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A sort synthesis of polyhydroxylated pyrrolizidines via sequential 1,3-dipolar cycloaddition and reductive amination

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ABSTRACT

Polyhydroxylated pyrrolizidines bearing a methyl group at C-5 have been synthesized by 1,3-dipolar cycloaddition of five membered cyclic nitrones with methyl vinyl ketone followed by a N–O reductive cleavage and in situ intramolecular reductive amination. The stereochemistry of the obtained compounds is examined in relation to the reactions mechanism.

1. Introduction

Polyhydroxylated pyrrolizidines belong to an important class of alkaloids that display a wide range of biological activities mainly due to their action as specific glycosidase inhibitors.[1] Most of the naturally occurring polyhydroxylated pyrrolizidines possess a further hydroxymethyl group and representative alkaloids of this type, such as alexine, australine, casuarine and hyacinthacine (Fig. 1), have gained considerable interest as antiviral and anticancer agents.[2] Since the biological activity varies substantially with the number, the position and the stereochemistry of the hydroxy groups on the pyrrolizine skeleton, the synthesis of both naturally occurring compounds and their stereoisomers and analogues has received much attention.[3]

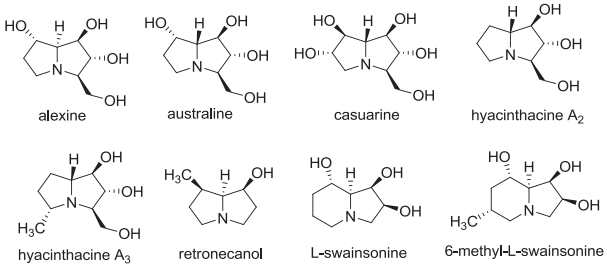
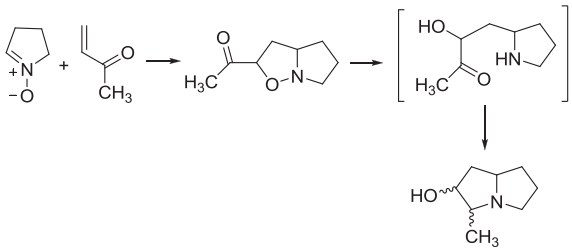


Fig. 1. Representative members of pyrrolizidine and indolizidine alkaloids.

A methyl group occurs also in many polyhydroxylated alkaloids as iminoaldilols, pyrrolizidines of hyacinthacine and necine families and indolizines.[1a,2b,4] In particular, the introduction of a methyl group at C-6 in L-swansonine increases its naringinase inhibition.[4]

In connection with our previous studies[5] on the synthesis of azasugars, we present in this paper a short and stereoselective synthesis of new polyhydroxylated pyrrolizidines bearing a methyl group at C-5. For this purpose we have planned a short reaction scheme comprised of 1,3-dipolar cycloaddition of five membered cyclic nitrones with methyl vinyl ketone followed by a N–O reductive cleavage and in situ intramolecular reductive amination to give pyrrolizidines (Scheme 1).



Scheme 1. General reaction scheme.

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The 1,3-dipolar cycloaddition of nitrones to alkenes and subsequent reductive cleavage is a well documented pathway for the formation of the pyrrolidine ring in many reaction schemes.[6] In most cases acrylates or allyl alcohol derivatives are chosen as alkenes and after the reductive cleavage of the N–O bond the cyclization to the pyrrolidine ring takes place through a nucleophilic attack by the amino group on the ester carbonyl or the activated hydroxymethyl group. Although the use of α,β-unsaturated ketones or aldehydes as dipolarophiles may offer a convenient alternative way for the formation of the pyrrolidine following an analogous methodology, to the best of our knowledge, has not received considerable attention with exception of a few cases.[7]

2. Results and discussion

For our study we chose the racemic protected *cis*-dihydroxy nitrone **1** and the enantiomerically pure nitrones **2**–**4** (Fig. 2). All these compounds were prepared from inexpensive starting materials applying previously described procedures with small modifications. In particular nitrone **1**[8a,b] and nitrone **4**[8e,f] were prepared from D-ribose, nitrone **2**[8c] from L-tartaric acid, and nitrone **3**[8d] from D-arabinose. The choice of these nitrones would permit to study the influence of the substituents geometry on both cycloaddition and reductive amination steps. Furthermore, the use of nitrones **3** and **4** bearing a 3,4-dihydroxy-5-hydroxymethyl substitution pattern will lead to hyacinthacine analogues.

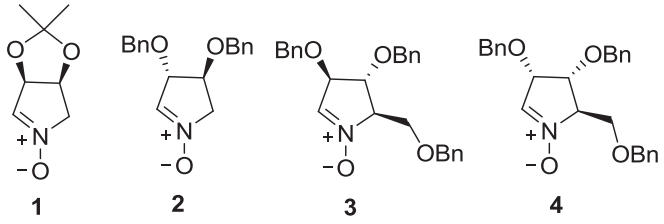
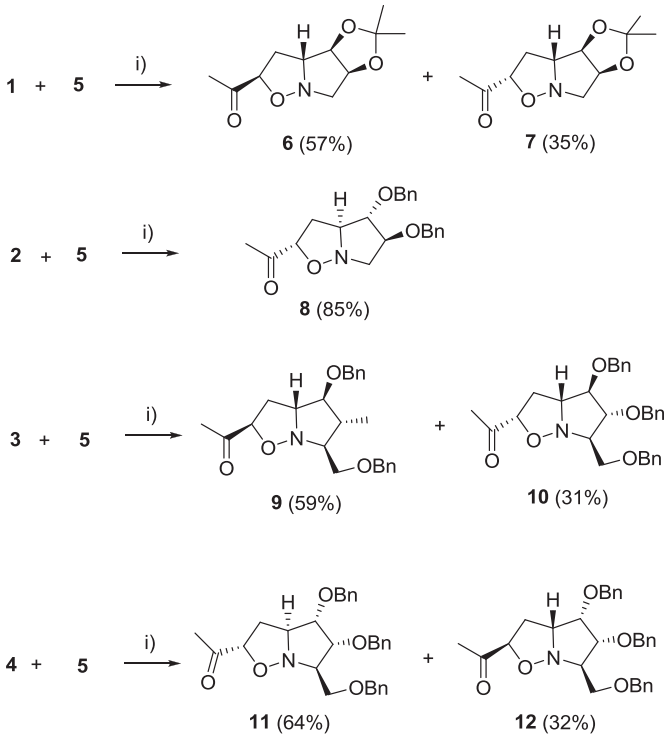


Fig. 2. Applied nitrones.

The cycloaddition reaction of the nitrones **1**–**4** with methyl vinyl ketone **5** took place under mild conditions (reflux in dichloromethane solution for 2 days) affording the expected cycloadducts in high yields. The reactions showed absolute regioselectivity and high stereoselectivity and among the eight possible isomers gave only isomers bearing the acetyl moiety at the 5-position of the isoxazolidine ring, two diastereoisomers in the case of nitrones **1**, **3** and **4** and one diastereoisomer in the case of nitrone **2** (Scheme 2). In particular, nitrone **1** gave the two cycloadducts **6** and **7** in a ratio 1.6:1 and 92% total yield. Cycloadducts **6** and **7** come from *exo*-anti and *endo*-anti transition states, respectively as a result of the tendency of the nitrone **1** to react from its less hindered face. The reaction of nitrone **2** was highly selective and afforded as sole product in 85% yield the isoxazolidine **8**, which comes from an *exo*-anti (relative the C-3 nitrone substituent) transition state. Nitrone **3** reacted also from its less hindered *Re*-face to give in a ratio 1.9:1 and 90% total yield cycloadducts **9** and **10** coming from *exo*-anti and *endo*-anti transition states, respectively. Nitrone **4** showed a lower face selectivity and gave in a ratio 2:1and 96% total yield cycloadducts **11** and **12** resulting from *exo*-anti and *exo*-syn transition states, respectively. The spectra data of the obtained cycloadducts are in accordance with the proposed structures.



