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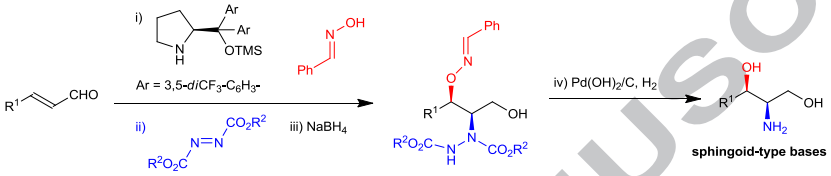

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Enantioselective synthesis of *syn*-2-amino-1,3-diols via organocatalytic sequential oxa-Michael/α-amination reactions of α,β-unsaturated aldehydes

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ABSTRACT

A general and efficient method for the enantioselective synthesis of *syn*-2-amino-1,3-diols is reported. It involves the methodology of secondary amine-catalyzed one-pot sequential oxa-Michael/α-amination reactions of α,β-unsaturated aldehydes. This method has also been successfully applied to highly efficient total syntheses of (+)-safingol and *D-threo*-clavaminol H with excellent stereoselectivities.

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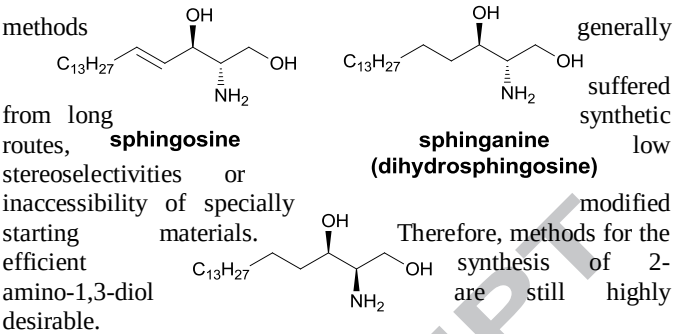
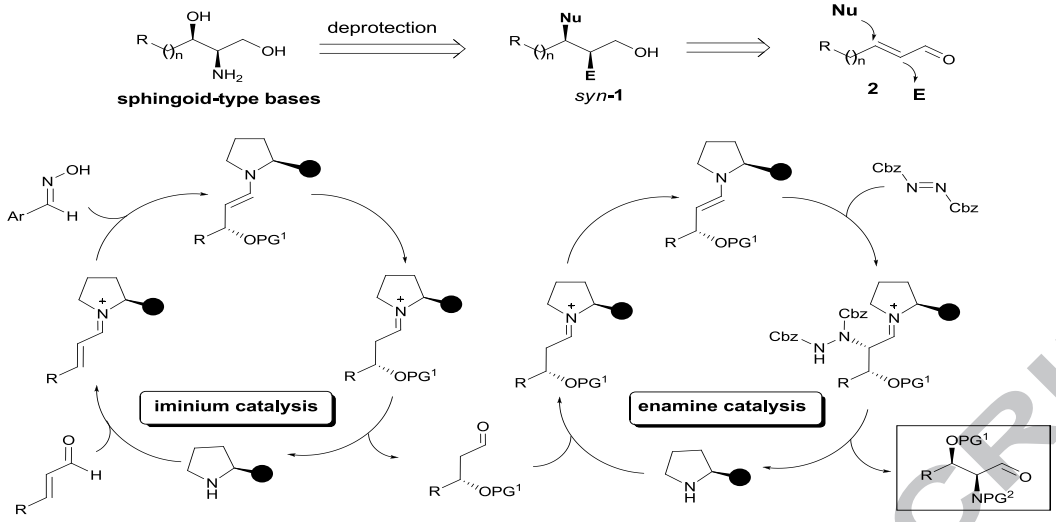
The 2-amino-1,3-diol moiety can be frequently found in many natural products and pharmaceutical molecules. The long-chain sphingoid-type bases are one of the most common 2-amino-1,3-diols, which are core fragments present in a large number of bioactive natural products.[1] Some of the representative examples are sphingosines, sphinganines (dihydrosphingosines) and safingol (Figure 1). Sphinganine is known to be an important precursor in the biosynthesis of ceramides, sphingomyelin, cerebrosides and gangliosides,[2] which are structural constituents of cell membranes and exhibit diverse biological activities in cell regulation, cell growth modulation, and signal transmission.[3] Safingol is a synthetic diastereoisomer of sphingosine and exhibits antineoplastic and antipsoriatic activities. Safingol was also used as a protein kinase Cα (PKCα)-selective inhibitor and has been under phase I clinical trial in combination with cisplatin for the treatment of advanced solid tumors.[4]

Due to the versatile and important bioactivities of 2-amino-1,3-diols, considerable efforts have been devoted to develop efficient and diverse synthetic approaches toward these compounds.[5] The traditional approaches for the preparation of 2-amino-1,3-diol motif involves the use of starting materials from the chiral pool, particularly serine derivatives[6] and carbohydrates[7]. Alternatively, a number of asymmetric transformations have also been employed for the syntheses of 2-amino-1,3-diol, such as Sharpless asymmetric dihydroxylation and epoxidation reactions,[8] asymmetric Henry reactions,[9] aldol reactions[10] and organocatalytic reactions.[11] These methods generally suffered from long synthetic routes, low stereoselectivities or inaccessibility of specially modified starting materials. Therefore, methods for the efficient synthesis of 2-amino-1,3-diol are still highly desirable.

