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A General Approach to 1-Hydroxymethylquinolizidine and 8-Hydroxymethylindolizidine Stereoisomers: Synthesis of (+)-Epitashiromine and Formal Syntheses of (+)-Epilupinine and (+)-Tashiromine

Rakesh G. Thorat^[a] and Sunil V. Pansare^{*[a]}**Keywords:** Alkaloids / Asymmetric synthesis / Cycloaddition / Natural products / Nitrones

A general strategy for the synthesis of structurally and stereochemically related indolizidine and quinolizidine alkaloids was developed. The methodology involves regio- and stereoselective 1,3-dipolar cycloadditions of simple nitrones with ephedrine-derived alkylidenemorpholinones. The intermediate isoxazolidines can be converted into either the

indolizidine or the quinolizidine motif depending on the nitron and the substituent on the dipolarophile. The approach was applied to the synthesis of (+)-epitashiromine and to the formal syntheses of (+)-epilupinine and (+)-tashiromine.

Introduction

The indolizidine and quinolizidine alkaloids constitute a prominent group of biologically relevant natural products that have engaged organic chemists for decades.^[1] In particular, the indolizidines (+)-tashiromine (**1**) and (+)-epitashiromine (**2**) and the corresponding quinolizidine alkaloids (–)-lupinine (**3**) and (+)-epilupinine (**4**, Figure 1) form an interesting set of structural motifs. Notably, the configuration of the hydroxymethyl substituent in the epi-isomer of the indolizidine is opposite to the orientation of the hydroxymethyl group in the epi-isomer of the quinolizidine (compare **2** and **4**, Figure 1), and a similar relationship is seen for **1** and **3**.

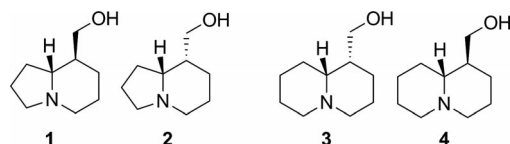


Figure 1. Structurally related pairs of indolizidine and quinolizidine alkaloids: (+)-tashiromine (**1**), (+)-epitashiromine (**2**), (–)-lupinine (**3**), and (+)-epilupinine (**4**).

The synthesis of lupinine,^[2] epilupinine,^[3] tashiromine,^[4] and epitashiromine^[5] has been extensively investigated. Most of the syntheses of these alkaloids have addressed one of the two possible diastereomers defined by the ring junction methine and the hydroxymethyl group. Consequently,

these syntheses are applicable to the stereochemically related motifs of epitashiromine/lupinine or tashiromine/epilupinine. A few syntheses of lupinine and tashiromine that also provide the corresponding epi-analogs are known, but these rely on either thermodynamically favorable isomerization of enolizable intermediates^[6] or separation of stereoisomeric intermediates at an early stage in the synthesis.^[7] Unified (stereodivergent) synthetic strategies that can provide access to epitashiromine and epilupinine or lupinine and tashiromine are rare.^[8] Herein, we describe a cohesive synthetic strategy that addresses this limitation. Application of our approach to the synthesis of (+)-epitashiromine and to the formal syntheses of (+)-epilupinine and (+)-tashiromine is described.

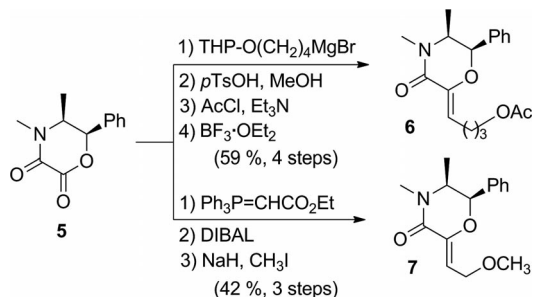
Results and Discussion

Our approach relies on the construction of only one of the two sets of contiguous stereocenters in the diastereomeric targets but ultimately provides access to either diastereomer of the targets by regioselective transformations of stereochemically matching intermediates. The strategy involves a stereoselective 1,3-dipolar cycloaddition of cyclic nitrones and chiral alkenes to provide functionalized isoxazolidines. These can be elaborated to the target molecules depending on the nature of the nitron and the alkene substituent. Notably, despite the possibility that nitron cycloaddition^[9] can potentially introduce both the stereocenters and more than half of all the required carbon atoms in the targets in a single step, the application of this strategy in the stereoselective synthesis of any of the targets **1–4** is prominently missing.^[10] This is in contrast to the nitron-based enantioselective syntheses of polyhydroxylated azacycles and azasugars.^[11]

