Note

Chemical Transformation of an Intermediate in the Synthesis of Huperzine A, Leading to a Diverse Array of Molecules

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Chemical transformation of an early intermediate in our synthesis of huperzine A provided a diverse array of molecules in which a variety of functional groups could be embedded.

Key words natural product; total synthesis; synthetic intermediate; chemical library; screening

Total synthesis of natural products provides a reliable entry to their derivatives in drug development.1–9) Since intermediates at a later stage of the synthesis tend to have similar structures to the target natural products, they could be used for the structure–activity relationship studies. On the other hand, intermediates at an early or middle stage of the synthesis may have scaffolds that are significantly different from the target natural products. These intermediates, however, may have some advantageous structural features for drug development; for example, they may be rich in stereogenic centers, have a fused or bridged ring system, or have non-flat three-dimensional structures. These structural features appear to contribute to the clinical success of drug candidates.10–15) Intermediates even at the early or middle stage of total synthesis could, therefore, form the basis of a fine library for drug discovery. In order to demonstrate an easy access to drug-like scaffolds, compound 1 (Chart 1), an early intermediate in our synthesis of huperzine A,16) was chosen for efficient chemical transformations.

We first prepared the key intermediate 1 according to the reported procedure.16) Chart 2 summarizes the synthesis. Tricyclic lactone 217,18) was successively treated with potassium hexamethyldisilazide (KHMDS, 2.5 eq) and then methallyl bromide to furnish 3. The vanadium-mediated epoxidation of 3 proceeded stereoselectively,19,20) giving 4, which was subjected to Swern oxidation to afford γ-hydroxy-α,β-unsaturated ketone 5. Upon treatment with trifluoromethanesulfonic acid (TfOH), 5 underwent cation-olefin cyclization to give 1.

With a sufficient amount of 1 in hand, the chemical elaboration of the bicyclo[3.3.1]nonane core in 1 was carried out (Chart 3). An attempted reduction of the ketone moiety in 1 with sodium borohydride in methanol afforded a 3 : 1 mixture of 6 and its diastereomer. To promote chelation to the secondary hydroxy group, the reaction with sodium borohydride was performed in acetic acid, in which sodium triacetoxyborohydride was formed in situ.21) Under such conditions, the diastereoselectivity was improved to 16 : 1, and the desired alcohol 6 was obtained in 72% yield. Treatment of 6 with TfOH induced the formation of an oxaadamantane skeleton,22–24) and the subsequent methanolysis of the lactone ring in 7 occurred under mild basic conditions to give diol 8. The primary alcohol moiety in 8 was selectively tosylated according to Tanabe’s protocol.25) Heating of the resulting tosylate facilitated the formation of a tetrahydrofuran ring to furnish 9 in 92% yield. For further functionalization, the methyl ester was hydrolyzed under basic conditions. The resulting carboxylic acid 10 and pyrrolidine were coupled via the formation of the corresponding acid chloride 11 to produce amide 12 in 86% yield. On the other hand, Curtius rearrangement of 10 using diphenylphosphoryl azide (DPPA) and benzyl alcohol furnished 14.26) Cleavage of the benzoxycarbonyl (Cbz) group in 14 by hydrogenolysis gave primary amine 15.

In conclusion, compound 1, an early intermediate in our synthesis of huperzine A, was efficiently converted to diverse molecules bearing three different ring systems in which a variety of functional groups were embedded. These compounds have been deposited in a chemical library and are currently employed in screening assays for drug discovery. The results of the screening assays will be reported in due course.

Experimental

General Remarks Nuclear magnetic resonance (¹H-NMR

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using a JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer, IR spectra were recorded (Hz). The chemical shifts in the C-NMR spectra are reported in parts per million (ppm) downfield of the tetramethylsilane (δ) signal, which provided the internal standard. Coupling constants are reported in hertz (Hz)

**Chart 3. Chemical Transformation of I**

(400 MHz), 1H-NMR (100 MHz) spectra were determined using a JEOL-ECS400 instrument. The chemical shifts in the 1H-NMR spectra were reported in parts per million (ppm) downfield from the tetramethylsilane (δ) signal, which provided the internal standard. Coupling constants are reported in hertz (Hz). The chemical shifts in the C-NMR spectra are reported in ppm relative to the centerline of the triplet at 77.0 ppm, corresponding to deuteriochloroform. IR spectra were recorded using a JASCO FTIR/IR-4100 Fourier Transform Infrared Spectrophotometer and were reported in wave numbers (cm⁻¹). High-resolution (HR)-MS were obtained using a JEOL JMS-T100LP AccuTOF LC-plus in positive electrospray ionization (ESI) method, using sodium trifluoroacetate as the internal standard. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical, 40-100 mesh) unless otherwise noted. Reagents were commercial grade and were used without purification. All reactions sensitive to oxygen were carried out under a nitrogen atmosphere.

