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Complementary stereoselective conjugate addition reactions on indolo[2,3-*a*]quinolizine templates

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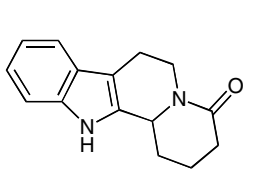
Abstract—We report a new and highly stereoselective approach for the construction of a range of functionalized indolo[2,3-*a*]quinolizine targets from a readily available, nonracemic chiral template. The methods developed allow us to predetermine relative product stereochemistries by judicious choice of substrate sub-structure.

The indolo[2,3-*a*]quinolizine ring system **1** is of considerable interest and significance since this heterocyclic template is found within a plethora of indole alkaloids, including geissoschizine **2**,[1] geissoschizol **3**[2] and hirsutine **4**.[3] The presence of the lactam carbonyl in templates such as **1** allows for possible further functionalization en route to the natural product targets. Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction,[4] Bischler–Napieralski reaction,[5] Fischer indole synthesis[6] and an asymmetric Pictet–Spengler reaction.[7]



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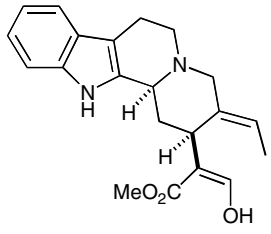

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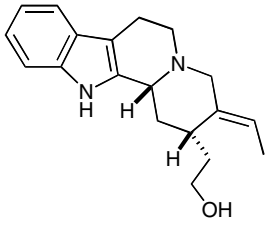

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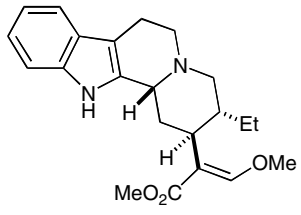

4

We have developed a new approach for the stereoselective synthesis of the indolo[2,3-*a*]quinolizine ring system that involves the cyclization of a pendent indole substituent onto an *N*-acyliminium intermediate as the key ring-forming step.[8] We have recently applied our methodology in natural product synthesis, and have reported the asymmetric preparation of some simple indole alkaloids, including deplancheine.[9] In order to access more advanced targets such as **2**–**4**, and their synthetic analogues, one would require suitable and flexible routes for the introduction of additional functionality to the indolo[2,3-*a*]quinolizine template, ideally with control over relative and absolute stereochemistry. One approach currently under study in our laboratory is to introduce appropriate functionality through conjugate addition to the lactam ring. Scheme 1 highlights the preparation of a model substrate for this investigation from indolizino[2,3-*a*]quinolizidine derivative **5**, obtained as a single diastereoisomer as previously reported.[8]

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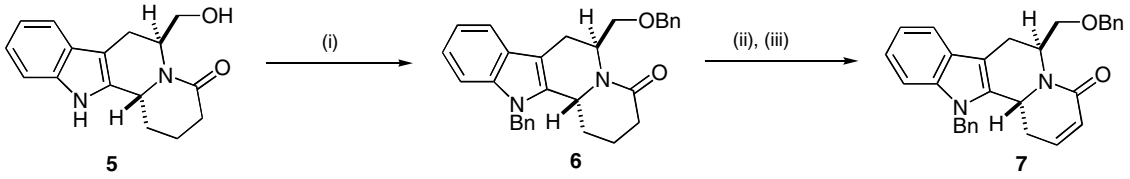
With α,β-unsaturated amide **7** in hand, we turned our attention to the proposed functionalization of the β-position through the conjugate addition chemistry shown in Scheme 2.

