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Catalytic Asymmetric Amination of N-Nonsubstituted α-Alkoxycarbonyl Amides: Concise Enantioselective Synthesis of Mycestericin F and G

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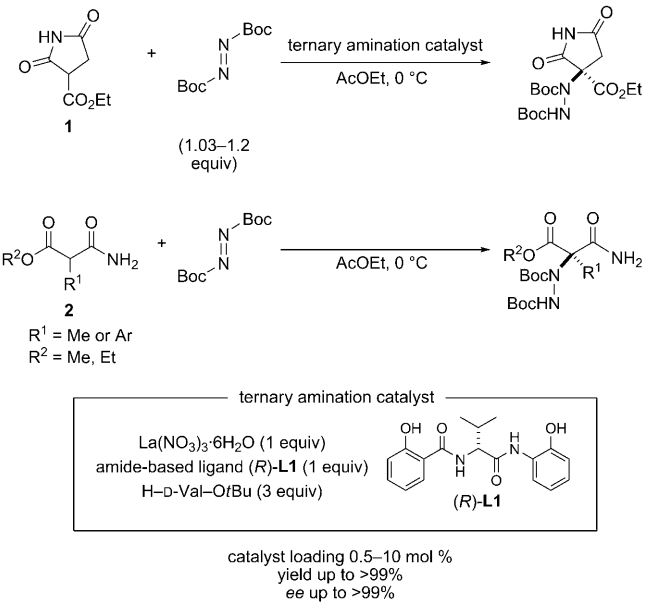
Abstract: In an attempt to explore the synthetic utility of a ternary asymmetric catalyst comprising $La(NO_3)_3{\cdot}6H_2O$, amide-based ligand (*R*)-**L1**, and D-valine *tert*-butyl ester H-D-Val-O*t*Bu, we investigated a catalytic, asymmetric amination of functionalized N-nonsubstituted α-alkoxycarbonyl amides using di-*tert*-butyl azodicarboxylate as an electrophilic aminating reagent. A highly functionalized, cyclic N-nonsubstituted α-alkoxycarbonyl amide delivered the desired amination product in up to 96% enantiometric excess, with the requisite functionalities of the polar heads of sphingosines with the appropriate stereochemical arrangement. The rapid asymmetric assembly of these functional groups allowed a concise enantioselective synthetic route to sphingosines to be established with a broad flexibility towards derivative synthesis. These studies have culminated in an efficient catalytic enantioselective total synthesis of immunosuppressive fungal metabolites mycestericin F (**3a**) and G (**3b**).

Keywords: amide-based ligands · asymmetric catalysis · asymmetric synthesis · cooperative effects · natural products

Introduction

The catalytic, asymmetric electrophilic α-amination of carbonyl compounds has received growing attention as a robust methodology that provides functionalized α-amino acid derivatives.[1–3] We recently developed a unique ternary catalytic system comprising $La(NO_3)_3{\cdot}6H_2O$, amide-based ligand (*R*)-**L1**, and D-valine *tert*-butyl ester H-D-Val-O*t*Bu, in which the three catalyst components are in dynamic equilibrium and work in a synergistic manner.[4–6] This catalytic system was specifically identified as being efficient for catalytic asymmetric amination of highly coordinative substrates exhibiting multiple coordination modes, such as succinimide derivative **1** and N-nonsubstituted α-alkoxycarbonyl amides **2** (Scheme 1). The cooperative stereocontrol that operates through both metal coordination and hydrogen bonding was proposed to be a key element in the high enantioselectivity with these substrates, which are seldom employed in asym-



Scheme 1. A ternary catalytic system for asymmetric amination of **1** and **2**. Boc = tert-butoxycarbonyl, *ee* = enantiomeric excess.

