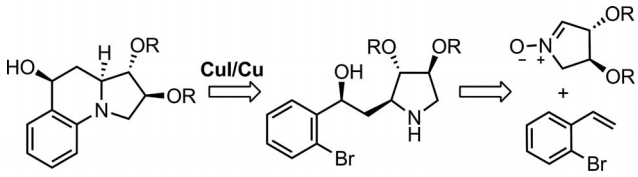
EurJOC European Journal of Organic Chemistry

Copper-Mediated *N*-Arylation



Highly hydroxy-functionalized hexahydropyrrolo[1,2-*a*]quinolines that have the same absolute configuration at stereocenters C-2, C-3 and C-3a as natural lentiginosine have been synthesized through a three-step sequence starting from enantiopure dialkoxypyrroline *N*-oxides derived from L-tartaric acid.

Keywords: Azasugars / Fused-ring systems / Copper catalysis / Cross-coupling / Cycloaddition

DOI: 10.1002/ejoc.201300440

Copper-Catalyzed Synthesis of a Highly Hydroxy-Functionalized Benzo[*e*]indolizidine by Intramolecular *N*-Arylation

Franca M. Cordero,*[a] Bhushan B. Khairnar,[a] Paola Bonanno,[a] Andrea Martinelli,[a] and Alberto Brandi*[a]

Dedicated to Professor Pierre Vogel on the occasion of his 70th birthday

Keywords: Azasugars / Fused-ring systems / Copper catalysis / Cross-coupling / Cycloaddition

The enantiopure (2*S*,3*S*,3a*S*,5*S*)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-2,3,5-triol (2,3,5-trihydroxybenzo[*e*]indolizidine) framework has been synthesized by a straightforward strategy consisting of 1,3-dipolar cycloaddition of a pyrroline *N*-oxide to 2-bromostyrene followed by isoxazolidine N–O bond reduction and cyclization by copper-catalyzed nucleophilic aromatic substitution of the intermediate pyrrolidine.

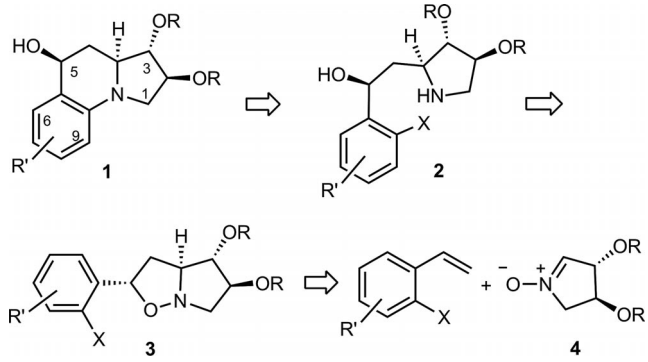
Introduction

Polyhydroxylated alkaloids (iminosugars) have attracted considerable attention for their remarkable biological activity and potential as pharmaceuticals tools.[1] Those with indolizidine structure, like castanospermine, swainsonine, or lentiginosine, are among the most studied for their broad activity. For example, castanospermine was brought to be a commercial drug against HCV infection.[2]

Lentiginosine [(1*S*,2*S*,8a*S*)-octahydroindolizine-1,2-diol], despite being one of the least-substituted exemplars, has shown interesting activity in addition to glycosidase inhibition. In particular, it was shown to be a potent inhibitor of HSP90.[3] Moreover, its enantiomer [(1*R*,2*R*,8a*R*)-octahydroindolizine-1,2-diol][4] and the corresponding 7-OH derivative [(1*R*,2*R*,7*S*,8a*R*)-octahydroindolizine-1,2,7-triol][5] have low cytotoxicity, but can induce apoptosis in cancer cell strains.

The search for new, more selective and potent candidates of this important class of compounds suggested the modification of the indolizidine skeleton through its conjugation with biorelevant substructures, like functionalized chains or amino acid structures. The six-membered ring of lentiginosine was the target of these functionalizations.[6] Proceeding on this idea, the synthesis of benzosubstituted lentiginosines was undertaken, supported by computational studies that suggested a better interaction of a benzolentiginosine with the enzymatic cavity. In addition, natural aryl-substituted polyhydroxylated pyrrolidines, like codonopsine or radicamine,[7] show interesting biological activities.

As outlined in Scheme 1, we envisioned a direct pathway to the creation of the benzo[*e*]indolizidine skeleton consisting of an intramolecular aromatic nucleophilic substitution of a suitable 2-[2-(2-halophenyl)ethyl]pyrrolidine such as **2**. The requisite intermediate **2** was envisioned to arise through reductive cleavage of the cycloadduct **3** between a 1-halo-2-ethenylbenzene and an enantiopure pyrroline *N*-oxide **4** derived, in turn, from tartaric acid. One particular advantage of this approach was anticipated to be the control of the regio- and stereochemistry of the 1,3-dipolar cycloaddition (1,3-DC).



Scheme 1. Retrosynthetic analysis of benzo[*e*]indolizidine **1**.

We report here the synthesis of pyrrolidine **2** (R = TBDMS or *t*Bu; R′ = H) and its cyclization to the corre-

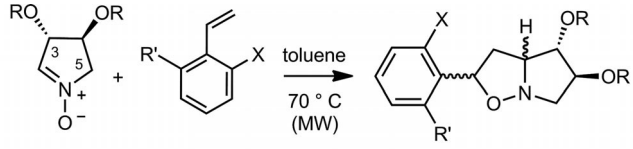
[a] Department of Chemistry "Ugo Schiff", University of Florence,
Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
Fax: +39-055-4573531
E-mail: franca.cordero@unifi.it
alberto.brandi@unifi.it
Homepage: http://www.unifi.it/dipchimica/CMpro-v-p-414.html
http://www.unifi.it/dipchimica/CMpro-v-p-382.html

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300440.

sponding tricyclic derivative **1**. The *tert*-butyl derivatives (R = *t*Bu) were synthesized in both enantiomeric forms, although only the compounds derived from L-tartaric acid (L-series) are discussed for the sake of brevity.

Results and Discussion

Initially, the 1,3-DC of dihydroxylated pyrroline *N*-oxides **5**[8,9] and **6**[5] with 1-halo-2-ethenylbenzenes was studied. The reactions of 2,6-dichlorostyrene (**7**) and 2-bromostyrene (**8**) with nitrones **5** and **6** in toluene at 70 °C under microwave heating (MW) afforded diastereomeric mixtures of the corresponding cycloadducts **9**–**11** in high overall yield (92–99%) (Scheme 2).



5: R = TBDMS
6: R = *t*Bu

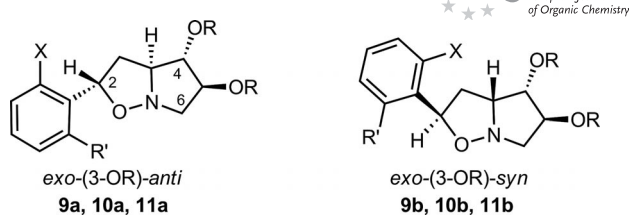
7: R' = X = Cl
8: R' = H, X = Br

9: R = TBDMS, R' = X = Cl
10: R = TBDMS, R' = H, X = Br
11: R = *t*Bu, R' = H, X = Br

Reagents	Time	Adduct	Yield	*exo-anti* : *exo-syn* : *endo-anti*
5 + **7**	1 h 45'	**9**	94%	6.8 : 6.4 : 1
5 + **8**	2 h	**10**	92%	18.4 : 11.6 : 1
6 + **8**	5 h	**11**	99%	12 : 3.5 : 1

Scheme 2. 1,3-DC of nitrones **5** and **6** with dipolarophiles **7** and **8**.

In all cases, the *exo*-(3-OR)-*anti* diastereomer (**9a**–**11a**) (Figure 1), which was derived from the *exo* attack of the alkene on the opposite face of the C-3 substituent of the nitrone, was the major adduct. The second and third isomers were, respectively, the *exo*-(3-OR)-*syn* and the *endo*-(3-OR)-*anti* isomers (**9b**–**11b** and **9c**–**11c**).[10] The 1,3-DC of nitrone **5** with dichlorostyrene **7** was less diastereoselective than the corresponding reaction with **8** (ca 1:1 vs. 1.6:1 *exo-anti*/*exo-syn* ratio). It is likely that the monosubstituted bromostyrene **8** can better accommodate the substituted phenyl ring in an *anti* approach. The highest stereoselectivity was obtained with the dipolarophile **8** and di-*tert*-butoxy nitrone **6**, which afforded the adduct *exo*-(3-OR)-*anti*-**11a** in as much as 73% yield (calculated). Diastereomeric adducts were not easily separable by chromatography on silica gel, and were often obtained as enriched fractions of isomers and separated at later steps (see the Exp. Sect.).



exo-(3-OR)-*anti*
9a, 10a, 11a

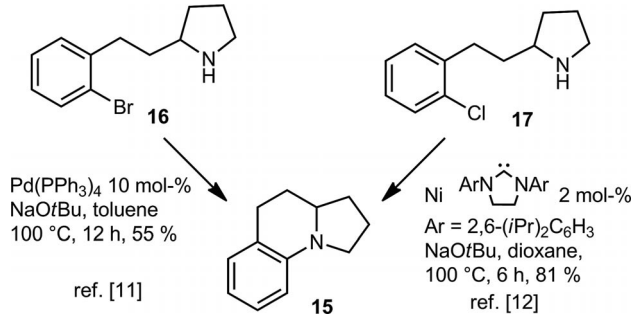
exo-(3-OR)-*syn*
9b, 10b, 11b

Figure 1. General structure of the two major diastereomers **9a**–**11a** and **9b**–**11b**.

