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ASYMMETRIC SYNTHESIS OF (*2R,3R,4R*)-3-HYDROXY-4- METHYL-PROPLINE *VIA* CHROMIUM(II) CHLORIDE-MEDIATED COUPLING REACTIONS OF (*S*)-GARNER ALDEHYDE WITH CROTYL BROMIDE

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Abstract–Efficient synthesis of (*2R,4R,4R*)-3-hydroxy-4-methylproline (**1a**), which is an antipode of the component of potent antifungal echinocandins, from (*S*)-Garner aldehyde (**2a**) has been established. The key step is chromium(II) chloride-mediated coupling reactions with crotyl bromide giving homoallyl alcohols (**4a**) and (**4a'**) in a ratio of 83:17.

INTRODUCTION

Compounds containing pyrrolidine or proline derivatives in the molecule found in nature are attracting attention today. Some polyhydroxylated pyrrolidine alkaloids from plants and micro-organisms were found to be potential therapeutic agents *i.e*. anticancer, immuneostimulating, antidiabetic, and antiviral agents.[1] Some peptide antibiotics containing proline derivatives in the molecule,[2] such as echinocandins from *Aspergillus ruglosus*, are known to have a potent antifungal activity,[3] and LY303366, which is a semisynthetic analogue of echinocandin B, to be a potential therapeutic agent for serious systemic *Candida* or *Aspergillus* infecton (Figure 1).[4] In these compounds, pyrrolidine moiety is considered to be responsible for the activity. Hence, a number of papers on stereoselective syntheses of polysubstituted pyrrolidines[5] have been published including our reports.[6]

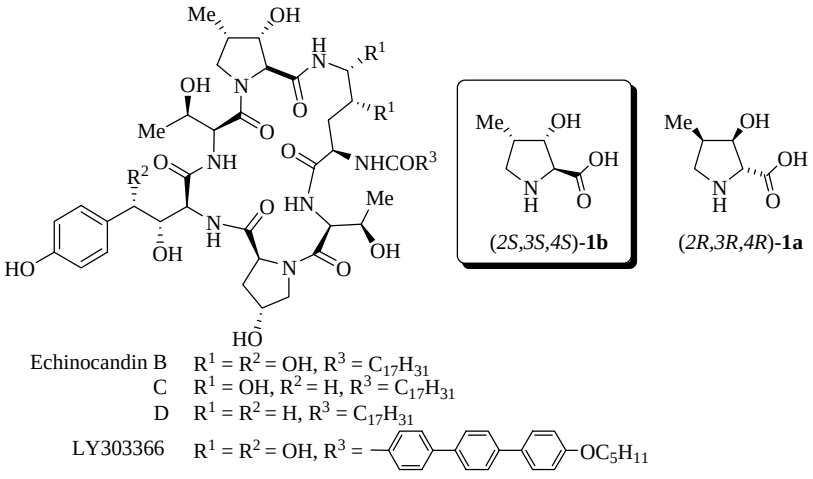
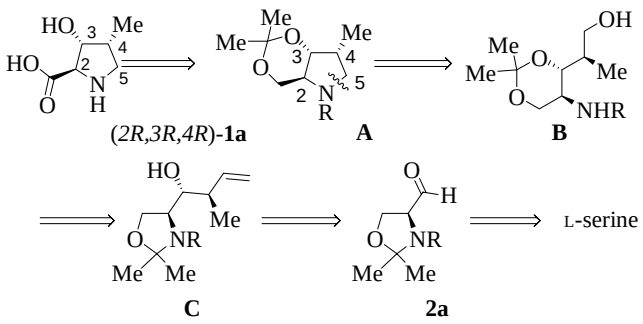


