# A Short and Efficient Route to Enantiopure 3,5-Diarylpyrrolizidines

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Since the isolation of xenovenine (Figure 1) from the venom of the cryptic thief ant *Solenopsis xenovenenum*,[1] several strategies for the preparation of 3,5-disubstituted pyrrolizidines, in racemic[1,2] or enantiopure form,[3] have been devised. Because of the important biological properties displayed by these compounds and, in general, by pyrrolizidine alkaloids,[4] the development of new efficient and concise routes to attain their preparation could be of great interest. For this reason, in continuation of our studies on the application of chiral nitrodiols to the synthesis of heterocyclic compounds,[5a,b] we decided to investigate if they were also amenable to conversion to enantiopure 3,5-disubstituted pyrrolizidines, in particular focusing our attention on the preparation of 3,5-diarylpyrrolizidines (Figure 1), a class of compounds that have never been described before.

The synthesis of nitrodiketones **2** from γ-nitroketones **1**, and the reduction to enantiopure nitrodiols **3** by using (+)- or (−)-diisopinocampheylchloroborane (DIP-Cl), as reported in Scheme 1, have been already described by us.[5a] Thus, with nitrodiols **3** in hand, we envisaged a synthetic strategy for the preparation of enantiopure 3,5-diarylpyrrolizidines based on the initial reduction of **3** to the corresponding amino derivatives **4** or **5**, then followed by the double intramolecular nucleophilic displacement of the two hydroxy groups by the amino functionality, which should take place as soon as the two OH are converted into leaving groups, for instance, mesylates. This process should lead to compounds **7** or their quaternary salts **6** with the stereocenters configurationally inverted with respect to their precursors **3**. In the cyclization reaction (Scheme 2) a pyrrolidine intermediate is formed as a 1:1 mixture of diastereoisomers. However, taking into account the relative configuration of the two aryl groups in final compounds **6** or **7**, only one diastereoisomer should be obtained with the second cyclization step, provided the pyrrolizidines have only the expected cis-fused stereochemistry at the ring junction.[6] To our knowledge, only one other synthesis of pyrrolizidines that started from nitrocompounds has been reported,[2b,c] but in that case aliphatic 4-nitro-1,7-diketones were used for the double cyclization step, under catalytic hydrogenation or different reduction conditions, thus leading to racemic mixtures of 3,5-dialkylpyrrolizidines.

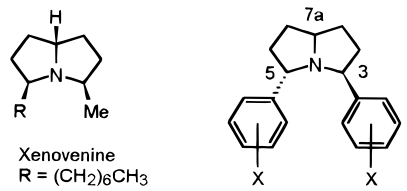


**Figure 1.**

Starting from enantiopure (1*R*,7*R*)-1,7-diaryl-4-nitroheptane-1,7-diols **3a**,**b**,[5a] the reduction of the nitro group was carried out by hydrogenation over Raney Nickel in MeOH at atmospheric pressure, providing aminodiols **4a**,**b** in 80−82% yield. Disappointingly, attempts at converting directly **4** to the corresponding pyrrolizidines by treatment with MsCl were quite ineffective, since only very small amounts (20−23%) of **7a**,**b** (see below for the structural and stereochemical assignments) were isolated after chromatography of complex crude mixtures containing *N*-mesyl pyrrolidines and *N*-mesyl aminodiols as the major products.[7]

Since the low yields in pyrrolizidines **7a**,**b** were due to the mesylation of the nitrogen atom in the aminodiols, we decided to convert **4a**,**b** into the corresponding *N*-benzyl derivatives **5a**,**b** (Scheme 1). These compounds appeared the best candidates to achieve the double cyclization: with a benzyl group on the N atom the increase of sterical hindrance could be sufficient to make the N-mesylation slower than the O-mesylation, and at the same time, the amino group should retain its nucleophilic character for displacing the *O*-mesylates soon after their formation. The cyclization should thus furnish quaternary ammonium salts to be eventually transformed into compounds **7a**,**b** by removal of the protecting *N*-benzyl group.

*N*-Benzyl aminodiols **5a**,**b** were prepared in good yields (84−86%) by reaction of **4a**,**b** with benzaldehyde and

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(6) Cis-fused pyrrolizidines are normally more stable than the corresponding trans-fused compounds (see ref 13a). 3,5-Dimethylpyrrolizidines having the cis relative configuration for the two methyl groups are instead reported to have a trans-fused stereochemistry for the ring junction. Antipova, I. V.; Negrebetskii, V. V.; Skvortsov, I. M. *Khim. Geterotsikl. Soed.* **1982**, 39−46.

(7) We also tried to generate the 4-amino group by hydrogenation (over Raney Nickel in MeOH) of the 4-nitro-1,7-dimesylate derivatives obtained by reaction of **3a**,**b** with MsCl in dichloromethane (route not shown in Scheme 1). However, this procedure was ineffective in yielding cyclization products, since solvolysis of the *O*-mesyl groups (to give mixtures of 1,7-dimethoxy-substituted products) was much faster than the reduction of the nitro to amino group.

