

An Efficient Asymmetric Synthesis of *allo*- and *pseudo*-7,8-Dimethoxyberbane Systems Through Tin-Mediated Three Component Coupling

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Dedicated to the memory of Professor Hidemasa Takaya

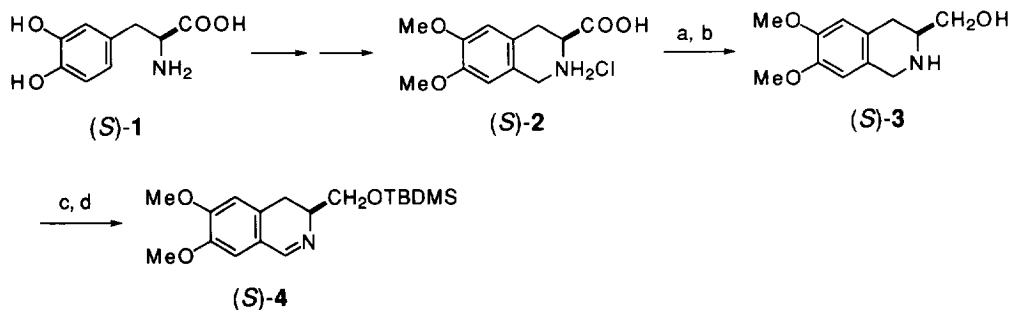
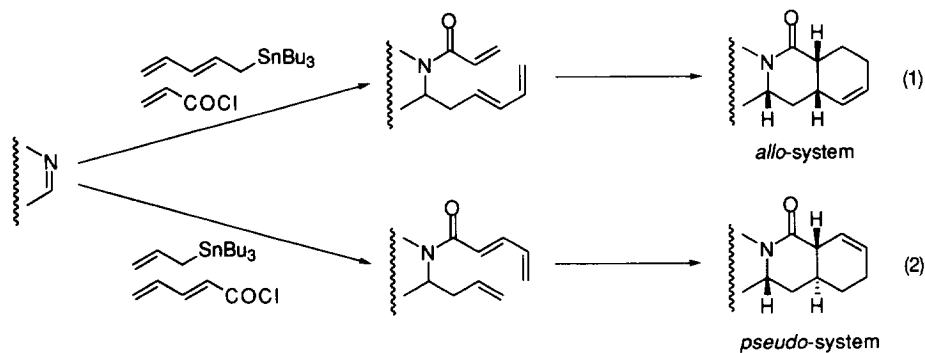
Abstract: Three component coupling reactions of chiral 3-substituted 6,7-dimethoxy-3,4-dihydroisoquinoline with allylic tin reagents and unsaturated acid chlorides followed by intramolecular Diels-Alder reactions afford *allo*- and *pseudo*-7,8-dimethoxyberbane systems in high diastereomeric excess.

Berberine alkaloids and their analogues have attracted much attention due to their inherent physiological activities for a past few decades.¹ Berbane compounds can be regarded as depyrrolo analogues of yohimbine and reserpine alkaloids and a number of their derivatives have been synthesized by Szantay and coworkers.² They have reported that 7,8-dialkoxyberbane derivatives possess interesting biological activities and that certain *allo*-berbane systems are extremely selective α 2-adrenoceptor antagonists.³

We have previously reported that several kinds of tin reagents react chemoselectively with cyclic C=N bonds activated acyl chlorides, providing a simple, effective method for the introduction of unsaturated carbon groups into nitrogen heterocycles.⁴ Taking advantage of these highly chemo-selective reactions and highly stereoselective intramolecular Diels-Alder cyclization, we have developed a highly efficient method for stereoselective construction of racemic *allo*- and *pseudo*-berbane systems, in which tin-mediated simultaneous 1,2-addition of diene and ene components to 3,4-dihydroisoquinoline systems (three-component coupling) is a key feature (Scheme 1).^{5,6} Thus, the normal electron demand Diels-Alder cycloaddition leads to the selective formation of the *allo*-system [eq. (1)],⁶ while the inverse electron demand cycloaddition results in that of the *pseudo*-system [eq. (2)].⁵ Moreover, we have found that the 1,2-addition to chiral 3-substituted 3,4-dihydroisoquinoline takes place in a highly diastereoselective manner through 1,3-asymmetric induction and that the diastereoselective bicycloannulation is possible.⁶ In this paper, we wish to report a new, efficient asymmetric synthesis of *allo*- and *pseudo*-7,8-dimethoxyberbane systems using tin-mediated three component coupling reactions followed by intramolecular Diels-Alder cycloadditions.