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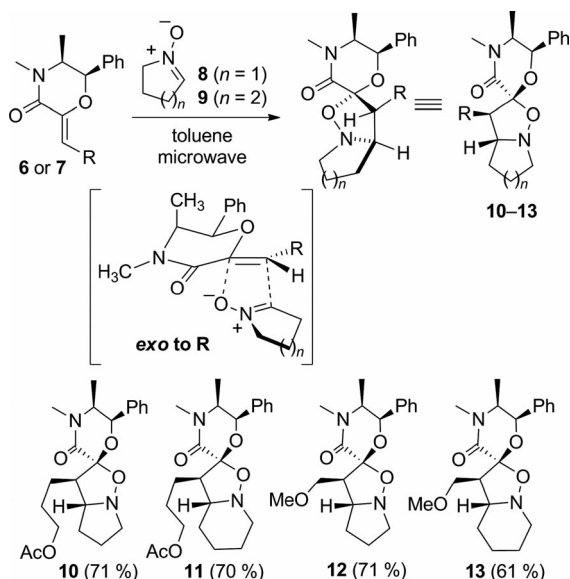
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201301078>.

The chiral alkenes with which we chose to examine the nitronc cycloadditions were alkylidenemorpholinones, which were obtained from ephedrine-derived morpholine-dione **5**^[12] (Scheme 1). Reaction of **5** with the Grignard reagent obtained from tetrahydropyran-2-yl (THP) protected 4-bromobutanol, replacement of the THP protecting group by an acetate group, and dehydration of the hemiacetal provided alkylidenemorpholinone **6**. Similarly, reaction of **5** with [(ethoxycarbonyl)methylene]triphenylphosphorane, reduction of the obtained ester to the allylic alcohol, and subsequent methylation provided alkylidenemorpholinone **7**. Both **6** and **7** were obtained exclusively as the *Z* isomers.^[13]



Scheme 1. Synthesis of ephedrine-derived alkylidenemorpholinones **6** and **7**. Ts = toluenesulfonyl, DIBAL = diisobutylaluminum hydride.

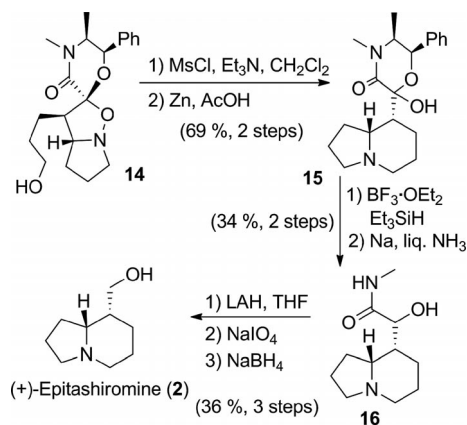
With the requisite alkenes in hand, we next examined their 1,3-dipolar cycloaddition reactions with pyrrolidine- and piperidine-derived nitrones **8** and **9**,^[14] respectively. Both **6** and **7** reacted stereoselectively and regioselectively with the nitrones upon heating in toluene. Microwave irradiation was found to be more effective than conventional heating for these reactions.^[15] Thus, spiroisoxazolidines **10–13** were obtained as single diastereomers^[16] in good yields within 30 min of microwave heating (Scheme 2).



Scheme 2. Stereoselective 1,3-dipolar cycloaddition reactions of **6** and **7** with nitrones **8** and **9**.

