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Enantioselective Synthesis of Lobeline via Nonenzymatic Desymmetrization

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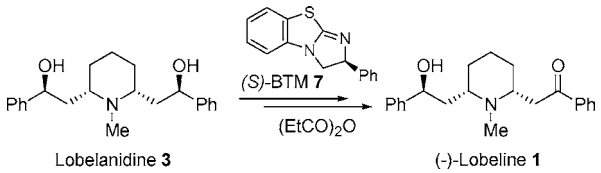
ABSTRACT



Lobelanidine **3** (-)-Lobeline **1**

Lobeline has been prepared in enantiopure form via desymmetrization of lobelanidine with use of BTM, a nonenzymatic enantioselective acyl transfer catalyst.

Lobeline **1** (Figure 1) is the major alkaloid and the active principle of *Lobelia inflata*, or Indian tobacco, which was among the most widely prescribed drugs in the 19th century. Lobeline has been used as an anti-asthmatic, expectorant, respiratory stimulant, and smoking-cessation aid.[1] Recently, it has received considerable attention as a potential treatment for psychostimulant abuse.[2,3] Lobeline's affinity for nicotinic cholinergic receptors is comparable to that of nicotine itself, despite the absence of any obvious structural resemblance between the two alkaloids. In fact, lobeline mimics many of the pharmacological effects of nicotine. Recent studies suggest, however, that it may also act as a nicotinic antagonist and some of its effects may be mediated by noncholinergic pathways.[2] It is noteworthy that lobeline's symmetrical natural congeners, lobelanine **2** and lobelanidine **3**, and "one-arm" analogues, sedamine **4** and sedaminone **6**, are far less biologically active.[4] So far, pharmacological study of lobeline's unnatural analogues has been limited mostly to its semisynthetic derivatives.[2,4] The availability of a flexible asymmetric route to lobeline and its analogues would greatly facilitate further exploration of their pharmacological potential.

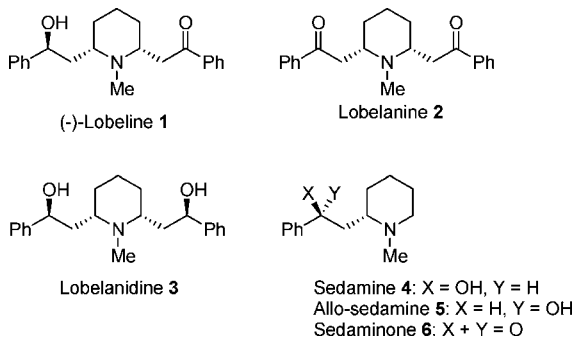


Figure 1. Lobeline and related alkaloids.

The first total syntheses of Lobelia alkaloids—racemic lobeline **1**, lobelanine **2**, and lobelanidine **3**—were achieved simultaneously by Wieland[5] and Scheuing[6] in 1929. Subsequently, the elegant biomimetic approach of Schöpf in 1935 provided lobelanine **2** in one step.[7] In 1959, Parker reported another synthesis of this compound.[8] Surprisingly, lobeline

(1) For a review of history, chemistry, and biology of *Lobelia* alkaloids, see: Felpin, F.-X.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10127.
(2) Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharmacol.* **2002**, *63*, 89.
(3) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 21.
(4) Flammia, D.; Dukat, M.; Damaj, M. I.; Martin, B.; Glennon, R. A. *J. Med. Chem.* **1999**, *42*, 3726.
(5) (a) Wieland, H.; Drishaus, I. *Annalen* **1929**, *473*, 102. (b) Wieland, H.; Koschara, W.; Dane, E. *Annalen* **1929**, *473*, 118.
(6) Scheuing, G.; Winterhalder, L. *Annalen* **1929**, *473*, 135.
(7) Schöpf, C.; Lehmann, G. *Annalen* **1935**, *518*, 1.

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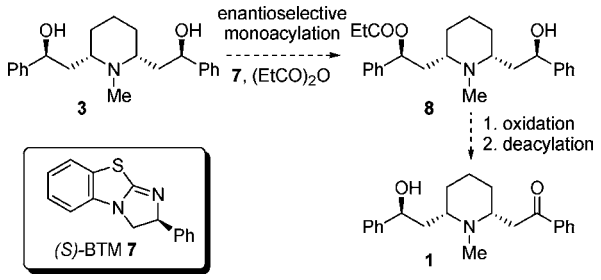
itself has not been prepared by asymmetric total synthesis until recently. Although its structure suggests desymmetrization[9] as the most obvious synthetic strategy, the first two asymmetric syntheses of lobeline—by Marazano (18 steps)[10] and by Lebreton (17 steps)[11]—did not take advantage of the symmetry considerations, opting instead for the stepwise construction of the three stereocenters. The first desymmetrization-based route to lobeline—via enantio- and stereoselective catalytic reduction of lobelanine—appeared in the patent literature in 2006,[12] shortly after we initiated the study described herein.