We started the preparation of chiral 3-substituted 6,7-dimethoxy-3,4-dihydroisoquinoline from *L*-DOPA [(*S*)-3,4-dihydroxyphenylalanine] **1** (Scheme 2). (*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinoline-carboxylic acid **2** was prepared from **1** according to the literature procedure.^{7,8} Then, (*S*)-**2** was converted to (*S*)-6,7-dimethoxy-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline **3** by the conventional methods in 75%

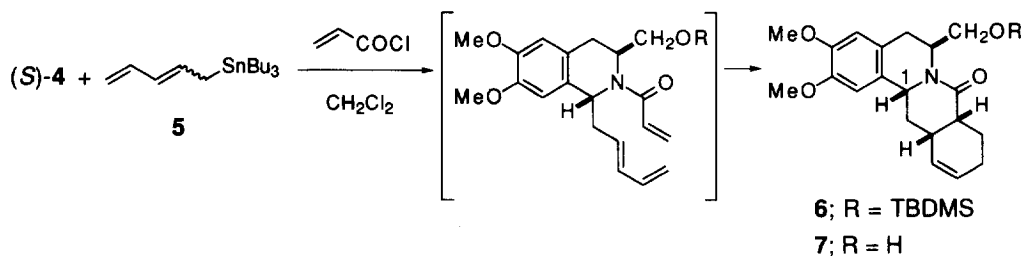
overall yield. The enantiomeric excess of **3** was determined to be 94% by ^{19}F NMR analysis of its MTPA ester. (*S*)-6,7-Dimethoxy-3-(*tert*-butyldimethylsiloxy)methyl-3,4-dihydroisoquinoline **4** was obtained from (*S*)-**3** in the usual way in 71% overall yield.



a: SOCl_2 , MeOH, then K_2CO_3 ; b: LiAlH_4 / Et_2O ; c: TBDMSCl, Imidazole / DMF; d: NCS, Bu_4NI , then aq. KOH

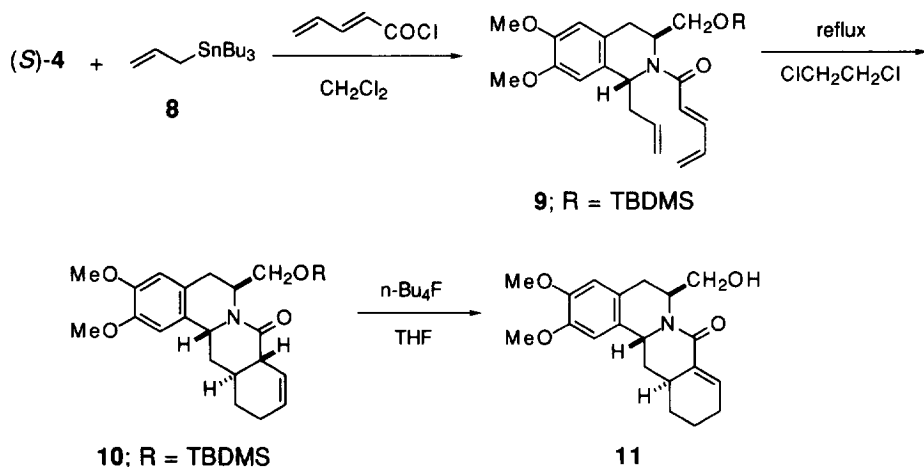
Scheme 2.