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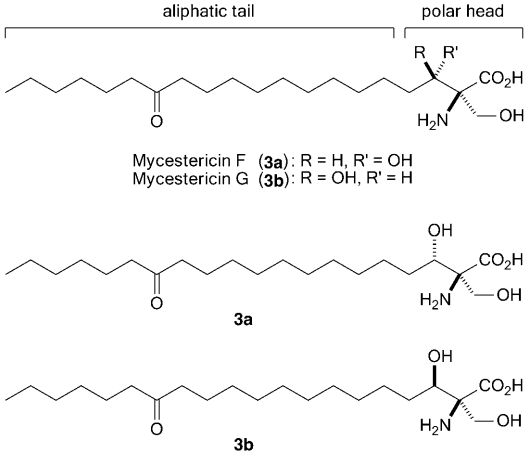
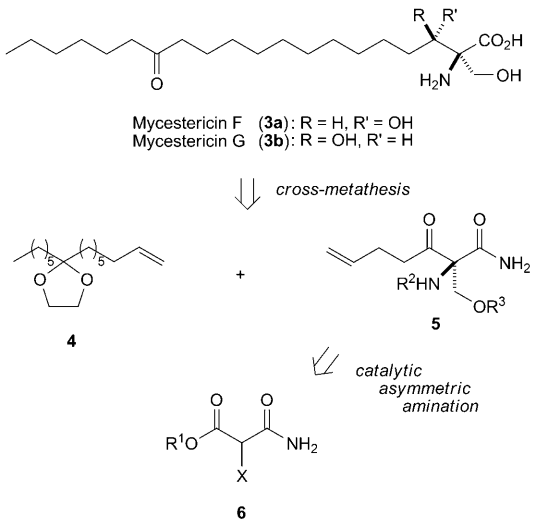
metric catalysis because multiple coordination modes usually compromise the enantioselection.[4c] A particular advantage of using these substrates in asymmetric catalysis is the ability to rapidly assemble functional groups in a stereocontrolled manner; this provides a powerful methodology with which to construct certain types of densely functionalized stereogenic substructures. In this context, the polar head groups of mycestericins drew our attention. Mycestericins were isolated from the culture broth of *Mycelia sterilia* and identified as potent immunosuppressants;[7,8] their mode of action is closely related to that of myriocin.[9] The characteristic densely functionalized α-trisubstituted amine motif, with adjacent carboxylic acid and hydroxyl groups, is accessible by catalytic asymmetric amination of functionalized N-nonsubstituted α-alkoxycarbonyl amides. Therefore, we envisioned exploiting our ternary catalytic system for a concise enantioselective total synthesis of mycestericin F (**3a**) and G (**3b**),[10–12] which would also contribute to the production of several useful analogues containing stereochemical diversity. The synthesis of this class of compounds was hampered by the difficulty in the stereoselective construction of the polar head group, because the known synthetic routes require lengthy transformations. Herein, we present details of a catalytic asymmetric amination of functionalized N-nonsubstituted α-alkoxycarbonyl amides and its application to the total synthesis of **3a** and **3b**.

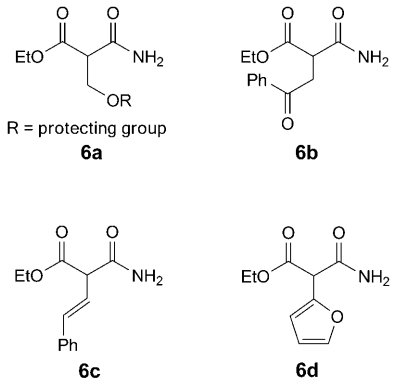


Results and Discussion

Design of N-nonsubstituted α-alkoxycarbonyl amides 6 and catalytic asymmetric amination with the ternary catalyst: The clear structural features of sphingosines, including mycestericins, led us to divide the structure of mycestericins into two parts, an aliphatic tail **4** and a polar head **5**, which we anticipated would be coupled by cross-metathesis (Scheme 2). The stereogenic tetrasubstituted carbon atom of the polar head group can be constructed through catalytic asymmetric amination of functionalized N-nonsubstituted α-alkoxycarbonyl amides **6**. Clear differentiation between the amide carbonyl and the ester carbonyl allowed stereoselective elaboration of the amination product. Initially, we designed the functionalized N-nonsubstituted α-alkoxycarbonyl amides **6a–6d** as candidate substrates for the catalytic asymmetric amination for the synthesis of **3a** and **3b** (Scheme 3). Although α-alkoxycarbonyl amide **6a**, with a