The products of conjugate addition were isolated in varying yields: **8** (52%), **9** (20%) and **10** (65%); we were pleased to observe the formation, in each case, of the desired product as a single diastereoisomer by examination of the crude reaction mixtures by 250 MHz ^{1}H NMR spectroscopy. The relative stereochemistry of each product was confirmed by NOE studies. Protons at positions 2 and 12b have *trans* relative stereochemistry, as seen in the natural product hirsutine, **4**.[3]

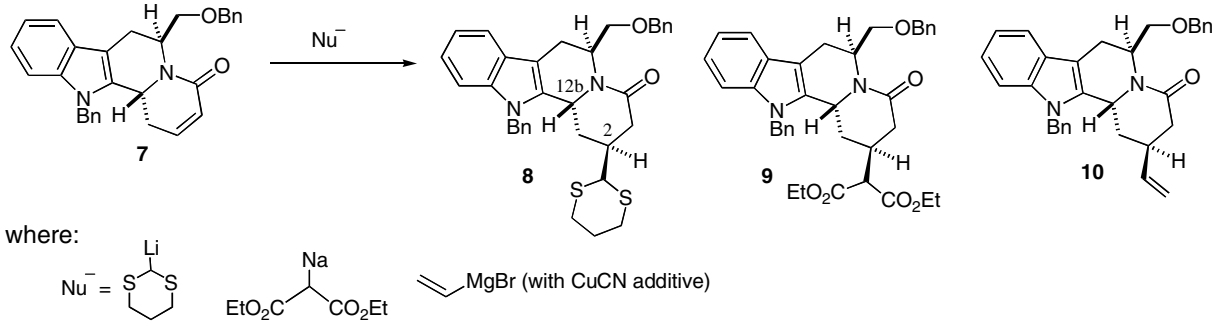
All nucleophiles gave the same sense of stereochemical induction with template **7**, and although this appears to result from the nucleophile approaching the face of the conjugated amide that carries the large benzyloxymethyl-substituent, the representations shown in Scheme 2 can be misleading, since the conformation of molecules such as **7** is bowl-like, and the nucleophiles are approaching from the outer (perhaps less hindered) face of the bowl; that is, from the same face as the H-atom at the proximate ring junction.

An intriguing and potentially very useful effect on the sense of nucleophilic addition was observed on further modification of the template sub-structure. Unsaturated substrate **16** was prepared as a single enantiomer following the method outlined in Scheme 3. Removal of the hydroxymethyl substituent in this way would be a natural progression en route to final targets such as **2**–**4** noted at the outset of this letter, and this protocol is now a standard transformation in our laboratory.[9]

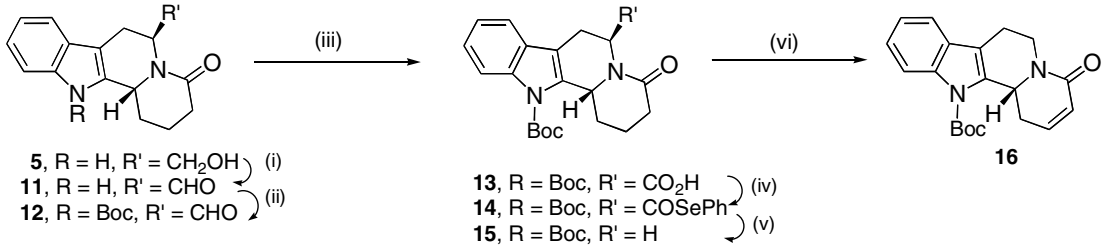
With the structures of potential targets **2**–**4** in mind we subjected compound **16** to the addition of 2 equiv of lithiated methyl 1,3-dithiolane-2-carboxylate and were pleased to observe the exclusive formation of the addition product **17** as a single diastereoisomer in 47% yield (Fig. 1). Analysis of compound **17** by X-ray crystallography[10] revealed that the addition had occurred on the opposite face to that observed in the studies outlined



Scheme 1. Reagents and conditions: (i) NaH (2 equiv), BnBr (2.2 equiv), DMF, rt, 1 h (90%); (ii) LDA, PhSeBr, THF, −78 °C to rt, 24 h, then (iii) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h (85% for two steps).



Scheme 2.



Scheme 3. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (70%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (98%); (iii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (83%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (83%); (v) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (73%); (vi) LDA, PhSeBr, THF, −78 °C to rt, 24 h, then $NaIO_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h (85% for two steps).

