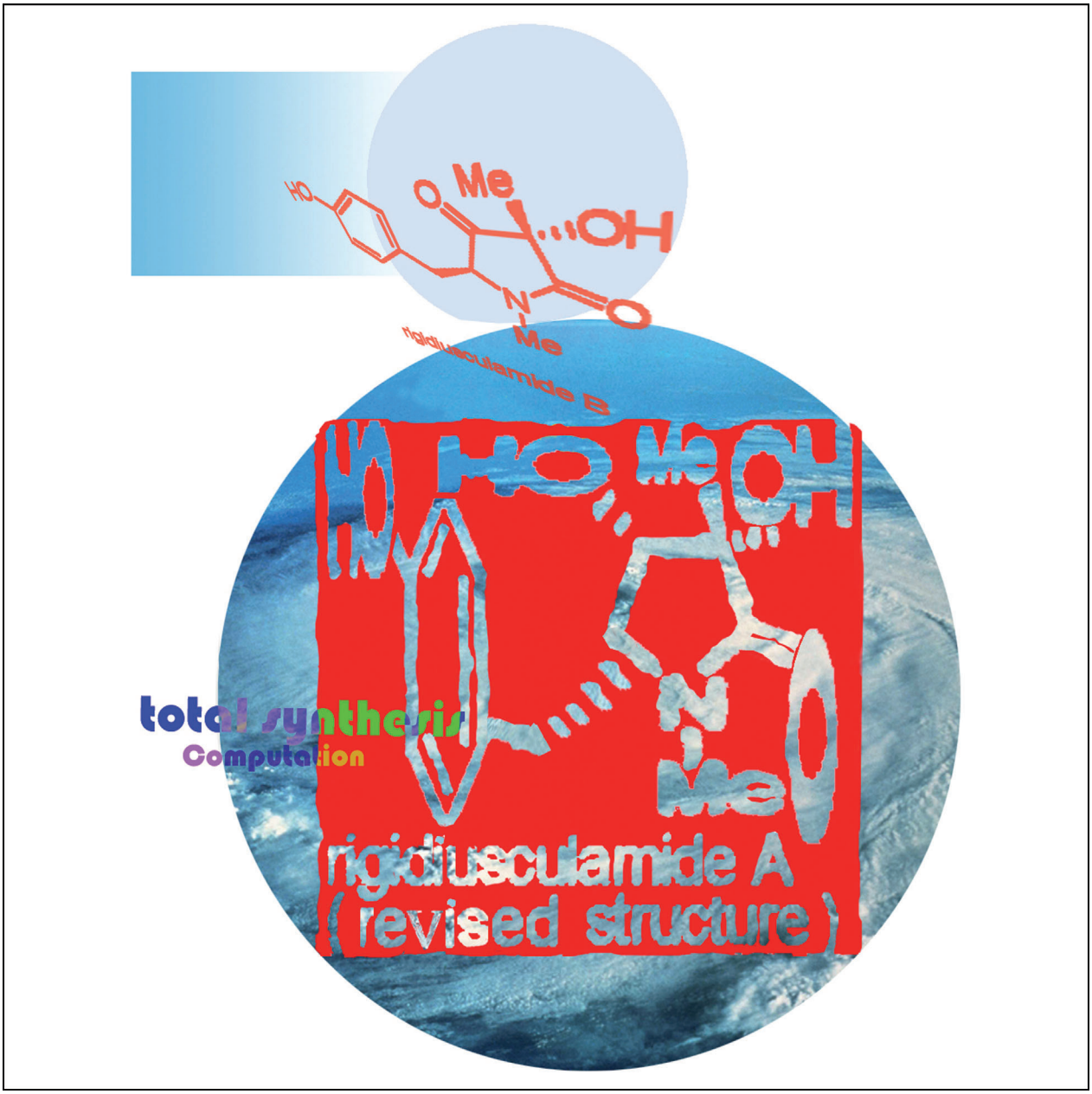
DOI: 10.1002/asia.201100809

Enantioselective Syntheses of Rigidiusculamides A and B: Revision of the Relative Stereochemistry of Rigidiusculamide A

Gui-Yang Chen, Huang Huang, Jian-Liang Ye, Ai-E Wang, Hui-Ying Huang, Hong-Kui Zhang, and Pei-Qiang Huang*[a]

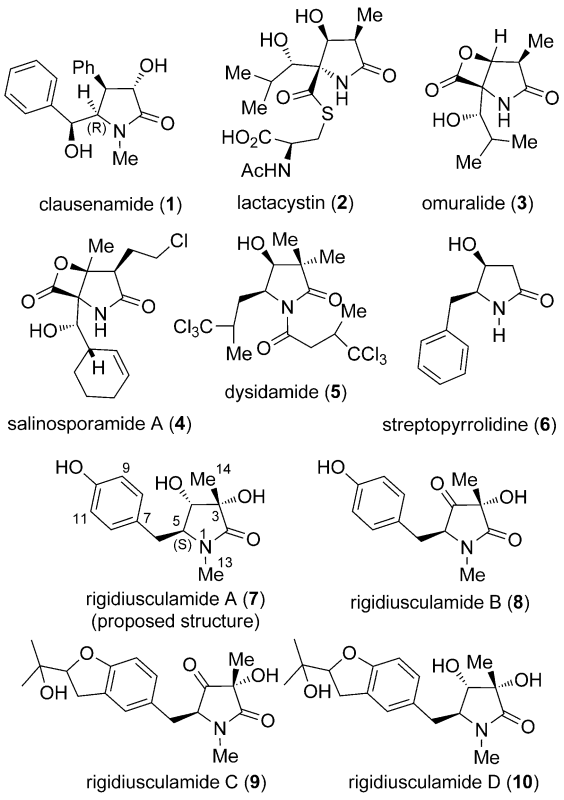


Abstract: The first enantioselective synthesis of cytotoxic natural products rigidiusculamides A (*ent*-**21**) and B (**8**) has been achieved by two synthetic routes. The first one is convergent based on the common intermediate **11**, obtained through a high yielding SmI_2-mediated Reformatsky-type reaction. A highly diastereoselective one-pot Dess–Martin periodinane-mediated bis-oxidation allowed the direct conversion of the diastereomeric mixture of **11** into rigidiusculamide B (**8**). Isolation of minor diastereomer **21**, in combination with computational work, allowed us to suggest the structure of the natural rigidiusculamide A to be *ent*-**21**, as synthesized by the second route. Four diastereomers (**7**, *ent*-**7**, **22a**, and **22b**) and an enantiomer (**21**) of rigidiusculamide A (*ent*-**21**) have been synthesized. On the basis of literature precedents and computational work, a biosynthetic pathway for rigidiusculamides A and B was proposed to account for the opposite configuration at C-5 of those two congeners.

Keywords: biosynthetic pathways · computational chemistry · natural products · structure elucidation · total synthesis

Introduction

Oxygenated pyrrolidines occur as key structural features in many bioactive natural products, such as azasugars,[1] tetramic acids (pyrrolidin-2,4-diones)/tetramates,[2] and γ-hydroxy-γ-lactams/γ-alkylidene-γ-lactams.[3] Although hydroxylated pyrrolidin-2-ones are not yet recognized as a distinct class of natural products, their bioactivity has attracted much attention. For example, clausenamide (**1**),[4] isolated from the leaves of *Clausena lansium* (*Lour*) Skeels, showed remarkable nootropic activity,[4b] and is under clinical trial for the treatment of Alzheimer's disease.[4c] Moreover, the discovery of lactacystin (**2**)[5] as a potent inhibitor of 20S proteosome[6] has aroused interest in research on hydroxylated pyrrolidin-2-ones (γ-lactams).[7–11] More and more bioactive hydroxylated γ-lactams have been isolated from sponges and microorganisms. The lactacystin series of lactams (omuralide (**3**),[6a,d] salinosporamides A–J,[7] and so on[8]) are of the most importance. Salinosporamide A (NPI-0052; **4**), which is a secondary metabolite of the marine actinomycete *Salinispora tropica*, is reported to be approximately thirty-five times more effective than omuralide as a proteosome inhibitor and is currently in clinical trials for the treatment of cancer.[9] On the other hand, in addition to the known dysidamide (**5**)[10a] and dysidamides B and C,[10b] which were isolated from the marine sponge *Dysidea herbacea*, five new members of polychlorinated pyrrolidinones have been isolated from the Red Sea marine sponge *Lamellodysidea herbacea*.[10c] The X-ray crystallographic diffraction analysis of compound **5** revealed the presence of two C-5 epimers in a ratio of 3:1. Structurally simple streptopyrrolidine (**6**), isolated from the fermentation broth of a marine *Streptomyces sp.* KORDI-3973 from the deep sea sediment,[5] was shown to significantly block capillary tube formation in cells.[11] Recently, Che and co-workers reported the isolation of rigidiusculamides A–D (**7**–**10**) from a crude extract of the ascomycete fungus *Albonectria rigidiuscula*,[12] and found that compounds **7** and **8** exhibited modest cytotoxicity against the human tumor cell lines HeLa and MCF-7. The structure and related stereochemistry of rigidiusculamide A were elucidated by NMR spectroscopy techniques, including NOESY, and the absolute stereochemistry was determined by the Snatzke circular dichroism technique.



In continuation of our studies on the asymmetric syntheses of bioactive *N*-containing heterocycles,[13] in particular, pyrrolidin-2-ones[14] and tetramic acids/tetramates,[15] we have been engaged in the total synthesis of rigidiusculamides A and B. We now report the results of this study, which include the first enantioselective and stereodivergent synthesis of rigidiusculamide B (**8**) and the proposed structure of

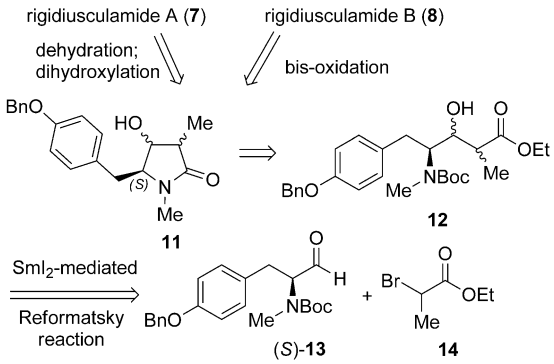
[a] G.-Y. Chen, H. Huang, Dr. J.-L. Ye, Dr. A.-E Wang, H.-Y. Huang, Prof. Dr. H.-K. Zhang, Prof. Dr. P.-Q. Huang
Department of Chemistry
and Key Laboratory for Chemical Biology of Fujian Province
College of Chemistry and Chemical Engineering
Xiamen University
Xiamen, Fujian 361005 (P.R. China)
Fax: (+86)-592-2186400
E-mail: pqhuang@xmu.edu.cn

rigidiusculamide A (**7**), as well as the revised structure of rigidiusculamide A (*ent*-**21**). On the basis of NMR spectroscopy and computation studies, the relative stereochemistry of the natural rigidiusculamide A was revised as 3*S*,4*S*,5*R*.

Results and Discussion

First Synthetic Route: Syntheses of Rigidiusculamide B (8) and the Proposed Structure of Rigidiusculamide A (7)

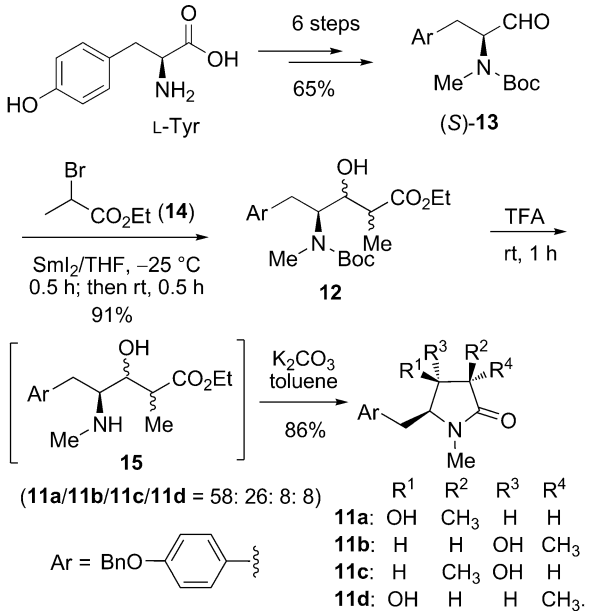
Our retrosynthetic analysis suggested (5*S*)-4-hydroxypyrrolidin-2-one (**11**) as a common intermediate for the synthesis of rigidiusculamides A and B (**7** and **8**; Scheme 1). Compound **11** would be available from compound **12** by cyclization, which in turn, could be accessed from **13** through either propionate enolate addition[16] or a Reformatsky reaction.[17,18] In view of the configurational instability of amino aldehydes,[16,19] the milder SmI_2-mediated[20] Reformatsky-type reaction[18] was envisioned for the coupling of aldehyde (*S*)-**13** and ethyl 2-bromopropionate (**14**).



Scheme 1. Retrosynthetic analysis of rigidiusculamide B (**8**) and the proposed structure of rigidiusculamide A (**7**). Bn = benzyl, Boc = *tert*-butyloxycarbonyl.

The configurationally labile α-amino aldehyde (*S*)-**13** was prepared by a known procedure from L-tyrosine in 65% overall yield.[21] For the Reformatsky reaction, the SmI_2-mediated version developed by Molander and Etter was used.[18a] By treating a solution of amino aldehyde (*S*)-**13** and **14** in tetrahydrofuran (THF) with a freshly prepared 0.1 M SmI_2[22] (4.0 equiv) in THF at −25 °C for 0.5 hours produced the desired product **12** as a diastereomeric mixture in 91% yield (Scheme 2). The ratio of the four diastereomers of compound **12** was not determined at this stage, but was deduced from their cyclization products **11a–d**.

As rigidiusculamides A and B were projected to be synthesized from **11** by dehydration–diastereoselective dihydroxylation and bis-oxidation, respectively, in principle, all four diastereomers of **11** can serve well for both purposes. Thus, all four diastereomers of **12** could be used in the next step without separation. Treatment of the diastereomeric mixture of **12** successively with TFA and K_2CO_3 in toluene provided pyrrolidin-2-one **11** in 86% yield. The four diastereomers of **11** could be separated into two fractions, **11a**/**11b** and **11c**/**11d**, in a ratio of 84:16 by flash column chromatography. ^1H NMR spectral analysis showed that the diastereomeric ratio of fraction **11a**/**11b** was 69:31 and that of the fraction **11c**/**11d** was 50:50. The diastereomeric ratio of **11** and its precursor **12** was thus determined to be 58:26:8:8.