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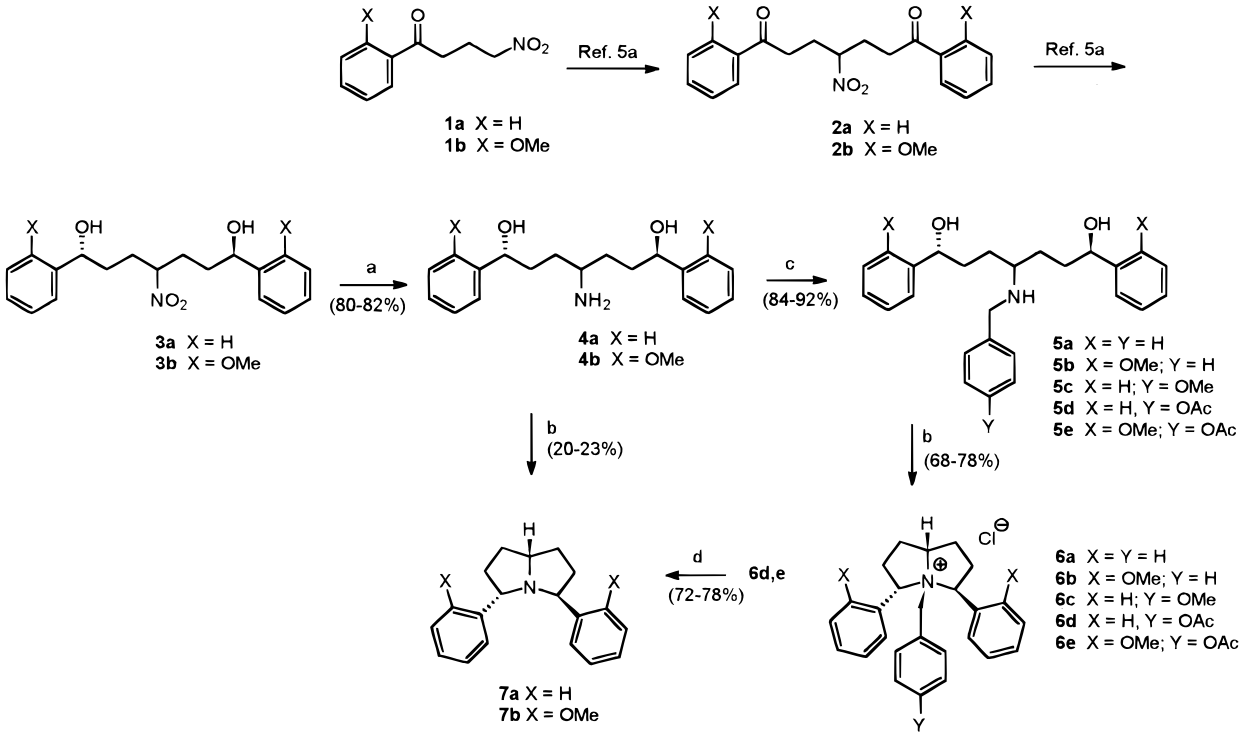
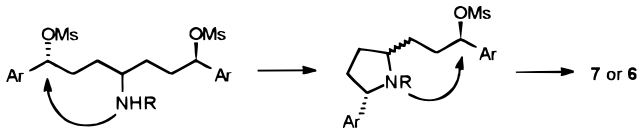
**Scheme 1**[a]

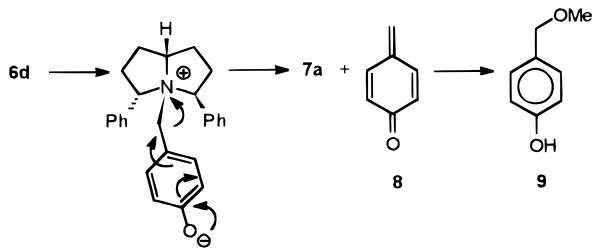



[a] Key: (a) $H_2$, Raney-Ni, MeOH, 24 h, 25 °C; (b) MsCl, $Et_3N$, 4 Å molecular sieves, $CH_2Cl_2$, 0 → 25 °C, 2 h; (c) ArCHO, $NaBH_3CN$, MeOH, $CH_3COOH$ up to pH 6, 0 → 25 °C, 24 h; (d) $K_2CO_3$, MeOH−$H_2O$, 25 °C, 2 h.

**Scheme 2**




**Scheme 3**




$NaBH_3CN$ in MeOH at pH 6. The next step was performed by adding 2 equiv of MsCl to solutions of **5a**,**b** and $Et_3N$ in anhydrous $CH_2Cl_2$ at 0 °C and then leaving the mixture under stirring for 2 h at room temperature. Since **5a**,**b** are very hygroscopic compounds and rapidly absorb water from the atmosphere, the dichloromethane solutions of these aminodiols were dried for 30 min with 4 Å molecular sieves prior to the addition of MsCl. With this expedient procedure the reactions were successful, and optically active salts **6a** ($[\alpha]^{25}_D$ −101.3, *c* 0.82, $CHCl_3$) and **6b** ($[\alpha]^{25}_D$ −62.2, *c* 0.24, $CHCl_3$) were obtained in 72 and 70% yield, respectively, after chromatographic purification. With the procedure employed for their isolation in the course of the workup (see the Experimental Section), these salts were obtained exclusively as chlorides soluble in water and organic solvents such as methanol and chloroform.

With compounds **6a**,**b** in hand, we tried to obtain the corresponding pyrrolizidines by debenzylation of the N atom. Unfortunately, deprotection to give **7a**,**b** proved very difficult with these simple *N*-benzyl derivatives. For example, catalytic hydrogenations over $Pd(OH)_2$ or Pd/C resulted in the cleavage of the internal benzylic bonds, providing mixtures of α-branched *N*-benzyl pyrrolidines and *N*-benzyl amines. Similarly, treatment with sodium thiophenate[8] in refluxing $CH_3CN$ afforded the α-branched *N*-benzyl pyrrolidine derived from nucleophilic attack of $PhS^-$ to the position 3 (or 5) of the pyrrolizidine ring.

Since quaternary salts **6a**,**b** were unsuitable to attain deprotection, we prepared pyrrolizidinium salts **6c** and **6d** (Scheme 1) bearing differently substituted *N*-benzyl groups in order to explore other deprotection methods. Unfortunately, the synthesis of *p*-methoxybenzyl derivative **6c**, obtained in 68% yield from aminodiol **5c**, was unproductive, since after treatment of this salt with cerium ammoniun nitrate (CAN)[9] or $CF_3COOH$[10] the starting material was recovered unreacted.

Finally, we found that *p*-acetyloxybenzyl derivative **6d**, prepared in 78% yield from aminodiol **5d**, was the right precursor to give **7a**. In fact, when the acetyl group in **6d** was subjected to hydrolysis with $K_2CO_3$ in MeOH/$H_2O$ at 25 °C, a complete debenzylation occurred, providing pyrrolizidine **7a** in 72% yield. This reaction should take place through the formation of a phenolate intermediate (Scheme 3) that immediately "eliminates" tertiary amine **7a** to form unsaturated ketone **8** (not isolated). This, in turn, undergoes nucleophilic attack by

(8) Shamma, M.; Deno, N. C.; Remar, J. F. *Tetrahedron Lett.* **1966**, 1375−1379.

(9) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371−2374.

(10) Buckle, D. R.; Rockell, J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627−630.

MeOH to give phenol derivative **9**, easily identified by the singlets at 4.34 ($CH_2$) and 3.33 ppm (MeO) in the $^1H$ NMR spectrum. According to these results, the *p*-acetyloxybenzyl group could find application as a protecting group of tertiary amines, as an alternative to the methyl group in the formation of quaternary ammonium salts.[11] The first in fact would require milder conditions to be removed, since alkaline hydrolysis at room temperature is sufficient for the deprotection reaction.

