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Versatile construction of functionalized tropane ring systems based on lactam activation: enantioselective synthesis of (+)-pervilleine B†

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The halo-assisted intramolecular addition of silyl enol ethers with *in situ* activated lactams yielded (hydroxylated) 1-halo-8-azabicyclo[3,2,1]octane and 1-halo-9-azabicyclo[3,3,1]nonane ring systems, which provided an easy enantioselective access to 6β-silyloxytropane-3-one, 3α,6β-dihydroxytropane, and pervilleine B. The absolute configuration of the natural (−)-pervilleine B was determined to be 1*R*,3*R*,5*S*,6*R*.

Recently more and more dihydroxytropane alkaloids derived from 3α,6β-tropanediol (**1**) have been isolated in forms of mono and di-esters.[1,2] For example, eleven such alkaloids have been isolated from the roots of *Erythroxylum pervillei* Baillon, collected in southern Madagascar.[2] Among them, pervilleines B, C and F (Fig. 1, **3**–**5**) displayed promising MDR-inhibitory activities,[3] and were selected for further development through a special program.[2c] In addition, 3α,6β-dihydroxytropane **1** (ref. 4*a*) and *O*-protected 6β-hydroxytropan-3-ones such as **2** (ref. 4*b* and *c*) have been used to develop highly active analogs of the muscarinic agonists,[4a] cocaine antagonists/partial agonists,[4b] and potent and selective M_2-receptor agonists.[4c] The bioactivities of this class of alkaloids have been shown to be highly enantiomer-dependent.[4] However, little attention has been paid to the enantioselective synthesis of dihydroxytropanes[5] although that of other tropane alkaloids and analogs has attracted considerable attention.[6]

In a program on the asymmetric synthesis of bioactive *N*-heterocycles and alkaloids,[7] we recently disclosed enantioselective synthesis of (−)-Bao Gong Teng A.[6a] As a continuation of that study, and on the basis of our development of the amide activation-based C–C bond formation reactions,[8] we envisaged that intramolecular cyclization of ketone–lactams **A** through addition of silyl enol ethers with *in situ* activated lactams could build the hydroxytropane-3-one ring systems **B** (Scheme 1). The compatibility of silyl enol ethers with amide activation conditions has been nicely demonstrated by Bélanger *et al.*,[9] while hydroxylactams **A** are easily available from chiral pools such as malic acid[10] *via* α-amidoalkylation. Herein we communicate the results of this investigation.

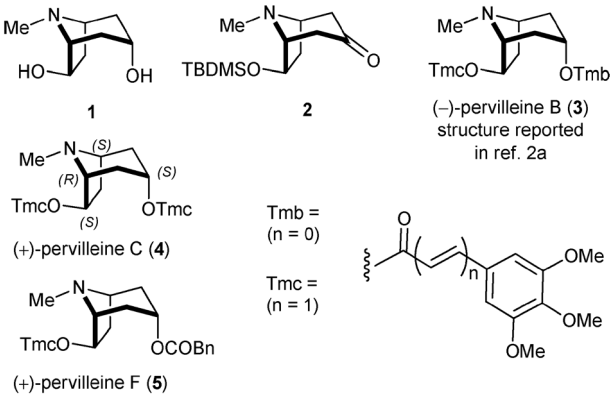
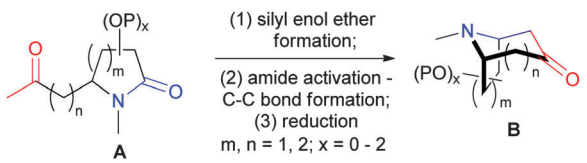


Fig. 1 Structures of some tropane alkaloids and the parent molecules.



Scheme 1 A new approach to hydroxylated tropan-3-ones.

