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Synthesis of Spirocyclopropyl γ-Lactams by a Highly Stereoselective Tandem Intramolecular Azetidine Ring-Opening/Closing Cascade Reaction

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A new tandem intramolecular azetidine ring-opening/closing cascade reaction affording spirocyclopropyl γ-lactams in high regio- and stereoselectivity is reported. The key step of the process is an S_N2-type ring-opening of TMSOTf-activated azetidine rings by silyl ketene acetals generated by treatment with TMSOTf and triethylamine. This study is a very rare example of nucleophilic ring opening of azetidines that does not require formation of quaternary azetidinium salts by *N*-alkylation or the use of *N*-electron-withdrawing groups.

Introduction

Although less popular than aziridines, pyrrolidines, and piperidines, azetidines constitute a class of attractive heterocycles present in many natural products and pharmacologically relevant compounds.[1] Until recently, the reactivity of azetidines was almost unexploited in comparison to that of the widely used aziridines because of their lower synthetic availability and reactivity.[2] For example, ring opening of azetidines usually requires stronger activation including formation of quaternary azetidinium salts by *N*-alkylation as a consequence of reduced ring strain and electrophilicity.[3] In a recent relevant study, azetidinium derivatives were indeed shown to be 17000 times less reactive than the corresponding aziridinium analogs towards nucleophilic ring opening.[3] Within the framework of a research program devoted to the design and biological evaluation of novel classes of iminosugars,[4,5] our objective was to access rapidly 2-azaspiro[3.3]heptane derivatives as precursors of original bicyclic spiranic iminosugars **1** (Figure 1). For example, compounds **2** may be viewed as a constrained analog of α-1-*C*-Nonyl-DIX (**3**) having a blocked $^1C_4$ conformation.

α-1-*C*-Nonyl-DIX (**3**) is a potent inhibitor of human β-glucocerebrosidase and acts as a pharmacological chaperone of the N370S mutant of this enzyme for patients with Gaucher disease.[6] The synthetic strategy we first envisioned to access 2-azaspiro[3.3]heptane derivatives was based on a Dieckmann reaction performed on diester **5** obtained in two steps from commercially available **4** (Scheme 1).[7] This was a short but challenging route, as formation of four-membered cycles by such a process is disfavored by ring strain and has almost no precedent.[8] First attempts performed under classical conditions (NaH, THF) failed to afford the desired 2-azaspiro[3.3]heptane derivative. We then turned our attention to a cationic variant of the Dieckmann reaction involving a silyl ketene acetal generated by treatment of enolizable ester **5** with TMSOTf and triethylamine (TEA).[9] In a first attempt, reaction of **5** following Hoye's protocol[9a] did not lead to the formation of the Dieckmann product but to functionalized 5-azaspiro[2.4]-heptane derivative **6a** in 65% yield as a single diastereoisomer (Scheme 1). The 5-azaspiro[2.4]heptane skeleton is a motif present in various biologically active molecules including antibacterial and antiautoimmune agents.[10,11]

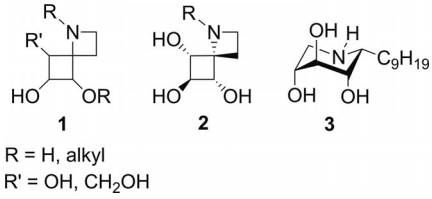

Figure 1. Iminosugars designed as pharmaceutical chaperones for Gaucher disease.

The structure of **6a** and relative configuration of the two asymmetric centers were determined by NMR spectroscopy and further confirmed by X-ray crystallographic analysis of primary alcohol **6b** obtained after selective reduction of the ester group (Figure 2).[12a] Access to the fully reduced pyrrolidine analog **6c** was also easily performed from **6a** by using LAH.

In this paper, we wish to report our first exploration of the synthetic scope of this novel tandem reaction and to provide some insights into its mechanism for rationalizing the unexpected formation of the azaspiro bicyclic products.