Figure 1

In the active echinocandins, (*2S,3S,4S*)-3-hydroxy-4-methylproline (**1b**) is the common constituent and is considered to be the most likely component which is related to the activity. For the elucidation of the definite structure-activity relationships and for the preparation of the analogues of these peptide antibiotics, it is essential, therefore, to establish an efficient method for the synthesis of **1**. A number of papers reported chiral synthesis of (*2S,3S,4S*)-3-hydroxy-4-methylproline (**1b**).[7, 8] Chiral synthesis of **1a**, the antipode of **1b** is also reported.[9] To study the effect of the segment of **1a** on the echinocandin activity, it may be significant to prepare **1a**. In the present paper, we performed chiral synthesis of (*2R,3R,4R*)-3-hydroxy-4-methylproline (**1a**) from (*S*)-Garner aldehyde (**2a**),[10] which can be easily derived from L-serine. Briefly, the method comprises the chromium(II) chloride-mediated coupling reaction of Garner aldehyde with allyl bromide and the conversion of its coupling product, homoallylic alcohol, to the target compound (**1a**). The chromium(II) chloride-mediated cross couplings of aldehydes with allyl halides are known to proceed chemo- and stereoselectively under mild reaction conditions to give coupling products in moderate to good yields.[6c, 11] The retrosynthetic analysis of **1a** is depicted in Scheme 1. The target amino acid (**1a**) was obtained *via* deprotection of the pyrrolidine derivative (**A**). The cleavage of the C5-N bond gave the intermediate (**B**). In turn, **B** should lead us back to the homoallylic alcohol (**C**), which can be prepared *via* the stereoselective chromium(II) chloride-mediated coupling reactions of the (*S*)-Garner aldehyde (**2a**) with (*E*)-crotyl bromide (**3**).

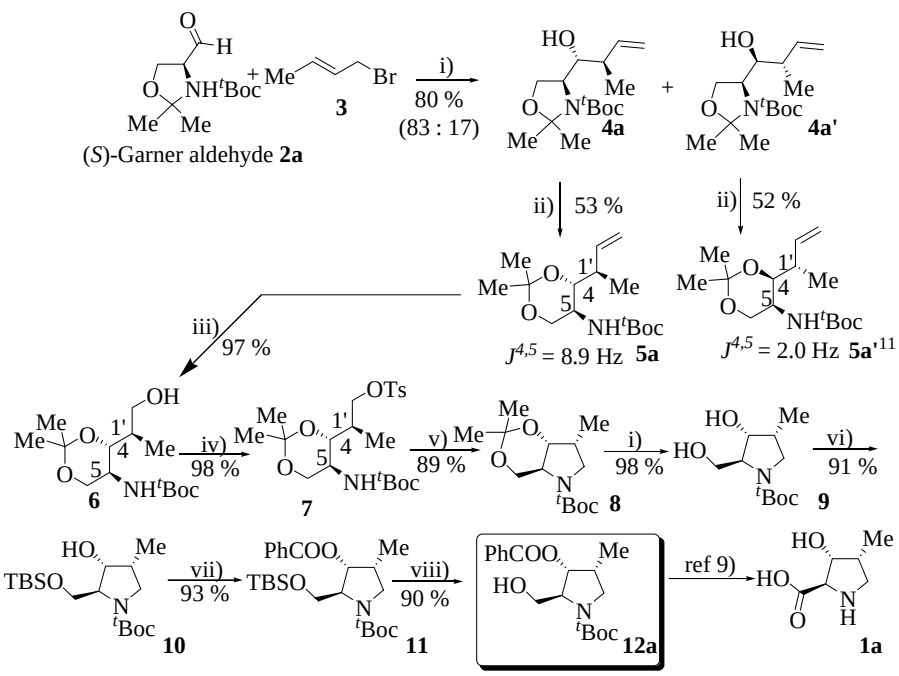


Scheme 1 Retrosynthetic analysis of 1a.