The stereochemistry of cycloadducts **9**–**11** was assigned by NMR analyses and then confirmed by the analysis of the corresponding derivatives (see Supporting Information).

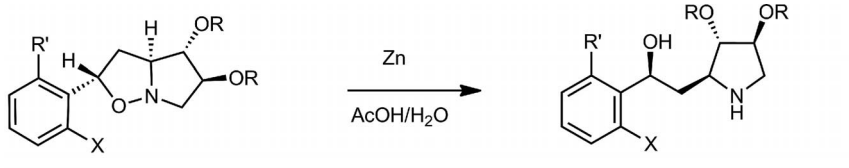
The selective reduction of the isoxazolidine N–O bond was carried out with Zn and acetic acid, and afforded the corresponding pyrrolidines in good yields (Scheme 3). NOE experiments on pyrrolidines derived from adducts **9a**–**11a** and **9b**–**11b** confirmed the assigned configurations (see Supporting Information).

Once the phenethyl pyrrolidines **12**–**14** were available in very few steps, the nucleophilic amine substitution of the halogenated aromatic ring was studied. An analysis of the literature showed that the unsubstituted 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (**15**) was obtained by Buchwald et al.[11] through a Pd-catalyzed amine aromatic substitution of the 2-Br-phenethylpyrrolidine (**16**) in 55% yield, and by Fort et al.[12] through the corresponding cyclization of the chloro derivative **17** in the presence of a Ni catalyst (81% yield) (Scheme 4).



Scheme 4. Previous syntheses of unsubstituted 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (**15**).

In our hands, such conditions, thoroughly investigated, were not able to afford the expected benzoindolizidine starting from derivatives **12** and **13**. The lack of reactivity of



9a	R' = X = Cl; R = TBDMS	60 °C, 4 h	72%
10a	R' = H, X = Br, R = TBDMS	60 °C, 4 h	88%
11a	R' = H, X = Br, R = *t*Bu	80 °C, 5 h	96%

12a R' = X = Cl; R = TBDMS
13a R' = H, X = Br, R = TBDMS
14a R' = H, X = Br, R = *t*Bu

Scheme 3. Reductive ring opening of the major adducts **9a**–**11a**.

these compounds under Buchwald reaction conditions could be explained by a steric hindrance effect, but most probably by the presence of the OH group in a suitable position to form a strong intramolecular hydrogen bond with the NH that, as a result, is no longer available for the coupling. Another possibility is that under the strongly alkaline conditions, the alcohol is deprotonated and the resulting alkoxide interferes with the vicinal metal coordinated with the benzene ring, quenching its catalytic effect. The presence of an intramolecular hydrogen bond in apolar solvents was proved by the persistence of the broad band in the 3100–3550 cm^{-1} region of the IR spectra of diluted solutions of **13a** (30–5 mM in $CDCl_3$). Attempts to convert the free OH group to a silyl ether with TBDMSCl and TMSCl in DMF, or TMSOTf in DCM failed or gave very small yields of the desired compound. Oxidation of the benzylic alcohol with MnO_2 also failed, in accord with a reduced reactivity of the OH group.

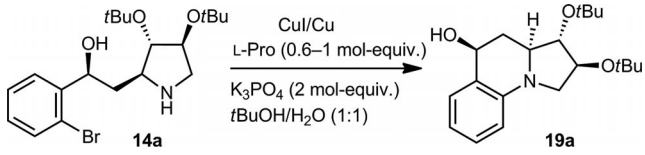
To verify these hypotheses, the cyclization under Ullmann reaction conditions[13] was then examined, because the highly polar solvents used in Cu^I catalyzed C–N coupling should effectively reduce the strength of the internal hydrogen bond in substrates **12**–**14**, and should shield the reactivity of the hydroxy group.

Cyclization of pyrrolidine **13a** in the presence of copper salts was tested using various combinations of catalyst sources, with or without proline, with an organic or inorganic base, and under anhydrous or aqueous conditions. It was found that CuI in the presence of metallic Cu was a more efficient catalyst than CuI alone or the $CuSO_4$/Cu couple, and that the use of proline as a copper ligand increased the yield. The catalytic effect of copper was proved by analyzing the thermal cyclization of **13a** (DMF, DBU or K_3PO_4, 120 °C, 2 h), which afforded only traces of **18a** along with a mixture of decomposition products. DBU and K_3PO_4 were more efficient than K_2CO_3 in DMF, but in protic solvents a higher yield was obtained when K_3PO_4 was used as base. Unfortunately, the desired compound **18a** could be isolated in only 30–46% yield at best (Scheme 5). A significant amount of decomposition products was always detected in the crude reaction mixtures, even when conversion was not complete. Generally, with longer reaction times or higher temperatures, decomposition increased with detrimental effect on the overall yield in accord with the relative instability of **18a** under the reaction conditions.

^1H NMR spectra of the crude mixtures showed a large excess of high field signals, suggesting that the TBDMS protecting group could be part of the problem. In fact, it has been reported that the TBDMS group can be removed in the presence of copper salts.[14]

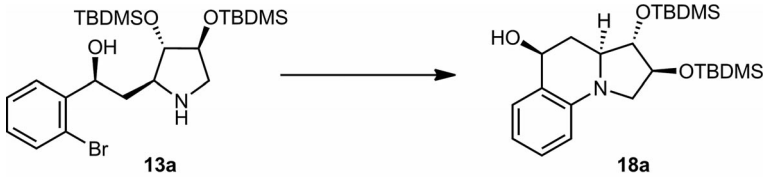
The copper-mediated cyclization of the di-*tert*-butyl derivative **14a** was studied using the best reaction conditions found, i.e. CuI/Cu/L-Pro as catalyst mixture, K_3PO_4 as base and a 1:1 mixture of *t*BuOH/H_2O as the solvent (Table 1). The replacement of the protecting group led to a significant reduction of decomposition products. Preliminary tests on **14a** revealed that a higher yield based on converted starting material could be achieved when the reaction was run at lower temperature and for longer time (Table 1, entries 1–2 and 5–7). A half mol equiv. of the CuI/Cu couple was found to be the best compromise between conversion percentage, overall yield and a reasonable reaction time (10–12 h) when the reaction was carried out at 90 °C. Due to the long reaction time, conventional heating was preferred over microwave irradiation that was only slightly more efficient (Table 1, entries 3, 4 and 9). Finally, the best reaction conditions (Table 1, entries 9 and 10) were applied to both the

Table 1. Copper-mediated cyclization of the *t*Bu derivative **14a**.



	CuI/Cu [%]	*T* [°C][a]	*t* [h]	RSM [%][b]	**19a** yield [%][c]
1	30:30	100 (MW)	3.5	61	36 (90)
2	30:30	120	1.5	32	48 (71)
3	50:50	90 (MW)	10	n.d.	75
4	50:50	90	10	n.d.	65
5	80:80	90 (MW)	13	15	62 (73)
6	80:80	110	2	n.d.	21
7	80:80	100 (MW)	3.5	30	31 (44)
8	50:50	95	10	28	58 (81)
9	50:50	90	12	n.d.	74
10	50:50	90	12	7[d]	77 (82)[d]

[a] MW: microwave heating. [b] RSM: recovered starting material (**14a**) after chromatography; n.d.: not determined. [c] Isolated yield after chromatography; values in parentheses refer to yields based on conversion. [d] The reaction was done on *ent*-**14a**.



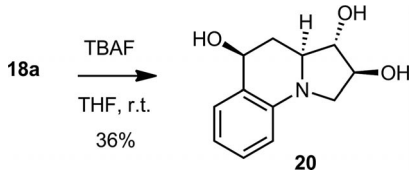
CuI/Cu/L-Pro (mol-%)	Base	Solvent	*T*	*t*	Yield
10/100/20	K_3PO_4	dry DMF	100 °C	48 h	37%
30/30/60	DBU	*t*BuOH	100 °C (MW)	10 h	30%
30/30/60	K_3PO_4	*t*BuOH/H_2O/THF	100 °C (MW)	5 h	46%

Scheme 5. Representative examples of copper-mediated cyclization of TBDMS derivative **13a**.

enantiomeric pyrrolidines **14a** and *ent*-**14a**. The corresponding tricyclic products **19a** and *ent*-**19a** were obtained in 74 and 77% yield, respectively, demonstrating no major effect of the use of the chiral L-proline as catalyst ligand with different enantiomers.

Under the same conditions, the dichloro derivative **12a** proved to be less reactive than **14a**, affording only traces of the corresponding benzoindolizidine after 48 h at 100 °C. The known reduced reactivity of chloro aromatic compounds in comparison with the corresponding bromo derivatives and the steric hindrance of the densely functionalized phenethyl pyrrolidines **12** compared to **13** and **14**, seem to explain the lack of reactivity.

Treatment of **18a** with tetrabutylammonium fluoride (TBAF) provided the deprotected triol **20** in 36% unoptimized yield (Scheme 6).



Scheme 6. Deprotection of benzoindolizidine **18a**.