Scheme 2. Reagents and conditions: i) CH_2Cl_2, reflux, 48 h.

The stereochemical assignment of the obtained cycloadducts was based mainly on NOE measurements performed either on the initial cycloadducts or on the sequential reductive amination products. In all cases the proton assignment was made by H,H, Cosy spectra. In Fig. 3 are given the observed crucial NOE enhancements, which strongly support the proposed stereochemistry for structures **7**–**11**. The stereochemistry of compound **6** the main product of the reaction with nitrone **1** was not possible to rely on NOE measurements due to the overlapping of the crucial for the structure determination protons. However, it was proved in its reduction products **13** and **14** as described below. Concerning the compound **12**, the minor product of the reaction with nitrone **4**, although NOE measurements are not so obvious due to the overlaps, offer considerable evidence. Thus the 3-H^1 is overlapped with methyl protons (δ 2.12–2.28), the 2-H with the methylene benzyl protons (δ 2.12–2.28), whereas 3a-H and 3-H^2 appear as separate peaks at δ 3.83 and 2.69, respectively. Saturation of 3a-H increases the intensity of the multiplet including 3-H^1 and not 3-H^2. Also saturation of 3-H^2 increases the intensity of the multiplet including 2-H and not 3a-H. These measurements show that 2-H is *cis* to the one of the two 3-H and 3a-H is *cis* to other one. So 2-H and 3a-H are in *trans*-disposition. This disposition is possible to the diastereoisomers that come from an *exo*-transition state. Since the structure from an *exo*-anti transition state was ascribed to the major cycloadduct **11**, the minor cycloadduct should have structure **12** from an *exo*-syn transition state.

The reductive cleavage of the N–O bond and the subsequent reductive amination of the obtained cycloadducts was carried out in one stage by hydrogenolysis over Pd/C catalyst at room temperature. Under these conditions the protective benzyl groups were not removed. For the cycloadducts **6**–**8** this procedure was not stereoselective and they gave both the expected isomers. Thus compound **6** gave the two pyrrolizidines **13** and **14** in a ratio 1.15:1 and 92% total yield, compound **7** the pyrrolizidines **15** and **16** in

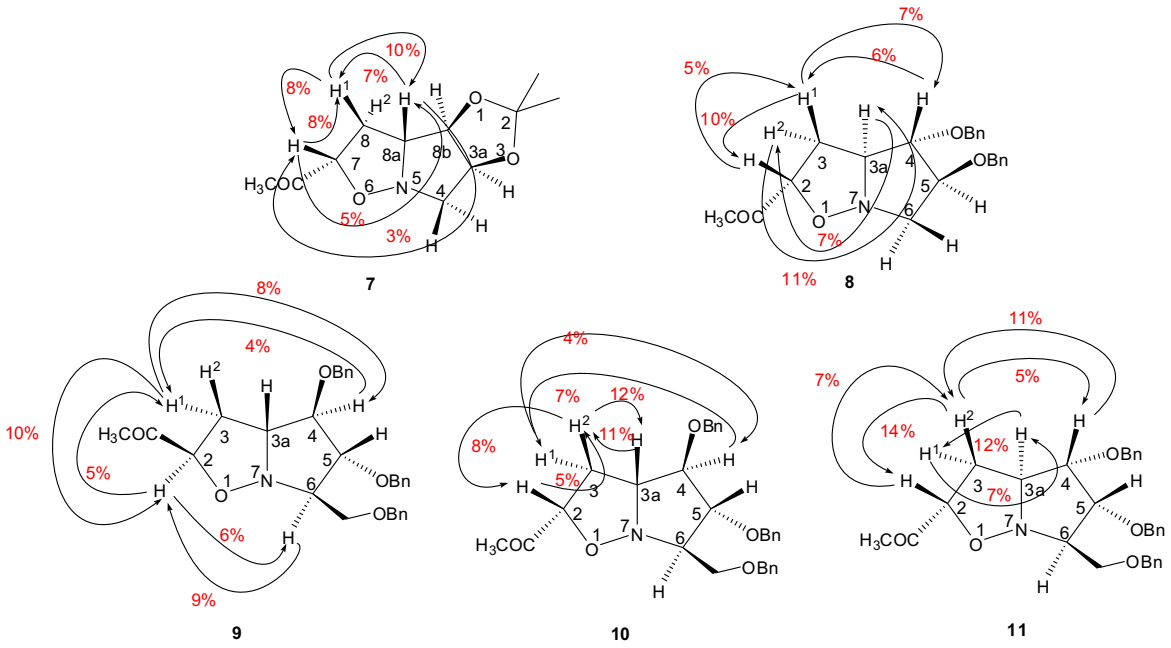
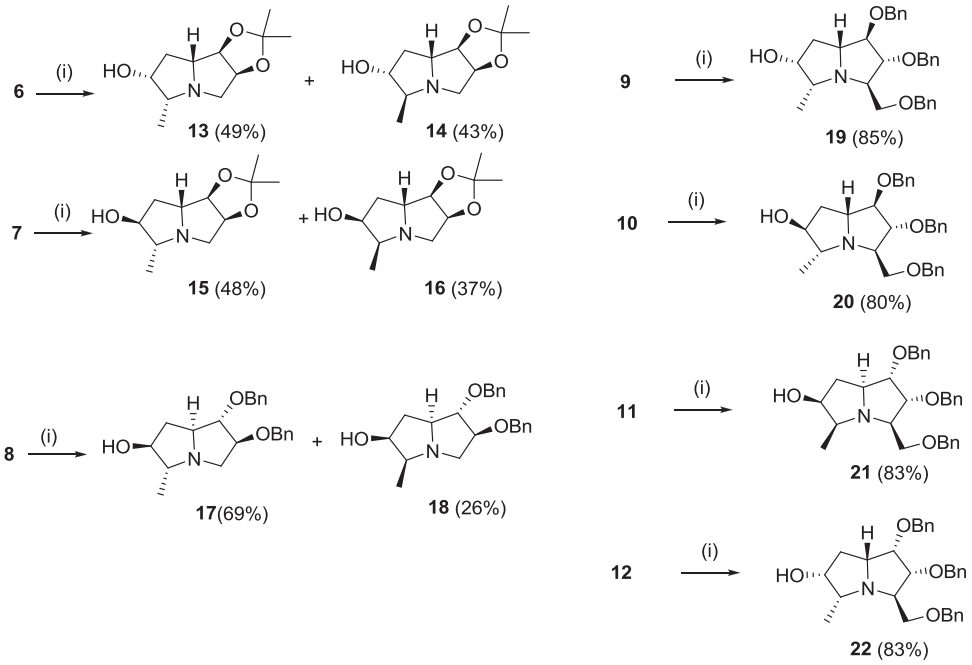


Fig. 3. NOE enhancements measured in compounds **7**–**11**.

a ratio 1.3:1 and 85% total yield and compound **8** the pyrrolizidines **17** and **18** in a ratio 1:2.7 and 95% total yield. On the contrary, the reductive amination of compounds **9**–**12** bearing a benzyloxymethyl group at the 6-position showed high stereoselectivity and gave only one of the possible two stereoisomers in 80–85% yields (Scheme 3). The spectra data of the obtained pyrrolizidines are in accordance with the proposed structures The stereochemical assignment was based on NOE measurements as depicted in Fig. 4. Due to the overlapping of the peaks informative NOE measurements were not possible in compounds **15**, **18** and **22**. The proposed stereochemistry of compounds **15** and **18** relies on the stereochemical assignment of their isomers **16** and **17**, respectively, whereas stereo structure of compound **22** is tentatively proposed in analogy with the other benzyloxymethyl derivatives.