RESULTS AND DISCUSSION

In our previous paper,[6c] we reported that the chromium(II) chloride-mediated coupling reaction of (*S*)-Garner aldehyde (**2a**) with **3** gave, of the 4 possible diastereomers, only two homoallylalcohol diastereomers (**4a**) and (**4a'**) in a ratio of 83:17. Silica gel chromatography separated **4a** and **4a'**, which were converted to acetonides (**5a**) and (**5a'**), respectively. The spectral data of **5a'** was identical with those in the literature.[12] In the ^{1}H NMR spectra of **5a**, the coupling constant ($J^{4,5}$) between the protons at C4 and C5 was 8.9 Hz, implying that the relative configuration between C4 and C5 was *anti*. The Nozaki-Hiyama reaction[13] or the reaction to produce **4a** and **4a'** is to proceed *via* a six-membered transition intermediate (**D**) (Figure 2) and the substituents attached to the α-position to the formyl group in **2** are considered to be arranged as in the Houk models.[14] Thus, the relative configuration between the

hydroxy group at C4 and the methyl group at C1' in **5a** should be also *anti*. However, at this stage, the stereochemistry of C1' on the side chain is not known and hence its absolute stereochemistry can not be defined, which is to be assigned later. Transformation of **5a** to a proline derivative (**12a**) was performed as shown in Scheme 2. By ozonolysis followed by sodium borohydride reduction, **5a** gave an alcohol (**6**) in 97 % yield. Tosylation of **6** and subsequent treatment of the tosylate (**7**) with sodium hydride gave **8**, and the removal of the acetonide in **8** gave the corresponding diol (**9**) in 98 % yield. A series of reactions, including protection of the primary hydroxyl group in **9** with the *t*-butyldimethylsilyl (TBS) group, esterification of the 3-hydroxyl group in the resulting **10** with benzoic acid, and deprotection of the TBS group in **11**, gave a proline derivative (**12a**). The spectral data and physical properties of **12a** including the specific rotation were identical with those in the literature.[8] Accordingly, the absolute configuration of C1' in **5a** and **4a** was determined to be *R*. The transformation of thus prepared **12a** is reported to give the target compound [(*2R,3R,4R*)-**1a**] in 88 %.[9] If (*R*)-Garner aldehyde (**2b**)[10] is employed as the starting material, the present method should give a very efficient method for the preparation of (*2S,3S,4S*)-**1b**. Because our present stereoselective synthesis of the target proline (**1a**) has the following advantageous features; it involves fewer steps (12 steps from the commercially available Garner aldehyde) than the procedures[9, 15] reported by Raghavan *et al.* (15 steps from the commercially available oxazolidinone) and gives final product, **12a** in a better overall yield (22 %) than that of the Raghavan's procedure (6 %), and the key step, the facile chromium(II) chloride-mediated stereoselective coupling reaction of the Garner aldehyde with crotyl bromide, produces, of the 4 possible



Reagents and conditions: i) $CrCl_2$, THF, rt; ii) a) *p*-TsOH·H_2O, MeOH, rt, b) 2,2-dimethoxypropane, *p*-TsOH·H_2O; iii) O_3 then $NaBH_4$; iv) TsCl; v) NaH; vi) TBSCl, imidazole, DMF; vii) PhCOCl, Et_3N, DMAP; viii) TBAF

Scheme 2 Formal synthesis of 1a.

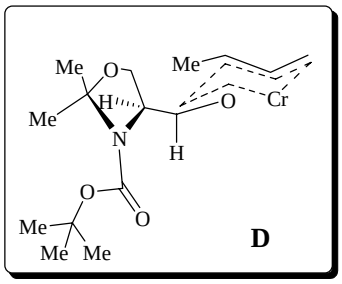


Figure 2

diastereomers, the aimed compound as the major product acompanied with a small amount of another diastereomer.

