General Route to 2,4,5-Trisubstituted Piperidines from Enantiopure β-Amino Esters. Total Synthesis of Pseudodistomin B Triacetate and Pseudodistomin F

Dawei Ma* and Haiying Sun

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

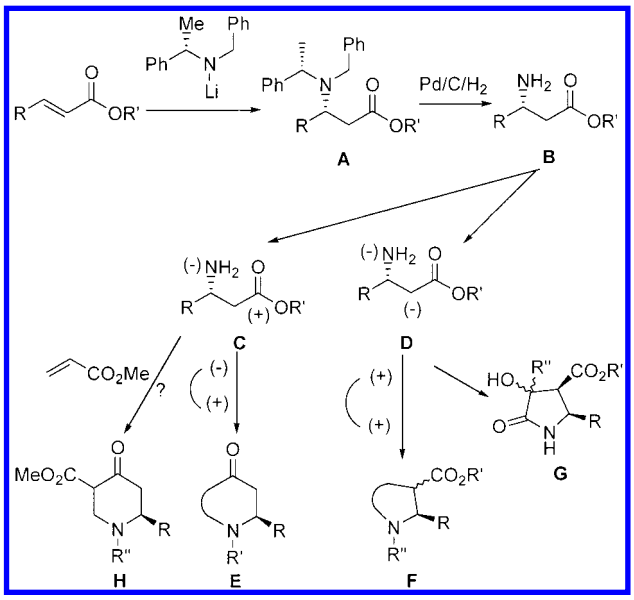
Received March 24, 2000

The Michael addition reaction of enantiopure β-amino esters with methyl acrylate followed by Dieckmann condensation and enol silylation affords the enol ethers **6**, which are hydrogenated with catalysis by Raney-Ni at 80 atm and 80 °C to provide 2,4,5-trisubstituted piperidines with high diastereoselectivity. In this case Ni−H attacks the C−C double bond from the direction of the 2-alkyl group to provide the products in which 2,4,5-trisubstrited groups are all cis to each other. While hydrogenation of enol ether **13** without a *N*-Boc protecting group gives the product **15** in which the 4-hydroxy group and 5-ester moiety are trans to the 2-alkyl group. By using the diastereoselective hydrogenation products **9d** and **9e** as key intermediates, pseudodistomin B triacetate and pseudodistomin F are synthesized. The key steps for these transformations include Curtius rearrangement and Julia olefination.

Introduction

Although α-amino acids have been widely used as chiral building blocks for several decades,[1] little attention has been directed to the synthesis from enantiopure β-amino acid derivatives because of their inconvenient availability. In 1991 Davies and Ichihara reported a convenient method to prepare *N*,*N*-disubstituted β-amino ester through a highly diastereoselective Michael addition reaction of a lithium amide with a suitable α,β-unsaturated ester.[2] This method makes it possible to assemble some complex molecules employing enantiopure β-amino esters as a chiral pool. Recently, several groups have demonstrated that this strategy could be applied in the synthesis of polyfunctionalized β-amino acid moieties that exist in many biologically important molecules,[3] chiral alcohols,[4] and chiral carbocycles.[5] Our interest in this field is based on the analysis shown in Scheme 1. The β-amino esters **B** can be regarded as the anion−cation synthons **C** or dianion synthons **D**. They can connect with either a suitable anion-cation reagent or a suitable dication reagent to form *N*-containing heterocycles **E** or **F**. We have found that polyfunctionalized pyrrolidinones **G** could be obtained diastereoselectively using ethyl glycoxalate or an α-ketoester as a dication reagent.[6] These polyfunctionalized pyrrolidinones have been successively used to synthesize necine alkaloids tussilagine, isotussilagine and (−)-petasinecine,[7] and plakoridine A, a fully substituted, functionally diverse pyrrolidine.[8] In this article we discuss how to build piperidines **H** employing methyl acrylate as an anion−cation reagent.[9] The polyfunctionlized piperidines

Scheme 1



(1) For reviews, see (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(2) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry*, **1991**, *2*, 183. (b) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141. (c) Davies, S. G.; Smyth, G. D. *Tetrahedron: Asymmetry*, **1996**, *7*, 1001. (e) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1998**, *39*, 6045.

(3) Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamota, Y. *J. Org. Chem.* **1995**, *60*, 143. (b) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett*. **1996**, 621. (c) Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry*, **1997**, *8*, 3387. (d) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313. (e) Davies, S. G.; Smyth, G. D.; Chippindale, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089.

(4) Davies, S. G.; Smyth, G. D. *Tetrahedron: Asymmetry*, **1996**, *7*, 1005.

(5) Urones, J. G.; Garrido, N. M.; Diez, D.; Dominguez, S. H.; Davies, S. G.; *Tetrahedron: Asymmetry* **1997**, *8*, 2683.

(6) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 575.

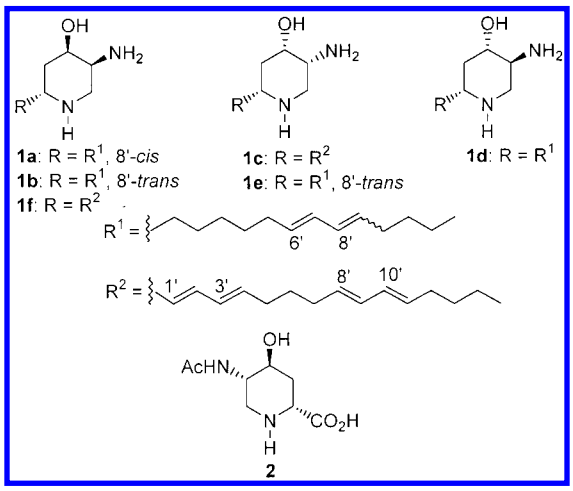
(7) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067. (b) Ma, D.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1703.

(8) Ma, D.; Sun, H. *Tetrahedron Lett.* **2000**, *41*, 1947.

(9) Part of these results was reported as a communication; see Ma, D.; Sun, H. *Tetrahedron Lett.* **1999**, *40*, 3609.

10.1021/jo000447q CCC: $19.00 © 2000 American Chemical Society
Published on Web 08/30/2000

Scheme 2



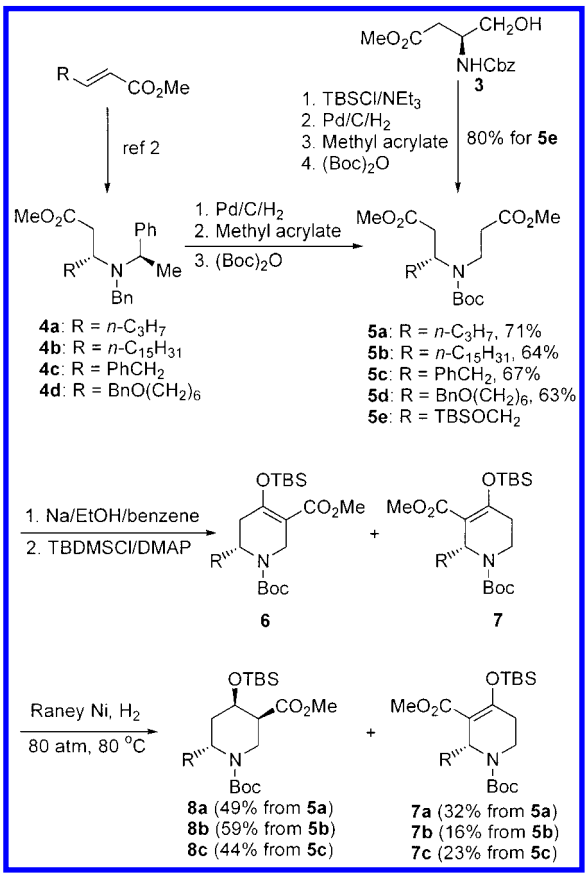
H are obviously valuable intermediates for assembling pseudodistomins A−F (**1a**−**f**, Scheme 2)[10] and sialidases inhibitor (2*R*,4*S*,5*S*)-5-acetamido-4-hydroxypipecolinic acid **2**.[11]

Pseudodistomins A **1a** and B **1b** are two piperidine alkaloids that were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and shown to have potent in vitro antineoplastic activity against L1210 and L5178 leukemia cells. In addition, they also displayed the inhibition of calmodulin-activated brain phosphodiesterase.[10a,10b] Four other pseudodistomins, C (**1c**), D (**1d**), E (**1e**), and F (**1f**), were isolated later from the same source, and they were found to be active in a cell-based assay for DNA damage induction.[10c,d] Their significant biological activity has made them targets of many synthetic studies.[12] Several asymmetric routes to these compounds or their analogues have appeared in which the enantiopure α-amino acids were employed to construct the piperidine systems.[12b−d] However, a more efficient synthetic protocol is still needed.