With the same protocol pyrrolizidine **7b** was prepared in 78% yield starting from aminodiol **5e**. In this particular case, the quaternary salt **6e** was not isolated from the crude reaction mixture, which was directly used in the following hydrolytic process.

The reactions leading to **6a**−**e** were highly diastereoselective, since a careful $^1H$ and $^{13}C$ NMR inspection of the crude mixtures containing **6a**−**e** and all the fractions collected during the chromatographic purification of these salts excluded the presence of *meso* forms of **6** (which derive from an ionic mechanism competing with that reported in Scheme 2). Homo- and hetereonuclear correlation NMR experiments allowed the unambiguous assignment of the $^1H$ and $^{13}C$ NMR signals of compounds **6a**−**e** and, accordingly, the relative stereochemistry of the three substituents on the pyrrolizidine ring.

In all these compounds, protons 3-H and 5-H, as well as carbon atoms C-3 and C-5, have different chemical shifts. For example, in **6a**, which can be taken as a model for all the 3,5-diphenyl-substituted pyrrolizidinium salts, 3-H and 5-H resonate at 4.74 and 5.05 ppm, and in **6b** at 4.91 and 5.64 ppm. With the two substituents at positions 3 and 5 being identical, the different resonances of 3-H and 5-H can be explained only by assuming that the two aryl groups have a trans relative configuration. As a direct consequence, because salts **6** were obtained as single nonracemic (they all are optically active) diastereoisomers, the absolute configuration of the stereocenters at C-3 and C-5 in the major enantiomer of these compounds, to which we refer in the discussion, must be *S*, the double nucleophilic displacement depicted in Scheme 2 occurring with inversion of configuration.

The cis-fused stereochemistry of these salts was determined by a NOESY experiment performed on **6a**. In a cis-fused compound, the bridgehead 7a-H and the benzylic $-CH_2-$ protons are on the same side and therefore should experience a mutual NOE enhancement. This actually occurs in compound **6a**, but quite to our surprise, only one of the two benzylic protons, in particular that resonating at 5.55 ppm (8-Ha, Figure 2), correlated with 7a-H. The other one, found considerably shielded up to 3.54 ppm (8-Hb), showed instead a NOESY cross-peak only with the proton resonating at 5.05 ppm (5-H). These data suggest that the benzyl group, which is cis with respect to the proton on C-7a, should have a preferred spatial orientation accounting for the very different chemical shift of 8-Ha and 8-Hb in the $^1H$ NMR spectrum but, most of all, for the NOE enhancements found in **6a**.

The inspection of the coupling constants for protons 3-H and 5-H in **6a**−**e** suggests that these compounds could be conformationally restricted. The averaged coupling constants of protons 3-H and 5-H with the vicinal protons on C-2 and C-6 are 12.7 and 5.3 Hz (3-H) and 13.1 and 5.1 Hz (5-H). Since the $^3J$ couplings for the two protons are practically identical, it is possible that these quaternary salts adopt in solution a predominant conformation in which the two phenyl groups are equatorially oriented. Only in this case, in fact, the protons on C-3 and C-5 would be both axially oriented (Figure 2), thus accounting for the large (∼13 Hz) and the small (∼5 Hz) couplings with the vicinal axial and equatorial protons, respectively. A complete conformational analysis[12] performed on **6a** confirmed that in the global minimum conformer (Figure 2) the two phenyl groups, which lie on parallel planes, are both in the equatorial position. Moreover, only one preferred position for the *N*-benzyl group was found, in accordance with the NOESY data reported above.

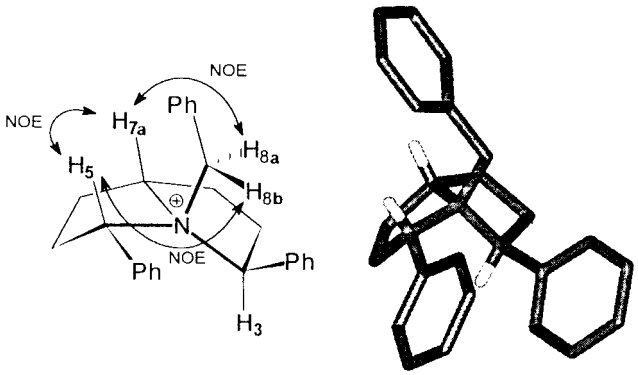



**Figure 2.** NOE correlations in **6a** (left) and MM2* global minimum conformer of **6a** (right).

The deprotection step carried out by alkaline hydrolysis of the acetyloxy group on **6d** and **6e** did not affect the relative trans stereochemistry in final pyrrolizidine **7a**,**b**, since protons 3-H and 5-H have different chemical shifts and resonate at 3.67 and 4.32 ppm in **7a** and at 4.14 and 4.44 ppm in **7b**. Furthermore, pyrrolizidines **7** retained the cis fusion of the ring junction. This assignment rests on the analysis of the chemical shifts of 7a-H, which resonates at 4.02 ppm in **7a** and 3.81 ppm in **7b**. In cis-fused pyrrolizidines, proton 7a-H is on the same side of the N lone pair and, therefore, should undergo a strong deshielding effect.[13] This is true, for example, for cis-fused 3,5-dialkylpyrrolizidines, in which 7a-H resonates in the 3.59−3.66 ppm range,[1,14] while in the corresponding trans-fused compounds 7a-H is found at 2.53−2.72 ppm.[1,2c] Moreover, the chemical shift values of C-7a in the $^{13}C$ NMR spectrum of **7a** (64.5 ppm) and **7b** (60.1 ppm) confirm the cis-fused stereochemistry, since they are consistent with those reported for C-7a in other cis-fused pyrrolizidines; instead, values of chemical shifts

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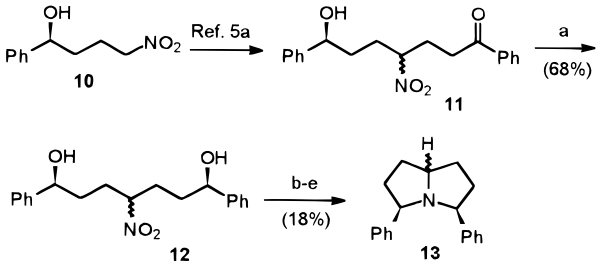
(12) The MacroModel (v4.5) molecular modeling software was used for molecular mechanics calculations and Monte Carlo conformational searchs (MM2* force field). Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(13) In cyclic systems, the protons adjacent to the nitrogen atom and on the same side of the N lone pair undergo a strong deshielding effect, whereas the protons on the opposite side are strongly shielded: (a) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109−126. (b) Wilson S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330−336. (c) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447−453. (d) Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *J. Heterocyclic Chem.* **1979**, *16*, 1041−1047. (e) Bohlmann, F.; Shumann, D. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol IX, Chapter 5.