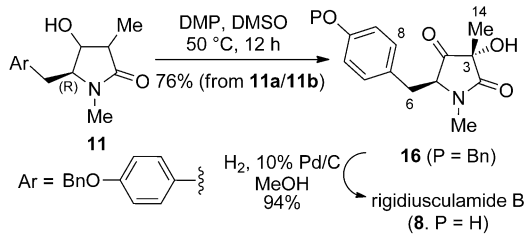
Scheme 2. Synthesis of pyrrolidin-2-one **11** by the SmI_2-mediated Reformatsky reaction. TFA = trifluoroacetic acid.

With the key intermediate **11** in hand, we first carried out the synthesis of **8**. For this purpose, both stereoselective α-hydroxylation and oxidation of the β-hydroxyl group were required. In connection with our recent interest in step-economy syntheses,[23,24] we anticipated to undertake a one-pot conversion of the diastereomeric mixture of **11** to **16**. In this context, Kirsch has reported[25] an 2-iodylbenzoic acid (IBX)-mediated one-pot α-hydroxylation of α-alkynyl alcohols.[26] In the total synthesis of decarbamoyloxysaxitoxin, Nagasawa and co-workers also attempted a one-pot β-hydroxyl oxidation/*N*-α-hydroxylation on a specific substrate by using IBX as an oxidant.[27]

To achieve our goal, and after unsuccessful trials with IBX, we elected to use Dess–Martin periodinane (DMP) as an oxidant.[28] It was hoped that the hydroxyl group could be oxidized by DMP to give a 1,3-dicarbonyl intermediate (tetramic acid), which would be further oxidized (hydroxylation) with DMP to give the desired product. To the best of our knowledge, hydroxylation with DMP has not been reported previously, whereas α-hydroxylation of 1,3-dicarbonyl compounds is well documented.[29] To our delight, exposure of the **11a**/**11b** fraction to DMP (4 equiv) in dimethylsulfoxide (DMSO) at 50 °C for 12 hours produced the desired compound **16** in 76% yield as the only isolable diastereomer (Scheme 3).

The relative stereochemistry of compound **16** was determined by NOESY experiments. The correlations between

CHEMISTRY
AN ASIAN JOURNAL



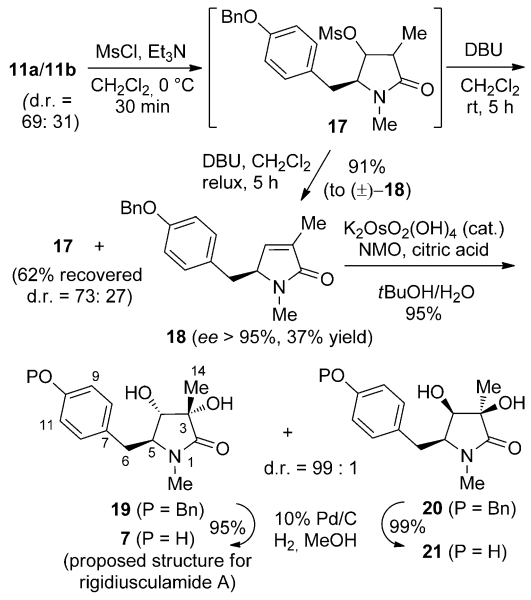
Scheme 3. Synthesis of rigidiusculamide B (**8**).

H-14 (Me at C-3), H-6, and H-8 indicated that the Me at C-3 and the benzyloxybenzyl group at C-5 were on the same face (see Figure S-2 in the Supporting Information). Thus, the configuration of compound **16** was determined to be 3*S*,5*S*. Catalytic hydrogenolysis of **16** (H_2, 1 atm, 10% Pd/C (cat.)) provided the *O*-debenzylation product **8** as a colorless oil in 94% yield. The physical ($[\alpha]_D^{20} = -20.2$ ($c = 1.0$, MeOH); lit.[12] $[\alpha]_D^{25} = -19.0$ ($c = 1.5$, MeOH)) and spectral data of **8** are identical to those reported for the natural rigidiusculamide B. Thus, both the structure and the stereochemistry of rigidiusculamide B (**8**) have been confirmed.

We next investigated the synthesis of the proposed structure of rigidiusculamide A (**7**). The diastereomeric mixture **11a**/**11b** (ratio: 69:31) was treated with methanesulfonyl chloride (MsCl)/Et_3N to give, after work up, crude mesylate **17**, which, without purification, was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2 equiv) in CH_2Cl_2 at reflux for 1.5 hours to afford racemic 3-pyrrolin-2-one[30] **18** in 91% yield (Scheme 4). To access to optically active product, the elimination reaction with DBU was first run in an ice-bath, then at room temperature for 5 hours, which gave the elimination product **18** in 37% yield (91% yield based on 62% of the recovered starting material **17**). The recovered mesylate was in a diastereomeric ratio of 73:27, which was similar to the original ratio of the starting mixture **11a**/**11b** (69:31). HPLC analysis of **18** on a chiral stationary phase showed that the enantiomeric excess (*ee*) of **18** ($[\alpha]_D^{20} = +146.6$ ($c = 1.0$, $CHCl_3$)) was at least 95% (see Figure S-9 in the Supporting Information).

We next turned our attention to the diastereoselective *cis*-dihydroxylation of **18**. For the diastereoselective *cis*-dihydroxylation of γ-substituted α,β-unsaturated lactams,[31,32] both Upjohn (OsO_4 (cat.), NMO, acetone/H_2O))[31a] and Mukaiyama conditions ($KMnO_4$, [18]crown-6, CH_2Cl_2)[32a] were generally adopted, both of which demonstrated complete *trans*-diastereoselectivity directed by the substituent at C-5 of the pyrrolidinones.[31b–d,32b,c] Recently, the Sharpless modification of the Upjohn procedure,[33] which uses easy to handle $K_2OsO_2(OH)_4$ as a catalytic oxidant, has shown great advantages in the *cis*-dihydroxylation of γ-substituted α,β-unsaturated lactams.[34] This high-yielding and highly diastereoselective method was then applied. Treatment of α,β-unsaturated lactam **18** with a catalytic amount of $K_2OsO_2(OH)_4$ (0.005 equiv), NMO (2.0 equiv), and citric acid (2.0 equiv) in *t*BuOH/H_2O (1:1, v/v) at room temperature for 8 hours produced diastereomer **19** in 94% yield, along with 1% of diastereomer **20**. Although vicinal coupling constants are usually used as an empiric rule to determine the related stereochemistry of simple 5-alkyl-4-hydroxypyrrolidin-2-ones, the observed anomalous small vicinal coupling constants[35] of H-4/H-5 ($J_{4,5} = 1.5$ Hz for *trans*-diastereomer **19**; $J_{4,5} = 3.5$ Hz for *cis*-diastereomer **20**) prevented a reliable assignment of the related stereochemistries of **19** and **20**. Compounds **19** and **20** were then debenzylated to give **7** and **21** in 95 and 99% yield, respectively, from which the related stereochemistries of **19** and **20** could be deduced.

A thorough structural study was undertaken on synthetic compounds **7** and **21**. The skeleton of **7** was first confirmed by NMR spectroscopy techniques (DEPT135, COSY, HSQC, and HMBC). The relative stereochemistries of compounds **7** and **21** were assigned by NOESY experiments. In the NOESY spectrum of **7** (Figure 1), the observed correlations between H-14 and H-6 as well as those between H-14 and H-4 indicated that the *p*-hydroxybenzyl group at C-5, Me at C-3 (H-14), and H-4 were on the same face, which established 3,4-*cis*-4,5-*trans* stereochemistry. The correlations between H-4/H-5 and H-4/H-14 (Me at C-3) shown in the NOESY spectrum of **21** indicate *all-cis* stereochemistry.



Scheme 4. Syntheses of the proposed structure of rigidiusculamide A (**7**) and its diastereomer **21**. NMO = *N*-methylmorpholine *N*-oxide.

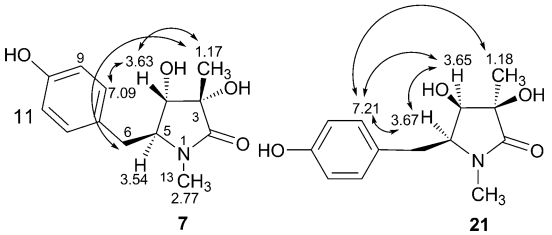


Figure 1. Observed key correlations in the NOESY spectra of compounds **7** and **21**.

The spectral data for synthetic compound **7** disagree with those reported for the natural rigidiusculamide A, although the magnitude of the optical rotation of **7** ($[\alpha]_D^{20}=+14.9$ ($c=$ 1.0, MeOH)) was in agreement with that of the natural rigidiusculamide A (lit.[12] $[\alpha]_D^{25}=-16.0$ ($c=0.1$, MeOH)). Nevertheless, both the optical rotation ($[\alpha]_D^{20}=+19$ ($c=0.1$, MeOH)) and spectral data of compound **21** were in agreement with those of the natural rigidiusculamide A, except the sense of optical rotation.

It is noteworthy that in work of Che et al. the 4,5-*trans* stereochemistry of rigidiusculamide A was assigned based on the observed NOEs between H-4 and Me at C-3 (H-14), as well as H-4 and benzene H-8.[12] However, no correlation between H_3-14 and H-6 has been reported, which is less convincing for the assignment. Indeed, quantum chemical calculations on the assumed structure, *ent*-**21**, at the B3LYP/6-31G* level showed that, in the most stable conformer of *ent*-**21** (Figure 2), the distance between H-4 and H-8, and H-4 and H_3-14 was only 2.961 and 2.645 Å, respectively, which is within the range of observable NOEs. Thus, the deduction of the 4,5-*trans* stereochemistry for rigidiusculamide A from only the correlations between H-4/H_3-14, and H-4/benzene H-8 by Che et al. might have led to the wrong conclusion.

On the basis of the above-mentioned evidence and considerations, natural rigidiusculamide A was tentatively deduced to have 3*S*,4*S*,5*R* configuration (*ent*-**21**).

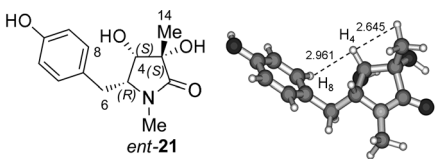
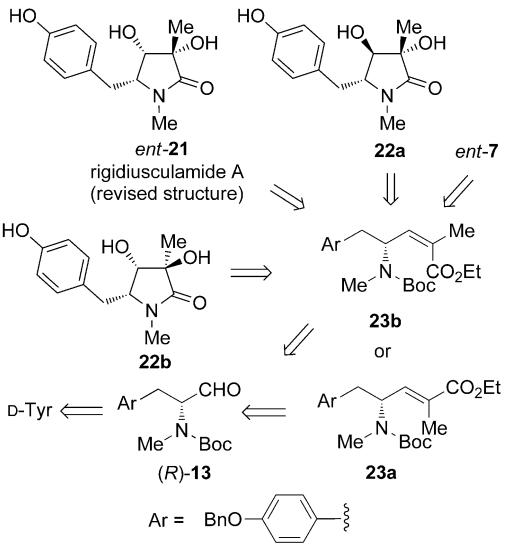


Figure 2. Structure and optimized stable conformer of *ent*-**21** at the B3LYP/6-31G* level.

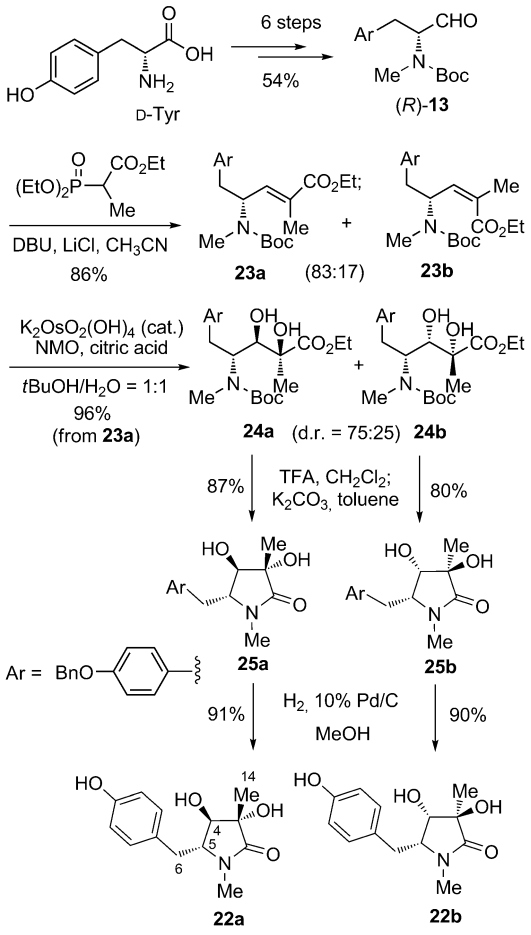
Second Synthetic Route: Synthesis of the Revised Structure of Rigidiusculamide A (*ent*-21) and Diastereomers *ent*-7 and 22a,b

To further confirm the structure of rigidiusculamide A, the synthesis of the revised structure of rigidiusculamide A (*ent*-**21**) and three diastereomers (**22a**,**b** and *ent*-**7**) by a new synthetic route was anticipated. The retrosynthetic analysis is outlined in Scheme 5 and features the use of the Horner–Wadsworth–Emmons (HWE) reaction and diastereoselective *cis*-dihydroxylation as the key steps.

The requisite protected α-amino aldehyde (*R*)-**13** was prepared from D-tyrosine by a known procedure.[21] The key HWE reaction was undertaken under Masamune–Roush conditions.[36] Thus, successive treatment of α-amino aldehyde (*R*)-**13** with LiCl/DBU and 2-(diethoxyphosphoryl)propanoate in CH_3CN at 0–5 °C for 3 hours produced the desired olefin as a separable geometric mixture of **23a** and **23b** in a ratio of 83:17 (determined by ^{1}H NMR spectroscopy) in 86% combined yield (Scheme 6). It should be mentioned that use of *n*BuLi as the base gave a poorer yield and



Scheme 5. Retrosynthetic analysis of the revised structure of rigidiusculamide A (*ent*-**21**) and other diastereomers.