Results and Discussion

Our detailed studies are outlined in Scheme 3. *N*,*N*-Disubstituted *β*-amino esters **4** could be obtained in high diastereoselectivity according to Davies's procedure.[2] Deprotection of **4** by Pd/C-catalyzed hydrogenation followed by Michael addition of the amine to methyl acrylate afforded the amino diesters, which were protected with a Boc group to yield **5a**−**d**. From the alcohol **3** derived from L-aspartic acid, diester **5e** was obtained by a four-step reaction shown in Scheme 3. Next, Dieckmann condensation of **5** mediated by sodium/methanol provided the cyclization products as two regioisomers, which were treated with *tert*-butyldimethylsilyl chloride to give a mixture of enol ethers **6** and **7**. These two isomers could not be separated by column chromatography, but their ratio could be determined by ^{1}H NMR. Thus, we could establish that the regioselectivity in the Dieckmann condensation step was about 1.5, 3.8, 1.7, 2.0, and 1.6 for **5a**, **5b**, **5c**, **5d**, and **5e**, respectively. For further conversion of **6** into the useful intermediates for synthesizing pseudodistomins, the key problem was how to reduce its C−C double bond diastereoselectively to create two stereogenic centers. After some experimentation, it was found that hydrogenation of the mixture of **6** and **7** at 80 atm and 80 °C under the action of Raney-Ni gave **8a**−**c** as a single isomer together with unreacted **7a**−**c**. Under these conditions, 100% conversion of **6** could be achieved while no hydrogenation of **7** was detected. However, it was found that part of **7** could be reduced by prolonging the reaction time and increasing the reaction temperature to 100 °C. The difference in reactivity of **6** and **7** might result from steric hindrance. It is notable that if the *tert*-butyl carbamate of **5** was changed to a methyl carbamate, much lower diastereoselectivity was observed. These results indicated that the Boc protecting group plays a crucial role in the diastereoselective hydrogenation.

Scheme 3



For diastereoselective hydrogenation of **6d**, its *O*-benzyl protecting group should be removed prior to Raney-Ni catalyzed hydrogenation because it was found that the phenyl ring was also hydrogenated under the reaction condition mentioned above. Thus, the benzyl ether moiety in the mixture of **6d** and **7d** was first cleaved under Pd/C-catalyzed hydrogenation, and then

(10) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.*, **1987**, *52*, 450. For studies on the structure revision, see (b) Ishibashi, M.; Deki, K.; Kobayashi, J. *J. Nat. Prod.* **1995**, *58*, 804. (c) Kobayashi, J.; Naitoh, K.; Doi, Y.; Deki, K.; Ishibashi, M. *J. Org. Chem*., **1995**, *60*, 6941. (d) Freyer, A. J.; Patil, A. D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod*. **1997**, *60*. 986.

(11) Clinch, K.; Vasella, A.; Schauer, R. *Tetrahedron Lett*., **1987**, *28*, 6425. (b) Glanzer, Gyorgydeak, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **1991**, *74*, 343.

(12) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 893. (b) Naito, T.; Yuumoto, Y.; Kiguchi, T.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 281. (c) Doi, Y.; Ishbashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573. (d) Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 773. (e) Knapp, S.; Hale, J. L. *J. Org. Chem*. **1993**, *58*, 2650. (f) Naito, T.; Yuumoto, Y.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett*. **1992**, *33*, 4033. (g) Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349.

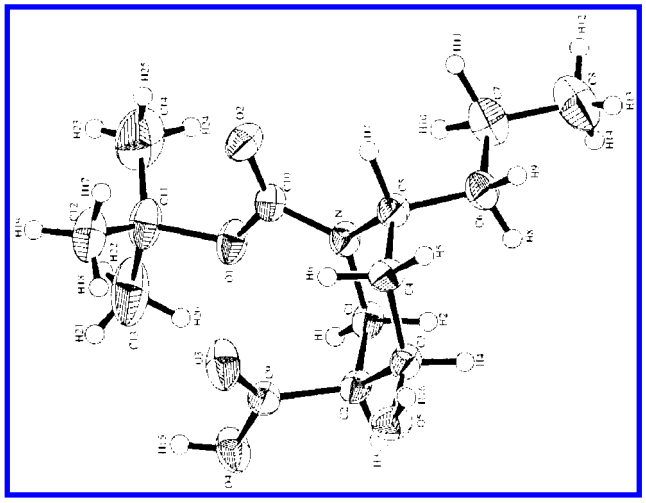
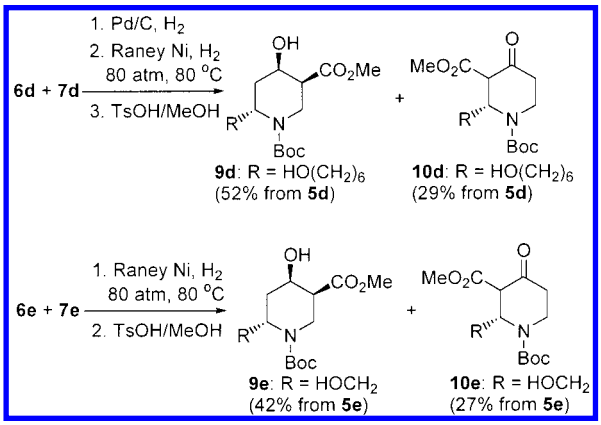
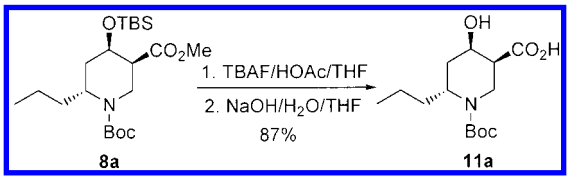


Figure 1. The X-ray structure of **11a**.

Scheme 4



Scheme 5



the C−C double bond was reduced by Raney-Ni catalyzed hydrogenation to afford a mixture of **8d** and unreacted **7d**. This mixture was not easy to separate, and it was therefore treated with TsOH in methanol to provide separable *β*-hydroxy ester **9d** and *β*-ketoester **10d**. The overall yield for **9d** from **5d** was about 52% (Scheme 4). In a similar manner, except for Pd/C-catalyzed hydrogenation, *β*-hydroxy ester **9e** was obtained from the mixture of **6e** and **7e**.

After the success in obtaining the reduction products **8**, **9d**, and **9e** diastereoselectively, the next problem was assignment of the stereochemistry of two new stereogenic centers. We planned to solve this problem by further conversion of these products. As shown in Scheme 5, treatment of **8a** with tetrabutylammonium fluoride followed by hydrolysis of the ester moiety with aqueous sodium hydroxide provided the corresponding *β*-hydroxy acid **11a**. Compound **11a** gave fine crystals which allowed us to determine its structure by X-ray analysis. As outlined in Figure 1, the X-ray studies of **11a** clearly indicated that the 4-hydroxy and 5-carboxylate groups are cis to each other and both trans to the *n*-propyl group.