The obtained results offer considerable evidence for the mechanism of the reaction. Reductive N–O cleavage of compounds A leads to the formation of the intermediate amino alcohols B, which are transformed to the bicyclic intermediates C via a nucleophilic attack of the NH group to the carbonyl bond. Intermediate C can be further transformed to the pyrrolizidines F via an iminium intermediate D or enamine E. Involvement of an enamine intermediate E should result in the lost of the stereogenic centre at the carbon bearing the hydroxyl group. The configuration of this



Scheme 3. Reagents and conditions: i) Pd/C, H_2, atm pressure, CH_3OH, rt, 48 h.

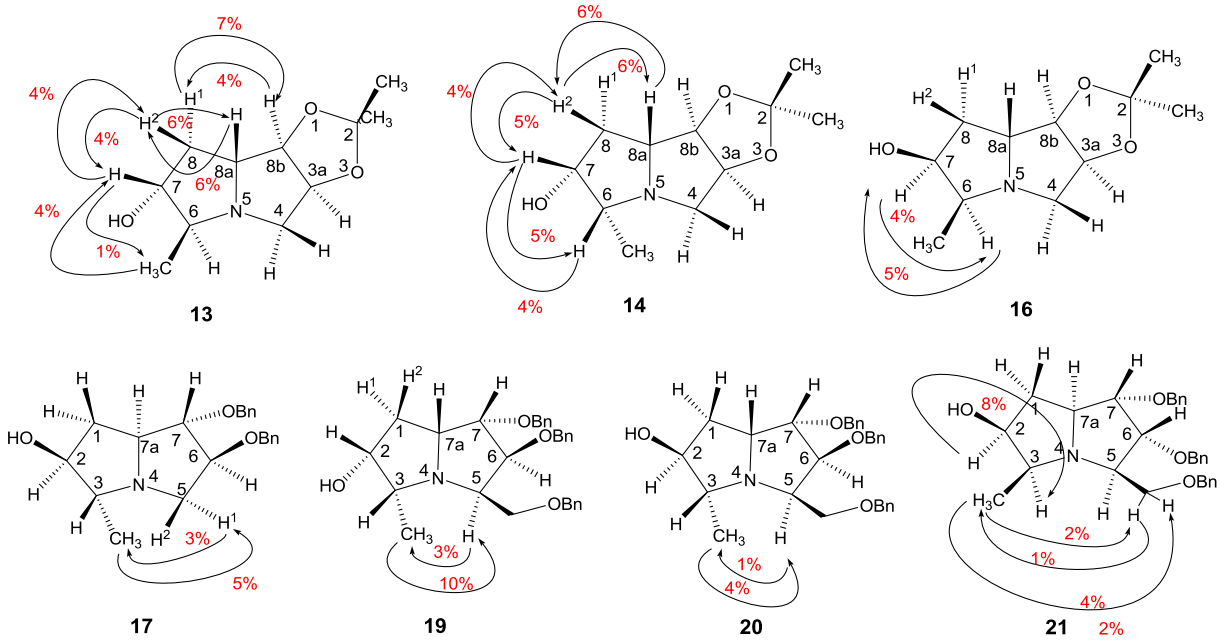
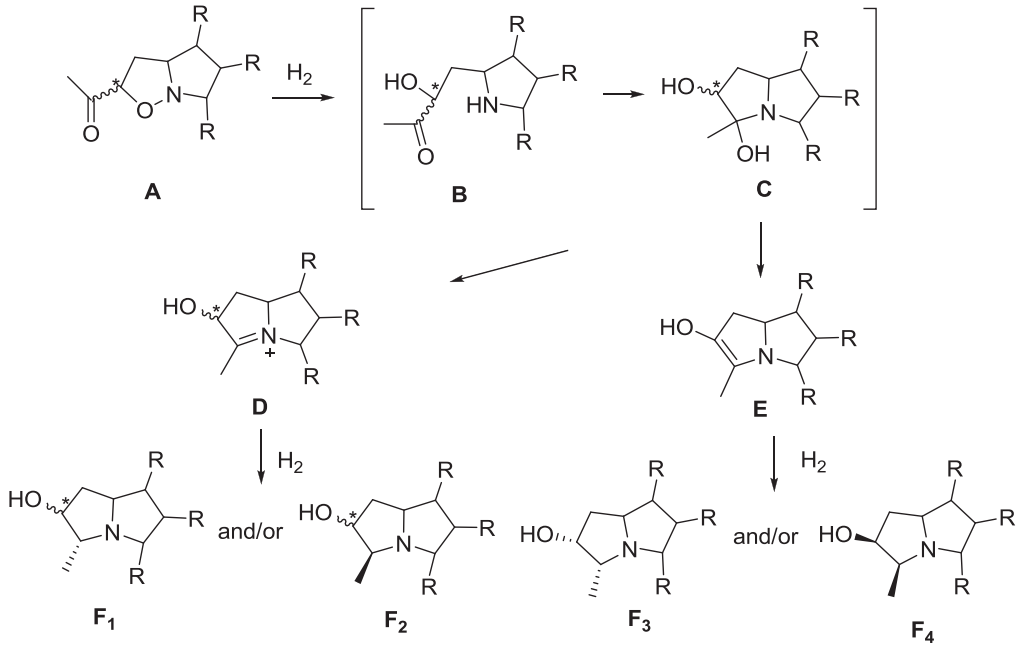


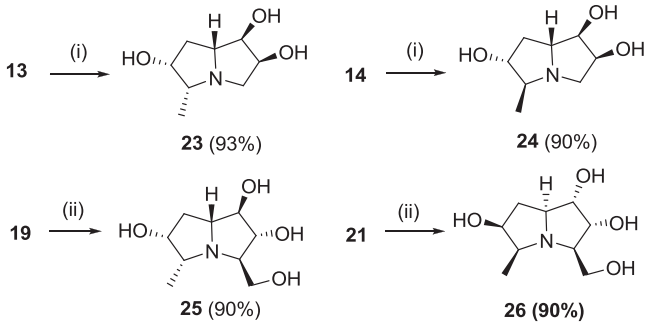
Fig. 4. NOE enhancements measured in compounds **13**, **14**, **16**, **17**, **19**–**21**.

stereocentre is determined by the arrangement of the acetyl group in the initial cycloadducts (marked with asterisk carbon in Scheme 4). Thus diastereomeric cycloadducts **6** and **7** as well as **9** and **10** differentiating at the stereochemistry of the carbon bearing the acetyl group should be expected to give the same reduction products bearing the 2-H and 3-H in *cis* disposition. The formation of different products and especially in the case of **6** and **7** the formation of four different products gives evidence for iminium ion D as intermediate, in which the configuration of the carbon bearing the hydroxyl group is retained. The formation of only one diasteoisomer in the case of compounds **9**–**12** bearing in addition to the C-4 and C-5 substituents a benzyloxymethyl substituent at C-6 can be attributed to a particular shape of the bicycle intermediate, which permits the hydrogen attack only from the *exo*-face directing the methyl group to the opposite face *trans* to the bridgehead hydrogen. Absolute stereoselectivity has been also mentioned in the hydrogenation reaction of analogous intermediates by Izquierdo and Franco in a series of papers.[9]

The removal of the protective groups can be done by standard procedures. Thus compounds **13** and **14** were transformed to the trihydroxypyrrolizidines **23** and **24**, respectively by acid hydrolysis, whereas compounds **19** and **21** were transformed to the tetrahydroxypyrrolizidines **25** and **26**, respectively by reductive debenzylation under pressure at 70 °C (Scheme 5).



