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A new approach to indolo[2,3-*a*]quinolizidines through radical cyclization of 2-acyl-1-phenylthiotetrahydro-β-carbolines bearing pendent α,β-unsaturated esters

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ABSTRACT

A new method is reported for the preparation of indolo[2,3-*a*]quinolizidines based on radical cyclization of a 2-acyl-1-phenylthiotetrahydro-β-carboline bearing a pendent α,β-unsaturated ester. The required radical cyclization precursor is efficiently assembled from *E*-5-ethoxycarbonyl-4-pentenoic acid and 3,4-dihydro-β-carboline through a DCC/HOBt-activation/N-acylation and $BF_3{\cdot}Et_2O$/PhSH iminium-ion trapping sequence. Tin-mediated radical cyclization of the radical cyclization precursor affords stereoselectively a *cis*-lactam (dr = 7:1) in good yield (81%), bearing the correct D/E ring fusion stereochemistry for the Tacaman alkaloids. The methodology has been applied to formal syntheses of the indoloquinolizidine alkaloids, (±)-eburnaminol and (±)-larutensine.

The indolo[2,3-*a*]quinolizidine framework **1** (Fig. 1) is a structural motif found within numerous natural products of varying structure and biological activity, including alkaloids such as the architecturally interesting (+)-N_a-methylvellosimine (**2**) and the well-known reserpine (**3**).[1] In addition to its importance within Nature's structural palette, this scaffold continues to present medicinally relevant leads for potential therapies against a range of diseases.[2]

Thus, given the significance of the indoloquinolizidine core in natural and clinical arenas alike, many methods have been developed for its preparation, including Bischler–Napieralski,[3] Pictet–Spengler,[4] Fischer indole synthesis[5] and vinylogous Mannich[6] approaches, as well as strategies based on formal aza-[3+3]-[7] and [3+2]-carbonyl ylide[8] cycloadditions. The Pictet–Spengler reaction has historically been particularly popular, and recently has been developed into synthetically useful asymmetric variants based on the use of tryptophan-derived substrates[4a–c] or asymmetric organocatalysis.[4d–g]

Despite these advances, indoloquinolizidine synthesis in the context of the pentacyclic alkaloids of the Eburnamine–Vincamine and Tacaman families (general framework, **4**, Scheme 1) has often suffered from low levels of stereocontrol. For this reason, we set out to develop a stereoselective method that would be particularly useful in accessing indoloquinolizidines of this type, specifically in the context of a total synthesis of the indole alkaloid tacamonine (**5**).[9]

Our planned method involved a novel disconnection[10] of the C3–C14 bond (tacamonine numbering) of the indoloquinolizidine, which we aimed to instal via a 6-*exo*-*trig* cyclization of a benzylic α-acylamino radical[11] **7**, itself generated from 2-acyl-1-phenylthiotetrahydro-β-carboline **8** (Scheme 1).

Herein we describe the development of the aforementioned method, and apply it to a brief formal synthesis of the Eburnamine–Vincamine alkaloids, (±)-eburnaminol and (±)-larutensine.

Our work began with the synthesis of the radical cyclization precursor **8**. As shown retrosynthetically in Scheme 1, we sought to assemble **8** from acid **9** and 3,4-dihydro-β-carboline[12] (**10**). From the outset, we envisaged achieving this N-acylation/iminium-ion

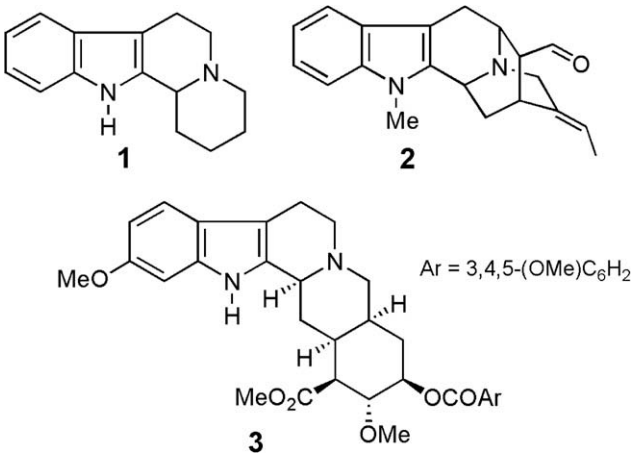

Figure 1. The indolo[2,3-*a*]quinolizidine framework **1** and examples of indoloquinolizidine natural products.