Figure 1. The structures of common sphingoid-type bases



In recent years, organocatalytic cascade reactions have attracted increasing attention and become a powerful tool for rapidly building molecular complexity.[12] As a part of our ongoing research on the application of organocatalysis for the preparation of biologically active compounds,[13] we set out to develop a highly efficient synthesis of long-chain 2-amino-1,3-diols via one-pot organocatalytic cascade reactions. Our synthetic strategy for the construction of 2-amino-1,3-diol motif is outlined in Scheme 1. We envisioned that the highly functional compound **1** could act as key precursor, which could be further converted to *syn*-2-amino-1,3-diols and related derivatives after deprotection.

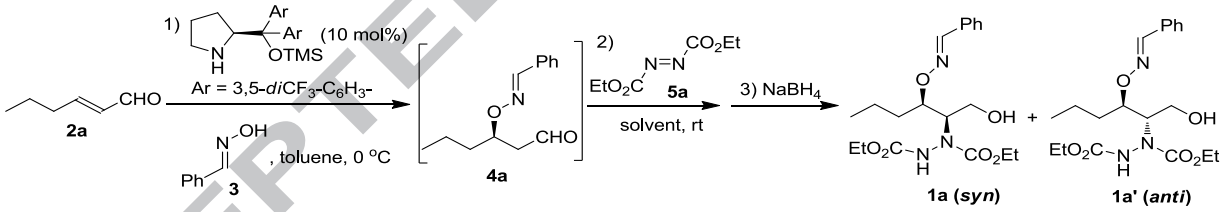


Scheme 1. Retro-synthetic analysis of *syn*-2-amino-1,3-diols and organocatalytic iminium/enamine cascade sequence

Herein compound **1** could be accessed through cascade oxa-Michael[14]/α-amination[15]/reduction reaction to generate both the amino and hydroxyl functionalities from α,β-unsaturated aldehyde via sequentially iminium- and enamine-catalyzed reactions

For the synthesis of 2-amino-1,3-diols, our primary goal was to prepare highly functional precusor **1** in one pot. Initially, the Michael reaction between *trans*-2-hexenal **2a** and (*E*)-benzaldoxime **3** in the presence of (*S*)-2-{bis[3,5-bis (trifluoromethyl)phenyl]trimethylsilanyloxymethyl}pyrrolidine in toluene was selected as the first step, which was developed by Jørgensen and coworkers.[14a] After the starting material **2a** was completely consumed, the aldehyde **4a** formed in situ was directly treated with diethyl azodicarboxylate (DEAD) **5a** at room temperature for another 12 h, followed by $NaBH_4$ reduction to give the corresponding alcohol **1a** in 31% overall yield and 98% *ee* (Table 1, entry 1). Next, the solvents and concentration of **5a** (entries 2-7) were evaluated. While the α-amination proceeded with 0.5 M of **5a** in toluene, the yield was improved to

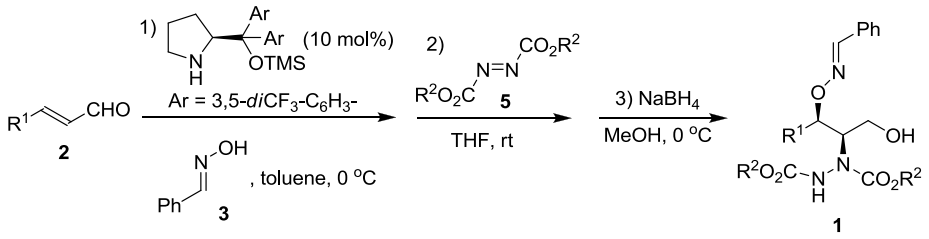
Table 1. Optimization of the cascade reaction[a]



entry	solvent	conc. of **5a** (M)	yield (%)[b]	*dr* (*syn*/*anti*)[c]	*ee* (%)[d]
1	toluene	2	31	6:1	98
2	toluene	1	35	6:1	98
3	toluene	0.5	40	7:1	98
4	MeCN	0.5	30	7:1	98
5	DCM	0.5	44	5:1	98
6	THF	0.5	51	12:1	97
7	Et_2O	0.5	28	9:1	98
8	THF	0.2	30	8:1	95
9[e]	THF	0.5	36	10:1	94