Having the desired chiral substrate (*S*)-**4** in hand, we have carried out the three-component coupling reactions to obtain *allo*-berbane system using normal electron demand Diels-Alder cyclization. When acryloyl chloride was added to a solution of (*S*)-**4** and 2,4-pentadienyltributyltin (**5**, *E* / *Z* = 75 / 25) in dichloromethane at 0 °C and the reaction mixture was stirred at room temperature, the 1,2-addition of acryloyl chloride and **5** to (*S*)-**4** and the subsequent intramolecular Diels-Alder cyclization took place smoothly to afford a tetracyclic *allo*-7,8-dimethoxyberbane derivative **6** in a highly stereoselective manner (Scheme 3). Thus, after the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 46 h, **6** was obtained in 56% yield. Inspection of the crude products by ^1H NMR (500 MHz) revealed that the diastereomeric excess was 94%.⁹ Lowering the reaction temperature to -15 °C did not improve the stereoselectivity but did decreased the yield (48%). Desilylation of **6** with tetrabutylammonium fluoride afforded the alcohol **7** in 77% yield. The enantiomeric excess of **7** was determined to be 95% by ^{19}F NMR analysis of its MTPA ester. Thus, the single stereogenic center of (*S*)-**4** can produce the three stereogenic centers of **6** stereoselectively, providing a highly efficient method for asymmetric synthesis of *allo*-berbane system.



Scheme 3.

We next turned our attention to a route of *pseudo*-berbane system using inverse electron demand Diels-Alder cyclization. When 2,4-pentadienyl chloride was added to a solution of (*S*)-**4** and allyltributyltin **8** in dichloromethane at 0 °C, the 1,2-addition took place very smoothly to give the adduct **9** in 94% yield (Scheme 4). Subsequent intramolecular cyclization of **9** was conducted in boiling 1,2-dichloroethane to afford *pseudo*-7,8-dimethoxyberbane derivative **10** in 90% yield. Inspection of the crude products by ¹H NMR (500 MHz) revealed that the diastereomeric excess was 92%,¹⁰ indicating the high anti-stereoselectivity in the 1,2-addition reaction. The above two reactions can be conducted in one-pot process: 1,2-dichloroethane was added to the reaction mixture of (*S*)-**4** with **8** and 2,4-pentadienyl chloride, and the solution was heated at reflux to afford **10** in 83% yield. Desilylation of **10** with tetrabutylammonium fluoride induced migration of the double bond to give the alcohol **11** in 64% yield. The enantiomeric excess of **11** was determined to be 94% by ¹⁹F NMR analysis of its MTPA ester.



Scheme 4.

In summary, we have developed a new, efficient method for asymmetric synthesis of *allo*- and *pseudo*-7,8-dialkoxyberbane systems based on the tin-mediated three component coupling reaction followed by the intramolecular Diels-Alder cycloaddition. Thus, *allo*- and *pseudo*-7,8-dimethoxyberbane systems can be synthesized in more than 94% ee.

Experimental

General. Infrared spectra were taken on a HORIBA FT-300 spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were measured with JEOL EX-270 (270 MHz) and JEOL A-500 (500 MHz) spectrometers using TMS as the internal standard. ^{13}C NMR spectra were measured with JEOL EX-270 and JEOL A-500 spectrometers using TMS as the internal standard. ^{19}F NMR spectra were measured with JEOL EX-270 and JEOL A-500 spectrometers using CF_3COOH as the external standard. Column chromatography was carried out by using Wako-gel C-200. TLC analysis was carried out by using DC-Alufolien Kieselgel 60 F254 (MERCK). High performance liquid chromatography (HPLC) analysis were conducted on a Waters 600E or TOSO CCPM. DAICEL CHIRALCEL OD (3.9 mm ϕ X 250 mm) was used as a chiral column, and Waters Nova Pak C18 (3.9 mm ϕ X 150 mm) as a reverse-phase column. All melting points were measured with Yanagimoto Micro Melting Point apparatus and not corrected. Optical rotations were measured with a JASCO DIP-360 spectrometer. The elemental analyses were performed by Kyoto University Elemental analysis center, and the high-resolution mass spectra were taken on a JEOL JMS 300 instrument. Tetrahydrofuran and diethyl ether were distilled over sodium-benzophenone ketyl under argon gas. Dichloromethane and 1,2-dichloroethane were distilled over P_2O_5 under argon gas before use. Methanol was distilled by magnesium methoxide under argon gas. Benzene, toluene and *N,N*-dimethylformamide (DMF) were distilled over CaH_2 . Most of reagents were purchased from Wako Pure Chemical Industry, Nakarai Tesque, Tokyo Kasei Industry, and Aldrich Chemical Company, Inc.. All manipulation of moisture-sensitive materials were conducted under argon atmosphere.