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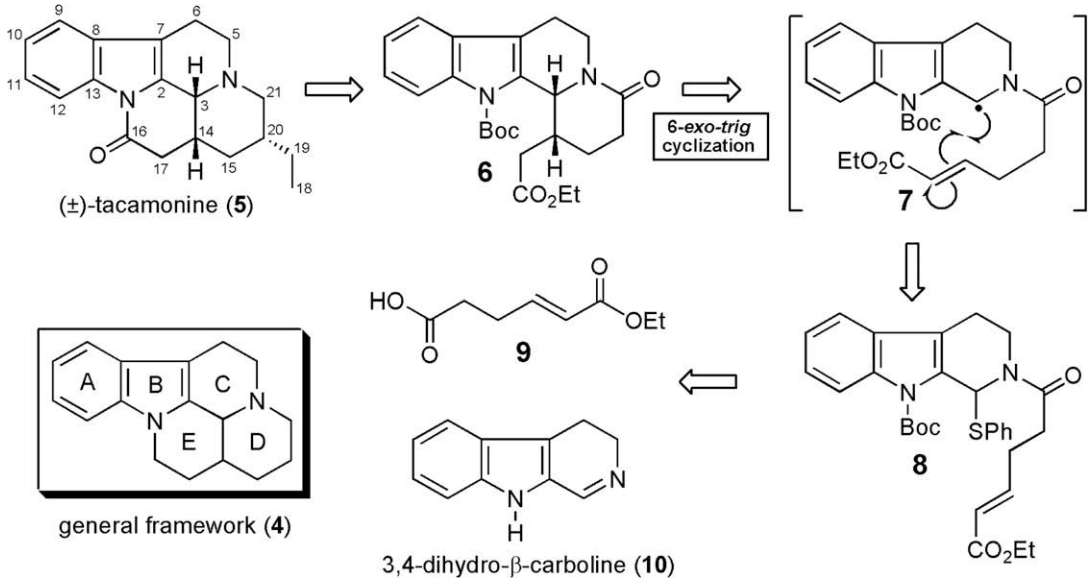
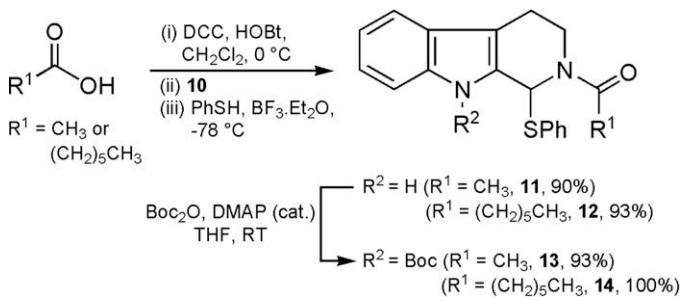


Scheme 1. Retrosynthesis of (±)-tacamonine (**5**) and general framework of the Tacaman and Eburnamine–Vincamine alkaloids (**4**).

trapping sequence under mild conditions, since this would allow for the potential use of sensitive acids bearing α-stereocentres (cf. structure of tacamonine, **5**). Mindful of these requirements, we began our search by exploring DCC/HOBt-activation of the acid, followed by N_b-acylation and low temperature $BF_3{\cdot}Et_2O$-mediated interception of the iminium ion with thiophenol in a one-pot sequence (DCC = *N*,*N*′-dicyclohexylcarbodiimide, HOBt = 1-hydroxybenzotriazole).