As a model study, racemic keto-lactam **6** was treated with TBDMSOTf–NEt_3,[11] and the resulting silyl enol ethers, formed as regioisomeric mixtures [**SL1a** (terminal) : **SL1b** (internal) = 6.4 : 1], were used directly in the cyclization reaction under the previously established lactam activation conditions (Tf_2O,[12] DTBMP, CH_2Cl_2, −78 °C) (Scheme 2).[8a] To our disappointment, the desired product **9** was not observed. Addition of Lewis acid such as $BF_3{\cdot}Et_2O$ or TMSOTf did not yield any product. However, use of 1.0 equiv. of TMSCl as a Lewis acid produced a 6-enolendo[13] cyclization product (**7a**) bearing a chlorine atom at the bridgehead carbon in 12% yield, instead of compound **9**. Other halo-containing Lewis acids including $TiCl_4$, $AlCl_3$, $SnCl_4$, $ZnBr_2$, and $ZnCl_2$ were

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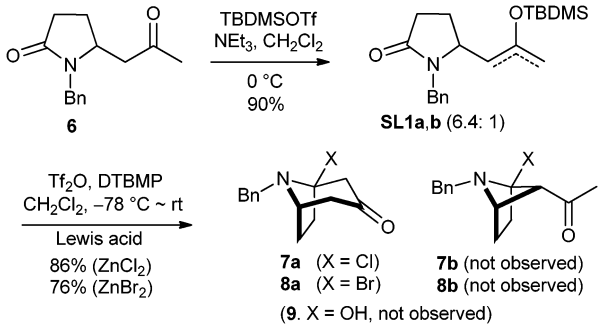


Scheme 2 The halo-assisted intramolecular addition of silyl enol ethers with *in situ* activated lactam. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

thus surveyed. The best result was obtained with the use of 1.2 equiv. of $ZnCl_2$ (86% yield based on the major regioisomer of the silyl enol ether). In all cases, no 4-enolexo cyclization product from the internal silyl enol ether **SL1b** was observed. The optimal conditions for the cyclization of silyl enol ether–lactams **SL1a,b** were thus established to be: Tf_2O (1.2 equiv.), DTBMP (1.2 equiv.), $ZnCl_2$ or $ZnBr_2$ (1.2 equiv.).

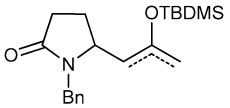
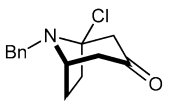
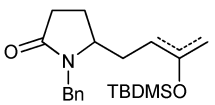
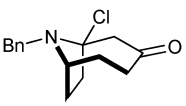
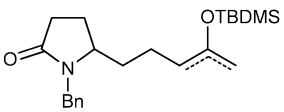
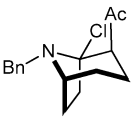
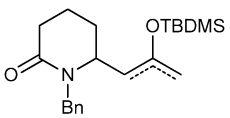
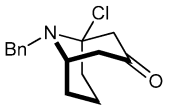
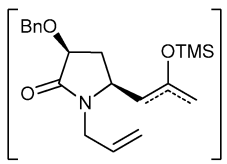
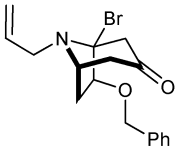
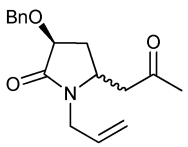
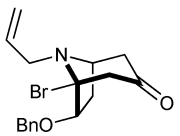
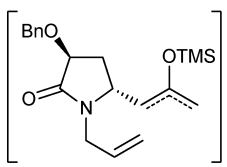
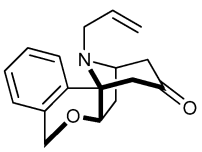
We then proceeded to investigate the reactions of other keto-lactams (*cf.* ESI†). All the silyl enol ethers, formed as regioisomeric mixtures, were directly used in the cyclization. The results are summarized in Table 1. As observed with silyl enol ethers **SL1a,b** (entry 1), the cyclization of **SL3a,b** (entry 3) led only to the formation of the 8-azabicyclo[3,2,1]octane ring system **11b** (isolated as a single diastereomer in 75% yield based on **SL3b**). From the cyclization of silyl enol ethers **SL2a,b**, the seven-membered (**10a**) and five-membered products were obtained only in trace amounts (entry 2) which precluded the full characterization of the products. Subjection of the regioisomeric mixture **SL4a,b** (ratio = 3.8 : 1) to the cyclization conditions produced the 9-azabicyclo [3,3,1]nonane ring system **12a** in 65% yield (entry 4).