EXPERIMENTAL

General Methods. Melting points were measured on a Yanagimoto micro melting point apparatus and are recorded uncorrected. ^{1}H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were obtained on a Varian Gemini A-300 and a Brucker DPX-400 instruments. Chemical shifts are reported in parts per million downfield from the internal standard. IR spectra (λ_{max} in cm^{-1}) were recorded on a Japan Spectroscopic Co. A-100 and MS spectra on a Fisons VG Auto Spec instrument. Flash chromatography and MPLC were performed with Merck silica gel Kieselgel 60 (230-400 mesh), and preparative thin layer chromatography (PTLC) with Merck Kieselgel 60 F254 precoated glass plates (0.25 or 0.50 mm). All solvents were of commercial grade and were distilled and dried as specified below before use: tetrahydrofuran (THF) with sodium benzophenone ketyl; CH_2Cl_2 with CaH_2. Garner aldehydes were prepared according to the procedures described by Garner *et al.*[10] Chromium(II) chloride was purchased from Aldrich Chemical Co. and used without further purification.

Preparation of compounds (4a) and (4a').

A THF solution (5 mL) containing **2a** (0.23 g, 1 mmol) and **3** (0.27 g, 2 mmol) was added uropwise to a suspension of $CrCl_2$ (0.61 g, 6.0 mmol) in dry THF (10 mL). After stirring for 2.5 h at rt, sat. aq. $NaHCO_3$ solution (10 mL) was added to the mixture and the organic layer was separated. The aqueous solution was then extracted with AcOEt (2 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give a residue, which was separated by silica gel flash chromatography (hexanes:AcOEt = 6:1) to give **4a** and **4a'**.

Compound (**4a**): Yield 0.19 g (66 %). Colorless oil, $[\alpha]_D$ -30.6° ($CHCl_3$, *c* = 1.04,). IR (neat): 3500 (OH), 1700 (C=O) cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz, 333K): 6.00 (1H, ddd, *J* = 18.0, 11.2, and 6.9 Hz), 5.03 (1H, ddd, *J* = 18.0, 1.9, and 1.0 Hz), 5.02 (1H, ddd, *J* = 11.2, 1.9, and 1.0 Hz), 4.09 (1H, dd, *J* = 8.9 and 2.5 Hz), 3.94 (2H, m), 3.67 (1H, dd, *J* = 8.9 and 6.9 Hz), 2.25 (1H, m), 1.90 (1H, bs), 1.71 (3H, s), 1.54 (3H, s), 1.44 (9H, s), 1.05 (3H, d, *J* = 6.9 Hz); MS (EI): 270 (M^+-Me). HRMS calcd for $C_{14}H_{24}NO_4$ (M^+-Me): *m/z* 70.1725, Found: *m/z* 270.1705.

Compound (**4a'**): Yield 0.04 g (14 %).Colorless solid, mp 65°C, $[\alpha]_D$ -25.2° ($CHCl_3$, *c* = 1.0,). *Anal.* Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.23; H, 9.48; N, 4.89. The physical and spectral data were identical with those reported.[10]

Preparation of compound (5a).

A mixture of MeOH (20 mL), **4a** (0.66 g, 2.3 mmol), and *p*-TsOH·H_2O (0.08 g, 0.4 mmol) was stirred for 2 h at rt.

After evaporation of the solvent *in vacuo*, sat. $NaHCO_3$-H_2O (1:1) solution (30 mL) was added to the residue. The aqueous solution was extracted with AcOEt (30 mL x 3), and the combined organic layer was, after washing with sat. NaCl (40 mL x 3), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography (hexanes-AcOEt) to give a diol (0.42 g, 75 % yield) as a colorless oil. A mixture of the diol (0.35 g, 1.4 mmoL), DMP (10 mL), and *p*-TsOH·H_2O (0.02 g, 0.1 mmol) was stirred at rt for 2 h. To the reaction mixture, 5 % aq. $NaHCO_3$ solution (30 mL) was added. The aqueous phase was then extracted with AcOEt (3 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography (hexanes:AcOEt = 15:1) to give **5a** (0.35 g, 53 %).