**Chart 3. Chemical Transformation of I**

(3aS*,7R*,9R*,9aS*,10R*)-9,10-Dihydroxy-5-methyl-7,8,9,9a-tetrahydro-1H-3a,7-methano[cycloocta]furan-1-one (6) To a stirred solution of 1 (660 mg, 2.97 mmol) in acetic acid (10 mL) was added sodium borohydride (669 mg, 17.7 mmol) portionwise at room temperature. After stirring for 12 h, additional sodium borohydride (112 mg, 2.96 mmol) was added. After stirring for another 3 h, the reaction mixture was quenched with water. The resulting solution was extracted with dichloromethane and then with 10% methanol in chloroform. The combined organic phases were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified using flash column chromatography (60-100% ethyl acetate in hexane) to give 6 (479 mg, 72.0%) as a white solid.

IR (neat, cm⁻¹) 3394, 2914, 1749, 1219, 1126, 1067, 1011, 820; 1H-NMR (CDCl₃) δ: 7.7, 7.7 Hz, 1H), 4.35 (dd, J = 7.7, 7.7 Hz, 1H), 4.28 (m, 1H), 4.10 (brs, 1H), 2.78 (m, 1H), 2.32 (brs, 1H), 2.23 (m, 1H), 2.11 (d, J = 12.4 Hz, 1H), 1.95 (d, J = 12.8 Hz, 1H), 1.93–1.87 (m, 2H), 1.74 (dd, J = 12.4, 2.8 Hz, 1H), 1.68 (d, J = 12.8 Hz, 1H), 1.22 (s, 3H); 13C-NMR (CDCl₃) δ: 179.2 (C), 72.8 (CH), 70.5 (C), 70.2 (CH₃), 68.2 (CH), 45.6 (CH), 44.5 (CH₂), 42.8 (CH₃), 40.7 (CH₂), 33.4 (CH), 27.9 (CH₃), 23.4 (CH₂); HR-MS (ESI) 247.0957 (Calcd for C₁₂H₁₆NaO₄ 247.0946).

(3aS*,4R*,6R*,8S*,9aS*,10R*)-10-Hydroxy-8-methyl-octahydro-1H-4,8-epoxy-6,9a-methanocyclooctal[c]furan-1-one (7) To a stirred solution of 6 (112 mg, 0.499 mmol) in 1,2-dichloroethane (1.7 mL) was added trifluoromethanesulfonic acid (4.4 µL, 0.050 mmol) at room temperature, and the reaction mixture was heated at 50°C. After stirring for 1 h, the reaction mixture was quenched with aqueous sodium hydrogen carbonate. The resulting solution was extracted with dichloromethane and then with 10% methanol in chloroform. The combined organic phases were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified using flash column chromatography (50% ethyl acetate in hexane) to give 7 (101 mg, 89.9%) as a white solid.

IR (neat, cm⁻¹) 3375, 2928, 1765, 1453, 1362, 1228, 1126, 1067, 1011, 820; 1H-NMR (CDCl₃) δ: 4.62 (dd, J = 12.4, 7.7 Hz, 1H), 4.35 (dd, J = 7.7, 7.7 Hz, 1H), 2.61 (dd, J = 14.6, 5.2, 5.2 Hz, 1H), 1.99 (d, J = 17.6 Hz, 1H), 1.75 (s, 3H), 1.69 (d, J = 14.6 Hz, 1H); 13C-NMR (CDCl₃) δ: 180.2 (C), 134.8 (C), 126.2 (CH), 70.0 (CH₃), 69.3 (CH₂), 64.3 (CH), 49.2 (CH), 46.3 (C), 41.0 (CH₃), 34.2 (CH), 28.4 (CH₂), 22.8 (CH₃); HR-MS (ESI) 279.1198 (Calcd for C₁₃H₁₈NaO₅ 279.1195).