The cyclization reactions of the enantiomeric keto-lactams **13** (*cis*-diastereomer) and **14** (*trans*-diastereomer), easily available from (*S*)-malic acid, were also investigated. The reaction of keto-lactam **13** with TMSOTf (NEt_3, CH_2Cl_2) yielded the terminal silyl enol ether **SL5a** in excellent regioselectivity (>20 : 1), which upon treatment with Tf_2O, DTBMP and $ZnBr_2$ cyclized to produce the 1-bromo-tropan-3-one **15** in 50% yield from keto-lactam **13** (entry 5). For *trans*-keto-lactam **14**, the terminal silyl enol ether **SL6a** was also formed in excellent regioselectivity (>20 : 1), which was subjected to the cyclization conditions to give the expected 1-bromo-tropan-3-one **16** in 23% yield from **14**, along with the tetracyclic compound **17** in a yield of 30% (from **14**).

The C–Cl bond was cleaved by heating a mixture of 1-chlorotropan-3-one **7a**, 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) and Bu_3SnH in toluene at 85 °C for 3.0 h, which gave **18** in 90% yield (Scheme 3).

We next turned to the enantioselective synthesis of pervilleine B (**3**). Since the absolute configuration of this alkaloid is unknown, we decided to synthesize pervilleine B with the absolute configuration displayed in Fig. 1. The requisite keto-lactam (+)-(4*S*,5*R*)-**19** was synthesized in 29% overall yield from (*S*)-malic acid (see ESI†). Treatment of **19** with TBDMSOTf–NEt_3 (CH_2Cl_2, 0 °C) yielded the silyl enol ether **20** in excellent

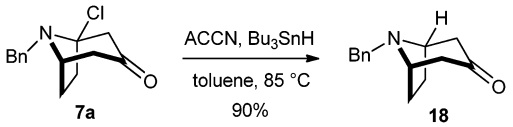
Table 1 Lactam activation-based cyclization reaction of keto-lactams *via* silyl enol ethers

Entry	Silyl enol ether[c]	Cyclization product (yield)[d]
1[a]	 **SL1a,b** (6.4: 1, 90%)	 **7a** (86%)
2[a]	 **SL2a,b** (1.3: 1, 84%)	 **10a** (trace)
3[a]	 **SL3a,b** (1.4: 1, 81%)	 **11b** (75%) single isomer
4[a]	 **SL4a,b** (3.8: 1, 40%)	 **12a** (65%)
5[b]	 **SL5a,b** (>20: 1) (from **13**)	 **15** (50% from **13**)
	 *cis*-**13** and *trans*-**14**	 **16** (23% from **14**)
6[b]	 **SL6a,b** (>20 : 1) (from **14**)	 **17** (30% from **14**)

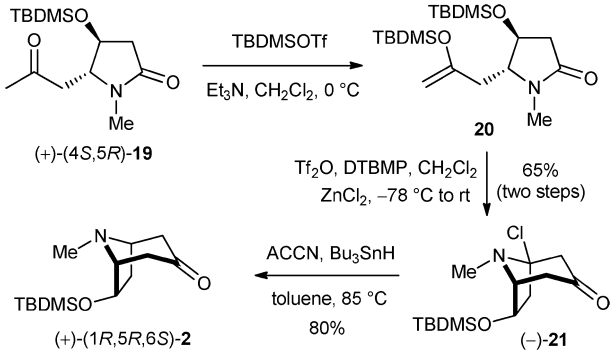
[a] Method A: (1) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C; (2) Tf_2O, DTBMP, $ZnCl_2$, −78 °C–rt. [b] Method B: (1) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (2) Tf_2O, DTBMP, $ZnBr_2$, −78 °C–rt. [c] Combined isolated yield of **SLXa** (terminal) and **SLXb** (internal), regioisomeric ratio determined using ^1H NMR. [d] Isolated yield obtained from the corresponding regioisomers of silyl enol ethers.