Scheme 4. Mechanistic scheme for the reductive amination.



Scheme 5. Reagents and conditions: i) *p*-$CH_3C_6H_4SO_3H$, CH_3OH acid, rt, 5 h ii) Pd/C, H_2, sealed tube, CH_3OH, 70 °C, rt, 48 h.

3. Conclusions

In conclusion, we have developed a convenient and short synthesis of polyhydroxylated pyrrolizidines starting from easily available cyclic nitrones. The stereochemical outcome of the reactions is determined by the stereochemistry of the starting nitrone. By choice of suitable nitrones hyacinthacine analogues as **19**–**22** can be obtained. The existence of a benzyloxymethoxy group at the C-5 position of the starting nitrone induces high stereoselectivity in the reductive amination step resulting one stereoisomer of the two possible ones in all cases.

4. Experimental

4.1. General

Melting points are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin–Elmer 297 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVANCE^{III} 300 spectrometer and ^{13}C NMR spectra at 75.5 MHz on the same spectrometer and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions, unless otherwise stated. Mass spectra were performed on a Shimadzu LCMS-2010 EV instrument under Electrospray Ionization conditions. High resolution mass spectra (HRESI) were obtained with a 7 T APEX II spectrometer. Microanalyses were performed on a Perkin–Elmer 2400-II element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. Optical rotations were measured with a A. KRÜSS Optronic P3002, operating at 589 nm (*l*=1 dm, 25 °C).

4.2. Reactions of nitrones 1–4 with methyl vinyl ketone 5

4.2.1. General procedure. A solution of the nitrone **1**, **2**, **3** or **4** (1 mmol) and methyl vinyl ketone (1.5 mmol) in dry dichloromethane (5 mL) was heated to reflux and the reaction was monitored by TLC for the consumption of the nitrone. After two days only traces of the nitrone were detected in the TLC. The heating was stopped and, after evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (3:1) as the eluent. From the reaction with nitrone **2** only one product **8** was isolated, whereas from the reactions with nitrones **1**, **3** and **4** the two diastereoisomeric products **6**/**7**, **9**/**10** and **11**/**12**, respectively were obtained separately.

*4.2.1.1. 1-[(3aSR, 7RS, 8aRS, 8bRS)-2,2-Dimethylhexahydro [1,3] dioxolo[4′,5′:3,4]pyrrolo[1,2-b]isoxazol-7-yl]-1-ethanone (**6**).* This compound was obtained from nitrone **1** in 57% yield (129 mg) as a colourless oil; R_f (hexane/EtOAc 3:1) 0.6; IR (liquid film): ν_{max} 1715 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.21 (s, 3H, $COCH_3$), 2.36 (dddd, *J*=13.2, 9.3, 4.2, 0.7 Hz, 1H, 8-H), 2.7 (dddd, *J*=13.2, 8.2, 4.3, 1.1 Hz, 1H, 8-H), 3.23 (dd, *J*=14.0, 4.0 Hz, 1H, 4-H), 3.51 (dd, *J*=14.0, 5.9 Hz, 1H, 4-H), 3.63 (ddd, *J*=8.2, 4.2, 2.4 Hz, 1H, 8a-H), 4.31 (dd, *J*=9.3, 4.3 Hz, 1H, 7-H), 4.52 (dd, *J*=7.2, 2.4 Hz, 1H, 8b-H), 4.89–4.98 (m, 1H, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 24.8, 25.4 and 26.9 (CH_3), 35.9 (C-8), 60.9, 70.8, 81.0, 81.2 and 85.8 (C-3a, C-4, C-7, C-8a and C-8b), 113.4 (C-2), 210.0 (CO). MS (*m*/*z*, %): 250 [100, $(M+Na)^+$]. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16%. Found: C, 58.40; H, 7.75; N, 5.99%.

*4.2.1.2. 1-[(3aSR, 7SR, 8aRS, 8bRS)-2,2-Dimethylhexahydro [1,3] dioxolo[4′,5′:3,4]pyrrolo[1,2-b]isoxazol-7-yl]-1-ethanone (**7**).* This compound was obtained from nitrone **1** in 35% yield (79 mg) as a white solid, mp 120–121 °C; R_f (hexane/EtOAc 3:1) 0.4; IR (KBr): ν_{max} 1715 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.22–2.33 (overlapped s and m, 4H, CH_3 and 8-H), 2.69 (dt, *J*=13.1, 8.4 Hz, 1H, 8-H), 3.47 (d, *J*=4.3 Hz, 2H, 4-H), 3.83 (ddd, *J*=8.4, 5.8, 2.3 Hz, 1H, 8a-H), 4.47 (t, *J*=8.4 Hz, 1H, 7-H), 4.58 (dd, *J*=6.5, 2.3 Hz, 1H, 8b-H), 4.98 (dt, 1H, *J*=6.5, 4.3 Hz, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 24.9, 26.8 and 27.1 (CH_3), 35.3 (C-8), 61.01, 71.7, 80.4, 83.3 and 84.5 (C-3a, C-4, C-7, C-8a and C-8b), 113.1 (C-2), 206.2 (CO). MS (*m*/*z*, %): 250 [100, $(M+Na)^+$]. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16%. Found: C, 58.38; H, 7.57; N, 5.94%.

*4.2.1.3. 1-[(2S, 3aS, 4S, 5S)-4,5-Bis(benzyloxy)hexahydropyrro lo [1,2-b]isoxazol-2-yl]ethanone (**8**).* This compound was obtained from nitrone **2** in 85% yield (312 mg) as a pale yellow oil; $[\alpha]_D^{25}$ 13.7 (*c* 3.8, $CHCl_3$); R_f (hexane/EtOAc 3:1) 0.5; IR (liquid film): ν_{max} 1715 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H, $COCH_3$), 2.42 (ddd, *J*=12.8, 8.2, 3.9 Hz, 1H, 3-H), 2.68 (ddd, *J*=12.8, 8.5, 5.5 Hz, 1H, 3-H), 3.44–3.58 (m, 2H, 6-H), 3.68 (ddd, *J*=8.5, 4.2, 3.9 Hz, 1H, 3a-H), 3.99 (dd, *J*=4.2, 2.7 Hz, 1H, 4-H), 4.11–4.17 (m, 1H, 5-H), 4.48 (dd, *J*=8.2, 5.5 Hz, 1H, 2-H), 4.52–4.63 (m, 4H, CH_2Ph), 7.25–7.42 (m, 10H, Ph-H). ^{13}C NMR ($CDCl_3$) δ: 25.5 (CH_3), 36.8 (C-3), 59.5, 69.9, 71.7, 71.8, 81.3, 84.3 and 89.1 (C-2, C-3a, C-4, C-5, C-6 and CH_2Ph), 127.4, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 137.5 and 137.6 (C–Ph), 209.8 (CO). MS (*m*/*z*, %): 390 [100, $(M+Na)^+$]. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81%. Found: C, 71.80; H, 6.90; N, 3.67%.