Our initial studies were carried out on the model acids, acetic and heptanoic acids. In the event, treatment of these acids (1.2 equiv) with DCC (1.2 equiv) and HOBt (1.2 equiv) at 0 °C, followed by addition of **10** (1.0 equiv) and subsequent exposure to PhSH (1.3 equiv) and $BF_3{\cdot}Et_2O$ (1.3 equiv) at −78 °C, cleanly afforded the corresponding α-sulfanyl amides as a mixture of rotamers (acetic, **11**: ~1.6:1; heptanoic, **12**: ~2.8:1) in good yield following chromatography (Scheme 2).[13] Indoles **11** and **12** could subsequently be *N*-Boc-protected [Boc_2O (1.3 equiv), DMAP (0.1 equiv), THF, RT] in near quantitative yield to give **13** and **14**, respectively.

Thus, with a reliable method in place, the preparation of **8** could be attempted. Acid **9** was prepared from 4-pentenoic acid (**15**) through a high-yielding ozonolysis/Horner–Wadsworth–Emmons sequence (80%, *E*:*Z* = 13:1; Scheme 3).[14] Thereafter, the coupling of **9** (1.0 equiv) with 3,4-dihydro-β-carboline (**10**) (1.2 equiv) proceeded smoothly, affording after treatment with benzenethiol the sulfanyl amide **17** in 88% yield (3 mmol scale) in a manner that was easily scalable (14 mmol: 83%). As before, indole *N*-Boc protection[15] proceeded in essentially quantitative yield to furnish **8** as a mixture of rotamers (~3.1:1) about the amide bond.[16]

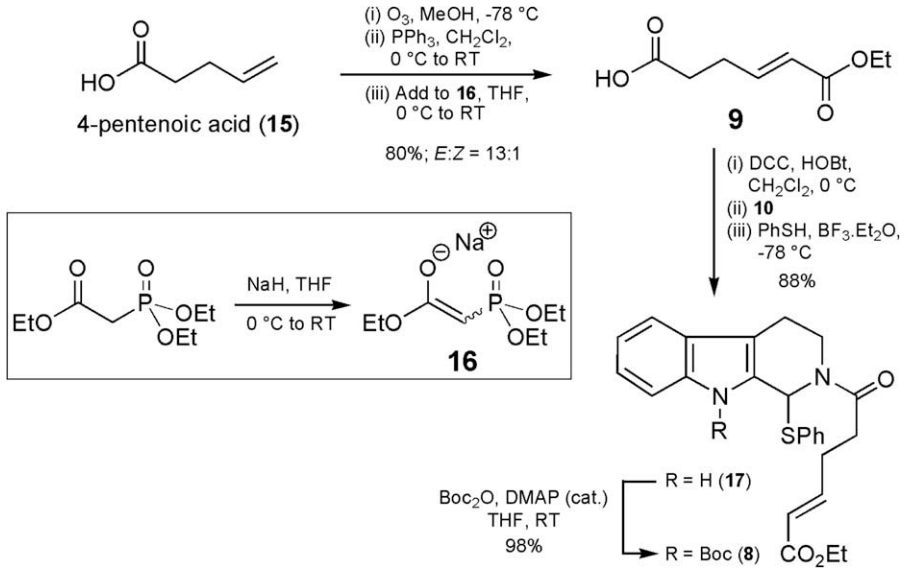


Scheme 2. Model α-sulfanyl amide synthesis.

