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Total Syntheses of (−) Epilupinine and (−)-Tashiromine Using Imino-Aldol Reactions

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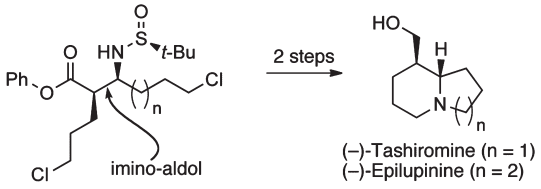
ABSTRACT



Short routes to enantiomerically pure indolizidine and quinolizidine alkaloids have been developed using imino-aldol reactions of enolates derived from phenyl 5-chlorovalerate. High levels of *syn* selectivity (dr ~13−16:1) were obtained using lithium enolates of phenyl esters in combination with *tert*-butylsulfinyl imines. The imino-aldol adducts were deprotected and cyclized to afford (−)-epilupinine ((−)-2) and (−)-tashiromine ((−)-1) in two further steps.

(+)-Tashiromine ((+)-**1**) and (+)-epilupinine ((+)-**2**) are 5-hydroxymethylated indolizidine and quinolizidine alkaloids respectively,[1] possessing common relative and absolute stereochemistry at C5 and C6 of their bicyclic ring systems. (+)-Tashiromine was first isolated in 1990 from *Maackia Tashoroi*,[2] whereas epilupinine has been known for considerably longer. (+)-Epilupinine was reported as a product of the epimerzation of (+)-lupinine,[3] but it exists naturally as a secondary metabolite in various members of the lupin family.[4] (+)-Epilupinine has been shown to exhibit *in vitro* inhibitory activity against Leukaemia P-388 (LD50 = 28 μg/mL) and lymphocytic Leukaemia L1210 (LD50 = 28 μg/mL) cells.[5] Both natural products

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(5) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970–974.

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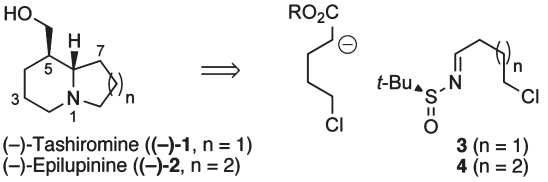
have been the focus of considerable synthetic attention and have been prepared by total synthesis in racemic and enantiomerically enriched form.[5–9]

Scheme 1. Imino-Aldol Approach to (−)-Tashiromine and (−)-Epilupinine

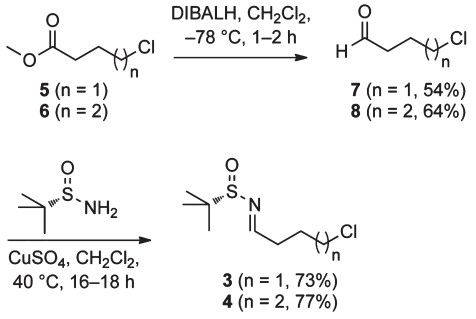


(−)-Tashiromine ((−)-**1**, n = 1)
(−)-Epilupinine ((−)-**2**, n = 2)

3 (n = 1)
4 (n = 2)

As part of studies toward quinolizidine and indolizidine containing natural products, we were attracted to an approach centered on imino-aldol reactions of *tert*-butanesulfinyl imines to correctly establish the required configurations at C5 and C6 (Scheme 1).[10,11] By incorporating chloroalkyl chains into the reacting enolate and imine, *N*-deprotection of the imino-aldol product would result in direct double cyclization to produce the required indolizidine and quinolizidine systems.[12]

Scheme 2. Synthesis of Sulfinyl Imines



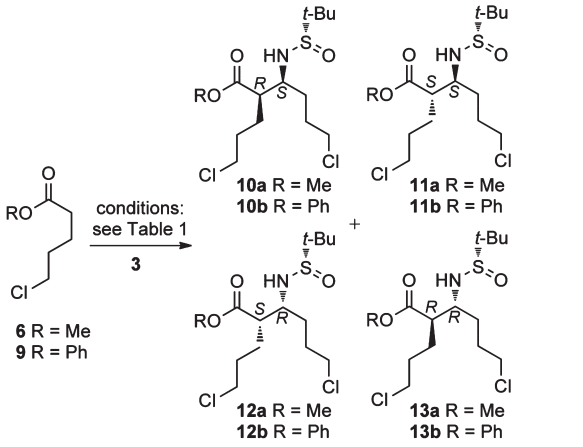
5 (n = 1)
6 (n = 2)

7 (n = 1, 54%)
8 (n = 2, 64%)

3 (n = 1, 73%)
4 (n = 2, 77%)