(*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride 2. This compound (*S*)-**2** was prepared from (*S*)-3,4-dihydroxyphenylalanine according to the literature's procedure.^{7,8}

(*S*)-6,7-Dimethoxy-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline 3. To a solution of (*S*)-**2** (2.40 g, 8.9 mmol) in MeOH (60 mL) was added SOCl_2 (1.2 mL) dropwise and the mixture was stirred at reflux for 3 h. Then the solvent was evaporated to give a white solid. The solid was dissolved in water (15 mL) and the solution was made basic with K_2CO_3 (pH = 8-9). The organic materials were extracted with CH_2Cl_2 and the organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated to give (*S*)-6,7-dimethoxy-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (2.17 g, 98%): IR (neat) 1739 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.59 (s, 3H), 6.52 (s, 3H), 4.04 (br s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.72 (dd, 1H, $J = 5$ and 10 Hz), 3.00 (dd, 1H, $J = 5$ and 16 Hz), 2.89 (dd, 1H, $J = 10$ and 16 Hz), 1.94 (br s, 1H); ^{13}C NMR (CDCl_3) δ 173.6 (C), 147.6 (C), 126.7 (C), 124.8 (C), 111.7 (CH), 108.8 (CH), 55.9 (CH), 55.9 (CH₃), 55.9 (CH₃), 52.1 (CH₃), 47.0 (CH₂), 31.1 (CH₂). To a suspension of LAH (3.3 g, 87.0 mmol) in Et_2O (100 mL) was added a suspension of (*S*)-6,7-dimethoxy-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (2.10 g, 8.4 mmol) in Et_2O (30 mL) and the mixture was stirred at reflux for 24 h. The reaction mixture was cooled to rt and was treated with saturated aq. Na_2SO_4 (13 mL) with ice cooling. White precipitates were formed. The reaction mixture was filtered and the precipitates were washed with CH_2Cl_2 . The solvent was evaporated to give (*S*)-**3** (1.44 g, 77%): mp 135-136 $^\circ\text{C}$; IR (KBr) 3423, 3257, 3113 cm^{-1} ; $[\alpha]_{\text{D}}^{20} = -89$ (c 1.30, CHCl_3); ^1H NMR (CDCl_3) δ 6.56 (s, 1H), 6.50 (s, 1H), 3.95 (d, 1H, $J = 16$ Hz), 3.93 (d, 1H, $J = 16$ Hz), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (dd, 1H, $J = 4$ and 11 Hz), 3.52 (dd, 1H, $J = 8$ and 11 Hz), 3.14 (br s, 2H), 3.00 (m, 1H), 2.57 (dd, 1H, $J = 4$ and 16 Hz), 2.49 (dd, 1H, $J = 11$ and 16 Hz); ^{13}C NMR (CDCl_3) δ 147.5 (C), 147.2 (C), 126.9 (C), 125.6 (C), 111.8 (CH), 108.8 (CH), 65.3 (CH), 55.8

(CH₃), 55.1 (CH), 47.4 (CH₂), 30.3 (CH₂) Anal. Calcd for C₁₂H₁₇NO₃: C, 64.56; H, 7.96; Found: C, 64.79; H, 7.96. The enantiomeric excess of (*S*)-**3** was determined to be 94% by ¹⁹F NMR analysis of its (+)-MTPA ester.