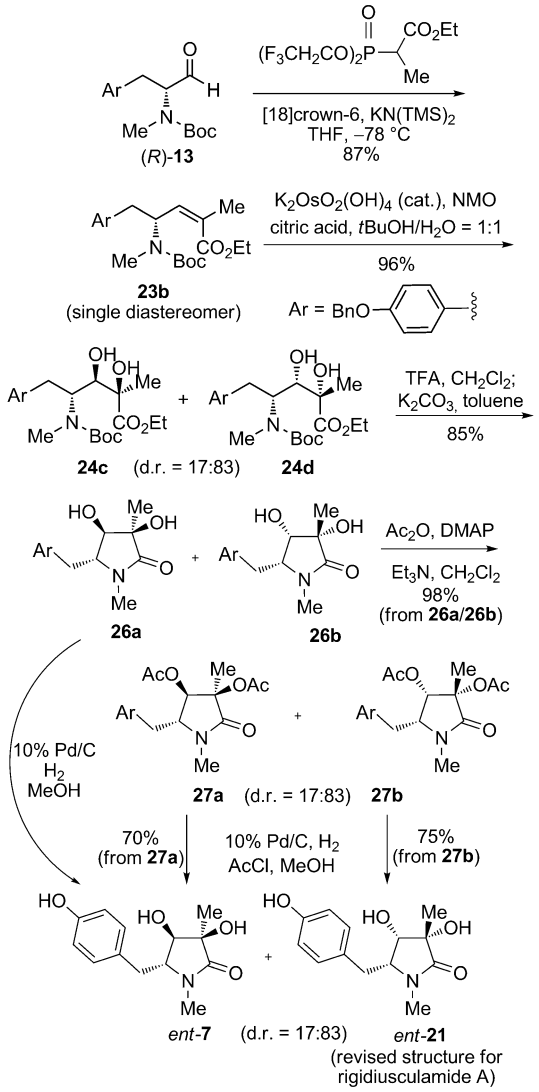
Scheme 6. Syntheses of two diastereomers (**22a**,**b**) of rigidiusculamide A.

stereoselectivity (45% yield, **23a**/**23b** = 67:33). The geometries of the olefins were determined by NOESY experi-

ments. A strong NOE correlation between the vinylic proton (at C-3) and methyl-H at C-2 was observed in the *Z* isomer, **23b**, whereas no similar correlation was observed for the *E* isomer, **23a**.

We next investigated the stereoselective *cis*-dihydroxylation of the major isomer (*E*)-**23a**. In sharp contrast to the cyclic cases for which excellent *trans* selectivities were always observed (see above), the catalytic *cis*-dihydroxylation of acyclic γ-amido-(*E*)-enoates with OsO_4/NMO showed variable stereochemistries with poor to modest diastereoselectivities.[37,38] The Sharpless asymmetric dihydroxylation usually showed decreased reaction rates with mixed results in terms of stereoselectivity.[37b,e–g,38] To get high stereoselectivities in such *cis*-dihydroxylations, aryl ketimine derivatives,[38a] bulky alkyl groups,[38b] and the OsO_4/*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) oxidation system[39] were introduced. For our particular substrate[37i] (*E*)-**23a**, the most convenient Sharpless modification of Upjohn conditions was applied.[33,34] A solution of (*E*)-**23a** in *t*BuOH/H_2O (1:1, v/v) was treated with $K_2OsO_2(OH)_4$ (cat.)/NMO in the presence of citric acid (2 equiv) and stirred for 8 hours to give **24a** and **24b** as a chromatographically separable 75:25 diastereomeric mixture in 96% combined yield (Scheme 6). The stereochemistry of the products were difficult to determine at this stage due to rotation of the Boc group, but could be deduced from derivatives **22a** and **22b** (see below). Cleavage of the *N*-Boc group in **24a** with TFA followed by treatment of the crude product with K_2CO_3 yielded the cyclization product **25a** in 87% yield, which gave **22a** after *O*-debenzylation (10% Pd/C, H_2; Scheme 6). The structure of **22a** was determined to be 3*S*,4*R*,5*R* by comprehensive NMR spectroscopy analysis (including ^1H, ^{13}C, DEPT135, COSY, and NOESY). In the NOESY spectrum of **22a** (see Figure S-5 in the Supporting Information), the observed correlations between H-4/H-6 and H-5/H-14 indicated that the *p*-hydroxybenzyl groups at C-5 and H-4 were on the same face. Thus, *all-trans* stereochemistry was established for **22a**. Except for the optical rotation data, the physical properties and spectral data for compound **22a** ($[\alpha]_D^{20} = -17.6$ ($c = 0.1$, MeOH)) are different from those of the natural product (lit.[12] $[\alpha]_D^{25} = -16.0$ ($c = 0.1$, MeOH)), thus implying that compound **22a** was not the natural product (rigidiusculamide A). By the same procedures, the minor diastereomer **24b** was converted into **22b**. A 3,4-*trans*-4,5-*cis* stereochemistry was revealed from the observed correlation between H-4/H-5 and H-6/H-14 in the NOESY spectrum of **22b** (see Figure S-5 in the Supporting Information). All physical ($[\alpha]_D^{20} = +5.5$ ($c = 0.9$, MeOH); lit.[12] $[\alpha]_D^{25} = -16.0$ ($c = 0.1$, MeOH)) and spectral data of compound **22b** are different from those of rigidiusculamide A, indicating that compound **22b** was also not the natural product (rigidiusculamide A).

We next focused on the synthesis of the revised structure of rigidiusculamide A (*ent*-**21**). For this purpose, the Still–Gennari *Z*-selective HWE reaction[40] was used for the stereoselective synthesis of (*Z*)-enoate **23b**. The carbanion generated in situ from ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate and $KN(TMS)_2$ in the presence of an excess of [18]crown-6 in THF at −78 °C, was treated with amino aldehyde (*R*)-**13** to produce (*Z*)-enoate **23b** as a single isomer in 87% yield (Scheme 7). As for the *cis*-dihydroxylation, mixed stereochemical outcomes[41] were usually obtained for



Scheme 7. Syntheses of the revised structure of rigidiusculamide A (*ent*-**21**) and diastereomer *ent*-**7**. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

N-Boc-protected γ-amino-(*Z*)-enoates with OsO_4/NMO as an oxidation system. By changing the *N*-protecting groups, stereoselection can be modulated.[42] In our case, the *cis*-dihydroxylation of (*Z*)-**23b** under Sharpless-modified Upjohn conditions[33,34] proceeded smoothly to give **24c** and **24d** (d.r. = 17:83, determined after bis-acetylation, see below) as a partially separable diastereomeric mixture in 96% yield, which, after removal of the *N*-protecting group, cyclized under basic conditions to afford the pyrrolidinones **26a/26b** as an inseparable diastereomeric mixture in 85% yield. *O*-Debenzylation of pyrrolidinones **26a/26b** gave two partially

separable diastereomers *ent*-**21** and *ent*-**7**. A sample of the major diastereomer *ent*-**21** was isolated, the physical and spectral data of which matched those reported for the natural rigidiusculamide A ($[\alpha]_D^{20}=-19.2$ ($c=1.0$, MeOH); lit.[12] $[\alpha]_D^{25}=-16.0$ ($c=0.1$, MeOH) for natural rigidiusculamide A), thereby demonstrating that *ent*-**21** is the natural rigidiusculamide A. To get complete separation of two diastereomers, the mixture of **26a/26b** was bis-acetylated to give **27a** and **27b** (d.r. = 17:83), which are separable by flash column chromatography. By comparing the coupling constants between H-4 and H-5 in two diastereomers (**27a**: $J_{4,5}=4.6$ Hz; **27b**: $J_{4,5}=6.0$ Hz), the stereochemistries of **27a** and **27b** were assigned as 4,5-*trans* and 4,5-*cis*, respectively, which was further confirmed by extensive NMR spectroscopy analysis (^{1}H, ^{13}C, DEPT135, COSY, and NOESY). There are correlations between H-4/H-14 (Me at C-3) and H-4/H-6 in the NOESY spectrum of **27a**, while the correlation between H-5/H-14 (Me at C-3) and H-5/H-4 were observed for diastereomers **27b** (Figure 3).

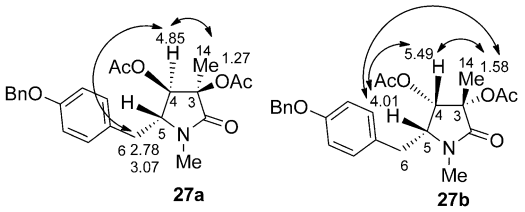


Figure 3. Observed characteristic correlations in the NOESY spectra of compounds **27a** and **27b**.

Catalytic hydrogenolysis of diastereomer **27a** under acidic conditions gave debenzylated and concomitantly deacetylated compound *ent*-**7** in 70% yield (Scheme 7). Similarly, compound *ent*-**21** was produced from diastereomer **27b**. Diastereomer *ent*-**21** showed correlations between H-4/H-14, H-5/H-14, H-4/H-5, and H-4/H-8 in the NOESY spectrum (Figure 4). The optical rotation ($[\alpha]_D^{20}=-19.2$ ($c=1.0$, MeOH); lit.[12] $[\alpha]_D^{25}=-16.0$ ($c=0.1$, MeOH)) and spectral data of *ent*-**21** were in agreement with those reported for the natural rigidiusculamide A. Thus, the stereochemistry of the natural rigidiusculamide A was revised as 3*S*,4*S*,5*R*.

At this stage, it is worthwhile to comment on the correlation between the coupling constants $J_{4,5}$ and the relative stereochemistry of 5-alkyl-4-hydroxypyrrolidin-2-ones. From the ^{1}H NMR spectroscopy data of all 5-alkyl-4-hydroxypyrrolidin-2-ones synthesized in this work, we can conclude without exception that the *cis* diastereomer always displays a larger coupling constant between H-4 and H-5 ($J_{4,5}$) than that of the corresponding *trans* diastereomer. This conclusion is in agreement with the previous empiric rule.[35] However, the values of $J_{4,5}$ may vary significantly from one to another molecule for polysubstituted *cis* (or *trans*) diastereomers.[38,42]

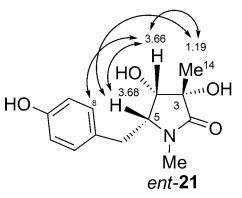
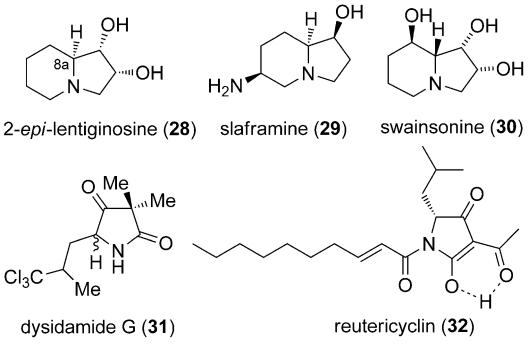


Figure 4. Observed characteristic correlations in the NOESY spectrum of compound *ent*-**21**.

With the structure of rigidiusculamide B (**8**) confirmed as 3*S*,5*S* and the stereochemistry of rigidiusculamide A revised as 3*S*,4*S*,5*R*, it is necessary to revise the biosynthesis of rigidiusculamides A–D proposed by Che et al.[12]

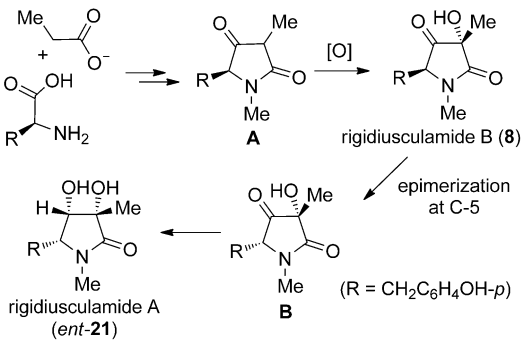
In fact, considerable efforts have been devoted to reveal the biosynthesis of oxygenated pyrrolidin-2-ones, including acyltetramic acids,[43] γ-hydroxy-γ-lactams/γ-alkylidene-γ-lactams,[3,44] and other hydroxylated γ-lactams.[45] In particular, several biosynthetic pathways involving epimerization have been suggested for different natural products. For example, epimerization has also been suggested to account for the different configuration at C-8a of swainsonine (**30**), relative to 2-*epi*-lentiginosine (**28**) and slaframine (**29**), all of which are produced by the fungus *Rhizoctonia leguminicola*.[46a] In addition, 2-*epi*-lentiginosine (**28**) has been reported to be a late intermediate in the biosynthesis of slaframine (**29**) and swainsonine (**30**) by Harris and co-workers.[46b] Epimerization at C-8a is apparently involved in the last stages of the biosynthesis of swainsonine, as well as in the oxidation of the piperidine ring.[47] Epimerization at C-5 might occur in the biosynthesis of natural dysidamide G (**31**), because it exists as a 3:1 C-5 epimeric mixture.[10c] Moreover, natural reutericyclin (**32**) is an *R* enantiomer,[48] whereas most naturally occurring tetramic acids possess an *S* configuration at C-5.[2]



Because rigidiusculamides A and B have the opposite configuration at C-5, and so might rigidiusculamides C and D, a simplified plausible biosynthetic pathway to rigidiusculamides A and B that involves an epimerization of tetramic acid derivative is suggested in Scheme 8. As outlined in Scheme 8, propionate-derived methylmalonyl coenzyme A (CoA)[45] first condenses with L-tyrosine to yield the tetramic acid derivative **A**,[43f,g] which is then oxidized to afford rigidiusculamide B (**8**). Rigidiusculamide B (**8**) could epimerize at C-5 to give intermediate **B**, which is reduced stereoselectively to produce the *all-cis* product rigidiusculamide A (*ent*-**21**). It is worth noting that the reduction of tetramic acids with $NaBH_4$ also gives 4,5-*cis*-lactams.[35a]

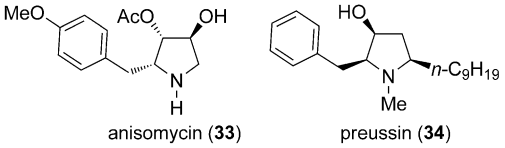
It is interesting that dysidamide (**5**) and dysidamides B–F also possess 4,5-*cis* stereochemistry.[10] Similar stereochemis-

CHEMISTRY
AN ASIAN JOURNAL

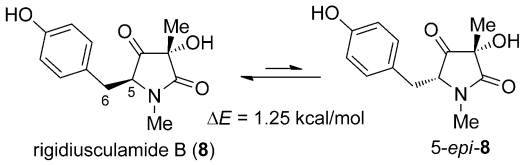


Scheme 8. A plausible biosynthesis of rigidiusculamides A and B.

try patterns can also be found in streptopyrrolidine (**6**),[11] anisomycin (**33**; first isolated from the fermentation broths of *Streptomyces griseolus* and *Streptomyces roseochromogenes*),[49] and preussin (**34**; a potent antifungal agent isolated from fermentation broths of *Preussia sp.* and *Aspergillus ochraceus*);[50] the last two actually possess relative 2,3-*cis* stereochemistry with opposite absolute configurations at those carbon atoms.



To test the feasibility of the suggested epimerization from **8** to intermediate **B**, the energy difference between **8** and 5-*epi*-**8** was calculated (Scheme 9). As the computational results at the B3LYP/6-31G* level showed, rigidiusculamide B (**8**) was more stable than 5-*epi*-**8** only by 1.25 kcal mol^{-1}, which, without taking kinetics into account, indicates that **8** and 5-*epi*-**8** exist in a ratio of 8:1. This deduction is essentially in agreement with the isolated yields of rigidiusculamides B and A (30 and 2 mg, respectively).[12] Thus, rigidiusculamide B (**8**) may be able to epimerize to intermediate **B** at room temperature. In fact, easy racemization of 5-alkyltetramic acids has been observed during the conversion of 5-alkyltetramic acids into the corresponding 5-alkyltetramates.[35a,51]



Scheme 9. Calculated energy difference between rigidiusculamide B (**8**) and 5-*epi*-**8** at B3LYP/6-31G* level.

