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An expedient synthesis of 7(*S*)-ethyl-8(*R* or *S*)-indolizidinols based on a thiophene reductive desulfurization

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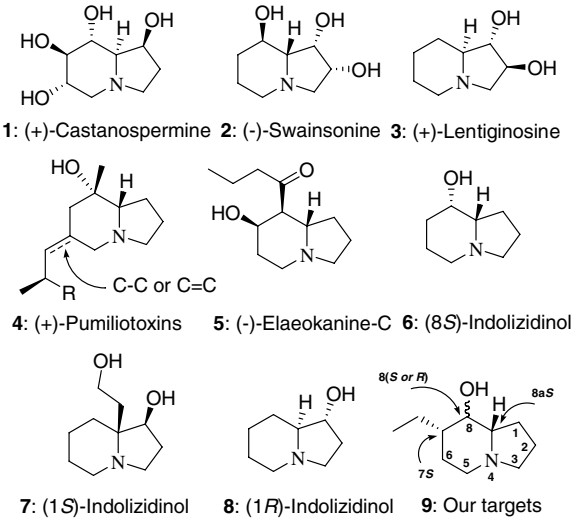
Abstract—Chiral hexahydrothieno[2,3-*f*]indolizine-4,7-dione (*S*)-**12** and the ancillary alcohol **13** were generated from thiophene-2-carboxaldehyde and (*S*)-glutamic acid in three and four steps, respectively, in good overall yields and both high enantio- and diastereomeric purities. Applying a thiophene reductive desulfurization, compound **12** was readily converted into 7(*S*)-ethyl-8(*S*)-indolizidinol **9**. The 8(*R*)-epimer of **9** was advantageously obtained using the Mitsunobu alcohol inversion or, starting from **13**, by chemical separation after O-benzylation and lactam reduction. During these studies, the reduction of regioisomers of **12** and **13**, namely **17** and **18**, was investigated and the results obtained are also discussed.

1. Introduction

Polyhydroxylated indolizidines alkaloids are excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins, potent glycosidase inhibitory activities,[1] activity against AIDS virus HIV and some carcinogenic cells as well as against other important pathologies.[2] In this line, castanospermine[3] (**1**), swainsonine[4] (**2**) and lentiginosine[5] (**3**) have shown respective glycosidase, mannosidase and amyloglycosidase inhibitory activities, respectively (see representative structures in Scheme 1).

While an impressive number of total syntheses of tetrahydroxylated, trihydroxylated and dihydroxylated indolizidines and their non-natural analogues in chiral or racemic forms have been reported, the mono hydroxylated indolizidines have attracted far less attention. These latter unique structures are exemplified by pumiliotoxins of type **4** as strong neurotoxins,[6] (−)-elaeokanine-C (**5**),[7]



Scheme 1. Representative indolizidines alkaloids **1**–**8** and our targets **9**.

the synthetic enantiopure (8*S*,8a*S*)-perhydro-8-indolizidinol (**6**),[8] the C_{8a} hydroxyethyl-substituted indolizidine (**7**)[9] and finally the (1*R*,8a*S*)-1-indolizidinol (**8**).[10] Whereas indolizidinols **5**–**7** have not revealed any significant biological activity yet, (1*R*,8a*S*)-1-indolizidinol (**8**)

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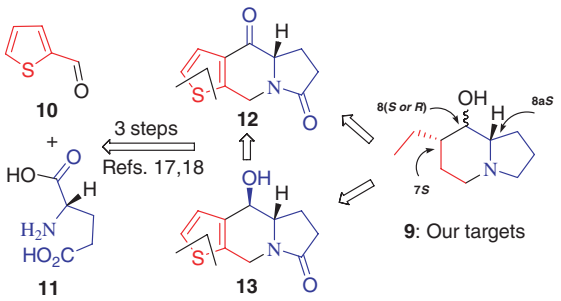
has, interestingly, been postulated as the biosynthetic congener of (−)-epilentiginosine (−)-**3** and as a metabolite of the fungus *Rhizoctonia leguminicola*,[11] the locoweeds *Astragalus oxyphysus*[12] and *A. lentiginosus*[13] (Scheme 1).