regioselectivity (terminal : internal > 20 : 1), which without purification was treated with Tf_2O, DTBMP, and $ZnCl_2$ (CH_2Cl_2, −78 °C to rt) to produce (−)-**21** in 65% yield (from **19**) as a single diastereomer. Radical de-chlorination (ACCN, Bu_3SnH, toluene, 85 °C) of **21** afforded (+)-(1*R*,5*R*,6*S*)-6β-silyloxytropane-3-one **2** in 80% yield (Scheme 4).

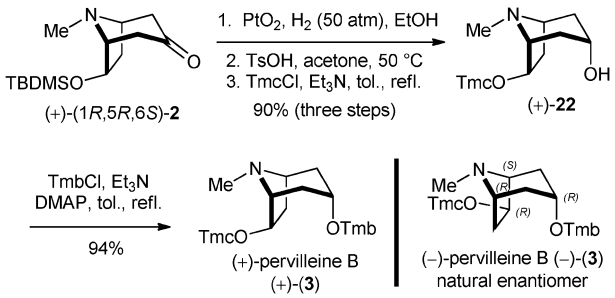
By stereoselective hydrogenation[5c] (PtO_2, H_2, 50 atm, EtOH), de-silylation (TsOH, acetone, 50 °C), and esterification of the resulting 3α,6β-dihydroxytropane **1** (TmcCl, Et_3N, tol., refl.), the key intermediate **2** was transformed into monoester **22** in 90%



Scheme 3 Radical de-chlorination of 1-chloro-tropane derivative **7a**.



Scheme 4 The construction of (1*R*,5*R*,6*S*)-tropan-3-one **2**.



Scheme 5 Final synthesis of (+)-(1*S*,3*S*,5*R*,6*S*)-pervilleine B, and the determined absolute configuration of the natural (−)-pervilleine B.

overall yield. Further esterification (TmbCl, NEt_3, DMAP, tol., refl.) of the sterically more hindered axial C-3 hydroxyl group of (+)-**22** furnished (+)-pervilleine B (**3**) in 94% yield. The spectroscopic data of our product matched those reported for the natural one,[2a] except for the sense of optical rotation {$[\alpha]_D^{20}$ +27 (*c* 1.0, $CHCl_3$); lit.[2a] $[\alpha]_D^{20}$ −22.5 (*c* 0.25, $CHCl_3$)}. Our synthetic product is thus the antipode of the natural (−)-pervilleine B and the absolute configuration of the latter is determined to be 1*R*,3*R*,5*S*,6*R* (Scheme 5).

In summary, a versatile method for construction of hydroxylated 8-azabicyclo[3,2,1]octane and 9-azabicyclo[3,3,1]nonane ring systems from keto-lactams has been disclosed. Based on this methodology, the enantioselective syntheses of (+)-6β-silyloxytropane-3-one **2** and 3α,6β-dihydroxytropane **1**, two versatile key intermediates for the synthesis of tropane alkaloids and highly bioactive analogs, were performed. The first enantioselective synthesis of pervilleine B (**3**) allowed determining the absolute configuration of natural pervilleine B to be 1*R*,3*R*,5*S*,6*R*. In addition, compounds **11b** and **12a** are valuable advanced intermediates for the syntheses of ferruginine[6h] and 9-azabicyclo[3.3.1]nonane type alkaloids such as euphococcinine[6j] and adaline,[6j] respectively.

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