Compound (**5a**): Colorless solid, mp 81°C (CH_2Cl_2), $[\alpha]_D$ +15.6° ($CHCl_3$, *c* = 0.90). IR (neat): 1680 (C=O) cm^{-1}; ^1H NMR (Pyridine-d_5, 400 MHz, 300 K): 6.12 (1H, ddd, *J* = 17.0, 10.3 and 8.2 Hz), 5.26 (1H, d, *J* = 17.0 Hz), 5.17 (1H, dd, *J* = 10.3 and 2.1 Hz), 4.09 (1H, dd, *J* = 11.8 and 2.0 Hz), 3.96 (1H, dd, *J* = 11.8 and 1.9 Hz), 3.91 (1H, m), 3.78 (1H, dd, *J* = 9.6 and 2.0 Hz), 2.75 (1H, m), 1.52 (9H, s), 1.47 (6H, s), 1.19 (3H, d, *J* = 6.9 Hz); MS (EI): m/z 270 (M^+-CH_3); MS (CI): m/z 286 (M^++1); *Anal.* Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.95; H, 9.60; N, 4.90.

Preparation of compound (5a').

According to the procedures described above, **5a'** was obtained in 52 % from **4a'**.

Compound (**5a'**): Colorless oil, $[\alpha]_D$ -7.72° ($CHCl_3$, *c* = 1.01). Physical and spectral data of **5a'** were identical with those reported in the literature.[10]

Preparation of compound (6).

A solution of **5a** (0.86 g, 3 mmol) in dry MeOH (30 mL) was treated with O_3 at -78 °C until the color of the solution turned blue (*ca*. 3 h). After the reaction mixture was purged with Ar gas, $NaBH_4$ (0.57 g, 15 mmol) was carefully added at the same temperature. Then the reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure and H_2O (30 mL) was added to the residue. The mixture was extracted with Et_2O (3 x 30 mL), and the organic layer was successively washed with H_2O (1 x 40 mL) and sat. aq. NaCl solution (1 x 40 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash column chromatography (hexanes:AcOEt = 4:1) to give **6** as a coloress oil (0.80 g, 97 %). Compound (**6**): $[\alpha]_D$ +20.8° ($CHCl_3$, *c* = 0.15). IR (neat): 3440 (OH), 3350 (NH), 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 300 K): 4.53 (1H, br s), 3.93 (1H, dd, *J* = 11.3 and 5.1 Hz), 3.83 (2H, m), 3.62 (1H, m), 3.56 (1H, dd, *J* = 9.3 and

3.6 Hz), 3.53 (1H, dd, *J* = 11.3 and 7.0 Hz), 2.62 (1H, br s), 1.93 (1H, m), 1.43 (9H, s), 1.41 (3H, s), 1.38 (3H, s), 1.05 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K): 155.2, 99.3, 77.2, 64.7, 63.7, 47.9, 36.3, 28.3, 27.5, 20.1, 14.2; MS (EI): m/z 290 (M^++H). *Anal.* Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.41; N, 4.84. Found: C, 57.97; H, 9.55; N, 4.77.

Preparation of compound (7).

p-TsCl (0.83 g, 4.4 mmol) was added to a solutions of **6** (0.80 g, 2.9 mmol), Et_3N (1.63 mL, 11.7 mmol), and DMAP (0.07 g, 0.58 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the mixture was then stirred at rt for 2.5 h. After dilution with $CHCl_3$ (30 mL), the organic phase was washed with H_2O (3 x 30 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash column chromatography (hexanes:AcOEt = 3:1) to give **7** as a colorless oil (1.28 g, 98 %). Compound (**7**): $[\alpha]_D$ +26.7° ($CHCl_3$, *c* = 0.32). IR (neat): 3400 (NH), 1690 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K): 7.47 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 4.57 (1H, br d), 4.11-3.97 (2H, m), 3.84 (1H, dd, *J* = 11.5 and 4.8 Hz), 3.71-3.44 (3H, m), 2.44 (3H, s), 2.08 (1H, m), 1.42 (9H, s), 1.33 (3H, s), 1.27 (3H, s). 1.0 (3H, d, *J* = 6.9 Hz); MS (EI): m/z 428 (M^+-CH_3). *Anal.* Calcd for $C_{21}H_{33}NO_7S$: C, 56.86; H, 7.50; N, 3.16. Found: C, 56.56; H, 7.57; N, 2.96.