In this sense, considerable efforts are continuously underway towards their synthesis and that of their stereoisomers and analogues. In other respects, some structural modifications of (−)-swainsonine (**2**) have recently been made and their pharmacological influence studied by Pearson's group and by Nagasawa and co-workers. During these studies, the incorporation for the first time of an hydroxymethyl, an arylalkyl-hydroxymethyl and a carbohydrate residue at the C_3 position[14] resulted in an increase of the α-manosidase activity compared to that exhibited by swainsonine itself, whereas the introduction of 6- or 7-ethyl and benzyloxyethyl-substituents in either equatorial and axial orientations resulted in a loss of activity.[15] During another exploration towards greater diversity, some new 5α-substituted swainsonine analogues were prepared and, in contrast to Pearson's 6- and 7-substituted analogues, were found to be more potent α-mannosidase inhibitors than swainsonine.[16]

Because there are few strategies amenable to these alkylated indolizidinols, and regarding their interesting biological profiles and potential as valuable candidates for novel therapeutic agents,[15–17] the development of new and straightforward routes for their production is therefore quite desirable. In this preliminary report, an expedient synthesis of prototypic alkyl substituted indolizidinols, namely 7-ethyl and 6-ethyl-8-indolizidinols, is described. This original chiron approach used a key step that creates the linkages between the C_7/ethyl group and the C_8/OH function of the bicyclic targets **9** in a quite uncommon manner, as illustrated in the disconnections depicted in Scheme 2.

Within our interest in the synthesis of fused azacyclic systems we have previously reported diverse indolizidines annulated to thiophene,[17,18] benzothiophene,[18,19] both benzene and thiophene,[20] and furan,[21] rings using the above strategy (Scheme 2). In connection with this work, we now selected optically active hexahydrothieno[2,3-*f*]indolizine-4,7-dione ((*S*)-**12**)[22] and the ancillary alcohol **13** as key templates for further elaborations directed towards the targeted compounds. These key intermediates were reported recently by us with high optical activity (>99% ee) by using the well known Friedel–Crafts type cyclization and stereospecific sodium borohydride reduction (Scheme 2).[17,18] Ultimately, the thiophene ring of compounds **12**–**13** could serve advantageously the role of reservoir for the ethyl substituent at position 7 of the indolizidine ring by means of the well established reductive desulfurization protocol. The potential utility of this technique is aptly illustrated in the literature with numerous examples given in different fields of organic chemistry, notably including the field of stereoselective total synthesis.[23,24]



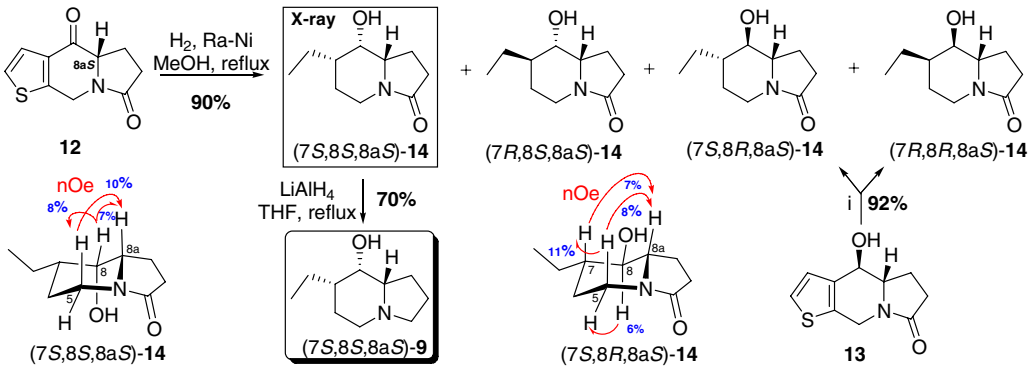
Scheme 2. Retrosynthetic scheme leading to the indolizidine targets **9**.

The requisite ketone skeleton **12** could be obtained in very good yield and in a large scale (up to 10 g) in a three step-sequence from the commercially available thiophene-2-carboxaldehyde (**10**) and (*S*)-glutamic acid (**11**) (overall yield of 55%). With large quantities of this material in hand, the present study started with the Raney-nickel hydrogenolysis of its thiophene ring (Scheme 3). The best experimental protocol turned out to be the contact of (*S*)-**12** with activated Ra-Ni in anhydrous methanol under stirring and 1 atm of hydrogen at reflux for 24 h. As might be expected, the four possible diastereomers of **14** were formed in a 68:12:10:10 ratio,[25] albeit in very good yield (90%). Repetition of the reaction gave the same stereomeric distribution; unfortunately, all attempts to separate this mixture failed. However, treating the crude mixture with dry acetone provided more satisfactory results, with the major stereoisomer crystallizing from the mixture in a synthetically useful yield of 52%. Further recrystallization from acetone upgraded the purity of this compound, the structure of which was unequivocally identified as (7*S*,8*S*,8a*S*)-**14** by means of ^{1}H and ^{13}C NMR spectroscopy and single X-ray crystallography (Fig. 1).[26] In line with other results in the furan series,[27] this result highlights the stereo-complementarity between the $NaBH_4$ and the hydrogenation reduction modes.