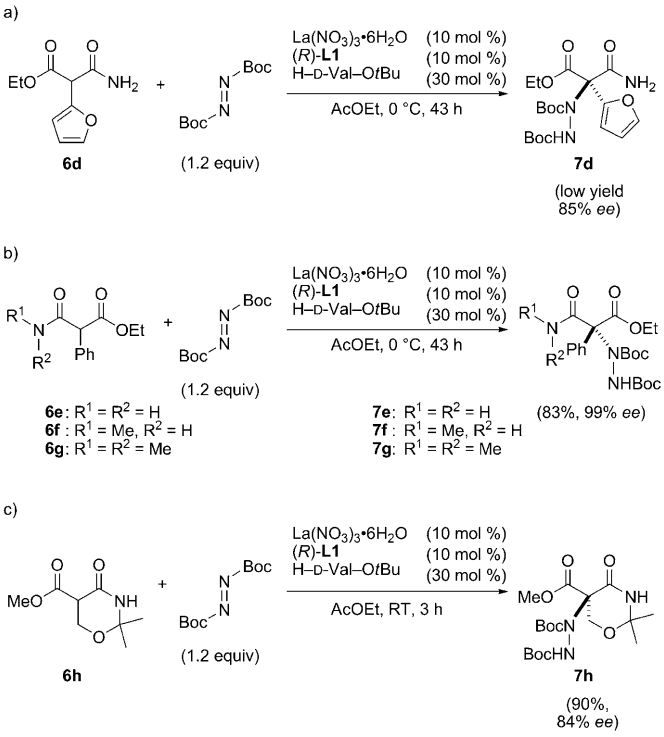
Scheme 2. Retrosynthetic analysis of mycestericin F (**3a**) and G (**3b**).



Scheme 3. Candidate substrates for catalytic asymmetric amination in the synthesis of mycestericin F (**3a**) and G (**3b**).

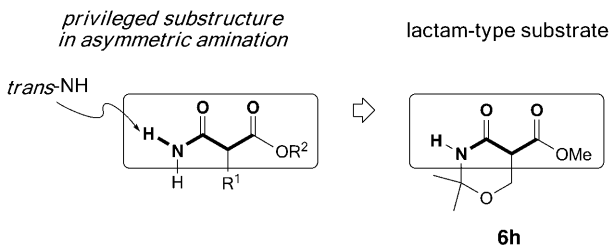
pendant O-protected α-hydroxylmethyl group, was a viable substrate to give the requisite functionalities quickly at the stereogenic tetrasubstituted carbon, all attempts to prepare these compounds resulted in failure due to a tendency of the 2-hydroxymethyl-1,3-dicarbonyl framework to undergo dehydration. This result prompted us to examine substrates with sp^2 α-substituents that are amenable to oxidation to introduce the requisite hydroxyl group. However, attempts at catalytic asymmetric aminations of **6b–6d** under the standard amination conditions[4c] suffered from poor catalytic performance and undesired side reactions leading to complex mixtures. For example, asymmetric amination of **6d** gave the desired product **7d** in low yield, albeit in 85% *ee*, at 0°C after 43 h together with several unidentified products

(Scheme 4a). Even worse results came from reactions with **6b** or **6c**, in which none of the desired amination products were obtained. A previous study revealed that the present



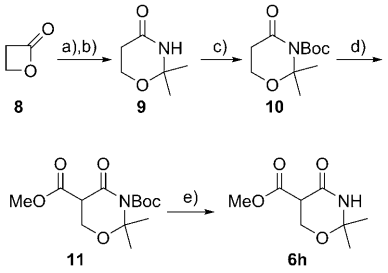
Scheme 4. Selected results of catalytic asymmetric amination of functionalized α-alkoxycarbonyl amides.