[a] Reaction conditions for the first step: **2a** (0.5 mmol), **3** (1.0 mmol), catalyst (0.05 mmol), $PhCO_2H$ (0.05 mmol) in toluene (0.5 mL), 0 °C, 12 h. Reaction conditions for the second step: **5a** (1.0 mmol), solvent, rt, 6 h. Reaction conditions for the third step: $NaBH_4$ (2.0 mmol), MeOH (2.0 mL), 0 °C, 0.5 h. [b] The isolated yields of **1a**. [c] The diastereomeric ratio of **1a** was determined by ^1H NMR analysis of the crude products. [d] The *ee* values of **1a** were determined by chiral HPLC analysis. [e] The second step was performed at 0 °C.

Table 2. The substrate scope of the one-pot sequential reactions[a]



Entry	2	5	product	yield (%)[b]	*dr* (*syn*/*anti*)[c]	*ee* (%)[d]
1	**2a**, R^1 = *n*-Pr	**5a**, R^2 = Et	**1a**	51	12:1	97
2	**2b**, R^1 = Me	**5a**, R^2 = Et	**1b**	47	10:1	>99
3	**2c**, R^1 = Et	**5a**, R^2 = Et	**1c**	46	10:1	>99
4	**2d**, R^1 = *n*-C_5H_{11}	**5a**, R^2 = Et	**1d**	48	10:1	99
5	(2*E*,6*Z*)-nona-2,6-dienal (**2e**)	**5a**, R^2 = Et	**1e**	45	9:1	99
6	**2a**, R^1 = *n*-Pr	**5b**, R^2 = *i*-Pr	**1f**	49	6:1	95
7	**2a**, R^1 = *n*-Pr	**5c**, R^2 = Bn	**1g**	52	7:1	>99
8	**2f**, R^1 = *i*-Pr	**5a**, R^2 = Et	**1h**	ND	ND	ND
9	**2a**, R^1 = *n*-Pr	**5d**, R^2 = *t*-Bu	**1i**	ND	ND	ND
10[e]	**2a**, R^1 = *n*-Pr	**5a**, R^2 = Et	**1a**	45	10:1	97
11[f]	**2a**, R^1 = *n*-Pr	**5a**, R^2 = Et	**1a+1a'**	43	1:1.2	85, 84

[a] Reaction conditions for the first step: **2** (0.5 mmol), **3** (1.0 mmol), catalyst (0.05 mmol), $PhCO_2H$ (0.05 mmol) in toluene (0.5 mL), 0 °C, 12 h. Reaction conditions for the second step: **5** (1.0 mmol), THF (1.5 mL), rt, 6 h. Reaction conditions for the third step: $NaBH_4$ (2.0 mmol), MeOH (2.0 mL), 0 °C, 0.5 h. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by chiral HPLC analysis. [e] This reaction was carried out at 5 mmol scale of **2**. [f] To obtain the *anti*-isomer of **1a**, *L*-proline (30 mol%) was added as catalyst in the second step.

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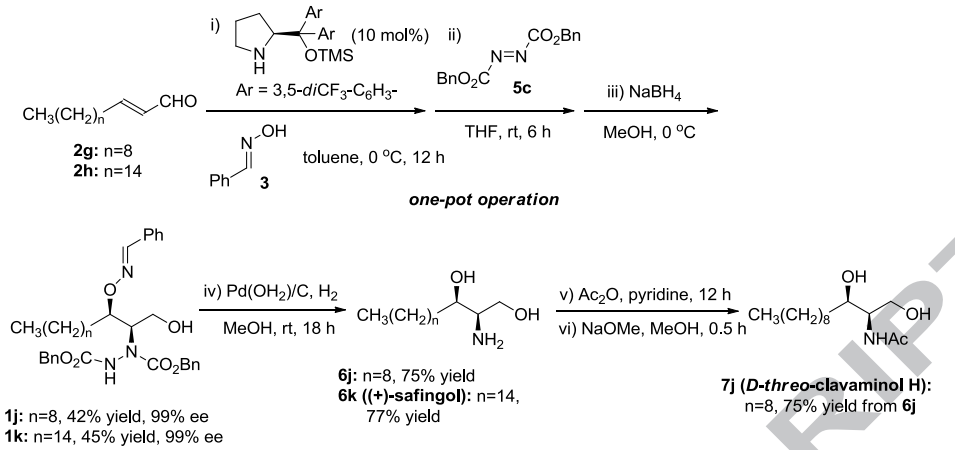
40% (entry 3). Other solvents including MeCN, CH_2Cl_2, THF and Et_2O were also evaluated (entries 4-7), and THF was identified as the optimal solvent for the α-amination reaction (entry 6). Further optimization of the THF reaction system on both the temperature and the concentration of **5a** resulted in lower yields and stereoselectivities (entries 8-9). Under optimal conditions, the desired product **1a** can be obtained in one-pot with 51% overall yield, 12:1 dr and 97% ee (entry 6). To further simplify the operation, we also tried to add the nucleophile oxime **3** and the electrophile DEAD **5a** simultaneously. Unfortunately, the resulting product was too complicated to isolate **1a** in high yield.

