Synthesis of Calycotomine *via* Pictet-Spengler Type Reaction of *N,O*-Acetal TMS Ethers as *N*-Acyliminium Ion Equivalents

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An efficient Pictet-Spengler type reaction of *N,O*-acetal TMS ethers for the practical synthesis of 1-substituted tetrahydroquinolines, medicinally important alkaloids, has been accomplished. To demonstrate the versatility of this novel procedure, the total synthesis of calycotomine, a representative 1-hydroxymethyl substituted tetrahydroisoquinoline, is also described.

Key Words : Tetrahydroisoquinoline, Pictet-Spengler reaction, *N,O*-Acetal TMS ether, Alkaloid

Introduction

The tetrahydroisoquinoline ring system (**1**) is an important structural motif[1] that is commonly encountered in naturally occurring alkaloids with interesting biological activities. In this regard, the tetrahydroisoquinoline framework has become widely identified as a "privileged" structure or pharmacophore, with representation in several medicinal agents of diverse therapeutic action.[2,3] In fact, a SciFinder search indicates that there are more than 5,000 tetrahydroisoquinolines that display a variety of structural diversity and are the potential drug candidates[2,3] such as β-adrenergic receptor antagonist **3**[4] and analgesic agent **4**.[5]

For the formation of tetrahydroisoquinoline ring system, the Pictet-Spengler and Bischler-Napieralski condensation are the most powerful methods,[6] but there are some limitations such as lack of substrate generality and harsh reaction condition at elevated temperature.

Recently, we reported a novel and versatile method for the preparation of the stable *N,O*-acetal TMS ether, as an excellent precursor of acyliminium ions which could be an optimal substrate for various electrophilic reaction.[7] In particular, *N,O*-acetal TMS ethers turned out to be most general and practical precursors, which is superior to other *N*-acyliminium ion precursors in terms of the ease of preparation, the functional group compatibility, substituents diversity, together with the facile conversion to the corresponding *N*-acyliminium ion. In an effort to expand the synthetic potential of our method, combined with our ongoing program to construct the small molecule library, we became interested in the Pictet-Spengler type reaction of acyclic *N*-acyliminium ion precursors and its application for rapid access to 1-substituted tetrahydroisoquinolines. Herein, we report the highly practical total synthesis of calycotomine (**2**),[6a,8] which is an representative 1-hydroxymethyl substituted tetrahydroisoquinoline.

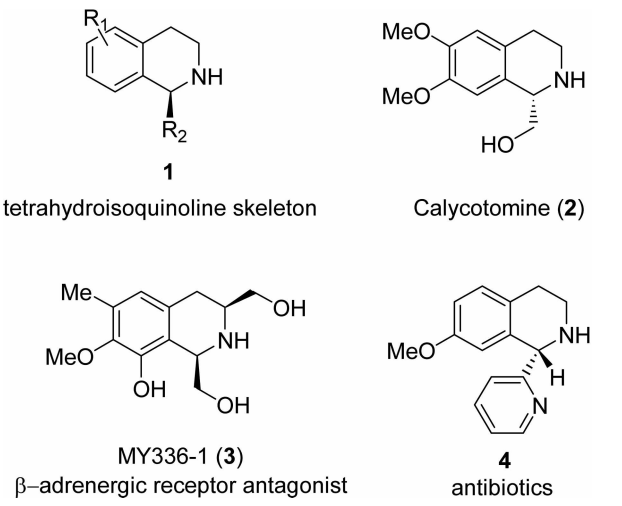
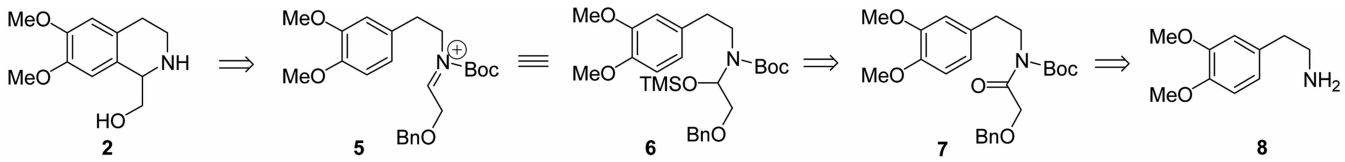


Figure 1. Structures of Representative 1-Substituted Tetrahydroisoquinolines.