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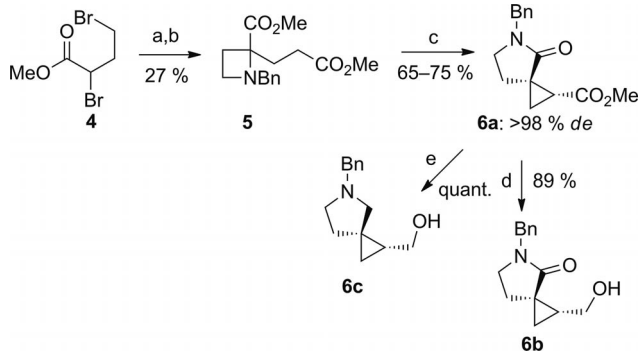


Scheme 1. Reagents and conditions: (a) $BnNH_2$ (1 equiv.), TEA (3 equiv.), MeCN, Δ, 4 h; (b) LDA (1.1 equiv.), HMPA (6.3 equiv.), methyl 3-bromopropionate (3 equiv.), THF, –78 °C to r.t.; (c) TMSOTf (2 equiv.), TEA (2.5 equiv.), CH_2Cl_2, r.t. or Δ; (d) $LiBHEt_3$ (4 equiv.), THF, –78 to –65 °C; (e) lithium aluminum hydride (LAH, 3.5 equiv.), THF, Δ.

Table 1. Reaction of **5** with Lewis acid and base.[a]

Entry	Lewis acid (equiv.)	Base (equiv.)	Temp.	Yield[b] [%]
1	TMSOTf (2)	TEA (2.5)	r.t.	65
2	TMSOTf (1)	TEA (2.5)	r.t.	–
3	TMSOTf (2)	TEA (1)	r.t.	–
4	TMSOTf (3)	TEA (2.5)	r.t.	65
5	TMSOTf (2)	TEA (3)	r.t.	68
6	TMSOTf (2)	TEA (2.5)	r.t.	75[c]
7	TMSOTf (2)	TEA (2.5)	Δ[d]	70
8	TMSOTf (2)	TEA (2.5)	r.t.	–[e]
9	TMSOTf (2)	DIPEA (2.5)	r.t.	38
10	ZnOTf (2)	TEA (2.5)	r.t.[f]	–
11	ScOTf (2)	TEA (2.5)	r.t.[f]	–
12	$BF_3{\cdot}Et_2O$ (2)	TEA (2.5)	r.t.	–[c]
13	CuOTf (2)	TEA (2.5)	r.t.	–[c]
14	TBDMSOTf (2)	TEA (2.5)	Δ	25

[a] Reaction performed in DCM for 5 to 7 h. [b] Isolated yield. [c] Reaction time: 24 h. [d] Reaction time: 3 h. [e] Reaction performed in THF. [f] Room temperature for 24 h then reflux for 3 h.

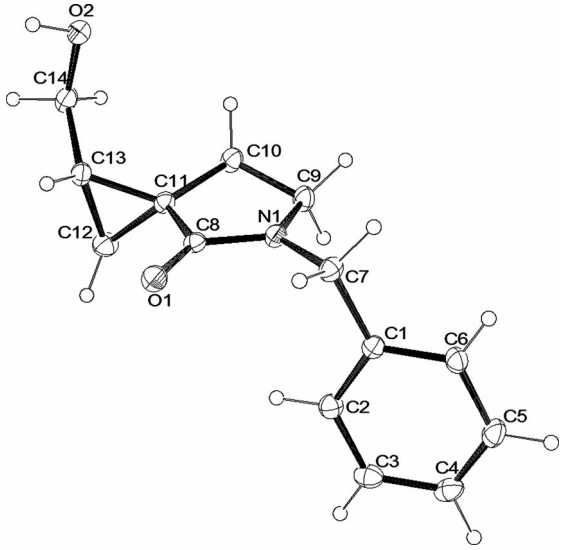


Figure 2. Molecule structure (ORTEP)[12b] of compound **6b**. Thermal ellipsoid at 30% probability.

Results and Discussion

Various experimental parameters were first examined with the TMSOTf/TEA system in DCM to improve the yield of the one-pot process. Decreasing the amount of TMSOTf or TEA to one equivalent was found to be detrimental, as no reaction took place (Table 1, Entries 2 and 3), whereas the addition of more equivalents of Lewis acid or base (Table 1, Entries 4 and 5) did not improve significantly the yield of the reaction. The best yields were obtained by increasing the reaction time to 24 h or by increasing the reaction temperature to reflux (Table 1, Entries 6 and 7).