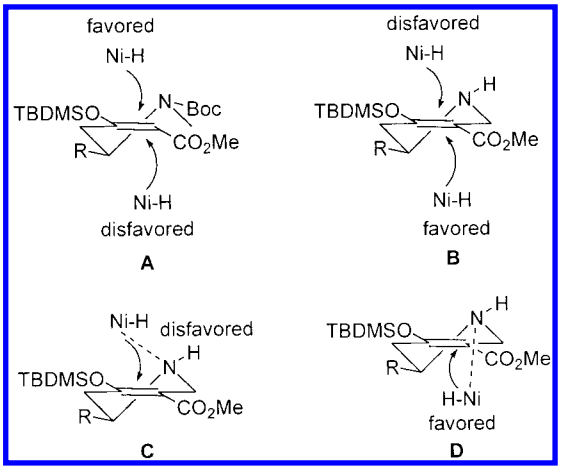
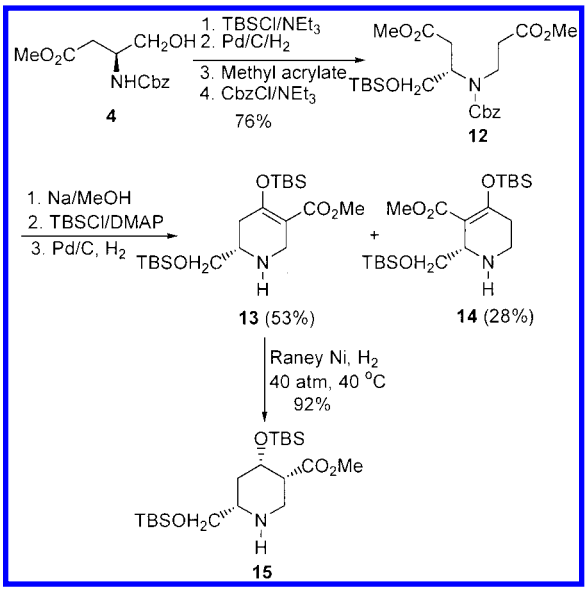


Figure 2. Stereochemistry analysis for hydrogenation of **6** (A) and **13** (B, C, and D).

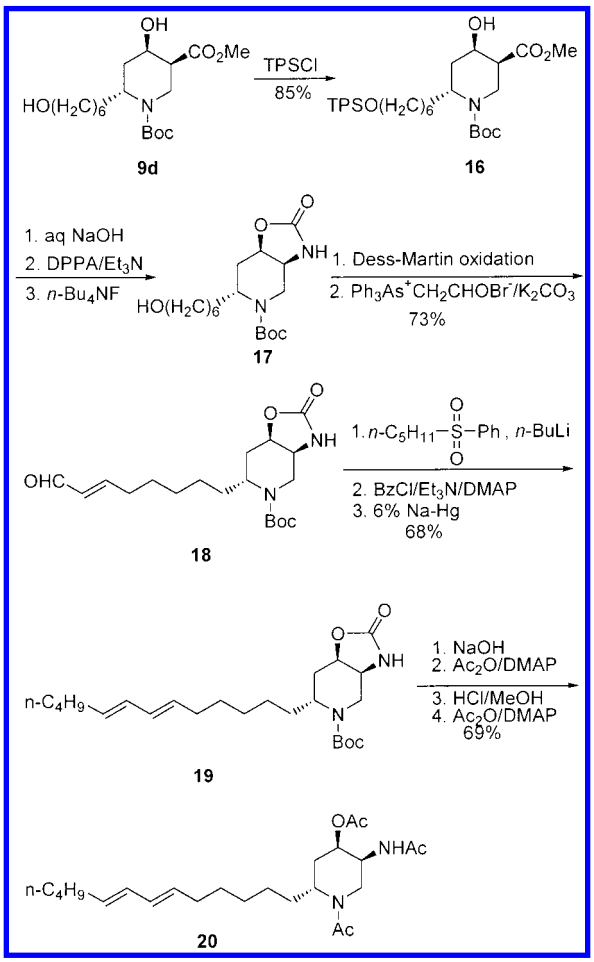
Scheme 6



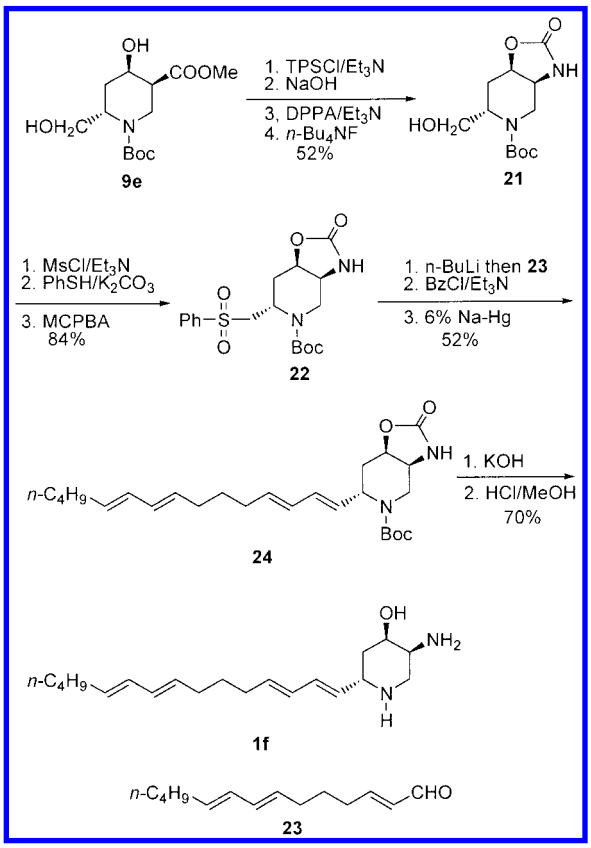
Thus, we concluded that the *β*-hydroxy acid **11a** has the (2*R*,4*R*,5*S*)-configuration.

The X-ray structure of **11a** also suggested an explanation for the diastereoselectivity in the Raney-Ni-catalyzed hydrogenation. As shown in Figure 2, because the Boc group and *n*-propyl are trans to each other, the active species Ni−H may attack the C−C double bond from the direction of *n*-propyl group (less-hindered face) to give the present stereochemistry. On the basis of this analysis, we realized that if a substrate without a *N*-protecting group at the 1-position was used, the active species Ni−H would attack the C−C double from the face with the 2-alkyl group (less-hindered face for either the normal case (**B**) or the case of *N*-chelation to the Ni (**C** and **D**)). This could lead to a change in stereochemistry of the hydrogenation products. With this idea in mind, we attempted the strategy that is outlined in Scheme 6. From the alcohol **4**, the diester **12** was prepared, and this diester was converted into the enol ether **13** in the following three steps: (1) Dieckmann condensation of **12** mediated by sodium/methanol provided the cyclization products; (2) treatment of the cyclization products with *tert*-butyldimethylsilyl chloride to give the corresponding enol ethers; (3) removal of the Cbz protecting group to produce the separable enol ethers **13** and **14**. As we

Scheme 7



Scheme 8



expected, the hydrogenation of **13** catalyzed by Raney-Ni delivered the piperidine **15** in which the three substituents at the 2-, 4-, and 5-positions are all cis to each other. This structure was assigned by its NOESY spectrum in which marked NOEs between 2-H and 4-H, 4-H and 5-H, and 5-H and 2-H were observed.

