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Efficient and Selective Synthesis of 6,7-Dehydrostipiamide via Zr-Catalyzed Asymmetric Carboalumination and Pd-Catalyzed Cross-Coupling of Organozincs†

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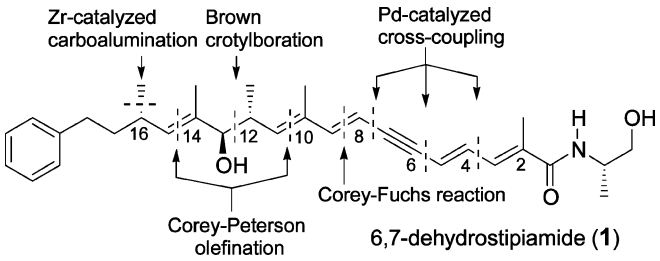
ABSTRACT



6,7-Dehydrostipiamide has been synthesized in 23% yield in 15 steps in the longest linear sequence through the application of the Zr-catalyzed asymmetric carboalumination and the Pd-catalyzed organozinc cross-coupling in addition to the Brown crotylboration, the Corey–Peterson olefination, and the Corey–Fuchs reaction for carbon–carbon bond formation.

We report herein an efficient and selective synthesis of 6,7-dehydrostipiamide[1] (**1**), a nonnatural multidrug resistance reversal agent of high potency and low toxicity, in 23% yield over 15 steps in the longest linear sequence. Of the eight crucial carbon−carbon bond-forming steps in the synthesis, three employed Pd-catalyzed organozinc cross-coupling reactions,[2] while two single bonds to the asymmetric carbon centers, i.e., C12 and C16, were constructed by using recently developed Zr-catalyzed asymmetric carboalumination[3] and Brown crotylboration,[4] respectively. Both of the trisubstituted alkenes at C10 and C14 were constructed through the use of the Corey version of the Peterson olefination (Corey−Peterson olefination hereafter),[5] while introduction of C8 was

† We wish to dedicate this paper to the memory of Professor S. Masamune.

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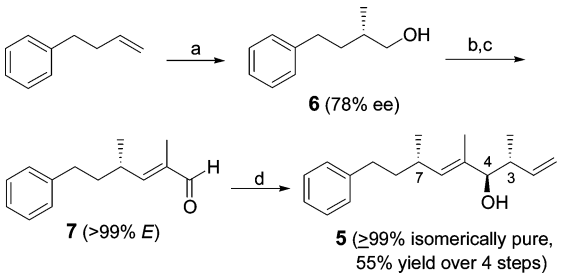
Scheme 1[a]



[a] Reagents and conditions: (a) (i) Me_3Al (2 equiv), 5% (+)-$(NMl)_2ZrCl_2$, IBAO (1 equiv); (ii) O_2; 85%. (b) $(COCl)_2$, DMSO. (c) (i) $Et_3SiCLiMeCH{=}NCy$, THF, −20 °C; (ii) CF_3CO_2H, 0 °C; 81%. (d) (+)-$lpc_2BCH_2CH{=}CHCH_3$-(*E*), THF−ether, −78 °C, 15 h, 80%.

achieved by the Corey−Fuchs reaction.[6] 6,7-Dehydrostipiamide,[1] as well as structurally related natural products, including stipiamide (phenalamide A_1) (**2**),[1,7] phenalamide A_2 (**3**),[8] and myxalamide A (**4**),[9] have been synthesized since 1997. With the exception of asymmetric crotylboration, however, none of the carbon−carbon bond-forming reactions mentioned above have been employed in previously reported syntheses.

