A Stereoselective and Short Total Synthesis of the Polyhydroxylated γ-Amino Acid (−)-Detoxinine, Based on Stereoselective Preparation of Dihydropyrrole Derivatives from Lithiated Alkoxyallenes

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Abstract: Based on our earlier results employing lithiated methoxyallene **2** as C_3 building block and imines **3** for the synthesis of dihydropyrrole derivatives **5**, we have investigated chiral imines **6**, **10**, and **15** as electrophilic components. Combined with lithiated alkoxyallenes, these imines provide the corresponding primary adducts and finally the dihydropyrrole derivatives **8**, **12**, **17**, **20**, and **22** in good yields and with high to excellent *syn* selectivities. This stereochemical outcome is interpreted as a result of α-chelate control. Treatment with hydrochloric acid converted *syn*-**8** and *syn*-**12** into bicyclic compounds **9** and **13**, whereas under more mildly acidic conditions adduct *syn*-**17** was transformed into diol *syn*-**18**. The total synthesis of the uncommon γ-amino acid (−)-detoxinine could be achieved by starting from (*S*)-malic acid, which was converted into imine **15** in four steps. Lithiated benzyloxyallene added to imine **15** and efficiently furnished the crucial dihydropyrrole derivative *syn*-**22**. The hydrogenolysis of this compound did not directly provide the protected triol **29** as anticipated, but a stepwise protocol made the triol available in a fairly satisfactory manner. A second crucial step of the synthesis was the selective oxidation of **29**, which could be achieved by employing platinum dioxide and oxygen. The resulting bicyclic lactone **30** was smoothly transformed into enantiopure (−)-detoxinine. Thus, a fairly short synthesis of this natural product based on a lithiated alkoxyallene could be performed, demonstrating the potential of these intermediates for syntheses of interesting functionalized heterocyclic compounds.

Keywords: allenes · amino acids · imines · pyrroles · total synthesis

Introduction

In a preliminary communication we reported an expedient synthesis of pyrrole derivatives with lithiated methoxyallene and imines as crucial building blocks.[1] Addition of the nucleophilic C_3 unit **2**—easily generated by lithiation of methoxyallene **1** with *n*-butyllithium—to the imines **3** and aqueous workup generally provided primary adducts **4** in excellent yields. Since methoxyallene **1** is easily available on large scale it is often used in excess to improve the conversion and yields of this reaction. The allenyl amines **4** can be cyclized to the dihydropyrrole derivatives **5** either under basic conditions (potassium *tert*-butoxide in DMSO) or alternatively by use of silver nitrate in acetone. Depending on the substituents at the nitrogen center, the cyclization may also occur at the stage of *N*-lithiated **4**, leading directly to dihydropyrroles **5**. Thus, the combination of **2** with **3** established a new and highly flexible synthesis of functionalized pyrrole derivatives by means of an efficient [3+2] cyclization (Scheme 1).[2, 3]

Herein we present our investigations on the diastereoselective additions of **2** and related lithiated alkoxyallenes to chiral imines,[4] which allow syntheses of enantiopure dihydropyrrole derivatives. As a first application we also present the straightforward synthesis of the unusual γ-amino acid (−)-detoxinine.

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Results and Discussion

Model reactions: Initial examples with chiral imines were already presented in our preliminary publication.[1] Treatment of lithiated methoxyallene **2** with the (*R*)-glyceraldehyde-derived *N*-phenyl imine **6** in tetrahydrofuran furnished an