Conclusions

1,3-DC of an enantiopure 3,4-dialkoxypyrroline *N*-oxide with 1-bromo-2-ethenylbenzene, followed by reduction of the isoxazolidine N–O bond and copper-catalyzed intramolecular *N*-arylation provided a convenient method for the synthesis of highly functionalized benzo[*e*]indolizidines. The bromophenylpyrrolidines underwent cyclization under Ullmann reaction conditions (copper catalyst, protic solvents), whereas Pd and Ni catalysts, which operate in apolar solvents, failed to give the same reaction. The required reaction conditions involving a high temperature (90 °C), stoichiometric copper, and a base were well tolerated by *tert*-butyl ether groups, whereas TBDMS ethers suffered partial decomposition. The method provided access to benzocondensed derivatives of iminosugars valuable as glycosidase inhibitors and apoptosis inducers.

Experimental Section

General Remarks: All the reactions requiring anhydrous conditions were carried out under nitrogen, and the solvents were appropriately dried before use. Chromatographic purifications were performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM, Merk) using the flash-column technique; R_f values refer to TLC on 0.25 mm silica gel plates (Merck F254, Macherey–Nagel precoated sheets) with the same eluant indicated for column chromatography unless otherwise stated. Melting points (m.p.) were determined with a RCH Kofler apparatus. Polarimetric measurements were performed with a JASCO DIP-370 polarimeter. NMR spectra were recorded with Varian Gemini (^{1}H, 200 MHz), Varian Mercury (^{1}H, 200 MHz), or Varian Mercuryplus (^{1}H, 400 MHz) instruments using $CDCl_3$ as the solvent, and were referenced internally to solvent reference frequencies. Assignments were made on the basis of ^{1}H–^{1}H COSY, HMQC, HSQC and HMBC experiments. IR spectra were recorded with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer on $CDCl_3$ solutions. Mass spectra were recorded with a QP5050 Shimadzu spectrometer with a GC–GC or direct inlet (70-eV ionizing voltage); relative percentages are shown in parentheses. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer. Microwave-assisted reactions were carried out in a CEM Discover™ single mode microwave reactor with an IR temperature sensor.

(3*S*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-Oxide (5): A mixture of (3*S*,4*S*)-1-benzyl-3,4-bis(*tert*-butyldimethylsilyloxy)-pyrrolidine (5.76 g, 13.66 mmol) and 20% $Pd(OH)_2$/C (2.02 g, 1.9 mmol) in MeOH (71 mL) was stirred under an H_2 atmosphere (1 atm) at room temp. overnight, then filtered through a short pad of Celite® and washed with MeOH. The filtrate was concentrated under reduced pressure to afford the debenzylated pyrrolidine (3.83 g, 85%) that was used in the next step without further purification. A mixture of crude (3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidine (1.868 g, 5.633 mmol) in a mixture of CH_3CN/THF (4:1, 10.8 mL) and aqueous Na_2EDTA (0.01 M, 8.3 mL) was stirred and cooled to 0 °C and then treated with $NaHCO_3$ (2.37 g, 28.16 mmol). Oxone®[15] (3.64 g, 5.91 mmol) was added portionwise over 2 h. The mixture was stirred at 0 °C for 30 min and then diluted with EtOAc (10 mL) and deionized H_2O (10 mL). The two phases were separated, and the aqueous solution was extracted with CH_2Cl_2 (2× 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and then concentrated under reduced pressure to afford crude **5** as a yellow oil. Purification by chromatography on silica gel (eluent: EtOAc/petroleum ether, 1:1) afforded **5** (1.43 g, 70%) as a white waxy solid.

Spectral properties were identical with those reported in the literature.[8]

(2*S*,3a*S*,4*S*,5*S*)-2-(2,6-Dichlorophenyl)-4,5-bis(*tert*-butyldimethylsilyloxy)hexahydropyrrolo[1,2-*b*][1,2]oxazole (9a): 2,6-Dichlorostyrene (**7**, 506 mg, 2.92 mmol) was added to a suspension of nitrone **5** (1.0 g, 2.89 mmol) in toluene (0.2 mL), and the reaction mixture was heated at 70 °C for 1 h 15 min in a microwave reactor (MW) using an irradiation power of 100 W. A second portion of nitrone (310 mg, 0.9 mmol) was added, and the reaction mixture was heated in the MW at 70 °C for 30 min. The solvent was evaporated under a nitrogen stream, and the residue was purified by chromatography on silica gel [eluent: EtOAc (1% Et_3N)/petroleum ether, 1:10]. Enriched fractions of the diastereoisomeric adducts were obtained in 94% overall yield (1.43 g, *exo-anti*:*exo-syn*:*endo-anti* ratio = 6.8:6.4:1). The major *exo-anti* diastereoisomer **9a** was obtained in 46% combined yield (696 mg), calculated by ^{1}H NMR of the mixed fractions, as a white solid.

9a (17:1 mixture with **9b**): R_f = 0.43; m.p. 72–73 °C. $[a]_D^{22}$ = +52.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 7.29 (pseudo d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.13 (dd, *J* = 8.5, 7.5 Hz, 1 H, H_{Ar}), 5.91 (pseudo t, *J* = 8.8 Hz, 1 H, 2-H), 4.09–4.04 (m, 2 H, 4-H, 5-H), 3.91 (ddd, *J* = 10.4, 4.3, 1.8 Hz, 1 H, 3a-H), 3.69 (dd, *J* = 12.5, 4.6 Hz, 1 H, 6-Ha), 3.12–3.06 (m, 1 H, 6-Hb), 2.83 (ddd, *J* = 12.2, 10.4, 9.4 Hz, 1 H, 3-Ha), 2.52 (ddd, *J* = 12.2, 8.3, 4.3 Hz, 1 H, 3-Hb), 0.93 [br. s, 9 H, $C(CH_3)_3$], 0.90 [br. s, 9 H, $C(CH_3)_3$], 0.12 (br. s, 6 H, $SiCH_3$), 0.10 (br. s, 6 H, $SiCH_3$) ppm. ^{13}C NMR (50 MHz): δ = 135.7 (s; 2 C, C_{Ar}), 132.9 (s; C_{Ar}), 129.3 (d; 3 C, CH_{Ar}), 83.8 (d; C-4), 77.8 (d; C-5), 74.7 (d; C-2), 73.2 (d; C-3a), 62.6 (t; C-6), 39.0 (t;C-3), 25.9 [q; 3 C, $C(CH_3)_3$], 25.8 [q; 3 C, $C(CH_3)_3$], 18.2 [s; $C(CH_3)_3$], 18.0 [s; $C(CH_3)_3$], –4.5 (q; 2 C, $SiCH_3$), –4.7 (q, 2 C, $SiCH_3$) ppm. IR: $\tilde{\nu}$ =

2956, 2931, 2857, 1564, 1472, 1439, 1259, 1108 cm^{-1}. $C_{24}H_{41}Cl_2NO_3Si_2$ (518.7): calcd. C 55.58, H 7.97, N 2.70; found C 55.52, H 8.23, N 2.79.

(2*S*,3a*S*,4*S*,5*S*)- and (2*R*,3a*R*,4*S*,5*S*)-2-(2-Bromophenyl)-4,5-bis(*tert*-butyldimethylsilyloxy)hexahydropyrrolo[1,2-*b*][1,2]oxazole (10a and 10b): 2-Bromostyrene (**8**, 609 mg, 3.32 mmol) was added to a suspension of nitrone **5** (1.147 g, 3.32 mmol) in toluene (2.5 mL), and the reaction mixture was heated at 70 °C for 3 h in the MW using an irradiation power of 100 W. The solvent was coevaporated with MeOH under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: EtOAc/petroleum ether, 1:14). Enriched fractions of the diastereoisomeric adducts were obtained in 92% overall yield (1.618 g, *exo-anti*:*exo-syn*:*endo-anti* ≈ 18.4:11.6:1). The *exo-anti* diastereoisomer **10a** was obtained in 55% combined yield (959 mg), calculated by ^{1}H NMR of the mixed fractions, as a white solid.