With β-hydroxy esters **9d** in hand, we developed a new route for synthesizing pseudodistomins B triacetate as shown in Scheme 7. First, we planned to convert the ester moiety of **9d** to the corresponding amino moiety by means of Curtius rearrangement. Accordingly, selective protection of the primary hydroxy group in **9d** with *tert*-butyldiphenylsilyl chloride (TPS-Cl) provided **16**. After hydrolysis of the ester **16** with aqueous NaOH, the resultant acid was treated with diphenylphosphoryl azide (DPPA) to form a carboxyl azide.[13] This intermediate was subjected to Curtius rearrangement to afford a cyclic carbamate, which was transformed to **17** by removing the TPS protecting group with *n*-Bu_4NF. Next, the alcohol **17** was converted into the corresponding aldehyde via a Dess−Martin oxidation, which was treated with triphenylarsonium salt of bromoacetaldehyde under the action of K_2CO_3 to deliver a formyl-olefination product **18**.[14] Now we decided to employ Julia olefination to introduce the desired *trans,trans*-diene moiety.[15] Thus, treatment of *n*-pentyl phenyl sulfone with *n*-BuLi followed by trapping the generated anion with the aldehyde **18** provided the coupling product, which was converted to the corresponding β-benzoyloxy sulfones and then subjected to sodium amalgam reduction to provide diene **19**. By ^{1}H NMR it was found that the purity for **19** is about 90%, which implied that other minor isomers of diene were also formed during the Julia olefination. Finally, the cyclic carbamate **19** was transformed into pseudodistomins B triacetate **20** by following deprotection and protection steps: (1) hydrolysis with aqueous NaOH; (2) protecting the free hydroxy and amino groups with acetyl group; (3) removal of the Boc group with saturated methanolic HCl; (4) acylation of the free amine with acetic anhydride. The spectral data of **20** were the same for those reported except for some small peaks in the ^{1}H NMR spectra displayed by some minor isomers (the ratio of **20** to minor isomers is about 6/1 as detected by ^{1}H NMR). The overall yield for this synthetic protocol is about 6.6% from β-amino ester **4d**.

The β-hydroxy acid **9e** is obviously a suitable intermediate for the total synthesis of pseudodistomin F. Our efforts to this goal are shown in Scheme 8. After transformation of **9e** to the cyclic carbamate **21** according to the procedure from **9d** to **17**, we tried to use Julia olefination to introduce the desired side chain. Accordingly, through its mesylate, the alcohol **21** was converted into the corresponding phenyl sulfide, which was oxidized to phenyl sulfone **22** with MCPBA. Next, coupling of **22** with aldehyde **23**[12c] followed by Julia olefination provided tetraene **24** in 52% yield. Finally, deprotection of **24** with aqueous KOH and subsequent HCl/MeOH gave **1f** in 70% yield. Its spectral data were identical with those reported.[10d] In this case only one isomer was observed in ^{1}H NMR, which implied that the purity of our synthetic pseudodistomin F was over 97%. To the best of our

(13) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(14) Huang, Y.; Shi, L.; Yang, J. *Tetrahedron Lett.* **1985**, *26*, 6447.
(15) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045, and references therein.

knowledge, the present result is the first total synthesis of pseudodistomin F. It is notable that if the β-hydroxy acid **15** was used as the starting material we could also synthesize pseudodistomin C by employing the same reaction sequence mentioned above.

In conclusion, we have developed a method to synthesize the chiral 2,4,5-trisubstituted piperidines starting from enantiopure β-amino esters. The key step for this synthetic method is the diastereoselective hydrogenation of enol ether intermediates. Varying the *N*-substituents at the 1-position of enol ethers could change the stereochemistry of hydrogenation products. The importance of this method was demonstrated by its capability for synthesis of pseudodistomin B triacetate and the first total synthesis of pseudodistomin F. The further application of this method to synthesize other biologically important alkaloids and the procedure improvement are in progress.

Experimental Section

General Procedure for Preparing Diesters 5 from β-Amino Esters 4. To a solution of β-amino ester **4** (10 mmol) in methanol (30 mL) was added 10% Pd/C (1 mmol). After the mixture was stirred under hydrogen for 10 h, the catalyst was filtered off. To the filtrate was added methyl acrylate (12 mmol) in a dropwise manner before the solution was stirred at room temperature for 24−48 h. After the solvent was evaporated and the residue was dissolved in 1,4-dioxane, di-*tert*-butyl dicarbonate (12 mmol) and $NaHCO_3$ (15 mmol) were added. The mixture was stirred at 30 °C for 5 h, and then the solvent was removed in vacuo. The residue was partitioned between water and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate for three times. The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was chromatographed to give the product.

(*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-carbomethoxyethyl)]aminohexanoic acid methyl ester 5a: 71% yield; $[\alpha]^{25}_D$ +7.0 (*c* 2.5, $CHCl_3$); IR (neat) 2956, 2932, 1725, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (m, 1H), 3.66 (s, 6H), 3.45 (m, 2H), 2.58 (m, 3H), 2.47 (m, 1H), 1.60 (m, 2H), 1.46 (s, 9H), 1.42 (m, 2H), 0.90 (t, *J* = 6.8 Hz, 3H); MS *m*/*z* 331 (M^+).

(*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-carbomethoxyethyl)]aminooctadecanoic acid methyl ester 5b: 64% yield; $[\alpha]^{15}_D$ −1.6 (*c* 8.0, $CHCl_3$); IR (neat) 2926, 2855, 1743, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (m, 1H), 3.67 (s, 6H), 3.45 (m, 2H), 2.59 (m, 3H), 2.48 (m, 1H), 1.59 (m, 2H), 1.46 (s, 9H), 1.25 (br s, 26H), 0.88 (t, *J* = 6.5 Hz, 3H); MS *m*/*z* 500 ($M^+ + H^+$); HRMS found *m*/*z* 499.3856, $C_{28}H_{53}NO_6$ requires 499.3873.

(*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-carbomethoxyethyl)]amino-4-phenylbutyric acid methyl ester 5c: 67% yield; $[\alpha]^{18}_D$ +34.0 (*c* 18.8, $CHCl_3$); IR (neat) 2976, 1739, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.05 (m, 1H), 3.55 (s, 6H), 3.19 (m, 2H), 2.77 (m, 3H), 2.55(m, 2H), 2.20 (m, 1H), 1.34 (s, 9H); MS *m*/*z* 379 (M^+); HRMS found *m*/*z* 379.1996, $C_{20}H_{29}NO_6$ requires 379.1986.

(*R*)-9-Phenylmethoxy-3-[*N*-(*tert*-butyloxycarbonyl)-*N*-(2-carbomethoxyethyl)]aminononanoic acid methyl ester 5d: 63% yield; $[\alpha]^{22}_D$ −1.1 (*c* 3.97, $CHCl_3$); IR (neat) 2934, 2859, 1740, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.46 (s, 2H), 4.23 (m, 1H), 3.66 (s, 6H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.41 (m, 2H), 2.60 (m, 3H), 2.45 (m, 1H), 1.60 (m, 4H), 1.45 (br s, 9H), 1.32 (m, 6H); MS *m*/*z* 480 ($M^+ + H^+$). Anal. Calcd for $C_{26}H_{41}NO_7$ requires C: 65.11, H: 8.62, N: 2.92. Found: C: 65.08, H: 8.77, N: 2.72.