Finally the synthesis of the targeted indolizidinol (7*S*,8*S*,8a*S*)-**9** was completed with LAH reduction of the lactam (7*S*,8*S*,8a*S*)-**14** in refluxing THF according to Greene's protocol.[10a] The reduction occurred cleanly within 4 h to afford the title compound 7(*S*)-ethyl-8(*S*)-indolizidinol **9** in 70% yield.[28]

In stark contrast to some literature reports claiming the robustness of the ketone function to various desulfurizing agents including Ra-Ni,[29] it is worth noting that the reductive cleavage of the thiophene ring of compound **12** was accompanied by that of the ketone function. At this stage, the question of both reduction kinetics and the order by which the two transformations proceeded, arose. In order to learn more about that point, and to further examine the possible influence of the C_8-substituent on the stereochemical course of the thiophene reductive cleavage, a set of additional experiments were conducted.

First, the enantiopure alcohol **13** was subjected to the same protocol used for its ketone precursor **12**. Interestingly, a non-separable mixture of (7*S*,8*R*,8a*S*)-**14** and (7*R*,8*R*,8a*S*)-**14** was obtained in a 78:22 ratio (92%



Scheme 3. Synthetic route to the 7(*S*)-ethyl-8(*S*)-indolizidinol target (7*S*,8*S*,8a*S*)-**9**. The four possible diastereomers (7*S*,8*S*,8a*S*)-**14**, (7*R*,8*S*,8a*S*)-**14**, (7*S*,8*R*,8a*S*)-**14** and (7*R*,8*R*,8a*S*)-**14** were obtained in a 68:12:10:10 ratio determined by NMR essays as well as X-ray analysis of (7*S*,8*S*,8a*S*)-**14**. Selected NOEs for the determination of relative configuration in the 7-ethylindolizidinols **14** were established by 1D-NOE ^{1}H NMR experiments.

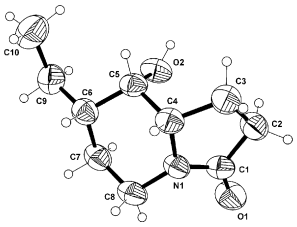
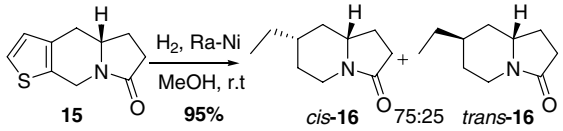


Figure 1. ORTEP drawing of indolizinone (7*S*,8*S*,8a*S*)-**14**. Thermal ellipsoids at 30% probability level.



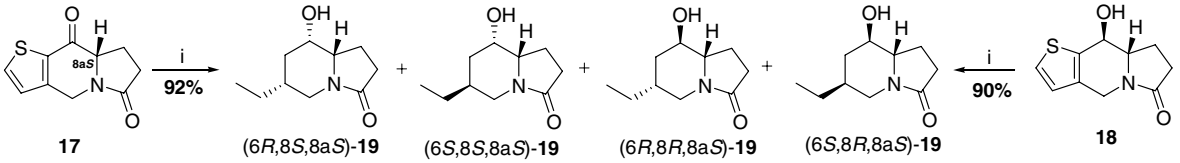
Scheme 4. Raney-nickel reduction of hexahydrothienoindolizinone **15**.

yield).[30] A parallel experiment was carried out starting from the C_8-deoxy analogue as **15** (Scheme 4), easily obtained from alcohol **13** as previously reported.[21b] An oily mixture of inseparable stereoisomers, surprisingly favouring the cis-isomer (the cis:trans ratio of **16** was determined as 75:25 by using NOE measurements),[30] resulted in an excellent 95% yield.