Conclusion

Starting from L-tyrosine, a divergent enantioselective synthesis of rigidiusculamide B (**8**) and the proposed structure of rigidiusculamide A (**7**) has been achieved in 9 steps, and 32% overall yield; starting from D-tyrosine, the revised structure of the natural rigidiusculamide A (*ent*-**21**) has been synthesized by another synthetic route in 11 steps with 22% overall yield. Through this work, the configuration of **8** was confirmed to be 3*S*,5*S*. By comparing the four diastereomers (**7**, *ent*-**7**, **22a**, and **22b**) and the enantiomer (**21**) of rigidiusculamine A (*ent*-**21**), the stereochemistry of natural rigidiusculamide A was established to be 3*S*,4*S*,5*R* (*ent*-**21**) without any ambiguity. A plausible biosynthesis of rigidiusculamides A and B has been proposed to account for the opposite configuration at C-5 of these two congeners. In addition, we have demonstrated, for the first time, that DMP is an excellent reagent for the direct bis-oxidation of β-hydroxy carbonyl compounds to give, in one-pot, the α-hydroxylation/β-hydroxyl oxidation product in a highly diastereomeric manner, and the power of computational chemistry in many aspects of total synthesis.

Experimental Section

General

Optical rotations were recorded on a Perkin–Elmer 341 automatic polarimeter. ^{1}H and ^{13}C NMR data were acquired with Bruker (at 400 MHz or 600 MHz) or Varian (at 500 MHz) spectrometers by using solvent signals ([D$_6$]acetone: δ_H=2.05/δ_C=29.8 ppm, 206.1 ppm; [D$_6$]DMSO: δ_H=2.50 ppm; CD$_3$OD: δ_H=3.35 ppm; CDCl$_3$: δ_H=7.26/δ_C=77.0 ppm) as references.

Tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl. CH_2Cl_2 was distilled over calcium hydride under N_2. DMSO was distilled from calcium hydride. Column chromatography was performed on silica gel eluting with EtOAc/petroleum ether (PE; 60–90 °C, unless otherwise stated) and a mixture of EtOAc/hexane.

For molecules with Boc groups, ^{1}H and ^{13}C NMR spectra were complicated by rotation of the *N*-Boc moiety.

*Synthesis of Compound **12***

A mixture of freshly prepared (*S*)-**13**[21a] (739 mg, 2.0 mmol) and **14** (0.38 mL, 3.0 mmol) in THF (3 mL) was added to a 0.1 N solution of SmI_2 in THF (prepared freshly by the addition of iodine (2.98 g) to samarium powder (2.04 g) in THF (80 mL)) and stirred at 60 °C for 2–3 h before being cooled to −25 °C. The mixture was stirred for 10 min at −25 °C and warmed to room temperature over 0.5 h. The reaction was quenched with a 0.1 M aqueous solution of HCl (30 mL) and extracted with EtOAc (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE=1:3) to afford compound **12** as a colorless oil (857 mg, 91%) as a mixture of four diastereomers, which was used in the next step without further separation. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ=1.06–1.60 (m, 15H; *t*Bu, CH*CH*$_3$, and CH$_2$*CH*$_3$), 2.40–3.01 (m, 5H; N*CH*$_3$ and CH*CH*$_2$), 3.15–3.26 (m, 1.2H; *CH*CH$_2$ and *OH*), 3.60–3.90 (m, 0.8H; *OH*), 4.05–4.25 (m, 3H; *CH*$_2$CH$_3$ and CH$_2$*CH*CH), 5.05 (s, 2H; Ph*CH*$_2$), 6.85–6.95 (m, 2H; ArH), 7.05–7.20 (m, 2H; ArH), 7.26–7.45 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C, TMS): δ=9.3, 13.9, 14.0 (2C), 14.1, 15.2, 15.7, 27.9, 28.2, 33.6, 40.6, 53.3, 58.1, 60.6, 60.7, 60.8, 70.0, 79.6, 114.6, 114.7, 114.8, 127.3 (2C), 127.8, 128.4, 129.9 (2C), 130.0, 131.2, 137.1, 155.4, 155.9, 157.2, 157.3, 176.6 ppm; IR (film):

$\tilde{\nu}$ = 3458, 2977, 2933, 1731, 1692, 1668, 1511, 1454, 1391, 1367, 1242, 1177, 1026 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{37}NO_6Na$: 494.2519 $[M+Na]^+$; found: 494.2510.

Procedure for the Preparation of Compound ***11***

TFA (0.76 mL, 10.2 mmol) was added to a solution of **12** (0.32 g, 0.68 mmol) in CH_2Cl_2 (5 mL) and cooled on an ice/water bath. After being stirred for 1 h at room temperature, the excess acid was removed under reduced pressure to give the deprotected amine. The residue was dissolved in toluene (4 mL) and treated with K_2CO_3 (1.66 g, 12 mmol). The mixture was stirred overnight and then the solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE = 2:1) to give the diastereomeric mixtures of **11a/11b** (159 mg, 74%, d.r. = 69:31, determined by ^{1}H NMR spectroscopy) and **11c/11d** (31 mg, 12%, d.r. = 50:50, determined by ^{1}H NMR spectroscopy).

Mixture of ***11a/11b***

White solid; m.p. 116.7–118.6 °C (EtOAc/PE); IR (KBr): $\tilde{\nu}$ = 3375, 2923, 1666, 1611, 1511, 1454, 1401, 1241, 1025 cm^{-1}.

Compound ***11a***

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture): δ = 1.12 (d, *J* = 7.4 Hz, 2.1H; CCH_3), 2.25–2.36 (m, homodec at δ = 1.12 ppm gave a d, $J_{3,4}$ = 5.7 Hz, 0.7H; H-3), 2.67 (dd, *J* = 14.0, 5.4 Hz, 0.7H; H-6), 2.81 (s, 2.1H; NCH_3), 3.05 (dd, *J* = 14.0, 7.6 Hz, 0.7H; H-6), 3.51 (ddd, *J* = 7.6, 5.4, 5.1 Hz, 0.7H; H-5), 3.69 (dd, *J* = 5.7, 5.1 Hz, 0.7H; H-4), 5.03 (s, 1.4H; PhCH_2), 6.97 (d, *J* = 8.6 Hz, 1.4H; ArH), 7.12 (d, *J* = 8.6 Hz, 1.4H; ArH), 7.29–7.43 ppm (m, 3.5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture): δ = 14.2, 27.9, 37.4, 45.1, 67.0, 70.0, 77.0 (observed in ^{13}C DEPT135), 115.3, 127.4, 127.9, 128.7, 128.9, 130.1, 136.8, 157.7, 175.2 ppm.

Compound ***11b***

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) (data read form the spectrum of the mixture): δ = 1.09 (d, *J* = 7.5 Hz, 0.9H; CCH_3), 2.12–2.25 (m, homodec at δ = 1.09 ppm gave a d, $J_{3,4}$ = 5.6 Hz, 0.3H; H-3), 2.64 (dd, *J* = 14.1, 5.1 Hz, 0.7H; H-6), 2.84 (s, 0.9H; NCH_3), 3.05 (dd, *J* = 14.1, 7.8 Hz, 0.7H; H-6), 3.56 (dd, *J* = 7.8, 5.1 Hz, 0.3H; H-5), 4.07 (dd, *J* = 5.6, 5.1 Hz, 0.3H; H-4), 5.02 (s, 0.6H; PhCH_2), 6.91 (d, *J* = 8.6 Hz, 0.6H; ArH), 7.05 (d, *J* = 8.6 Hz, 0.6H; ArH), 7.29–7.43 ppm (m, 1.5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture): δ = 8.3, 28.6, 35.5, 40.0, 68.9, 71.2, 77.0 (observed in ^{13}C DEPT135), 115.1, 127.4, 127.9, 128.5, 128.9, 130.0, 136.8, 157.7, 175.3 ppm; MS (ESI): *m/z* (%): 348 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found: C 73.68, H 7.38, N 4.46.

Mixture of ***11c/11d***

White solid; m.p. 125.6–126.4 °C (EtOAc/PE); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.4, 13.2, 27.6, 28.9, 32.0, 32.8, 42.6, 43.4, 64.1, 64.3, 68.6, 70.0, 74.1, 115.0, 127.4, 127.9, 128.5, 129.4, 130.2, 130.3, 130.4, 136.9, 157.5 (2C), 175.4, 176.3 ppm; IR (KBr): $\tilde{\nu}$ = 3376, 2930, 1672, 1610, 1511, 1454, 1401, 1240, 1177, 1109, 1080, 1025 cm^{-1}; MS (ESI): *m/z* (%): 348 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found: C 73.68, H 7.38, N 4.46.

Compound ***11c***

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.19 (d, *J* = 7.4 Hz, 1.5H; CCH_3), 2.15–2.35 (m, homodec at δ = 1.19 ppm gave a d, $J_{3,4}$ = 5.1 Hz, 1.5H; H-3), 2.83 (s, 1.5H; NCH_3), 2.92–3.03 (m, 1H; H-6), 3.62 (ddd, *J* = 9.0, 6.6, 3.8 Hz; homodec at δ = 3.99 ppm gave a dd, $J_{5,6}$ = 9.0, 6.6 Hz, 0.5H; H-5), 3.94–4.04 (m, 0.5H; H-4), 5.04 (s, 1H; PhCH_2), 6.93 (d, *J* = 8.6 Hz, 1H; ArH), 7.23 (d, *J* = 8.6 Hz, 1H; ArH), 7.30–7.43 ppm (m, 2.5H; ArH).

Compound ***11d***

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.15 (d, *J* = 7.5 Hz, 1.5H; CCH_3), 2.67 (s, 1.5H; NCH_3), 2.80 (dd, *J* = 14.0, 6.6 Hz, 0.5H; H-6), 3.02–3.12 (m, 1H; H-6), 3.71 (ddd, *J* = 6.6, 6.6, 5.1 Hz; homodec at δ = 3.99 ppm gave a dd, $J_{5,6}$ = 6.6, 6.6 Hz, 0.5H; H-5), 3.94–4.04 (m, 0.5H; H-4), 5.03 (s, 1H; PhCH_2), 6.91 (d, *J* = 8.6 Hz, 1H; ArH), 7.20 (d, *J* = 8.6 Hz, 1H; ArH), 7.30–7.43 ppm (m, 2.5H; ArH).

Synthesis of Compound ***16***

DMP (550 mg, 1.28 mmol) was added to a stirred solution of a diastereomeric mixture **11a/11b** (105 mg, 0.32 mmol) in DMSO (1.5 mL) at room temperature. Then the mixture was stirred at 55 °C for 12 h. After cooling to room temperature, the reaction was quenched with H_2O (15 mL). The precipitate was filtered off and the filtrate was extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE = 2:1) to afford compound **16** as a white solid (83 mg, 76%). M.p. 185.2–186.4 °C (EtOAc/PE); $[\alpha]_D^{20}$ = −18.3 (*c* = 0.8 in acetone); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.49 (s, 3H; CCH_3), 2.99 (s, 3H; NCH_3), 3.02 (d, *J* = 4.3 Hz, 2H; H-6), 4.09 (t, *J* = 4.3 Hz, 1H; H-5), 4.96 (s, 2H; PhCH_2), 6.81 (d, *J* = 8.7 Hz, 2H; ArH), 6.85 (d, *J* = 8.7 Hz, 2H; ArH), 7.26–7.40 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.0, 28.4, 33.9, 67.8, 70.0, 70.8, 115.4, 126.6, 127.4, 128.0, 128.6, 131.0, 136.6, 158.2, 173.1, 208.1 ppm; IR (KBr): $\tilde{\nu}$ = 3305, 3030, 2924, 1777, 1672, 1610, 1511, 1252, 1125, 1039 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{20}H_{22}NO_4$: 340.1549 $[M+H]^+$; found: 340.1550.

Synthesis of Compound ***8***

A solution of **16** (25 mg) in MeOH (1 mL) was added to a suspension of 10% Pd/C (15 mg) in MeOH (1 mL). The mixture was stirred under 1 atm of hydrogen for 6 h at room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE = 3:1) to give **8** as a colorless oil (17 mg, 94%). $[\alpha]_D^{20}$ = −20.2 (*c* = 1.0 in MeOH) (lit.[12] $[\alpha]_D^{25}$ = −19.0 (*c* 1.5, MeOH)); ^{1}H NMR (500 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 0.52 (s, 3H; CCH_3), 3.01 (dd, *J* = 14.6, 4.4 Hz, 1H; H-6), 3.04 (s, 3H; NCH_3), 3.14 (dd, *J* = 14.6, 4.4 Hz, 1H; H-6), 4.22 (t, *J* = 4.4 Hz, 1H; H-5), 6.74 (d, *J* = 8.5 Hz, 2H; ArH), 6.89 ppm (d, *J* = 8.5 Hz, 2H; ArH); ^{13}C NMR (125 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 19.9, 28.1, 34.3, 68.0, 71.1, 116.1 (2C), 127.0, 132.0 (2C), 157.5, 173.3, 210.6 ppm; IR (film): $\tilde{\nu}$ = 3300, 2928, 1775, 1686, 1613, 1515, 1444, 1228, 1122 cm^{-1}; HRMS (ESI): *m/z* calcd (%) for $C_{13}H_{16}NO_4$: 250.1079 $[M+H]^+$; found: 250.1081.

Syntheses of Compounds ***17*** *and* ***18***

Freshly distilled Et_3N (98 μL, 0.72 mmol) and MsCl (28 μL, 0.36 mmol) were added successively to a solution of a diastereomeric mixture of **11a/11b** (40 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) and was cooled on an ice/water bath. After being stirred for 30 min, the reaction was quenched with an aqueous solution of $NaHCO_3$ and the organic phase was separated, and washed successively with water and brine. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mesylate **17** was used in the next step without further purification.

DBU (18 μL, 0.12 mmol) was added dropwise to a solution of the crude mesylate **17** in CH_2Cl_2 (3 mL) at 0 °C. The reaction was stirred for 5 h at room temperature, and then quenched with an aqueous solution of NH_4Cl at 0 °C. The mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE = 1:2) to give the recovered compound **17** (31 mg, 62%) and **18** (14 mg, 37%, 91% yield based on recovered **17**). The diastereomeric mixture of **11c/11d** was dehydrated in a similar manner to give the recovered compound **17** (55%) and **18** (37%, 82% yield based on recovered **17**).

