Total Syntheses of (−)-7-epi-Alexine and (+)-Alexine Using Stereoselective Allylation

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Received: 11.04.2019
Accepted after revision: 09.05.2019
Published online: 12.06.2019

Abstract Total syntheses of (−)-7-epi-alexine and (+)-alexine were achieved by using stereoselective allylation via a functionalized pyrrolidine obtained from an extended chiral 1,3-oxazine. The synthetic strategies include pyrrolidine formation via oxazine cleavage and diastereoselective allylations of a pyrrolidine aldehyde. (−)-7-epi-Alexine and (+)-alexine were synthesized from anti, syn, anti-oxazine in 12 steps.

Key words allylation, alkaloids, amino alcohols, diastereoselectivity, asymmetric synthesis, cyclization

With the aim of synthesizing biologically active and important compounds, our research group has synthesized polyhydroxylated alkaloids using extended chiral 1,3-oxazines.1 Recently, we reported the synthesis of a novel chiral building block, functionalized pyrrolidine 2, from anti, syn, syn-oxazine 1, and successfully extended the chirality to the synthesis of pyrrolidine 3 (Scheme 1).2 In this work, the synthesis of functionalized pyrrolidine 5 from anti, syn, anti-oxazine 4 and stereoselective allylation of functionalized pyrrolidine 5 were achieved.

(+)-Alexine (7, Figure 1) is a naturally occurring tetrahydroxylated pyrrolizidine, whose isolation from Alexa leio-petal was reported in 1988.3 Polyhydroxylated pyrrolizidine alkaloids are a class of sugar mimics wherein an oxygen atom in the ring is replaced by a nitrogen atom.4 (+)-Alexine (7) and its structurally related congeners have attracted interest due to their significant biological activities, including potent inhibitory activity toward glycosidases and antiviral and antiretroviral activities.5 Due to their biological activities and structural features, many syntheses of (+)-alexine (7) and (−)-7-epi-alexine (8) have been reported.6 Our main tactic involved individual syn- and anti-selective allylations. Herein we report the stereocontrolled total syntheses of (+)-alexine (7) and (−)-7-epi-alexine (8).

Our retrosynthetic analyses are shown in Scheme 2. (−)-7-epi-Alexine (8) could be derived from the cyclization of 6a, which could be obtained via stereoselective allylation of the functionalized pyrrolidine 5. Functionalized pyrrolidine 5 could be derived from anti, syn, syn-oxazine 4.

Scheme 1 Syntheses involved in previous work and this work

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Through the same series of transformations, (+)-alexine (7) could be obtained via compounds 6b, 5, and 4. The preparation of 5 is shown in Scheme 3, and begins with anti,syn,anti-oxazine 4, which was prepared using previously reported methods.14,7 To obtain the pyrrolidine ring via oxazine ring cleavage, we tested various methods. Primary selective monotosylation of the diol 4 and base treatment furnished an epoxide.8 We then tried to synthesize the pyrrolidine ring using Pd-catalyzed hydrogenation but only decomposition products were obtained (Scheme 3A). The epoxide derived from the diol 4 was treated with dimethylsulfonium methylium to generate allylic alcohol.9 Drawing from our previously reported method,2 we attempted the oxazine ring cleavage with CbzCl, but the desired product was not obtained, and the dimethylsulfonium methylium reaction gave a very low yield of allylic alcohol (Scheme 3B). Primary selective pivaloylation of the diol 4 furnished compound 5 (Scheme 3C).10 Mesylation of 4 was carried out with Pd(OH)2/C under H2 to afford the pyrrolidine 10. The secondary alcohol 10 was protected by a methoxymethyl (MOM) group, and the pivaloyl group was deprotected using DIBAL-H,11 to furnish the primary alcohol 5 (Scheme 3C).

The results of the allylation of the aldehyde after Dess–Martin oxidation of the corresponding primary alcohol 5 are shown in Table 1. The reaction mediated by SnCl4 with allyltributyltin afforded 6a/6b in a 10:1 ratio and in 57% yield (entry 1). The reaction mediated by TiCl4 resulted in the same 6a/6b ratio as in entry 1, but in lower yield (entry 2). The MgBr2·OEt2 reaction using allyltributyltin as the nucleophile afforded 6a/6b in a 15:1 ratio and in 78% yield (entry 3). The reaction mediated by BF3·OEt2 furnished 6a/6b in a 1:6 ratio and in 73% yield (entry 4). The reaction using allylmagnesium bromide with no Lewis-acid afforded 6a/6b in a 6:1 ratio and in 42% yield (entry 5).