The (*S*)-*tert*-butanesulfinyl imines **3** and **4** were prepared from the corresponding chloroalkyl esters **5** and **6** in two steps (Scheme 2).[13] Initial imino-aldol reaction between titanium enolates derived from commercially available methyl 5-chlorovalerate (**6**) and imine **3** gave a modest level of diastereocontrol (entry 1, Table 1: dr = 7:2:1). The

Table 1. Influence of Ester Structure and Reaction Conditions on the Stereoselectivity of the Imino-Aldol Reaction



entry	R	conditions[a]	yield (%)[b]	dr[c] (**10**:**11**:**12**:**13**)
1	Me	A	43	7:2:1:–
2	Me	B	56	9:1:–:–
3	Ph	A	56	9:1:–:–
4	Ph	B	78	16:1:–:–

[a] Conditions A: (i) LDA, **6** or **9**, THF, −78 °C; (ii) $TiCl(OiPr)_3$; (iii) imine **3**. Conditions B: (i) LDA, **6** or **9**, THF, −78 °C; (ii) imine **3**. [b] Combined yield of the indicated mixture of diastereomers isolated by column chromatography. [c] dr estimated by integration of crude ^{1}H NMR for **10**:**11**:**12**:**13** respectively. "–" indicates that the isomer was not observed in the crude ^{1}H NMR spectra.

observed stereoisomers were identified as *syn*-adducts **10a**, **12a** (isolated as a mixture), and *anti*-aduct **11a** respectively, by elaboration to known compounds.[14] In comparison to propionate imino-aldol reactions, which are often highly diastereoselective, modest levels of stereoselectivity have been noted previously for imino-aldol reactions of methyl and *para*-methoxybenzyl esters of functionalized straight-chain carboxylic acids.[10b,15,16]

The diastereoselectivity and product distribution was influenced significantly with respect to the choice of ester

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(11) For examples of imino-aldol reactions of aryl *N*-sulfinyl imines: (a) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413–2416. (b) Davis, F. A.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 848–851.

(12) For some sequences involving additions of organometallic species to *tert*-butylsulfinyl imines followed by cyclization: (a) Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705–4708. (b) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222–224. For an example using *p*-tolylsulfinyl imines:(c) Ruano, J. L. G.; Aleman, J.; Cid, M. B. *Synthesis* **2006**, 687–691.

(13) An unusual sulfonamide byproduct, *t*-BuSNHSO$_2$*t*-Bu, was isolated after prolonged reaction times for the formation of sulfinyl imines. The structure was confirmed by X-ray crystallography. For the formation of a similar compound, see: Drabowicz, J. *Heteroat. Chem.* **2002**, *13*, 437–442.

(14) Conversion of the *syn* adducts **10a** and **12a** to tashiromine and the *anti* adduct **11a** to 5-epitashiromine is described in the Supporting Information.

(15) Thomas, E. J.; Vickers, C. F. *Tetrahedron: Asymmetry* **2009**, *20*, 970–979.

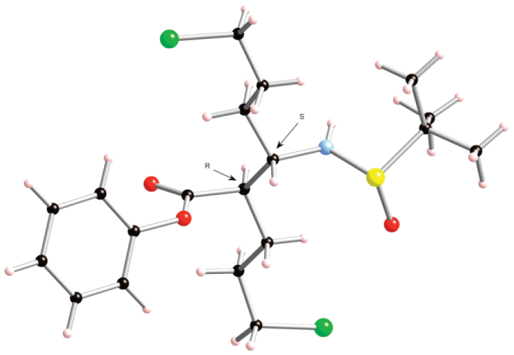

Figure 1. X-ray structure of the major imino-aldol product **10b**.

and the enolization conditions. The lithium enolate of the methyl ester **6**, generated using LDA in THF, gave an enhanced selectivity for **10a** (entry 2). However, the phenyl ester **9**[17] afforded the highest levels of selectivity in the imino-aldol reaction with sulfinyl imine **3**, and most effectively when the lithium enolate was employed (entries 3 and 4). Significantly, the minor *syn*-diastereoisomer **12b** was not observed, and separation of the *syn* and *anti* diastereomers **10b** and **11b** was possible by either column chromatography or crystallization. Furthermore, the stereochemistry of **10b** was determined using X-ray diffraction (Figure 1).

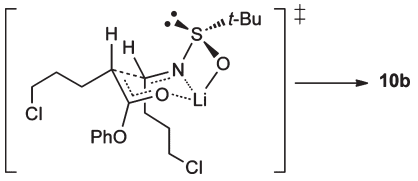

Figure 2. Proposed transition state model to account for the observed diastereocontrol in the imino-aldol reaction.