(1S*,3R*,4S*,5S*,6R*,7R*)-Methyl 6-Hydroxy-4-(hydroxy-methyl)-1-methyl-2-oxaadamantane-5-carboxylate (8) To a stirred solution of 7 (74.0 mg, 0.330 mmol) in methanol (1.1 mL) was added potassium carbonate (91.2 mg, 0.660 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with water. The resulting solution was extracted with dichloromethane and then with 10% methanol in chloroform. The combined organic phases were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified using flash column chromatography (70-100% ethyl acetate in hexane) to give 8 (58.8 mg, 69.6%) as a white solid.

IR (neat, cm⁻¹) 3405, 3290, 2970, 1721, 1444, 1374, 1258, 1130, 1072, 1034, 803; 1H-NMR (CDCl₃) δ: 4.23 (s, 1H), 4.18 (brs, 1H), 3.89–3.80 (m, 2H), 3.78 (s, 1H), 2.51 (m, 1H), 2.27 (m, 1H), 2.19 (d, J = 13.6 Hz, 1H), 1.05 (dd, J = 12.8, 2.8 Hz, 1H), 1.88 (ddd, J = 13.2, 2.8, 2.8 Hz, 1H), 1.74 (d, J = 13.6 Hz, 1H), 1.66 (d, J = 12.8 Hz, 1H), 1.63 (d, J = 13.2 Hz, 1H), 1.17 (s, 3H); 13C-NMR (CDCl₃) δ: 176.3 (C), 72.8 (CH), 69.7 (CH), 69.4 (C), 62.2 (CH₂), 52.1 (CH₃), 47.5 (C), 47.0 (CH), 44.9 (CH₂), 41.0 (CH₃), 32.2 (CH), 28.0 (CH), 24.6 (CH₃); HR-MS (ESI) 279.1198 (Calcd for C₁₃H₂₀NaO₅ 279.1198).

(3S*,3aS*,5S*,7R*,9aR*,9R*)-Methyl 5-Methylocyclohydro-5,3,7-(epoxyethane[1,1,2]trityl)benzofuran-3a-carboxylate
To a stirred solution of 8 (178 mg, 0.696 mmol) in acetonitrile (2.3 mL) were added N,N,N′,N′-tetramethylethylene-1,3-diamine (0.250 mL, 1.50 mmol) and p-toluenesulfonyl chloride (160 mg, 0.837 mmol) at 0°C. The reaction mixture was then allowed to warm to room temperature. After stirring for 30 min, the reaction mixture was heated at 50°C. After stirring for 2 h, the reaction mixture was quenched with water. The resulting solution was extracted with dichloromethane and then with 10% methanol in chloroform. The combined organic phases were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give carboxylic acid (47 mg, 12.89%).

To a solution of 9 (146 mg, 91.8% as a pale yellow oil. IR (neat, cm⁻¹) 2931, 1733, 1522, 1169, 1036, 972, 872, 773; ¹H-NMR (CDCl₃) δ: 4.56 (d, J=5.0 Hz, 1H), 2.36 (s, 1H), 2.11 (d, J=12.8 Hz, 1H), 1.79 (dd, J=12.8, 2.8 Hz, 1H), 3.84 (dd, J=6.0 Hz, 1H), 4.08 (d, J=2.8 Hz, 1H), 3.84 (dd, J=8.2 Hz, 2H), 3.55 (br, 3H), 3.10 (dd, J=4.6, 4.6 Hz, 1H), 2.35 (s, 1H), 2.08–1.76 (m, 8H), 1.61–1.56 (m, 2H), 1.25 (s, 3H); ¹³C-NMR (CDCl₃) δ: 171.1 (C), 77.1 (CH), 71.0 (CH), 69.0 (CH3), 67.9 (C), 52.2 (C), 47.8 (CH2), 42.1 (CH), 38.7 (CH2), 38.7 (CH3), 34.0 (CH), 30.3 (CH2), 28.1 (CH3), 27.2 (br), 22.9 (br); HR-MS (ESI) 300.1576 (Calcd for C₁₄H₂₃NNaO₃ 300.1576).