With optimal reaction conditions for the one-pot sequential reaction in hand, we examined the scope of this reaction using various *α,β*-unsaturated aldehydes and azodicarboxylates. The results were summarized in Table 2. For aldehydes **2a-d** with linear alkyl chains, the reactions proceeded smoothly to give the desired products in good yields (46~51%) and excellent enantioselectivities (97~>99% *ee*) (Table 2, entries 1-4). Similar result was also obtained for *α,β*-unsaturated aldehyde **2e** with an extra double bond (entry 5). To expand the scope of the reaction, we also investigated different amine sources and the results indicated that *dii*sopropyl- and *di*benzylazodicarbxylates (**5b** and **5c**) were suitable candidates (entries 6-7). However, no desired product was isolated when *di*-*tert*-butyl azodicarboxylate **5d** (entry 9) or branched *α,β*-unsaturated aldehyde **2f** (entry 8) were employed, which is probably due to steric hindrance effect of these substituent groups. Moreover, an additional scaled-up experiment showed that this reaction could be performed in gram scale without obvious loss of stereoselectivity and with slightly lower yield (entry 10).

The major drawback of this methodology is that *anti*-2-amino-1,3-diols couldn't be generated as the major products, while biologically relevant sphingoids are *anti*-isomers. To overcome this problem, we have tried the concomitant use of two cycle-specific catalysts as developed by MacMillan.[16] When 30 mol% *L*-proline was added in the amination step, the *anti*-isomer **1a'** was obtained as the major product, albeit the *dr* value was just 1.2:1 (*anti*/*syn*) and the *ee* value was 84% (Table 2, entry 11).

Finally, the practical utility of this organocatalytic sequential oxa-Michael/*α*-amination reaction was demonstrated by the short asymmetric synthesis of (+)-safingol and *D-threo*-clavaminol H (Scheme 2). Clavaminol H also belong to sphingoid-type bases and was isolated from the Mediterranean ascidian *Clavelina phlegraea*.[17] Although clavaminol H did not exhibit significant biological activity, the corresponding des-acteyl product has showed cytotoxic activities against gastric carcinoma cell lines.[17b] Starting from readily available (*E*)-dodec-2-enal **2g** and (*E*)-octadec-2-enal **2h**, the asymmetric sequential oxa-Michael/*α*-amination reactions with oxime **3** and DBAD **5c** in the presence of 10 mol% catalyst



Scheme 2. Total synthesis of (+)-safingol and *D-threo*-clavaminol H

provided the corresponding alcohols **1j** (42% isolated yield, 99% *ee*) and **1k** (45% isolated yield, 99% *ee*), respectively. Then the deprotection of **1j** and **1k** afforded the target sphingoid bases. Several reductive conditions including hydrogenation with $Pd(OH)_2/C$, Pd/C and PtO_2 have been investigated, and corresponding 2-amino-1,3-diols **6j** and **6k** (*i.e.* (+)-safingol) were obtained through concomitant cleavage of the N-N and N-O bonds via hydrogenation with $Pd(OH)_2/C$ in MeOH,while hydrogenation with Pd/C and PtO_2 couldn't give **6j** and **6k**.[18] Then the amine group of compound **6j** was acetylated to give **7j** (*i.e. D-threo*-clavaminol H) in 75% yield. The absolute configuration of these products were determined by comparison of the optical rotation of (+)-safingol **6k** with previously reported in literature.[19]

In summary, we have developed a one-pot sequential oxa-Michael/*α*-amination reaction through combining iminium and enamine activation of *α,β*-unsaturated aldehydes. The enantioenriched *syn-β,γ*-functional alcohols were obtained in good to excellent diastereo- and enantioselectivities. Those alcohols could be facilely transformed to *syn*-2-amino-1,3-diols via hydrogenation. Moreover, this method has been successfully applied to highly efficient syntheses of (+)-safingol and *D-threo*-clavaminol H with excellent stereoselectivities.

Acknowledgments

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Supplementary Material

Supplementary data (typical experimental procedures, physical data of new compounds, copies of ^1H and ^{13}C NMR, and HPLC spectra) associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx.

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Highlights

- a one-pot sequential oxa-Michael/α-amination reaction has been described.
- highly enantioenriched *syn-β,γ*-functional alcohols were obtained.
- *(+)*-safingol and *D-threo*-clavaminol *H* were prepared with this method as key step.