ternary catalytic system recognizes the α-alkoxycarbonyl amide motif with a *trans*-N–H proton as a privileged substructure to promote the reaction in a highly enantioselective manner (Scheme 5).[4c] Indeed, α-alkoxycarbonyl amide **6e**, which has such a *trans*-NH proton, afforded the desired amination product in 83% yield with 99% *ee*, whereas the reaction of neither *N*-methyl nor *N*,*N*-dimethyl analogues **6f** or **6g**, both lacking a *trans*-NH proton, proceeded (Scheme 4b). To both minimize the steric bias and comply with the privileged structure, including a *trans*-amide NH proton, we designed the lactam-type substrate **6h**, with the requisite oxygen functionality incorporated into a 1,3-oxazinane ring system (Scheme 5). In contrast to acyclic **6a**, the



Scheme 5. Privileged structure in the catalytic asymmetric amination with the ternary catalytic system.

cyclic compound **6h** is sufficiently stable under both acidic and basic conditions, probably as a result of conformational restriction of the α-hydroxymethyl group, which prevents β-elimination. Catalytic asymmetric amination of the lactam-type substrate **6h** proceeded smoothly at room temperature, affording **7h** in 90% yield and 84% *ee* after 3 h (Scheme 4c). The synthesis of **6h** commenced with commercially available β-propiolactone (**8**), the ring opening of which proceeded quantitatively with concentrated aqueous ammonia to give β-hydroxypropionamide, followed by intramolecular protection/cyclization using 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid, affording 2,2-dimethyl-1,3-oxazin-4-one (**9**) in 58% yield in two steps (Scheme 6). Unsuccessful installation of a methoxycarbonyl

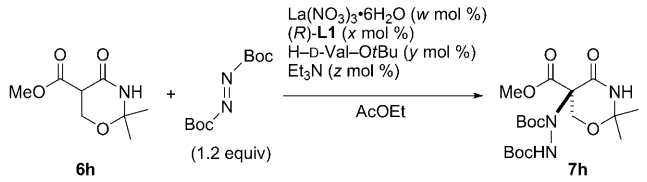


Scheme 6. Synthesis of lactam-type substrate **6h** for asymmetric amination. a) Aq 25% NH_3, RT, 18 h; b) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, toluene, reflux, 20 h, 58% (two steps); c) Boc_2O, 4-dimethylaminopyridine (DMAP), Et_3N, CH_3CN, reflux, 48 h, 96%; d) lithium diisopropylamide (LDA), methyl chloroformate, THF, −78 °C, 2 h, 86%; e) trifluoroacetic acid (TFA), CH_2Cl_2, RT, 2 h, 78%.

group with **9** led us to protect the lactam nitrogen. After installation of the *N*-Boc protecting group under standard conditions in 96% yield, methoxycarbonylation of the lithium enolate of **10**, generated by LDA, proceeded smoothly with methyl chloroformate in 86% yield. Subsequent Boc removal of compound **11** using TFA in dichloromethane gave the amination substrate **6h** in 78% yield.

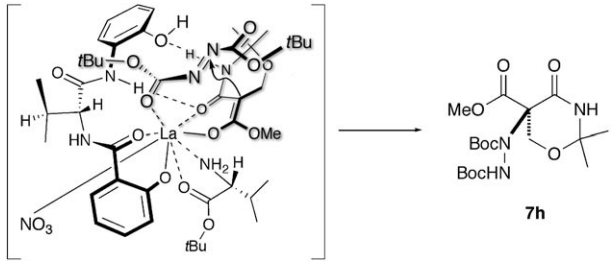
Further optimization of the catalytic asymmetric amination of **6h** was the next focus; the results are summarized in Table 1. The catalyst was prepared by mixing the three components of $La(NO_3)_3 \cdot 6H_2O$ (US$392.5/500 g, Aldrich),[13] amide-based ligand (*R*)-**L1**,[14] and D-valine *tert*-butyl ester H-D-Val-O*t*Bu in a ratio of 1:1:3 in ethyl acetate. The reaction temperature could be lowered from room temperature to 0 °C to increase the enantioselectivity to 96% *ee* while maintaining high catalytic efficiency (Table 1, entries 1 and 2). The absolute configuration of the amination product **7h** was temporarily assigned by analogy to other acyclic N-nonsubstituted α-alkoxycarbonyl amides, assuming that a similar transition state was operative for the lactam-type substrate **6h** (Scheme 7).[4c] The catalyst loading was successfully reduced to 3 mol% after an extended period of reaction time (Table 1, entry 3). In some cases, adjunctive triethylamine accelerated the reaction in this catalytic system by enhancing the formation of the La/(*R*)-**L1**/H-D-Val-O*t*Bu ternary

Table 1. Catalytic asymmetric amination of **6h** with $La(NO_3)_3$/(*R*)-**L1**/H-D-Val-O*t*Bu ternary catalyst.