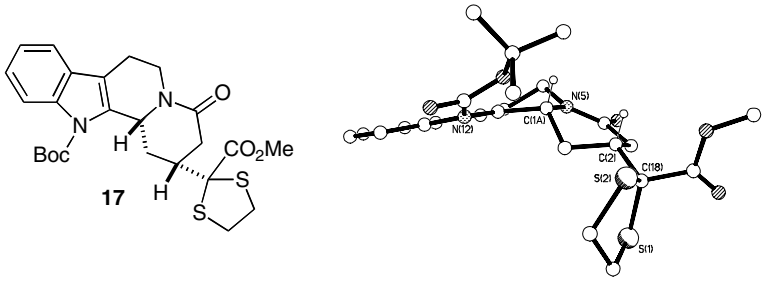
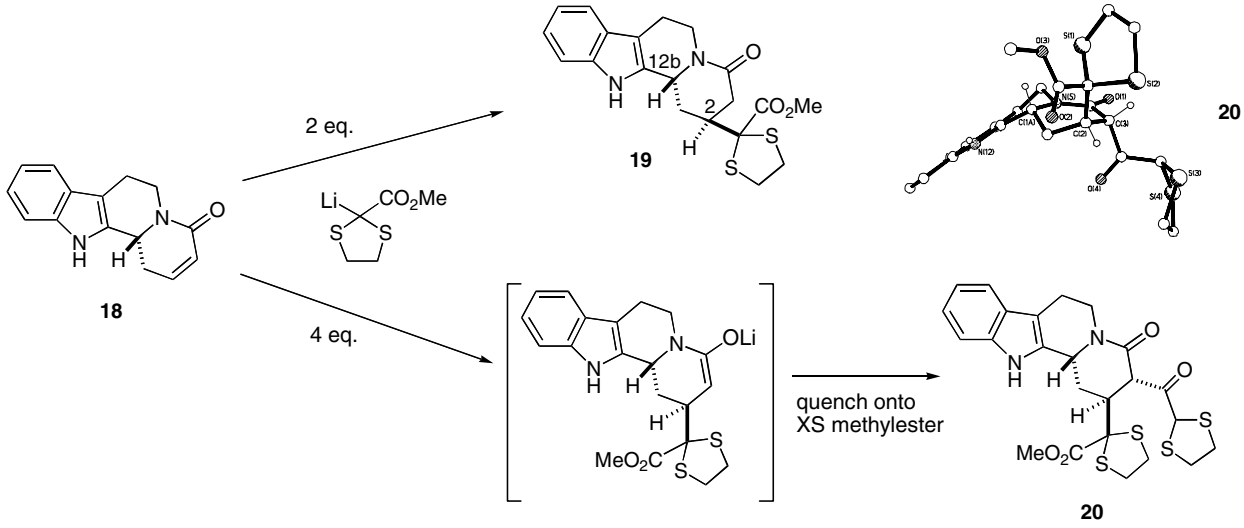


Figure 1.



Scheme 4.

above, with the protons at positions 2 and 12b now having *cis* relative stereochemistry, as in the natural products geissoschizine **2**[1] and geissoschizol **3**.[2]

A remarkable manipulation in the sense of stereochemical induction can be achieved with template **18**, that lacks any *N*-protection at the indole nitrogen (obtained through formic acid-mediated deprotection of **16** [neat, rt, 22 h, 71% yield]). In this case, addition of the lithiated dithiolane nucleophile (2 equiv) led to selective formation of product **19** in which the protons at positions 2 and 12b were found to be of *trans* relative stereochemistry, as seen previously with template **7**, and as required in the natural product hirsutine, **4**.[3]

The full potential of our approach for the efficient stereoselective total synthesis of indole natural products can be demonstrated with the addition of an excess of the lithiated dithiolane nucleophile (4 equiv) to substrate **18**. We reasoned that the dithiolane moiety could serve a dual role: as both a nucleophile and subsequently, in the same pot, as an electrophile for derivatization of an intermediate lactam enolate. This domino process would provide a highly economic route to access advanced heterocyclic templates. We were pleased to isolate product **20** in 64% yield and as a single diastereoisomer (Scheme 4). Product **20** has the correct relative stereochemistry at all three chiral centres required for a future synthesis of hirsutine, **4**, as confirmed by X-ray crystallography (Scheme 4).[11]