Enantioselective acyl transfer catalyst BTM **7** recently developed by our group proved to be highly effective for the kinetic resolution of secondary benzylic alcohols.[13] Desymmetrization of the meso-diol lobelanidine **3** (Scheme 1) presented an irresistible opportunity to apply BTM to the

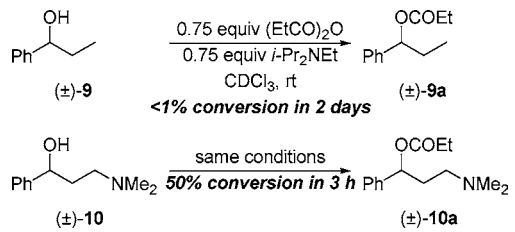
Scheme 1. Proposed Desymmetrization of Lobelanidine via Enantioselective Acylation



synthesis of natural products. Despite the simplicity of the proposed synthetic scheme, there was one potential problem: since none of the substrates employed in our previous studies contained basic functionality, we did not know whether the tertiary amino group present in lobelanidine would be compatible with the enantioselective acylation.

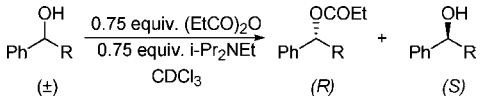
An experiment with the simplest model substrate **10** confirmed our misgivings. In contrast to the structurally similar alcohol **9** lacking the basic amine moiety, **10** was rapidly acylated with propionic anhydride in the absence of any catalyst at room temperature (Scheme 2; Table 1, entries

Scheme 2. Influence of an Amino Group on the Rate of Uncatalyzed Acylation



1 and 3). The low selectivity factor obtained in its kinetic resolution was tentatively ascribed to the interference from the background reaction, which was still significant at 0 °C

Table 1. Acylation of Model Substrates[a]



entry	substrate	catalyst loading (mol %)	temp (°C)	% convn	time (h)	*s*
1	**9**		rt	<1	48	
2	**9**	8	0	51	8	93
3	**10**		rt	50	2.9	
4	**10**		0	50	12	
5	**10**		−20	50	40	
6	**10**	8	0	44	5.5	8.2
7	**10**	8	−20	19	10.5	ND
8	**4**		rt	50	0.73	
9	**4**	8	0	52	0.83	29
10	**4**	8	−20	54	3.5	50
11	**5**		rt	50	3.7	
12	**5**	8	0	49	7	4.6

[a] Conditions: 0.25 M substrate, (*R*)-**7**, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, $CDCl_3$.

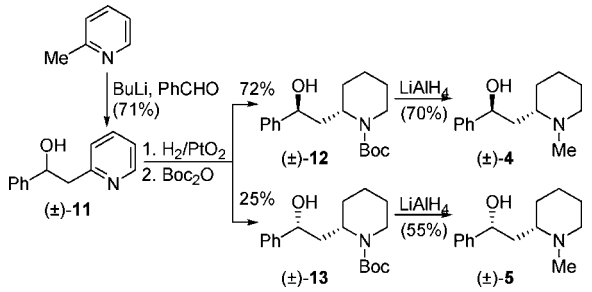
(Table 1, entries 4 and 6). Further lowering the reaction temperature to −20 °C led to greatly diminished reaction rates of both the uncatalyzed and the catalyzed acylations (Table 1, entries 5 and 7). The rapid uncatalyzed reaction of **10** was attributed to the strong hydrogen bond between the hydroxyl and the dimethylamino group, which effectively increased the nucleophilicity of the former.[14]

Despite this discouraging first result, we decided to examine the enantioselective acylation of a more precise model substrate: sedamine **4** having the same relative configuration as lobelanidine **3**. The short sequence shown in Scheme 3[15−18] provided us with racemic sedamine (±)-**4** as well as its naturally occurring epimer *allo*-sedamine (±)-**5**.[19]

Both (±)-sedamine **4** and (±)-*allo*-sedamine **5** underwent rapid uncatalyzed acylation (entries 8 and 11). To our delight, however, the kinetic resolution of sedamine **4** proceeded with