Benzyl ((3S,3aS,5S,5′R,7aR,9R)-5-Methyloctahydro-3,7-epoxyethane[1,1,2]triyl)benzofuran-3a-yl)carbamate (14) To a solution of 10 (57 mg, 0.25 mmol) in benzene (0.8 mL) were added triethylamine (0.11 mL, 0.79 mmol) and DPPA (82 µL, 0.38 mmol) at room temperature. After stirring for 50 min, the mixture was concentrated in vacuo. The residue was dissolved in benzene (0.8 mL) and triethylamine (0.10 mL, 0.72 mmol) were added. The resulting mixture was heated at 80°C for 2 h. After cooling to room temperature, benzyl alcohol (52 µL, 0.50 mmol) and triethylamine (0.10 mL, 0.72 mmol) were added. The resulting mixture was heated at 80°C for 1.5 h before it was concentrated in vacuo. The residue was partitioned between dichloromethane and aqueous sodium hydrogen carbonate, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified with flash column chromatography (30–100% ethyl acetate in hexane) to give 14 (63 mg, 76%) as an amorphous solid. IR (neat, cm⁻¹) 3301, 2930, 1712, 1527, 1282, 1240, 1113, 1035, 969; ¹H-NMR (CDCl₃) δ: 7.35 (s, 5H), 5.07 (s, 2H), 4.85 (s, 1H), 4.19 (s, 1H), 4.10 (s, 1H), 3.99–3.95 (m, 1H), 3.68 (d, J=8.7 Hz, 1H), 2.75 (s, 1H), 2.49 (d, J=12.8 Hz, 1H), 2.36 (s, 1H), 2.05 (d, J=12.8 Hz, 1H), 1.97 (d, J=13.3 Hz, 1H), 1.73 (d, J=13.3 Hz, 1H), 1.61–1.56 (m, 2H), 1.20 (s, 3H); ¹³C-NMR (CDCl₃) δ: 165.2 (C), 136.3 (C), 128.6 (CH2), 128.2 (CH2), 128.1 (CH), 79.9 (CH), 71.3 (CH), 70.4 (C), 68.6 (CH3), 66.4 (CH2), 59.6 (C), 44.3 (CH), 40.2 (CH2), 38.5 (CH3), 34.4 (CH), 29.8 (CH), 27.9 (CH3); HR-MS (ESI) 352.1534 (Calcd for C₁₅H₂₄NNaO₃ 352.1525).

Benzyl ((3S,3aS,5S,5′R,7aR,9R)-5-Methyloctahydro-3,7-epoxyethane[1,1,2]triyl)benzofuran-3a-yl)amine (15) To a flask charged with benzyl carbamate 14 (40 mg, 0.12 mmol) and palladium on carbon (10%, 26 mg, 0.012 mmol) was added methanol (0.5 mL). The solution was then purged with hydrogen gas. After stirring for 2 h, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated in vacuo, and the residue was purified using flash column chromatography (NH₂ silica gel, dichloromethane) to give 15 (22 mg, 94%) as an oil. IR (neat, cm⁻¹) 3456, 2927, 1375, 1031, 966; ¹H-NMR (CDCl₃) δ: 4.08–4.04 (m, 2H), 3.81 (d, J=5.51 Hz, 1H), 3.68 (d, J=8.71 Hz, 1H), 2.33 (s, 1H), 2.16 (d, J=4.61 Hz, 1H), 1.91 (dd, J=12.8, 12.8, 2.81 Hz, 2H), 1.71 (dd, J=17.0, 13.3 Hz, 2H), 1.56–1.49 (m, 2H), 1.20 (s, 3H); ¹³C-NMR (CDCl₃) δ: 83.2 (CH), 71.8 (CH), 70.3 (C), 68.5 (CH2), 56.7 (C), 48.6 (CH), 43.6 (CH2), 39.1 (CH3), 34.5 (CH), 29.2 (CH3), 28.1 (CH3); HR-MS (ESI) 196.1332 (Calcd for C₁₅H₂₀NO₂ 196.1338).

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Conflict of Interest The authors declare no conflict of interest.

References and Notes

18) While a racemic sample was used for this study, asymmetric synthesis of 2 has been reported. See ref. 16.