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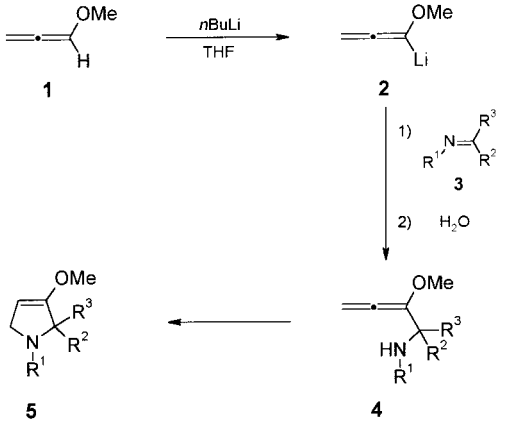
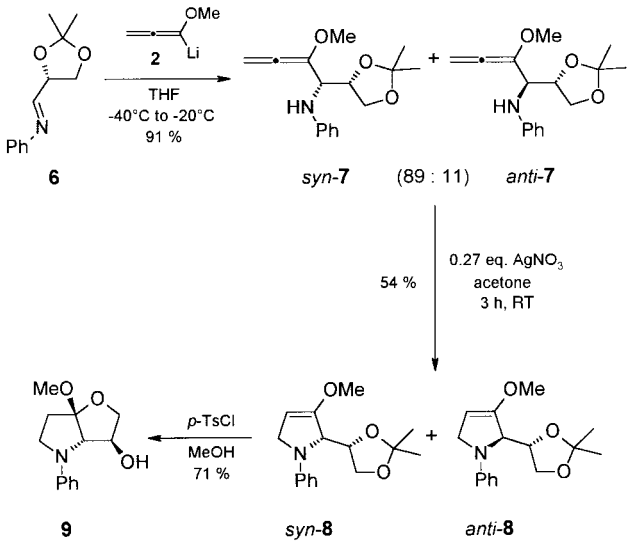


Scheme 1. Synthesis of dihydropyrrole derivatives **5** from methoxyallene **1** and imines **3**.

89:11 mixture of the two diastereomeric adducts *syn*-**7** and *anti*-**7** in excellent yield (Scheme 2). Treatment of this mixture with silver nitrate afforded a moderate yield of the two expected cyclization products *syn*-**8** and *anti*-**8** in a similar ratio of isomers. Chromatography allowed isolation and characterization of the major diastereomer *syn*-**8**, and an X-ray analysis of a crystal unequivocally confirmed the anticipated *syn* configuration (Figure 1).[5] Treatment of *syn*-**8** with hydrochloric acid (generated by methanolysis of *p*-toluenesulfonyl chloride (*p*-TsCl)) provided bicyclic acetal **9** in good yield, a transformation which demonstrates the potential of enantiopure dihydropyrroles of type **8** for further synthetic elaboration. Compound **9** was also used to establish the configuration by NMR spectroscopy (NOE).



Scheme 2. Diastereoselective addition of lithiated methoxyallene **2** to chiral imine **6**.

Similar results were obtained with the (*R*)-glyceraldehyde-derived *N*-benzyl imine **10** (Scheme 3). Addition of lithiated methoxyallene **2** to this imine in tetrahydrofuran gave *syn*-configured products exclusively. Under standard conditions with aqueous quenching at $-20\,^{\circ}C$, a 1:1 mixture of primary adduct *syn*-**11** and its cyclization product *syn*-**12** was isolated

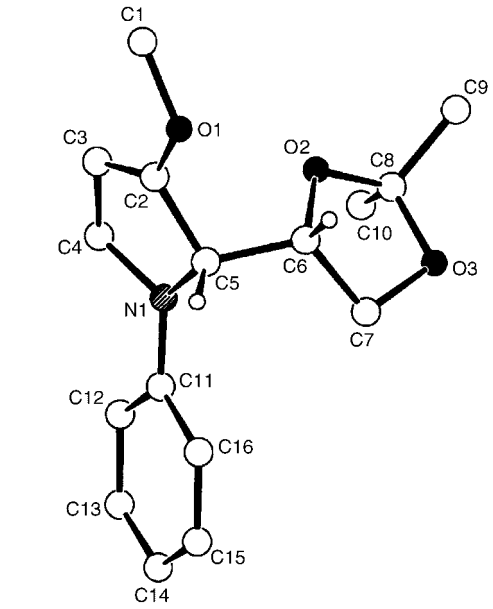
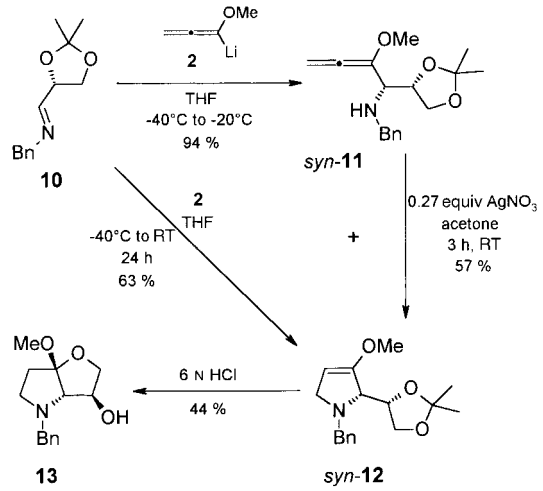


Figure 1. Structure of dihydropyrrole *syn*-**8** (Schakal representation, hydrogen atoms are shown only at the stereogenic centers).