(*S*)-4-*tert*-Butyldimethylsiloxy-3-[*N*-(*tert*-butyloxycarbonyl)-*N*-(2-carbomethoxyethyl)]aminobutyric Acid Methyl Ester 5e. To a stirring solution of **3** (12 g, 45 mmol) in 30 mL of CH_2Cl_2 were added DMAP (50 mg, 0.41 mmol), *tert*-butyldimethylsilyl chloride (8 g, 54 mmol), and 10 mL of triethylamine. The mixture was stirred at room temperature for 6 h before it was partitioned between CH_2Cl_2 and brine. The organic phase was dried over Na_2SO_4 and concentrated, and the residue was chromatographed to give the corresponding silyl ether, which was dissolved in 100 mL of methanol. After this solution was added 1 g of 10% Pd/C, the mixture was stirred under hydrogen for 10 h, and then the catalyst was filtered off. To the filtrate was added methyl acrylate (5 mL, 55 mmol) in a dropwise manner. The solution was stirred at room temperature for 48 h, and then the solvent was evaporated. After the residue was dissolved in 100 mL of 1,4-dioxane, di-*tert*-butyl dicarbonate (12 g, 55 mmol) and $NaHCO_3$ (5.7 g, 68 mmol) were added. The resultant mixture was stirred at 30 °C for 5 h and then concentrated in vacuo. The residue was partitioned between 50 mL of water and 100 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was chromatographed to give 15.5 g (80%) of **5e**: $[\alpha]^{25}_D$ −11.1 (*c* 1.2, $CHCl_3$); IR (neat) 2956, 2932, 1742, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (m, 1H), 3.80 (m, 1H), 3.66 (s, 7H), 3.48 (m, 2H), 2.72 (m, 1H), 2.63 (m, 3H), 1.44 (s, 9H), 0.87 (s, 9H), 0.35 (s, 6H); MS *m*/*z* 434 ($M^+ + H^+$). Anal. Calcd for $C_{20}H_{39}NO_7Si$: C: 55.40, H: 9.06, N: 3.23. Found: C: 55.60, H: 9.49, N: 3.16.

(3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsiloxy-6-propylpiperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 8a. To a solution of **5a** (6.0 g, 18 mmol) in 50 mL of benzene were added sodium (0.5 g, 22 mmol) in small pieces and 0.2 mL of methanol. After the reaction mixture was stirred under N_2 at room temperature for 48 h, saturated aqueous NH_4Cl was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate for three times, the combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed to give the crude Dieckmann condensation products, which were dissolved in CH_2Cl_2. To this solution were added *tert*-butyldimethylsilyl chloride (3.0 g, 20 mmol), 70 mg of DMAP, and 3 mL of triethylamine. After the mixture was stirred at room temperature for 24 h, it was partitioned between CH_2Cl_2 and brine. The organic layer was concentrated, and the residue was chromatographed to give the corresponding silyl ethers **6** and **7**. This mixture was dissolved in ethyl acetate, and then 1.0 g of Raney-Ni (50% slurry in water) was added. After the mixture was stirred under hydrogen (80 atm) at 80 °C for 24 h, the catalyst was filtered off, and the filtrate was concentrated followed by chromatography to give 3.7 g (49%) of **8a**: $[\alpha]^{15}_D$ +3.7 (*c* 1.07, $CHCl_3$); IR (neat) 2937, 2860, 1745, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.34 (m, 1H), 4.20 (m, 1H), 4.11 (m, 1H), 3.63 (s, 3H), 3.05 (dd, *J* = 14.4, 3.8 Hz, 1H), 2.70 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.55 (m, 1H), 1.44 (s, 9H), 1.28 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); MS *m*/*z* 416 ($M^+ + H^+$). Anal. Calcd for $C_{21}H_{41}NO_5Si$: C: 60.68, H: 9.94, N: 3.37. Found: C: 60.96, H: 10.30, N: 3.45.

(3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsiloxy-6-pentadecylpiperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 8b. Following the procedure for preparation of **8a** from **5a**, **8b** was obtained from **5b** in 59% overall yield: $[\alpha]^{15}_D$ +3.1 (*c* 1.04, $CHCl_3$); IR (neat) 2928, 2856, 1747, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (m, 1H), 4.20 (m, 1H), 4.10 (m, 1H), 3.63 (s, 3H), 3.05 (dd, *J* = 14.5, 3.9 Hz, 1H), 2.70 (m, 1H), 2.23 (m, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.44 (s, 9H), 1.24 (m, 26H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H); MS *m*/*z* 584 ($M^+ + H^+$); HRMS found *m*/*z* 526.3901 ($M^+ - t$-Bu), $C_{29}H_{56}NO_5Si$ requires 526.3927.

(3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsiloxy-6-phenylmethylpiperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 8c. Following the procedure for preparation of **8a** from **5a**, **8c** was obtained from **5c** in 44% overall yield: $[\alpha]^{18}_D$ +24.9 (*c* 0.5, $CHCl_3$); IR (neat) 2953, 2858, 1744, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 5H), 4.5 (m, 1H), 4.23 (m, 2H), 3.62 (s, 3H), 3.22 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.92 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.76 (m, 2H), 2.12 (m, 1H), 1.58 (m, 1H), 1.33 (s, 9H), 0.8 (s, 9H), 0.05 (s, 6H); MS *m*/*z* 464 ($M^+ +$

H^+); HRMS found *m*/*z* 406.2054 ($M^+ - t$-Bu), $C_{21}H_{32}NO_5Si$ requires 406.2049.

(3*S*,4*R*,6*R*)-4-Hydroxy-6-(6-hydroxyhexyl)piperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 9d. To a solution of **5d** (10 g, 21 mmol) in 100 mL of benzene were added sodium (0.58 g, 25 mmol) in small pieces and 0.2 mL of methanol. The mixture was stirred under N_2 at room temperature for 48 h before 30 mL of saturated aqueous NH_4Cl was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed to give the corresponding Dieckmann condensation products. The crude products were dissolved in 30 mL of CH_2Cl_2, and then *tert*-butyldimethylsilyl chloride (3.5 g, 23 mmol), 30 mg DMAP, and 5 mL of triethylamine were added. The reaction mixture was stirred at room temperature for 24 h before it was partitioned between 200 mL of CH_2Cl_2 and 50 mL of brine. The organic layer was dried and concentrated, and the residue was allowed to pass through a short column of silica gel to give a mixture of **6d** and **7d**. This mixture was dissolved in 100 mL of ethyl acetate, and then 1 g of 10% Pd/C was added. After this suspension solution was stirred under hydrogen (30 atm) at 50 °C for 24 h, the catalyst was filtered off. To the filtrate was added 2 g of Raney-Ni (50% slurry in water) before the mixture was stirred under hydrogen (80 atm) at 80 °C for 24 h. The catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in 50 mL of methanol. To this solution was added TsOH (5 g, 29 mmol) before the solution was stirred at room temperature for 1 h. After the solvent was removed, the residue was chromatographed to give 3.9 g (52%) of **9d**: $[\alpha]^{22}_D$ −17.3 (*c* 1.44, $CHCl_3$); IR (neat) 3422, 2933, 2860, 1739, 1693, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.53 (brs, 1H), 4.32 (m, 1H), 3.95 (m, 1H), 3.71 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 3.33 (m, 1H), 2.95 (dt, J = 14.3, 3.6 Hz, 1H), 2.84 (br s, 1H), 1.95 (ddd, J = 12.4, 12.4, 6.1 Hz, 1H), 1.79 (m, 1H), 1.60 (m, 4H), 1.42 (br s, 9H), 1.32 (m, 6H); MS *m*/*z* 360 ($M^+ + H^+$). Anal. Calcd for $C_{18}H_{33}NO_6$: C: 58.76, H: 9.57, N: 4.03. Found: C: 58.91, H: 9.34, N: 3.59.