	Cat. concentration [mol%]				*T* [°C]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
	w	*x*	*y*	*z*				
1	10	10	30	0	RT	3	90	84
2	10	10	30	0	0	3	96	96
3	3	3	9	0	0	24	83	92
4	3	3	9	9	0	24	81	88
5	3	3	12	0	0	24	92	95
6	2	2	8	0	0	24	76	82
7	0	10	30	0	0	24	trace	ND[c]
8	10	10	0	0	0	24	trace	ND[c]
9	10	0	30	0	0	24	63	4

[a] Yield of the isolated product. [b] Determined by chiral stationary phase HPLC analysis. [c] ND = not determined.

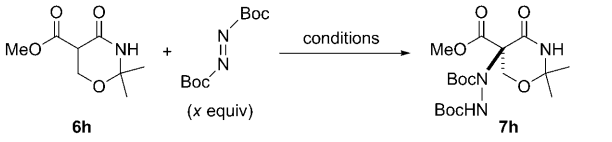


Scheme 7. Proposed transition state for the asymmetric amination of **6h** and the assumed absolute configuration of **7h**.

complex in equilibrium; however, this was not the case for this specific substrate (Table 1, entry 4). Instead, additional use of H-D-Val-O*t*Bu (4 equiv relative to La) increased both the chemical yield and the *ee* value, whereas at least 3 mol% of La was essential to achieve satisfactory catalytic efficiency (Table 1, entries 5 and 6). Further studies confirmed that every catalyst component $La(NO_3)_3 \cdot 6H_2O$, (*R*)-**L1**, and H-D-Val-O*t*Bu was indispensable for the promotion of the reaction with a high level of stereocontrol (Table 1, entries 7–9).

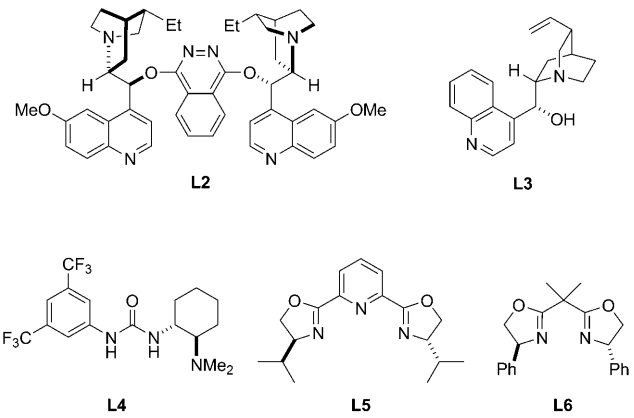
Taking the particular functional group arrangement of substrate **6h** into account, we examined the amination reaction of **6h** using other known organocatalysts and metal-based catalysts for asymmetric amination. A series of organocatalysts, **L2** (10 mol%, RT),[3k] **L3**; (20 mol%, −25°C),[3b] or **L4** (10 mol%, RT),[3d] were evaluated under the recommended reaction conditions; however, the catalytic efficiency was unsatisfactory, with no reaction at all being observed with **L2** or **L3**, and only 40% yield and 63% *ee* being obtained with **L4** (Table 2, entries 1–3). On the other hand, metal-based catalysts exhibited better performance in the amination. Catalyst **L5**[2f] (10 mol%) gave the desired product **7h** in 53% yield at −40°C, albeit with almost no

Table 2. Catalytic asymmetric amination of **6h** with known catalysts.