No reaction took place in THF (Table 1, Entry 8), and the yield was divided by almost a factor of 2 by using DIPEA instead of TEA as a base (Table 1, Entry 9). Screening of various azaphilic and oxophilic Lewis acids[13] revealed that the nature of the Lewis acid was crucial, as conversion of the azetidine starting material was observed only with TMSOTf (Table 1, Entries 10–13). The use of a more sterically demanding trialkylsilyl triflate (TBDMSOTf) led to low yields and modest conversion (Table 1, Entry 14). The influence of diverse structural parameters in the outcome of the spirocyclization reaction was then studied (Figure 3 and Scheme 2). Deactivation of the azetidine endocyclic nitrogen atom was found to be detrimental to the process, as no spiranic product could be obtained from *N*-Tos or *N*-Boc azetidines **7** and **8** (Figure 3).

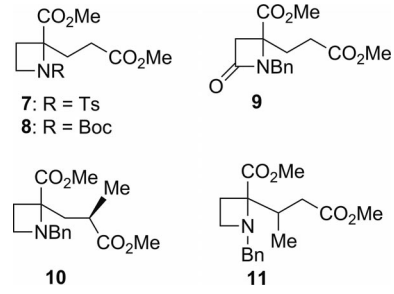
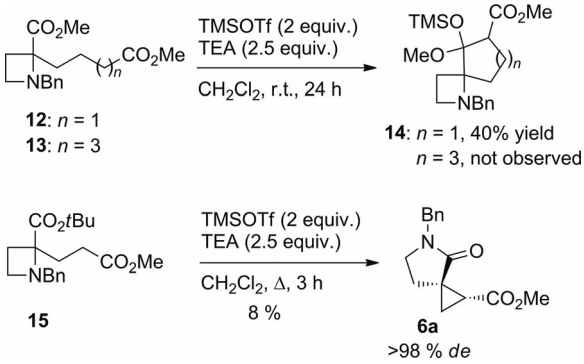


Figure 3. Test substrates for investigating the scope of the tandem reaction.

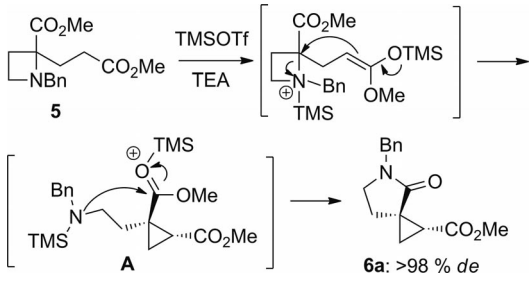
No desired product was obtained from lactam **9** either.[14] The reaction was found to be highly sensitive to the introduction of substituents in the α or β position to the primary ester group; azetidines **10** and **11**,[15] the methylated analogs of **5**, did not partake in the spirocyclization reaction. Not surprisingly, conversion of **12** provided the expected spirocyclopentane **14** as the increase of the alkyl chain length by one methylene unit favored the Dieckmann reaction

(Scheme 2). Further increase in the alkyl chain length by two methylene units to favor azetidine ring opening (formation of a six-membered ring) over the Dieckmann reaction (formation of a disfavored seven-membered ring)[9a] led to substrate **13**, which was not reactive under our typical cyclization conditions. The influence of steric effects on the cyclization process was explored with *tert*-butyl ester **15**, which afforded the expected spiranic lactam in a much lower yield than that of corresponding methyl ester analog **5** (Scheme 2).



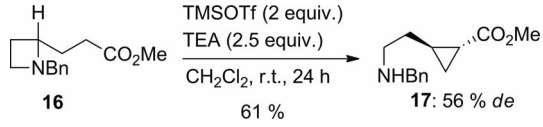
Scheme 2.

A tentative mechanism for the formation of spirocyclopropyl γ-lactam **6a** is proposed in Scheme 3. We believe that the key step of the process is an S_N2-type ring opening[2,16] of the TMSOTf-activated azetidine ring by the silyl ketene acetal generated by treatment with TMSOTf and TEA.[9a] Amino ester **A**, thus obtained, finally undergoes an intramolecular cyclization to afford five-membered lactam **6a** by reaction of the amine function with the ester group in the γ position. This reaction proceeds in high regioselectivity, as no formation of the six-membered lactam was detected. Remarkably, in this process TMSOTf plays a triple role by generating the reactive nucleophilic intermediate (the silyl ketene acetal), by activating the azetidinine for the nucleophilic ring opening, and by activating the carbonyl group of the tertiary ester group for the final amide bond formation.[17]



Scheme 3. Proposed mechanism for the tandem reaction.