(*S*)-6,7-Dimethoxy-3-*tert*-butyldimethylsiloxymethyl-3,4-dihydroisoquinoline 4. To a solution of (*S*)-**3** (1.20 g, 5.4 mmol) and imidazole (0.73 g, 11 mmol) in DMF (6 mL) was added TBDMSCl (0.89 g, 5.9 mmol) and the mixture was stirred at rt for 2 h. To the reaction mixture was added CH₂Cl₂ and the mixture was washed with water and brine. The organic layer was separated and dried (Na₂SO₄). The solvent was evaporated to give (*S*)-6,7-dimethoxy-3-*tert*-butyldimethylsiloxymethyl-1,2,3,4-tetrahydroisoquinoline (1.74 g, 100%): ¹H NMR (CDCl₃) δ 6.58 (s, 3H), 6.53 (s, 3H), 4.00 (d, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.75 (dd, 1H), 3.61 (dd, 1H), 2.98 (m, 1H), 2.57 (d, 2H), 1.99 (broad s, 1H), 0.92 (s, 9H), 0.088 (s, 6H); ¹³C NMR (CDCl₃) δ 147.4 (C), 147.2 (C), 127.4 (C), 126.1 (C), 112.0 (CH), 109.0 (CH), 66.9 (CH₂), 55.9 (CH₃ X 2), 55.0 (CH), 47.9 (CH₂), 30.6 (CH₂), 26.0 (CH₃), 18.3 (C), -5.38 (CH₃). To a solution of (*S*)-6,7-dimethoxy-3-*tert*-butyldimethylsiloxymethyl-1,2,3,4-tetrahydroisoquinoline (1.67 g, 5.0 mmol) in CH₂Cl₂ (10 mL) was added *N*-chlorosuccinimide (0.73 g, 5.5 mmol) and the mixture was stirred at rt for 1 h. Then, ⁿBu₄NI (0.22 g) and 30% aq. KOH (15 mL) was added to the reaction mixture and stirred for 1.5 h at rt. The organic layer was washed with water and brine. The organic layer was separated and dried (Na₂SO₄). The solvent was evaporated and the residue was distilled with a bulb-to-bulb apparatus to give (*S*)-**4** (1.18 g, 71%): bp 175 °C / 0.15 mmHg (bath temp); IR (neat) 1625, 1608 cm⁻¹; [α]_D²² = +50 (c 1.08, CHCl₃); ¹H NMR (CDCl₃) δ 8.21 (d, 1H, *J* = 2 Hz), 6.81 (s, 1H), 6.70 (s, 1H), 4.06 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.72 (m, 2H), 2.83 (dd, 1H, *J* = 6 and 16 Hz), 2.60 (dd, 1H, *J* = 12 and 16 Hz), 0.92 (s, 9H), 0.08 (s, 6H); ¹³C NMR (CDCl₃) δ 159.7 (CH), 151.3 (C), 147.8 (C), 129.6 (C), 121.6 (C), 110.8 (CH), 110.3 (CH), 66.7 (CH₂), 58.9 (CH), 56.1 (CH₃), 56.0 (CH₃), 27.6 (CH₂), 26.0 (CH₃), 18.4 (C), -5.3 (CH₃). Anal. Calcd for C₁₈H₂₉NO₃Si: C, 64.44; H, 8.71. Found: C, 64.30; H, 8.95.

