Synthetic Study towards (-)-Allosedridine

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Abstract. The synthesis of (R)-3-((4-methoxybenzyl)oxy)butanal, which is an intermediate of (-)-Allosedridine, a 2-substituted piperidine alkaloid, was described, The route started from (R)-methyl 3-hydroxybutanoate via a PMB protection, a $LiAlH_4$ reduction and a Swern oxidation.

Introduction

2-Substituted piperidine alkaloids (**Figure 1**) are a series of nature products with novel biological activities, which were widely distributed in nature [1]. As these alkaloids are obtained in only trace amounts from natural sources, there is a great need to develop diverse methods for their syntheses. Piperidine, the core unit for these alkaloids, has occupied an important position as bioactive targets and useful synthetic intermediates. Consequently, several synthetic approaches have been developed for the synthesis of these alkaloids[2].

(-)-Allosedridine **1** and (+)-allosedridine **2**[3] were both isolated from *Sedum nudum*[4], which were observed to exhibit memory-enhancing properties upon their isolation and may be effective for the treatment of Alzheimer' s disease[5]. For the novel biological activity, we became interested in the synthesis of such natural products. Herein, we explored our synthetic study towards (-)-allosedridine **1**.

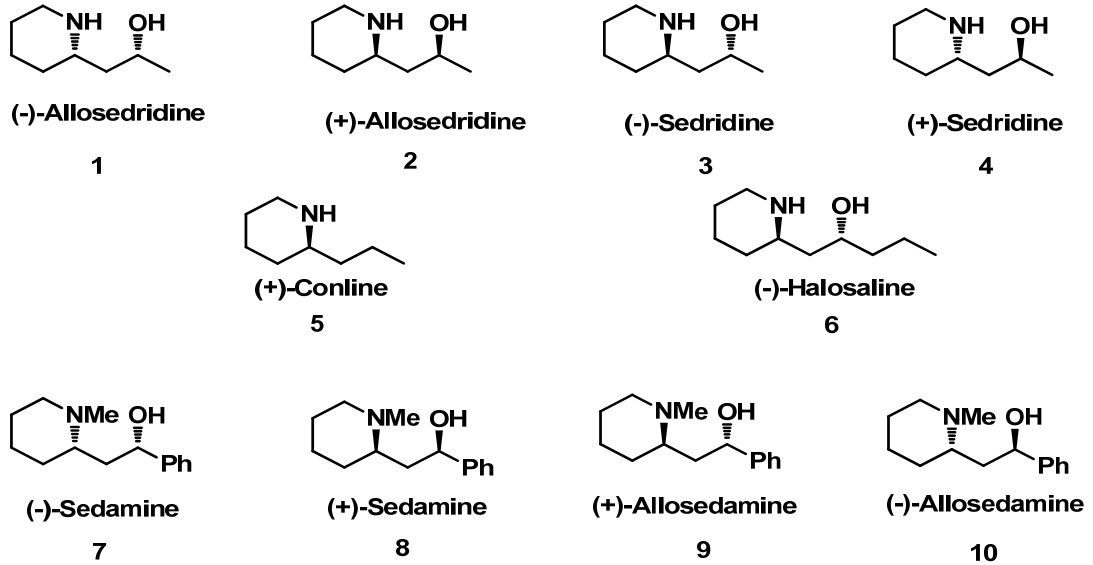
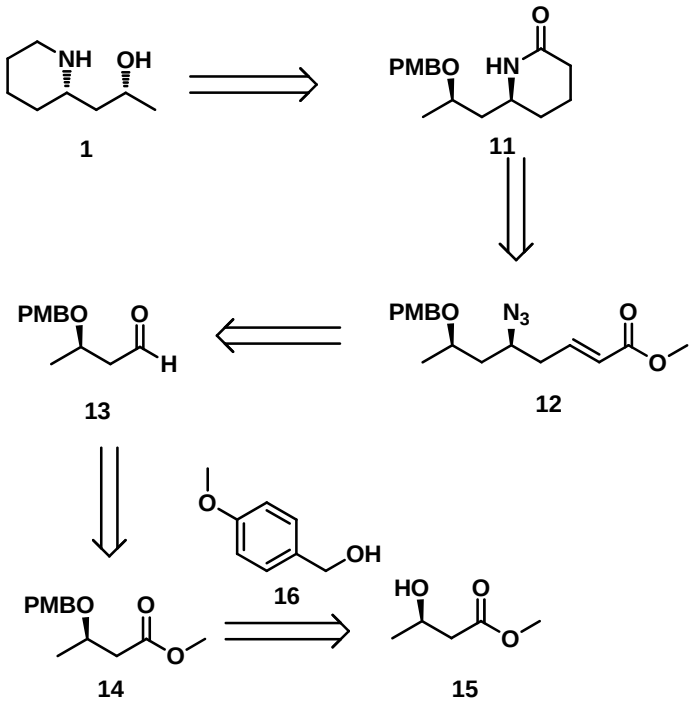