From this first set of results, it clearly appeared that the thiophene reductive cleavages of **12**, **13** and **15** occurred in a stereoselective manner with, quite interestingly, similar stereomeric distributions with respect to the stereogenicity at carbon C_7 ($S/R \sim 80/20$) regardless of the substitution pattern at carbon C_8 (=O; H,OH: Scheme 3, H,H: Scheme 4). These results strongly point out that inherent stereocontrol exerted by the vicinity at C_8 during the thiophene reductive cleavage poorly contributes to the observed stereoselectivities, which, therefore, would be better interpreted in terms of a uniform preferential hydrogen approach from the *exo* (convex) face of the thienoindolizinone tricyclic skeleton, in line with our earlier report in the furan series.[21b] Moreover, the discrepancy outlined in Scheme 3 in the ratios (7*S*,8*R*,8a*S*)-**14**/(7*R*,8*R*,8a*S*)-**14** starting from either **12** (50:50 ratio) or **13** (78:22 ratio) strongly supports a thiophene opening-first pathway, since a ketone reduction-first pathway of compound **12** should probably have led to an 80:20 ratio.

To complete this study, we have also investigated the reduction of the regioisomeric ketone **17** and its hydroxyl derivative **18**, readily available from thiophene-3-carboxaldehyde, with the expectation of providing a rapid entry to 6-ethylindolizidin-8-ols. Thus, treatment of **17** under the well established reductive-desulfurization protocol led to an oily mixture of three inseparable diastereomers in a 24:69:7 ratio favouring product (6*S*,8*S*,8a*S*)-**19** (see Scheme and results in Table 1). The structures of these isomers, respectively (6*R*,8*S*,8a*S*)-**19**, (6*S*,8*S*,8a*S*)-**19** and (6*S*,8*R*,8a*S*)-**19**, were

Table 1. Results of the reductive desulfurization reaction[a] of ketone **17** and corresponding alcohol **18**[b]



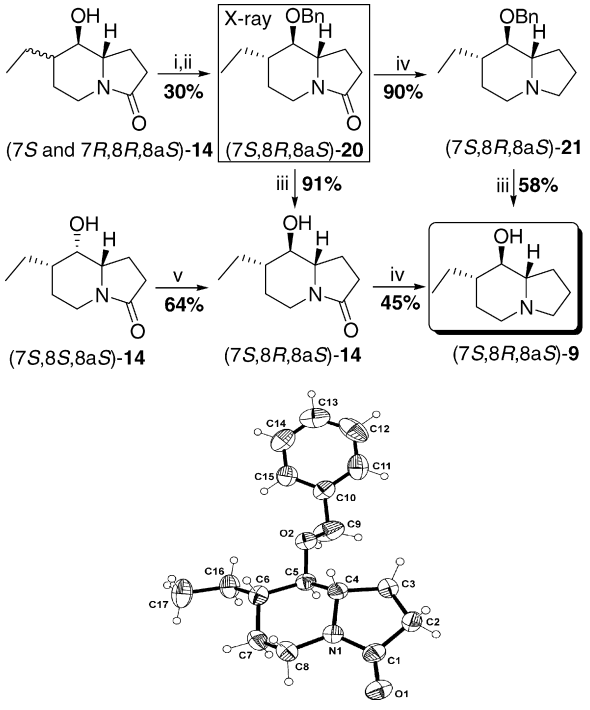
Starting material: ketone **17**	24	69	0	7	Yield: 92%
Starting material: alcohol **18**	b	b	77	23	Yield: 90%

[a] (i) Ra-Ni, MeOH, reflux.

[b] Only two possible diastereomers (6*R*,8*R*,8a*S*)-**19** and (6*S*,8*R*,8a*S*)-**19** were obtained in a 77:23 ratio. The diastereomers (6*R*,8*S*,8a*S*)-**19** and (6*S*,8*S*,8a*S*)-**19** could not obtained from the alcohol **18**.

unequivocally identified by NMR spectroscopy (Table 1) including notably NOE measurements. This experiment revealed a dr similar as above regarding the orientation of the ethyl group but, importantly, the sense of hydride delivery was reversed (down/up ethyl–C_6 24:76, Table 1 vs up/down ethyl–C_7 78:22 starting from ketone **12**, Scheme 3). Otherwise reductive-desulfurization of alcohol **18** produced the two possible diastereomers (6*R*,8*R*,8a*S*)-**19** and (6*S*,8*R*,8a*S*)-**19** with restoration of the usual sense '*exo*-approach' and level '77:23 ratio' of stereo-induction. Though the literature is rather unclear regarding the stereoselectivity of hydrogenation, it is nevertheless general that addition of hydrogen occurs from the less hindered face of the double bond of the thiophene ring. However, the discrepancies of certain results observed herein during notably the reduction of ketones **12** and **17** could be ascribed to the so called haptophilic effect which causes H_2 to be added from the same side as a polar substituent such as an hydroxyl group.[31]