***allo*-(1*R*,3*S*,12*R*,17*R*)-7,8-Dimethoxy-3-[(*tert*-butyldimethylsiloxy)methyl]-13,14-didehydro-18-oxoberbane [(6*S*,8*aR*,12*aR*,13*aR*)-5,6,8*a*,9,10,12*a*,13,13*a*-Octahydro-6-[(*tert*-butyldimethylsiloxy)methyl]-2,3-dimethoxy-8*H*-dibenzo[*a,g*]quinolizin-8-one] 6.** To a solution of (*S*)-**4** (335 mg, 1.0 mmol) and **5** (366 mg, 1.0 mmol) in CH₂Cl₂ (3 mL) was added acryloyl chloride (0.10 mL, 1.1 mmol) at 0 °C and the mixture was stirred for 2 h. Then the reaction mixture was stirred for 69 h at rt. The solvent was evaporated and the residue was chromatographed on silica gel (12 g, hexane-AcOEt from 1:0 to 0:1) to give **6** (258 mg, 56%): bp 220 °C / 0.15 mmHg (bath temp); IR (neat) 1637 cm⁻¹; ¹H NMR (CDCl₃) δ 6.65 (s, 1H), 6.56 (s, 1H), 5.88 (br d, 1H, *J* = 10 Hz), 5.76 (dd, 1H, *J* = 4 and 10 Hz), 5.36 (dd, 1H, *J* = 6 and 14 Hz), 4.63 (dd, 1H, *J* = 3 and 11 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 3.64 (m, 2H), 3.03 (dd, 1H, *J* = 6 and 16 Hz), 2.78 (d, 1H, *J* = 16 Hz), 2.64–2.80 (m, 3H), 2.50 (d, 1H, *J* = 13 Hz), 2.15–2.27 (m, 3H), 1.65 (m, 2H), 0.81 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H); ¹³C NMR (CDCl₃) δ 172.9 (C), 147.9 (C), 147.5 (C), 128.4 (CH), 128.2 (CH), 127.7 (C), 124.5 (C), 111.8 (CH), 108.1 (CH), 61.2 (CH₂), 56.0 (CH₃), 55.7 (CH₃), 53.3 (CH), 47.6 (CH), 40.7 (CH), 35.1 (CH₂), 32.1 (CH), 28.5 (CH₂), 25.6 (CH₃), 25.1 (CH₂), 23.2 (CH₂), 17.9 (C), -5.6 (CH₃), -5.6 (CH₃). Anal. Calcd for C₂₆H₃₉NO₄Si: C, 68.23; H, 8.59. Found: C, 67.94; H, 8.60.

***allo*-(1*R*,3*S*,12*R*,17*R*)-7,8-Dimethoxy-3-hydroxymethyl-13,14-didehydro-18-oxoberbane [(6*S*,8*aR*,12*aR*,13*aR*)-5,6,8*a*,9,10,12*a*,13,13*a*-Octahydro-2,3-dimethoxy-6-hydroxymethyl-8*H*-dibenzo[*a,g*]quinolizin-8-one] 7.** To a solution of **6** (230 mg, 0.50 mmol) in THF (7 mL) was added 1.0 M solution of ⁿBu₄NF in THF (1.7 mL, 1.7 mmol) dropwise at rt. After 0.5 h, water (9 mL)

was added to the reaction mixture slowly. The organic materials were extracted with CH_2Cl_2 and the organic layer was dried (MgSO_4). The solvent was evaporated and the residue was column chromatographed (silica gel 18 g, hexane: AcOEt = 6:4, 4:6, 2:8, 0:10) to give **7** (132 mg, 77%): mp 81–4 °C; IR (KBr) 3390, 1608 cm^{-1} ; $[\alpha]_{\text{D}}^{23} = +190$ (c 0.50, CHCl_3); ^1H NMR (CDCl_3) δ 6.67 (s, 1H), 6.58 (s, 1H), 5.80 (m, 1H), 5.67 (d, 1H, $J = 9$ Hz), 5.32 (m, 1H), 4.61 (dd, 1H, $J = 3$ and 11 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.62 (dd, 1H, $J = 6$ and 11 Hz), 3.54 (t, 1H, $J = 10$ Hz), 3.00 (dd, 1H, $J = 6$ and 16 Hz), 2.60–2.70 (m, 3H), 2.42 (d, 1H, $J = 13$ Hz), 2.12 (m, 3H), 1.96 (br s, 1H), 1.60 (m, 2H); ^{13}C NMR (CDCl_3) δ 174.6 (C), 148.0 (C), 147.8 (C), 128.4 (CH), 128.2 (CH), 127.2 (C), 124.0 (C), 111.7 (CH), 108.3 (CH), 62.2 (CH_2), 56.1 (CH_3), 55.8 (CH_3), 53.2 (CH), 48.5 (CH), 40.8 (CH), 35.4 (CH), 32.1 (CH_2), 29.0 (CH_2), 25.1 (CH_2), 23.3 (CH_2). HRMS (FAB⁺). Calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4$ [(MH⁺)]: 344.1862. Found: 344.1874. The enantiomeric excess of **7** was determined to be 95% by ^{19}F NMR of its (+)-MTPA ester.