Scheme 3. Diastereoselective addition of lithiated methoxyallene **2** to chiral imine **10**.

in excellent yield. This mixture was converted into pure *syn*-**12** by silver nitrate catalysis in 57% yield. A more efficient preparation of this compound was achieved when imine **10** and lithiated methoxyallene **2** were combined at $-40\,^{\circ}C$ and the reaction mixture was allowed to warm up to room temperature over 24 h. This reaction protocol furnished pure *syn*-**12** in 63% yield. Generally, lithiated primary adducts bearing an *N*-alkyl substituent are prone to cyclization under conditions considerably milder than those required for substrates with electron-withdrawing groups such as phenyl, tosyl, or *tert*-butoxycarbonyl substituents.[2, 6, 7] Dihydropyrrole **12** was converted into bicyclic acetal **13** by treatment with 6 N hydrochloric acid in methanol. The moderate yield of only 44% may be due to loss of material by formation of the highly polar hemiacetal related to **13**.

Whereas only *syn*-configured products were observed in tetrahydrofuran as solvent, treatment of **2** with imine **10** was

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considerably less diastereoselective in diethyl ether (*syn*-**11**/*anti*-**11** 63:37, 83% yield of crude product) or in toluene (*syn*-**11**/*anti*-**11** 57:43, conversion ca. 90%, 72% yield of crude product).[2] Interestingly, only primary adducts **11** and no cyclized dihydropyrroles **12** were isolated when these less polar solvents were employed.[8] It is evident that the excellent *syn* selectivity requires polar solvents such as tetrahydrofuran, which also enhance the cyclization rate, due to the increased nucleophilicity of the intermediate *N*-lithiated addition product. The *syn* selectivity may be explained in terms of a chelate-controlled addition of lithiated methoxyallene **2** to imine **10** involving the α-oxygen of the dioxolane ring in complex formation (Figure 2).[9] Chelation of the lithium ion by the

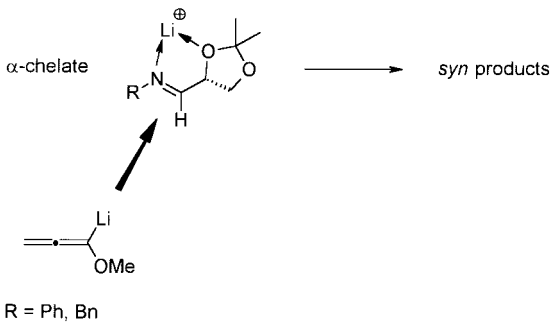


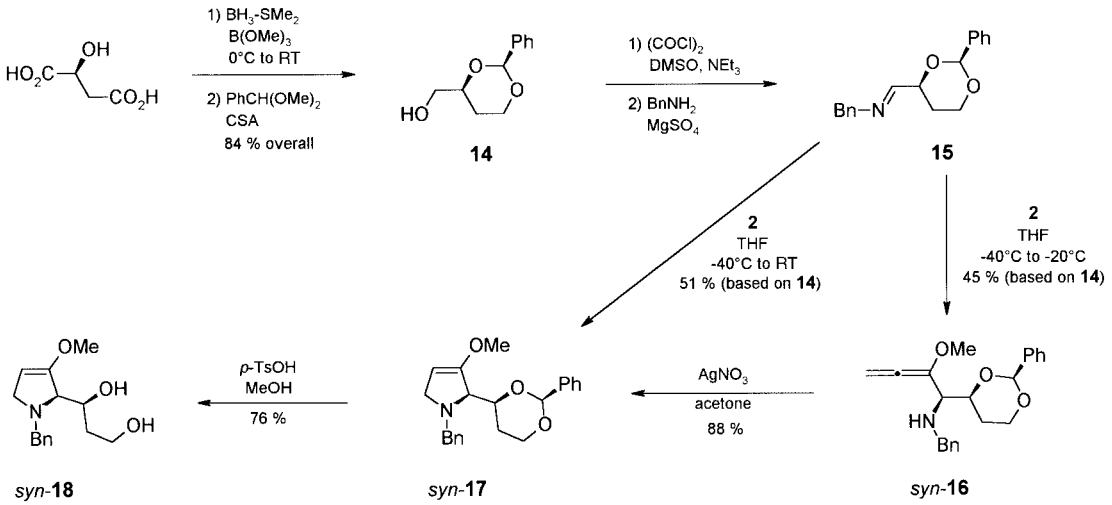
Figure 2. α-Chelate model for the addition of **2** to imines **6** and **10**.