(3*S*,4*R*,6*S*)-4-Hydroxy-6-hydroxymethylpiperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 9e. Following the procedure for preparing **6d** and **7d** from **5d**, the mixture of **6e** and **7e** was obtained from **5e**, and it was dissolved in 100 mL of ethyl acetate. To this solution was added 2 g of Raney-Ni (50% slurry in water) before the mixture was stirred under H_2 (80 atm) at 80 °C for 24 h. The catalyst was filtered off, and the filtrate was concentrated. The residue was dissolved in 50 mL of methanol before TsOH was added. After the solution was stirred at room temperature for 1 h, the solvent was removed under reduced pressure. The residue was chromatographed to afford **9e** in 42% overall yield: $[\alpha]^{21}_D$ −64.0 (*c* 0.58, $CHCl_3$); IR (neat) 3452, 2978, 1732, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (m, 2H), 4.15 (m, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.40 (dd, J = 14.0, 3.5 Hz, 1H), 3.28 (dm, J = 8.3 Hz, 1H), 2.79 (dd, J = 8.6, 4.3 Hz, 1H), 2.68 (br s, 1H), 1.93 (m, 2H), 1.47 (s, 9H); MS *m*/*z* 290 ($M^+ + H^+$). Anal. Calcd for $C_{13}H_{23}NO_6$: C: 53.96, H: 8.01, N: 4.79. Found: C: 53.96, H: 7.96, N: 4.77.

(3*S*,4*R*,6*R*)-4-Hydroxy-6-propylpiperidine-1,3-dicarbolylic Acid 1-*tert*-Butyl Ester 11a. To a solution of **8a** (0.5 g, 1.2 mmol) in 5 mL of THF were added TBAF (0.9 g, 3.4 mmol) and 0.01 mL of HOAc. After the solution was stirred at room temperature for 24 h, the solvent was removed in vacuo, and the residue was chromatographed to give the corresponding alcohol. This alcohol was dissolved in 3 mL of methanol, and then 3 mL of 10% aqueous NaOH was added. The mixture was stirred at room temperature for 3 h before methanol was evaporated. The residue was acidified to pH = 4 by adding 3 N HCl and then extracted with ethyl acetate. The combined organic phase was dried and concentrated to give crude product, which was recrystallized to give 286 mg (87%) of **11a** as a fine crystals: $[\alpha]^{20}_D$ −10.9 (*c* 0.6, $CHCl_3$); IR (neat) 3317, 2920, 1741, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.5 (br s, 1H), 4.57 (dm, J = 14.1 Hz, 1H), 4.35 (m, 1H), 4.05 (m, 1H), 2.98 (dd, J = 14.1, 3.2 Hz, 1H), 2.88 (br s, 1H), 2.01 (m, 1H), 1.80 (m, 1H), 1.62 (m, 2H), 1.44 (br s, 9H), 1.30 (m, 2H), 0.91 (t, J = 8.2 Hz, 3H); MS *m*/*z* 287 (M^+). Anal. Calcd for $C_{14}H_{25}NO_5$: C: 58.54, H: 8.71, N: 4.88. Found: C: 58.34, H: 8.88, N: 4.75.

(*S*)-4-*tert*-Butyldimethylsiloxy-3-[*N*-(phenylmethoxycarbonyl)-*N*-(2-carbomethoxyethyl)]aminobutyric Acid Methyl Ester 12. To a stirring solution of **4** (1.2 g, 4.5 mmol) in 5 mL of CH_2Cl_2 were added 20 mg of DMAP, *tert*-butyldimethylsilyl chloride (0.8 g, 5.3 mmol), and 1 mL of triethylamine. After the mixture was stirred at room temperature for 6 h, it was partitioned between 30 mL of CH_2Cl_2 and 10 mL of brine. The organic phase was dried and evaporated, and the residue was chromatographed to give the corresponding silyl ether. This silyl ether was dissolved in 10 mL of methanol, and then 100 mg of 10% Pd/C was added. After the mixture was stirred under H_2 for 10 h, the catalyst was filtered off. The filtrate was added methyl acrylate (0.5 mL, 5.5 mmol) in a dropwise manner. The resultant solution was stirred at room temperature for 48 h before the solvent was evaporated. The residue was dissolved in 5 mL of 1,4-dioxane, and then benzyl chloroformate (1.0 g, 5.9 mmol) and $NaHCO_3$ (0.6 g, 7 mmol) were added. After the mixture was stirred at 30 °C for 5 h, the solvent was removed in vacuo. The residue was diluted with 10 mL of water and 20 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed to afford 1.6 g (76%) of **12**: $[\alpha]^{20}_D$ −10.2 (*c* 4.3, $CHCl_3$); IR (neat) 2955, 2858, 1741, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 5H), 5.28 (s, 2H), 4.10 (m, 1H), 4.01 (m, 1H), 3.83 (s, 6H), 3.81 (m, 3H), 2.98 (m, 1H), 2.81 (m, 3H), 1.03 (s, 9H), 0.18 (s, 6H); MS *m*/*z* 467 (M^+); HRMS found *m*/*z* 467.2331, $C_{23}H_{37}NO_7Si$ requires 467.2323.

(3*R*,4*S*,6*S*)-4-*tert*-Butyldimethylsiloxy-6-*tert*-butyldimethylsiloxymethylpiperidine-3-carboxylic Acid Methyl Ester 15. To a solution of **12** (0.8 g, 1.7 mmol) in 10 mL of dry benzene were added sodium (70 mg, 3 mmol) in small pieces and 0.05 mL of methanol. After the mixture was stirred under N_2 at room temperature for 48 h, 5 mL of saturated aqueous NH_4Cl was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. After the combined organic phase was washed with brine and dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed to provide the crude Dieckmann condensation products. This mixture was dissolved in 3 mL of CH_2Cl_2, and then *tert*-butyldimethylsilyl chloride (300 mg, 2 mmol), DMAP (20 mg, 0.16 mmol), and 0.3 mL of triethylamine were added. After the reaction solution was stirred at room temperature for 24 h, it was partitioned between 20 mL of CH_2Cl_2 and 10 mL of brine. The organic layer was concentrated, and the residue was chromatographed to give the corresponding silyl ethers. They were dissolved in 10 mL of methanol, and then 100 mg of 10% Pd/C was added. The mixture was stirred under H_2 at room temperature for 5 h before the catalyst was filtered off. The filtrate was concentrated and chromatographed to give crude **1**3, which was dissolved in 15 mL of ethyl acetate. After this solution was added to 100 mg of Raney-Ni (50% slurry in water), the mixture was stirred under H_2 (40 atm) at 40 °C for 12 h. The catalyst was filtered off, and the filtrate was concentrated followed by chromatography to give 0.35 g (49% overall yield from **12**) of **15**: $[\alpha]^{22}_D$ −47.6 (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (m, 1H), 3.75 (dd, J = 9.8, 5.6 Hz, 1H), 3.65 (s, 3H), 3.53 (dd, J = 9.8, 4.8 Hz, 1H), 3.26 (dd, J = 13.5, 3.5 Hz, 1H), 2.76 (dd, J = 13.5, 3.7 Hz, 1H), 2.69 (m, 1H), 2.66 (m, 1H), 1.95 (s, 1H), 1.74 (m, 2H), 0.90 (s, 9H), 0.86 (s, 9H), 0.59 (s, 6H), 0.49 (s, 6H); MS *m*/*z* 417 (M^+); HRMS found *m*/*z* 417.2727; $C_{20}H_{43}NSi_2O_4$ requires 417.2723.