In conclusion, we have found that the relative stereochemistry of the products of conjugate addition to indolo[2,3-*a*]quinolizine molecules can be influenced through careful selection of the template structure, allowing complementary approaches to diastereoisomeric addition products.[12] With either the hydroxymethyl auxiliary group present, or judicious choice of indole *N*-protection, nucleophilic addition occurs to give *cis* relative stereochemistry between the newly added substituent and the proton at ring junction 12b. An alternative manipulation of the template structure can lead to the introduction of *trans* relative stereochemistry between these two groupings. In addition, we have discovered that the use of a dithiolane reagent in a domino-type process can lead to highly efficient and stereoselective functionalization of our template. Current work is focused on extending the methodology described in this paper to other, more complex indole alkaloid targets. Our progress will be reported in due course.

Acknowledgements

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10. Crystallography for **17**: $C_{25}H_{30}N_2O_5S_2$, $M = 502.63$, monoclinic, $P2_1$, $a = 10.5505(7)$, $b = 9.3807(6)$, $c = 12.4921(8)$ Å, $\beta = 100.281(2)°$, $V = 1216.51(14)$ Å^3, $Z = 2$, 10,789 data measured, $R_{int} = 0.0192$, $wR2 = 0.0905$ for all 5594 unique data, $R1 = 0.0379$ for 5007 data with $F^2 \geqslant 2\sigma(F^2)$. Absolute structure parameter $= -0.03(6)$—thus reliably determined. CCDC 286786 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.).
11. Crystallography for **20**: $C_{24}H_{26}N_2O_4S_4$, $M = 534.71$, orthorhombic, $P2_12_12_1$, $a = 7.6895(7)$, $b = 17.2611(16)$, $c = 18.2799(17)$ Å, $V = 2426.3(4)$ Å^3, $Z = 4$, 21508 data measured, $R_{int} = 0.0208$, $wR2 = 0.0705$ for all 5875 unique data, $R1 = 0.0287$ for 5417 data with $F^2 \geqslant 2\sigma(F^2)$. Absolute structure parameter $= -0.03(5)$—thus reliably determined. H-bonded chains along *a* via N(12)–H(12)···O(1′), CCDC 286787.
12. Data for selected compounds: Compound **7**: δ_H (400 MHz; $CDCl_3$) 2.21–2.30 (1H, m), 2.52–2.59 (1H, m), 3.02 (1H, ddd, *J* 16, 8, 4), 3.15 (1H, d, *J* 16), 3.30–3.38 (2H, m), 4.45 (2H, s), 4.59–4.63 (1H, m, C=CC*H*), 5.23 (2H, dd, *J* 36, 16), 5.42–5.46 (1H, m), 6.06 (1H, dd, *J* 8, 4), 6.49–6.50 (1H, m), 6.83–6.85 (2H, m), 7.14–7.23 (11H, m), 7.60–7.62 (1H, m); δ_C (100 MHz, $CDCl_3$) 21.9 (*C*H$_2$), 32.0 (*C*H$_2$), 47.3 (*C*H), 48.3 (*C*H$_2$), 49.8 (*C*H), 68.0 (*C*H$_2$), 72.5 (*C*H$_2$), 107.6 (*C*), 109.8 (*C*H), 118.7 (*C*H), 119.9 (*C*H), 122.3 (*C*H), 125.6 (2 × *C*H), 125.9 (*C*H), 127.0 (*C*), 127.3 (2 × *C*H), 127.3 (*C*H), 127.5 (*C*H), 128.2 (2 × *C*H), 128.9 (2 × *C*H), 132.6 (*C*), 137.0 (*C*), 138.1 (*C*), 138.2 (*C*), 138.2 (*C*H), 164.9 (N*C*=O); MS (EI) *m*/*z* 448 [M$^+$, 100.0%] (Found: M$^+$, 448.21406. $C_{30}H_{28}N_2O_2$ requires 448.21507). Compound **16**: δ_H (400 MHz, $CDCl_3$) 1.69 (9H, s), 2.13–2.22 (1H, m), 2.72–2.80 (2H, m), 2.82–2.92 (1H, m), 3.03 (1H, ddd, *J* 17.2, 6.6, 3.8), 5.02 (1H, ddd, *J* 12.5, 4.8, 1.4), 5.24–5.30 (1H, m), 6.09 (1H, dd, *J* 9.7, 1.5), 6.67–6.71 (1H, m), 7.26–7.35 (2H, m), 7.47–7.49 (1H, m), 8.08 (1H, d, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*H$_2$), 28.2 (3 × *C*H$_3$), 31.6 (*C*H$_2$), 37.6 (*C*H$_2$), 53.3 (*C*H), 84.5 (*C*), 115.8 (*C*H), 118.0 (*C*), 118.4 (*C*H), 123.1 (*C*H), 124.7 (*C*H), 125.4 (*C*H), 128.5 (*C*), 134.1 (*C*), 136. 6 (*C*), 139.2 (*C*H), 150.0 (N*C*(O)O′Bu), 164.8 (N*C*=O); MS (EI) *m*/*z* 338 [M$^+$, 24.4%] (Found: M$^+$, 338.16318. $C_{20}H_{22}N_2O_3$ requires 338.16384). Compound **17:** δ_H (400 MHz, $CDCl_3$) 1.38–1.47 (1H, m), 1.70 (9H, s), 2.53 (1H, dd, *J* 17.4, 11.7), 2.69–2.80 (2H, m) 2.81–2.85 (2H, m), 2.87–2.89 (1H, m), 2.95–3.03 (1H, m), 3.28–3.33 (2H, m), 3.35–3.39 (2H, m), 3.81 (3H, s), 5.10–5.17 (2H, m), 7.23–7.33 (2H, m), 7.43–7.45 (1H, m), 8.02–8.04 (1H, m); δ_C (100 MHz, $CDCl_3$) 21.7 (*C*H$_2$), 28.1 (3 × *C*H$_3$), 33.8 (*C*H$_2$), 35.7 (*C*H$_2$), 38.4 (*C*H), 39.0 (*C*H$_2$), 40.1 (*C*H$_2$), 40.3 (*C*H$_2$), 53.5 (*C*H$_3$), 55.4 (*C*H), 74.1 (*C*), 84.5 (*C*), 115.5 (*C*H), 118.4 (*C*H), 118.7 (*C*), 123.1 (*C*H), 124.8 (*C*H), 128.5 (*C*), 134.7 (*C*), 136.8 (*C*), 150.3 (N*C*(O)O′Bu), 168.7 (*C*=O), 171.9 (N*C*=O); MS (EI) *m*/*z* 502 [M$^+$, 3.5%] (Found: M$^+$, 502.15989. $C_{25}H_{30}N_2O_5S_2$ requires 502.15962). Compound **20**: δ_H (400 MHz, $CDCl_3$) 2.29–2.33 (1H, m), 2.79–2.89 (2H, m), 2.79–2.89 (1H, m), 3.15–3.27 (4H, m), 3.35–3.37 (2H, m), 3.45–3.48 (2H, m), 3.49–3.52 (1H, m), 3.88 (3H, s), 4.33–4.36 (1H, m), 4.98 (1H, t , *J* 8.4), 5.11–5.13 (1H, m), 5.92 (1H, s), 7.10–7.20 (2H, m), 7.32–7.34 (1H, m), 7.49 (1H, d, *J* 7.6), 7.87 (1H, br s); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*H$_2$), 29.3 (*C*H$_2$), 30.9 (*C*H), 38.2 (*C*H$_2$), 38.3 (*C*H$_2$), 39.1 (*C*H$_2$), 40.4 (*C*H$_2$), 41.3 (*C*H$_2$), 51.0 (*C*H), 53.8 (*C*H$_3$), 54.8 (*C*H), 56.3 (*C*H), 73.9 (*C*), 109.7 (*C*) 110.9 (*C*H), 118.4 (*C*H), 119.9 (*C*H), 122.2 (*C*H), 126.8 (*C*), 131.9 (*C*), 136.3 (*C*), 164.8 (*C*=O), 171.8 (N*C*=O), 198.1 (*C*=O); MS (FAB) *m*/*z* 535 [MH$^+$, 5.2%] (Found: MH$^+$, 535.08460. $C_{24}H_{26}N_2O_4S_4$ requires 535.08537).