2 h	96 [c]
7 [c]	 **5g**	 **6g**	5 min	82
8 [c]	 **5h**	 **6h**	5 min	66 [f]

[a] Condition A: BF_3•OEt_2 (1.1 equiv), CH_2Cl_2, rt. [b] Condition B: CF_3SO_3H (1.1 equiv), CH_3CN, rt. [c] Condition C: BF_3•OEt_2 (2.2 equiv), CH_2Cl_2, rt. [d] Yield of isolated product. [e] Diastereoselectivity ratio was 3:1 determined by ^1H NMR (400 MHz) analysis of crude reaction mixtures. [f] Accompanied by 5% unidentified byproduct.

To effect the proposed electrophilic olefin cyclization of allylic α,β-epoxy ketone **5a**, an extensive investigation toward reaction condition was carried out (Table 1). Among all acids studied, BF_3•OEt_2 and CF_3SO_3H were found to be the ideal choices to promote 3-exo cyclization of the allylic epoxide to give the desired angularly fused 6,3,5-tricyclic product in satisfactory yields (Table 1, entries 3 and 11).

The reaction was complete in CH_2Cl_2 or CH_3CN within 3−5 min at room temperature. Other Lewis acids (e.g., $SnCl_4$, $SnBr_4$, $TiCl_4$, and TMSOTf) resulted in complex mixtures, while relatively weaker Lewis acids such as $InCl_3$ and $ZnCl_2$, as well as weaker protic acids (e.g., *p*-TsOH, CF_3CO_2H), resulted in no apparent reaction or only trace conversion (starting material was recovered).

Scheme 2. Chirality Transfer in the Epoxide-Initiated Cascade Cyclization



With this encouraging result in hand, we investigated more substrates under the optimized reaction conditions that were proven to be general and versatile, as shown in Table 2. For example, the α,*β*-unsaturated substrate **5b** and lactone **5c** were prepared and also successfully converted to the corresponding products **6b** and **6c** in 95% and 84% yields, respectively (entries 2 and 3). To our delight, olefinic epoxides **5d**, **5e**, and **5f** similarly gave the corresponding products **6d**, **6e**, and **6f** in excellent yields, demonstrating that substitutes on olefin are not essential to the cascade process (entries 4, 5, and 6). In most of the aforementioned examples, the reactions proceeded with uniformly exclusive diastereoselectivity. However, a pendant phenyl group was found to have a deleterious effect on this selectivity, providing **6f** as a 3:1 diastereomeric mixture. We propose that the resulting benzylic ion, a more stable cyclopropylcarbinyl cation intermediate, was trapped relatively slowly by the oxygen resulting in the low stereoselectivity. The dihydroxyl adduct **5g** underwent a 3-exo cascade cyclization to furnish the single diastereomeric adduct **6g**, which demonstrated that the free hydroxyl group did not disturb the transformation (entry 7). Finally, it is interesting to note that in the case of entry 8, an unexpected triol cyclopropyl product **6h** was obtained in moderate yield after quenching with aqueous sodium bicarbonate and no tricyclic product was observed. This indicated that the single-step transformation afforded the thermodynamically favored compound.

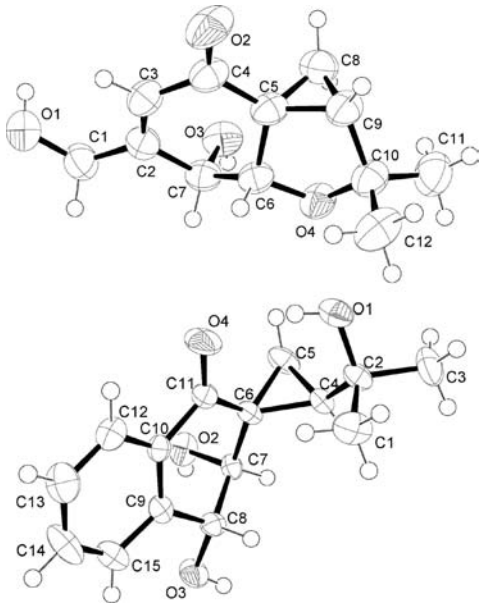


Figure 2. ORTEP drawing of **6g** (top CCDC no. 709206) and **6h** (bottom CCDC no. 709207).

With the optically active substrates **5i** and **5j**, acid-induced cyclization gave the expected products **6i** and **6j** in excellent yields with high stereochemical fidelity (Scheme 2).[9] Moreover, these two cases disclosed that the presence of a carbonyl group adjacent to epoxide in the substrate did not play an important role in this reaction.

The structures of all the products were established on the basis of spectroscopic data (see the Supporting Information). To assign the relative stereochemistry of the products beyond doubt, the structures of **6g** and **6h** were determined unambiguously by X-ray crystallography—the former has a 5,6-membered trans-fused configuration while the latter is an acyclic triol (Figure 2).[10] It is noteworthy that compared with other products in Table 2, **6g** prensents the most similar structural feature of mycorrhizin A, which enables the potential investigation for further diversity-oriented synthesis[8] of the angularly fused 6,3,5-tricyclic natural products.

In conclusion, we have developed an efficient method for constructing an angularly fused 6,3,5-tricyclic system via a cation-olefin cascade cyclization. The reaction can be

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(8) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(9) Enantiomeric purity was determined by HPLC (see the Supporting Information).

(10) Crystallographic data of **6g** and **6h** were deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 709206 and 709207). The stereochemistries of the remaining products in Table 2 were assigned by analogy (see the Supporting Information for further details).

promoted by either Brønsted acid (CF_3SO_3H) or Lewis acid (BF_3•OEt_2), offering excellent yields and high stereochemical fidelity. Efforts directed toward the total synthesis of natural products bearing similar skeletons are currently being investigated in our laboratory.

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Supporting Information Available: Experimental details, ^1H and ^{13}C NMR spectra of products, and X-ray structure of **6g** and **6h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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