(3*S*,4*R*,6*R*)-(4-Hydroxy-6-(6-*tert*-butyldiphenylsiloxyhexyl)piperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester 16. To a stirring solution of **9d** (1.1 g, 3 mmol) in 3 mL of CH_2Cl_2 were added *tert*-butyldiphenylsilyl chloride (900 mg, 3.3 mmol) 20 mg of DMAP, and 0.5 mL of triethylamine. The resultant solution was stirred at room temperature

for 6 h before it was partitioned between 20 mL of CH_2Cl_2 and 10 mL of brine. The organic phase was separated, dried, and concentrated, and the residue was chromatographed to give 1.55 g (85%) of **16**. $[\alpha]^{15}_D$ −16.5 (*c* 3.2, $CHCl_3$); IR (neat) 3460, 2933, 2859, 1740, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.39 (m, 6H), 4.55 (m, 1H), 4.32 (m, 1H), 3.95 (m, 1H), 3.72 (s, 3H), 3.63 (t, J = 6.4 Hz, 2H), 3.43 (dm, J = 10.8 Hz, 1H), 2.95 (dd, J = 13.2, 3.4 Hz, 1H), 2.83 (br s, 1H), 1.97 (m, 1H), 1.72 (m, 1H), 1.55 (m, 4H), 1.42 (s, 9H), 1.30 (m, 6H), 1.05 (s, 9H); MS *m*/*z* 498 (M^+ − Boc + $2H^+$). Anal. Cacld for $C_{34}H_{51}NO_6Si$: C: 68.31, H: 8.60, N: 2.34. Found: C: 68.44, H: 8.75, N: 2.00.

(3*S*,4*R*,6*R*)-6-(6-Hydroxyhexyl)-2-oxohexahydrooxazlolo[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 17. To a solution of **16** (1.2 g, 2 mmol) in 3 mL of methanol was added 3 mL of 10% NaOH solution. After the mixture was stirred at room temperature for 6 h, methanol was removed in vacuo. The residue was acidified to pH = 4 by adding 3 N HCl, and then the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated. After the residue was dissolved in 15 mL of dry benzene, DPPA (0.66 g, 2.4 mmol) and 1 mL of triethylamine were added. The solution was heated at reflux for 16 h, and then solvent was evaporated. The residue was chromatographed to give the corresponding oxazolidinone, which was dissolved in 5 mL of THF. After this solution was added TBAF (0.65 g, 2.5 mmol), it was stirred at room temperature for 6 h. The solvent was evaporated, and the residue was chromatographed to provide 467 mg (68%) of **17**: $[\alpha]^{22}_D$ −63.8 (*c* 1.02, $CHCl_3$); IR (neat) 3298, 2935, 2856, 1748, 1733, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (br s, 1H), 4.91 (m, 1H), 4.04 (m, 2H), 3.95 (m, 1H), 3.64 (t, J = 6.5 Hz, 2H), 2.87 (m, 2H), 2.27 (m, 1H), 1.56 (m, 3H), 1.45 (s, 9H), 1.33 (m, 8H); MS *m*/*z* 342 (M^+), HRMS found *m*/*z* 342.2122 (M^+), $C_{17}H_{30}N_2O_5$ requires 342.2090.

(3*S*,4*R*,6*R*)-2-Oxo-6-(8-oxooct-6-enyl)hexahydrooxazlolo-[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 18. To a solution of **17** (220 mg, 0.64 mmol) in 5 mL of CH_2Cl_2 was added Dess−Martin oxidant (330 mg, 0.78 mmol). The solution was stirred at room temperature for 2 h before it was filtered through silica gel. The filtrate was concentrated, and the residue was chromatographed to give the corresponding aldehyde, which was dissolved in 3.5 mL of dry ethyl ether and 1.5 mL of dry THF. To this solution was added triphenylarsonium salt of bromoacetaldehyde (338 mg, 0.96 mmol), K_2CO_3 (106 mg, 0.77 mmol), and 30 μL of water. The resultant mixture was stirred at room temperature for 20 h, and then it was filtered through silica gel. The filtrate was concentrated, and the residue was chromatographed to give 172 mg (73%) of unsaturated aldehyde **18**: $[\alpha]^{22}_D$ −56.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, J = 7.8 Hz, 1H), 6.85 (dd, J = 15.6, 6.8 Hz, 1H), 6.12 (dd, J = 15.6, 7.8 Hz, 1H), 5.60 (m, 1H), 4.92 (m, 1H), 4.1 (m, 2H), 3.95 (m, 1H), 2.88 (m, 1H), 2.33 (m, 3H), 1.61 (m, 3H), 1.44 (s, 9H), 1.32 (br s, 6H); MS *m*/*z* 366 (M^+), HRMS found *m*/*z* 311.1634 (M^+ − *t*-Bu + $2H^+$), $C_{15}H_{23}N_2O_5$ requires 311.1661.

(3*S*,4*R*,6*R*)-2-Oxo-6-trideca-6,8-dienylhexahydrooxazlolo[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 19. A solution of n-pentyl phenyl sulfone (52 mg, 0.24 mmol) in 1 mL of dry THF was cooled to −78 °C, and then *n*-BuLi (2 M solution in hexane, 0.24 mmol) was added. The reaction mixture was stirred at this temperature for 2 h before a solution of **18** (40 mg, 0.11 mmol) in 0.5 mL of dry THF was added. The stirring was continued for another 1 h, and then 1 mL of saturated aqueous NH_4Cl was added at −78 °C to quench the reaction. After the mixture was warmed to room temperature, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed to give the corresponding alcohol. This alcohol was dissolved in 1 mL of dry CH_2Cl_2, and then benzoyl chloride (15.5 mg, 0.11 mmol), 1 mg of DMAP, and 20 mL of triethylamine were added. After the solution was stirred at room temperature for 3 h, the solvent was removed in vacuo, and the residue was chromatographed to give the corresponding ester. This ester was dissolved in 1 mL of methanol and 0.5 mL of ethyl acetate, and the solution was cooled to −25 °C. To this solution was added 0.42 g of 6% sodium amalgam. The mixture was stirred at this temperature for 1 h before the liquid was decanted into water. The residue was washed with ethyl acetate for three times, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was chromatographed to give 31.7 mg (69%) of **19**: $[\alpha]^{22}_D$ −47.6 (*c* 0.82, $CHCl_3$); IR (neat) 3300, 2932, 2859, 1749, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 2H), 5.50 (m, 3H), 4.92 (m, 1H), 4.10 (m, 2H), 3.95 (m, 1H), 2.88 (m, 1H), 2.21 (m, 1H), 2.02 (m, 4H), 1.84 (m, 1H), 1.44 (m, 2H), 1.39 (br s, 9H), 1.26 (m, 10H), 0.86 (t, J = 6.4 Hz, 3H); MS *m*/*z* 420 (M^+), HRMS found *m*/*z* 420.3008 (M^+); $C_{24}H_{40}N_2O_4$ requires 420.3028.

Pseudodistomin B Triacetate 20. To a solution of **19** (15 mg, 0.036 mmol) in 1 mL of methanol was added 1 mL of 10% aqueous NaOH. The resultant mixture was refluxed for 3 h before it was extracted with CH_2Cl_2. The combined organic phase was dried and evaporated, and the residue was dissolved in 2 mL of CH_2Cl_2. To this stirring solution were added 1 mg of DMAP, 50 μL of Ac_2O, and 50 μL of triethylamine. The stirring was continued for 3 h, and then the solvent was evaporated. The residue was chromatographed to give the crude acylation product. This product was dissolved in 1 mL of ethyl acetate, and then 1 mL of saturated methanolic HCl was added. After the solution was stirred at room temperature for 30 min, 3 mL of 20% aqueous K_2CO_3 was added to quench the reaction. The resultant mixture was extracted with CH_2Cl_2, and the combined organic phase was dried and concentrated. The residue was dissolved in 1 mL of CH_2Cl_2 before 1 mg of DMAP, 50 μL of Ac_2O, and 50 μL of triethylamine were added. The stirring was continued for 2 h, and then the solvent was evaporated. The residue was chromatographed to give 10 mg (69%) of **20**: $[\alpha]^{22}_D$ 35.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 2H), 5.50 (m, 2H), 5.15 (br s, 1H), 4.92 (br s, 3/4H), 4.61 (m, 1/4H), 4.51 (br s, 1/4H), 4.37 (br s, 3/4H), 4.01 (br s, 1/4H), 3.96 (m, 3/4H), 3.29 (m, 3/4H), 2.93 (m, 1/4H), 2.14 (br s, 2H), 2.04 (br s, 13H), 1.74 (m, 2H), 1.55 (m, 2H), 1.30 (br s, 10H), 0.89 (t, J = 6.5 Hz, 3H); MS *m*/*z* 420 (M^+).