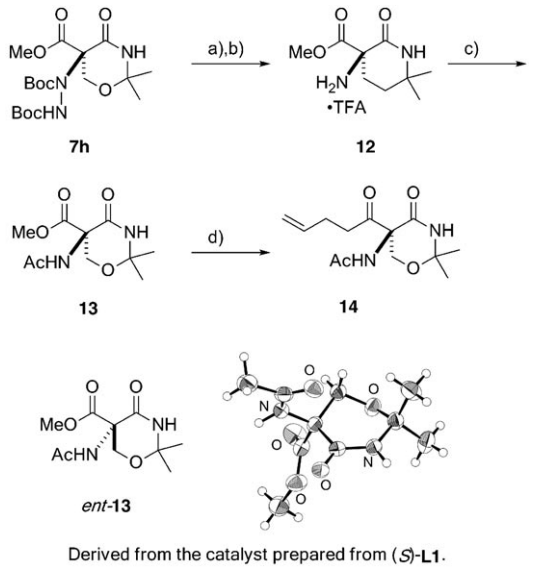
	x	Conditions	Yield [%]	*ee* [%]
1	1.0	**L2** (10 mol%), 1,1,2-trichloroethane, RT	0	ND
2	1.05	**L3** (20 mol%), CH_2Cl_2, −25°C	0	ND
3	0.91	**L4** (10 mol%), toluene, RT	40[a]	63[b]
4	1.6	$La(OTf)_3$/**L5** (10 mol%), CH_3CN, MS 4 Å, −40°C	53	1
5	1.2	$Cu(OTf)_2$/**L6** (10 mol%), CH_2Cl_2, RT	quant.	95

[a] Based on *tert*-butyl azodicarboxylate. [b] *ent*-**7h** was obtained as the major enantiomer.

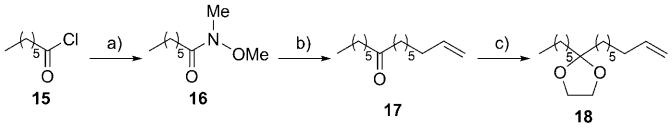


enantioselection (1% *ee*; Table 2, entry 4). Catalyst **L6** (10 mol%)[2a] gave the desired product **7h** in quantitative yield with 95% *ee* at room temperature (Table 2, entry 5), indicating that the Cu catalyst was similarly effective for the amination of **6h**.

Enantioselective total synthesis of mycestericin F and G: By harnessing metal coordination/hydrogen-bond cooperative catalysis for stereocontrol and substrate activation exerted by our ternary catalyst system, we succeeded in the asymmetric amination of the functionalized α-alkoxycarbonyl amides **6h** to afford amination product **7h** with the requisite functionality for the synthesis of mycestericins in high yield and excellent enantioselectivity with a minimum catalyst loading of 3 mol%. We then set out to achieve the enantioselective total synthesis of **3a** and **3b**. The di-Boc hydrazine moiety of **7h** was first converted into amine **12** in a two-step sequence (Scheme 8). Whereas an attempt at removing the Boc groups with a small excess (6 equiv) of TFA in dichloromethane led to the formation of considerable amounts of byproducts, a large excess (130 equiv) of TFA allowed clean conversion into the deprotected hydrazine TFA salt. The hydrogenative conditions used for cleavage of the N–N bond with Raney nickel were unsuccessful for this specific substrate.[15] Moreover, none of the transition-metal catalysts, including palladium on carbon,[16] palladium hydroxide,[17] or



Scheme 8. Conversion of the amination product **7h**. a) TFA, CH_2Cl_2, 0 °C, 3 h; b) H_2 (1 atm), Rh/C, MeOH, RT, 18 h, 96 %; c) acetyl chloride, Et_3N, CH_2Cl_2, RT, 98 %; d) vinylmagnesium bromide (10 equiv), CuCN, THF, −45 °C to RT, 18 h, 81 %.



Scheme 9. Synthesis of the aliphatic tail bearing a terminal olefin. a) MeONHMe·HCl, pyridine, CH_2Cl_2, RT, 3 h, 88 %; b) 7-octen-1-ylmagnesium bromide, THF, 0 °C, 2 h, 93 %; c) ethylene glycol, *p*-toluenesulfonic acid, toluene, reflux, 18 h, quant.