10a (ca 7:1 mixture with two minor isomers): R_f = 0.50; m.p. 52–53 °C. $[\alpha]_D^{22}$ = +6.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 7.62 (dd, *J* = 7.8, 1.6 Hz, 1 H, H_{Ar}), 7.51 (dd, *J* = 8.0, 1.1 Hz, 1 H, H_{Ar}), 7.31 (pseudo dt, *J* = 1.1, 7.6 Hz, 1 H, H_{Ar}), 7.12 (pseudo dt, *J* = 1.6, 7.6 Hz, 1 H, H_{Ar}), 5.44 (pseudo t, *J* = 7.4 Hz, 1 H, 2-H), 4.09 (pseudo dt, *J* = 4.1, 5.5 Hz, 1 H, 5-H), 4.02 (pseudo t, *J* = 3.8 Hz, 1 H, 4-H), 3.64 (dd, *J* = 12.1, 5.4 Hz, 1 H, 6-Ha), 3.67–3.61 (m, 1 H, 3a-H), 3.14 (dd, *J* = 12.1, 5.7 Hz, 1 H, 6-Hb), 2.83 (ddd, *J* = 12.4, 6.7, 4.2 Hz, 1 H, 3-Ha), 2.21 (ddd, *J* = 12.4, 9.2, 8.1 Hz, 1 H, 3-Hb), 0.92 [s, 9 H, $C(CH_3)_3$], 0.88 [s, 9 H, $C(CH_3)_3$], 0.12 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz): δ = 139.9 (s; C_{Ar}), 132.5 (d; CH_{Ar}), 128.8 (d; CH_{Ar}), 127.7 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 121.7 (s; C_{Ar}), 83.6 (d; C-4), 78.0 (d; C-5), 77.3 (d; C-2), 71.8 (d; C-3a), 62.2 (t; C-6), 41.5 (t; C-3), 25.9 [q; 3 C, $C(CH_3)_3$], 25.8 [q; 3 C, $C(CH_3)_3$], 18.1 [s, $C(CH_3)_3$], 17.9 [s, $C(CH_3)_3$], –4.4 (q; $SiCH_3$), –4.5 (q; $SiCH_3$), –4.6 (q; $SiCH_3$), –4.7 (q, $SiCH_3$) ppm. IR: $\tilde{\nu}$ = 2955, 2930, 2858, 1471, 1440, 1361, 1258, 1110 cm^{-1}. MS (EI): *m*/*z* (%) = 529 (6) $[(M + 2)]^+$, 527 (5) $[M]^+$, 286 (3), 241 (5), 212 (3), 187 (3), 185 (3), 171 (19), 147 (25), 133 (10), 128 (10), 115 (11), 73 (100). 55, (76). $C_{24}H_{42}BrNO_3Si_2$ (528.7): C 54.52, H 8.01, N 2.65; found C 54.66, H 8.27, N 2.61.

10b ^{1}H NMR (400 MHz, 18:1 mixture with **10a**): δ = 7.65 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.30 (pseudo dt, *J* = 1.2, 7.8 Hz, 1 H, H_{Ar}), 7.11 (pseudo dt, *J* = 1.7, 7.6 Hz, 1 H, H_{Ar}), 5.27 (dd, *J* = 8.8, 6.4 Hz, 1 H, 2-H), 4.25 (pseudo dt, *J* = 3.1, 4.9 Hz, 1 H, 5-H), 4.08–4.00 (m, 2 H, 3a-H, 4-H), 3.37 (dd, *J* = 12.5, 5.2 Hz, 1 H, 6-Ha), 3.22 (dd, *J* = 12.5, 4.7 Hz, 1 H, 6-Hb), 2.93 (ddd, *J* = 12.4, 6.4, 2.0 Hz, 1 H, 3-Ha), 2.03 (pseudo dt, *J* = 12.4, 8.7 Hz, 1 H, 3-Hb), 0.95 [s, 9 H, $C(CH_3)_3$], 0.90 [s, 9 H, $C(CH_3)_3$], 0.14 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.09 (s, 6 H, $SiCH_3$) ppm.

(2*S*,3a*S*,4*S*,5*S*)-, (2*R*,3a*R*,4*S*,5*S*)-, (2*R*,3a*S*,4*S*,5*S*)-, and (2*S*,3a*R*,4*S*,5*S*)-2-(2-Bromophenyl)-4,5-di-*tert*-butoxyhexahydropyrrolo[1,2-*b*][1,2]oxazole (11a, 11b, 11c, and 11d): 2-Bromostyrene (**8**, 595 mg, 3.27 mmol) was added to a suspension of nitrone **6**[5] (0.5 g, 2.18 mmol) in toluene (1.16 mL), and the reaction mixture was heated at 70 °C for 5 h in the MW using an irradiation power of 100 W. The solvent was evaporated under a nitrogen stream, and the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether, 1:4), affording fractions enriched of diastereoisomers, especially the minor ones in 99% overall yield (0.889 g). The *exo-anti* adduct **11a** and the *exo-syn* isomer **11b** were obtained in 73% and 22% yield, respectively (677 and 191 mg), calculated by ^{1}H NMR of the mixed fractions, as colourless oils.

11a (6.7:1 mixture of **11a** and **11c**): R_f = 0.40. $[\alpha]_D^{25}$ = +12.8 (*c* = 0.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.30 (pseudo dt, *J* = 1.2, 7.6 Hz, 1 H, H_{Ar}), 7.11 (pseudo dt, *J* = 1.7, 7.7 Hz, 1 H, H_{Ar}), 5.51 (pseudo t, *J* = 7.3 Hz, 1 H, 2-H), 3.97 (pseudo dt, *J* = 8.0, 5.6 Hz, 1 H, 5-H), 3.87 (dd, *J* = 5.3, 4.1 Hz, 1 H, 4-H), 3.57 (dd, *J* = 10.7, 5.9 Hz, 1 H, 6-Ha), 3.60–3.55 (m, 1 H, 3a-H), 3.02 (dd, *J* = 10.7, 8.0 Hz, 1 H, 6-Hb), 2.82 (ddd, *J* = 12.5, 7.1, 5.3 Hz, 1 H, 3-Ha), 2.23 (ddd, *J* = 12.5, 9.0, 7.5 Hz, 1 H, 3-Hb), 1.22 [s, 9 H, $C(CH_3)_3$], 1.19 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.1 (s; C_{Ar}), 132.4 (d; CH_{Ar}), 128.8 (d; CH_{Ar}), 127.7 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 121.8 (s; C_{Ar}), 81.6 (d; C-4), 77.3 (d; C-2), 76.2 (d; C-5), 74.1 (s; Me_3CO), 74.0 (s; Me_3CO), 70.1 (d; C-3a), 60.3 (t; C-6), 41.6 (t; C-3), 28.7 (q; 3 C, CH_3), 28.5 (q; 3 C, CH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2977, 2935, 2872, 1472, 1390, 1365, 1190, 1105 cm^{-1}. MS (EI): *m*/*z* (%) = 413 (6) $[(M + 2)]^+$, 411 (6) $[M]^+$, 356 (12), 354 (12), 300 (6), 298 (6), 284 (2), 282 (2), 228 (7), 226 (8), 116 (8), 57 (100), 55 (36). $C_{20}H_{30}BrNO_3$ (412.4): calcd. C 58.25, H 7.33, N 3.40; found C 57.94, H 7.41, N 3.24.

11b (6.9:1 mixture of **11b** and **11d**): R_f = 0.22. $[\alpha]_D^{25}$ = +58.2 (*c* = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.30 (pseudo dt, *J* = 1.2, 7.6 Hz, 1 H, H_{Ar}), 7.10 (pseudo dt, *J* = 1.7, 7.7 Hz, 1 H, H_{Ar}), 5.29 (pseudo t, *J* = 7.3 Hz, 1 H, 2-H), 4.11 (pseudo dt, *J* = 5.1, 6.5 Hz, 1 H, 5-H), 3.96–3.86 (m, 2 H, 3a-H, 4-H), 3.40 (dd, *J* = 13.1, 6.3 Hz, 1 H, 6-Ha), 3.09 (dd, *J* = 13.1, 6.8 Hz, 1 H, 6-Hb), 3.02 (ddd, *J* = 12.4, 6.8, 2.9 Hz, 1 H, 3-Ha), 2.01 (pseudo dt, *J* = 12.4, 8.0 Hz, 1 H, 3-Hb), 1.22 (s, 9 H, $CH_3 \times 3$), 1.20 (s, 9 H, $CH_3 \times 3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.9 (s; C_{Ar}), 132.4 (d; CH_{Ar}), 128.6 (d; CH_{Ar}), 127.6 (d; CH_{Ar}), 127.2 (d; CH_{Ar}), 121.7 (s; C_{Ar}), 78.6 (d; C-2), 77.4 (d; C-4), 76.4 (d; C-5), 74.0 (s; Me_3CO), 73.6 (s; Me_3CO), 66.6 (d; C-3a), 60.7 (t; C-6), 38.7 (t; C-3), 28.5 (q; 6 C, CH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2977, 2934, 2907, 2872, 1568, 1472, 1390, 1365, 1193, 1096, 1020 cm^{-1}. MS (EI): *m*/*z* (%) = 413 (3) $[(M + 2)]^+$, 411 (3) $[M]^+$, 356 (8), 354 (7), 300 (5), 298 (5), 284 (2), 282 (2), 228 (5), 226 (6), 116 (7), 57 (100), 55 (36). $C_{20}H_{30}BrNO_3$ (412.4): calcd. C 58.25, H 7.33, N 3.40; found C 58.40, H 7.35, N 3.60.

11c: (6.7:1 mixture of **11a** and **11c**): ^{1}H NMR ($CDCl_3$, 400 MHz, discernible signals): δ = 7.74 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.49 (dd, *J* = 7.9, 1.2 Hz, 1 H, H_{Ar}), 7.29 (pseudo dt, *J* = 1.2, 7.5 Hz, 1 H, H_{Ar}), 5.28 (dd, *J* = 9.9, 6.1 Hz, 1 H, 2-H), 4.05 (pseudo dt, *J* = 4.1, 5.7 Hz, 1 H, 5-H), 3.84 (pseudo t, *J* = 3.8 Hz, 1 H, 4-H), 3.70 (pseudo dt, *J* = 3.5, 8.3 Hz, 1 H, 3a-H), 3.53 (dd, *J* = 11.8, 5.6 Hz, 1 H, 6-Ha), 3.25 (dd, *J* = 11.8, 5.9 Hz, 1 H, 6-Hb), 3.06 (ddd, *J* = 12.2, 7.8, 6.1 Hz, 1 H, 3-Ha), 2.01 (ddd, *J* = 12.2, 9.9, 8.6 Hz, 1 H, 3-Hb), 1.21 [s, 9 H, $C(CH_3)_3$], 1.16 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, discernible signals): δ = 82.4 (d; C-4), 80.1 (d; C-2), 79.0 (d; C-5), 73.9 (s; Me_3CO), 72.6 (d; C-3a), 61.8 (t; C-6), 41.8 (t; C-3), 28.6 (q; 3 C, CH_3), 28.5 (q; 3 C, CH_3) ppm.