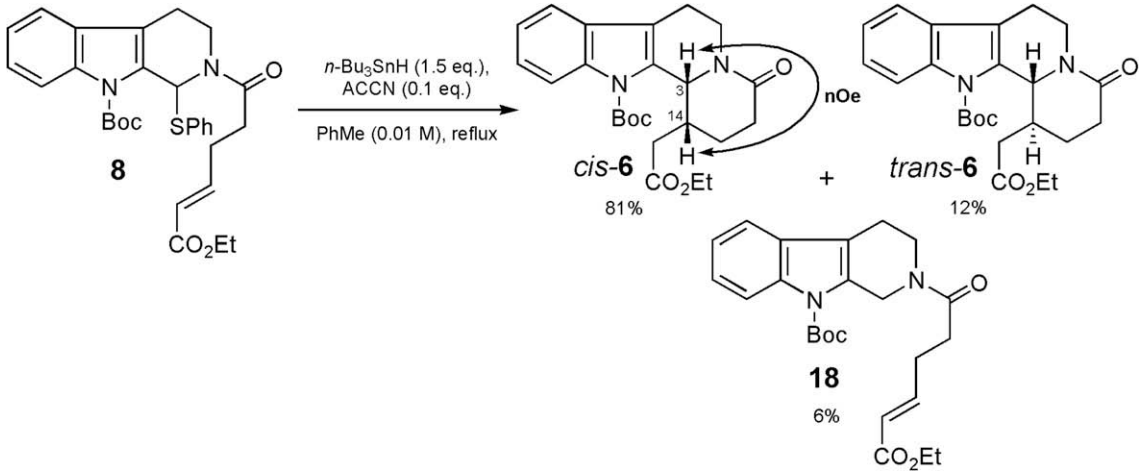
With **8** in hand, we next investigated the key radical cyclization. Subjecting **8** to standard radical cyclization conditions [*n*-Bu_3SnH (3.0 equiv), ACCN (0.1 equiv), degassed PhMe (0.02 M), reflux] gratifyingly resulted in the consumption of starting material and formation of more polar products [ACCN = 1,1′-azobis(dicyclohexylcarbonitrile)]. Careful chromatography of this mixture revealed the major component to be the desired *cis*-lactam (*cis*-**6**, 51%, Scheme 4),[17] accompanied by a smaller amount of the trans-isomer (*trans*-**6**, 15%)[17] and radical reduction product (**18**, 20%). After further optimization, we found, as expected, that conducting the reaction under more dilute conditions (0.01 M), lowering the equivalents of *n*-Bu_3SnH (1.5 equiv) and slowing the addition of the *n*-Bu_3SnH/ACCN/PhMe solution (over 1.5 h), all resulted in a decrease in the amount of reduction product (down to 6%), together with an increase in the yield and diastereoselectivity (*cis*:*trans* = 81%:12%) (Scheme 4).

The structures of *cis*- and *trans*-**6** were assigned on the basis of 2D NMR experiments (COSY, HSQC, NOESY and HMBC), with key stereochemical information being afforded by the cross-peak obtained in the NOESY spectrum of *cis*-**6** between H-3 (δ 5.39) and H-14 (δ 3.23). Unfortunately, signal overlap in the ^1H NMR spectrum of *trans*-**6** precluded the use of a similar NOESY experiment to show the absence of this cross-peak in the trans-isomer. Moreover, the coupling constants between these two protons yielded little information, as in both isomers, the *J* values were small and very similar [J_{H3-H14} (*cis*) = 2.0 Hz; J_{H3-H14} (*trans*) = 1.8 Hz], indicating significant distortion from the chair-like conformers. Thus, with the NMR data unable to confirm the stereochemistry of the major isomer, we sought definitive proof in the form of an X-ray crystal structure determination. While this was not possible for *cis*-**6** (formed as a gum), its saponification [LiOH (2.5 equiv), THF/H_2O (3:1), 76%] yielded the crystalline acid **19**, which could be recrystallized from MeOH to provide crystals suitable for a single crystal X-ray determination. The X-ray structure[18] (Fig. 2) clearly confirms the desired cis-arrangement of H-3 and H-14.

The observed diastereoselectivity in the radical cyclization can be rationalized by examining the possible transition states leading to each isomer (Fig. 3). Assuming reasonably that the larger indole substituent at the reacting radical centre adopts a pseudoequatorial position in the transition states, *cis*-**6** would arise from one in which the enoate ester group adopts a pseudoaxial orientation (**TS-1**), while in the transition state leading to *trans*-**6** this group



Scheme 3. Preparation of radical cyclization precursor **8**.



Scheme 4. Radical cyclization of **8**.