At that stage, the stereochemistry of isoxazolidines **10–13** was tentatively assigned as shown, on the basis of two factors: (1) Approach of the nitronc *exo* to the alkene substituent (R, Scheme 2) to minimize steric interactions. (2) Reaction of the alkene from the face opposite to the methyl and phenyl groups in the morpholinone.^[17] The regiochemistry of the nitronc cycloaddition was assigned on the basis of a characteristic resonance at approximately 100 ppm for the spiroacetal carbon atom in isoxazolidines **10–13**.^[18]

The synthesis of epitashiromine was then initiated from **10** (Scheme 3). Hydrolysis of the acetate in **10** provided primary alcohol **14**, which was converted into the mesylate (Ms). Owing to its unstable nature, the crude mesylate was immediately reduced with Zn/AcOH directly to provide **15**, obtained from in situ cyclization of the secondary amine (Scheme 3). With most of the epitashiromine components established in **15**, removal of the ephedrine portion was examined. Surprisingly, **15** was resistant to dissolving-metal reduction (Na/NH₃), the usual protocol for this transformation. However, reduction of the hemiacetal in **15** (BF₃·OEt₂, Et₃SiH) followed by dissolving-metal reduction successfully generated hydroxy amide **16**. Conversion of **16** into (+)-epitashiromine (**2**) was achieved by reduction of the hydroxy amide to the amino alcohol, oxidative cleavage of the amino alcohol to the aldehyde, and in situ reduction of the aldehyde^[19] to the primary alcohol (Scheme 3). The formation of (+)-epitashiromine confirmed the stereochemistry of **10**.

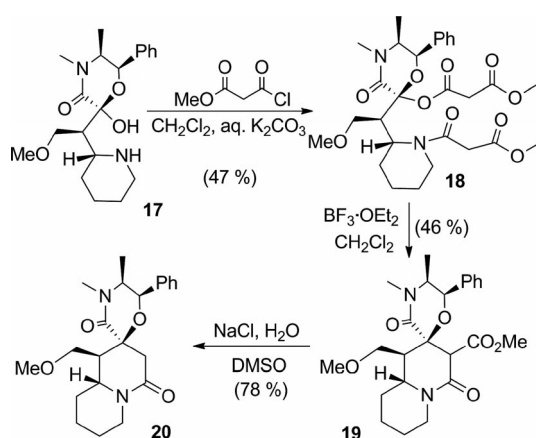


Scheme 3. Conversion of isoxazolidine **14** into (+)-epitashiromine. LAH = lithium aluminum hydride.

The racemic version of the aldehyde intermediate obtained from **16** (Scheme 3) has previously been converted into (±)-tashiromine through epimerization. Thus, the present synthesis of (+)-epitashiromine also constitutes a formal synthesis of (+)-tashiromine.

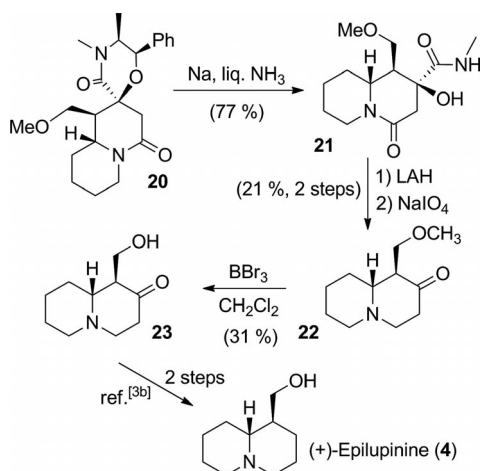
Having established the stereochemical course of the nitronc cycloaddition reaction, we proceeded to examine the second objective of our synthetic plan, namely, the preparation of (+)-epilupinine (**4**), which has a *cis* orientation of the ring junction methine and the hydroxymethyl

group in the piperidine ring. The difference between this approach and the one described for epitashiromine lies in the construction of the second ring in the target. In the epitashiromine synthesis, the alkene substituent was employed for ring formation. In the approach to epilupinine, the alkene substituent was chosen to provide the hydroxymethyl side chain in the final product. Hence, isoxazolidine **13** (Scheme 1) served as the starting material for this study. Reduction of **13** (Zn, AcOH, 90%) provided amino hemiacetal **17**, which was bis(acylated) with methyl (chloroformyl)acetate to provide **18**. Lewis acid mediated oxonium ion formation from the acetal in **18** and subsequent cyclization of the *N*-acyl fragment led to **19**. Krapcho decarboxylation^[20] of **19** provided **20**, which has the required azabicyclic framework for epilupinine (Scheme 4).