11d: (6.9:1 mixture of **11b** and **11d**): ^{1}H NMR ($CDCl_3$, 400 MHz, discernible signals): δ = 7.57 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.13 (pseudo dt, *J* = 1.7, 7.7 Hz, 1 H, H_{Ar}), 5.20 (dd, *J* = 9.8, 6.2 Hz, 1 H, 2-H), 4.27 (pseudo dt, *J* = 9.1, 6.2 Hz, 1 H, 5-H), 3.55 (dd, *J* = 13.9, 6.4 Hz, 1 H, 6-Ha), 2.90 (dd, *J* = 13.9, 9.1 Hz, 1 H, 6-Hb), 2.65 (ddd, *J* = 12.4, 8.6, 6.2 Hz, 1 H, 3-Ha), 2.35–2.27 (m, 1 H, 3-Hb), 1.21 [s, 9 H, $C(CH_3)_3$], 1.13 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, discernible signals): δ = 132.5 (d; CH_{Ar}), 128.9 (d; CH_{Ar}), 127.5 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 78.9 (d; C-2), 77.6 (d; C-4), 76.0 (d; C-5), 66.5 (d; C-3a), 58.9 (t; C-6), 37.9 (t; C-3) ppm.

(1*S*)-1-(2,6-Dichlorophenyl)-2-[(2*S*,3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]ethanol (12a): A 17:1 mixture of isoxazoli-

dines **9a** and **9b** (63 mg, 0.119 mmol of **9a** and 3 mg of **9b**) was mixed with zinc powder (36 mg, 0.56 mmol) in AcOH/H_2O [9:1 (v/v), 1.08 mL], and the suspension was heated in an oil bath at 60 °C for 4 h and then filtered through cotton wool. The solid residue was washed with EtOAc, the solution was basified to pH = 9 with a saturated aq. $NaHCO_3$ solution, and then it was extracted with EtOAc (5× 10 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography on silica gel (eluent: initially CH_2Cl_2, then CH_2Cl_2/MeOH with 1% NH_4OH, 15:1) afforded pyrrolidine **12a** in 72% yield (45 mg) as a white solid. R_f = 0.30 (CH_2Cl_2/MeOH with 1% NH_4OH, 15:1); m.p. 113–114 °C. $[\alpha]_D^{25}$ = +14.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.27 (pseudo d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.10 (dd, *J* = 8.4, 7.6 Hz, 1 H, H_{Ar}), 5.69 (dd, *J* = 9.7, 3.2 Hz, 1 H, C*H*OH), 4.00–3.97 (m, 1 H, 4-H), 3.87–3.84 (m, 1 H, 3-H), 3.24 (pseudo dt, *J* = 8.7, 3.6 Hz, 1 H, 2-H), 3.11 (dd, *J* = 11.9, 4.6 Hz, 1 H, 5-Ha), 2.84 (dd, *J* = 11.9, 2.4 Hz, 1 H, 5-Hb), 2.46 (ddd, *J* = 14.5, 9.7, 3.8 Hz, 1 H, C*H*HCHOH), 1.80 (ddd, *J* = 14.5, 8.6, 3.1 Hz, 1 H, CH*H*CHOH), 0.87 [s, 9 H, $C(CH_3)_3$], 0.86 [s, 9 H, $C(CH_3)_3$], 0.07 (s, 3 H, $SiCH_3$), 0.066 (s, 3 H, $SiCH_3$), 0.058 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (50 MHz): δ = 138.1 (s; C_{Ar}), 134.2 (s; 2 C, C_{Ar}), 129.3 (d; 2 C, CH_{Ar}), 128.4 (d; CH_{Ar}), 83.7 (d; C-3), 79.9 (d; C-4), 70.0 (d; *C*HOH), 64.6 (d; C-2), 53.4 (t; C-5), 36.3 (t; *C*H_2CHOH), 25.8 [q; 6 C, C(*C*H_3)$_3$], 18.0 [s; 2 C, *C*(CH_3)$_3$], –4.4 (q; $SiCH_3$), –4.5 (q; 2 C, $SiCH_3$), –4.6 (q; $SiCH_3$) ppm. IR: $\tilde{\nu}$ = 3600, 3200 (br), 2954, 2923, 2862, 1582, 1562, 1472, 1437, 1258, 1089 cm^{-1}. MS (EI): *m*/*z* (%) = 521 (2) [M + 2]$^+$, 519 (2) [M]$^+$, 504 (1), 484 (1), 462 (2), 352 (2), 330 (5), 276 (5), 171 (63), 73 (88), 56 (100). $C_{24}H_{43}Cl_2NO_3Si_2$ (520.68): calcd. C 55.36, H 8.32, N 2.69; found C 55.04, H 8.05, N 2.62.

(1*R*)-1-(2,6-Dichlorophenyl)-2-[(2*R*,3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]ethanol (12b), (1*R*)-1-(2,6-Dichlorophenyl)-2-[(2*S*,3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]ethanol (12c), and (1*S*)-1-(2,6-Dichlorophenyl)-2-[(2*R*,3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]ethanol (12d): Following the same procedure used to prepare **12a**, the diastereomeric pyrrolidines **12b**, **12c** and **12d** were obtained starting from mixtures of cycloadducts **9**. The diastereomeric pyrrolidines could only partially be separated by chromatography on silica gel.

12b (48:3:1 mixture with **12d** and **12c**): M.p. 119–120 °C. $[\alpha]_D^{26}$ = –0.84 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.27 (pseudo d, *J* = 8.1 Hz, 2 H, H_{Ar}), 7.11 (dd, *J* = 8.5, 7.6 Hz, 1 H, H_{Ar}), 5.64 (dd, *J* = 8.3, 5.0 Hz, 1 H, C*H*OH), 4.02 (pseudo dt, *J* = 4.9, 1.3 Hz, 1 H, 4-H), 3.91 (dd, *J* = 3.3, 1.3 Hz, 1 H, 3-H), 3.50–3.45 (m, 1 H, 2-H), 3.36 (dd, *J* = 12.2, 4.9 Hz, 1 H, 5-Ha), 3.38–2.87 (br. s, 2 H, NH, OH) 2.75 (dd, *J* = 12.2, 1.3 Hz, 1 H, 5-Hb), 2.32 (ddd, *J* = 14.3, 8.3, 4.7 Hz, 1 H, C*H*HCHOH), 2.01 (ddd, *J* = 14.3, 9.3, 5.0 Hz, 1 H, CH*H*CHOH), 0.87 [s, 9 H, $C(CH_3)_3$], 0.86 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, $SiCH_3$), 0.06 (s, 6 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0 (s; CAr), 134.4 (s; 2 C, CAr), 129.4 (d; 2 C, CHAr), 128.6 (d; CHAr), 79.8 (d; C-3), 78.2 (d; C-4), 70.0 (d; *C*HOH), 58.4 (d; C-2), 53.2 (t; C-5), 33.7 (t; *C*H_2CHOH), 25.8 [q; 3 C, C(*C*H_3)$_3$], 25.7 [q; 3 C, C(*C*H_3)$_3$], 18.0 [s; *C*(CH_3)$_3$], 17.9 [s; *C*(CH_3)$_3$], –4.4 (q; $SiCH_3$), –4.6 (q; $SiCH_3$), –4.7 (q; $SiCH_3$), –4.8 (q; $SiCH_3$) ppm.

12c: (1:1.2:0.2 mixture with **12b** and **12a**): ^1H NMR (400 MHz, discernible signals): δ = 3.79–3.77 (m, 1 H, 3-H), 3.34 (dd, *J* = 12.4, 5.5 Hz, 1 H, 5-Ha), 2.97 (dd, *J* = 12.4, 2.9 Hz, 1 H, 5-Hb), 2.64 (pseudo dt, *J* = 14.4, 11.4 Hz, 1 H, C*H*HCHOH), 1.65 (pseudo dt, *J* = 14.4, 3.0 Hz, 1 H, CH*H*CHOH) ppm.

12d: (1.3:1 mixture with **12b**): ^1H NMR (400 MHz, discernible signals): δ = 5.71 (dd, *J* = 10.8, *J* = 2.9 Hz, 1 H, C*H*OH), 3.37 (dd, *J* = 12.4, 4.5 Hz, 1 H, 5-Ha), 2.88 (br. d, *J* = 12.4 Hz, 1 H, 5-Hb), 2.61 (pseudo dt, *J* = 14.6, 11.0 Hz, 1 H, C*H*HCHOH), 1.72 (pseudo dt, *J* = 14.6, 2.8 Hz, 1 H, CH*H*CHOH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, discernible signals): δ = 137.8 (s; C_{Ar}), 134.5 (s; 2 C, C_{Ar}), 129.2 (d; 2 C, CH_{Ar}), 128.4 (d; CH_{Ar}), 80.0 (d; C-3), 77.9 (d; C-4), 77.1 (d; *C*HOH), 61.4 (d; C-2), 52.9 (t; C-5), 32.2 (t; *C*H_2CHOH), 25.8 [q; 6 C, C(*C*H_3)$_3$], 18.1 [s; *C*(CH_3)$_3$], 18.0 [s; *C*(CH_3)$_3$] ppm.