The preparation of a key intermediate **5** corresponding to the C11−C18 moiety was achieved only in four steps from 4-phenyl-1-butene in 55% overall yield, as summarized in Scheme 1.The Zr-catalyzed asymmetric carboalumination[3] of 4-phenyl-1-butene with Me_3Al (2 molar equiv), 5 mol % (+)-$(NMI)_2ZrCl_2$,[10] where NMI is 1-neomenthylindenyl derived from (+)-menthol, and isobutylaluminoxane[3e] (IBAO), prepared by the reaction of 1 molar equiv each of $^iBu_3Al$ and H_2O, in CH_2Cl_2 at 0 °C produced, after oxidation with O_2, (2*S*)-2-methyl-4-phenyl-1-butanol[1] (**6**) in 85% yield and 78% ee. Although the Mosher ester analysis[11] of **6** indicated an approximately 80% ee for **6**, signal overlappings in ^1H NMR spectra did not permit an accurate measurement of enantioselectivity for this case. So, **6** was oxidized by Swern oxidation[12] (96% yield) and then converted to the corresponding carboxylic acid with $KMnO_4-KH_2PO_4$ in aqueous ^tBuOH[13] (70% yield). The resultant carboxylic acid was treated with both *R* and *S* isomers of α-(1-aminoethyl)-naphthalene, $NCPO(OEt)_2$, and NEt_3 in DMF;[14] the carboxamide thus obtained in 92% yield was analyzed by GLC and NMR spectroscopy, both of which indicated an enantiomeric excess of 78%. The results presented above have also confirmed that little or no racemization occurs in the Swern oxidation step.

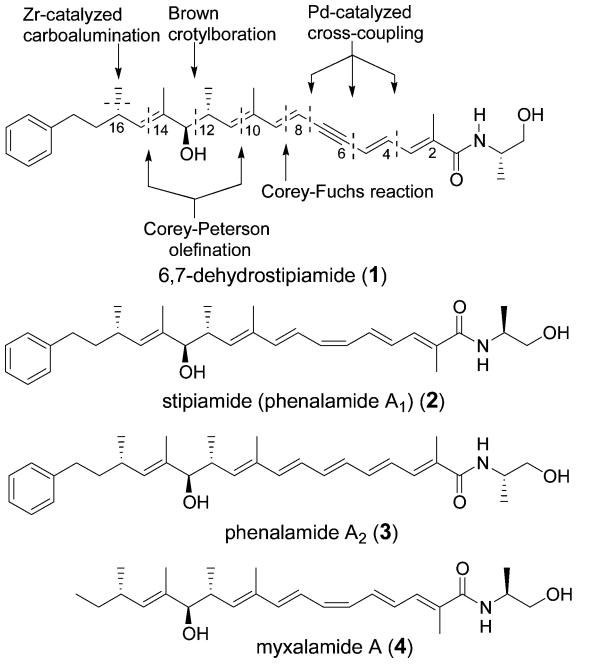


Figure 1.

After Swern oxidation of **6**, the crudely obtained aldehyde was subjected to the Corey−Peterson olefination with a reagent generated in situ by treating *N*-cyclohexyl(2-triethylsilylpropylidene)imine with ^sBuLi at −78 °C.[5] After treatment with CF_3COOH, the desired aldehyde **7** of >99% *E* was obtained in 81% yield. We initially converted **6** into **7** in four steps. Following the Swern oxidation of **6** as stated above, the Corey−Fuchs reaction,[6] followed by conversion of the 1,1-dibromo-1-alkene thus formed into the corresponding methylalkyne (92% yield based on **6**), and subsequent hydrozirconation and carbonylation with ^nBuNC[15] (87% yield) provided **7** in 80% combined yield from **6**. Clearly, the route shown in Scheme 1 is more efficient than either that described above or that involving the Horner−Emmons olefination reported previously.[1]

Brown's asymmetric crotylboration[4] of **7** using (+)-(*E*)-$(CH_3CH{=}CHCH_2)BIpc_2$ produced the desired **5** in 80% yield. The ^1H NMR spectra of the crude product obtained without isomeric separation revealed only two sets of doublets at 3.70 (d, $J = 8.7$ Hz) and 3.86 (d, $J = 7.2$ Hz) for the methine proton at C4 in ratio of ≥30:1. Evidently, the configuration at C7 exerts little or no effect on the ^1H NMR signals for protons bonded to C3 and C4. The 3*R*,4*R*