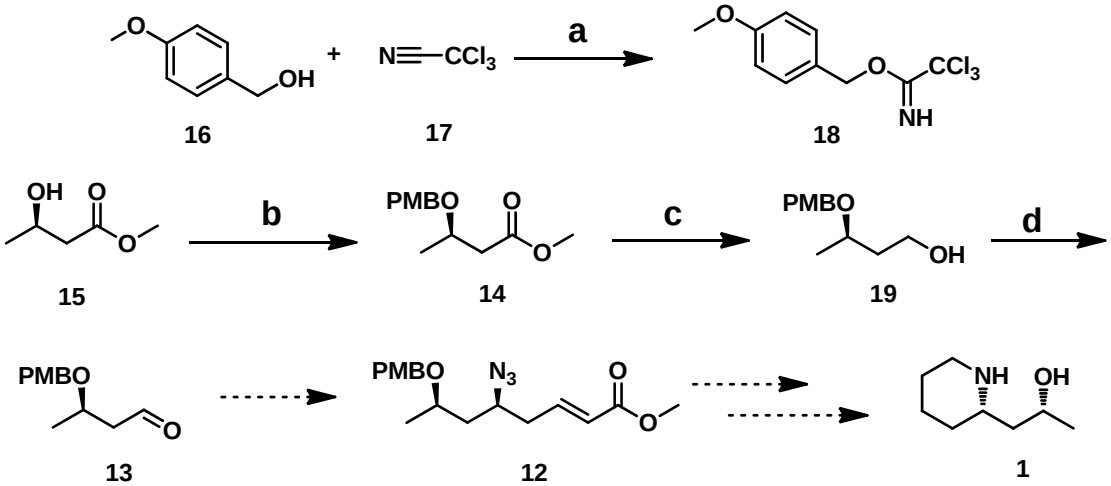
Figure 1. 2-Substituted piperidine alkaloids

Our retrosynthetic analysis of (-)-allosedridine **1** is outlined in **Scheme 1**，which actually represented a general stereoselective synthetic method for preparing **1** and **2**.



Scheme 1. Retrosynthetic route of (-)-Allosedridine

In our retrosynthetic analysis, we envisioned that the target molecule **1** could be achieved from (S)-6-((R)-2-((4-methoxybenzyl)oxy)propyl)piperidin-2-one **11** via a deprotection of PMB group and few transformation steps. Compound **11** was designed to be obtained from azide **12**, which in turn obtained from aldehyde **13** via a few steps. For the compound **13**, it could be easily obtained from ester **14** via a reduction, such using $LiAlH_4$ and following a Swern oxidation. The compound **14** could be got from the commercial available material (R)-methyl 3-hydroxybutanoate **15** via a protection. In this paper, we just reported the synthesis of compound **13**. The detailed route of **13** was show in **scheme 2**. The synthetic study towards the total synthesis of (-)-allosedridine **1** is going on based on **13**.



a) NaH (60%), Et_2O, 0ºC to r.t., 2h; b) **18**, CSA, DCM, r.t.,18h; c) $LiAlH_4$, Et_2O, 0ºC, 30 min; d) $(COCl)_2$, DMSO, Et_3N, DCM, -78ºC, 3h

Scheme 2. Synthetic route of compound **13**

Experimental

NMR spectra were recorded on Bruker AV-400MHz spectrometers. The solvents and reagents were purified and dried according to standard procedures: CH_2Cl_2, THF, DMF were distilled from CaH_2 prior to use.