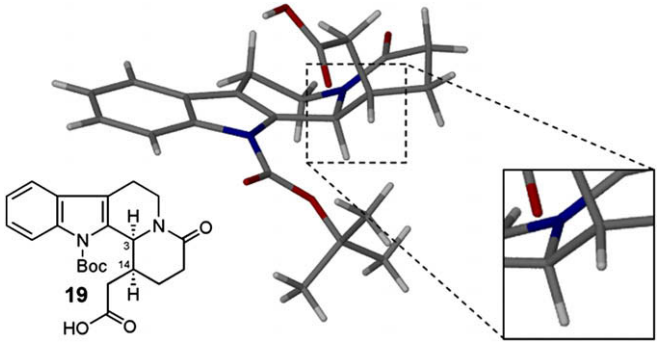


Figure 2. X-ray crystal structure of acid **19** showing the cis-arrangement of H-3 and H-14.

would be pseudoequatorial (**TS-2**). In the latter orientation, the ester suffers significant steric interaction with the bulky *N*-*t*-butoxycarbonyl group, which destabilizes **TS-2** and thereby disfavours the formation of *trans*-**6**; **TS-1**, on the other hand, avoids such clashing and for this reason *cis*-**6** predominates.[19]

Having established the requisite stereochemistry to be in place for (±)-tacamonine, we sought to demonstrate the utility of *cis*-**6** in a short formal synthesis of the natural products, eburnaminol (**20**) and larutensine (**21**) (Scheme 5). These two Eburnamine–Vincamine alkaloids were isolated[20] in 1991 from *Kopsia larutensis* and had previously been synthesized by Lounasmaa and Karvinen from indoloquinolizidine ester **22** in six and seven steps, respectively.[21] Thus, lactam **6** was converted through a three-step sequence (final two steps unoptimized) into **22**. First, the *N*-Boc group of **6** was removed by treatment with TFA in the presence of thioanisole as a cation scavenger to give free indole **23** in excellent yield (93%) (Scheme 5). Thereafter, conversion of **23** into thiolactam **24** was achieved with Lawesson's reagent (64%), and which was then reduced with excess Raney Nickel (77%) to deliver **22**. The spectral data (^{1}H, ^{13}C, IR and HRMS) of **22** were in good agreement with those reported by Lounasmaa, except that the melting point of our material differed significantly from that reported by Husson et al.,[22] although the solvent used in their case was different from ours [120–124 °C (EtOAc/hexanes); lit. mp: 160 °C (benzene/hexane)[22]].

In summary, we have developed an efficient method for the preparation of indolo[2,3-*a*]quinolizidines that is particularly