imine nitrogen atom and the β-oxygen atom should lead to the *anti* products, which would also predominate if stereoelectronic Felkin–Anh control were operative in these additions to **10**. Among the solvents examined, tetrahydrofuran is apparently the most suitable solvent to steer the reaction pathway via the α-chelate. This interpretation is in accordance with other reported nucleophilic addition reactions involving chiral imine **10**.[5]

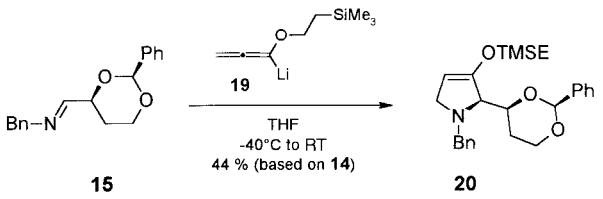
Another model reaction involved imine **15**, since alkoxyallene adducts derived thereof might be highly suitable for the planned (−)-detoxinine synthesis (see below). The ultimate precursor of **15** was (*S*)-malic acid, which was smoothly reduced to a chiral 1,2,4-butanetriol.[10] Regioselective protection of this triol furnished 1,3-dioxane derivative **14** in excellent overall yield (Scheme 4).[11] Swern oxidation of this alcohol and condensation of the resulting aldehyde with benzylamine in the presence of magnesium sulfate provided crude imine **15**, which was not purified but directly treated with lithiated methoxyallene **2**. Standard conditions (aqueous quenching at −20 °C) furnished the desired primary adduct **16** exclusively as the required *syn* diastereomer in 45% overall yield (with respect to alcohol **14**). Silver nitrate treatment converted *syn*-**16** into dihydropyrrole *syn*-**17** in good yield. This compound was available even more efficiently by direct cyclization of the lithiated primary adduct derived from **15** and **2**, when the reaction mixture was allowed to warm up to room temperature. The overall yield for *syn*-**17** of 51%, based on alcohol **14**, is very satisfactory since four reaction steps are involved (oxidation, condensation, addition, cyclization). Again, the *syn* diastereomer of **17** was isolated exclusively. The assignment as the *syn* isomer was first assumed by analogy to the outcome with the related imines **6** and **10**, but later confirmed by conversion of derivative *syn*-**22** into (−)-detoxinine and the X-ray analysis of intermediate **30** (see below).

Interestingly, compound *syn*-**17** could be hydrolyzed in good yield just to the stage of diol *syn*-**18**—and not to the expected cyclic acetal related to compounds **9** or **13**—by application of *p*-toluenesulfonic acid. Apparently, the weaker sulfonic acid attacks the enol ether unit of *syn*-**17** and *syn*-**18** only slowly, although this behavior was not studied systematically.[7] A second model reaction with imine **15** involved lithiated 2-(trimethylsilyl)ethoxyallene (**19**) which was generated under standard conditions from the corresponding alkoxyallene derivative (Scheme 5).[12] The cyclized product *syn*-**20** was isolated exclusively, and the overall yield of 44% (based on alcohol **14**) was again fair.