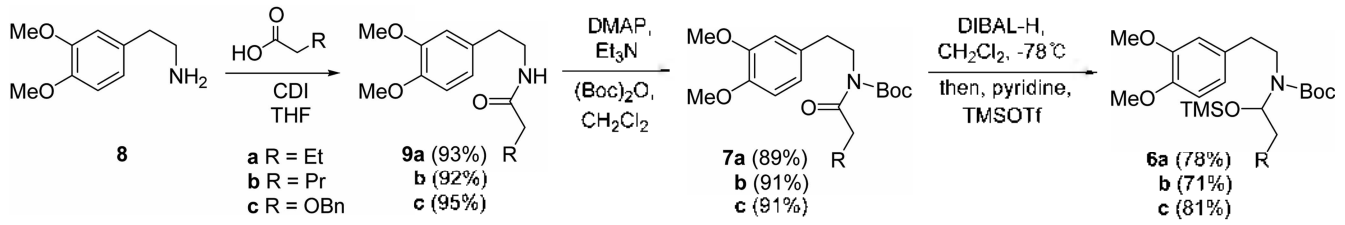
Results and Discussion

For the concise synthesis of calycotomine (**2**), we contemplated options for using an amidoalkylation for effecting the Pictet-Spengler type ring closure as indicated in Scheme 1. It was envisioned that calycotomine (**2**) would be obtained by Lewis-acid mediated cyclization of the *N,O*-acetal TMS ether **6** *via* *N*-acyliminium ion **5**. On basis of our methodology, the requisite *N,O*-acetal TMS ether **6** was considered accessible from an amidation of the phenethyl amine **8**, followed by a reductive silylation of the resulting amide **7**. Taken together, this strategy would permit significant flexibility and thereby adapt a platform that leads to a variety of 1-substituted tetrahydroquinolines.

As illustrated in Scheme 2, our synthesis commenced with the preparation of the amide **7** as a precursor for the formation of the *N,O*-acetal TMS ethers **6**. Amidation of the starting amine **8** by treatment of the various acids and CDI, followed by protection with Boc anhydride gave the corresponding amides **7** in excellent yields (83-86% for 2

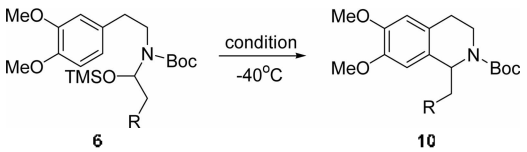


Scheme 1. Retrosynthetic Plan.



Scheme 2. Preparation of the *N,O*-acetal TMS ethers **6**.

Table 1. Optimization of the Pictet-Spengler Type Cyclization



Entry	6	R	Lewis Acid	Solvent	Yield (%)[a]
1	**6a**	Et	BF_3·OEt_2	CH_2Cl_2	84
2	**6a**	Et	$SnCl_4$	CH_2Cl_2	35
3	**6a**	Et	$TiCl_4$	CH_2Cl_2	47
4	**6a**	Et	BF_3·OEt_2	CH_3CN	61
5	**6a**	Et	BF_3·OEt_2	THF	–[b]
6	**6b**	*n*-Pr	BF_3·OEt_2	CH_2Cl_2	87
7	**6c**	OBn	BF_3·OEt_2	CH_2Cl_2	85

[a]Isolated yields. [b]Decomposed.

steps). According to a standard procedure,[7] an initial treatment of the amide **7** with DIBAL in CH_2Cl_2 at –78 °C, followed by the sequential addition of pyridine and TMSOTf, afforded the desired *N,O*-acetal TMS ethers **6** possessing various alkyl substituent, key intermediates for the projected cyclization.

