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Complementary routes for the stereoselective synthesis of functionalized benzoquinolizidine targets

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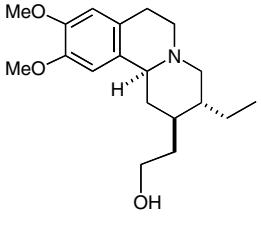
Abstract—We report new and complementary routes for the highly stereoselective construction of functionalized benzoquinolizidine targets from readily available, non-racemic chiral templates. The methods developed allow us to predetermine relative product stereochemistries by judicious choice of substrate sub-structure, and provide ready access to alternative stereoisomers.

The benzo[*a*]quinolizidine ring system is of considerable interest and significance since this heterocyclic template is found within a range of pharmacologically interesting alkaloids. For example (−)-protoemetinol **1**,[1] isolated by Battersby from *Alangium lamarckii*, is structurally related to psychotrine **2** and *O*-methylpsychotrine **3**, and indeed **1** has formed the basis of synthetic approaches to these more functionalized derivatives.[2] Alangine, **4**, a recently isolated natural product also from *A. lamarckii* differs stereochemically from compounds **1**–**3** in that it has trans relative stereochemistry at positions 2 and 11b.[3] Compounds **2** and **3** are known to be potent inhibitors of HIV-1 reverse transcriptase, and such biological significance earmarks the development of new asymmetric routes for accessing functionalized benzo[*a*]quinolizidine targets as an important task.[4]

Over recent years our research teams have, independently, developed a new approach for the stereoselective synthesis of heterocyclic ring systems that involves the cyclization of a pendent aromatic substituent onto an *N*-acyliminium intermediate as the key ring-forming step.[5] We now wish to report the development of complementary routes for the highly stereoselective synthesis of functionalized benzo[*a*]quinolizidine targets that allow at will, the efficient preparation of targets with a



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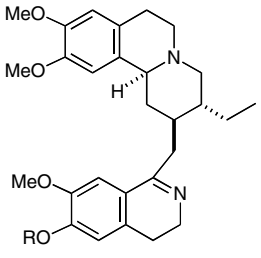
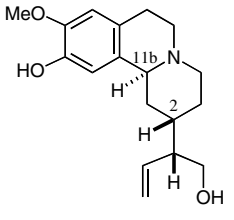


2 (R = H)
3 (R = Me)



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range of relative product stereochemistries through judicious choice of substrate structure and reaction protocol.

We envisaged one route to the chosen functionalized targets through application of conjugate addition chemistry to an α,β-unsaturated tetrahydroisoquinoline substrate, since in related work on an indolo[2,3-*a*]quinolizine skeleton the use of appropriate nucleophilic reagents in conjugate addition reactions has proved to be very successful, proceeding with good yield and with exclusive diastereoselectivity.[6,7]

In an attempt to influence the approach of the attacking nucleophile we generated template **6** through TBDPS-protection of the hydroxyl group of **5** before introducing unsaturation (Scheme 1). Substrate **5** was obtained as a single diastereoisomer on Lewis acid induced cyclization of the corresponding bicyclic lactam precursor, as previously reported by our group.[8] Our aim here was to shield the 'upper' face of the heterocycle to encourage attack from below, and hence produce the desired cis product stereochemistry (relative to the H-atoms at stereocentres 2 and 11b).

The results of conjugate addition studies on template **6** are highlighted in Scheme 2, with product **7** isolated in 70% yield as a single diastereoisomer, and product **8** in 55% yield but as a 1:1 mixture of diastereoisomers. The relative stereochemistry of **7** was confirmed by nOe studies, and found to have trans relative stereochemistry with respect to the H-atoms at the chiral centres.[9]

One possible explanation for the observed stereochemical outcome of the conjugate addition reactions to unsaturated lactam **6** could be, as highlighted in Figure 1, an axial attack of the vinyl cuprate, under stereoelectronic control, to give the kinetic product **7**. However, the conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate may be reversible, affording the 1:1 mixture of isomers **8a** (2,11b trans, kinetic):**8b** (2,11b cis, thermodynamic) under the reaction conditions (−78 °C to 25 °C, 24 h).

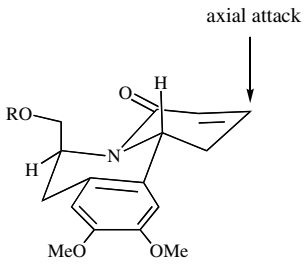
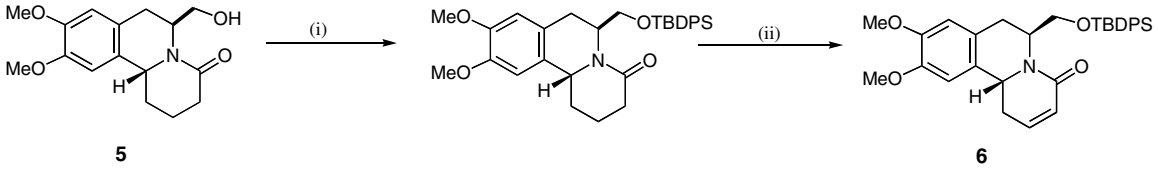


Figure 1.