(8) Parker, W.; Raphael, R. A.; Wilkinson, D. I. *J. Chem. Soc.* **1959**, 2433.
(9) (a) Rovis, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2007; 275−311. (b) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.
(10) Compere, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528
(11) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, *9192*.
(12) Klingler, F.-D.; Sobotta, R. (Boehringer Ingelheim) US 2006014791.
(13) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.
(14) A similar effect was recently utilized in the design of asymmetric organocatalysts: (a) Wayman, K. A.; Sammakia, T. *Org. Lett.* **2003**, *5*, 4105. (b) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502.
(15) Solladie-Cavallo, A.; Roje, M.; Isarno, T.; Sunjic, V.; Vinkovic, V.; *Eur. J. Org. Chem.* **2000**, *6*, 1077.
(16) Yu, C.-Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6665.
(17) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213.
(18) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982.
(19) For a review of syntheses of *Sedum* alkaloids, see: Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.

Scheme 3. Synthesis of (±)-Sedamine and (±)-*allo*-Sedamine



a synthetically useful selectivity factor of 29 (entry 9). Furthermore, the catalyzed acylation of **4** proved to be much more rapid than that of any previously studied alcohols. Therefore, we were able to lower the temperature to −20 °C and improve the enantioselectivity even further (entry 10). Clearly, the presence of the amino group accelerated both the catalyzed and the uncatalyzed acylations to comparable extents in this case. At the same time, the catalyzed acylation of *allo*-sedamine **5** produced a rather disappointing result (entry 12), indicating that the influence of the amino group is strongly affected by its spatial orientation.

Encouraged by the success in the kinetic resolution of sedamine **4**, we initiated the asymmetric synthesis of (−)-lobeline **1**. Preparation of lobelanine **2** was accomplished by using the classical biomimetic Mannich reaction of glutaraldehyde, methylamine hydrochloride, and benzoylacetic acid developed by Schöpf and Lehmann[7] (Scheme 4). Lobelanine hydrochloride was obtained in 45% (unoptimized) yield as an 85/15 mixture of cis/trans isomers (by ^{1}H NMR). Borohydride reduction of the mixture afforded an 85/15 mixture of diastereomeric diols, from which the major isomer, lobelanidine **3**, was efficiently isolated in pure form by recrystallization. The high stereoselectivity observed in the reduction of each of the diastereomers of lobelanine is in contrast to the reduction of sedaminone **6** with $NaBH_4$ reported to give a 1:1 mixture of **4** and **5**.[15] We also obtained lobelanidine as the major product of borohydride reduction of commercial (−)-lobeline hydrochloride.[20]

Uncatalyzed acylation of lobelanidine **3** with 1 equiv of propionic anhydride at room temperature rapidly gave rise to the monoester (**8**), with only negligible diester formation (**14**), which indicated that the second acylation step was much

Scheme 4. Preparation of Lobelanidine **3**

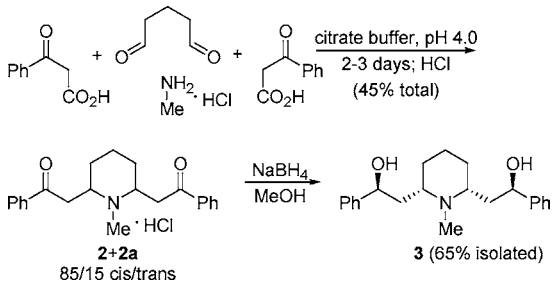
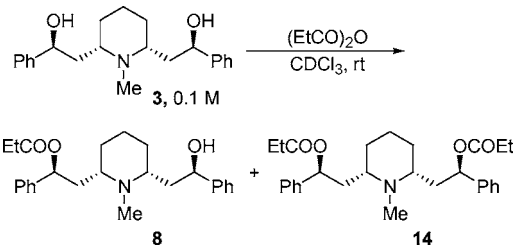


Table 2. Acylation of Lobelanidine



entry	catalyst loading (mol %)	condn[a]	time	% **3**[b]	% **8**[b] (% ee)	% **14**[b]
1		A	60 min	57	42	1
2	10	A	60 min	38	58 (89)	4
3	20	A	60 min	26	71 (>99)	3
4	20	B	60 min	21	76 (>99)	3
5	20	C	2 d	ND[c]	92[d] (>99)	8[d]
6[e]	20	D	2 d	8[d]	88[d] (>99)	≤4
7		A	1 min	99	1	ND[c]
8	20	A	1 min	85	15 (91)	ND[c]