We next directed our attention towards accessing the C_8-epimer of indolizidinol **9** referred to as (7*S*,8*R*,8a*S*)-**9**. In a first sequence, alcohol (7*S*,8*S*,8a*S*)-**14** isolated above was efficiently converted into the expected alcohol-lactam (7*S*,8*R*,8a*S*)-**14**[32] in 64% yield by a one pot two-step Mitsunobu inversion/saponification sequence.[33] The target (7*S*,8*R*,8a*S*)-**9** was finally reached in 45% yield by repeating a LAH reduction protocol (Scheme 5). Alternatively, (7*S*,8*R*,8a*S*)-**9** was also obtained in four steps from the 78:22 mixture of 7(*S* and *R*)-ethyl-8(*R*)-hydroxyindolizin-3-ones **14** prepared from alcohol **13** (see Scheme 3). Thus, O-benzylation of the stereomeric mixture using standard conditions led to the expected products which, furnished by simple deposition in hexane, the major benzylated product in pure form as a white solid in 30% yield. Its structure was identified as (7*S*,8*R*,8a*S*)-**20** by spectroscopic means and crystallographic analysis.[26,34] Finally, the latter product **20** was efficiently converted into the target indolizidinol (7*S*,8*R*,8a*S*)-**9** using a debenzylation-lactam reduction route or the inverted sequence in 41% and 52% yields via alcohol-lactam (7*S*,8*R*,8a*S*)-**14** or ether (7*S*,8*R*,8a*S*)-**21**, respectively.



Scheme 5. Scheme leading to 7(*S*)-ethyl-8(*R*)-indolizidinol (7*S*,8*R*,8a*S*)-**9** and the ORTEP plot (thermal ellipsoids at 30% probability level) of its congener 8-benzyloxyindolizidinone (7*S*,8*R*,8a*S*)-**20**. Reagents and conditions: (i) NaH, BnBr, DMF, 40–50 °C, 24 h; (ii) hexane, separation of diastereomers; (iii) H_2, 10% Pd/C, MeOH, 12 h; (iv) LAH, THF, reflux, 4 h and (v) $PhCO_2H$, DEAD, PPh_3, toluene, rt, 1 h then K_2CO_3, MeOH, THF, 1 h.

2. Conclusion

In this letter, we have successfully introduced a new and expedient synthetic entry to 7(*S*)-ethyl-8(*R* or *S*)-indolizidinol alkaloid cores **9** in five- and eight steps and overall yields of 20% or 8%, respectively. Our uncommon strategy uses as key step a reductive desulfurization of the thiophene ring with a Raney-nickel reductant in which the thiophene constitutes an original alkyl source. The targets (7*S*,8*S*,8a*S*)-**9** and (7*S*,8*R*,8a*S*)-**9** were obtained ultimately by lactam reduction or by a configurational alcohol inversion with Mitsunobu reaction followed by lactam reduction, respectively. In the latter case, a chemical separation via an easy O-benzylation reaction, lactam reduction and debenzylation were also advantageously used.

Finally, thanks to the mild experimental conditions and to the cheap and modular chiral source and thiophene aldehydes, this method is probably the most straightforward for the synthesis of indolizidinols bearing an alkyl group at C_6 or C_7 positions. In addition, it is shorter and more direct than the rarely available but longer methods starting from enantiopure lactones[15a] or α,β-unsaturated δ-lactams[15b] both derived from sugars. Consequently, this route opens the way to the design and synthesis of a wide variety of novel polyhydroxylated indolizidine alkaloids comprising of different substituents and stereochemistry with promising pharmacological profiles.