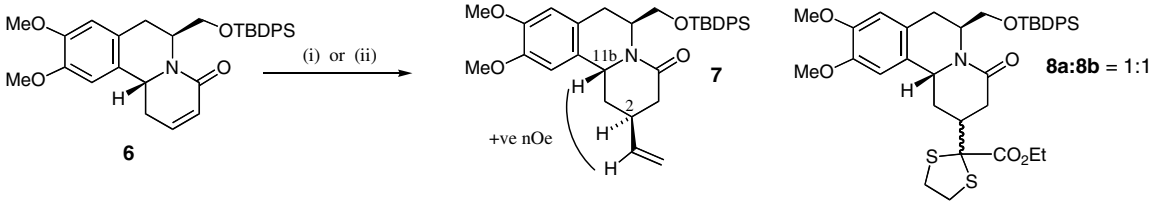
In an attempt to determine the effect, if any, of the hydroxymethyl substituent on the stereoselectivity of the conjugate addition process, we decided to examine the reaction of substrate **13**, having removed the hydroxymethyl substituent by the route highlighted in Scheme 3.

With α,β-unsaturated amide **13** in hand, we turned our attention to the proposed functionalization of the β-position of the unsaturated lactam through conjugate addition chemistry using the more successful vinyl nucleophile (Scheme 4).

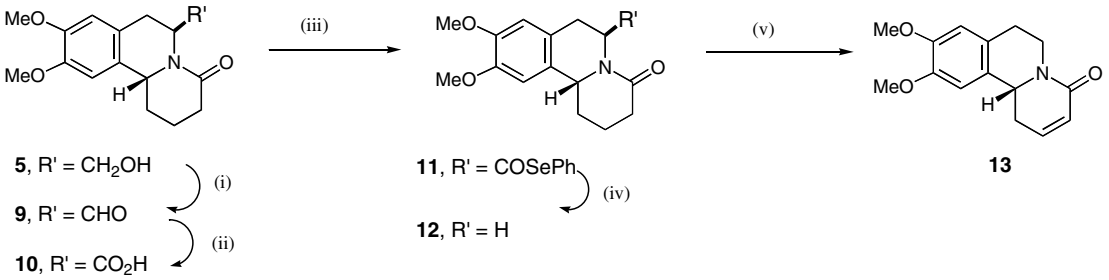
Product **14** was isolated in good yield (67%), and we were pleased to observe the formation of a single diastereoisomer by examination of the crude reaction mixture by 250 MHz ^{1}H NMR spectroscopy. The relative stereochemistry of **14** was confirmed by nOe studies, and again found to have the H-atoms at the chiral centres showing trans relative stereochemistry.[9] We also attempted the addition reaction with the lithiated dithiolane nucleophile, but in this case we only obtained an intractable product mixture.



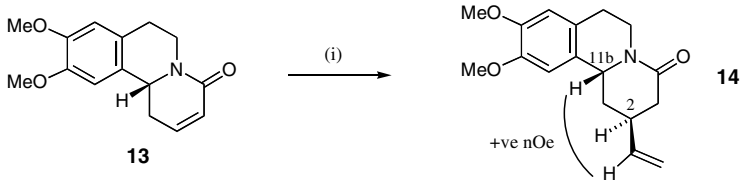
Scheme 1. Reagents and conditions: (i) imidazole (3 equiv), DMAP (cat.), TBDPSCl (2 equiv), DCM, rt, 24 h, (97%); (ii) LDA, PhSeBr, THF, −78 °C to rt, 24 h; then $NaIO_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h (42%, two steps).



Scheme 2. Reagents and conditions: (i) vinylmagnesium bromide (10 equiv), CuCN (7.5 equiv), TMSCl (7.5 equiv), THF, −78 °C to rt, 24 h; (ii) LDA (2 equiv), ethyl 1,3-dithiolane-2-carboxylate (1.2 equiv), THF, −78 °C to rt, 24 h.



Scheme 3. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (70%); (ii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (86%); (iii) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (76%); (iv) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (81%); (v) LDA, PhSeBr, THF, −78 °C to rt, 24 h; then $NaIO_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h (61% for two steps).