*4.2.1.4. 1-[((2R, 3aR, 4R, 5R, 6R)-4,5-Bis(benzyloxy)-6-benzyl oxymethyl)hexahydropyrrolo[1,2-b]isoxazol-2-yl] ethanone (**9**).* This compound was obtained from nitrone **3** in 59% yield (287 mg) as a pale yellow oil; R_f (hexane/EtOAc 3:1) 0.6; $[\alpha]_D^{25}$ −16.1 (*c* 3.46, $CHCl_3$); IR (liquid film): ν_{max} 1715(CO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H, $COCH_3$), 2.42 (ddd, *J*=12.7, 8.3, 5.2 Hz, 1H, 3-H), 2.58 (ddd, *J*=12.7, 8.5, 6.2 Hz, 1H, 3-H), 3.52 (q, *J*=5.4, 1H, 6-H), 3.58–3.76 (m, 3H, 3a-H and CH_2O), 4.01 (t, *J*=5.4 Hz, 1H, 4-H), 4.12 (t, *J*=5.4 Hz, 1H, 5-H), 4.48 (dd, *J*=8.3, 6.2 Hz, 1H, 2-H), 4.52–4.68 (m, 6H, CH_2Ph), 7.21–7.45 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 25.9 (CH_3), 36.9 (C-3), 68.0, 69.9, 70.5, 72.0, 72.3, 73.4, 81.4, 84.8 and 87.8 (C-2, C-3a, C-4, C-5, C-6, CH_2O and CH_2Ph), 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 137.6, 137.9 and 138.2 (C–Ph), 208.9 (CO). MS (*m*/*z*, %): 510 [100, $(M+Na)^+$]. Anal. Calcd for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87%. Found: C, 73.80; H, 6.90; N, 2.67%.

*4.2.1.5. 1-[((2S, 3aR, 4R, 5R, 6R)-4,5-Bis(benzyloxy)-6-benzyl oxymethyl)hexahydropyrrolo[1,2-b]isoxazol-2-yl] ethanone (**10**).* This compound was obtained from nitrone **3** in 31% yield (149 mg) as a pale yellow oil; R_f (hexane/EtOAc 3:1) 0.5; $[\alpha]_D^{25}$ −32.3 (*c* 3.46, $CHCl_3$); IR (liquid film): ν_{max} 1715 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H, $COCH_3$), 2.37 (ddd, *J*=12.7, 8.3, 7.5 Hz, 1H, 3-H), 2.62 (ddd, *J*=12.7, 8.3, 7.5 Hz, 1H, 3-H), 3.51 (q, *J*=5.4, 1H, 6-H), 3.60–3.73 (m, 2H, CH_2O), 3.78 (dt, *J*=7.5, 4.1 Hz, 1H, 3a-H), 4.01 (t, *J*=4.1 Hz, 1H, 4-H), 4.12 (dd, *J*=5.4, 4.1 Hz, 1H, 5-H), 4.45 (t, *J*=8.3 Hz, 1H, 2-H), 4.52–4.63

(m, 6H, CH_2Ph), 7.21–7.45 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 26.4 (CH_3), 36.6 (C-3), 68.8, 69.6, 70.4, 72.0, 72.2, 73.3, 83.8, 85.3 and 87.1 (C-2, C-3a, C-4, C-5, C-6, CH_2O and CH_2Ph), 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 137.5, 137.9 and 138.1 (C–Ph), 207.1 (CO). MS (*m*/*z*, %): 510 [100, $(M+Na)^+$]. Anal. Calcd for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87%. Found: C, 73, 81; H, 6.75; N, 2.77%.

*4.2.1.6. 1-[((2S, 3aS, 4S, 5R, 6R)-4,5-Bis(benzyloxy)-6-benzyl oxymethyl)hexahydropyrrolo[1,2-b]isoxazol-2-yl] ethanone (**11**).* This compound was obtained from nitrone **4** in 64% (312 mg) yield as a pale yellow oil; R_f (hexane/EtOAc 3:1) 0.6; $[\alpha]_D^{25}$ +77.2 (*c* 6.7, $CHCl_3$); IR (liquid film): ν_{max} 1710 (CO) cm^{-1}. ^1H NMR ($CDCl_3/C_6D_6$ 4:1) δ: 1.93 (ddd, *J*=12.8, 8.8, 2.9 Hz, 1H, 3-H), 2.15 (s, 3H, $COCH_3$), 2.69 (ddd, *J*=12.8, 8.7, 3.7 Hz, 1H, 3-H), 3.51 (dd, *J*=5.6, 3.7 Hz, 1H, 4-H), 3.55–3.62 (m, 1H, 3a-H), 3.66–3.77 (m, 2H, CH_2O), 3.82–3.92 (m, 2H, 5-H and 6-H), 3.95 (dd, *J*=8.8, 3.7 Hz, 1H, 2-H), 4.32–4.53 (m, 6H, CH_2Ph), 7.10–7.30 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 25.2 (CH_3), 36.3 (C-3), 67.6, 69.4, 69.7, 71.8, 72.5, 73.1, 78.6, 80.8 and 81.7 (C-2, C-3a, C-4, C-5, C-6, CH_2O and CH_2Ph), 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 137.5, 137.7 and 138.1 (C–Ph), 211.8 (CO). MS (*m*/*z*, %): 510 [100, $(M+Na)^+$]. Anal. Calcd for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87%. Found: C, 73, 77; H, 6.90; N, 2.71%.

*4.2.1.7. 1-[((2R, 3aR, 4S, 5R, 6R)-4,5-Bis(benzyloxy)-6-benzyl oxymethyl)hexahydropyrrolo[1,2-b]isoxazol-2-yl] ethanone (**12**).* This compound was obtained from nitrone **4** in 32% yield (156 mg) as a pale yellow oil; R_f (hexane/EtOAc 3:1) 0.4; $[\alpha]_D^{25}$ −7.6 (*c* 2.8, $CHCl_3$); IR (liquid film): ν_{max} 1710 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.12–2.28 (overlapped s and m, 4H, 3-H and $COCH_3$), 2.69 (ddd, *J*=12.1, 7.5, 4.4 Hz, 1H, 3-H), 3.53 (q, *J*=4.5 Hz, 1H, 6-H), 3.68 (d, *J*=4.5 Hz, 2H, CH_2O), 3.83 (dt, *J*=9.0, 4.4 Hz, 1H, 3a-H), 3.92–3.03 (m, 2H, 4-H and 5-H), 4.50–4.68 (m, 6H, CH_2Ph and 2-H), 4.77 (d, *J*=11.8 Hz, 1H, CH_2Ph) 7.22–7.44 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 26.0 (CH_3), 32.9 (C-3), 65.7, 69.6, 70.1, 72.5, 73.1, 73.4, 77.1, 79.0 and 82.5 (C-2, C-3a, C-4, C-5, C-6, CH_2O and CH_2Ph), 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 137.9, 138.0 and 138.2 (C–Ph), 207.9 (CO). MS (*m*/*z*, %): 510 [100, $(M+Na)^+$]. Anal. Calcd for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87%. Found: C, 73.88; H, 6.97; N, 2.63%.

4.3. Reductive amination of compounds 6–12

4.3.1. General procedure. The cycloaddition product **6**, **7**, **8**, **9**, **10**, **11**, or **12** (0.4 mmol) was dissolved in methanol (5 mL), a catalytic amount of Pd/C (a spatula tip) was added and the reaction mixture was stirred for two days under a hydrogen atmosphere at room temperature. After, the crude reaction mixture was passed over Celite and concentrated. The residue was chromatographed on a silica gel column with ethyl acetate–methanol (4:1) (for the reactions of **6**–**8**), ethyl acetate (for the reactions of **9**, **10**) or ethyl acetate–hexane (1:1) (for the reactions of **11**, **12**) as the eluent. From the reactions of **6**–**8** there were isolated two diastereomeric products **13**/**14**, **15**/**16** and **17**/**18**, respectively partially separately and partially as a mixture. From the reactions of **9**–**12** only one product was isolated, **19**–**22**, respectively.