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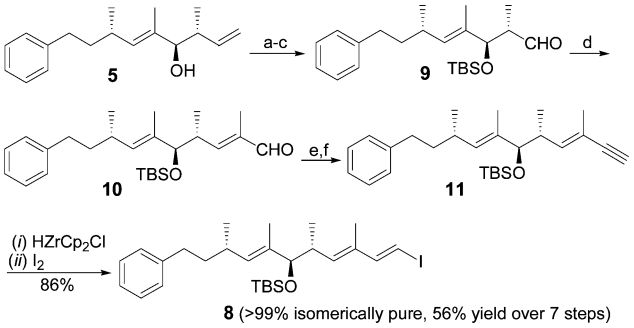
Scheme 2[a]



8 (>99% isomerically pure, 56% yield over 7 steps)

[a] Reagents and conditions: (a) TBSCl, DMAP, imidazole. (b) AD-mix-α. (c) $NaIO_4$; 90% (over three steps); (d) (i) $Et_3SiCLiMe$-CH=NCy, THF, −20 °C; (ii) CF_3CO_2H, 0 °C; 80%. (e) CBr_4, PPh_3, Zn. (f) (i) ^{n}BuLi; (ii) NH_4Cl; 90%.

configuration may be tentatively, but safely, assigned to the major isomer on the basis of the use of (+)-(*E*)−(CH_3CH=$CHCH_2$)$BIpc_2$,[4] and the diastereomeric ratio of ≥30:1 mandates that the configuration at both C3 and C4 is ≥97% *R*.

Although the *S* and *R* configurations at C7 were indistinguishable by ^{1}H NMR spectroscopy (vide supra), ^{13}C NMR spectra of crudely isolated **5** showed two sets of signals separated by at least 0.1 ppm for eight carbon atoms, including C7 (δ 31.79 (*S*) and 31.96 (*R*), *S*:*R* = 9:1). Column chromatography (silica gel, 1/25 ethyl acetate/hexanes) provided **5** (≥80:1 dr) in 80% yield from **7**. Thus, the stereoisomeric purity at C7 was improved to ≥99% *S* by simple chromatography, and the overall enantiomeric purity of **5** may safely be estimated to be >99.9% ee.

Conversion of **5** into another key intermediate **8** was achieved in seven steps in 56% combined yield. Protection of **5** with ^{t}BuMe$_2$SiCl (TBSCl) proceeded in 96% yield, and the resultant product was converted to aldehyde **9** by two successive oxidations; first with AD-mix-α[16] (Aldrich), and then with $NaIO_4$, as reported previously,[1] in 94% combined yield. Conversion of **9** into **10** was achieved by using the Corey−Peterson olefination in 80% yield (>99% *E*). The Corey−Fuchs reaction[6] of **10** with CBr_4, PPh_3, and Zn (98% yield), treatment of the product with ^{n}BuLi followed by acidification to give **11** (92% yield), and its hydrozirconation−iodinolysis (86% yield) provided **8** as a ≥99% isomerically pure compound (Scheme 2).

In the previously reported synthesis of stipiamide and 6,7-dehydrostipiamide,[1] **10** was directly converted to **8** by the reaction of **10** with CHI_3 and $CrCl_2$[17] in 70% yield. It reduces the number of steps by two but also reduces the yield by 7%. In our hands, an *E*/*Z* ratio of approximately 5 was observed, and a concern about the scalability of the process was also expressed.[1] We also investigated the applicability of a tandem alkynylation−methylation reaction of 1,1-dibromo-1-alkenes, recently reported by us.[18] To this end, aldehyde **9** was subjected to the Corey−Fuchs reaction[6] (98% yield). The product was first alkynylated with BrZnC≡$CSiMe_3$ in the presence of 5% Cl_2Pd(DPEphos), where DPEPhos is bis(*o*-diphenylphosphinophenyl) ether, and 10% DIBAL-H in 75% yield; subsequent methylation with Me_2-Zn in the presence of Pd(^{t}Bu$_3$P)$_2$ in quantitative yield, followed by desilylation with K_2CO_3 and MeOH (98% yield), gave **11** (>98% stereoisomerically pure) in 72% combined yield over three steps from **9**. The combined yield indicated above is the same as that shown in Scheme 2. We judge that the two procedures are of comparable merits.