Scheme 4. Synthesis of epilupinine intermediate **20**.

The conversion of **20** into an advanced epilupinine intermediate was readily achieved in a few steps. Dissolving-metal reduction of **20** provided hydroxy amide **21**. Simultaneous reduction of both amide linkages in **21** and oxidative cleavage of the product provided ketone **22** (Scheme 5). Demethylation of **22** generated **23**, which can be converted into (+)-epilupinine by reduction of the derived dithiolane.



Scheme 5. Completion of the formal synthesis of (+)-epilupinine.

Thus, isoxazolidines **10** and **13** with matching stereochemistry (*cis* R group and N-CH) provide access to **2** and **4**, respectively, which have opposite configuration at the hydroxymethyl-group-bearing stereocenter.

Conclusions

A stereodivergent synthetic strategy involving a 1,3-dipolar cycloaddition reaction of achiral nitrones with chiral dipolarophiles was developed for the synthesis of selected indolizidine and quinolizidine alkaloids. The methodology was applied in the total synthesis of (+)-epitashiromine and in the formal syntheses of (+)-epilupinine and (+)-tashiromine. The approach can potentially be extended to the synthesis of (+)-lupinine by engaging isoxazolidine **11** as the starting material in a synthetic route similar to that developed with **10**. Similarly, isoxazolidine **12** can lead to (+)-tashiromine. Current efforts focus on reactions of functionalized nitrones with **6** and **7** as well as other applications of related alkyldenemorpholinones.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for the compounds prepared.

Acknowledgments

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- Recent reviews: a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139; b) T. Honda, *Heterocycles* **2011**, *83*, 1; c) S. Perreault, T. Rovis, *Chem. Soc. Rev.* **2009**, *38*, 3149; d) R. Remuson, Y. Gelas-Mialhe, *Mini-Rev. Org. Chem.* **2008**, *5*, 193; e) J. P. Michael, *Beilstein J. Org. Chem.* **2007**, *3*, 10 (DOI: 10.1186/1860-5397-3-10).
- For recent enantioselective syntheses of lupinine, see: a) M. Hajri, C. Blondelle, A. Martinez, J.-L. Vasse, J. Szymoniak, *Tetrahedron Lett.* **2013**, *54*, 1029; b) S. Fustero, J. Moscardó, M. Sánchez-Roselló, S. Flores, M. Guerola, *Tetrahedron* **2011**, *67*, 7412; c) L. Silva Santos, Y. Mirabal-Gallardo, N. Shankaraiah, M. J. Simirgiotis, *Synthesis* **2011**, 51; d) E. Airiau, T. Spangenberg, N. Girard, B. Breit, A. Mann, *Org. Lett.* **2010**, *12*, 528; e) R. Noël, M.-C. Fargo-Bellassoued, C. Vanucci-Bacqué, G. Lhommet, *Synthesis* **2008**, 1948; f) S. Ma, B. Ni, *Chem. Eur. J.* **2004**, *10*, 3286; g) A. Agami, L. Dechoux, S. Hebbe, C. Ménard, *Tetrahedron* **2004**, *60*, 5433; for recent syntheses of racemic lupinine, see: h) P. Pohmakotr, A. Seubsai, P. Numeechai, P. Tuchinda, *Synthesis* **2008**, 1733; i) M. Y. Chang, H.-M. Tai, C.-H. Lin, N.-C. Chang, *Heterocycles* **2005**, *65*, 395.
- For recent enantioselective syntheses of epilupinine, see: a) A. C. Cutter, I. R. Miller, J. F. Kelly, R. K. Bellingham, M. E. Light, R. C. D. Brown, *Org. Lett.* **2011**, *13*, 3988; b) D. Su, X. Wang, C. Shao, J. Xu, R. Zhu, Y. Hu, *J. Org. Chem.* **2011**, *76*, 188; c) M. Ahari, A. Perez, C. Menant, J.-L. Vasse, J. Szymoniak, *Org. Lett.* **2008**, *10*, 2473; also see ref.^[2f]; for recent syntheses of racemic epilupinine, see: d) S. M. Amorde, R. T. Jewett, S. F. Martin, *Tetrahedron* **2009**, *65*, 3222; e) S. F. Martin, *Pure Appl. Chem.* **2009**, *81*, 195. Also see ref.^[2h]
- For selected enantioselective syntheses of tashiromine, see: a) J. C. Conrad, J. Kong, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640; b) O. David, C. Bellec, M.-C. Fargeau-Bellassoued, G. Lhommet, *Heterocycles* **2001**, *55*,