4-methoxybenzyl 2, 2, 2-trichloroacetimidate 18

At 0°C, sodium hydride (60%, 40.2 mg, 1.01 mmol) was added to (4-methoxyphenyl)methanol **16** (556 mg, 4.02 mmol) under nitrogen, which was previously solubilized in anhydrous ether (1.5 mL). The mixture was stirred for 30 min at room temperature and then cooled at 0 °C. Trichloroacetonitrile **17** (403 mL, 4.024 mmol) was then added. The mixture was allowed to be stirred for 2 h at room temperature, then it was neutralized with saturated $NaHCO_3$ solution and washed with hexane (5 mL). Organic layer was extracted and then dried over $MgSO_4$ and subsequently concentrated to give the crude compound **18** (1.090 g, 3.858 mmol, 96%) as oil. R_f (petroleum ether/AcOEt: 1:1)=0.78; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H, -CH_3O), 5.18 (s, 2H, -CH_2O), 6.81 (d, 2H, -2CH aromatics, 8.7 Hz), 7.27 (d, 2H, -2CH aromatic).

(R)-methyl 3-((4-methoxybenzyl)oxy)butanoate 14

Under a nitrogen atmosphere, p-Methoxybenzyl trichloroacetimidate **18** (987 mL, 4.754 mmol) was added to (R)-methyl 3-hydroxybutanoate**15** (351 mg, 2.971 mmol) dissolved in dichloromethane (30 mL) dropwise and camphorsulfonic acid (69 mg, 0.297 mmol) was added. After 18 h, the mixture was treated with saturated $NaHCO_3$. After extraction with DCM (3×30 mL), organic phases were dried over $MgSO_4$, filtered and then concentrated. Crude product was purified on silica gel (petroleum ether/AcOEt: 1:20) to furnish the pure compound **14** (680 mg, 2.852 mmol, 96%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, 3H), 2.42-2.68 (m, 2H), 3.69 (s, 3H), 3.81 (s, 3H), 4.00 (m, 1H), 4.485 (m, 2H), 6.89 (d, 2H), 7.27 (d, 2H). ^{13}C NMR (400 MHz, CDCl3) δ: 171.46, 158.67, 130.11, 128.75, 113.44, 113.27, 71.07, 70.02, 54.77, 51.06, 41.36, 19.37.

(R)-3-((4-methoxybenzyl)oxy)butan-1-ol 19

To an ice-cold suspension of $LiAlH_4$ (2.32 g, 61.1 mmol) in ether (90 mL) was added a solution of **14** (14.56 g, 61.1 mmol) dissolved in ether (30 mL), and the mixture was stirred at 0℃ for 30 min and warmed to room temperature. Then the mixture was cooled to 0℃ again, EtOAc (27 mL, 0.31 mol), H_2O (22 mL, 1.22 mol) were added to the mixture. The resulting mixture was stirred vigorously at room temperature for 1 h and filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography (hexane/EtOAc) to afford alcohol **19** (9.61 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27(d, J = 4.2 Hz, 2H), 6.89(d, J = 4.2 Hz, 2H), 4.58(d, J = 5.6 Hz, 1H), 4.38(d, J = 5.6 Hz, 1H), 3.81(s, 3H), 3.79-3.73(m, 3H), 2.71(s, 1H), 1.79-1.74(m, 2H), 1.25(d, J = 3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 159.21, 130.46, 129.37, 113.88, 74.43, 70.09, 61.02, 55.29, 38.75, 19.39.

(R)-3-((4-methoxybenzyl)oxy)butanal 13

Under a nitrogen atmosphere, to a solution of $(COCl)_2$ (3.8 mL, 43.6 mmol) in CH_2Cl_2 (90 mL) was injected DMSO (6.14 mL, 86.5 mmol) at -78 ℃. The solution was stirred at the same temperature for 15 min, and a solution of alcohol **19** (6.1 g, 29.0 mmol) dissolved in CH_2Cl_2 (30 mL) was added. After 1 h of stirring at -78 ℃, Et_3N (28.3 mL, 204 mmol) was added, and the resulting mixture was warmed gradually to 0 ℃ over 2 h. Brine was added to the mixture, and the product was extracted with Et_2O three times. The combined ethereal solutions were washed with brine, dried, and concentrated to give aldehyde **13** as a yellow oil (5.34 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67(s, 1H), 7.15(d, J = 4.2Hz, 2H), 6.78(d, J = 4.2 Hz, 2H), 4.44(d, J = 5.6 Hz, 1H), 4.31(d, J = 5.6 Hz, 1H), 3.98-3.95(m, 1H), 3.70(s, 3H), 2.62-2.55(m, 1H), 2.43-2.38(m, 1H), 1.19(d, J = 3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 201.06, 158.75, 129.81, 128.81, 113.34, 69.78, 69.38, 54.78, 50.01.

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