The transition states for the allylation reactions are shown in Figure 2. Additions to the aldehyde derived from 5 mediated by SnCl4, TiCl4, and MgBr2·OEt2 could proceed via the α-chelation model (Figure 2A), which results in the syn-alcohol 6a (entries 1–3). Addition to the aldehyde derived...
The resulting allylation products 6a and 6b were used in the syntheses of (−)-epi-alexine (8) and (+)-alexine (7), respectively, as shown in Scheme 4, which further confirmed the relative stereochemistries of 6a and 6b. Allylation products 6a and 6b were first protected with a MOM group. Ozonolysis and hydrogenolysis of 13 and 15 afforded pyrrolizidine compounds 14 and 16, respectively. Global deprotections of 14 and 16 with 1 N aq HCl furnished 8 and 7 as HCl salts (8-HCl and 7-HCl), which were neutralized with an ion-exchange resin to afford (−)-epi-alexine (8) and (+)-alexine (7), respectively. The spectroscopic (1H and 13C NMR) data and other properties of the synthesized (−)-epi-alexine (8) and (+)-alexine (7) were in good agreement with the previously reported values. The optical rotation of 8, [α]D20 = −10.7 (c 0.4, H2O), was similar to the reported value, [α]D20 = −11.0 (c 1.0, H2O), thereby confirming its absolute configuration. The optical rotation of 7, [α]D20 = +40.7 (c 0.4, H2O), was also similar to the reported value, [α]D23 = +40.4 (c 0.3, H2O), which confirmed its absolute configuration. Thus, (−)-epi-alexine (8) and (+)-alexine (7) were synthesized from anti, syn, anti-oxazine 4, in 14.6% and 15.1% yields, respectively, in 12 steps.

In summary, (−)-7-epi-alexine (8) and (+)-alexine (7) were synthesized from anti, syn, anti-oxazine 4 via formation of pyrrolidines, stereoselective allylation, and pyrrolizidine cyclization. Notably, syn- and anti-selective allylations were successfully carried out by using MgBr2·OEt2 and BF3·OEt2, respectively. Further applications of using functionalized pyrrolidines are currently in progress.

Commercially available reagents were used without additional purification, unless stated otherwise. Unless stated otherwise, all non-aqueous reactions were performed under an argon atmosphere by using commercial-grade reagents and solvents. THF was distilled from sodium and benzophenone (as an indicator). CH2Cl2 was distilled from CaH2. Optical rotations were measured with a Jasco P1020 polarimeter, in the solvent reported alongside the data. Specific rotations are reported in 10−1 deg cm2/g, and concentrations in g/100 mL. IR spectra were obtained using a Jasco FT/IR-4100 spectrophotometer. 1H and 13C NMR spectroscopic data were recorded at the Yonsung R&D center using a Bruker FT-NMR 300 MHz spectrometer. Chemical shift values are reported in ppm relative to TMS or CDCl3 as the internal standard, and coupling constants are reported in Hz. Mass spectroscopic data were obtained using an Agilent 6530 Accurate-Mass Q-TOF LC/MS high-resolution mass spectrometer equipped with a magnetic-sector–electric-sector double-focusing analyzer. Flash chromatographic separations were performed using mixtures of hexanes and EtOAc or MeOH and CHCl3 as the eluents.

(R)-2-[(4R,5R,6R,5’)-tert-Butyldimethylsilyloxy]-4-[(tert-butyldimethylsilyloxy)methyl]-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)-2-hydroxyethyl Pivalate (9)

To a solution of 4 (0.5 g, 0.86 mmol) in CH2Cl2 (8.6 mL) was added pyridine (1 mL) followed by PivCl (0.16 mL, 1.29 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with sat. aq NH4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with Et2O (20 mL). The combined organic layers were washed successively with CuSO4 and brine, dried over MgSO4, and concentrated in vacuo. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 15:1); this afforded 9.
Yield: 0.45 g (0.78 mmol, 91%); colorless oil; \( R_f = 0.4 \) (hexanes–EtOAc, 6:1); [\( \delta \) (500 MHz, CDCl\(_3\))] = 4.26, 0.94 (each, 12 H).

IR (500 MHz, CDCl\(_3\)): \( \nu \) 3474, 2955, 2928, 2857, 1708, 1471, 1219, 1099, 1045, 837, 772 cm\(^{-1}\).

HRMS (EI): \([M + H]^+\) calcd for C\(_{28}\)H\(_{51}\)NO\(_7\)Si\(_2\): 569.3204; found: 569.3280.