Preparation of compound (8).

A solution of **7** (0.36 g, 0.81 mmol) in dry THF (1 mL) was added to a suspension of 60 % NaH in mineral oil (0.11 g, 2.8 mmol) at 0 °C. After stirring at rt for 15 h, the resulting mixture was poured into ice-water (10 mL) and the whole was treated with Et_2O (3 x 20 mL). The organic phase was washed with sat. aq. NaCl solution (3 x 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue, which was purified by flash column chromatography (hexanes:AcOEt = 4:1) to give **8** as a colorless oil (0.20 g, 89 %). Compound (**8**): $[\alpha]_D$ +118° ($CHCl_3$, *c* = 0.13). IR (neat): 1695 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K): 3.75 (1H, dd, *J* = 10.5 and 6.4 Hz), 3.94-3.63 (2H, m), 3.50 (1H, dd, *J* = 10.5 and 6.4 Hz), 3.23 (1H, br s), 3.14 (1H, br d), 2.46-2.39 (1H, m), 1.48, 1.46 (6H, 2 x s), 1.451, 1.446 (9H, 2 x s), 1.06, 1.01 (3H, 2 x d, *J* = 7.0 Hz); MS (EI): m/z 271 (M^+). *Anal.* Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.70; H, 9.11; N, 5.20.

Preparation of compound (9).

A mixture of **8** (0.20 g, 0.72 mmol), *p*-TsOH·H_2O (0.04 g, 0.21 mmol), and MeOH (5 mL) was stirred at rt for 2 h. To this reaction mixture, 5 % aq. $NaHCO_3$ solution (30 mL) was added. The aqueous phase was then extracted with AcOEt (3 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated *in*

vacuo. The residue was subjected to silica gel flash chromatography (hexanes:AcOEt = 1:2) to give **9** as a colorless oil (0.17 g, 98 %). Compound (**9**): $[\alpha]_D$ +34.8° ($CHCl_3$, *c* = 0.41). IR (neat): 3400 (OH), 1665 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 300 K): 4.12-3.64 (4H, m), 3.47 (1H, br m), 3.15 (1H, br m), 2.31, 2.14 (1H, 2 x br s), 1.70 (2H, s), 1.46 (9H, 2 x s), 1.06 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K): (CO not visible) 80.1, 75.0, 68.4, 64.8, 51.4, 36.2, 28.4, 11.0; MS (EI): m/z 231 (M^+), 200 (M^+-CH_2OH). HRMS calcd for $C_{11}H_{21}NO_4$ (M^+): m/z 231.1471, Found: m/z 231.1471.

Preparation of compound (10).

TBSCl (1.02 g, 6.72 mmol) was added in one portion to a solution of **9** (0.52 g, 2.24 mmol), Et_3N (0.91 g, 8.96 mmol), and DMAP (0.05 g, 0.45 mmol) in CH_2Cl_2 (16 mL) at 0 °C. The mixture was stirred at rt for 3 h. After dilution with $CHCl_3$ (30 mL), the organic layer was washed with H_2O (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was subjected to silica gel flash chromatography (hexanes:AcOEt = 6:1) to give monosilylated pyrrolidine (**10**) as a colorless oil (0.702 g, 91 %). Compound (**10**): $[\alpha]_D$ +40.4° ($CHCl_3$, *c* = 0.26). IR (neat): 3430 (OH), 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 300 K): 4.16 (1H, m), 3.86-3.83 (1H, m), 3.77-3.43 (3H, m), 3.15, 3.08 (1H, 2 x t, *J* = 10.1 Hz), 2.39 (1H, m), 1.58 (1H, d, *J* = 2.0 Hz), 1.39 (9H, s), 1.06 (3H, m), 0.89 (9H, s), 0.07 (6H, s); MS (EI): m/z 288 (M^+-*t*-Bu). *Anal.* Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.19; H, 10.02; N, 4.12.

Preparation of compound (11).