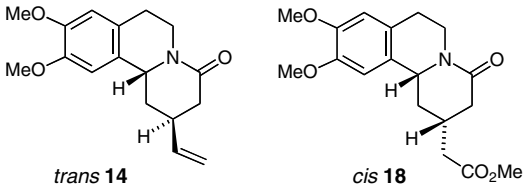
Scheme 4. Reagents and conditions: (i) vinylmagnesium bromide (10 equiv), CuCN (7.5 equiv), TMSCl (7.5 equiv), THF, −78 °C to rt, 24 h.

Clearly the (protected) hydroxymethyl group of substrate **6** plays no major role in determining the approach of the nucleophile, with the inherent conformation of the parent heterocyclic template being responsible for the stereochemical induction, with the nucleophile approaching from the least hindered (convex) face of the ring system. In summary, products **7** and **14** are formed as single diastereoisomers and with trans relative stereochemistry at positions 2 and 11b, as required for alkaloids such as alangine, **4**.

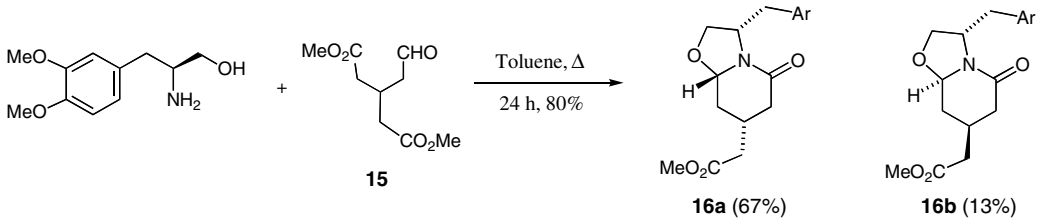
An alternative route for the introduction of substituents onto the lactam ring would involve the incorporation of functionality at an earlier stage in the sequence. The development of synthetic routes to prochiral or racemic glutarates,[10] such as **15**, and the subsequent use of these oxo diesters in stereoselective cyclocondensation reactions with chiral amino alcohols has previously been demonstrated.[5b] In this current approach, cyclocondensation of the appropriate substrates leads to the formation of functionalized bicyclic lactams **16a** and **16b** in a process that involves the discrimination of two enantiotopic acetate chains (Scheme 5).

Lactams **16a**,**b** were separable, and their relative stereochemistry was established by X-ray crystallography. *N*-Acyliminium ion precursor **16a**, on treatment with $TiCl_4$ in DCM at reflux for 3 days, gave **17** in 36% yield as a single product diastereoisomer (Scheme 6). X-ray crystallography[11] confirmed the relative stereochemistry of this product to be as shown in Scheme 6, with the H-atoms at the chiral centres now having *cis* relative stereochemistry, as required in benzo[*a*]quinolizidine targets, such as **1**–**3**.

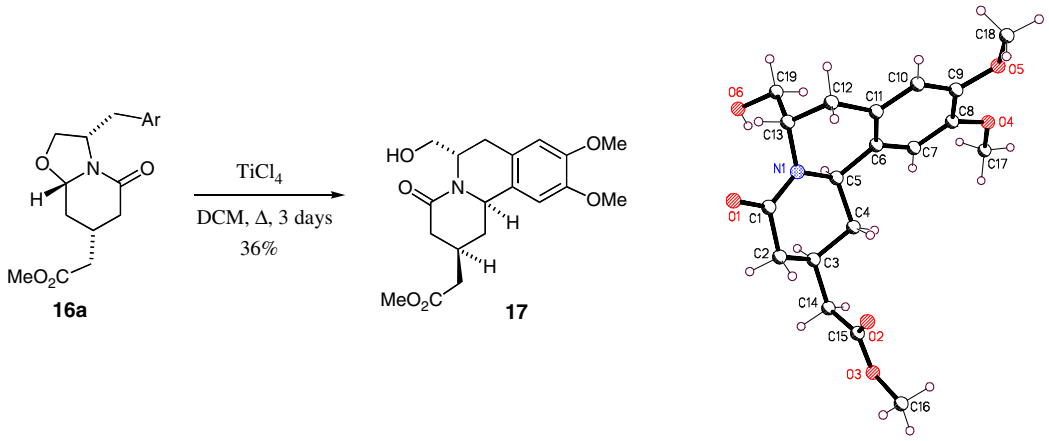
Removal of the hydroxymethyl moiety from **17** by an analogous route to that described in Scheme 3 gave the desired functionalized benzo[*a*]quinolizidine target **18**.



In conclusion, we have developed new and highly stereoselective routes to functionalized benzo[*a*]quinolizidine targets, both in the 2,11b-cis and -trans series. The relative stereochemistry of the products can be influenced through appropriate selection of synthetic approach, allowing complementary routes to diastereoisomerically



Scheme 5.