**Benzyl (2R,3R,4R,5S)-3-[(tert-Butyldimethylsilyloxy)-2-[(tert-butyldimethylsilyloxy)methyl]-4-hydroxy-5-[(pivaloyloxy)methyl]pyrroline-1-carboxylate (12)**

To a solution of 9 (350 mg, 0.66 mmol) in CH\(_2\)Cl\(_2\) (6 mL), Et\(_3\)N (0.2 mL, 1.2 mmol), followed by MsCl (0.1 mL, 1.2 mmol) at 0 °C were added. The reaction mixture was stirred at 0 °C for 1 h and quenched with sat. aq NaHCO\(_3\) solution (20 mL). The layers were separated, and the aqeous layer was extracted with Et\(_2\)O (20 mL). The combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 20:1) to give compound 12. Yield: 218 mg (0.33 mmol, 83%); colorless oil; \( R_f = 0.7 \) (hexanes–EtOAc, 4:1); [\( \delta \) (500 MHz, CDCl\(_3\))] = 6.83, 5.01–5.30 (each, 1 H).

IR (500 MHz, CDCl\(_3\)): \( \nu \) 3474, 2955, 2928, 2857, 1708, 1471, 1219, 1099, 1045, 837, 772 cm\(^{-1}\).

HRMS (EI): \([M + H]^+\) calcd for C\(_{30}\)H\(_{54}\)NO\(_6\)Si\(_2\): 580.3484; found: 580.3485.

**Benzyl (2R,3R,4R,5S)-3-[(tert-Butyldimethylsilyloxy)-2-[(tert-butyldimethylsilyloxy)methyl]-4-hydroxy-5-[(methoxymethyl)methyl]pyrroline-1-carboxylate (5)**

To a solution of 4 (569 mg, 0.651 mmol) in CH\(_2\)Cl\(_2\) (6.5 mL) was added 1.0 M DIBAL-H in cyclohexane (1.63 mL, 1.632 mmol). The reaction mixture was stirred at –78 °C for 1 h and then quenched with sat. aq potassium sodium tartrate (20 mL). The layers were separated and the aqeous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 6:1) to give compound 5. Yield: 315 mg (0.55 mmol, 85%); colorless oil; \( R_f = 0.3 \) (hexanes–EtOAc, 4:1); [\( \delta \) (500 MHz, CDCl\(_3\))] = 1.88, 1.83, 18.3, 18.0, –4.5, –4.7, –5.4.

IR (500 MHz, CDCl\(_3\)): \( \nu \) 2956, 2930, 2858, 1735, 1678, 1512, 1472, 1362, 1281, 1215, 1220, 1151, 1014, 1046, 1004, 838, 773 cm\(^{-1}\).

HRMS (EI): \([M + H]^+\) calcd for C\(_{30}\)H\(_{50}\)NO\(_6\)Si\(_2\): 575.3255; found: 575.3247.

**Benzyl (2R,3R,4R,5S)-3-[(tert-Butyldimethylsilyloxy)-2-[(tert-butyldimethylsilyloxy)methyl]-5-[(methoxymethyl)methyl]pyrroline-1-carboxylate (11)**

To a solution of 10 (240 mg, 0.44 mmol) in CH\(_2\)Cl\(_2\) (4 mL) were added DMAP (5 mg, 0.04 mmol) and DIPEA (0.15 mL, 0.8 mmol), followed by MOMCl (0.07 mL, 0.8 mmol). The reaction mixture was stirred at 40 °C for 4 h and then quenched with H\(_2\)O (20 mL). The layers were separated, and the aqeous layer was extracted with Et\(_2\)O (20 mL). The combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The resulting substance was purified by column chromatography (silica gel, hexanes–EtOAc, 20:1) to give compound 11. Yield: 226 mg (0.37 mmol, 78%); colorless oil; \( R_f = 0.5 \) (hexanes–EtOAc, 4:1); [\( \delta \) (500 MHz, CDCl\(_3\))] = 6.83, 5.01–5.30 (each, 1 H).

IR (500 MHz, CDCl\(_3\)): \( \nu \) 3474, 2955, 2928, 2857, 1735, 1678, 1512, 1472, 1362, 1281, 1215, 1220, 1151, 1014, 1046, 1004, 838, 773 cm\(^{-1}\).

HRMS (EI): \([M + H]^+\) calcd for C\(_{30}\)H\(_{52}\)NO\(_6\)Si\(_2\): 579.3255; found: 579.3247.
Benzyl (2R,3R,4R,5S)-3-[(tert-Butyldimethylsilyloxy)-2-[(tert-butyldimethylsilyloxy)methyl]-5-[(5S)-1-hydroxybut-3-ene-3-ynyl]-4-[(methoxymethoxy)but-3-enyl]pyrrolidine-1-carboxylate (6b) Yield: 111 mg (0.18 mmol, 63%); colorless oil; \( R_f = 0.50 \) (hexanes–EtOAc, 6:1); \([\alpha]_D^{20} = +3.6 \) (c 0.1, CHCl3).