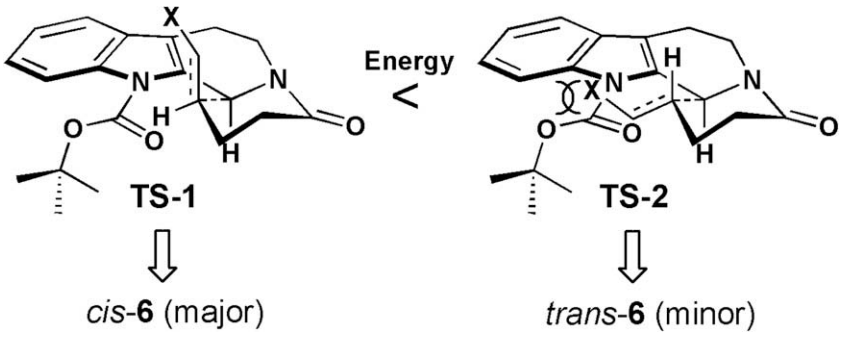
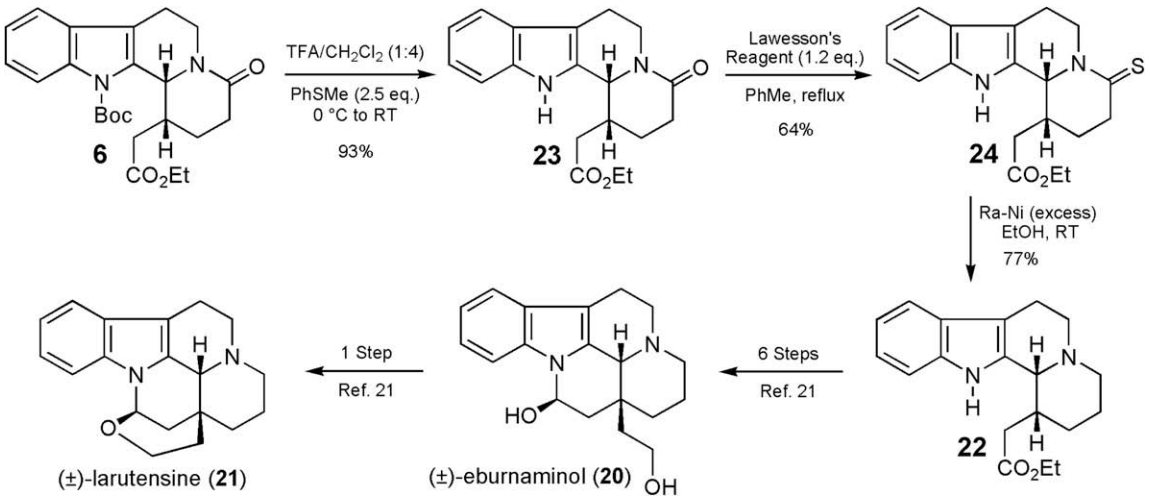


Figure 3. Proposed transition state model for the observed stereoselectivity (X = CO_2Et).



Scheme 5. Formal syntheses of (±)-eburnaminol (**20**) and (±)-larutensine (**21**) via **22**.

applicable to the synthesis of pentacyclic alkaloids of the Tacaman family. Our method involves a high-yielding assembly of the required radical cyclization precursor using a mild DCC/HOBt-activation and $BF_3{\cdot}Et_2O$/HSPh iminium-ion trapping sequence, as well as an *n*-Bu_3SnH-mediated radical cyclization that is selective for the desired cis-isomer. From this cis-product, the formal syntheses of (±)-eburnaminol and (±)-larutensine were completed through the preparation of a common indoloquinolizidine intermediate. Efforts to expand the scope of this method and apply it to a racemic total synthesis of tacamonine are underway in our laboratory, and will be reported in due course.

Acknowledgements

We thank the University of Cape Town and the South African National Research Foundation for funding.