(14) Skvortsov, I. M.; Elvidge, J. A. *J. Chem. Soc. B* **1968**, 1589−1595.

**Scheme 4**[a]




[a] Key: (a) (+)-DIP−Cl, $CH_2Cl_2$, −25 °C, 5 h; (b) $H_2$, Raney-Ni, MeOH, 24 h, 25 °C; (c) *p*-$AcOC_6H_4CHO$, $NaBH_3CN$, MeOH, $CH_3COOH$ up to pH 6, 0 → 25 °C, 24 h; (d) MsCl, $Et_3N$, 4 Å molecular sieves, $CH_2Cl_2$, 0 → 25 °C, 2 h; (e) $K_2CO_3$, MeOH−$H_2O$, 25 °C, 2 h.

greater than 70 ppm for this carbon atom are typical of trans-fused compounds.[1,15]

The complete enantioselectivity of the process leading to pyrrolizidines **7** was ascertained by determining the enantiomeric excess in the case of pyrrolizidine (3*S*,5*S*)-**7a**. This was accomplished by the analysis of the $^1$H NMR spectrum of the pyrrolizidinium salt obtained by treatment of **7a** with 1 equiv of (+)-MPTA (Mosher's acid)[16] in $CDCl_3$. The ee was calculated by measuring the areas of the signals of the MeO group, splitted at 3.59 and 3.52 ppm in the diastereomeric salts, and corresponded, as expected, to the enantiomeric purity of the starting nitro alcohol **3a** (96%).

Since most of the biologically active pyrrolizidine alkaloids have a cis relative configuration at C-3 and C-5, we considered it useful to ascertain if the strategy described above could be applied to the synthesis of *cis*-3,5-diarylpyrrolizidines, choosing compound **13** as the simplest target (Scheme 4), i.e., the diaryl analogue of **7a** with the 3,5-cis relative configuration as in xenovenine (Figure 1). However, the direct reduction of nitrodiketone **2a** by (+)- or (−)-DIP-Cl is in this case unsuitable for the preparation of *meso*-nitrodiol **12**, which instead could be obtained as depicted in Scheme 4. Addition of (*S*)-nitro alcohol **10**,[5d] in the presence of Amberlyst A21, to phenyl vinyl ketone gave nitro compound **11** as a 1:1 diastereomeric mixture.[5a] The stereoselective reduction of the carbonyl group in **11** was then performed by using (+)-DIP-Cl, affording the expected *meso*-diols **12** with 1*S*,4*R*,7*R* and 1*S*,4*S*,7*R* configuration in 1:1 ratio and 68% yield. (In the $^{13}$C NMR spectrum of the mixture only the signals at 88.9 and 87.8 ppm attributable to the C-4 atom of the two *meso*-nitrodiols are present).[5a] The mixture of diols **12** was then converted by the usual methodology into pyrrolizidine **13**, obtained in 18% overall yield as a 1:1 mixture of meso isomers having a 3,5-cis relative configuration. Although separation of the two isomers was not carried out, this stereochemical assignment is immediate from the analysis of the $^1$H NMR spectrum of the mixture: protons 3-H and 5-H, which are enantiotopic in compounds such as **13**, have in fact the same chemical shift and resonate at 3.91 ppm in one isomer and at 3.20 ppm in the other one. Proton 7a-H resonates below 3 ppm (2.81 and 2.49 ppm) in both isomers, and in the $^{13}$C NMR spectrum of the mixture, two doublets attributable to C-7a are found at 70.0 and 72.6 ppm. These values, as mentioned in discussing the stereochemistry of pyrrolizidines **7**, could be accounted for by assuming a trans-fused stereochemistry for the ring junction in **13**.[1,2c,15] This would be also consistent with the observation that 3,5-dimethylpyrrolizidines with cis relative stereochemistry of the substituents are more stable in the trans-fused form.[6]

In conclusion, we have presented a short and efficient route for the preparation of enantiomerically pure 3,5-diarylpyrrolizidines **7**, obtained in 41−56% overall yield after four steps. The methodology was based on a double nucleophilic displacement occurring in chiral 1,7-diaryl-4-[(*N*-benzyl)amino]heptane-1,7-diols as soon as the two hydroxy groups were converted into mesylates. The cyclization reactions were diastereo- and enantioselective, affording configurationally inverted, cis-fused 3,5-disubstituted pyrrolizidinium salts **6**. The presence of a *p*-acetyloxy substituent on the *N*-benzyl group in these salts was a prime requirement to permit the removal of the N-protection by alkaline hydrolysis, thus providing target tertiary amines **7**. Cis-3,5-diaryl-substituted pyrrolizidines such as **13** can be also prepared by using the same methodology. The synthesis of pyrrolizidines **7** and **13** was accomplished starting from chiral nitro alcohols or nitrodiols, which in turn can be prepared by enantioselective reduction of nitroketones or nitrodiketones using either yeasts or chemical reducing reagents depending on the type of substrate. This should allow for the preparation of a wide range of chiral precursors that can be easily converted into the corresponding 3,5-disubstituted pyrrolizidines by the methodology described in this paper.

## Experimental Section

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel using flash-column techniques; $R_f$ values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. $^1$H and $^{13}$C NMR spectra were recorded at 200 and 50.33 MHz, respectively. NOESY spectra were recorded at 500 MHz. Mass spectra were carried out in EI at 70 eV ionizing voltage. $CH_2Cl_2$ was distilled from $CaH_2$. All reactions requiring anhydrous conditions were performed in flame-dried glassware. Compounds **1**−**3**, **10**, and **11** were prepared as reported.[5a,d]

**(1*R*,7*R*)-(+)-1,7-Diphenyl-4-aminoheptane-1,7-diol (4a).** A solution of **3a** (3.31 g, 10.5 mmol) in MeOH (40 mL) was added under stirring to a prehydrogenated suspension of wet Raney-Ni (3.99 g, washed three times with 5 mL of MeOH before the addition of the solution of **3a**) in the same solvent (20 mL). The mixture was left under a hydrogen atmosphere for 24 h at room temperature and then filtered twice on a Celite layer and finally evaporated to give pure **4a** (2.59 g, 82%) as a white solid: mp 35−36 °C; $[\alpha]^{25}_D$ +43.6 (*c* 0.78, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.15 (m, 10 H), 4.61 (m, 2 H), 3.03 (m, 1 H), 1.90−1.45 (m, 8 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 144.6 (s), 144.4 (s), 128.4 (d, 4 C), 127.2 (d, 2 C), 125.8 (d, 4 C), 74.1 (d), 73.4 (d), 51.9 (d), 36.4 (t), 34.8 (t), 32.2 (t), 31.9 (t); MS *m*/*z* 299 ($M^+$, 1), 146 (100); IR ($CDCl_3$) 3601, 3550−3150 $cm^{-1}$. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.01; H, 8.53; N, 4.52.