Compound ***17***

Colorless oil; $[\alpha]_D^{20}=+29.7$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=0.95$ (d, $J=7.8$ Hz, 2.2 H; CHCH_3), 1.05 (d, $J=7.3$ Hz, 0.8 H; CHCH_3), 2.10 (dq, $J=7.3$, 3.2 Hz, 0.28 H; CH_3CH), 2.52 (dq, $J=7.8$, 3.2 Hz, 0.72 H; CH_3CH), 2.50–2.60 (m, 2.2 H; SO_2Me and CHCH_2), 2.63–2.75 (m, 1.8 H; SO_2Me and CHCH_2), 2.80–2.88 (m, 3.25 H; NMe and CHCH_2), 3.01 (dd, $J=14.3$, 4.8 Hz, 0.75 H; CHCH_2), 3.73–3.80 (m, 1 H; CH_2CH), 4.50 (dd, $J=2.8$, 2.8 Hz, 0.75 H; CHCHCH), 4.88 (d, $J=6.1$ Hz, 0.25 H; CHCHCH), 4.99 (s, 0.5 H; PhCH_2), 5.05 (s, 1.5 H; PhCH_2), 6.85–6.91 (m, 2 H), 6.97–7.05 (m, 2 H; ArH), 7.23–7.36 ppm (m, 5 H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=8.9$, 14.3, 18.3, 28.1, 28.4, 34.9, 36.1, 37.9, 38.6, 43.7, 58.2, 65.6, 66.8, 69.9, 79.6, 82.1, 115.4, 127.3, 127.4, 127.5, 127.9, 128.5, 130.2, 136.6, 157.9 (2 C), 173.3, 173.7 ppm; IR (film): $\tilde{\nu}=2934$, 1693, 1607, 1512, 1243, 1174, 1024 cm^{-1}; MS (ESI): m/z (%): 426 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{21}H_{25}NO_5S$: C 62.51, H 6.25, N 3.47; found: C 62.29, H 6.14, N 3.26.

Compound ***18***

Colorless oil; $[\alpha]_D^{20}=+146.6$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.83$ (t, $J=1.7$ Hz, 3 H; CHCCH_3), 2.51 (dd, $J=13.5$, 8.9 Hz, 1 H; CHCH_2), 3.01 (s, 3 H; NMe), 3.11 (dd, $J=13.5$, 5.2 Hz, 1 H; CHCH_2), 3.98 (ddd, $J=8.9$, 5.2, 1.8 Hz, 1 H; CHCH$_2$), 5.06 (s, 2 H; PhCH_2), 6.51 (dq, $J=1.8$, 1.7 Hz, 1 H; CCHCH), 6.92 (d, $J=8.6$ Hz, 2 H; ArH), 7.08 (d, $J=8.6$ Hz, 2 H; ArH), 7.31–7.45 ppm (m, 5 H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=11.2$, 27.6, 37.0, 63.4, 70.0, 114.9 (2 C), 127.4 (2 C), 127.9, 128.5 (2 C), 128.7, 130.1 (2 C), 135.2, 136.9, 139.5, 157.7, 171.9 ppm; IR (film): $\tilde{\nu}=2918$, 2847, 1677, 1640, 1503, 1387, 1250, 1026 cm^{-1}; MS (ESI): m/z (%): 330 (100) $[M^+$+Na]; HRMS (ESI): m/z calcd (%) for $C_{20}H_{21}NO_2Na$: 330.1470 $[M+Na]^+$; found: 330.1466.

Synthesis of Compound ***19***

Compound **18** (172 mg, 0.56 mmol) and citric acid (212 mg, 1.12 mmol) were dissolved in a 1:1 (v/v) mixture of *t*BuOH and H_2O (8.0 mL). Aqueous $K_2OsO_2(OH)_4$ (0.1 mL, 0.027 M) was added followed by NMO (130 mg, 1.12 mmol). The solution turned gray–green and, after stirring for 8 h at room temperature, a nearly colorless solution formed. At that point, the reaction was quenched with an excess of $Na_2S_2O_3$ (5.0 g). The solid was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE = 3:1) to give a product that was recrystallized from PE/EtOAc to give compound (3*S*,4*S*,5*S*)-**19** (178 mg, 94 %). The mother liquid was subjected to flash column chromatography to afford (3*R*,4*R*,5*S*)-**20** (ca. 1.6 mg, 1 %). White solid; m.p. 131.7–133.2 °C (EtOAc/PE); $[\alpha]_D^{20}=+12.5$ ($c=1.0$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.36$ (s, 3 H; CCH_3), 2.76 (dd, $J=14.4$, 8.2 Hz, 1 H; H-6), 2.80 (s, 3 H; NCH_3), 2.98 (dd, $J=14.4$, 6.0 Hz, 1 H; H-6), 3.31 (br s, 1 H; CHOH), 3.61 (ddd, $J=8.2$, 6.0, 1.5 Hz, 1 H; H-5), 3.72 (d, $J=1.5$ Hz, 1 H; H-4), 4.49 (br s, 1 H; COH), 5.05 (s, 2 H; PhCH_2), 6.94 (d, $J=8.4$ Hz, 2 H; ArH), 7.11 (d, $J=8.4$ Hz, 2 H; ArH), 7.30–7.43 ppm (m, 5 H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=23.8$, 29.0, 36.5, 67.3, 70.0, 73.2, 74.4, 115.2 (2 C), 127.4 (2 C), 128.0, 128.6 (2 C), 128.8, 130.1 (2 C), 136.8, 157.8, 175.0 ppm; IR (KBr): $\tilde{\nu}=3370$, 2927, 1678, 1610, 1511, 1241 cm^{-1}; MS (ESI): m/z (%): 364 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{20}H_{23}NO_4$: C 70.36, H 6.79, N 4.10; found: C 70.27, H 6.91, N 3.99.

Compound ***20***

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.26$ (s, 3 H; CCH_3), 2.86 (s, 3 H; NCH_3), 2.95 (dd, $J=13.1$, 5.0 Hz, 1 H; H-6), 3.09 (dd, $J=13.1$, 10.1 Hz, 1 H; H-6), 3.60 (ddd, $J=10.1$, 5.0, 3.5 Hz, 1 H; H-5), 3.72 (d, $J=3.5$ Hz, 1 H; H-4), 5.06 (s, 2 H; PhCH_2), 6.95 (d, $J=8.6$ Hz, 2 H; ArH), 7.30 (d, $J=8.6$ Hz, 2 H; ArH), 7.32–7.45 ppm (m, 5 H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): $\delta=21.4$, 27.9, 31.8, 62.5, 70.1, 71.7, 74.9, 115.0, 127.5, 128.0, 128.6, 129.2, 130.6, 137.0, 157.7, 175.4 ppm; IR (film): $\tilde{\nu}=3337$, 2930, 1678, 1610, 1512, 1241, 1075 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{20}H_{24}NO_4$: 342.1705 $[M+H]^+$; found: 342.1702.

Synthesis of Compound ***7***

Hydrogenolysis of **19** (18 mg, 0.05 mmol) by the procedure described for **8** produced compound **7**, the proposed structure for rigidiusculamide A (12 mg, 95 %), as a white solid. M.p. 175.9–178.0 °C (EtOAc/PE); $[\alpha]_D^{20}=+14.9$ ($c=1.0$ in MeOH); ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): $\delta=1.22$ (s, 3 H; CCH_3), 2.77 (s, 3 H; NCH_3), 2.78 (dd, $J=14.3$, 7.4 Hz, 1 H; H-6), 2.99 (dd, $J=14.3$, 5.6 Hz, 1 H; H-6), 3.54 (ddd, $J=7.4$, 5.6, 3.4 Hz, 1 H; H-5), 3.63 (d, $J=3.4$ Hz, 1 H; H-4), 6.78 (d, $J=8.5$ Hz, 2 H; ArH), 7.09 ppm (d, $J=8.5$ Hz, 2 H; ArH); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): $\delta=23.6$, 28.5, 36.6, 66.8, 73.5, 75.2, 116.1 (2 C), 128.8, 131.2 (2 C), 157.0, 175.1 ppm; MS (ESI): m/z (%): 274 (100) $[M+Na]^+$; IR (KBr): $\tilde{\nu}=3404$, 2926, 1672, 1615, 1516, 1407, 1242, 1065 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{13}H_{17}NO_4K$: 290.0795 $[M+K]^+$; found: 290.0793.

Synthesis of Compound ***21***

Hydrogenolysis of **20** (1.6 mg, 4.7×10^{-3} mmol) by the procedure described for **8** produced compound **21** (1 mg, 99 %) as a colorless oil. $[\alpha]_D^{20}=+19$ ($c=0.1$ in MeOH) (lit.[12] $[\alpha]_D^{25}=-16.0$ ($c=0.1$ in MeOH)); ^{1}H NMR (600 MHz, [D$_6$]acetone+D_2O, 25 °C, TMS): $\delta=1.25$ (s, 3 H; CCH_3), 2.76 (s, 3 H; NCH_3), 2.95–3.05 (m, 2 H; H-6), 3.73 (d, $J=4.4$ Hz, 1 H; H-4), 3.77 (dt, $J=7.4$, 4.4 Hz, 1 H; H-5), 6.81 (d, $J=7.9$ Hz, 2 H; ArH), 7.22 ppm (d, $J=7.9$ Hz, 2 H; ArH); ^{13}C NMR (125 MHz, [D$_6$]acetone, 25 °C, TMS): $\delta=21.7$, 28.0, 33.1, 63.1, 73.1, 75.2, 116.0 (2C), 129.7, 131.4 (2C), 156.8, 175.4 ppm; IR (film): $\tilde{\nu}=3381$, 2919, 1674, 1613, 1515, 1407, 1259, 1095 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{13}H_{17}NO_4Na$: 274.1055 $[M+Na]^+$; found: 274.1057.

Synthesis of Compounds ***23a/23b***

Method A: LiCl (404 mg, 9.63 mmol) and DBU (1.5 mL, 9.63 mmol) were added to a solution of ethyl 2-(diethoxyphosphoryl)propanoate (2.293 g, 9.63 mmol) in predried CH_3CN (39 mL). The reaction mixture was stirred at room temperature for 20 min until the LiCl dissolved completely. After being cooled to 0 °C, aldehyde (*R*)-**13** (1.423 g, 3.85 mmol) in CH_3CN (4 mL) was added dropwise by means of a syringe and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with an aqueous solution of NH_4Cl (30 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:30) to give **23a** (1.253 g, 72 %) and **23b** (250 mg, 14 %).

Method B: A solution of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate (26 mg, 0.075 mmol) and [18]crown-6 (100 mg, 0.38 mmol) in anhydrous THF (1.5 mL) was cooled to −78 °C under nitrogen and treated with $KN(TMS)_2$ (0.11 mL, 0.075 mmol, 0.7 M in toluene). The aldehyde (*R*)-**13** (28 mg, 0.075 mmol) was then added and the resulting mixture was stirred for 1 h at −78 °C. The reaction mixture was quenched with an aqueous solution of NH_4Cl (2 mL) and extracted with Et_2O (4 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:20) to give **23b** as a colorless viscous oil (30 mg, 87 %).

Compound ***23a***

Colorless viscous oil; $[\alpha]_D^{20}=+14.0$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.26$–1.34 (m, 12 H; *t*Bu and CH_2CH_3), 1.78 (s, 3 H; CCH_3), 2.75 (br s, 4 H; NCH_3 and CH_2CH), 2.88 (dd, $J=13.9$, 8.9 Hz, 1 H; CH_2CH), 4.20 (q, $J=7.0$ Hz, 2 H; CH_2CH_3), 5.03 (s, 2 H; PhCH_2), 5.04 (br m, 1 H; CH_2CHCH), 6.74 (dd, $J=8.4$, 1.4 Hz, 1 H; CH=C), 6.89 (d, $J=8.5$ Hz, 2 H; ArH), 7.09 (br s, 2 H; ArH), 7.31–7.43 ppm (m, 5 H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): $\delta=12.7$, 14.2, 28.2 (3 C), 29.3, 37.9, 55. 4, 60.7, 70.0, 79.6, 114.8 (2 C), 127.4 (2 C), 127.8, 128.5 (3 C), 130.0 (2 C), 130.7, 137.1, 138.4, 155.1, 157.5, 167.8 ppm; IR (film): $\tilde{\nu}=2975$, 2928, 1711, 1691, 1611, 1584, 1512, 1453, 1390, 1366, 1243, 1124, 1027, 862, 772, 743, 697 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{27}H_{35}NO_5Na$: 476.2413 $[M+Na]^+$; found: 476.2406.

*Compound **23b***

Colorless viscous oil; $[\alpha]_D^{20} = -63.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.26$–1.34 (m, 12H; *t*Bu and CH_2CH_3), 1.93 (s, 3H; CCH_3), 2.78 (br m, 5H; NCH_3 and CH_2CH), 4.21 (q, $J = 7.1$ Hz, 2H; CH_2CH_3), 5.02 (s, 2H; $PhCH_2$), 5.44 (br m, 1H; CH_2CHCH), 6.10 (br m, 1H; CH=C), 6.88 (d, $J = 8.6$ Hz, 2H; ArH), 7.14 (m, 2H; ArH), 7.28–7.42 ppm (m, 5H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.2$, 20.5, 28.3 (3C), 29.6, 37.7, 56.3, 60.3, 69.9, 79.2, 114.6 (2C), 127.3 (2C), 127.8, 128.4 (3C), 130.0 (2C), 130.6, 137.1, 138.9, 155.4, 157.3, 167.1 ppm; IR (film): $\tilde{\nu} = 2976$, 2927, 1710, 1690, 1611, 1584, 1512, 1453, 1390, 1366, 1229, 1130, 1026, 860, 774, 739, 697 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{27}H_{35}NO_5Na$: 476.2413 $[M+Na]^+$; found: 476.2409.

*Synthesis of Compounds **24a/24b***

N-Methylmorpholine oxide (566 mg, 2.95 mmol), citric acid (345 mg, 2.95 mmol), and aqueous $K_2OsO_2(OH)_4$ (0.3 mL, 0.027 M) were added to a solution of **23a** (668 mg, 1.47 mmol) in *t*BuOH/H_2O (1:1, 3 mL). The mixture was stirred at room temperature for 8 h (monitored by TLC). The reaction was quenched with $Na_2S_2O_3 \cdot 5H_2O$ and stirred for 0.5 h. After removing the solid by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 1:6) to give **24a** (514 mg, 72%) and **24b** (171 mg, 24%).