pseudo-(1R,3S,12S,17R)-7,8-Dimethoxy-3-[(tert-butyldimethylsiloxy)methyl]-15,16-didehydro-18-oxoberbane [(6S,8aR,12aS,13aR)-5,6,8,8a,12,12a,13,13a-Octahydro-2,3-dimethoxy-6-[(tert-butyldimethylsiloxy)methyl]-11H-dibenzo[a,g]quinolizin-8-one] 10.

(1) To a solution of (*S*)-**4** (335 mg, 1.0 mmol) and **8** (334 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added 2,4-pentadienoyl chloride (0.10 mL, 1.0 mmol) dropwise at 0 °C, and the reaction mixture was stirred at this temperature for 2 h and at rt for 5 h. The solvent was evaporated and the residue was chromatographed on silica gel to give 1-Allyl-3-(*S*)-*tert*-butyldimethylsilyloxymethyl-6,7-dimethoxy-*N*-pentadienoyl-1,2,3,4-tetrahydroisoquinoline (**9**, 432 mg, 94%): ^1H NMR (CDCl_3) δ 7.34 (dd, 1H, $J = 11$ and 15 Hz), 6.42–6.71 (m, 4H), 5.54–5.72 (m, 2H), 5.42 (d, 1H, $J = 10$ Hz), 4.84–5.15 (m, 3H), 4.65–4.23 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.27 (dd, 1H, $J = 4$ and 10 Hz), 2.92–3.16 (m, 3H), 2.67 (m, 1H), 2.28 (m, 1H), 0.81 (s, 9H), -0.02–0.08 (s, 6H); ^{13}C NMR (CDCl_3) δ 166.0 (C), 147.8 (C), 147.1 (C), 142.7 (CH), 135.2 (CH), 134.6 (CH), 128.8 (C), 124.6 (C), 124.1 (CH_2), 121.9 (CH), 117.6 (CH_2), 11.9 (CH), 111.2 (CH), 63.8 (CH_2), 56.0 (CH_3), 55.8 (CH_3), 55.5 (CH), 54.1 (CH), 41.2 (CH_2), 31.5 (CH_2), 25.8 (CH_3), 18.1 (C), -5.6 (CH_3). The 1,2-adduct **9** is relatively labile and should be used immediately. A solution of **9** (0.181 g, 0.395 mmol) and 2,6-di-*tert*-butylphenol (5 mg) in 1,2-dichloroethane (40 mL) was heated at reflux for 144 h. Then the solvent was evaporated and the residue was chromatographed on silica gel to give **10** (164 mg, 90%): bp 210 °C / 0.20 mmHg (bath temp); IR (neat) 1641 cm^{-1} ; $[\alpha]_{\text{D}}^{20} = +38$ (c 1.13, CHCl_3); ^1H NMR (CDCl_3) δ 6.65 (s, 1H), 6.56 (s, 1H), 6.18 (dd, 1H, $J = 2$ and 10 Hz), 5.74 (m, 1H), 4.69 (m, 1H), 4.57 (t, 1H, $J = 7$ Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.56 (dd, 1H, $J = 5$ and 10 Hz), 3.43 (dd, 1H, $J = 9$ and 10 Hz), 2.94 (dd, 1H, $J = 4$ and 15 Hz), 2.76–2.84 (m, 2H), 2.09 (m, 3H), 1.89 (m, 2H), 1.75 (m, 1H), 1.51 (m, 1H), 0.82 (s, 9H), -0.03 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (CDCl_3) δ 172.0 (C), 148.0 (C), 147.5 (C), 128.9 (C), 127.7 (CH), 125.6 (C), 124.2 (CH), 112.2 (CH), 108.1 (CH), 61.7 (CH_2), 56.2 (CH_3), 55.9 (CH_3), 51.5 (CH), 49.6 (CH), 43.9 (CH), 36.8 (CH_2), 32.0 (CH), 29.6 (CH_2), 28.6 (CH_2), 25.7 (CH_3), 25.2 (CH_2), 18.2 (C), -5.5 (CH_3), -5.6 (CH_3). Anal. Calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_4\text{Si}$: C, 68.23; H, 8.59. Found: C, 68.00; H, 8.61.