Scheme 6.

substituted products **14** and **18** as single diastereoisomers.[12] The absolute stereochemistry of such products can, if required, be tuned by the choice of appropriate enantiomer of the β-aminoalcohol starting material.

Acknowledgements

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References and notes

1. Battersby, A. R.; Kapil, R. S.; Bhakuni, B. S.; Popli, S. P.; Merchant, J. R.; Salgar, S. S. *Tetrahedron Lett.* **1965**, 4965–4971.
2. Takacs, J. M.; Boito, S. C. *Tetrahedron Lett.* **1995**, *36*, 2941–2944, and references therein.
3. Itoh, A.; Ikuta, Y.; Tanahashi, T.; Nagakura, N. *J. Nat. Prod.* **2000**, *63*, 723–725; Takayama, H.; Arai, M.; Kitajima, M.; Aimi, N. *Chem. Pharm. Bull.* **2002**, *50*, 1141–1143.
4. Tan, G. T.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *J. Biol. Chem.* **1991**, *266*, 23529–23536.
5. For recent examples, see: (a) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357–359; (b) Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820.
6. Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, *47*, 1961–1964.
7. For related conjugate additions, see: Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693.
8. Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661–3663.
9. For compounds **7** and **14**, a positive NOE effect was observed between the proton at position 11b and a proton of the newly added vinyl substituent. No positive NOE effect was observed between the proton substituents at positions 11b and 2.
10. Amat, M.; Bassas, O.; Cantó, M.; Llor, N.; Santos, M. M. M.; Bosch, J. *Tetrahedron* **2005**, *61*, 7693–7702.
11. X-ray data for **17**: Data collected at 150 K on a Bruker SMART 1000 diffractometer; solution by direct methods and refinement by full-matrix least-squares on F^2 using all the data.[13] Non-hydrogen atoms refined with anisotropic atomic displacement parameters; hydrogen atoms inserted at calculated positions using a riding model, except for the alcohol proton which was located and refined with a fixed isotropic displacement parameter. Crystal dimensions $0.36 \times 0.24 \times 0.22$ mm^3, monoclinic, $P2_1$, $a = 5.1398(4)$, $b = 11.7652(8)$, $c = 14.524(1)$ Å, $\beta = 94.274(1)°$ and $V = 875.8(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.378$ M g/m^3. 7592 Refl., 2156 independent ($R_{int} = 0.0212$), $\mu = 0.102$ mm^{-1}, $F(000) = 388$, 238 least-squares parameters, $R1 = 0.0303$, $wR = 0.0777$ (2σ data). CCDC 297432 contains supplementary crystallographic data in cif format. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk).
12. Data for selected compounds: Compound **14**: $[\alpha]_D^{22}$ +43.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 2.02–2.08 (1H, m), 2.30–2.37 (1H, m), 2.54 (2H, t, $J = 4$), 2.63 (1H, dt, $J = 2.8$, 15.2), 2.67–2.73 (1H, m), 2.78–2.85 (1H, m), 2.91–2.90 (1H, m), 3.86 (3H, s), 3.87 (3H, s), 4.63–4.66 (1H, m), 4.83–4.88 (1H, m), 5.12–5.18 (2H, m), 5.91–6.00 (1H, m), 6.62 (1H, s), 6.64 (1H, s); δ_C (100 MHz; $CDCl_3$) 28.5, 33.1, 34.8, 36.3, 40.1, 53.5, 55.9, 56.1, 107.8, 11.7, 115.4, 127.6, 129.0, 139.4, 146.8, 146.9, 169.0 (Found (EI): M^+ 288.15935. $C_{17}H_{21}NO_3$ requires 288.15940). Compound **18**: $[\alpha]_D^{22}$ +124.9 (*c* 1.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.34–1.43 (1H, m), 2.07 (1H, dd, $J = 17$, 12), 2.34–2.36 (2H, m), 2.43–2.49 (1H, m), 2.55–2.68 (3H, m), 2.74–2.92 (2H, m), 3.70 (3H, s), 3.83 (3H, s), 3.84 (3H, s), 4.65 (1H, dd, $J = 11$, 4), 4.81–4.85 (1H, m), 6.59 (1H, s), 6.63 (1H, s); δ_C (100 MHz; $CDCl_3$) 28.4 (2C), 37.0, 38.1, 39.5, 39.9, 51.7, 55.8, 56.0, 56.1, 108.2, 111.5, 127.1, 128.6, 147.7, 147.8, 168.1, 172.1 (Found (EI): M^+, 333.1576. $C_{18}H_{23}NO_5$ requires 333.1576).
13. Sheldrick, G. M. SHELXTL version 6.12, Bruker-AXS, Madison WI, 2001.