*Compound **24a***

Colorless viscous oil; $[\alpha]_D^{20} = +76.7$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.20$–1.46 (m, 15H), 2.04 (s, 1H), 2.38 (br s, 2H), 2.68–3.07 (m, 3H), 3.24 (br s, 1H), 3.59 (s, 1H), 4.12 (q, $J = 7.2$ Hz, 1H), 4.21–4.35 (m, 2H), 5.02 (s, 2H; $PhCH_2$), 6.89 (d, $J = 8.5$ Hz, 2H; ArH), 7.09 (d, $J = 8.5$ Hz, 2H; ArH), 7.29–7.43 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.1$, 20.9, 22.2, 28.3 (3C), 32.3, 56.6, 60.3, 62.0, 62.4, 70.0, 77.5, 114.7 (2C), 127.3 (2C), 127.4, 127.8, 128.4 (2C), 129.9 (2C), 137.1, 155.1, 157.2, 175.7 ppm; IR (film): $\tilde{\nu} = 3456$, 2977, 2931, 1732, 1690, 1666, 1611, 1584, 1511, 1454, 1391, 1366, 1242, 1175, 1024, 949, 863, 774, 739, 697 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{27}H_{37}NO_7Na$: 510.2468 $[M+Na]^+$; found: 510.2457.

*Compound **24b***

Colorless viscous oil; $[\alpha]_D^{20} = +71.3$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.12$–1.57 (m, 18H), 2.51 (br s, 2H), 2.72 (s, 1H), 2.85–2.92 (m, 1H), 3.58–3.80 (m, 2H), 4.23 (br m, 2H), 5.03 (s, 2H; $PhCH_2$), 6.89 (d, $J = 8.5$ Hz, 2H; ArH), 7.13 (d, $J = 8.5$ Hz, 2H; ArH), 7.29–7.43 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.0$, 21.0, 28.3 (3C), 30.6, 34.7, 56.0, 60.3, 61.9, 62.6, 70.0, 80.6, 114.8 (2C), 127.4 (2C), 127.8, 128.5 (2C), 129.8, 130.0 (2C), 137.1, 157.4, 158.1, 176.2 ppm; IR (film): $\tilde{\nu} = 3456$, 2978, 2932, 1730, 1692, 1664, 1612, 1512, 1454, 1393, 1367, 1243, 1176, 1148, 1025, 949, 863, 774, 737, 697 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{27}H_{37}NO_7Na$: 510.2468 $[M+Na]^+$; found: 510.2465.

*Synthesis of Compound **25a***

A solution of **24a** (163 mg, 0.33 mmol) in CH_2Cl_2 (1.7 mL) was cooled on an ice/water bath and TFA (0.51 mL, 30% CH_2Cl_2) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 3.5 h (monitored by TLC). The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in toluene (3.4 mL). The mixture was cooled with an ice/water bath and K_2CO_3 (455 mg, 3.3 mmol) was added. The reaction mixture was stirred at room temperature for 16 h (monitored by TLC). The reaction mixture was then concentrated under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 and H_2O. The reaction mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1:40) to give **25a** as a white solid (99 mg, 87%). M.p. 154–155 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20} = -36.8$ ($c = 1.0$ in MeOH); ^{1}H NMR (400 MHz, [D_6]DMSO+D_2O, 25 °C, TMS): $\delta = 1.07$ (s, 3H; CCH_3), 2.69 (s, 3H; NCH_3), 2.86 (dd, $J = 14.4$, 6.6 Hz, 1H; H-6), 2.92 (dd, $J = 14.4$, 5.4 Hz, 1H; H-6), 3.29 (ddd, $J = 6.6$, 5.4, 4.8 Hz, 1H; H-5), 3.59 (d, $J = 4.8$ Hz, 1H; H-4), 5.07 (s, 2H; $PhCH_2$), 6.96 (d, $J = 8.6$ Hz, 2H; ArH), 7.18 (d, $J = 8.6$ Hz, 2H; ArH), 7.29–7.50 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 18.6$, 28.0, 30.9, 36.9, 63.2, 70.1, 78.4, 115.3 (2C), 127.5 (2C), 128.0, 128.6 (2C), 128.9, 130.2 (2C), 136.9, 157.8, 175.2 ppm; IR (KBr): $\tilde{\nu} = 3453$, 2925, 1686, 1610, 1513, 1238, 990, 748, 700 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{20}H_{24}NO_4$: 364.1525 $[M+H]^+$; found: 364.1522.

*Synthesis of Compound **25b***

A solution of **24b** (50 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was cooled on an ice/water bath and TFA (0.15 mL, 30% CH_2Cl_2) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 3.5 h (monitored by TLC). The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in toluene (1 mL). The mixture was cooled on an ice/water bath and K_2CO_3 (140 mg, 1.0 mmol) was added. The reaction mixture was stirred at room temperature for 16 h (monitored by TLC). The reaction mixture was then concentrated under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 and H_2O. The reaction mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1:40) to give **25b** as a white solid (28 mg, 80%). M.p. 169–170 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20} = +6.5$ ($c = 0.5$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD+D_2O, 25 °C, TMS): $\delta = 1.31$ (s, 3H; CCH_3), 2.72 (s, 3H; NCH_3), 2.86 (dd, $J = 13.5$, 6.0 Hz, 1H; H-6), 3.04 (dd, $J = 13.5$, 8.5 Hz, 1H; H-6), 3.82 (d, $J = 6.0$ Hz, 1H; H-4), 3.93 (dt, $J = 8.5$, 6.0 Hz, 1H; H-5), 5.06 (s, 2H; $PhCH_2$), 6.94 (d, $J = 8.6$ Hz, 2H; ArH), 7.23 (d, $J = 8.6$ Hz, 2H; ArH), 7.34–7.43 ppm (m, 5H; ArH); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 18.9, 29.0, 33.5, 64.5, 71.0, 75.2, 77.8, 116.0 (2C), 128.5 (2C), 128.8, 129.5 (2C), 131.5 (2C), 131.9, 138.9, 158.9, 177.4 ppm; IR (KBr): $\tilde{\nu} = 3424$, 2924, 1702, 1613, 1514, 1254, 1060, 740, 669 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{20}H_{24}NO_4$: 364.1525 $[M+H]^+$; found: 364.1521.

*Synthesis of Compound **22a***

Compound **25a** (45 mg, 0.13 mmol) in MeOH (2 mL) was added to a suspension of 10% Pd/C (25 mg) in MeOH (2 mL). The mixture was stirred under 1 atm of hydrogen for 10 h at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1:20) to give compound **22a** as a white solid (30 mg, 91%). M.p. 194–196 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20} = -17.6$ ($c = 1.0$ in MeOH); ^{1}H NMR (500 MHz, [D_6]acetone, 25 °C, TMS): $\delta = 1.20$ (s, 3H; CCH_3), 2.76 (s, 3H; NCH_3), 2.94 (dd, $J = 13.5$, 6.8 Hz, 1H; H-6), 2.99 (dd, $J = 13.5$, 5.7 Hz, 1H; H-6), 3.42 (ddd, $J = 6.8$, 5.7, 4.9 Hz, 1H; H-5), 3.83 (dd, $J = 5.2$, 4.9 Hz, 1H; H-4), 4.21 (br m, 1H, D_2O exchangeable; COH), 4.32 (d, $J = 5.2$ Hz, 1H, D_2O exchangeable; $CHOH$), 6.80 (d, $J = 8.5$ Hz, 2H; ArH), 7.03 (d, $J = 8.5$ Hz, 2H; ArH), 8.19 ppm (s, 1H; ArOH); ^{13}C NMR (125 MHz, [D_6]acetone, 25 °C, TMS): $\delta = 19.0$, 28.3, 37.0, 66.1, 77.2, 77.7, 116.1 (2C), 129.6, 131.4 (2C), 156.9, 175.5 ppm; IR (KBr): $\tilde{\nu} =$ 3387, 2923, 1679, 1613, 1515, 1406, 1269, 1079, 619 cm^{-1}; HRMS (ESI): *m*/*z* calcd (%) for $C_{13}H_{17}NO_4Na$: 274.1055 $[M+Na]^+$; found: 274.1051.

*Synthesis of Compound **22b***

Compound **25b** (27 mg, 0.079 mmol) in MeOH (1 mL) was added to a suspension of 10% Pd/C (15 mg) in MeOH (1 mL). The mixture was stirred under 1 atm of hydrogen for 10 h at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1:20) to give **22b** as a white solid (18 mg, 90%). M.p. 193–195 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20} = +5.5$ ($c = 0.9$ in MeOH); ^{1}H NMR (500 MHz, [D_6]acetone, 25 °C, TMS): $\delta = 1.30$ (s, 3H; CCH_3), 2.66 (s, 3H; NCH_3), 2.82 (dd, $J = 13.6$, 6.0 Hz, 1H; H-6), 3.05 (dd, $J = 13.6$, 8.2 Hz, 1H; H-6), 3.87 (dt, $J = 13.6$, 6.0 Hz, 1H; H-5), 3.93 (t, $J =$

6.0 Hz; H-4), 4.23 (br m, 1H, D_2O exchangeable; C*OH*), 4.46 (d, J= 5.7 Hz, 1H, D_2O exchangeable; CH*OH*), 6.77 (d, J=8.5 Hz, 2H; ArH), 7.17 (d, J=8.5 Hz, 2H; ArH), 8.23 ppm (s, 1H; Ar*OH*); ^{13}C NMR (125 MHz, [D_6]acetone, 25 °C, TMS): δ=19.6, 28.6, 33.4, 63.8, 74.9, 77.0, 116.1 (2C), 130.5, 131.2 (2C), 156.8, 175.6 ppm; IR (KBr): $\tilde{\nu}$=3436, 2927, 1679, 1613, 1517, 1403, 1234, 1099, 830, 796 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{13}H_{17}NO_4Na$: 274.1055 [M+Na]$^+$; found: 274.1051.

*Synthesis of Compounds **24c** and **24d***

NMO (412 mg, 2.14 mmol), citric acid (450 mg, 2.14 mmol), and an aqueous solution of $K_2OsO_2(OH)_4$ (0.2 mL, 0.027 M) were added to a solution of **23b** (487 mg, 1.07 mmol) in *t*BuOH/H_2O (1:1, 3 mL). The mixture was stirred at room temperature for 8 h (monitored by TLC). The reaction was quenched with $Na_2S_2O_3$·5H_2O and stirred for 0.5 h. After removing the solid by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane=1:6) to give **24c/24d** as an inseparable mixture (500 mg, 96%, colorless viscous oil), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture, M=major diastereomer; m=minor diastereomer): δ=1.24–1.50 (m, 15H, M+m), 1.73 (s, 1H, M+m), 2.16–2.38 (m, 2H, M+m), 2.58–2.90 (m, 3H, M+m), 3.20–3.34 (m, 1H, M+m), 3.76–3.86 (m, 1H, M+m), 4.12–4.51 (m, 3H, M+m), 5.03 (s, 2H, M+m), 6.86–6.90 (m, 2H, M+m), 7.05–7.10 (m, 2H, M+m), 7.30–7.43 ppm (m, 5H, M+m); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture): δ=14.1, 24.0, 28.3 (3C), 33.5, 58.3, 61.7, 62.2, 70.0, 75.6, 80.6, 114.8 (2C), 127.4 (2C), 127.8, 128.5 (2C), 129.8, 129.9 (2C), 137.1, 157.2, 157.4, 175.7 ppm.

*Synthesis of Compounds **26a** and **26b***

TFA (0.35 mL, 30% CH_2Cl_2) was added dropwise to a cooled solution (ice/water bath) of the mixture **24c/24d** (115 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL). After 5 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 3.5 h. The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in toluene (2.4 mL). The mixture was cooled on an ice/water bath and K_2CO_3 (331 mg, 2.4 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure and resulting residue was dissolved in CH_2Cl_2 and H_2O. The reaction mixture was extracted with CH_2Cl_2 (5× 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1:40) to give **26a/26b** as an inseparable mixture (68 mg, 85%, white solid), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture, M=major diastereomer; m=minor diastereomer): δ=1.29 (s, 0.42H; CCH_3), 1.31 (s, 2.43H; CCH_3), 2.83 (s, 0.45H, m; NCH_3), 2.86 (s, 2.33H, M; NCH_3), 2.98 (dd, J=13.2, 5.0 Hz, 1H, M+m; H-6), 3.12 (dd, J=13.2, 10.1 Hz, 1H, M+m; H-6), 3.31 (s, 0.78H, M; *OH*), 3.45 (s, 0.16H, m; *OH*), 3.63 (ddd, J=10.1, 5.0, 2.6 Hz, 1H, M+m; H-5), 3.75 (d, J=2.6 Hz, 1H, M+m; H-4), 4.55 (s, 0.58H, M; *OH*), 4.66 (s, 0.19H, M; *OH*), 4.79 (s, 0.15H, m; *OH*), 5.08 (s, 2H, M+m; PhCH_2), 6.97 (d, J=8.6 Hz, 2H, M; ArH), 7.14 (d, J=8.6 Hz, 0.35H, m; ArH), 7.29 (d, J=8.6 Hz, 1.66H, M; ArH), 7.31–7.47 ppm (m, 5H, M+m; ArH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS) (data read from the spectrum of the mixture): δ=21.3, 23.8, 27.9, 31.9, 36.5, 62.6, 67.3, 70.0, 72.1, 73.3, 74.6, 74.9, 114.9, 115.2, 127.4, 127.9, 128.5, 128.9, 129.3, 130.1, 130.5, 137.0, 157.6, 175.9 ppm.

*Synthesis of Compounds ent-**21** and ent-**7***

The mixture of **26a/26b** (20 mg, 0.06 mmol) in MeOH (1 mL) was added to a suspension of 10% Pd/C (10 mg) in MeOH (1 mL). The mixture was stirred under 1 atm of hydrogen for 10 h at room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1:20) to give compounds *ent*-**21** and *ent*-**7** as a mixture (3 mg, 21%), from which a sample of *ent*-**21** was separated (10 mg, 69%) for characterization, and the remaining major part of the mixture was separated by acetylation.

*Compound ent-**21***

White solid; m.p. 182–183 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20}$=−19.2 (c=1.0 in MeOH) (lit.[12] colorless oil, $[\alpha]_D^{25}$=−16.0 (c=0.1 in MeOH)); ^{1}H NMR (500 MHz, [D_6]acetone+D_2O, 25 °C, TMS): δ=1.19 (s, 3H; CCH_3), 2.70 (s, 3H; NCH_3), 2.92 (dd, J=13.3, 5.6 Hz, 1H; H-6), 2.97 (dd, J=13.3, 8.6 Hz, 1H; H-6), 3.66 (d, J=4.4 Hz, 1H; H-4), 3.68 (ddd, J=8.6, 5.6, 4.4 Hz, 1H; H-5), 6.75 (d, J=8.5 Hz, 2H; ArH), 7.17 ppm (d, J=8.5 Hz, 2H; ArH); ^{13}C NMR (125 MHz, [D_6]acetone, 25 °C, TMS): δ=21.8, 28.0, 33.1, 63.2, 73.2, 75.2, 116.0 (2C), 129.8, 131.4 (2C), 156.8, 175.5 ppm; IR (KBr): $\tilde{\nu}$=3415, 2925, 1665, 1613, 1517, 1403, 1235, 1090, 848, 792, 713, 628 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{13}H_{17}NO_4Na$: 274.1055 [M+Na]$^+$; found: 274.1048.