- 1689; also see ref.^[3a,5b,5c,7a,7b] for recent syntheses of racemic tashiromine, see: c) W.-H. Chiou, Y.-H. Lin, G.-T. Chen, Y.-K. Gao, Y.-C. Tseng, C.-L. Kao, J.-C. Tsai, *Chem. Commun.* **2011**, 47, 3562; d) S. P. Marsden, A. D. McElhinney, *Beilstein J. Org. Chem.* **2008**, 4, 8 (DOI: 10.1186/1860-5397-4-8); e) M. Pohmakotr, S. Prateptongkum, S. Chooprayoon, P. Tuchinda, V. Reutrakul, *Tetrahedron* **2008**, 64, 2339; f) G. Bélanger, R. Larouche-Gauthier, F. Ménard, M. Nantel, F. Barabé, *J. Org. Chem.* **2006**, 71, 704; g) A. D. McElhinney, S. P. Marsden, *Synlett* **2005**, 2528.
- [5] For recent enantioselective syntheses of epitashiromine, see: a) E. Pereira, C. F. Alves, M. A. Böeckelmann, R. A. Pilli, *Quim. Nova* **2008**, 31, 771; b) K. R. Dieter, N. Chen, R. T. Watson, *Tetrahedron* **2005**, 61, 3221; for an enantioselective approach to (–)-epitashiromine, see: c) K. K. S. Reddy, B. V. Rao, S. S. Raju, *Tetrahedron: Asymmetry* **2011**, 22, 662; for syntheses of racemic epitashiromine, see: d) M. G. Banwell, D. A. S. Beck, J. A. Smith, *Org. Biomol. Chem.* **2004**, 2, 157; e) K. R. Dieter, R. T. Watson, *Tetrahedron Lett.* **2002**, 43, 7725; see also ref.^[2g] for syntheses of epitashiromine prior to 2002, see ref.^[5e]
- [6] a) For epimerization of an epitashiromine intermediate to provide tashiromine, see: K. Paulvannan, J. R. Stille, *J. Org. Chem.* **1994**, 59, 1613; b) for epimerization of a lupinine intermediate to provide epilupinine, see ref.^[2h]
- [7] For enantioselective syntheses of tashiromine and epitashiromine that rely on the separation of diastereomeric intermediates, see: a) J. L. Gage, B. P. Branchaud, *Tetrahedron Lett.* **1997**, 38, 7007; b) D.-C. Ha, S.-H. Park, K.-S. Choi, C.-S. Yun, *Bull. Korean Chem. Soc.* **1998**, 19, 728; also see ref.^[2g,5a,5b,5d]
- [8] For the synthesis of tashiromine and epitashiromine by stereodivergent reduction of a common intermediate, see: S. H. Kim, S.-I. Kim, S. Lai, J. K. Cha, *J. Org. Chem.* **1999**, 64, 6771.
- [9] Reviews: a) P. N. Confalone, E. M. Huie, in *Organic Reactions*, Wiley, Hoboken, NJ, USA, **1988**, vol. 36, pp. 1–173; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, 98, 863; c) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449; d) M. Frederickson, *Tetrahedron* **1997**, 53, 403.
- [10] For approaches to the lupine alkaloids through nitroncycloaddition, see a) J. J. Tufariello, J. J. Tegeler, *Tetrahedron Lett.* **1976**, 17, 4037; b) F. M. Cordero, B. Anichini, A. Goti, A. Brandi, *Tetrahedron* **1993**, 49, 9867; notably, the key cycloaddition step in these reports is not diastereoselective; c) for a review on approaches to racemic alkaloids from nitrones, see: J. J. Tufariello, *Acc. Chem. Res.* **1979**, 12, 396.