Total synthesis of (−)-detoxinine: (−)-Detoxinine is an uncommon polyhydroxylated γ-amino acid and the parent component of several depsipeptide metabolites produced by *Streptomyces caespitosus* var. *detoxicus* 7072 GC1 and known as detoxin complex.[13] Glasshouse tests have shown that



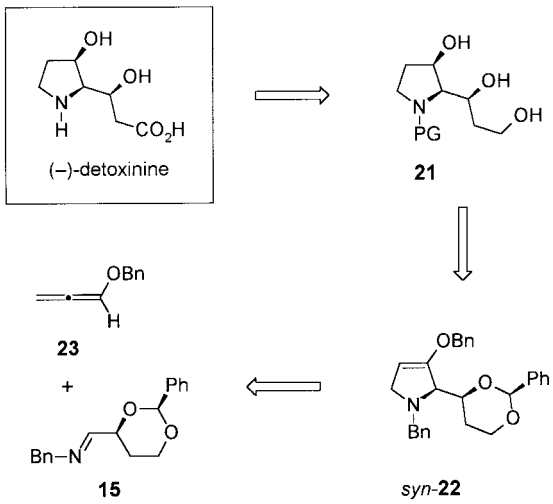
Scheme 4. Synthesis of chiral imine **15** and its diastereoselective reaction with lithiated methoxyallene **2**.



Scheme 5. Diastereoselective addition of lithiated alkoxyallene **19** to chiral imine **15**.

detoxins decrease the phytotoxicity of the rice blast fungicide Blasticidin S—a nucleoside antibiotic—without interfering with its desired properties. Total syntheses of racemic[14] and enantiopure detoxinine[15] have been reported. In general, these involve many steps with complex reagents, since the dense sequence of functional groups and the three stereogenic centers of the natural product are rather challenging.

Our retrosynthetic analysis of (−)-detoxinine first goes back to (protected) trihydroxylated pyrrolidine derivative **21**, which should be available from the appropriately functionalized dihydropyrrole *syn*-**22** (Scheme 6). This compound disconnects into C_3 building block benzyloxyallene **23** and chiral

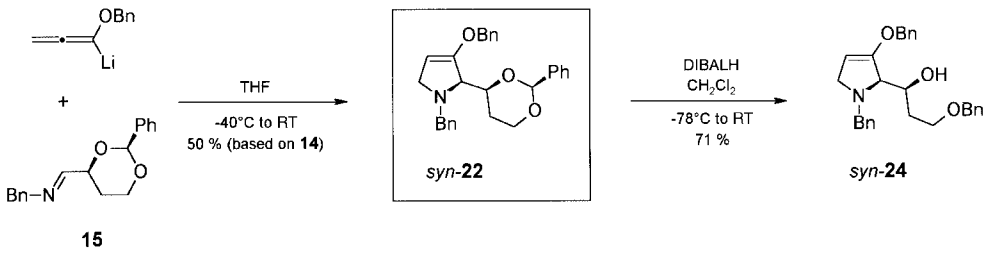


Scheme 6. Retrosynthetic analysis of (−)-detoxinine.

imine **15**. Since our model studies suggested that *syn*-**22** should be readily available—see the synthesis of compounds *syn*-**17** and *syn*-**20**—the first crucial step of our approach should be the conversion of *syn*-**22** into triol **21** or its equivalents. For this purpose we initially planned a one-step transformation with hydrogen and an appropriate catalyst, which should first reduce the enol ether double bond to deliver the required configuration at the missing stereogenic center, and then transform the benzyl ether and *N*-benzylamine moieties into free hydroxyl groups and the secondary amine function under mild conditions. The second, crucial, reaction would involve the selective oxidation of the primary alcohol of **21** or its equivalent to the carboxylic acid of (−)-detoxinine, a problem which could be solved in a satisfactory manner.