**(1*R*,7*R*)-(+)-1,7-Bis(2-methoxyphenyl)-4-aminoheptane-1,7-diol (4b).** According to the procedure reported above, starting from **3b** (1.85 g, 4.75 mmol) aminodiol **4b** (1.37 g, 80%) was obtained as a white solid: mp 56−57 °C; $[\alpha]^{25}_D$ +33.0 (*c* 0.20, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.35 (m, 2 H), 7.24−7.12 (m, 2 H), 6.91−6.75 (m, 4 H), 4.91 (m, 2 H), 3.73 (s, 6 H), 3.27 (m, 1 H), 3.20−2.40 (m, 4 H), 1.80−1.60 (m, 8 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.8 (s), 155.7 (s), 132.5 (s, 2 C), 127.8 (d, 2 C), 126.5 (d), 126.4

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(d), 120.6 (d, 2 C), 110.0 (d), 109.9 (d), 69.0 (d), 68.0 (d), 55.0 (q, 2 C), 52.0 (d), 34.2 (t), 32.7 (t), 30.6 (t), 28.3 (t); MS *m*/*z* 359 ($M^+$, 5), 83 (100); IR ($CDCl_3$) 3607, 3600−3000 $cm^{-1}$. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.10; H, 8.43; N, 3.71.

**(1*R*,7*R*)-(+)-1,7-Diphenyl-4-[(*N*-benzyl)amino]heptane-1,7-diol (5a).** $NaBH_3CN$ (121 mg, 1.93 mmol) and benzaldehyde (213 μL, 2.11 mmol) were added to a stirred solution of **4a** (578 mg, 1.93 mmol) in MeOH (2 mL) cooled at 0 °C. A few drops of glacial $CH_3COOH$ were added up to pH 6, and the solution was left under stirring at room temperature. After 24 h, the solution was diluted with water (10 mL), and $Na_2CO_3$ (s) was added to adjust pH 9−10. The resulting mixture was saturated with NaCl (s), and finally the product was extracted with chloroform (3 × 15 mL). The organic layer was dried over $Na_2SO_4$, filtered, and evaporated, furnishing crude **5a**. This was purified by chromatography ($CH_2Cl_2$−MeOH, 20:1, 1% $NH_4OH$ in MeOH, $R_f$ 0.18), obtaining pure **5a** (632 mg, 84%) as a low-melting compound: $[\alpha]^{25}_D$ +29.9 (*c* 0.60, $CH_3OH$); $^1H$ NMR ($CDCl_3$) δ 7.40−7.15 (m, 15 H), 4.66 (m, 2 H), 3.77 (AB system, *J* = 12.8 Hz, 2 H), 2.69 (m, 1 H), 1.90−1.45 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 145.1 (s), 145.0 (s), 138.6 (s), 128.4 (d, 4 C), 128.1 (d, 2 C), 127.2 (d, 2 C), 127.0 (d), 126.9 (d, 2 C), 125.7 (d, 4 C), 73.8 (d), 73.7 (d), 56.4 (d), 50.6 (t), 36.1 (t), 35.1 (t), 29.9 (t), 29.2 (t); MS *m*/*z* 389 ($M^+$, 20), 91 (100); IR ($CDCl_3$) 3605 $cm^{-1}$. Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 79.85; H, 8.30; N, 3.20.

**(1*R*,7*R*)-(+)-1,7-Bis(2-methoxyphenyl)-4-[(*N*-benzyl)amino]heptane-1,7-diol (5b).** According to the procedure reported for the preparation and purification of **5a**, *N*-benzyl aminodiol **5b** (920 mg) was obtained starting from **4b** (856 mg, 2.38 mmol) as a low-melting compound in 86% yield: $[\alpha]^{25}_D$ +52.2 (*c* 1.13, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 7.39−7.16 (m, 9 H), 6.97−6.82 (m, 4 H), 4.89 (m, 2 H), 3.87−3.67 (m, 8 H), 2.65 (m, 1 H), 2.60−2.50 (br s, 3 H), 1.88−1.78 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 159.9 (s, 2 C), 139.2 (s), 133.2 (s), 133.1 (s), 128.4 (d, 2 C), 127.7 (d, 2 C), 127.6 (d, 2 C), 127.1 (d), 126.5 (d, 2 C), 120.5 (d, 2 C), 110.1 (d), 110.0 (d), 69.3 (d), 69.0 (d), 56.6 (d), 55.0 (q, 2 C), 50.6 (t), 34.4 (t), 33.3 (t), 30.3 (t), 29.6 (t); MS *m*/*z* 449 ($M^+$, 42), 266 (100), 91 (100); IR ($CDCl_3$) 3609, 3480−3120 $cm^{-1}$. Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.47; H, 7.64; N, 2.98.

**(1*R*,7*R*)-(+)-1,7-Diphenyl-4-[*N*-((4-methoxyphenyl)methyl)amino]heptane-1,7-diol (5c).** As reported for **5a**, starting from **4a** (332 mg, 1.11 mmol) and *p*-anisaldehyde (150 μL, 1.24 mmol), pure **5c** (396 mg) was obtained as a low-melting compound in 85% yield: $[\alpha]^{25}_D$ +40.0 (*c* 0.18, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 7.40−7.15 (m, 12 H), 6.84 (m, 2 H), 4.62 (m, 2 H), 3.76 (s, 3 H), 3.72 (AB system, *J* = 12.4 Hz, 2 H), 2.66 (m, 1 H), 1.90−1.45 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 145.1 (s), 145.0 (s), 130.4 (s), 130.0 (d, 2 C), 128.4 (d, 4 C), 127.3 (d), 127.2 (d), 125.8 (d, 4 C), 114.1 (d, 2 C), 113.6 (s), 74.2 (d), 74.0 (d), 56.6 (d), 55.2 (q), 50.0 (t), 36.3 (t), 35.1 (t), 30.0 (t), 29.2 (t); MS *m*/*z* 419 ($M^+$, 1), 121 (100); IR ($CDCl_3$) 3614 $cm^{-1}$. Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found: C, 77.11; H, 8.10; N, 3.15.