(1*S*)- and (1*R*)-1-(2-Bromophenyl)-2-[(2*S*,3*S*,4*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]ethanol (13a and 13b): Following the same procedure used to prepare **12a**, pyrrolidines **13a** and **13b** were obtained starting from a mixture of cycloadducts **10a** and **10b**.

13a: White solid, 88% yield, R_f = 0.34 [eluent: CH_2Cl_2/MeOH (1% NH_4OH) 20:1]; m.p. 102–103 °C. $[\alpha]_D^{25}$ = +12.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.65 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.48 (dd, *J* = 7.9, 1.2 Hz, 1 H, H_{Ar}), 7.33 (pseudo dt, *J* = 1.2, 7.5 Hz, 1 H, H_{Ar}), 7.09 (pseudo dt, *J* = 1.7, 7.6, Hz, 1 H, H_{Ar}), 5.28 (dd, *J* = 6.4, 3.2 Hz, 1 H, C*H*OH), 3.98–3.94 (m, 1 H, 4-H), 3.82–3.80 (m, 1 H, 3-H), 3.16 (dd, *J* = 11.9, 4.9 Hz, 1 H, 5-Ha), 3.02 (pseudo dt, *J* = 9.6, 2.7 Hz, 1 H, 2-H), 2.89 (dd, *J* = 11.9, 2.8 Hz, 1 H, 5-Hb), 2.14 (ddd, *J* = 14.6, 9.6, 3.2 Hz, 1 H, C*H*HCHOH), 1.88 (ddd, *J* = 14.6, 6.4, 3.3 Hz, 1 H, CH*H*CHOH), 0.89 [s, 9 H, $C(CH_3)_3$], 0.79 [s, 9 H, $C(CH_3)_3$], 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.00 (s, 3 H, $SiCH_3$), –0.07 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz): δ = 143.7 (s; C_{Ar}), 132.5 (d; CH_{Ar}), 128.2 (d; CH_{Ar}), 127.9 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 121.2 (s; C_{Ar}), 84.0 (d; C-3), 79.9 (d; C-4), 71.6 (d; CHOH), 64.4 (d; C-2), 53.2 (t; C-5), 36.2 (t; *C*H_2CHOH), 25.8 [q; 3 C, C(*C*H_3)$_3$], 25.7 [q; 3 C, C(*C*H_3)$_3$], 17.9 [s; *C*(CH_3)$_3$], 17.8 [s; *C*(CH_3)$_3$], –4.6 (q; $SiCH_3$), –4.67 (q; $SiCH_3$), –4.71 (q; $SiCH_3$), –4.8 (q; $SiCH_3$) ppm. IR: $\tilde{\nu}$ = 3661, 3190, 2930, 2858, 1471, 1463, 1258, 1088, 1082 cm^{-1}. MS (EI): *m*/*z* (%) = 531 (1) [(M + 2)]$^+$, 529 (1) [M]$^+$, 450 (2), 432 (5), 171 (54), 97 (44), 83 (45), 71 (59), 57 (100). $C_{24}H_{44}BrNO_3Si_2$ (530.69): calcd. C 54.32, H 8.36, N 2.64; found C 54.32, H 8.28, N 2.68.

13b: White solid; m.p. 155–156 °C. $[\alpha]_D^{26}$ = +46.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.65 (dd, *J* = 7.8, 1.6 Hz, 1 H, H_{Ar}), 7.49 (dd, *J* = 7.9, 1.2 Hz, 1 H, H_{Ar}), 7.33 (pseudo dt, *J* = 1.2, 7.5 Hz, 1 H, H_{Ar}), 7.10 (pseudo dt, *J* = 1.6, 7.6, Hz, 1 H, H_{Ar}), 5.31 (pseudo t, *J* = 4.6 Hz, 1 H, C*H*OH), 3.94 (pseudo dt, *J* = 4.6, 1.6 Hz, 1 H, 4-H), 3.74 (dd, *J* = 4.1, 1.6 Hz, 1 H, 3-H), 3.24 (dd, *J* = 12.4, 4.6 Hz, 1 H, 5-Ha), 3.19 (pseudo dt, *J* = 11.3, 3.6 Hz, 1 H, 2-H), 2.69 (dd, *J* = 12.4, 1.6 Hz, 1 H, 5-Hb), 2.11 (ddd, *J* = 14.7, 11.3, 4.2 Hz, 1 H, C*H*HCHOH), 1.93 (ddd, *J* = 14.7, 5.0, 3.1 Hz, 1 H, CH*H*CHOH), 0.87 [s, 9 H, $C(CH_3)_3$], 0.82 [s, 9 H, $C(CH_3)_3$], 0.033 (s, 3 H, $SiCH_3$), 0.031 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), –0.01 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz): δ = 143.7 (s; C_{Ar}), 132.7 (d; CH_{Ar}), 128.3 (d; CH_{Ar}), 127.8 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 121.4 (s; C_{Ar}), 80.4 (d; C-3), 78.4 (d; C-4), 71.5 (d; CHOH), 57.4 (d; C-2), 52.9 (t; C-5), 32.8 (t; *C*H_2CHOH), 25.8 [q; 3 C, C(*C*H_3)$_3$], 25.7 [q; 3 C, C(*C*H_3)$_3$], 18.0 [s; *C*(CH_3)$_3$], 17.8 [s; *C*(CH_3)$_3$], –4.6 (q; $SiCH_3$), –4.67 (q; $SiCH_3$), –4.68 (q; $SiCH_3$), –4.9 (q, $SiCH_3$) ppm.

(1*S*)- and (1*R*)-1-(2-Bromophenyl)-2-[(2*S*,3*S*,4*S*)-3,4-di-*tert*-butoxypyrrolidin-2-yl]ethanol (14a and 14c): A 6.7:1 mixture of isoxazolidines **11a** and **11c** (686 mg, 1.66 mmol) and zinc powder (544 mg, 8.32 mmol) in AcOH:H_2O = 9:1 (15.9 mL) was heated in an oil bath at 80 °C for 5 h and then diluted with MeOH and filtered through cotton wool. The filtrate was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2, and the solution was basified to pH = 9 with a saturated aq. $NaHCO_3$ solution and solid Na_2CO_3 at 0 °C. The resulting suspension was sequentially extracted with CH_2Cl_2 (3× 30 mL) and EtOAc (2× 30 mL). The combined organic phases were washed with brine (50 mL), dried

with Na_2SO_4, filtered and concentrated under reduced pressure. Filtration on silica gel [eluent: CH_2Cl_2/MeOH (1% NH_4OH) 95:5] afforded a 6.2:1 mixture of pyrrolidines **14a** and **14c** in 96% yield (658 mg) as a yellow viscous oil.

14a: (6.2:1 mixture with **14c**): R_f = 0.20. $[\alpha]_D^{25}$ = –15.1 (*c* = 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (dd, *J* = 7.8, 1.7 Hz, 1 H, H_{Ar}), 7.48 (dd, *J* = 7.9, 1.2 Hz, 1 H, H_{Ar}), 7.33 (pseudo dt, *J* = 1.2, 7.5 Hz, 1 H, H_{Ar}), 7.09 (pseudo dt, *J* = 1.7, 7.6 Hz, 1 H, H_{Ar}), 5.31 (dd, *J* = 5.9, 3.5 Hz, 1 H, C*H*OH), 4.94–4.15 (br. s, 2 H, NH, OH) 3.85–3.80 (m, 1 H, 4-H), 3.66 (pseudo t, *J* = 2.2 Hz, 1 H, 3-H), 3.16 (dd, *J* = 12.1, 5.6 Hz, 1 H, 5-Ha), 3.03 (pseudo dt, *J* = 10.2, 2.7 Hz, 1 H, 2-H), 2.92 (dd, *J* = 12.1, 4.3 Hz, 1 H, 5-Hb), 2.21 (ddd, *J* = 14.7, 10.2, 3.5 Hz, 1 H, C*H*HCHOH), 1.96 (ddd, *J* = 14.7, 5.9, 3.2 Hz, 1 H, CH*H*CHOH), 1.18 (s, 9 H, $CH_3 \times 3$), 1.06 (s, 9 H, $CH_3 \times 3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.5 (s; C_{Ar}), 132.5 (d; CH_{Ar}), 128.2 (d; CH_{Ar}), 128.1 (d; CH_{Ar}), 127.3 (d; CH_{Ar}), 121.1 (s; C_{Ar}), 83.1 (d; C-3), 79.2 (d; C-4), 73.9 (s; Me_3CO), 73.8 (s; Me_3CO), 71.8 (d; CHOH), 63.0 (d; C-2), 52.3 (t; C-5), 34.8 (t; CH_2CHOH), 28.6 (q; 3 C, CH_3), 28.5 (q; 3 C, CH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3500–2500 (br), 3068, 2979, 2934, 2873, 1464, 1391, 1365, 1235, 1191, 1071, 1023 cm^{-1}. MS (EI): *m*/*z* (%) = 415 (1) [(M + 2)]$^+$, 413 (1) [M]$^+$, 358 (1), 356 (1), 342 (1), 340 (1), 334 (1), 260 (5), 228 (3), 187 (5), 185 (6), 148 (9), 116 (34), 98 (12), 57 (100).