*Synthesis of Compounds **27a** and **27b***

Triethylamine (0.10 mL, 0.66 mmol) was added dropwise to a solution of mixture of **26a/26b** (50 mg, 0.15 mmol) and DMAP (15 mg (cat.)) in CH_2Cl_2 (3.7 mL). The reaction was cooled on an ice/water bath and Ac_2O (0.06 mL, 0.59 mmol) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane=1:4) to give **27a** (10 mg, 16%) and **27b** (51 mg, 82%).

*Compound **27a***

Colorless oil; $[\alpha]_D^{20}$=+32.6 (c=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=1.27 (s, 3H; CCH_3), 1.84 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 2.78 (dd, J=14.0, 7.3 Hz, 1H; H-6), 2.94 (s, 3H; NCH_3), 3.07 (dd, J=14.0, 4.6 Hz, 1H; H-6), 3.73 (dt, J=7.3, 4.6 Hz, 1H; H-5), 4.85 (d, J=4.6 Hz, 1H; H-4), 5.04 (s, 2H; PhCH_2), 6.90 (d, J= 8.5 Hz, 2H; ArH), 7.07 (d, J=8.5 Hz, 2H; ArH), 7.29–7.42 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=20.1, 20.4, 23.1, 28.7, 36.5, 64.1, 69.9, 73.5, 77.3, 115.1 (2C), 127.3 (2C), 127.6, 127.9, 128.5 (2C), 130.6 (2C), 136.8, 157.8, 169.5, 169.6, 171.6 ppm; IR (film): $\tilde{\nu}$= 2924, 1747, 1711, 1610, 1512, 1243, 1072, 902, 798, 696 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{24}H_{27}NO_6Na$: 448.1736 [M+Na]$^+$; found: 448.1737.

*Compound **27b***

Colorless oil; $[\alpha]_D^{20}$=−11.2 (c=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=1.58 (s, 3H; CCH_3), 2.00 (s, 3H; CH_3CO), 2.08 (s, 3H; CH_3CO), 2.76 (s, 3H; NCH_3), 2.94 (d, J=6.4 Hz, 2H; H-6), 4.01 (dd, J=13.2, 6.4 Hz, 1H; H-5), 5.04 (s, 2H; PhCH_2), 5.49 (d, J=6.4 Hz, 1H; H-4), 6.91 (d, J=8.6 Hz, 2H; ArH), 7.10 (d, J=8.6 Hz, 2H; ArH), 7.30–7.43 ppm (m, 5H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=20.4, 20.9, 20.9, 29.0, 32.8, 60.5, 70.0, 71.7, 78.7, 115.1 (2C), 127.4 (2C), 127.9, 128.5 (2C), 129.4, 129.6 (2C), 136.8, 157.5, 169.1, 169.2, 171.0 ppm; IR (film): $\tilde{\nu}$=2928, 1754, 1709, 1610, 1512, 1239, 1072, 859, 740, 698 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{24}H_{27}NO_6Na$: 448.1736 [M+Na]$^+$; found: 448.1739.

*Synthesis of Compound ent-**7** (by Deacetylation of **27a**)*

Compound **27a** (10 mg, 0.023 mmol) in MeOH (0.5 mL) was added to a suspension of 10% Pd/C (10 mg) in MeOH (0.5 mL). The reaction was cooled on an ice/water bath and AcCl (0.05 mL, 0.69 mmol) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was stirred under 1 atm of hydrogen for 10 h at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1:20) to give compound *ent*-**7** (4 mg, 70%).

*Compound ent-**7***

Colorless oil; $[\alpha]_D^{20}$=−12.9 (c=1.0 in MeOH); ^{1}H NMR (400 MHz, [D_6]acetone+D_2O, 25 °C, TMS): δ=1.22 (s, 3H; CCH_3), 2.75 (s, 3H;

NCH_3), 2.77 (dd, J=14.3, 7.4 Hz, 1H; H-6), 2.97 (dd, J=14.3, 5.6 Hz, 1H; H-6), 3.54 (ddd, J=7.4, 5.6, 3.4 Hz, 1H; H-5), 3.62 (d, J=3.4 Hz, 1H; H-4), 6.77 (d, J=8.5 Hz, 2H; ArH), 7.09 ppm (d, J=8.5 Hz, 2H; ArH); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ=23.7, 28.5, 36.9, 67.0, 73.6, 75.6, 116.3 (2C), 129.2, 131.3 (2C), 157.1, 174.6 ppm; IR (film): $\tilde{\nu}$=3331, 2923, 1666, 1613, 1592, 1515, 1384, 852, 790 cm^{-1}; HRMS (ESI): m/z calcd (%) for $C_{13}H_{17}NO_4Na$: 274.1055 $[M+Na]^+$; found: 274.1051.

*Synthesis of Compound ent-**21** (by Deacetylation of **27b**)*

Compound **27b** (40 mg, 0.094 mmol) in MeOH (1.5 mL) was cooled to 0 °C on an ice/water bath and added to a suspension of 10% Pd/C (20 mg) in MeOH (1.5 mL). Subsequently, AcCl (0.2 mL, 2.76 mmol) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was stirred under 1 atm of hydrogen for 10 h at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1:20) to give *ent*-**21** as a white solid (20 mg, 75%).

Acknowledgements

We are grateful to the National Basic Research Program (973 Program) of China (grant no. 2010CB833200), the NSF of China (20832005, 21072160), the NFFTBS (no. J1030415), and the NSF of Fujian Province of China (2011J01056) for financial support. We thank Dr. Zhi-Hong Guo for valuable discussions. We also thank Ming-Gui Lin for assistance in the preparation of some starting materials.

[1] For leading reviews on synthesis and biological activities, see: a) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; b) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295; c) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625–649; d) B. G. Winchester, *Tetrahedron: Asymmetry* **2009**, *20*, 645–651.

[2] For reviews on isolation and synthesis of tetramic acids/tetramates, see: a) B. J. L. Royles, *Chem. Rev.* **1995**, *95*, 1981–2001; b) E. L. Ghisalberti in *Studies in Natural Products Chemistry*, *Vol. 28*, **2003**, pp. 109-163; c) R. Schobert, A. Schlenk, *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221; for a special example, see: d) A. Höltzel, M. G. Gänzle, G. J. Nicholson, W. P. Hammes, G. Jung, *Angew. Chem.* **2000**, *112*, 2886–2888; *Angew. Chem. Int. Ed.* **2000**, *39*, 2766–2768; for selected recent syntheses, see: e) Y. Jin, Y. Liu, Z. Wang, S. Kwong, Z. Xu, T. Ye, *Org. Lett.* **2010**, *12*, 1100–1103; f) S. Suntornchashwej, K. Suwanborirux, M. Isobe, *Tetrahedron* **2007**, *63*, 3217–3226; g) Z. Gu, A. Zakarian, *Angew. Chem.* **2010**, *122*, 9896–9899; *Angew. Chem. Int. Ed.* **2010**, *49*, 9702–9705; h) E. A. Ilardi, A. Zakarian, *Chem. Asian J.* **2011**, *6*, 2260–2263.

[3] For a review, see: B. Nay, N. Riache, L. Evanno, *Nat. Prod. Rep.* **2009**, *26*, 1044–1062.

[4] For isolation, see: a) M.-H. Yang, Y.-Y. Chen, L. Huang, *Phytochemistry* **1988**, *27*, 445–450; for a review on bioactivities, see: b) X. Z. Zhu, X.-Y. Li, J. Liu, *Eur. J. Pharmacol.* **2004**, *500*, 221–230; c) J. J. Xue, X. M. Yu, *Chin. Chem. Lett.* **2011**, *22*, 761–764; for a recent synthesis, see: d) L. Yang, D.-X. Wang, Q.-Y. Zheng, J. Pan, Z.-T. Huang, M.-X. Wang, *Org. Biomol. Chem.* **2009**, *7*, 2628–2634.

[5] For isolation, see: a) S. Omura, T. Fujimoto, K. Otoguro, K. Matsuzaki, R. Moriguchi, H. Tanaka, Y. Sasaki, *J. Antibiot.* **1991**, *44*, 113–116; b) S. Omura, K. Matsuzaki, T. Fujimoto, K. Kosuge, T. Furuya, S. Fujita, A. Nakagawa, *J. Antibiot.* **1991**, *44*, 117–118.

[6] a) E. J. Corey, W.-D. Z. Li, *Chem. Pharm. Bull.* **1999**, *47*, 1–10 (review); b) E. J. Corey, G. A. Reichard, R. Kania, *Tetrahedron Lett.* **1993**, *34*, 6977–6980; c) E. J. Corey, G. A. Reichard, *J. Am. Chem. Soc.* **1992**, *114*, 10677–10678; d) G. Fenteany, R. F. Standaert, G. A. Reichard, E. J. Corey, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 3358–3362.

[7] For isolation, see: a) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem.* **2003**, *115*, 369–371; *Angew. Chem. Int. Ed.* **2003**, *42*, 355–357 (salinosporamide A); b) P. G. Williams, G. O. Buchanan, R. H. Feling, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2005**, *70*, 6196–6203 (salinosporamides B, C); c) K. A. Reed, R. R. Manam, S. S. Mitchell, J. Xu, S. Teisan, T.-H. Chao, G. Deyanat-Yazdi, S. T. C. Neuteboom, K. S. Lam, B. C. M. Potts, *J. Nat. Prod.* **2007**, *70*, 269–276 (salinosporamides D–J); for selected recent total syntheses, see: d) N. Satoh, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2011**, *13*, 3028–3031; e) H. Nguyen, G. Ma, T. Gladysheva, T. Fremgen, D. Romo, *J. Org. Chem.* **2011**, *76*, 2–12; f) Y. Kaiya, J. Hasegawa, T. Momose, T. Sato, N. Chida, *Chem. Asian J.* **2011**, *6*, 209–219; g) T. Fukuda, K. Sugiyama, S. Arima, Y. Harigaya, T. Nagamitsu, S. Omura, *Org. Lett.* **2008**, *10*, 4239–4242; h) A. Endo, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 8298–8299.

[8] a) R. R. Manam, V. R. Macherla, G. Tsueng, C. W. Dring, J. Weiss, S. T. C. Neuteboom, K. S. Lam, B. C. Potts, *J. Nat. Prod.* **2009**, *72*, 295–297 (antiprotealide); b) M. Stadler, J. Bitzer, A. Mayer-Bartschmid, H. Muller, J. Benet-Buchholz, F. Gantner, H.-V. Tichy, P. Reinemer, K. B. Bacon, *J. Nat. Prod.* **2007**, *70*, 246–252 (cinnabaramides A–G).

[9] a) D. Chauhan, L. Catley, G. Li, K. Podar, T. Hideshima, M. Velankar, C. Mitsiades, N. Mitsiades, H. Yasui, A. Letai, H. Ovaa, C. Berkers, B. Nicholson, T.-H. Chao, S. T. C. Neuteboom, P. Richardson, M. A. Palladino, K. C. Anderson, *Cancer Cell* **2005**, *8*, 407–419; b) V. R. Macherla, S. S. Mitchell, R. R. Manam, K. A. Reed, T.-H. Chao, B. Nicholson, G. Deyanat-Yazdi, B. Mai, P. R. Jensen, W. Fenical, S. T. C. Neuteboom, K. S. Lam, M. A. Palladino, B. C. M. Potts, *J. Med. Chem.* **2005**, *48*, 3684–3687.

[10] a) T. Gebreyesusa, T. Yosief, S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1988**, *29*, 3863–3864; b) S. Isaacs, R. Berman, Y. Kashman, T. Gebreyesus, T. Yosief, *J. Nat. Prod.* **1991**, *54*, 83–91; c) P. Sauleau, P. Retailleau, J. Vacelet, M.-L. Bourguet-Kondracki, *Tetrahedron* **2005**, *61*, 955–963.

[11] H.-J. Shin, T.-S. Kim, H.-S. Lee, J.-Y. Park, I.-K. Choi, H.-J. Kwon, *Phytochemistry* **2008**, *69*, 2363–2366.

[12] J. Li, S.-C. Liu, S.-B. Niu, W.-Y. Zhuang, Y.-S. Che, *J. Nat. Prod.* **2009**, *72*, 2184–2187.

[13] For an account, see: a) P.-Q. Huang, *Synlett* **2006**, 1133–1149; for two recent examples, see: b) S.-T. Ruan, J.-M. Luo, Y. Du, P.-Q. Huang, *Org. Lett.* **2011**, *13*, 4938–4941; c) S.-C. Tuo, J.-L. Ye, A.-E. Wang, S.-Y. Huang, P.-Q. Huang, *Org. Lett.* **2011**, *13*, 5270–5273.

[14] For recent examples, see: a) J. Chen, P.-Q. Huang, Y. Queneau, *J. Org. Chem.* **2009**, *74*, 7457–7463; b) S.-H. Xiang, H.-Q. Yuan, P.-Q. Huang, *Tetrahedron: Asymmetry* **2009**, *20*, 2021–2026; c) Z.-B. Ye, J. Chen, W.-H. Meng, P.-Q. Huang, *Tetrahedron: Asymmetry* **2010**, *21*, 895–902.

[15] a) P.-Q. Huang, T.-J. Wu, Y.-P. Ruan, *Org. Lett.* **2003**, *5*, 4341–4344; b) P.-Q. Huang, J. Deng, *Synlett* **2004**, 0247–0250; c) L.-J. Jiang, H.-Q. Lan, J.-F. Zheng, J.-L. Ye, P.-Q. Huang, *Synlett* **2009**, 297–301; d) L.-J. Jiang, B. Teng, J.-F. Zheng, J.-L. Ye, P.-Q Huang, *Tetrahedron* **2010**, *66*, 172–175; e) J.-M. Luo, C.-F. Dai, S.-Y. Lin, P.-Q. Huang, *Chem. Asian J.* **2009**, *4*, 328–335; f) G. Liu, T.-J. Wu, Y.-P. Ruan, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 5755–5768; g) H.-Q. Lan, P.-Q Huang, *Chem. Commun.* **2010**, *46*, 5319–5321; h) H.-Q. Lan, J.-L. Ye, A.-E Wang, P.-Q. Huang, *Chem. Eur. J.* **2011**, *17*, 958–968.

[16] a) A. K. Ghosh, Z. L. Dawson, *Synthesis* **2009**, 2992–3002; b) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947; c) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65–75.

[17] For two recent reviews on Reformatsky-type reactions, see: a) W. R. Dolbier Jr., R. Ocampo, *Tetrahedron* **2004**, *60*, 9325–9374; b) P. G. Cozzi, *Angew. Chem.* **2007**, *119*, 2620–2623; *Angew. Chem. Int. Ed.* **2007**, *46*, 2568–2571.