**(1*R*,7*R*)-(+)-1,7-Diphenyl-4-[*N*-((4-acetyloxyphenyl)methyl)amino]heptane-1,7-diol (5d).** As reported for **5a**, but in the workup, $NaHCO_3$ is added to adjust pH 7. Starting from **4a** (434 mg, 1.45 mmol) and *p*-acetyloxybenzaldehyde (228 μL, 1.62 mmol), pure **5d** (597 mg) was obtained as a low-melting compound in 92% yield: $[\alpha]^{25}_D$ +32.5 (*c* 0.27, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 7.40−7.15 (m, 12 H), 7.02 (m, 2 H), 4.63 (m, 2 H), 3.72 (AB system, *J* = 12.9 Hz, 2 H), 2.65 (m, 1 H), 2.27 (s, 3 H), 1.90−1.40 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) δ: 169.6 (s), 149.9 (s), 145.2 (s), 145.0 (s), 136.6 (s), 129.6 (d, 2 C), 128.4 (d, 4 C), 127.2 (d, 2 C), 125.8 (d, 4 C), 121.8 (d, 2 C), 74.3 (d), 74.1 (d), 56.8 (d), 50.4 (t), 36.3 (t), 35.2 (t), 30.4 (t), 29.6 (t), 21.1 (q); MS *m*/*z* 447 ($M^+$, 1), 107 (100); IR ($CDCl_3$) 3612, 1755 $cm^{-1}$. Anal. Calcd for $C_{28}H_{33}NO_4$: C, 75.14; H, 7.43; N, 3.13. Found: C, 75.43; H, 7.62; N, 3.04.

**(1*R*,7*R*)-(+)-1,7-Bis(2-methoxyphenyl)-4-[*N*-((4-acetyloxyphenyl)methyl)amino]heptane-1,7-diol (5e).** As reported for **5a**, but in the workup $NaHCO_3$ is added to adjust pH 7. Starting from **4b** (334 mg, 0.93 mmol) and *p*-acetyloxybenzaldehyde (147 μL, 1.04 mmol), pure **5e** (425 mg) was obtained as a low-melting compound in 90% yield: $[\alpha]^{25}_D$ +30.7 (*c* 0.21, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 7.40−7.30 (m, 3 H), 7.25−7.05 (m, 3 H), 7.00−6.75 (m, 6 H), 4.87 (m, 2 H), 3.80 (s, 3 H), 3.79 (m, 2 H), 3.78 (s, 3 H), 2.70 (m, 1 H), 2.27 (s, 3 H), 1.90−1.40 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 169.6 (s), 156.2 (s, 2 C), 151.2 (s), 136.7 (s), 132.9 (s, 2 C), 129.6 (d, 2 C), 128.1 (d), 128.0 (d), 126.7 (d, 2 C), 121.7 (d, 2 C), 120.7 (d, 2 C), 110.3 (d, 2 C), 70.1 (d), 69.6 (d), 56.9 (d), 55.2 (q, 2 C), 50.2 (t), 34.5 (t), 33.3 (t), 30.5 (t), 29.8 (t), 21.1 (q); MS *m*/*z* 489 ($M^+$ − 18, 3), 324 (100); IR ($CDCl_3$) 3595, 3050−2850, 1756 $cm^{-1}$. Anal. Calcd for $C_{30}H_{37}NO_6$: C, 70.98; H, 7.35; N, 2.76. Found: C, 70.89; H, 7.55; N, 2.55.

**(3*S*,4*S*,5*S*,7a*R*)-(−)-3,5-Diphenyl-4-benzylpyrrolizidinium Chloride (6a).** A solution of **5a** (453 mg, 1.09 mmol) and $Et_3N$ (765 μL, 5.45 mmol) in anhydrous $CH_2Cl_2$ (39 mL) was stirred for 30 min over activated 4 Å molecular sieves under a nitrogen atmosphere. After the solution was cooled to 0 °C, MsCl (186 μL, 2.40 mmol) was added dropwise and the resulting solution left under stirring at room temperature. After 2 h, the solution was diluted with water (50 mL), the aqueous layer was saturated with NaCl (s), and the two phases were separated. The organic layer was dried over $Na_2SO_4$, filtered, and evaporated, affording a crude that was purified by chromatography, first eluting with $CH_2Cl_2$−MeOH, 20:1, and then with MeOH, obtaining pure **6a** (306 mg, 72%) as a white solid: mp 109−110 °C; $[\alpha]^{25}_D$ −101.3 (*c* 0.82, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 8.09 (m, 2 H), 7.70−7.35 (m, 8 H), 7.17 (d, *J* = 7.3 Hz, 1 H), 7.04 (m, 2 H), 6.54 (d, *J* = 7.7 Hz, 2 H), 5.68 (m, 1 H), 5.55 (d, *J* = 12.6 Hz, 1 H), 5.05 (dd, *J* = 13.5, 5.1 Hz, 1 H), 4.74 (dd, *J* = 13.5, 5.1 Hz, 1 H), 3.84 (m, 1 H), 3.54 (d, *J* = 12.6 Hz, 1 H), 2.79 (m, 1 H), 2.68 (m, 1 H), 2.20−1.80 (m, 3 H), 1.74 (m, 1 H), 1.14 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 133.5 (d, 2 C), 131.3 (d, 2 C), 130.9 (d, 2 C), 130.9 (s), 129.9 (s), 129.9 (d, 2 C) 129.7 (d, 2 C), 129.3 (d), 129.0 (d, 2 C), 128.5 (s), 127.8 (d, 2 C), 78.4 (d), 77.6 (d), 72.3 (d), 62.2 (t), 31.0 (t), 30.8 (t), 27.5 (t), 27.1 (t); MS *m*/*z* 389 ($M^+$, 3), 91 (100). Anal. Calcd for $C_{26}H_{28}NCl$: C, 80.08; H, 7.24; N, 3.59. Found: C, 79.96; H, 7.37; N, 3.22.