For a convergent final assembly of the carbon framework of 6,7-dehydrostipiamide, ethyl (2*E*,4*E*)-2-methyl-2,4-heptadien-6-ynoate (**12**) was prepared, as recently reported by us.[19] Thus, (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne,[20] obtained in 81% yield by treating commercially available (Aldrich) (*E*)-ICH=CHBr with Me_3SiC≡CZnBr in the presence of 2% Pd(PPh_3)$_4$, was successively treated with ^{t}BuLi (2.0 equiv) in ether, $ZnBr_2$, THF, and (*E*)-BrCH=C(Me)COOEt in the presence of 2% Cl_2Pd(PPh_3)$_2$ and 4% DIBAL-H in THF (95% yield). After desilylation with K_2-CO_3 and EtOH, **12** was obtained in 76% combined yield over three steps from (*E*)-ICH=CHBr, Me_3SiC≡CZnBr, and (*E*)-BrCH=C(Me)CO_2Et. The ^{13}C NMR spectrum of **12** indicated it to be >98% *E*,*E*. For the critical cross-coupling between **8** and **12**, **12** was first converted to its Zn derivative (**13**) via lithiation with LDA (1 equiv) in THF, followed by treatment with dry $ZnBr_2$ in THF. Its cross-coupling with **8**, in the presence of 5% Cl_2Pd(PPh_3)$_2$ and 10% DIBAL-H,[2] proceeded cleanly to give **14** (>99% isomerically pure) in 94% yield. Thus, the synthesis of **14** was achieved in 29% yield over 12 steps in the longest linear sequence (Schemes 1−3).

As recently reported by us,[19] **12** can be converted to (*E*,*E*,*E*)-BrCH=CHC≡CCH=CHCH=C(Me)COOEt (**15**) in 82% yield by the Pd-catalyzed reaction of the zinco derivative of **12** with (*E*)-ICH=CHBr. We therefore sought a more convergent and potentially superior route to **14** through the use of **15**. To this end, **9** was converted to >99% pure **16** via the Corey−Fuchs reaction in 96% yield over two steps (Scheme 4). To our disappointment, however, hydrozirconation of **16** with HZrCp_2Cl (2 equiv),[21] followed by successive addition of $ZnCl_2$ (2 equiv), **15** (1.2 equiv), and a catalyst consisting of 5 mol % Cl_2Pd(PPh_3)$_2$, 10 mol % tris(*o*-furyl)-phosphine (TFP), and 10 mol % DIBAL-H in THF at 23 °C for 20 h, led to the formation of the desired compound **14** only in 57% yield. Upon iodinolysis of the hydrozirconation mixture derived from **16**, the corresponding 2-iodo derivative **17** and its 3-iodo isomer were isolated in 74 and 18% yields, respectively, after chromatographic separation. The formation of the unwanted regioisomer must be partially responsible for the low yield of **14**. To probe this issue further, the