[a] Conditions: (A) 1.0 equiv of $(EtCO)_2O$, 1.0 equiv of *i*-Pr_2NEt; (B) 1.0 equiv of $(EtCO)_2O$, no base added; (C) 1.1 equiv of $(EtCO)_2O$, no base added; (D) 1.0 equiv of $(EtCO)_2O$, 1.0 equiv of *i*-Pr_2NEt. [b] Yields were estimated by ^{1}H NMR unless stated otherwise. [c] Not detected. [d] Isolated yields are given. [e] (*R*)-BTM was used resulting in the opposite enantiomer of **8a**.

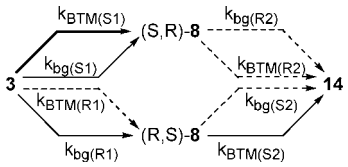
slower than the first one (cf. entry 1, Table 2). In fact, addition of the second equivalent of propionic anhydride led to only slow conversion of **8** to **14**, despite the obvious similarity of the monoester **8** to sedamine **4**, which is rapidly acylated under similar conditions (vide supra).

Desymmetrization of lobelanidine was examined next. We were pleased to obtain high enantiomeric excess (89%) at room temperature using 10 mol % of (*S*)-BTM, which is equivalent to 5 mol % in kinetic resolutions (Table 2, entry 2). At 20 mol % catalyst loading, the monoester product was enantiomerically pure within the limits of detection by HPLC (entry 3). In the absence of Hünig's base, the reaction was found to proceed with essentially the same rate and enantioselectivity (entry 4). Conducting desymmetrization of **3** for 2 days, **8** was isolated in an excellent yield and enantiopurity, in addition to small amounts of diester **14** (entry 5). Similar results were produced in the presence or absence of Hünig's base (cf. entries 5 and 6).

The high ee of monoester **8** and the low yield of diester **14** obtained in the above experiments seemed surprising at first glance, given the significant rate of the background reaction. Thus, an additional control study was carried out.[21] By stopping the reactions at low conversions, we estimated the initial rate of the reaction catalyzed by 20 mol % BTM to be ca. 15 times higher than that of the background reaction (entries 7 and 8). Furthermore, the ee of **8** was found to increase during the first hour of the reaction (cf. entries 8 and 3) indicating that the "wrong" (*R*,*S*)-enantiomer of **8** produced by the background reaction was consumed by the BTM-catalyzed acylation to the diester. Finally, we estab-

lished that (*S*,*R*)-monoester **8** was rapidly acylated in the presence of 20 mol % of (*R*)-BTM, but did not undergo any appreciable reaction in its absence. These additional data lend support to the overall scheme of the desymmetrization processs depicted below (Scheme 5) and account, within experimental error, for its surprising efficiency.

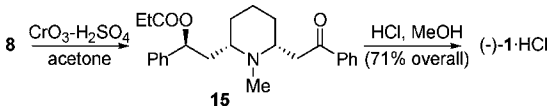
Scheme 5. Catalyzed vs Background Acylation[a]



[a] Relative order of reaction rates: $k_{BTM(S1)} > k_{bg(S1)} = k_{bg(R1)} \approx k_{BTM(S2)} > k_{BTM(R2)} \approx k_{bg(S2)} = k_{bg(R2)}$ (k_{BTM} = rate of catalyzed acylation; k_{bg} = rate of background acylation).

Monoester **8** underwent smooth oxidation with the Jones reagent affording lobeline propionate **15** (Scheme 6). Transesterification of the crude **15** with methanol in the presence of HCl was chosen for its deprotection due to the known facile epimerization of lobeline base.[10] (−)-Lobeline hydrochloride was obtained in 71% yield after recrystallization. Its spectral data and optical rotation matched those of a commercial sample. In the same manner, the unnatural enantiomer (+)-lobeline was obtained by using (*R*)-BTM in the key desymmetrization step (Table 2, entry 6).

Scheme 6. Preparation of (−)-Lobeline



In conclusion, we have achieved a concise asymmetric synthesis of (−)- and (+)-lobeline via desymmetrization of lobelanidine. The synthetic route is expected to be suitable for the preparation of unnatural lobeline analogues in nonracemic form.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Reduction of lobelanine and lobeline with $LiAlH_4$ was reported to give lower selectivities: Ebnother, A. *Helv. Chim. Acta* **1958**, *41*, 386.

(21) See the Supporting Information for details.