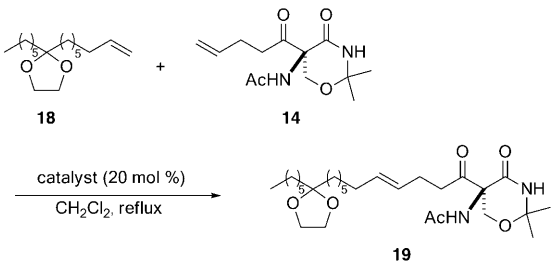
platinum oxide,[18] achieved the reaction. A two-step sequence of di-trifluoroacetylation/SmI_2 treatment[19] resulted in the formation of a complex reaction mixture. Eventually, the N−N bond cleavage was effected by using rhodium on carbon under a hydrogen atmosphere.[20] By using 30 wt % of 5 % Rh/C as catalyst, a mixture of starting material and amine **12** was obtained with concomitant formation of some byproducts, but with 60 wt % of the catalyst a very clean conversion was observed and amine **12** was obtained as the TFA salt[21] in 96 % overall yield from **7h**. The free amino group of **12** was then capped with an acetyl group to give **13** in 98 % yield before the subsequent alkylation. The absolute configuration was unequivocally determined at this stage by single-crystal X-ray crystallographic analysis of *ent*-**13**, which was derived from the catalyst prepared from (*S*)-**L1**.[22]

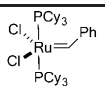
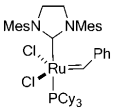
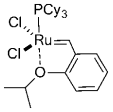
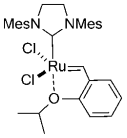
Installation of the 3-butenyl group at the ester carbonyl to provide γ,δ-unsaturated ketone **14**, which is a requisite handle for the attachment of the aliphatic tail of mycestericins, was the next focus. The multiple coordinative functional groups in the periphery of the ester carbonyl hampered the introduction of a C_4 alkyl chain. Moreover, potential overalkylation of the ester by using organometallic reagents to give a tertiary alcohol was also an issue that needed to be addressed. An attempted reaction using commercially available 3-butenylmagnesium bromide resulted in the formation of the desired product **14** in 30 % yield together with a number of byproducts, most notably the tertiary alcohol, because of overalkylation. We turned our attention to the use of a less sterically demanding nucleophile and applied the protocol reported by Lubell and co-workers, who developed a sequential addition of vinylmagnesium bromide on esters in the presence of a copper salt to afford the γ,δ-unsaturated ketones through collapse of the tetrahedral intermediate followed by selective 1,4-addition to the resulting vinyl ketone.[23] Ester **13** underwent twofold alkylation under Lubell's conditions with a slight modification, delivering the desired γ,δ-unsaturated ketone **14** in 81 % yield with 10 equivalents of vinylmagnesium bromide and a stoichiometric amount of copper(I) cyanide. When the amounts of Grignard reagent and copper(I) cyanide were reduced, the yield of **14** decreased significantly and the product was accompanied by the formation of unidentified byproducts.

The aliphatic tail group of mycestericins with a terminal olefin was synthesized in three steps from commercially available *n*-heptanoyl chloride (**15**) following the reported procedure (Scheme 9).[24] Formation of the Weinreb amide **16** followed by alkylation with freshly prepared 7-octen-1-ylmagnesium bromide gave the C_{15} linear chain **17**, with C=O and C=C functionalities at the requisite positions, in high yield. The ketone was protected as the dioxolane under standard conditions to give the aliphatic tail substrate **18** in quantitative yield, which was used for the coupling reaction. Cross-metathesis of **14**, which was composed of the polar head group attached to the aliphatic tail with the terminal olefin, with **18** was then examined (Table 3). Among the readily available Ru-based metathesis catalysts tested, the Grubbs first generation catalyst exhibited the best performance to give the coupling product **19**.[25] The NMR spectrum suggested that a trace amount of the coupling product with *Z*-configured olefin was also formed; however, the olefin geometry is not an issue for the synthesis of **3a** and **3b** with a saturated alkyl chain.