**(3*S*,4*S*,5*S*,7a*R*)-(−)-3,5-Bis(2-methoxyphenyl)-4-benzylpyrrolizidinium Chloride (6b).** Prepared as reported for **6a**. Starting from **5b** (189 mg, 0.42 mmol), pure **6b** (132 mg, 70%) was obtained, after chromatography ($CH_2Cl_2$−MeOH, 20:1, $R_f$ 0.19), as a white solid: mp 82−83 °C; $[\alpha]^{25}_D$ −62.2 (*c* 0.24, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.60−7.38 (m, 4 H), 7.30−7.20 (m, 3 H), 7.00−6.63 (m, 4 H), 5.64 (dd, *J* = 12.8, 5.8 Hz, 1 H), 5.22 (m, 1 H), 4.98 (d, *J* = 12.8 Hz, 1 H), 4.91 (dd, *J* = 10.6, 6.2 Hz, 1 H), 4.50 (d, *J* = 12.8 Hz, 1 H), 3.73 (s, 3 H), 3.70 (m, 1 H), 3.65 (s, 3 H), 2.96 (m, 1 H), 2.75 (m, 1 H), 2.22 (m, 2 H), 2.00−1.70 (m, 2 H), 0.97 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 158.8 (s), 158.5 (s), 133.2 (d, 2 C), 132.9 (d), 132.5 (d), 131.6 (d), 131.4 (d), 130.1 (d), 129.6 (s), 129.2 (d, 2 C), 121.8 (d), 120.8 (d), 119.3 (s), 118.8 (s), 111.5 (d), 111.4 (d), 77.9 (d), 71.7 (d), 70.2 (d), 62.2 (t), 55.6 (q), 54.9 (q), 31.0 (t), 29.3 (t), 28.0 (t), 27.8 (t); MS *m*/*z* 449 ($M^+$, 0.1), 91 (100). Anal. Calcd for $C_{28}H_{32}NO_2Cl$: C, 74.73; H, 7.17; N, 3.11. Found: C, 74.55; H, 7.21; N, 3.01.

**(3*S*,4*S*,5*S*,7a*R*)-(−)-3,5-Diphenyl-4-[(4-methoxyphenyl)methyl]pyrrolizidinium Chloride (6c).** Prepared and purified as reported for **6a**. Starting from **5c** (298 mg, 0.71 mmol), pure **6c** (203 mg, 68%) was obtained, after chromatography ($CH_2Cl_2$−MeOH, 20:1, $R_f$ 0.12), as a white solid: mp 118−119 °C; $[\alpha]^{25}_D$ −112.8 (*c* 1.10, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2 H), 7.58 (m, 4 H), 7.20 (m, 2 H), 7.00 (m, 4 H), 6.54 (d, *J* = 7.7 Hz, 2 H), 5.69 (m, 1 H), 5.57 (d, *J* = 16.0 Hz, 1 H), 5.06 (dd, *J* = 12.8, 4.7 Hz, 1 H), 4.70 (dd, *J* = 13.1, 5.1 Hz, 1 H), 3.90 (m, 1 H), 3.83 (s, 3 H), 3.56 (d, *J* = 16.0 Hz, 1 H), 2.87−2.58 (m, 2 H), 2.20−1.90 (m, 3 H), 1.75 (m, 1 H), 1.22 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 160.5 (s), 135.0 (d, 2 C), 131.3 (d, 2 C), 130.9 (d, 2 C), 130.0 (s), 129.9 (s), 129.9 (d) 129.7 (d, 2 C), 129.3 (d), 129.0 (d, 2 C), 120.1 (s), 114.3 (d, 2 C), 78.1 (d), 77.2 (d), 71.9 (d), 61.9 (t), 55.0 (q), 31.1 (t), 30.9 (t), 27.6 (t), 27.1 (t); MS *m*/*z* 419 ($M^+$, 1), 121 (100). Anal. Calcd for $C_{27}H_{30}NOCl$: C, 77.22; H, 7.20; N, 3.34. Found: C, 77.48; H, 7.47; N, 3.17.

**(3*S*,4*S*,5*S*,7a*R*)-(−)-3,5-Diphenyl-4-[(4-acetyloxyphenyl)methyl]pyrrolizidinium Chloride (6d).** Prepared as reported for **6a**. Starting from **5d** (300 mg, 0.67 mmol), pure **6d** (234 mg, 78%) was obtained, after chromatography ($CH_2Cl_2$−MeOH, 20:1, $R_f$ 0.10), as a white solid: mp 122−123 °C; $[\alpha]^{25}_D$ −102.3 (*c* 0.27, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2 H), 7.57 (m, 4 H), 7.20 (m, 2 H), 7.05 (m, 4 H), 6.54 (d, *J* = 7.7 Hz, 2 H), 5.70 (m, 1 H), 5.66 (d, *J* = 12.8 Hz, 1 H), 5.00 (dd, *J* = 13.1, 4.7 Hz, 1 H), 4.71 (dd, *J* = 13.5, 5.1 Hz, 1 H), 3.90 (m, 1 H), 3.50 (d, *J* = 12.8 Hz, 1 H), 2.90−2.55 (m, 2 H), 2.35−1.90 (m, 3 H), 2.29

(s, 3 H), 1.78 (m, 1 H), 1.22 (m, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.8 (s), 151.9 (s), 134.9 (d, 2 C), 131.6 (d, 2 C), 131.3 (d), 131.1 (d, 2 C), 130.1 (s), 129.9 (d, 2 C), 129.8 (s), 129.7 (d), 128.1 (d, 2 C), 126.3 (s), 122.4 (d, 2 C), 78.7 (d), 77.9 (d), 72.6 (d), 61.7 (t), 31.3 (t), 30.9 (t), 27.8 (t), 27.3 (t), 20.9 (q); MS *m*/*z* 294 (21), 83 (100); IR ($CDCl_3$) 1762 cm$^{-1}$. Anal. Calcd for $C_{28}H_{30}NO_2Cl$: C, 75.07; H, 6.75; N, 3.13. Found: C, 74.88; H, 6.92; N, 2.97.

**(3*S*,5*S*,7a*S*)-(−)-3,5-Diphenylpyrrolizidine (7a).** To a solution of salt **6d** (90 mg, 0.2 mmol) in MeOH (2.5 mL) was added a solution of $K_2CO_3$ (160 mg, 1.16 mmol) in water (1.6 mL), and the resulting suspension was left under stirring at room temperature. After 2 h, 2 N HCl was added up to pH 1−1.5, and the solution was extracted with $Et_2O$ (2 × 5 mL). To the aqueous layer was then added $K_2CO_3$ (s) up to pH 9−10, followed by extraction with chloroform (2 × 10 mL). The latter organic layer was dried over $Na_2SO_4$, filtered, and evaporated to give pure **7a** (38 mg, 72%) as a white solid: mp 40−41 °C; $[\alpha]^{25}_D$ −78.5 (*c* 0.61, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.00 (m, 8 H), 6.89 (m, 2 H), 4.32 (m, 1 H), 4.02 (m, 1 H), 3.67 (dd, $J$ = 9.2, 6.3 Hz, 1 H), 2.25−1.90 (m, 4 H), 1.85−1.40 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 131.5 (s), 129.5 (s), 129.2 (d, 2 C), 127.6 (d, 4 C), 127.2 (d), 126.7 (d, 2 C), 125.9 (d), 66.4 (d), 64.5 (d), 66.2 (d), 37.8 (t), 33.3 (t), 31.4 (t), 28.6 (t); MS *m*/*z* 263 ($M^+$, 44), 104 (100). Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.81; H, 8.13; N, 5.21.