The proposed mechanism is supported by experimental evidence and explains why azetidines **7**, **8**, and **9** are not substrates of the cyclization reaction; the best activation of the azetidine ring with TMSOTf is indeed expected for an endocyclic amine. To isolate the aminocyclopropane intermediate of type **A** by avoiding the formation of the β-lactam, the tertiary ester group was replaced by a hydrogen atom, and the reaction was performed from azetidine **16**.[18] Treatment of **16** with TMSOTf and TEA afforded cyclopropane **17** in 61 % yield with 56 %*de* in favor of the *trans* product (Scheme 4). Disappointing results obtained with **10**, **11**, and azetidine **15** bearing a bulky *t*Bu ester group or with higher trialkylsilyl triflate (Table 1, Entry 14) are compatible with the fact that an S_N2 process is a mechanism known to be sensitive to steric hindrance.



Scheme 4.

Conclusions

In conclusion, a novel, highly stereoselective tandem intramolecular azetidine ring-opening/closing cascade reaction is reported. In this one-step process, two cycles – a cyclopropane and a γ-butyrolactam – and two asymmetric centers are created. This study represents a very rare example[19] of nucleophilic ring opening of azetidines without formation of quaternary azetidinium salts by *N*-alkylation or the use of *N*-electron-withdrawing groups.[20,21] Further applications and mechanistic exploration of this methodology are currently under investigation in our laboratory.

Experimental Section

General Methods: Tetrahydrofuran (THF) was dried by passage through an activated alumina column under an atmosphere of argon. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 under an atmosphere of argon. Triethylamine (TEA) was distilled from KOH under an atmosphere of argon and stored over KOH. All reactions were performed in standard glassware under an atmosphere of argon. Flash chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm) purchased from E. Merck. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F_{254} purchased from E. Merck. IR spectra were recorded with a Perkin–Elmer Spectrum One Spectrophotometer. NMR spectra were recorded with a Bruker AC 300 or AC 400 with solvent peaks as reference. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The ^1H signals were assigned by 2D experiments (COSY). ESI-HRMS was carried out with a Bruker MicroTOF spectrometer.

5-Benzyl-1-methoxycarbonyl-5-azaspiro[2.4]heptan-4-one (6a): To a solution of azetidine **5** (80 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) cooled to 0 °C was added TEA (96 μL, 0.69 mmol, 2.5 equiv.) and TMSOTf (0.1 mL, 0.55 mmol, 2 equiv.). The solution was stirred at room temperature for 24 h. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/pentane, 1:5 to 1:1) to afford **6a** (54 mg, 75 %) as a yellow oil. TLC: R_f = 0.30 (silica gel; AcOEt/

petroleum ether, 1:2). IR (film): $\tilde{\nu}$ = 1728, 1688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H, Ph), 4.51 (d, J = 14.7 Hz, 1 H, CH_2Ph), 4.45 (d, J = 14.7 Hz, 1 H, CH_2Ph), 3.71 (s, 3 H, CO_2Me), 3.32 (m, 2 H, 6-H), 2.28 (dd, J = 6.1, 8.8 Hz, 1 H, 1-H), 2.19 (dd, J = 8.3, 6.3 Hz, 2 H, 7-H), 1.58 (dd, J = 8.8, 4.0 Hz, 1 H, 2a-H), 1.35 (dd, J = 5.9, 4.1 Hz, 1 H, 2b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (CO), 172.0 (NCO), 136.3 (*C*q-Ar), 128.8 (2 *C*H-Ar), 128.4 (2 *C*H-Ar), 127.8 (1 *C*H-Ar), 52.0 (OMe), 47.6 (*C*H_2Ph), 44.2 (C-6), 31.6 (C-3), 25.3 (C-1), 22.9 (C-7), 19.3 (C-2) ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO_3Na$ $[M + Na]^+$ 282.110; found 282.110.