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10. To the best of our knowledge, this is the first time this bond has been installed by radical means. Generally, indoloquinolizidine synthesis via the C3–C14 bond involves annulation or cycloaddition onto 3,4-dihydro-β-carboline or its derivatives, which simultaneously forms the N4–C21 bond. For examples, see: (a) Nagata, K.; Sekishiro, Y.; Itoh, T. *Heterocycles* **2007**, *72*, 175–179; (b) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533–1536; (c) Oppolozer, W.; Hauth, H.; Pfaffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801–1810.
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13. All new compounds delivered ^{1}H and ^{13}C NMR and IR spectral data consistent with the assigned structures, as well as satisfactory microanalyses or accurate HRMS masses.
14. The small amount of *Z*-isomer could be separated by careful chromatography after conversion into **8** but was more conveniently carried through the radical cyclization, as both isomers were converted into product. Moreover, alkene isomerization is known to occur under tributyltin radical conditions, see, for example: Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099–6101.
15. Indole protection was necessary as radical cyclization of free indole **17** resulted in a complex mixture (>6 products), which only contained a small amount of the desired lactam **23** (<10%).
16. Although only one rotamer of **8** has the correct configuration to undergo radical cyclization, equilibration to the reactive rotamer seemingly occurs under the reaction conditions, as all starting material is consumed to form product.
17. 12-(*tert*-Butoxycarbonyl)-1-(ethoxycarbonylmethyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**6**). [Numbering for NMR assignments follows the IUPAC name] *cis*-**6** (major): IR (thin film) 2931, 1732, 1645, 1456, 1410, 1369, 1309, 1141, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 1H, H-11), 7.44 (d, *J* = 7.7 Hz, 1H, H-8), 7.31 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H, H-10), 7.25 (m, 1H, H-9), 5.39 (d, *J* = 2.0 Hz, 1H, H-12b), 5.14 (ddd, *J* = 12.0, 4.1, 1.2 Hz, 1H, 1 × H-6), 3.82 (dq, *J* = 10.9, 7.1 Hz, 1H, 1 × OCH_2CH_3), 3.68 (dq, *J* = 10.9, 7.1 Hz, 1H, 1 × OCH_2CH_3), 3.23 (m, 1H, H-1), 2.84-2.65 (m, 3H, H-7 + 1 × H-6), 2.55 (m, 2H, H-3), 2.20–2.03 (m, 2H, 1 × H-2 + 1 × CH_2CO), 1.96-1.82 (m, 2H, 1 × CH_2CO + 1 × H-2), 1.72 (s, 9H, $OC(CH_3)_3$), 0.99 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (CH_2CO), 169.6 (C-4), 150.0 (NCO_2t-Bu), 136.7 (C-11a), 132.0 (C-12a), 128.1 (C-7b), 124.8 (C-10), 122.9 (C-9), 120.2 (C-7a), 118.2 (C-8), 115.8 (C-11), 84.4 ($OC(CH_3)_3$), 60.3 (OCH_2CH_3), 58.2 (C-12b), 38.3 (C-6), 33.0 (C-1), 31.8 (CH_2CO), 28.2 ($OC(CH_3)_3$), 28.0 (C-3), 24.1 (C-2), 21.3 (C-7), 13.8 (OCH_2CH_3); HRMS (ESI): $[M+H]^+$, 427.2212; $C_{24}H_{31}N_2O_5$ requires 427.2233. *trans*-**6** (minor): IR (thin film) 2979, 2927, 1727, 1648, 1456, 1419, 1370, 1357, 1307, 1156, 1139, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H, H-11), 7.45 (dd, *J* = 7.5, 0.7 Hz, 1H, H-8), 7.37–7.24 (m, 2H, H-9 + H-10), 5.11 (d, *J* = 1.8 Hz, 1H, H-12b), 5.02 (m, 1H, 1 × H-6), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.98–2.61 (m, 6H, CH_2CO + 1 × H-6 + H-1 + H-7), 2.55 (m, 1H, 1 × H-3), 2.40 (dt, *J* = 8.1, 4.3 Hz, 1H, 1 × H-3), 1.78–1.65 (m, 11H, $OC(CH_3)_3$ + H-2), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (CH_2CO), 170.6 (C-4), 150.9 (NCO_2t-Bu), 136.6 (C-11a), 135.0 (C-12a), 129.0 (C-7b), 124.7 (C-10), 123.1 (C-9), 120.7 (C-7a), 118.3 (C-8), 115.5 (C-11), 84.7 ($OC(CH_3)_3$), 60.5 (OCH_2CH_3), 60.3 (C-12b), 41.8 (C-6), 36.8 (C-1), 35.1 (CH_2CO), 28.3 (C-3), 28.2 ($OC(CH_3)_3$), 22.2 (C-2), 21.5 (C-7), 14.2 (OCH_2CH_3); HRMS (ESI): $[M+H]^+$, 427.2236; $C_{24}H_{31}N_2O_5$ requires 427.2233.
18. The molecule of **19** selected from the racemate by the X-ray analyst had absolute stereochemistry opposite to that depicted in the preceding schemes. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 737199. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. Attempts to test this model with the less sterically demanding methoxycarbonyl-carbonyl-protected analogue of **8** were complicated by the instability of this group to the cyclization conditions. Nevertheless, the methoxycarbonyl-protected analogue of *cis*-**6** could be isolated as the major product in 53% yield.
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