**(3*S*,5*S*,7a*S*)-(−)-3,5-Bis(2-methoxyphenyl)pyrrolizidine (7b).** Aminodiol **5e** (99 mg, 0.195 mmol) was converted into crude salt **6e** (92 mg, 93%) as reported above. This was not purified but used directly for the deprotection step performed as described for **7a**. Pyrrolizidine **7b** (49 mg) was obtained as a low-melting compound in 78% yield: $[\alpha]^{25}_D$ −57.2 (*c* 0.13, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.51 (d, $J$ = 7.0 Hz, 1 H), 7.31 (d, $J$ = 7.6 Hz, 1 H), 7.00−6.80 (m, 2 H), 6.74 (m, 2 H), 6.36 (d, $J$ = 8.0 Hz, 1 H), 6.23 (d, $J$ = 8.4 Hz, 1 H), 4.44 (m, 1 H), 4.14 (dd, $J$ = 10.3, 5.2 Hz, 1 H), 3.81 (m, 1 H), 3.43 (s, 3 H), 3.40 (s, 3 H), 2.25−1.90 (m, 4 H), 1.60−1.30 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2 (s), 155.8 (s), 128.3 (d, 2 C), 128.1 (d, 2 C), 120.0 (s), 119.7 (d), 119.1 (s), 118.8 (d), 108.8 (d, 2 C), 65.6 (d), 65.4 (d), 60.1 (d), 54.9 (q), 54.5 (q), 36.0 (t), 33.7 (t), 31.3 (t), 26.2 (t); MS *m*/*z* 323 ($M^+$, 46), 91 (100). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.00; H, 7.79; N, 4.33. Found: C, 78.39; H, 7.42; N, 4.08.

**(1*S*,4*R*,7*R*)- and (1*S*,4*S*,7*R*)-1,7-Diphenyl-4-nitroheptane-1,7-diol (12).** To a solution of (+)-DIP-Cl (343 mg, 1.07 mmol) in $CH_2Cl_2$ (5 mL) cooled at −25 °C was added a solution of **11** (313 mg, 0.96 mmol) in $CH_2Cl_2$ (2 mL), under stirring and $N_2$ atmosphere. After 5 h, the solvent was evaporated and the α-pinene removed under high vacuum (0.15 mbar). The residue was then dissolved in $Et_2O$, and diethanolamine (205 $\mu$L) was added. The resulting suspension was stirred for 2 h, filtered, and concentrated. The residue was chromatographed, eluting first with $CH_2Cl_2$ and then with $CH_2Cl_2$−MeOH, 20:1, to give the 1:1 diastereomeric mixture **12** (215 mg, 68%) as a low-melting solid ($R_f$ 0.25): $^1$H NMR ($CDCl_3$) $\delta$ 7.30−7.00 (m, 10 H + 10 H), 4.30 (m, 3 H + 3 H), 2.20−1.40 (m, 8 H + 8 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 143.8 (s, 2 C + 2 C), 128.5 (d, 2 C + 2 C), 128.3 (d, 2 C + 2 C), 127.7 (d, 2 C + 2 C), 125.6 (d, 4 C + 4 C), 88.9 (d), 87.8 (d), 73.5 (d, 2 C), 73.0 (d, 2 C), 34.8 (t, 2 C), 34.6 (t, 2 C), 30.2 (t, 2 C), 29.6 (t, 2 C).

**(3*S*,5*R*,7a*R*)- and (3*S*,5*R*,7a*S*)-3,5-Diphenylpyrrolizidine (13).** Nitrodiol **12** (215 mg, 0.65 mmol) was subjected to the usual hydrogenation over Raney-Ni, and as reported for the preparation of **5d**, the resulting amine (170 mg) was transformed into the corresponding *p*-acetyloxybenzylamine (79 mg, 31%): $^1$H NMR ($CDCl_3$) $\delta$: 7.20−7.10 (m, 12 H + 12 H), 7.03 (d, $J$ = 8.4 Hz, 2 H + 2 H), 4.65 (m, 2 H + 2 H), 3.77 (s, 2 H), 3.69 (s, 2 H), 2.72 (m, 1 H), 2.60 (m, 1 H), 2.29 (s, 3 H + 3 H), 1.90−1.50 (m, 8 H + 8 H).

This secondary amine was then converted into the pyrrolizidinium salt according to the usual procedure, and the crude reaction mixture (66 mg) was dissolved in MeOH (2 mL) and treated with a solution of $K_2CO_3$ (120 mg) in $H_2O$ (2 mL). After 2 h, the usual workup afforded a crude oil that was chromatographed, eluting first with $CH_2Cl_2$−MeOH, 20:1, and then with MeOH, obtaining the 1:1 diastereomeric mixture **13** (26 mg, 68%) as a pale yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.40−6.70 (m, 10 H + 10 H), 3.91 (t, $J$ = 6.6 Hz, 2 H), 3.20 (t, $J$ = 7.6 Hz, 2 H), 2.81 (m, 1 H), 2.49 (m, 3 H), 2.30−1.50 (m, 8 H + 6 H);$^{13}$C NMR ($CDCl_3$) $\delta$ 131.5 (s, 2 C), 130.5 (s, 2 C), 127.9 (d, 4 C), 127.8 (d, 4 C), 127.2 (d, 4 C), 126.8 (d, 4 C), 126.1 (d, 2 C), 126.0 (d, 2 C), 72.6 (d), 70.0 (d), 65.1 (d, 2 C), 65.0 (d, 2 C), 40.3 (d, 2 C), 35.7 (d, 2 C), 32.4 (d, 2 C), 26.2 (d, 2 C); MS *m*/*z* 263 ($M^+$, 30), 104 (100); IR ($CDCl_3$) 2872, 2794, 2713, 2650 cm$^{-1}$ (Bohlmann bands).

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