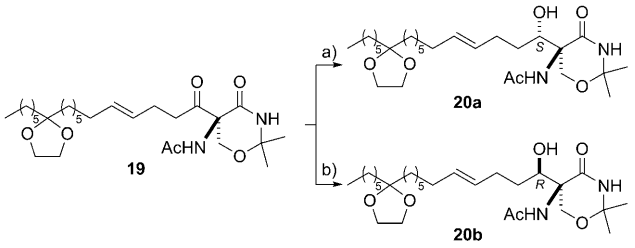
The next objective was the diastereoselective reduction of the ketone of **19**. We anticipated that the rigid structure of the neighboring six-membered lactam with densely located polar functional groups could induce high diastereoselectivity (Scheme 10). Hydride reduction with $NaBH_4$ in methanol either at room temperature or at 0 °C produced the desired homoallylic alcohol in favor of the *S*-configured secondary alcohol **20a** with 9:1 diastereoselectivity determined by ^1H NMR spectroscopic analysis of the crude mixture. Use of the sterically demanding L-selectride in THF at −78 °C significantly enhanced the diastereoselectivity to afford **20a** in 93 % yield as a single diastereomer. Chelate formation with $CeCl_3$ at the 1,3-dicarbonyl moiety altered the stereochemical course of the reduction with $NaBH_4$ to provide *R*-configured alcohol **20b**.[26] Whereas the reaction at room temperature in methanol gave the reduced product as a diastereo-

Table 3. Cross-metathesis of the polar head group **14** and the aliphatic tail group **18**.



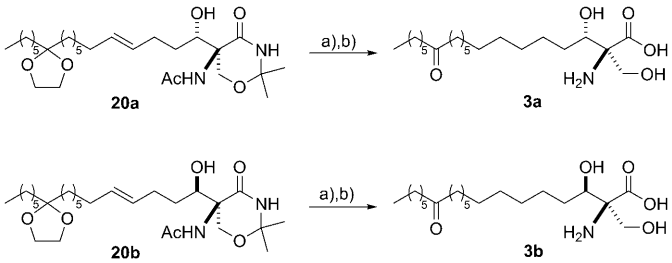
	Catalyst[a]	*t* [h]	Isolated yield [%]
1		24	62
2		18	46
3		24	54
4		18	46

[a] Mes = mesityl.



Scheme 10. Diastereoselective reduction of **19**. a) L-Selectride, −78 °C, THF, 93 %; b) $NaBH_4$ (1 equiv), $CeCl_3$ (10 equiv), MeOH, −78 °C, 91 %.

meric mixture in favor of **20b** (**20a**/**20b** = 35:65), isomer **20b** was obtained exclusively in 91 % yield without any trace of **20a** when the same transformation was performed at −78 °C. Both **20a** and **20b** were hydrogenated at room temperature under atmospheric pressure using palladium on charcoal to give **21a** and **21b**, with saturated alkyl chains, in quantitative yield (Scheme 11). Global deprotection and hydrolysis of the amides was achieved in a single-step procedure by treatment with 6 M aqueous hydrochloric acid at reflux temperature for 15 h. With this procedure, compounds **21a** and **21b** were successfully transformed into **3a** and **3b**, respectively. ^{1}H NMR spectra of the final products were in full accord with the reported data.[22]



Scheme 11. Final global deprotection to produce **3a** and **3b**. a) H_2 (1 atm), Pd/C, MeOH, RT, 18 h, quant (for **18a** and **18b**); b) aq 6 M HCl, reflux, 18 h, 61 % (for **3a**), 69 % (for **3b**).

Conclusion

We have achieved an efficient asymmetric total synthesis of mycestericin F (**3a**) and G (**3b**), which are sphingosine-like fungal metabolites that exhibit immunosuppressive activity. A lanthanum/amide-based ligand (*R*)-**L1**/H-D-Val-O*t*Bu ternary catalyst system for asymmetric amination developed by our group was crucial for the construction of the tetrasubstituted stereogenic center that is a requisite for this class of compounds. The design of an amination substrate **6h** with an α-alkoxycarbonyl amide motif with a *trans*-amide N−H, which is a privileged structural motif required for specific recognition by the catalyst, allowed for rapid stereoselective assembly of functional groups in the polar head group. Continuing efforts will be devoted to the synthesis of several analogues and sphingosines based on this synthetic methodology. The results, including biological evaluation, will be reported in due course.

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