IR (neat): 3442, 2954, 2929, 2857, 1709, 1735, 1428, 1411, 1384, 1277, 1258, 1178, 1162, 1046, 983, 846, 1384, 1325, 1281, 1278, 1162, 971, 84, 73, 73.9, 70.5, 68.4, 67.4, 66.4, 61.4, 56.2, 38.8, 25.9, 14.7, 9.4, –4.7, –5.4, –5.5.

HRMS (EI): \( m/z \) [M + H]+ calcd for C31H56NO7Si2: 610.3590; found: 610.3591.

Benzyl (2R,3R,4R,5S)-3-[(tert-Butyldimethylsilyloxy)-2-[(tert-butyldimethylsilyloxy)methyl]-5-[(5S)-hydroxybut-3-ene-3-ynyl]-4-[(methoxymethoxy)but-3-enyl]pyrrolidine-1-carboxylate (13)

Yield: 35 mg (0.073 mmol, 69%); colorless oil; \( R_f = 0.45 \) (hexanes–EtOAc, 6:1); \([\alpha]_D^{20} = +9.4 \) (c 0.1, CHCl3).

IR (neat): 3475, 2952, 2930, 2857, 1709, 1741, 1428, 1411, 1384, 1277, 1258, 1178, 1162, 971, 84, 73, 73.9, 70.5, 68.4, 67.4, 66.4, 61.4, 56.2, 38.8, 25.9, 14.7, 9.4, –4.7, –5.4, –5.5.

HRMS (EI): \( m/z \) [M + H]+ calcd for C33H59NO8Si2: 653.3779; found: 653.3777.

Synthesis

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13C NMR (75 MHz, CDCl3): δ = 96.4, 96.1, 81.6, 74.8, 72.7, 68.8, 62.2, 55.8, 55.5, 46.6, 35.0, 29.7, 25.9, 25.7, 18.3, 17.9, −4.6, −4.7, −5.4, −5.5. HRMS (EI): m/z [M+] calcd for C41H60NO14Si2: 506.3328; found: 506.3331.

(1R,2R,3R,7R,7aS)-3-(Hydroxymethyl)hexahydro-1H-pyrrolizine-1,2,7-triol ([–]-7-epi-Alexine; 8)

To a solution of 14 (33 mg, 0.07 mmol) in MeOH (3 mL) at r.t., 1 N aq HCl solution (3 mL) was added. The reaction mixture was stirred for 6 h. The solvent was removed in vacuo, furnishing the HCl salt of 2 (2-HCl) as a white solid. This was purified on an ion-exchange column (DOWEX 50WX8-200). The column was washed with MeOH (20 mL) and H2O (20 mL) to remove products not containing amines, and then with 6 M aq NH4OH (60 mL) to yield a solution of compound 8. Evaporation of the solvent afforded product 8.

Yield: 12 mg (0.06 mmol, 93%); white solid; [α]D20 10.7 (c 0.4, H2O).
IR (neat): 3338, 2922, 2865, 2844, 1456, 1346, 1054, 1032, 1013 cm⁻¹.
HRMS (EI): m/z [M + H]+ calcd for C41H60NO14Si2: 506.3328; found: 506.3331.

(1R,2R,3R,7R,7aS)-3-(Hydroxymethyl)hexahydro-1H-pyrrolizine-1,2,7-triol ([+]-Alexine; 7)

Yield: 11.6 mg (0.058 mmol, 87%); white solid; [α]D20 10.7 (c 0.4, H2O).
IR (neat): 3338, 2919, 2309, 1558, 1437, 1109, 1046, 791, 598 cm⁻¹.
1H NMR (300 MHz, CDCl3): δ = 4.47 (td, J = 3.9, 1.5 Hz, 1 H), 4.22 (t, J = 8.1 Hz, 1 H), 3.81–3.96 (m, 3 H), 3.52 (dd, J = 8.3, 4.2 Hz, 1 H), 3.21 (dd, J = 11.6, 9.4, 6.3 Hz, 1 H), 2.92–3.05 (m, 2 H), 1.75–1.94 (m, 2 H).
13C NMR (75 MHz, CDCl3): δ = 77.4, 75.0, 72.0, 66.0, 63.5, 59.0, 45.7, 33.7.
HRMS (EI): m/z [M + H]+ calcd for C41H60NO14: 190.1074; found: 190.1076.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611566.

References


(12) Peaks in 1H NMR and 13C NMR spectra of compounds are broad and split due to the presence of N-Chz rotamers.

Funding Information

This work was supported by Yonsung Fine Chemicals Co., Ltd.

Acknowledgement

We thank the Yonsung R&D Center analysis research department for the HRMS measurements.

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