- [11] a) Recent review: A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Eur. J.* **2009**, 15, 7808; b) N. G. Argypoulos, T. Panagiotidis, E. Coutouli-Argypoulou, C. Raptopoulou, *Tetrahedron* **2007**, 63, 321; c) B. Alcaide, C. Pardo, E. Saez, *Synlett* **2002**, 85; d) P. Gębarowski, W. Sas, *Chem. Commun.* **2001**, 915; e) A. B. Holmes, B. Bourdin, I. Collins, E. C. Davison, A. J. Rudge, T. C. Stork, J. A. Warner, *Pure Appl. Chem.* **1997**, 69, 531.
- [12] a) V. F. Rudchenko, V. G. Shtamburg, A. P. Pleshkova, R. G. Kostyanovskii, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1981**, 30, 825; b) S. V. Pansare, A. Bhattacharyya, *Tetrahedron Lett.* **2001**, 42, 9265; for synthetic applications of other amino alcohol derived morpholinones, see: c) G. G. Cox, L. M. Harwood, *Tetrahedron: Asymmetry* **1994**, 5, 1669; d) R. M. Williams, *Aldrichim. Acta* **1992**, 25, 11; e) S. V. Pansare, B. A. Shinkre, A. Bhattacharyya, *Tetrahedron* **2002**, 58, 5985.
- [13] The Z stereochemistry was assigned by comparison of the chemical shift of the alkene CH signal to those of related alkylidenemorpholinones, see ref.^[17]
- [14] Prepared by oxidation of the corresponding amines, see: S.-I. Murahashi, T. Shiota, *Tetrahedron Lett.* **1987**, 28, 2383.
- [15] Parallel studies with alkenes related to **6** and **7**, with methyl or ethoxycarbonyl substitution, indicated that their reactions with nitrones are not subject to Lewis acid catalysis [MgBr_2 , ZnCl_2 , $\text{Ti}(\text{O}i\text{Pr})_4$, $\text{Sc}(\text{OTf})_3$, or $\text{In}(\text{OTf})_3$]. For reactions of acyclic nitrones with *exo*-glycols, see: G. Enderlin, C. Taillefumier, C. Didierjean, Y. Chapleur, *Tetrahedron: Asymmetry* **2005**, 16, 2459.
- [16] Determined by ^1H NMR spectroscopy. Signal broadening is seen in the ^1H NMR spectra of **11** and **13** as a result of pyramidal inversion at the nitrogen atom; this has been observed for other isoxazolidines, see: a) E. Tyrrell, J. Allen, K. Jones, R. Beauchet, *Synthesis* **2005**, 2393; b) B. A. Moosa, M. I. M. Waizer, M. B. Fettouhi, S. A. Ali, *J. Phys. Org. Chem.* **2009**, 22, 212. Hence, the diastereomeric excess of **11** and **13** was determined from the ^1H NMR spectrum of the corresponding amines obtained by N–O bond reduction; see compounds **S2** (Supporting Information) and **17**.
- [17] Previous studies with the ephedrine-derived morpholinone system indicated a strong preference for reactions from the less hindered face of the morpholinone, see: a) S. V. Pansare, V. A. Adsool, *Org. Lett.* **2006**, 8, 5897; b) S. V. Pansare, R. G. Ravi, R. P. Jain, *J. Org. Chem.* **1998**, 63, 4120.
- [18] The regioisomeric cycloadducts would have a spiro carbon atom the signal of which is expected to appear at $\delta \approx 75$ –80 ppm, as seen for compounds **19** and **20**.
- [19] Purification of the aldehyde precursor of epitashiromine by chromatography caused significant epimerization. This was conveniently avoided by in situ reduction to diastereomerically pure epitashiromine.
- [20] A. P. Krapcho, *Synthesis* **1982**, 805.

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