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25. (a) Composition of 7-ethyl-8-hydroxyindolizidinones **14** was determined by HPLC analysis of the crude reaction mixture and ^{1}H NMR essays. (b) Spectroscopic data of (7*S*,8*S*,8a*S*)-*7-ethyl-8-hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizin-3-one* (**14**). Activated Raney-nickel (9.00 g) was added to a solution of thienoindolizidinedione **12** (1.00 g, 4.8 mmol) in anhydrous methanol (20 mL) and the mixture was stirred at reflux under hydrogen (1 atm) for 24 h. The solution was filtered through a Celite pad to remove the catalyst. After concentration in vacuo, the crude product was treated with acetone (10 mL). The resulting precipitate of **14** was filtered and recrystallized from acetone. Yield: 52% (0.46 g), mp 123–127 °C; $[\alpha]_D$ −1.6 (*c* 1, EtOH); IR (ν, cm^{-1}, KBr): 3291, 2961, 2989, 1655, 1643 (C=O), 1471, 1457; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.95 (t, 3H, CH_3, $J = 7.2$ Hz), 1.38 (qd, 1H, H-6, $J = 2.9$ and 12.8 Hz), 1.42–1.52 (m, 4H, 2 × H-9, H-6 and H-7), 2.03 (dddd, 1H, H-1peq, $J = 5.7$, 8.8, 10.6 and 13.7 Hz), 2.14 (tdd, 1H, H-1pax, $J = 5.0$, 11.0 and 12.9 Hz), 2.31 (br s, 1H, OH), 2.33 (dddd, 1 H, H-2pax, $J = 1.2$, 6.5, 10.6 and 16.7 Hz), 2.45 (ddd, 1H, H-2peq, $J = 5.6$, 10.6 and 16.7 Hz), 2.66 (t, 1H, H-5ax, $J = 11.8$ Hz), 3.53 (ddd, 1H, H-8a, $J = 1.4$, 5.3 and 8.5 Hz), 3.61 (s, 1H, H-8), 4.11

(dd, 1H, H-5eq, $J = 4.2$ and 12.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4 (C-10), 19.3 (C-1), 23.9 (C-6), 25.2 (C-9), 30.6 (C-2), 39.6 (C-5), 42.3 (C-7), 61.8 (C-8a), 68.7 (C-8), 174.7 (C-3); MS (*m*/*z*, (%)): 183 (M^+, 59), 166 (18), 155 (10), 154 (20), 112 (15), 98 (100), 97 (11), 86 (75). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25) C, 65.54; H, 9.35; N, 7.64. Found C, 65.42; H, 9.15; N, 7.49.

26. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC references numbers 614535 and 614534 for products (7*S*,8*S*,8a*S*)-**14** and (7*S*,8*R*,8a*S*)-**20**), respectively. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk.
27. While the $NaBH_4$ reduction of furanic keto amide analogue to **12** furnishes the OH at C8- with a (*R*) stereogenicity as single isomer, [21a] hydrogenation over an appropriate catalyst led to the formation of the 8*S* epimer in good stereoselectivity (manuscript under preparation).
28. *(7S,8S,8aS)-7-Ethyl-1,2,3,5,6,7,8,8a-octahydroindolizin-8-ol* (**9**). Mp 38–40 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.09–1.23 (m, 1H, H-7), 1.29 (dq, 1H, H-9, $J = 7.1$ and 13.8 Hz), 1.38–1.53 (m, 3H, 2 × H-6 and H-9), 1.60–1.76 (m, 3H, 2 × H-2 and H-1), 1.77–1.88 (m, 1H, H-1), 1.95 (t, 1H, H-8a, $J = 10.8$ Hz), 1.97 (t, 1H, H-5ax, $J = 10.8$ Hz), 2.07 (q, 1H, H-3pax, $J = 8.9$ Hz), 2.28 (br s, 1H, OH), 2.95–2.99 (m, 1H, H-3peq), 3.00–3.04 (m, 1H, H-5eq), 3.51 (s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5 (C-10), 21.4 (C-2), 25.0 (C-1), 25.1 (C-9), 26.3 (C-6), 43.1 (C-7), 52.4 (C-5), 54.2 (C-3), 67.4 (C-8), 68.3 (C-8a). Anal. Calcd for $C_{10}H_{19}NO$ (169.27): C, 70.96; H, 11.31; N, 8.27. Found: C, 70.79; H, 11.23; N, 8.18.
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30. The stereochemistries of **14** were determined on the basis of both the X-ray analysis of (7*S*,8*S*,8a*S*)-**14** and their NMR study obtained separately from ketone **12** and alcohol **13**, respectively. The ratio of lactams **16** *cis* and *trans* was determined by using NOE measurements.
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32. *(7S,8R,8aS)-7-Ethyl-8-hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizin-3-one* (**14**). This product was isolated as a colourless oil; $[\alpha]_D$ −59.1 (*c* 1, EtOH); IR (*v*, cm^{-1}, KBr): 3379 (OH), 2962, 2874, 1666 (C=O), 1460, 1423, 1269, 1133, 1072, 882; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3, $J = 7.4$ Hz), 1.09 (dq, 1H, H-6, $J = 5.0$ and 13.0 Hz), 1.18 (qdd, 1H, H-9, $J = 7.4$, 7.8 and 13.9 Hz), 1.37 (ttd, 1H, H-7, $J = 3.3$, 9.3 and 12.5 Hz), 1.81–1.85 (m, 1H, H-1), 1.86 (dd, 1H, H-6, $J = 1.3$ and 13.4 Hz), 1.88 (dqd, 1H, H-9, $J = 3.2$, 7.6 and 13.4 Hz), 2.33 (tdd, 1H, H-1, $J = 6.8$, 12.2 and 13.8 Hz), 2.39 (dd, 2H, 2 × H-2, $J = 7.6$ and 9.0 Hz), 2.62 (dt, 1H, H-5ax, $J = 3.3$ and 13.2 Hz), 2.91 (t, 1H, H-8, $J = 9.5$ Hz), 3.06 (br s, 1H, OH), 3.23 (ddd, 1H, H-8a, $J = 6.4$, 7.6 and 8.9 Hz), 4.06 (ddd, 1H, H-5eq, $J = 1.7$, 5.0 and 13.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.6 (C-10), 22.5, 23.6 (C-1 and C-9), 28.0 (C-6), 30.3 (C-2), 39.3 (C-5), 44.1 (C-7), 62.3 (C-8a), 76.5 (C-8), 173.8 (C-3); MS (*m*/*z*, (%)): 184 (12), 183 (43), 168 (5), 166 (17), 155 (17), 154 (18), 126 (9), 112 (16), 111 (5), 99 (73), 98 (100), 86 (32), 84 (20), 83 (12). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25) C, 65.54; H, 9.35; N, 7.64. Found C, 65.42; H, 9.15; N, 7.49.
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34. *(7S,8R,8aS)-8-Benzyloxy-7-ethyl-1,2,3,5,6,7,8,8a-octahydroindolizin-3-one* (**20**). This product was isolated as a white solid; mp 82–85 °C (acetone); $[\alpha]_D$ −68.8 (*c* 1, EtOH); IR (*v*, cm^{-1}, KBr): 3032, 2975, 2922, 2964, 1681 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3, $J = 7.5$ Hz), 1.10 (dq, 1H, H-6, $J = 4.8$ and 12.9 Hz), 1.22 (qdd, 1H, H-9, $J = 7.4$, 7.8 and 13.8 Hz), 1.47–1.54 (m, 1H, H-7), 1.74–1.83 (m, 1H, H-1), 1.85 (dd, 1H, H-6, $J = 1.3$ and 13.4 Hz), 1.94 (dqd, 1H, H-9, $J = 3.2$, 7.6 and 13.7 Hz), 2.29–2.40 (m, 3H, 2 × H-2 and H-1), 2.57 (dt, 1H, H-5ax, $J = 2.9$ and 13.0 Hz), 2.84 (t, 1H, H-8, $J = 9.6$ Hz), 3.36 (td, 1H, H-8a, $J = 7.2$ and 8.4 Hz), 4.06 (dd, 1H, H-5eq, $J = 3.7$ and 13.2 Hz), 4.66 (s, 2H, OCH_2), 7.25–7.40 (m, 5H, H-arom.); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.8 (C-10), 24.0, 24.1 (C-1 and C-9), 28.0 (C-6), 30.6 (C-2), 39.3 (C-5), 43.8 (C-7), 61.5 (C-8a), 74.6 (OCH_2), 85.3 (C-8), 127.8, 128.0, 128.5, 138.1 (C-arom), 173.7 (C-3); MS (*m*/*z*, (%)): 273 (M^+, 15), 183 (15), 182 (100), 167 (25), 99 (68), 98 (48), 91 (88), 84 (23). Anal. Calcd for $C_{17}H_{23}NO_2$ (273.38) C, 74.69; H, 8.48; N, 5.12. Found C, 74.51; H, 8.39; N, 5.01.