(3*S*,4*R*,6*S*)-6-Hydroxymethyl-2-oxohexahydrooxazlolo-[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 21. To a stirring solution of **9e** (1.2 g, 4.1 mmol) in 3 mL of CH_2Cl_2 were added *tert*-butyldiphenyl chloride (1.2 g, 4.4 mmol), 20 mg of DMAP, and 0.5 mL of triethylamine. The resultant solution was stirred at room temperature for 6 h, and then it was partitioned between 20 mL of CH_2Cl_2 and 10 mL of brine. The organic phase was dried and concentrated, the residue was chromatographed to give the corresponding silyl ether. This silyl ether was dissolved in 3 mL of methanol, and then 3 mL of 10% aqueous NaOH was added. The mixture was stirred at room temperature for 6 h before methanol was removed in vacuo. The residue was added 3 N HCl to adjust pH to 4, and then it was extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was dissolved in 15 mL of dry benzene, and then DPPA (1.2 g, 4.4 mmol) and 1.5 mL of triethylamine were added. After the resultant solution was heated at reflux for 16 h, the cooled solution was concentrated, and the residue was chromatographed to give the corresponding oxazolidinone, which was dissolved in 3 mL of THF. After TBAF (1.2 g, 4.6 mmol) was added to this solution, it was stirred at room temperature for 6 h. The solvent was evaporated, and the residual oil was chromatographed to provide 0.59 g (52%) of **21**: $[\alpha]^{21}_D$ −111.4 (*c* 0.92, CH_3OH); IR (neat) 3456, 3298, 2970, 1744, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 1H), 5.05 (m, 1H), 4.13 (m, 2H), 4.04 (m, 1H), 3.91 (m, 1H), 3.62 (m, 1H), 3.10 (m, 1H), 2.20 (m, 1H), 2.03 (m, 1H), 1.51 (br s, 9H); MS *m*/*z* 272 (M^+); HRMS found *m*/*z* 272.1374, $C_{12}H_{20}N_2O_5$ requires 272.1376.

(3*S*,4*R*,6*S*)-6-Benzenesulfonylmethyl-2-oxohexahydrooxazlolo[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 22. To a stirring solution of **21** (110 mg, 0.4 mmol) in 3 mL of CH_2Cl_2 were added MsCl (58 mg, 0.5 mmol), 2 mg

of DMAP, and 0.1 mL of triethylamine. The resulting solution was stirred at room temperature for 6 h before it was partitioned between 15 mL of CH_2Cl_2 and 5 mL of brine. The organic phase was separated, dried, and concentrated, and then the residue was chromatographed to give the corresponding mesylate. After this product was dissolved in 3 mL of 1,4-dioxane, $NaHCO_3$ (50 mg, 0.6 mmol) and thiophenol (66 mg, 0.6 mmol) were added. The resulting mixture was stirred at room temperature for 24 h before it was filtered through silica gel. The filtrate was concentrated, and the residue was chromatographed to give the corresponding thiol ether, which was dissolved in 3 mL of dry CH_2Cl_2. To this solution was added MCPBA (60%, 287 mg, 1 mmol). After the mixture was stirred at room temperature for 3 h, 5 mL of 10% aqueous K_2CO_3 was added. The stirring was continued for 10 min, and then the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. After the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo, the residue was chromatographed to give 133 mg (87%) of **22:** $[\alpha]^{15}_D$ −69.2 (*c* 0.4, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.61 (m, 3H), 5.1 (s, 1H), 4.97 (m, 1H), 4.37 (m, 1H), 4.02 (m, 1H), 3.99 (m, 1H), 3.40 (m, 2H), 3.07 (m, 1H), 2.60 (m, 1H), 2.15 (m, 1H), 1.29 (br s, 9H); MS *m*/*z* 396 (M^+); HRMS found *m*/*z* 396.1369, $C_{18}H_{24}SN_2O_6$ requires 396.1383.

(3*S*,4*R*,6*S*)-2-Oxo-6-pentadeca-1,3,8,10-tetraenylhexahydrooxazolo[4,5-*c*]piperidine-5-carboxylic Acid *tert*-Butyl Ester 24. A solution of **22** (85 mg, 0.21 mmol) in 3 mL of DME was cooled to −78 °C. To this stirring solution was added *n*-BuLi (2 M solution in hexane, 0.21 mmol). After the solution was stirred at this temperature for 2 h, a solution of aldehyde **23** (108 mg, 0.53 mmol) in 1 mL of DME was added in a dropwise manner. The stirring was continued for 30 min before saturated aqueous NH_4Cl was added to quench the reaction. The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was washed with brine and dried. After the solvent was evaporated, the residue was chromatographed to give the corresponding coupling products. This mixture was dissolved in 1 mL of CH_2Cl_2, and then at 0 °C benzoyl chloride (33 mg, 0.23 mmol), 3 mg of DMAP, and 50 mL of triethylamine were added with stirring. The ice bath was removed, and the stirring was continued for 3 h. After the mixture was filtered through silica gel, the filtrate was concentrated, and then the residue was dissolved in 1 mL of methanol and 0.5 mL of ethyl acetate. The resultant solution was cooled to −25 °C, and then 0.8 g of 6% sodium amalgam was added. After the mixture was stirred at this temperature for 1 h, the liquid was decanted into water, and the residue was washed with ethyl acetate for three times. The aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was chromatographed to give 48 mg (52%) of **24**. $[\alpha]^{11}_D$ +10.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.09 (m, 4H), 5.65 (m, 5H), 4.99 (m, 1H), 4.60 (m, 1H), 4.08 (m, 2H), 3.08 (m, 1H), 2.45 (m, 1H), 2.23 (m, 6H), 1.71 (m, 1H), 1.48 (br s, 9H), 1.55−1.35 (m, 6H), 0.95 (t, J = 6.8 Hz, 3H); MS *m*/*z* 444 (M^+); HRMS found *m*/*z* 444.2982, $C_{26}H_{40}N_2O_4$ requires 444.2976.

Pseudodistomin F. To a solution of 24 (10 mg, 0.023 mmol) in 1 mL of methanol was added 1 mL of 30% aqueous KOH. After the resultant mixture was refluxed for 3 h, it was extracted with CH_2Cl_2. The combined organic phase was dried and concentrated. The residue was dissolved in 1 mL of ethyl acetate, and then 1 mL of saturated methanolic HCl was added. After the resultant solution was stirred at room temperature for 30 min, 3 mL of 20% aqueous K_2CO_3 was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the combined organic phase was dried and concentrated. The residue was chromatographed to afford 5 mg (70%) of **1f**: $[\alpha]^{11}_D$ −12.6 (*c* 0.2, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.17 (dm, J = 14.6 Hz, 1H), 6.05 (dm, J = 14.6 Hz, 1H), 6.00 (dm, J = 14.6 Hz, 2H), 5.67 (dm, J = 14.6 Hz, 1H), 5.55 (dm, J = 14.6 Hz, 3H), 3.95 (m, 1H), 3.45 (m, 1H), 2.73 (m, 3H), 2.06 (m, 6H), 1.85 (m, 2H), 1.48 (m, 3H), 1.36 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); MS *m*/*z* 318 (M^+).

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grants 29725205 and 29972049), and Qiu Shi Science & Technologies Foundation for their financial support.

Supporting Information Available: ^{1}H NMR spectra of compounds **5b**, **5c**, **8b**, **12**, **15**, **17**−**19**, **21**, **22**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000447Q