Benzyloxyallene **23** was prepared and lithiated under standard conditions.[16] Addition of freshly generated imine **15** to the solution of lithiated **23** at −40 °C followed by slow warming up to room temperature led to the formation of *syn*-**22** in 50 % overall yield (based on the precursor of **15**, alcohol **14**, Scheme 7). When this reaction was performed on a larger scale it was possible to isolate the second diastereomer *anti*-**22** in small amounts by HPLC separation.[17] On the basis of this experiment, the diastereoselectivity of the addition of lithiated **23** to **15** was calculated to be higher than 97:3 in favor of the *syn* isomer. To explore the reactivity of compounds of type *syn*-**22** we treated it with diisobutylaluminum hydride (DIBALH), which induced a reductive cleavage of the 1,3-dioxane ring. Surprisingly, the secondary hydroxy group in the resulting product *syn*-**24** was unprotected, but not the expected primary hydroxyl group as expected according to a literature report.[18] The additional functional groups of *syn*-**22** may undergo complexation with the reducing agent and thus lead to altered ring-opening behavior. Our hope of selectively deprotecting the primary alcohol function incorporated in *syn*-**22**, which should facilitate its smooth conversion into a carboxylic group as required in (−)-detoxinine, was thus frustrated by this unexpected regioselectivity.

We therefore followed our initial plan (Scheme 6) and examined the reductive conversion of *syn*-**22** into triol **21**. Although we employed several catalysts and a variety of different reaction conditions, we disappointingly did not succeed in performing this transformation directly.[7, 19] Hydrogenolysis of *syn*-**22** in the presence of Pearlman's catalyst $Pd(OH)_2$ and Boc anhydride gave dihydropyrrole **25** as major product, together with smaller amounts of pyrrolidinone **26** (Scheme 8). This experiment reveals to our surprise that the reductive *N*-debenzylation of *syn*-**22** is apparently the fastest step in the anticipated sequence of hydrogenolysis leading to *N*-Boc-protected compounds **25** and **26**. It also demonstrates that debenzylation of the enol ether unit of the dihydropyrrole core is probably faster than debenzylation of the 1,3-dioxane ring and, most importantly, faster than hydrogenation of the enol ether double bond. *O*-Debenzylation leads to an enol intermediate, which is evidently the precursor of the



Scheme 7. Stereoselective synthesis of enantiopure dihydropyrrole derivative *syn*-**22**.

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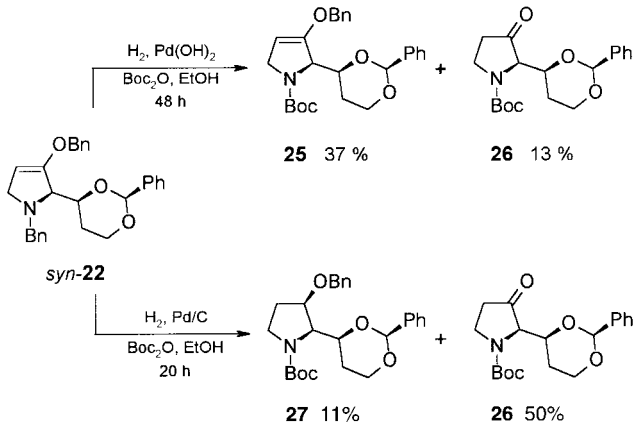
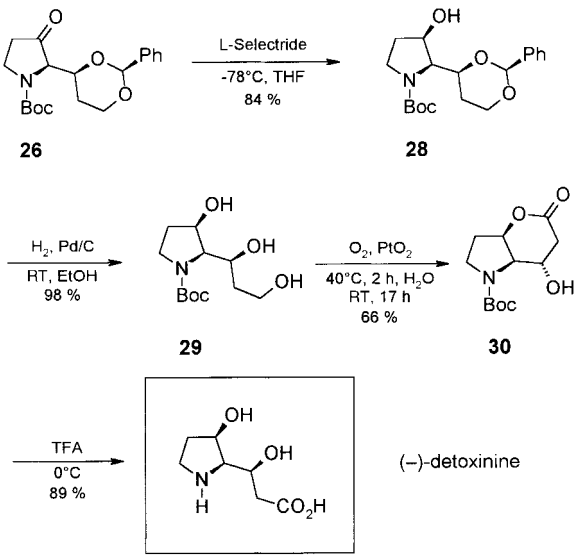


Scheme 8. Hydrogenolyses of *syn*-**22** to provide pyrrolidinone derivative **26**.