*4.3.1.1. 1-(3aSR, 6RS, 7RS, 8aRS, 8bRS)-2,2-6-Trimethyl hexa hydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**13**).* This compound was obtained from cycloadduct **6** in 49% yield (42 mg) as a white solid, mp 108–111 °C; R_f (EtOAc/CH_3OH 4:1) 0.2; IR (KBr): ν_{max} 3300 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.26 (d, *J*=7.0 Hz, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.57 (ddd, *J*=14.4, 8.4, 2.8 Hz, 1H, 8-H), 2.41 (ddd, *J*=14.4, 9.2, 7.1 Hz, 1H, 8-H), 3.09 (d, *J*=11.6, 1H, 4-H), 3.18 (qd, *J*=7.1, 4.7 Hz, 1H, 6-H), 3.33 (dd, *J*=11.6, 4.9 Hz, 1H, 4-H), 3.47 (br s, 1H, OH), 3.53 (ddd as t, Σ*J*=17.6 Hz, 1H, 8a-H), 4.26 (ddd, *J*=7.1, 4.7, 2.8 Hz, 1H, 7-H), 4.56 (d, *J*=6.0 Hz, 1H, 8b-H), 4.80 (ddd as t, Σ*J*=10.9 Hz, 1H, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 11.1, 24.5 and 26.5 (CH_3), 38.5 (C-8), 52.3, 61.9, 69.9, 75.3, 80.6 and 84.6 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 111.5 (C-2). HRESIMS for $C_{11}H_{20}NO_3$ $(M+H)^+$: calcd 214.1443, found 214.1438.

*4.3.1.2. (3aSR, 6SR, 7RS, 8aRS, 8bRS)-2,2-6-Trimethylhexa hydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**14**).* This compound was obtained from cycloadduct **6** in 43% yield (37 mg) as a white solid, mp 118–121 °C; R_f(EtOAc/CH_3OH 4:1) 0.3; IR (KBr): ν_{max} 3300 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.13 (d, *J*=6.4 Hz, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.68 (dt, *J*=13.2, 6.7 Hz, 1H, 8-H), 2.47 (ddd, *J*=13.2, 8.3, 6.7 Hz, 1H, 8-H), 2.53 (br s, 1H, OH), 2.63 (qn, *J*=6.4 Hz, 1H, 6-H), 3.16 (dd, *J*=10.9, 4.6 Hz, 1H, 4-H), 3.26 (dd, *J*=10.9, 5.6 Hz, 1H, 4-H), 3.59 (ddd, *J*=8.3, 6.7, 3.2 Hz, 1H, 8a-H), 3.93 (psq, Σ*J*=19.8 Hz, 1H, 7-H), 4.58 (dd, *J*=6.2, 3.2 Hz, 1H, 8b-H), 4.90 (ddd as q, Σ*J*=16.4 Hz, 1H, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 18.6, 25.4 and 27.5 (CH_3), 38.0 (C-8), 58.2, 68.0, 68.6, 78.6, 80.9 and 87.2 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 112.8 (C-2). HRESIMS for $C_{11}H_{20}NO_3$ $(M+H)^+$: calcd 214.1443, found 214.1437.

*4.3.1.3. (3aSR, 6RS, 7SR, 8aRS, 8bRS)-2,2-6-Trimethyl hexa hydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**15**).* This compound was obtained from cycloadduct **7** in 48% yield (31 mg as a mixture with **16** determined from ^1H NMR and 10 mg separately as a white solid, mp 142–144 °C); R_f (EtOAc/CH_3OH 4:1) 0.2; IR (KBr): ν_{max} 3450 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.42 (d, *J*=6.6 Hz, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.01 (ddd, *J*=13.9, 8.6, 4.7 Hz, 1H, 8-H), 2.53 (dd, *J*=13.9, 8.3 Hz, 1H, 8-H), 2.88–2.98 (m, 1H, 6-H), 3.23 (dd, *J*=13.0, 6.2 Hz, 1H, 4-H), 3.40 (br s, 1H, OH), 3.55 (dd, *J*=13.00, 4.7 Hz, 1H, 4-H), 4.23 (t, *J*=4.7 Hz, 1H, 7-H), 4.38 (ddd, *J*=8.6, 8.3, 4.7 Hz, 1H, 8a-H), 4.56 (dd, *J*=5.5, 3.0 Hz, 1H, 8b-H), 4.80 (ddd as q, Σ*J*=16.4 Hz, 1H, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 11.9, 25.4 and 27.4 (CH_3), 38.7 (C-8), 55.7, 69.0, 69.2, 74.6, 80.1 and 85.4 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 114.1 (C-2). HRESIMS for $C_{11}H_{20}NO_3$ $(M+H)^+$: calcd 214.1443, found 214.1448.

*4.3.1.4. (3aSR, 6RS, 7SR, 8aRS, 8bRS)-2,2-6-Trimethylhexa hydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**16**).* This compound was obtained from cycloadduct **7** in 37% yield (22 mg as a mixture with **15** determined from ^1H NMR and 10 mg separately as a white solid, mp 145–147 °C); R_f (EtOAc/CH_3OH 4:1) 0.1; IR (KBr): ν_{max} 3450 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.13 (d, *J*=6.4 Hz, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.89 (ddd, *J*=14.0, 7.7, 5.0 Hz, 1H, 8-H), 2.04 (br s, 1H, OH), 2.28 (dd, *J*=14.0, 8.0 Hz, 1H, 8-H), 2.63–2.73 (m, 1H, 6-H), 3.08 (dd, *J*=13.0, 6.1 Hz, 1H, 4-H), 3.18 (dd, *J*=13.00, 4.7 Hz, 1H, 4-H), 3.8 (ddd as td, Σ*J*=19.2 Hz, 1H, 8a-H), 4.13 (dd as t, Σ*J*=8.1 Hz, 1H, 7-H), 4.42 (dd, *J*=6.2, 3.5 Hz, 1H, 8b-H), 4.87 (ddd as q, Σ*J*=17.0 Hz, 1H, 3a-H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 25.4 and 27.6 (CH_3), 39.1 (C-8), 56.7, 55.4, 69.1, 75.7, 81.3 and 87.3 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 112.9 (C-2). HRESIMS for $C_{11}H_{20}NO_3$ $(M+H)^+$: calcd 214.1443, found 214.1435.

*4.3.1.5. (2S, 3R, 6S, 7S, 7aS)-6,7-Bis(benzyloxy)-3-methylhexa hydro-1H-pyrrolizin-2-ol (**17**).* This compound was obtained from cycloadduct **8** in 69% yield (77 mg as a mixture with **18** determined from ^1H NMR and 20 mg separately as a pale yellow oil); R_f (EtOAc/CH_3OH 4:1) 0.2; IR (liquid film): ν_{max} 3300 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.41 (d, *J*=6.6 Hz, 3H, CH_3), 2.03 (br s, 1H, OH), 2.28–2.38 (m, 2H, 1-H), 3.32 (dd, *J*=11.0, 3.1 Hz, 1H, 5-H), 3.50 (d, *J*=11.0, 1H, 5-H), 3.62–3.72 (m, 1H, 3-H), 4.02 (d, *J*=5.0 Hz, 1H, 7-H), 4.10–4.20 (m, 2H, 2-H and 6-H), 4.43 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.49–4.71 (m, 3H, 7a-H and CH_2Ph), 4.77 (d, *J*=12.0 Hz, 1H, CH_2Ph), 7.17–7.49 (m, 10H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 9.9 (CH_3), 32.4 (C-1), 49.7 (C-5), 62.4, 67.1, 71.4, 73.6, 74.2, 80.4 and 81.3 (C-2, C-3, C-6, C-7, C-7a and CH_2Ph), 127.9, 128.0, 128.2, 128.6, 128.9, 129.0, 135.8 and 137.1 (C–Ph). HRESIMS for $C_{22}H_{28}NO_3$ $(M+H)^+$: calcd 354.2069, found 354.2061.