(2) To a solution of (*S*)-**4** (335 mg, 1.0 mmol) and **8** (334 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added 2,4-pentadienoyl chloride (0.10 mL, 1.0 mmol) dropwise at 0 °C, and the reaction mixture was stirred at this temperature for 2 h and at rt for 4 h. After the solvent was removed by reduced pressure, 1,2-dichloroethane and a small amount of 2,6-di-*tert*-butylphenol were added to the residue, and the mixture was heated at reflux for 70 h. The solvent was evaporated and the residue was chromatographed on silica gel to give **10** (379 mg, 83%).

(1R,3S,12S)-7,8-Dimethoxy-3-hydroxymethyl-16,17-didehydro-18-oxoberbane

[(6S,8aR,13aR)-5,6,10,11,12,12a,13,13a-Octahydro-2,3-dimethoxy-6-hydroxymethyl-8H-dibenzo[a,g]quinolizin-8-one] 11. To a solution of **10** (151 mg, 0.33 mmol) in THF (5 mL) was added 1.0 M solution of ⁿBu₄NF in THF (0.99 mL, 0.99 mmol) at rt and the mixture was stirred for 32 h. To the reaction mixture was added water (15 mL) slowly and the mixture was stirred for 30 min. The organic materials were extracted with AcOEt and dried (MgSO₄). The solvent was evaporated and the residue was chromatographed on silica gel to give **18** (73 mg, 64%): mp 233 °C (decomp); [α]_D²⁴ = -91 (c 1.73, CHCl₃); IR (KBr) 3372, 1646, 1612 cm⁻¹; ¹H NMR (CDCl₃) δ 6.95 (s, 1H), 6.75 (s, 1H), 6.73 (s, 1H), 4.63 (m, 1H), 4.55 (br s), 4.47 (dd, 1H, *J* = 3 and 6 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (d, 2H, *J* = 6 Hz), 2.99 (dd, 1H, *J* = 7 and 15 Hz), 2.50—2.64 (m, 3H), 2.25 (m, 2H), 2.03 (m, 1H), 1.84—1.95 (m, 2H), 1.72 (br s), 1.53 (m, 1H), 1.32 (m, 1H); ¹³C NMR (CDCl₃) δ 167.0 (C), 148.6 (C), 147.6 (C), 136.5 (CH), 131.5 (C), 129.9 (C), 127.9 (C), 111.8 (CH), 107.3 (CH), 66.5 (CH₂), 56.6 (CH₃), 56.1 (CH₃), 53.9 (CH), 50.7 (CH), 31.0 (CH₂), 29.9 (CH₂), 29.8 (CH₂), 29.5 (CH), 25.9 (CH₂), 21.2 (CH₂). HRMS (FAB⁺). Calcd for C₂₀H₂₆NO₄ [(MH⁺)]: 344.1862. Found: 344.1859. The enantiomeric excess of **11** was determined to be 94% by ¹⁹F NMR of its (+)-MTPA ester.

References and Notes

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- 9) ¹H NMR differential NOE experiments showed that there is 4.5% NOE between the methylene protons of the siloxymethyl group and H1.
- 10) ¹H NMR differential NOE experiments showed that there is 3.7% NOE between the methylene protons of the siloxymethyl group and H1.

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