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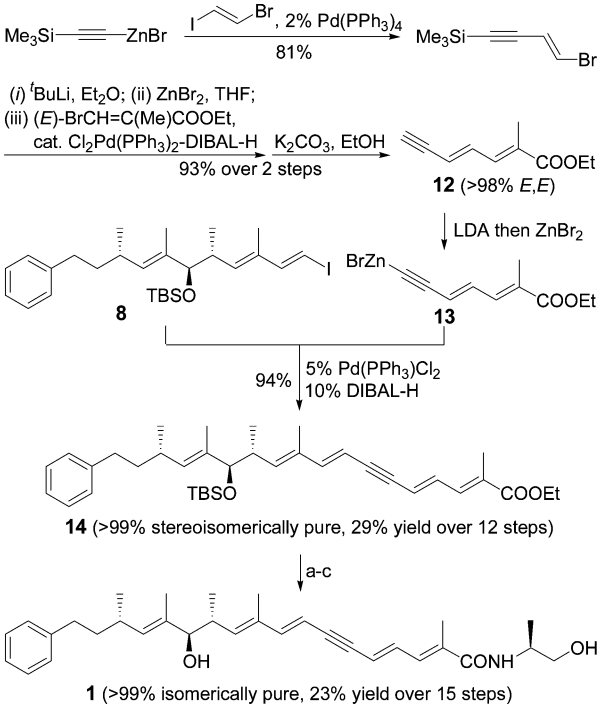
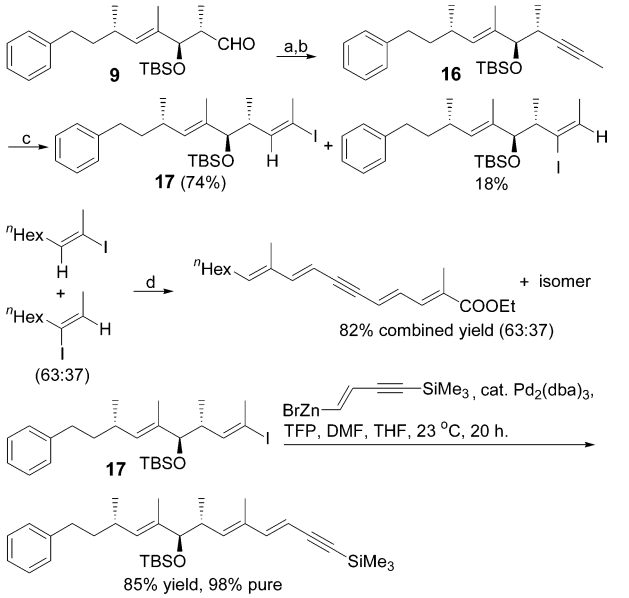
Scheme 3[a]



[a] Reagents and conditions: (a) TBAF, THF, 23 °C, 24 h; (b) LiOH, THF−MeOH−H_2O; (c) (*S*)-MeCH(NH_2)CH_2OH, PyBroP, $^iPr_2NEt$, CH_2Cl_2; 78% yield over three steps.

Scheme 4[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, Zn; (b) (i) ^nBuLi (3.3 equiv); (ii) MeI (5 equiv); 96% over two steps. (c) (i) $HZrCp_2Cl$ (2 equiv); (ii) I_2 (1.6 equiv). (d) (i) ^nBuLi then $ZnBr_2$; (ii) (*E*,*E*,*E*)-BrCH═CHC═CCH═CHCH═C(Me)COOEt (**15**), cat. $Pd_2(dba)_3$, TFP [tris(2-furyl)phosphine], DMF, THF, 23 °C, 20 h.

regioisomerically pure 2-iodo isomer **17** was zincated via lithiation and cross-coupled with **15** under various sets of catalytic conditions, but the yields of **14** were mysteriously and uniformly low (≤30%); the major side reaction is deiodination of **17** (∼60%). Attempts to generate the zinco derivatives of **15** were also disappointing. And yet, both **15** and **17** were shown to be highly satisfactory cross-coupling partners in favorable cases, as shown in Scheme 4.

As summarized in Scheme 3, no difficulty was encountered in converting **14** into the final product **1** in 78% combined yield over three steps. After desilylation with TBAF (85%), ester hydrolysis with LiOH in THF−MeOH−H_2O (96%), followed by amidation with 2 equiv of (*S*)-MeCH(NH_2)CH_2OH (97% ee, Aldrich) using $^iPr_2NEt$ (3 equiv) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, Fluka),[1,22] provided >99% isomerically pure **1** in 95% yield. This linear three-step final assembly of **1** adds a couple of steps in the longest linear sequence relative to a more convergent synthesis involving the use of preamidated intermediates.[1] However, the significantly higher amidation yield of 91% combined yield indicated above, as compared with those reported (54−59%), and an opportunity for readily introducing different amines well justify this strategy. The synthesis of 6,7-dehydrostipiamide (**1**) in 23% overall yield over the 15-step longest linear sequence should prove to be practically attractive as a synthetic route not only to **1** but also to related compounds, including **2**−**4**.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**−**17** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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