14c: (6.2:1 mixture of **14a**/**14c**): ^1H NMR ($CDCl_3$, 400 MHz, discernible signals): δ = 5.13 (dd, *J* = 10.2, 1.1 Hz, 1 H, C*H*OH), 3.87 (pseudo dt, *J* = 2.3, 5.9 Hz, 1 H, 4-H), 3.60 (pseudo t, *J* = 2.2 Hz, 1 H, 3-H), 3.35 (pseudo dt, *J* = 12.1, 2.2 Hz, 1 H, 2-H), 3.24 (dd, *J* = 12.6, 6.4 Hz, 1 H, 5-Ha), 2.83 (dd, *J* = 12.6, 5.5 Hz, 1 H, 5-Hb), 1.69–1.58 (m, 1 H, C*H*HCHOH), 1.19 (s, 9 H, $CH_3 \times 3$), 1.15 (s, 9 H, $CH_3 \times 3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, discernible signals): δ = 143.8 (s; C_{Ar}), 132.3 (d; CH_{Ar}), 128.2 (d; CH_{Ar}), 127.6 (d; CH_{Ar}), 127.5 (d; CH_{Ar}), 121.4 (s; C_{Ar}), 84.1 (d; C-3), 79.9 (d; C-4), 74.1 (s; Me_3CO), 73.9 (d; CHOH), 73.6 (s; Me_3CO), 66.5 (d; C-2), 52.2 (t; C-5), 37.0 (t; CH_2CHOH), 28.7 (q; 3 C, CH_3), 28.5 (q; 3 C, CH_3) ppm.

(1*R*)-1-(2-Bromophenyl)-2-[(2*R*,3*S*,4*S*)-3,4-di-*tert*-butoxypyrrolidin-2-yl]ethanol (14b): Following the same procedure used to prepare **14a**, the diastereomeric pyrrolidine **14b** was obtained starting from a mixture of cycloadducts **11b** and **11d**.

14b: ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (dd, *J* = 7.7, 1.7 Hz, 1 H, H_{Ar}), 7.48 (dd, *J* = 7.9, 1.2 Hz, 1 H, H_{Ar}), 7.33 (pseudo dt, *J* = 1.2, 7.6 Hz, 1 H, H_{Ar}), 7.09 (pseudo dt, *J* = 1.7, 7.7 Hz, 1 H, H_{Ar}), 5.29 (pseudo t, *J* = 4.3 Hz, 1 H, C*H*OH), 4.20–2.92 (br. s, 2 H, NH, OH) 3.87 (pseudo dt, *J* = 6.2, 3.5 Hz, 1 H, 4-H), 3.64 (dd, *J* = 5.7, 3.6 Hz, 1 H, 3-H), 3.26 (dd, *J* = 12.5, 6.2 Hz, 1 H, 5-Ha), 3.06 (pseudo dt, *J* = 9.4, 5.4 Hz, 1 H, 2-H), 2.66 (dd, *J* = 12.5, 3.4 Hz, 1 H, 5-Hb), 2.06–2.00 (m, 2 H, CH_2CHOH), 1.14 (s, 9 H, $CH_3 \times 3$), 1.08 (s, 9 H, $CH_3 \times 3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.8 (s; C_{Ar}), 132.6 (d; CH_{Ar}), 128.2 (d; CH_{Ar}), 128.0 (d; CH_{Ar}), 127.2 (d; CH_{Ar}), 121.2 (s; C_{Ar}), 80.0 (d; C-3), 77.9 (d; C-4), 73.7 (s; Me_3CO), 73.5 (s; Me_3CO), 72.1 (d; CHOH), 56.8 (d; C-2), 51.8 (t; C-5), 31.8 (t; CH_2CHOH), 28.6 (q; 3 C, CH_3), 28.3 (q; 3 C, CH_3) ppm.

(2*S*,3*S*,3a*S*,5*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolin-5-ol (18a). Method A: DBU (40 μL, 0.267 mmol) and degassed *t*BuOH (2.6 mL) were added to a mixture of **13a** (69.8 mg, 0.132 mmol), CuI (2.5 mg, 0.013 mmol), copper powder (1.0 mg, 0.015 mmol) and L-proline (3.0 mg, 0.026 mmol) under nitrogen atmosphere in a microwave vial. The reaction mixture was heated at 100 °C for 10 h in the MW and then concentrated. The crude product was dissolved in $CHCl_3$, filtered through a short pad of Celite® and concentrated under reduced pressure. Purification by chromatography on silica gel (eluent: petroleum ether/EtOAc, 20:1) afforded **18a** in 30% yield (18 mg) as a white solid.

Method B: Degassed DMF (0.3 mL) was added to a mixture of **13a** (100 mg, 0.19 mmol), CuI (4.5 mg, 0.024 mmol), copper powder (14 mg, 0.22 mmol), K_3PO_4 (81 mg, 0.38 mmol), and L-proline (4.7 mg, 0.04 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 48 h in an oil bath and then concentrated. The crude product was dissolved in CH_2Cl_2, filtered through a short pad of Celite®/Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel afforded **18a** in 37% yield (31 mg) as a white solid.

Method C: Degassed *t*BuOH/H_2O (1:1, 0.6 mL) and THF (0.15 mL) were added to a mixture of **13a** (22 mg, 0.04 mmol), CuI (2.4 mg, 0.013 mmol), copper powder (1.0 mg, 0.015 mmol), K_3PO_4 (17 mg, 0.08 mmol), and L-proline (2.8 mg, 0.024 mmol) under nitrogen atmosphere in a microwave vial. The reaction mixture was heated at 100 °C for 5 h in the MW and then filtered through a short pad of Celite®/Na_2SO_4. The solution was concentrated under reduced pressure. Purification by chromatography on silica gel afforded **18a** in 46% yield (8 mg) as a white solid.

18a: R_f = 0.45 (petroleum ether/EtOAc, 9:1); m.p. 142–144 °C. $[\alpha]_D^{24}$ = +67.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.38 (pseudo dt, *J* = 7.6, 1.2 Hz, 1 H, 6-H), 7.12 (dt, *J* = 8.1, 7.3, 1.5, 0.6 Hz, 1 H, 8-H), 6.67 (pseudo dt, *J* = 0.8, 7.4 Hz, 1 H, 7-H), 6.30 (dd, *J* = 8.1, 0.8 Hz, 1 H, 9-H), 4.86 (br. ddd, *J* = 11.0, 8.8, 5.5 Hz, 1 H, 5-H), 4.23 (pseudo dt, *J* = 7.7, 6.7 Hz, 1 H, 2-H), 3.78 (dd, *J* = 8.0, 6.7 Hz, 1 H, 3-H), 3.51 (dd, *J* = 9.4, 7.7 Hz, 1 H, 1-Ha), 3.38 (ddd, *J* = 11.9, 8.0, 3.0 Hz, 1 H, 3a-H), 3.01 (dd, *J* = 9.4, 6.7 Hz, 1 H, 1-Hb), 2.47 (ddd, *J* = 11.5, 5.5, 3.0 Hz, 1 H, 4-Ha), 1.71 (d, *J* = 8.8 Hz, 1 H, OH), 1.58 (pseudo q, *J* = 11.5 Hz, 1 H, 4-Hb), 0.92 [s, 9 H, $C(CH_3)_3$], 0.91 [s, 9 H, $C(CH_3)_3$], 0.14 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz): δ = 143.2 (s; C_{Ar}), 128.6 (d; C-8), 125.3 (d; C-6), 124.7 (s; C_{Ar}), 115.9 (d; C-7), 109.4 (d; C-9), 82.2 (d; C-3), 76.6 (d; C-2), 67.1 (d; C-5), 59.5 (d; C-3a), 52.2 (t; C-1), 35.8 (t; C-4), 25.9 [q; 3 C, $C(CH_3)_3$], 25.8 [q; 3 C, $C(CH_3)_3$], 18.0 [s; $C(CH_3)_3$], 17.9 [s; $C(CH_3)_3$], –3.8 (q; $SiCH_3$), –4.2 (q; $SiCH_3$), –4.4 (q; $SiCH_3$), –4.5 (q, $SiCH_3$) ppm. IR: $\tilde{\nu}$ = 3586, 2955, 2929, 2857, 1605, 1500, 1472, 1462, 1259, 1156, 1113 cm^{-1}. MS (EI): *m*/*z* (%) = 449 (65) [M]$^+$, 434 (2), 430 (7), 392 (12), 374 (10), 168 (56), 161 (69), 143 (48), 132 (19), 73 (100). $C_{24}H_{43}NO_3Si_2$ (449.77): calcd. C 64.09, H 9.64, N 3.11; found C 64.48, H 9.36, N 2.76.