BzCl (0.089 g, 0.63 mmol) was added to a solution of **10** (0.086 g, 0.25 mmol), Et_3N (0.101 g, 1.0 mmol), and DMAP (0.006 g, 0.05 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C with stirring. The mixture was stirred at rt for 4 h and then refluxed for 5 h. After dilution with H_2O (10 mL), the aqueous phase was extraced with $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography (hexanes:AcOEt = 10:1) to give **11** as a colorless oil (0.101 g, 93 %). Compound (**11**): $[\alpha]_D$ +20.7° ($CHCl_3$, *c* = 0.37). IR (neat): 1710, 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 300 K): 8.04 (2H, dd, *J* = 6.2 and 6.2 Hz), 7.57 (1H, m), 7.16 (2H, m), 5.45 (1H, dd, *J* = 11.9 and 4.3 Hz), 3.99-3.73 (3H, m), 3.67-3.55 (1H, m), 3.25, 3.16 (1H, 2 x t, *J* = 10.5 Hz), 2.76-2.69 (1H, m), 1.47, 1.46 (9H, 2 x s), 1.08 (3H, t, *J* = 7.3 Hz), 0.902, 0.896 (9H, 2 x s), 0.07, 0.065 (overlapped), 0.05 (6H, 4 x s); ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K):166.0, 154.3, 133.1, 133.0, 130.22, 130.15, 129.6, 128.43, 128.36, 79.7, 79.5, 79.4, 79.1, 65.9, 62.5, 61.9, 52.4, 51.9, 35.7, 34.7, 28.5, 25.9, 18.2, 11.5, -5.5; MS (EI): m/z 450 (M^++H). *Anal.* Calcd for $C_{24}H_{39}NO_5Si$: C,

64.10; H, 8.75; N, 3.12. Found: C, 63.82; H, 8.69; N, 3.27.

Preparation of compound (12a).

A 1.0 M TBAF solution in THF (0.44 mL, 0.44 mmol) was added to a solution of **11** (0.101 g, 0.22 mmol) in THF (0.25 mL) at 0 °C. The mixture was stirred at rt for 48 h. After the addition of sat. aq. $NaHCO_3$ solution (30 mL) to the reaction mixture, the aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was subjected to silica gel flash chromatography (hexanes:AcOEt = 3:1) to give **12a** as a colorless oil (0.067 g, 90 %). Compound (**12a**): $[\alpha]_D$ +31.4° ($CHCl_3$, *c* = 1.31) [$[\alpha]_D$ -30.4° ($CHCl_3$, *c* = 1.34)].[8] IR (neat): 3420 (OH), 1715, 1692 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 300 K): 8.04 (2H, d, *J* = 7.3 Hz), 7.59 (1H, m), 7.46 (2H, dd, *J* = 7.3 and 7.3 Hz), 5.36, 5.21 (1H, 2 x m), 4.10 (1H, m), 3.92-3.62 (4H, m), 3.25 (1H, m), 2.59 (1H, br s), 1.47 (9H, s), 1.10 (3H, d, *J* = 6.3 Hz) [lit.,[8] ^1H NMR ($CDCl_3$, 300 MHz, 300 K): 8.05 (2H, d), 7.60 (1H, dd), 7.47 (2H, dd), 5.36, 5.21 (1H, 2m), 4.10 (1H, m), 3.85 (masked m), 3.90, 3.75 (OCH_2), 3.66 (1H, m), 3.26 (1H, m), 2.60 (1H, m),1.47 (9H, s), 1.10 (3H, d, *J* = 6)]; ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K): (CO not visible) 133.3, 129.8, 129.6, 128.5, 80.5, 77.8, 66.2, 64.7, 52.3, 35.5, 28.4, 11.4 [lit.,[8] ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) (CO not visible) 133.36, 129.95, 129.74, 128.56, 80.57, 78.01, 66.33, 64.66, 52.35, 35.65, 28.50, 11.48]; MS (CI): m/z 336 (M^++H). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.30; H, 7.53; N, 4.20.

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