*4.3.1.6. (2S, 3S, 6S, 7S, 7aS)-6,7-Bis(benzyloxy)-3-methylhexahydro-1H-pyrrolizin-2-ol (**18**).* This compound was obtained from cycloadduct **8** in 26% yield (27 mg as a mixture with **17** determined from ^{1}H NMR and 10 mg separately as a pale yellow oil); R_f (EtOAc/CH_3OH 4:1) 0.1; IR (liquid film): ν_{max} 3280 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.51 (d, J=6.8 Hz, 3H, CH_3), 1.93 (dd, J=14.0, 3.2 Hz, 1H, 1-H), 2.03 (br s, 1H, OH), 2.35 (ddd, J=14.0, 10.7, 5.9 Hz, 1H, 1-H), 3.32–3.58 (m, 3H, 3-H and 5-H), 3.96–4.07 (m, 1H, 7a-H), 4.13 (t, J=4.9 Hz, 1H, 7-H), 4.21–4.36 (m, 2H, 2-H and 6-H), 4.53–4.70 (m, 4H, CH_2Ph), 7.21–7.49 (m, 10H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 10.2 (CH_3), 38.4 (C-1), 49.8 (C-5), 63.2, 67.0, 72.3, 73.2, 74.5, 82.6 and 86.7 (C-2, C-3, C-6, C-7, C-7a and CH_2Ph), 127.8, 128.0, 128.1, 128.3, 128.5, 128.7, 136.8 and 137.5 (C–Ph). HRESIMS for $C_{22}H_{28}NO_3$ $(M+H)^+$: calcd 354.2069, found 354.2073.

*4.3.1.7. (2R, 3R, 5R, 6R, 7R, 7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-2-ol (**19**).* This compound was obtained from cycloadduct **9** in 85% yield (160 mg) as pale yellow oil; R_f (EtOAc) 0.4; $[\alpha]_D^{25}$ −20.9 (c 2.78, $CHCl_3$); IR (liquid film): ν_{max} 3300 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.32 (d, J=6.4 Hz, 3H, CH_3), 1.78 (dd, J=14.6, 3.7 Hz, 1H, 1-H), 2.01 (br s, 1H, OH), 2.29 (ddd, J=14.6, 10.4, 6.2 Hz, 1H, 1-H), 3.08–3.20 (m, 1H, 3-H), 3.41 (d, J=7.7 Hz, 2H, CH_2OPh), 3.67 (dd, J=10.4, 3.7 Hz, 1H, 7a-H), 3.85 (t, J=7.7, 1H, 5-H), 3.90–3.98 (br m, 1H, 2-H), 4.08 (s, 1H, 7-H), 4.12 (s, 1H, 6-H), 4.41–4.62 (m, 6H, CH_2Ph), 7.15–7.37 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 11.8 (CH_3), 39.8(C-1), 62.8, 62.85, 68.6, 71.3, 71.8, 73.0, 73.1, 75.3, 85.9 and 88.2 (C-2, C-3, C-5, C-6, C-7, C-7a and CH_2Ph), 127.4, 127.6, 128.0, 128.0, 128.1, 128.2, 128.3, 137.0, 138.0 and 138.5 (C–Ph). HRESIMS for $C_{30}H_{36}NO_4$ $(M+H)^+$: calcd 474.2644, found 474.2651.

*4.3.1.8. (2S, 3R, 5R, 6R, 7R, 7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-2-ol (**20**).* This compound was obtained from cycloadduct **10** in 80% yield (151 mg) as a pale yellow oil; R_f (EtOAc) 0.3; $[\alpha]_D^{25}$ −31.1 (c 1.28, $CHCl_3$); IR (liquid film): ν_{max} 3350 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.19 (d, J=6.4 Hz, 3H, CH_3), 1.97 (ddd, J=13.4, 8.5, 4.5 Hz, 1H, 1-H), 2.19 (dt, J=13.4, 7.6 Hz, 1H, 1-H), 2.48 (br s, 1H, OH), 3.14 (qd, J=6.4, 3.5 Hz, 1H, 3-H), 3.25 (dt, J=7.5, 3.3 Hz, 1H, 5-H), 3.49–3.61 (m, 2H, CH_2OPh), 3.84–3.98 (m, 2H, 7-H and 7a-H), 4.08–4.17 (m, 2H, 2-H και 6-H), 4.41–4.62 (m, 6H, CH_2Ph), 7.15–7.45 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 14.4 (CH_3), 39.9 (C-1), 66.8, 67.3, 68.3, 71.4, 71.8, 72.1, 73.3, 75.9, 87.0 and 88.8 (C-2, C-3, C-5, C-6, C-7, C-7a and CH_2Ph), 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 138.0, 138.3 and 138.5 (C–Ph). HRESIMS for $C_{30}H_{36}NO_4$ $(M+H)^+$: calcd 474.2644, found 474.2641.

*4.3.1.9. (2S, 3S, 5R, 6R, 7S, 7aS)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-2-ol (**21**).* This compound was obtained from cycloadduct **11** in 83% yield (157 mg) as a pale yellow oil; R_f (hexane/EtOAc 1:1) 0.4; $[\alpha]_D^{25}$ +2.1 (c 4.85, $CHCl_3$); IR (liquid film): ν_{max} 3380 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.12 (d, J=6.3 Hz, 3H, CH_3), 1.35 (ddd, J=13.1, 10.2, 6.0 Hz, 1H, 1-H), 1.89 (br s, 1H, OH), 2.41 (ddd, J=13.1, 7.0, 6.0 Hz, 1H, 1-H), 2.49 (qn, J=6.3 Hz, 1H, 3-H), 2.82 (ddd as q, ΣJ=14.0 Hz, 1H, 5-H), 2.88 (ddd, J=8.7, 7.0, 6.0 Hz 1H, 7a-H), 3.44 (dd, J=10.1, 5.8 Hz, 1H, CH_2OPh), 3.56 (dd, J=10.1, 4.2 Hz, 1H, CH_2OPh), 3.65 (dd, J=8.7, 6.3 Hz, 1H, 7-H), 4.08 (dd, J=6.3, 4.0 Hz, 1H, 6-H), 4.24 (ddd as q, ΣJ=22.5 Hz, 1H, 2-H), 4.49–4.65 (m, 5H, CH_2Ph), 4.74 (d, J=12.0 Hz, 1H, CH_2Ph), 7.22–7.42 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 37.4 (C-1), 60.6, 66.1, 69.0, 70.9, 71.7, 72.1, 73.2, 77.5, 79.4 and 83.3 (C-2, C-3, C-5, C-6, C-7, C-7a and CH_2Ph), 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 138.0, 138.3 and 138.5 (C–Ph). HRESIMS for HRESIMS for $C_{30}H_{35}NNaO_4$ $(M+Na)^+$: calcd 496.2464, found 496.2465.

*4.3.1.10. (2R, 3R, 5R, 6R, 7S, 7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-2-ol (**22**).* This compound was obtained from cycloadduct **12** in 83% yield (157 mg) as a pale yellow oil; R_f (hexane/EtOAc 1:1) 0.3; $[\alpha]_D^{25}$ −8.1 (c 2.28, $CHCl_3$); IR (liquid film): ν_{max} 3380 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.21 (d, J=6.9 Hz, 3H, CH_3), 2.20 (br s, 1H, OH), 2.38 (dd, J=18.8, 8.9 Hz, 1H, 1-H), 2.72 (ddd, J=18.8, 3.4, 1.5 Hz, 1H, 1-H), 3.19–3.28 (m, 2H, 3-H and 5-H), 3.60 (t, J=4.5 Hz, 2H, CH_2OPh), 3.71 (dt, J=8.9, 3.4 Hz, 1H, 7a-H), 3.96 (t, J=3.4 Hz, 1H, 7-H), 4.11 (dd, J=8.1, 3.4 Hz, 1H, 6-H), 4.49–4.68 (m, 6H, CH_2Ph and 2-H), 4.74 (d, J=11.8 Hz, 1H, CH_2Ph), 7.20–7.40 (m, 15H, Ph–H). ^{13}C NMR ($CDCl_3$) δ: 17.8 (CH_3), 35.6 (C-1), 60.2, 68.1, 69.8, 71.9, 73.1, 73.2, 73.3, 73.4, 78.5 and 84.0 (C-2, C-3, C-5, C-6, C-7, C-7a and CH_2Ph), 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 137.8, 138.2 and 138.3 (C–Ph). HRESIMS for $C_{30}H_{35}NNaO_4$ $(M+Na)^+$: calcd 496.2464, found 496.2469.