(2*S*,3*S*,3a*S*,5*S*)-2,3-Di-*tert*-butoxy-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-*a*]quinolin-5-ol (19a): The mixed solvent *t*BuOH/H_2O (1:1, 3 mL) was added to a mixture of **14a**/**14c** (103 mg, 0.248 mmol of **14a** and 14 mg of **14c**), CuI (23.6 mg, 0.124 mmol), copper powder (7.9 mg, 0.124 mmol), K_3PO_4 (105.5 mg, 0.497 mmol) and L-proline (28.6 mg, 0.248 mmol) under nitrogen atmosphere in a vial. Nitrogen was bubbled through the reaction mixture to remove oxygen. The reaction mixture was heated at 90 °C in an oil bath for 12 h and then was filtered through a small pad of Celite®. The solution was diluted with H_2O and sequentially extracted with CH_2Cl_2 (3× 20 mL) and EtOAc (2× 20 mL). The combined organic phases were washed with NH_4OH (1% H_2O solution) and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel [eluent: CH_2Cl_2/MeOH (1% NH_4OH) 98:2] afforded **19a** in 74% yield (61.2 mg) as a white solid.

19a: R_f = 0.42; m.p. 167–169 °C. $[\alpha]_D^{23}$ = +151.76 (*c* = 0.42, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.38 (pseudo dt, *J* = 7.5, 1.3 Hz,

1 H, 6-H); 7.12 (dddd, J = 8.1, 7.4, 1.5, 0.6 Hz, 1 H, 8-H), 6.67 (pseudo dt, J = 0.9, 7.4 Hz, 1 H, 7-H), 6.31 (dd, J = 8.1, 0.9 Hz, 1 H, 9-H), 4.92–4.82 (m, 1 H, 5-H), 4.09–4.03 (m, 1 H, 2-H), 3.74 (dd, J = 8.6, 7.2 Hz, 1 H, 3-H), 3.45 (dd, J = 9.6, 7.9 Hz, 1 H, 1-Ha), 3.33 (ddd, J = 11.8, 8.6, 2.8 Hz, 1 H, 3a-H), 3.04 (dd, J = 9.6, 6.5 Hz, 1 H, 1-Hb), 2.56 (ddd, J = 11.5, 5.7, 2.8 Hz, 1 H, 4-Ha), 1.73 (br. d, J = 7.9 Hz, 1 H, OH), 1.59 (pseudo q, J = 11.5 Hz, 1 H, 4-Hb) 1.26 (s, 9 H, $CH_3 \times 3$), 1.24 (s, 9 H, $CH_3 \times 3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.4 (s; C_{Ar}), 128.6 (d; C-8), 125.5 (d; C-6), 124.8 (s; C_{Ar}), 115.9 (d; C-7), 109.5 (d; C-9), 80.3 (d; C-3), 75.2 (d; C-2), 74.3 (s; Me_3CO), 73.9 (s; Me_3CO), 67.2 (d; C-5), 57.9 (d; C-3a), 52.1 (t; C-1), 35.9 (t; C-4), 29.4 (q; 3 C, CH_3), 28.6 (q; 3 C, CH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3619, 3587, 3069, 3043, 2934, 2977, 2934, 1605, 1497, 1462, 1364, 1193, 1091 cm^{-1}. MS (EI): m/z (%) = 333 (21) $[M]^+$, 314 (1), 276 (12), 258 (5), 220 (2), 202 (22), 186 (4), 161 (13), 130 (10), 71 (14), 69 (15), 57 (100). $C_{20}H_{31}NO_3$ (333.4): calcd. C 72.04, H 9.37, N 4.20; found C 71.79, H 9.75, N 4.40.

(2*R*,3*R*,3a*R*,5*R*)-2,3-Di-*tert*-butoxy-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-*a*]quinolin-5-ol (*ent*-19a): Following the same procedure as for **19a**, the enantiomeric trihydroxy-benzo[*e*]indolizidine *ent*-**19a** was prepared starting from **8** and nitrone *ent*-**6**.

(2*S*,3*S*,3a*S*,5*S*)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-2,3,5-triol (20): A 1 M solution of tetrabutlyammonium fluoride (TBAF) in THF (0.26 mL, 0.26 mmol) was added to a solution of **18a** (26 mg, 0.057 mmol) in dry THF (3 mL). The reaction mixture was stirred overnight at room temp. under nitrogen atmosphere and then concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel [eluent: CH_2Cl_2/MeOH (1% NH_4OH) 9:1] afforded **20** in 36% yield (5 mg) as a white solid.

20: R_f = 0.25; m.p. 161–163 °C (dec.). $[\alpha]_D^{25}$ = +85.06 (c = 0.45, MeOH); ^1H NMR (CD_3OD, 400 MHz): δ = 7.31 (pseudo dt, J = 7.6, 1.3 Hz, 1 H, 6-H); 7.05–7.00 (m, 1 H, 8-H), 6.59 (pseudo dt, J = 0.9, 7.5 Hz, 1 H, 7-H), 6.30 (dd, J = 8.1, 0.9 Hz, 1 H, 9-H), 4.79 (br. dd, J = 11.4, 5.5 Hz, 1 H, 5-H), 4.20 (pseudo dt, J = 7.9, 6.9 Hz, 1 H, 2-H), 3.66 (dd, J = 8.3, 7.1 Hz, 1 H, 3-H), 3.53 (dd, J = 9.7, 7.9 Hz, 1 H, 1-Ha), 3.56–3.29 (m, 1 H, 3a-H), 3.02 (dd, J = 9.7, 6.7 Hz, 1 H, 1-Hb), 2.46 (ddd, J = 11.6, 5.5, 2.9 Hz, 1 H, 4-Ha), 1.58 (pseudo q, J = 11.6 Hz, 1 H, 4-Hb) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 144.8 (s; C_{Ar}), 129.2 (d; C-6), 126.6 (d; C-8), 126.4 (s; C_{Ar}), 116.9 (d; C-7), 110.6 (d; C-9), 82.8 (d; C-3), 76.6 (d; C-2), 67.5 (d; C-5), 61.3 (d; C-3a), 52.8 (t; C-1), 36.4 (t; C-4) ppm.

Supporting Information (see footnote on the first page of this article): Diagnostic NOE interactions in compounds **12a**–**14a**, **12b**–**14b** and **19a**; copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

The authors thank the Italian Ministry of University and Research (MIUR) for financial support (PRIN20109Z2XRJ)

[1] a) E. Borgesde Melo, A. da Silveira Gomes, I. Carvalho, *Tetrahedron* **2006**, *62*, 10277–10302; b) N. Asano, *Glycobiology* **2003**, *13*, 93R–104R; c) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; d) P. Compain, O. Martin, *Iminosugars: From Synthesis to Therapeutic Applications*; John Wiley & Sons, New York, **2007**.

[2] L. A. Sorbera, J. Castañer, L. García-Capdevila, *Drugs Future* **2005**, *30*, 545–552.

[3] F. Dal Piaz, A. Vassallo, M. G. Chini, F. M. Cordero, F. Cardona, C. Pisano, G. Bifulco, N. De Tommasi, A. Brandi, *PLoS ONE* **2012**, *7*, e43316.

[4] a) B. Macchi, A. Minutolo, S. Grelli, F. Cardona, F. M. Cordero, A. Mastino, A. Brandi, *Glycobiology* **2010**, *20*, 500–506; b) A. Minutolo, S. Grelli, F. Marino-Merlo, F. M. Cordero, A. Brandi, B. Macchi, A. Mastino, *Cell Death Disease* **2012**, *3*, e358.

[5] F. M. Cordero, P. Bonanno, B. B. Khairnar, F. Cardona, A. Brandi, B. Macchi, A. Minutolo, S. Grelli, A. Mastino, *ChemPlusChem* **2012**, *77*, 224–233.

[6] a) F. M. Cordero, P. Bonanno, S. Neudeck, C. Vurchio, A. Brandi, *Adv. Synth. Catal.* **2009**, *351*, 1155–1161; b) F. M. Cordero, P. Bonanno, M. Chioccioli, P. Gratteri, I. Robina, A. J. Moreno Vargas, A. Brandi, *Tetrahedron* **2011**, *67*, 9555–9564.

[7] a) A. Kotland, F. Accadbled, K. Robeyns, J.-B. Behr, *J. Org. Chem.* **2011**, *76*, 4094–4098; b) J.-K. Su, Y.-M. Jia, R. He, P.-X. Rui, N. Han, X. He, J. Xiang, X. Chen, J. Zhu, C.-Y. Yu, *Synlett* **2010**, 1609–1616.

[8] A. Goti, F. Cardona, A. Brandi, S. Picasso, P. Vogel, *Tetrahedron: Asymmetry* **1996**, *7*, 1659–1674.

[9] Nitrone **5** was synthesized following the procedure reported in ref.[8] except for the last step, where the more environmentally friendly Oxone® was used as the oxidant instead of H_2O_2/SeO_2 cat (see the Exp. Sect. and ref.[15]).

[10] Only traces (<1%) of *endo*-(3-O*t*Bu)-*syn*-**11d** were detected after chromatographic separation.

[11] J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525–7546.

[12] R. Omar-Amrani, A. Thomas, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* **2003**, *5*, 2311–2314.

[13] For selected reviews, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, *15*, 2428–2439; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; d) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460; e) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; f) G. Evano, M. Toumib, A. Costea, *Chem. Commun.* **2009**, 4166–4175.

[14] Z. P. Tan, L. Wang, J. B. Wang, *Chin. Chem. Lett.* **2000**, *11*, 753–756.

[15] C. Gella, È. Ferrer, R. Alibés, F. Busqué, P. de March, M. Figueredo, J. Font, *J. Org. Chem.* **2009**, *74*, 6365–6367.

Received: March 25, 2013
Published Online: ■