5-Benzyl-1-hydroxymethyl-5-azaspiro[2.4]heptan-4-one (6b): To a solution of **6a** (84 mg, 0.32 mmol) in THF (0.5 mL) cooled to –78 °C was added $LiBHEt_3$ (1 M in THF, 1.3 mL, 1.30 mmol, 4 equiv.). The solution was stirred for 1 h at –78 °C and 1.5 h at –65 °C. Saturated aqueous $NaHCO_3$ (0.4 mL) was added, and the solution was warmed to 0 °C. H_2O_2 (35%, 90 μL) was added, and the solution was stirred at 0 °C for 20 min. The solution was concentrated under reduced pressure. Water was added, and the solution was extracted with CH_2Cl_2 (3×). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography ($MeOH/CH_2Cl_2$, 5:95) to afford **6b** (67 mg, 89%) as a white powder. TLC: R_f = 0.30 (silica gel; $MeOH/CH_2Cl_2$, 5:95). IR (film): $\tilde{\nu}$ = 3389, 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 5 H, Ph), 4.60 (d, J = 14.6 Hz, 1 H, CH_2Ph), 4.45 (d, J = 14.6 Hz, 1 H, CH_2Ph), 3.89 (dd, J = 11.5, 5.7 Hz, 1 H, CH_2OH), 3.46 (m, 1 H, CH_2OH), 3.39 (m, 2 H, 6-H), 2.31 (m, 1 H, 1-H), 2.01 (m, 1 H, 7a-H), 1.77 (m, 1 H, 7b-H), 1.38 (dd, J = 9.1, 4.2 Hz, 1 H, 2a-H), 0.64 (dd, J = 6.3, 4.4 Hz, 1 H, 2b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1 (NCO), 136.7 (Cq-Ar), 128.8 (2 *C*H-Ar), 128.3 (2 *C*H-Ar), 127.7 (1 *C*H-Ar), 63.1 (*C*H_2OH), 47.4 (*C*H_2Ph), 44.5 (C-6), 27.2 (C-3), 25.1 (C-1), 22.4 (C-7), 17.6 (C-2) ppm. HRMS (ESI): calcd. for $C_{14}H_{17}NO_2Na$ $[M + Na]^+$ 254.115; found 254.117.

5-Benzyl-1-hydroxymethyl-5-azaspiro[2.4]heptane (6c): LAH (34 mg, 0.89 mmol, 3.5 equiv.) was added to a solution of **6a** (66.2 mg, 0.26 mmol) in THF (1.4 mL). The solution was stirred at reflux for 3 h. After cooling, H_2O (1 mL) followed by 10% NaOH (2 mL) and H_2O (3 mL) were added. The solution was filtered through Celite and concentrated under reduced pressure to afford **6c** (55 mg, quant.) as a yellow oil. IR (film): $\tilde{\nu}$ = 3342 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.16 (m, 5 H, Ph), 4.12–3.88 (br. s, 1 H, OH), 3.64–3.51 (m, 3 H, CH_2OH, CH_2Ph), 3.25 (dd, J = 11.1, 8.6 Hz, 1 H, CH_2OH), 2.80 (m, 1 H, 5a-H), 2.61 (m, 1 H, 5b-H), 2.49 (d, J = 9.1 Hz, 1 H, 4a-H), 2.37 (d, J = 9.1 Hz, 1 H, 4b-H), 1.97 (m, 1 H, 7a-H), 1.62 (m, 1 H, 7b-H), 1.04 (m, 1 H, 1-H), 0.68 (dd, J = 8.8, 4.9 Hz, 1 H, 2a-H), 0.27 (t, J = 5.2 Hz, 1 H, 2b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (*C*q-Ar), 129.1 (2 *C*H-Ar), 128.4 (2 *C*H-Ar), 127.2 (*C*H-Ar), 63.9 (C-4 or *C*H_2OH), 63.7 (C-4 or *C*H_2OH), 60.9 (*C*H_2Ph), 50.0 (C-6), 28.8 (C-7), 25.25 (C-1), 25.2 (C-3), 17.0 (C-2) ppm. HRMS (ESI): calcd. for $C_{14}H_{20}NO$ $[M + H]^+$ 218.154; found 218.153.

Supporting Information (see footnote on the first page of this article): ^1H NMR, ^1H–^1H NOESY NMR, and ^{13}C NMR spectra for compound **6a**.

Acknowledgments

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