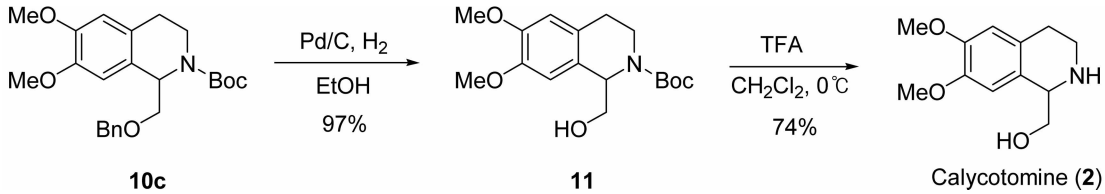
With the sufficient quantities of **6** in hand, various Lewis acids and solvent systems for the intramolecular amidoalkylations of **6** were explored. As shown in Table 1, among the Lewis acids tested, BF_3 etherate was most effective, yielding the desired compound **10** in good yield (entry 1 *vs.* entry 2 and 3). As anticipated, CH_2Cl_2 turned out to be the most effective solvent (entry 1 *vs.* entry 4 and 5). This result implies that the *N,O*-acetal TMS ethers **6** could be potential substrates for a facile electrophilic aromatic substitution reaction.

Having successfully addressed the synthesis of 1-substituted tetrahydroisoquinolines **10**, we turned our attention to the synthesis of calycotomine (**2**) as a representative target (Scheme 3). Consequently, hydrogenolysis of **10c** followed by removal of the Boc group of the resulting alcohol **11** with TFA produced the synthetic calycotomine (**2**) in 95% overall yield, which is identical with the natural **2** (^{1}H, ^{13}C-NMR, IR, and MS).[8a]

In conclusion, we have developed a convenient method for the synthesis of calycotomine **2** (6 steps, 43% overall yield) employing Pictet-Spengler type reaction of *N,O*-acetal TMS ether **6** as a *N*-acyliminium ion equivalent. This procedure appears to be quite useful for synthetic and medicinal chemistry, in terms of efficiency and functional diversity. Further application of this method to syntheses of medicinally important tetrahydroquinolines and tetrahydro-*β*-carbolines is currently underway and will be reported in due course.

Experimental

Material and methods. Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and were used without furtherher purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, and pyridine were freshly distilled from calcium hydride. All solvents used for



Scheme 3. Completion of the Synthesis of Calycotomine (**2**).

routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh. Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Infrared spectra were recorded on a Jasco FT-IR 300E spectrometer. Mass spectra were obtained with VG Trio-2 GC-MS instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPS300 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

2-Benzyloxy-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (9). To a solution of benzyloxy-acetic acid (100 mg, 0.602 mmol) in dry THF at room temperature was added CDI (146 mg, 0.903 mmol). After stirring for 1 h, amine **8** (164 mg, 0.903 mmol) was added to the reaction mixture and was stirred for 6-12 h. The reaction mixture was then extracted with EtOAc with 1 *N* HCl solution. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through paper and concentrated. The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 2:1) to afford **9** (282 mg, 95%).

FT-IR (thin film) 3320, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (t, J = 7.0 Hz, 2H), 3.54 (m, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.98 (s, 2H), 4.51 (s, 2H), 6.65 (brs, 1H), 6.80-6.72 (m, 3H), 7.34-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.2, 39.9, 55.8, 55.9, 69.6, 73.5, 111.4, 111.8, 120.6, 127.7, 128.1, 128.5, 131.2, 136.8, 147.7, 149.1, 169.3.

(2-Benzyloxy-acetyl)-[2-(3,4-dimethoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (7). To a solution of **9** (100 mg, 0.304 mmol), DMAP (7.43 mg, 0.061 mmol), and Et_3N (0.170 mL, 1.22 mmol) in dry CH_2Cl_2 was added $(Boc)_2O$ (199 mg, 0.912 mmol). The reaction mixture was stirred for 6 h, and was then extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered through paper and concentrated. The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 1:2) to afford **7** (118 mg, 91%).

FT-IR (thin film) 1725, 1720, 1594, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.78 (t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 3.89-3.92 (m, 2H), 4.60 (s, 2H), 4.62 (s, 3H), 6.81-6.72 (m, 3H), 7.42-7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.9, 34.4, 45.9, 55.8, 55.9, 71.9, 73.2, 83.4, 111.3, 112.2, 120.8, 127.7, 127.9, 128.4, 131.3, 137.7, 147.7, 148.9, 152.6, 172.9.