The formation of the major observed stereoisomer is consistent with the closed transition state model presented by Ellman for the imino-aldol reactions of *E*-enolates of propionate esters with *tert*-butylsulfinyl imines (Figure 2).[10] Although, we were not able to trap the enolate derived from **9**, enolization of phenyl propionate with LDA in THF has been reported to give predominantly the *E*-silyl ketene acetal.[18]

Having achieved high levels of diastereoselectivity in the imino-aldol reactions of phenyl ester **9**, attention returned

(16) For an example of a prionate imino-aldol reaction with a functionalized *tert*-butylsulfinyl imine: Wen, S. J.; Carey, K. L.; Nakao, Y.; Fusetani, N.; Packham, G.; Ganesan, A. *Org. Lett.* **2007**, *9*, 1105–1108.

(17) The phenyl ester was obtained in one step from commercial 5-chloropentanoyl chloride.

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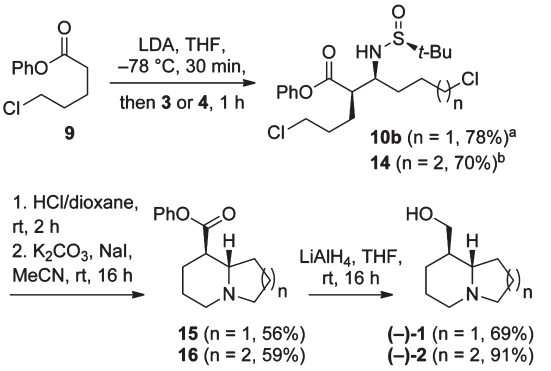
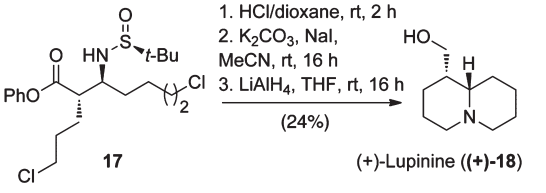
Scheme 3. Synthesis of (−)-Epilupinine and (−)-Tashiromine



[a] dr = 16:1 with **11b** (^{1}H NMR). [b] dr = 13:1 with **17** (^{1}H NMR).

to the synthesis of the indolizidine and quinolizidine alkaloids (Scheme 3). The *syn* imino-aldol product **10b** contained the entire framework of (−)-tashiromine (**(−)-1**), and the correctly established stereochemistry. Removal of the *N*-sulfinyl protecting group using HCl in dioxane afforded the primary amine, which underwent the key double cyclization under basic conditions to give the indolizidine **15**. Finally, ester reduction was carried out using $LiAlH_4$ to produce a mixture of phenol and (−)-tashiromine (**(−)-1**). Ion exchange chromatography gave (−)-tashiromine, which exhibited physical and spectroscopic characteristics consistent with those reported for the authentic material,[19] with the exception that our material was obtained as a low melting solid.

Scheme 4. Synthesis of (+)-Lupinine: Confirmation of Stereochemistry of Minor Imino-Aldol Stereoisomer



Similarly, chemoselective reaction of the lithium enolate derived from phenyl ester **9** with the homologous sulfinyl imine **4** secured the *β*-amino ester precursor **14** in 70% yield (**14**:**17**, dr = 13:1 by ^{1}H NMR). Subjecting pure **14** to the deprotection−double cyclization−reduction sequence described above afforded (−)-epilupinine (**(−)-2**, Scheme 3), which also gave physical and spectroscopic data that were consistent with reported values.[18] The the minor amino-aldol product **17** was converted to (+)-lupinine (**(+)-19**), thereby providing confirmation of its relative and absolute stereochemistry (Scheme 4).[19,20]

(19) Physical and spectroscopic data for (−)-tashiromine, (−)-epilupinine, and (+)-lupinine are provided in the Supporting Information.

In summary, lithium enolates derived from chloroalkanoic acid phenyl esters have been shown to undergo highly chemoselective and *syn* selective imino-aldol reactions with chloroalkyl sulfinyl imines, and the resulting adducts have been elaborated to yield indolizidine and quinolizidine systems. Six-step total syntheses of (−)-tashiromine (**(−)-1**) and (−)-epilupinine (**(−)-2**) were realized in 12% and 15% overall yields respectively.

(20) Davis and Xu have recently reported that *anti* imino aldol products can be obtained by diastereoselective alkylation of acetate imino-aldol adducts: Davis, F. A.; Xu, P. *J. Org. Chem.* **2011**, *76*, 3329–3337.

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Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray crystallographic data for **10b**, **14**, and *t*-BuSNHSO$_2$*t*-Bu. This material is available free of charge via the Internet at http://pubs.acs.org.