[18] For selected SmI_2-promoted Reformatsky-type reactions, see: a) G. A. Molander, J. B. Etter, *J. Am. Chem. Soc.* **1987**, *109*, 6556–6558; b) G. A. Molander, J. B. Etter, L. S. Harring, P.-J. Thorel, *J. Am. Chem. Soc.* **1991**, *113*, 8036–8045; c) M. F. Jacobsen, M. Turks,

R. Hazell, T. Skrydstrup, *J. Org. Chem.* **2002**, *67*, 2411–2417; d) T. Nagano, J. Motoyoshiya, A. Kakehi, Y. Nishii, *Org. Lett.* **2008**, *10*, 5453–5456.

[19] a) K. E. Rittle, C. F. Homnick, G. S. Ponticello, B. E. Evans, *J. Org. Chem.* **1982**, *47*, 3016–3018; for two reviews on the use of α-amino aldehydes in asymmetric synthesis, see: b) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149–164; c) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559–1573; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546.

[20] For recent reviews on the chemistry of SmI_2, see: a) K. Gopalaiah, H. B. Kagan, *New J. Chem.* **2008**, *32*, 607–637; b) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351–10372; c) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371–3404; d) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem.* **2009**, *121*, 7276–7301; *Angew. Chem. Int. Ed.* **2009**, *48*, 7140–7165.

[21] a) T. Honda, H. Mizutani, J. Takayama, Y. Soeda, *Heterocycles* **2004**, *62*, 343–355; b) D. Ma, W. Tang, A. P. Kozikowski, N. E. Lewin, P. M. Blumberg, *J. Org. Chem.* **1999**, *64*, 6366–6373; c) J.-G. Kim, D. O. Jang, *Tetrahedron Lett.* **2009**, *50*, 688–692.

[22] a) P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698; b) Y.-G. Xiang, X.-W. Wang, X. Zheng, Y.-P. Ruan, P.-Q. Huang, *Chem. Commun.* **2009**, 7045–7047.

[23] For reviews on efficiency in organic synthesis, see: a) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202; b) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49; c) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25–31; for an example, see: d) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505–7511.

[24] a) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem.* **2010**, *122*, 3101–3104; *Angew. Chem. Int. Ed.* **2010**, *49*, 3037–3040; b) K.-J. Xiao, Y. Wang, K.-Y. Ye, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 12792–12796; for a related method, see: c) S.-H. Xiang, J. Xu, H.-Q. Yuan, P.-Q. Huang, *Synlett* **2010**, 1829–1832.

[25] For a review on IBX, see: a) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2011**, *123*, 1562–1590; *Angew. Chem. Int. Ed.* **2011**, *50*, 1524–1552; b) H. Pati, V. Satam, A. Harad, R. Rajule, *Tetrahedron* **2010**, *66*, 7659–7706; c) T. Wirth, *Angew. Chem.* **2001**, *113*, 2893–2895; *Angew. Chem. Int. Ed.* **2001**, *40*, 2812–2814.

[26] S. F. Kirsch, *J. Org. Chem.* **2005**, *70*, 10210–10212.

[27] a) O. Iwamoto, H. Koshino, D. Hashizume, K. Nagasawa, *Angew. Chem.* **2007**, *119*, 8779–8782; *Angew. Chem. Int. Ed.* **2007**, *46*, 8625–8628; b) O. Iwamoto, R. Shinohara, K. Nagasawa, *Chem. Asian J.* **2009**, *4*, 277–285.

[28] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; c) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899; d) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552; for a minireview, see: e) A. Speicher, V. Bomm, T. Eicher, *J. Prakt. Chem.* **1996**, *338*, 588–590; for selected general reviews on hypervalent iodine reagents, see: f) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185–1197; g) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358; h) H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111–124; i) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584.

[29] For selected examples on the α-hydroxylation of β-dicarbonyl compounds, see: a) S. Takechi, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2011**, *52*, 2140–2143; b) A. M. R. Smith, H. S. Rzepa, A. J. P. White, D. Billen, K. K. Hii, *J. Org. Chem.* **2010**, *75*, 3085–3096; c) B. Gong, Q. Meng, T. Su, Z. Gao, *Chin. J. Org. Chem.* **2010**, *30*, 401–408; d) S. F. Kirsch, A. Duschek, *Chem. Eur. J.* **2009**, *15*, 10713–10717; e) A. M. R. Smith, D. Billen, K. K. Hii, *Chem. Commun.* **2009**, 3925–3927; f) D. Li, K. Schröder, B. Bitterlich, M. K. Tse, M. Beller, *Tetrahedron Lett.* **2008**, *49*, 5976–5979; g) J. Christoffers, T. Werner, M. Rössle, *Catal. Today* **2007**, *121*, 22–26; h) M. R. Acocella, O. G. Mancheño, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2004**, *69*, 8165–8167; i) J. Christoffers, T. Werner, S. Unger, W. Frey, *Eur. J. Org. Chem.* **2003**, 425–431; j) P. Y. Toullec, C. Bonaccorsi, A. Mezzetti, A. Togni, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5810–5814; k) J. Christoffers, T. Werner, *Synlett* **2002**, 119–121; l) T. Watanabe, T. Ishikawa, *Tetrahedron Lett.* **1999**, *40*, 7795–7798; m) F. A. Davis, H. Liu, B.-C. Chen, P. Zhou, *Tetrahedron* **1998**, *54*, 10481–10492; n) R. Z. Andriamialisoa, N. Langlois, Y. Langlois, *Tetrahedron Lett.* **1985**, *26*, 3563–3566.

[30] a) M. Yu, D. L. J. Clive, V. S. C. Yeh, S. Kang, J. Wang, *Tetrahedron Lett.* **2004**, *45*, 2879–2881; b) A. Murray, G. R. Proctor, *Tetrahedron Lett.* **1995**, *36*, 291–294.

[31] a) V. Vanrheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973–1976; b) N. Ikota, A. Hanaki, *Chem. Pharm. Bull.* **1989**, *37*, 1087–1089; c) B. Dudot, L. Micouin, I. Baussanne, J. Royer, *Synthesis* **1999**, 688–694; d) T. Muramatsu, S. Yamashita, Y. Nakamura, M. Suzuki, N. Mase, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2007**, *48*, 8956–8959.

[32] a) T. Mukaiyama, K. Suzuki, T. Yamada, F. Tabusa, *Tetrahedron* **1990**, *46*, 265–276; b) G. Casiraghi, G. Rassu, P. Spanu, L. Pinna, *J. Org. Chem.* **1992**, *57*, 3760–3763; c) P. Spanu, G. Rassu, L. Pinna, L. Battistini, G. Casiraghi, *Tetrahedron: Asymmetry* **1997**, *8*, 3237–3243.

[33] P. Dupau, R. Epple, A. A. Thomas. V. V. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421–433.

[34] a) C. J. Hayes, A. E. Sherlock, M. D. Selby, *Org. Biomol. Chem.* **2006**, *4*, 193–195; b) C. Hayes, A. E. Sherlock, M. P. Green, C. Wilson, A. J. Blake, M. D. Selby, J. C. Prodger, *J. Org. Chem.* **2008**, *73*, 2041–2051.

[35] a) P. Jouin, B. Castro, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177–1182; b) A. Bernardi, F. Micheli, D. Potenza, C. Scolastico, R. Villa, *Tetrahedron Lett.* **1990**, *31*, 4949–4952; c) P.-Q. Huang, S.-L. Wang, J.-L. Ye, Y.-P. Ruan, Y.-Q. Huang, H. Zheng, J.-X. Gao, *Tetrahedron* **1998**, *54*, 12547–12560; d) G. Rassu, G. Casiraghi, P. Spanu, L. Pinna, G. G. Fava, M. B. Ferrari, G. Pelosi, *Tetrahedron: Asymmetry* **1992**, *3*, 1035–1048; e) G.-N. Wang, L. Yang, L.-H. Zhang, X.-S. Ye, *J. Org. Chem.* **2011**, *76*, 2001–2009.

[36] a) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186; see, also: b) A. J. Pearson, H. Sun, X. Wang, *J. Org. Chem.* **2007**, *72*, 2547–2557; c) A. J. Pearson, X. Wang, *Tetrahedron Lett.* **2005**, *46*, 3123–3126.

[37] a) S. P. Kotkar, V. B. Chavan, A. Sudalai, *Org. Lett.* **2007**, *9*, 1001–1004; b) P. Coutrot, S. Claude, C. Didierjean, C. Grison, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 417–420; c) Y. Huang, D. R. Dalton, *J. Org. Chem.* **1997**, *62*, 372–376; d) M. T. Reetz, T. J. Strack, F. Mutulis, R. Goddard, *Tetrahedron Lett.* **1996**, *37*, 9293–9296; e) I. Izquierdo, M. T. Plaza, J. A. Tamayo, *Tetrahedron: Asymmetry* **2004**, *15*, 3635–3642; f) A. T. Carmona, J. Fuentes, P. Vogel, I. Robina, *Tetrahedron: Asymmetry* **2004**, *15*, 323–333; g) A. N. Hulme, C. H. Montgomery, *Tetrahedron Lett.* **2003**, *44*, 7649–7653; h) R. S. D. Broady, J. E. Rexhausen, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1083–1094; i) P. M. Kauppinen, A. M. P. Koskinen, *Tetrahedron Lett.* **1997**, *38*, 3103–3106; j) M. F. Dee, R. L. Rosati, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 949–952; k) M. Gurjar, L. Ghosh, M. Syamala, V. Jayasree, *Tetrahedron Lett.* **1994**, *35*, 8871–8872; l) F. Yokokawa, Y. Hmada, T. Shioiri, *Synlett* **1992**, 703–705.

[38] a) J. S. Oh, J. Jeon, D. Y. Park, Y. G. Kim, *Chem. Commun.* **2005**, 770–771; b) J. Jeon, S.-H. Kim, J. H. Lee, J. S. Oh, D. Y. Park, Y. G. Kim, *Bull. Korean Chem. Soc.* **2009**, *30*, 1003–1008, and references therein.

[39] a) E. Vedejs, A. W. Kruger, *J. Org. Chem.* **1999**, *64*, 4790–4797; b) T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe, G. Stemp, *J. Org. Chem.* **2002**, *67*, 7946–7956; c) K. Csatayová, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, J. E. Thomson, D. L. Wilson, *Org. Lett.* **2011**, *13*, 2606–2609, and references therein.

[40] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

[41] a) D. J. Krysan, T. W. Rockway, A. R. Haight, *Tetrahedron: Asymmetry* **1994**, *5*, 625–632; see, also: b) H. J. Yoon, Y.-W. Kim, B. K. Lee, W. K. Lee, Y. Kim, H.-J. Ha, *Chem. Commun.* **2007**, 79–81.

[42] a) J. Jeon, J. H. Lee, J.-W. Kim, Y. G. Kim, *Tetrahedron: Asymmetry* **2007**, *18*, 2448–2453; b) J. Jeon, M. Shin, J. W. Yoo, J. S. Oh, J. G. Bae, S. H. Jung, Y. G. Kim, *Tetrahedron Lett.* **2007**, *48*, 1105–1108;

c) J. Jeon, S.-K. Hong, J. S. Oh, Y. G. Kim, *J. Org. Chem.* **2006**, *71*, 3310–3313; d) ref. [34].
[43] a) W. Xu, X. Cai, M. E. Jung, Y. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 13604–13607; b) A. A. Yakasai, J. Davison, Z. Wasil, L. M. Halo, C. P. Butts, C. M. Lazarus, A. M. Bailey, T. J. Simpson, R. J. Cox, *J. Am. Chem. Soc.* **2011**, *133*, 10990–10998; c) L. Lou, G. Qian, Y. Xie, J. Hang, H. Chen, K. Zaleta-Rivera, Y. Li, Y. Shen, P. H. Dussault, F. Liu, L. Du, *J. Am. Chem. Soc.* **2011**, *133*, 643–645; d) X. Liu, C. T. Walsh, *Biochemistry* **2009**, *48*, 11032–11044; e) X. Liu, C. T. Walsh, *Biochemistry* **2009**, *48*, 8746–8757; f) J. W. Sims, E. W. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11149–11155; g) H. Chen, S. G. Olesen, P. H. M. Harrison, *Org. Lett.* **2006**, *8*, 5329–5332 (leading reference); h) H. Chen, P. H. M. Harrison, *Org. Lett.* **2004**, *6*, 4033–4036; i) P. Duspara, S. I. Jenkins, D. W. Hughes, P. H. M. Harrison, *Chem. Commun.* **1998**, 2643–2644.
[44] H. Oikawa, *J. Org. Chem.* **2003**, *68*, 3552–3557.
[45] L. L. Beer, B. S. Moore, *Org. Lett.* **2007**, *9*, 845–848.
[46] a) T. M. Harris, C. M. Harris, J. E. Hill, F. S. Ungemach, H. P. Broquist, B. M. Wickwire, *J. Org. Chem.* **1987**, *52*, 3094–3098; b) C. M. Harris, M. J. Schneider, F. S. Ungemach, J. E. Hill, T. M. Harris, *J. Am. Chem. Soc.* **1988**, *110*, 940–949.
[47] M. P. Heitz, L. E. Overman, *J. Org. Chem.* **1989**, *54*, 2591–2596.
[48] A. Höltzel, M. G. Gänzle, G. J. Nicholson, W. P. Hammes, G. Jung, *Angew. Chem.* **2000**, *112*, 2886–2888; *Angew. Chem. Int. Ed.* **2000**, *39*, 2766–2768.
[49] H. Taube, E. L. King, *J. Am. Chem. Soc.* **1954**, *76*, 4053–4054.
[50] a) J. H. Johnson, D. W. Phillipson, A. D. Kahle, *J. Antibiot.* **1989**, *42*, 1184–1185; b) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, *J. Antibiot.* **1988**, *41*, 1774–1779.
[51] a) K. Akaji, Y. Hayashi, Y. Kiso, N. Kuriyama, *J. Org. Chem.* **1999**, *64*, 405–411; b) S. Paik, S. Carmeli, J. Cullingham, R. E. Moore, G. M. L. Patterson, M. A. Tius, *J. Am. Chem. Soc.* **1994**, *116*, 8116–8125; c) G. R. Pettit, T. J. Thornton, J. T. Mullaney, M. R. Boyd, D. L. Herald, S.-B. Singh, E. J. Flahive, *Tetrahedron* **1994**, *50*, 12097–12108; d) N. Patino, E. Frérot, N. Galeotti, J. Poncet, J. Coste, M.-N. Dufour, P. Jouin, *Tetrahedron* **1992**, *48*, 4115–4122; e) G. R. Pettit, D. L. Herald, S. B. Singh, T. J. Thornton, J. T. Mullaney, *J. Am. Chem. Soc.* **1991**, *113*, 6692–6693.

Received: September 27, 2011
Published online: February 7, 2012