(2-Benzyloxy-1-trimethylsilanyloxy-ethyl)-[2-(3,4-dimethoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (6c). To a solution of **7** (100 mg, 0.233 mmol) in dry CH_2Cl_2 at −78 °C was added 1 M solution of DIBAL-H (0.698 mL, 0.698 mmol). After stirring for 30 min, the reaction mixture was treated with pyridine (0.094 mL, 1.17 mmol) and then TMSOTf (0.148 mL, 0.816 mmol). The mixture was stirred at −78 °C for 10 min, and then slowly warmed to 0 °C, quenched with 15% aqueous sodium potassium tartrate, and diluted with Et_2O. The resultant mixture was warmed to room temperature and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in reduced pressure. The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 1:3) to afford **6c** (95 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ 0.06 (s, 9H), 1.45 and 1.46 (s, 9H), 2.61-2.79 (m, 2H), 3.08-3.24 (m, 2H), 3.40 (d, J = 5.7 Hz, 2H), 3.77 (s, 6H), 4.41-4.57 (m, 2H), 5.69 and 5.84 (m, 1H), 6.60-6.76 (m, 3H), 7.19-7.26 (m, 5H).

Standard procedure for the synthesis of 10. To a solution of **6c** (100 mg, 0.199 mmol) in dry CH_2Cl_2 at −40 °C was added BF_3 etherate (0.096 mL, 0.596 mmol) and stirred for 1 h. It was cooled again to 0 °C and quenched with Et_3N. The reaction mixture was then extracted with EtOAc with $NaHCO_3$. The combined organic layers were dried and concentrated. The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 1:2) to afford **10c** (69.9 mg, 85%).

10a: ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ 1.15 (m, 3H), 1.40 (s, 9H), 1.58-1.85 (m, 2H), 2.52-4.21 (m, 4H), 3.77 (s, 3H), 3.79 (s, 3H), 4.79 and 4.82 (m, 1H), 6.52 (s, 2H); MS (FAB) *m/z* 322 (M + H$^-$). **10b**: ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ 1.09 (m, 3H), 1.37 (s, 9H), 1.51-1.83 (m, 4H), 2.54-4.13 (m, 4H), 3.60 (s, 3H), 3.79 (s, 3H), 4.88 and 4.99 (m, 1H), 6.50 (s, 2H); MS (FAB) *m/z* 336 (M + H$^+$). **10c**: FT-IR (thin film) 1687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ 1.47 and 1.49 (s, 9H), 2.61 and 2.67 (m, 1H), 2.84 (m, 1H), 3.21 and 3.34 (m, 1H), 3.55-4.32 (m, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 4.51 (m, 2H), 5.13 and 5.31 (m, 1H), 6.61-6.74 (m, 2H), 7.27 (m, 5H); MS (FAB) *m/z* 414 (M + H$^+$).

1-Hydroxymethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (11). To a solution of **10c** (80.0 mg, 0.193 mmol) in EtOH was added 10% Pd/C (10 mg). The reaction mixture was stirred under an atmosphere of H_2 filled in a balloon for 18 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (ethyl acetate:*n*-hexane = 1:1) to afford **11** (60.4 mg, 97%).

FT-IR (thin film) 3513, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ 1.47 (s, 9H), 2.62-3.24 (m, 3H), 3.57-4.02 (m, 3H), 3.80 (s, 6H), 5.10 and 5.19 (m, 1H), 6.60 (s, 1H), 6.66 (s, 1H); MS (FAB) *m/z* 324 (M + H$^+$).

Calycotomine (2). To a solution of **11** (50.0 mg, 0.155 mmol) in dry CH_2Cl_2 at 0 °C was added TFA (0.060 mL, 0.773 mmol) and stirred for 3 h. The reaction mixture was poured into sat. $NaHCO_3$. The organic layer was extracted

with EtOAc and the combined organic layers were washed with aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated to give **2** (25.5 mg, 74%) as a solid.

FT-IR (thin film) 3450 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.92 (t, J = 6.3 Hz, 2H), 3.25 (dd, J = 6.0, 12.4 Hz, 1H), 3.42 (dd, J = 6.4, 12.8 Hz, 1H), 3.70 (s, 6H), 4.00 (m, 2H), 4.34 (dd, J = 4.0, 8.8 Hz, 1H), 6.70 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 26.2, 39.9, 56.6, 56.8, 58.0, 63.1, 110.9, 113.3, 122.3, 126.0, 150.0, 150.8; MS (FAB) m/z 224 ($M + H^-$).

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