4.4. Deprotection of isopropylidene group

4.4.1. General procedure. The pyrrolizidine **13** or **14** (0.1 mmol) was dissolved in methanol (2 mL), *p*-toluenesulfonic acid (0.2 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. After the acid was neutralized by addition of potassium carbonate and the formed solids were removed by filtration. The solvent was evaporated from the filtrate and the residue was chromatographed on a silica gel column with methanol as eluent.

*4.4.1.1. (1RS, 2SR, 5RS, 6RS, 7aRS)-5-Methylohexahydro-1H-pyrrolizine-1,2,6-triol (**23**).* This compound was obtained from pyrrolizidine **13** in 93% yield (16 mg) as a colourless oil; R_f(CH_3OH) 0.2; IR (liquid film): ν_{max} 3420 (OH) cm^{-1}. ^{1}H NMR (CD_3OD) δ: 1.17 (d, J=6.2 Hz, 3H, CH_3), 1.65 (dt, J=12.5, 8.6 Hz, 1H, 7-H), 2.43 (dt, J=125, 6.6 Hz, 1H, 7-H), 2.49–2.59 (br m, 1H, 5-H), 2.89 (dd, J=11.5, 4.1 Hz, 1H, 3-H), 3.06 (dd, J=11.5, 3.9 Hz, 1H, 3-H), 3.38–3.46 (br m, 1H, 7a-H), 3.75 (ddd as q, ΣJ=23.0 Hz, 1H, 6-H), 3.91 (t, J=5.2 Hz 1H, 1-H), 4.26 (ddd as q, ΣJ=13.2 Hz, 1H, 2-H). ^{13}C NMR (CD_3OD) δ: 17.4 (CH_3), 38.3 (C-7), 58.5 (C-3), 66.6, 69.7, 73.3, 78.6 and 79.4 (C-1, C-2, C-5, C-6 and C-7a). HRESIMS for $C_8H_{16}NO_3$ $(M+H)^+$: calcd 174.1130, found 174.1138.

*4.4.1.2. (1RS, 2SR, 5SR, 6RS, 7aRS)-5-Methylohexahydro-1H-pyrrolizine-1,2,6-triol (**24**).* This compound was obtained from pyrrolizidine **14** in 90% yield (16 mg as white solid, mp 112–114 °C); R_f (CH_3OH) 0.1; IR (KBr): ν_{max} 3425 (OH) cm^{-1}. ^{1}H NMR (CD_3OD) δ: 1.30 (d, J=7.0 Hz, 3H, CH_3), 1.86 (ddd, J=14.8, 3.2, 1.8 Hz, 1H, 7-H), 2.17 (ddd, J=14.8, 8.4, 5.1 Hz, 1H, 7-H), 2.86 (dd, J=10.7, 2.4, 1H, 3-H), 2.96–3.05 (m, 1H, 5-H), 3.38–3.49 (m, 2H, 3-H, 7a-H), 4.11 (dd, J=6.3, 4.1, 1H, 1-H), 4.14–4.25 (m, 2H, 2-H, 6-H). ^{13}C NMR (CD_3OD) δ: 11.0 (CH_3), 39.3 (C-7), 53.8 (C-3), 62.3, 68.9, 73.7, 76.5 and 80.2 (C-1, C-2, C-5, C-6 and C-7a). HRESIMS for $C_8H_{16}NO_3$ $(M+H)^+$: calcd 174.1130, found 174.1128.

4.5. Deprotection of benzyl group

4.5.1. General procedure. To a vial equipped with a screw cap there were added a solution of pyrrolizidine **19** or **21** (0.1 mmol) in methanol (2 mL) and a catalytic amount Pd/C (a spatula tip) was added. A balloon, filled with hydrogen was adapted to the reaction flask by means of a septum. After repeated evacuations and flashings with hydrogen gas the vial was closed and it was heated at 70 °C for two days. After the reaction mixture was passed over Celite and concentrated to give compounds **25** or **26** in satisfactory pure form.

*4.5.1.1. (1R, 2R, 3R, 5R, 6R, 7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,6-triol (**25**).* This compound was obtained from pyrrolizidine **19** in 90% yield (18 mg as a pale yellow oil); $[\alpha]_D^{25}$ −9.3 (c 6.2, CH_3OH); IR (liquid film): ν_{max} 3420 (OH) cm^{-1}. ^{1}H

NMR (CD_3OD) δ: 1.51 (d, J=6.9 Hz, 3H, CH_3), 2.24 (br d, J=13.8 Hz, 1H, 7H), 2.35 (ddd, J=13.8, 9.3, 4.6 Hz, 1H, 7-H), 3.29–3.39 (m, 3H, 5-H and CH_2OH), 3.63–4.04 (m, 3H, 1-H, 3-H and 7a-H), 4.20–4.36 (m, 2H, 2-H and 6-H). ^{13}C NMR (CD_3OD) δ: 10.5 (CH_3), 37.5 (C-7), 58.4 (C-3), 66.6, 66.9 (C-5, CH_2OH), 71.1, 74.7, 76.3 and 80.7 (C-1, C-2, C-6 and C-7a). HRESIMS for $C_9H_{18}NO_4$ $(M+H)^+$: calcd 204.1236, found 204.1235.

*4.5.1.2. (1S, 2R, 3R, 5S, 6S, 7aS)-3-(Hydroxymethyl)-5-methyl hexahydro-1H-pyrrolizine-1,2,6-triol (**26**).* This compound was obtained from pyrrolizidine **21** in 90% yield (18 mg as a pale yellow oil); $[\alpha]_D^{25}$ −7.2 (*c* 4.0, CH_3OH); IR (liquid film): ν_{max} 3560, 3300 (OH) cm^{-1}. ^{1}H NMR (CD_3OD) δ: 1.35 (d, J=6.5 Hz, 3H, CH_3), 1.98 (ddd, J=13.2, 9.4, 1.4 Hz, 1H, 7-H), 2.60 (ddd, J=13.2, 7.6, 5.1 Hz, 1H, 7-H), 3.00 (dt, J=5.4, 3.3 Hz, 1H, 3-H), 3.17 (dq, J=4.0, 6.5 Hz, 1H, 5-H), 3.52–3.57 (m, 1H, 7a-H), 3.85 (dd, J=11.1, 3.3 Hz, 1H, CH_2OH), 3.92 (dd, J=11.1, 3.3 Hz, 1H, CH_2OH), 4.05 (br, 1H, 1-H), 4.31–4.42 (m, 2H, 2-H and 6-H). ^{13}C NMR (CD_3OD) δ: 15.6 (CH_3), 33.1 (C-7), 63.1 (C-4), 66.0, 68.0 (C-5, CH_2OH), 70.7, 73.7, 77.2 and 77.6 (C-1, C-2, C-6 and C-7a). HRESIMS for $C_9H_{18}NO_4$ $(M+H)^+$: calcd 204.1236, found 204.1235.

References and notes

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