Scheme 9. Completion of the total synthesis of (−)-detoxinine.

carbonyl group in compound **26**. The moderate mass balance (50 % yield) of this experiment indicates that further products are generated during this reduction, but these could not be isolated, due to their higher polarity. We believe that free secondary amines are formed and that these poison the palladium catalyst, which is then not able to catalyze the subsequent desired steps. Experiments performed in the absence of Boc anhydride or with longer reaction times provided rather complex product mixtures that could not be characterized. This is interpreted as further evidence that free secondary amines generated during the hydrogenolysis complicate this reductive transformation. The 1,3-dioxane ring with benzylic bonds can be smoothly cleaved under similar conditions as shown by transformation of **28** into **29** (see below).

We came closer to our goal when performing the reduction with palladium on carbon in the presence of Boc anhydride. Pyrrolidinone **26** was now the major component, isolated in 50 % yield together with saturated pyrrolidine derivative **27**. Formation of **26** is explained by consecutive *N*- and *O*-debenzylation followed by enol ketone tautomerism and *N*-Boc protection. The isolation of the benzyl ether **27** demonstrates that the reduction of the enol ether double bond of *syn*-**22** is apparently only slightly slower than the *O*-debenzylation under these conditions. The configuration of **27** was not rigorously established, but we assume that the double bond was reduced from the less shielded back side, forming the stereogenic center as depicted. Again, the catalyst was probably poisoned by produced amines, since the 1,3-dioxane ring of **26** and **27** survived under the reductive conditions.

Although *syn*-**22** could be transformed into pyrrolidinone **26** in 50 % yield only, this compound is a very good precursor for the remaining steps of our (−)-detoxinine synthesis. Reduction of the carbonyl group of **26** proceeded with excellent diastereoselectivity and efficiency, furnishing pyrrolidinol derivative **28** in 84 % yield (Scheme 9). Reductive cleavage of the 1,3-dioxane ring of **28** now occurred without any problems, leading to an almost quantitative yield of *N*-Boc-protected triol **29**, which is equivalent to the desired triol **21** as introduced in our plan (see Scheme 6). We mentioned above that the next hurdle in our route might be the selective oxidation of the primary hydroxy group. We tried several methods—including variants which first provide an intermediate aldehyde[20, 7] to be further oxidized into the carboxylic acid—but finally found that direct oxidation of **29** with platinum dioxide and oxygen provided the most satisfactory result.[21, 15c] The generated carboxylic acid immediately cyclized to δ-lactone **30**, isolated in 66 % yield. The constitution and configuration of this bicyclic lactone was verified by an X-ray structure analysis (Figure 3), which clearly demonstrates that the anticipated *syn* configuration of all precursors

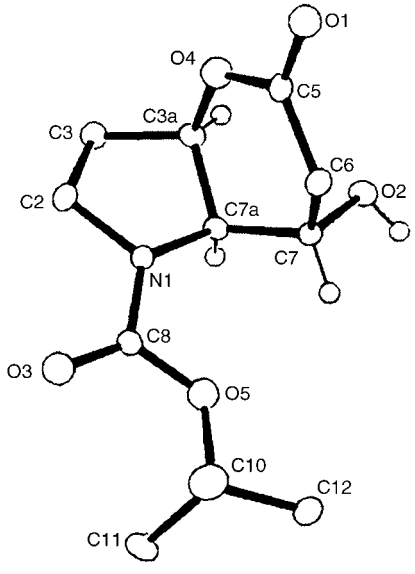


Figure 3. Structure of lactone **30** (ORTEP representation, hydrogen atoms are shown only at the stereogenic centers).

of this compound was correct. This crystal structure makes it very likely that the assignments for model compounds *syn*-**17** and *syn*-**20** as discussed are also correct. Finally, lactone **30** was treated with trifluoroacetic acid, which induced Boc-deprotection and opening of the lactone ring to provide (−)-detoxinine in 89 % yield as colorless crystals. The optical

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rotation of our sample (−5.0 in water), the melting point, and the spectroscopic data agree well with values reported in literature for the enantiopure natural product.[15] Most importantly, these results establish that no racemization occurred during our multistep synthesis.

A new and short synthesis of (−)-detoxinine, based on a compound derived from the pool of chiral compounds (malic acid), was thus established. Our route to this natural product also opens the way to analogues by exploitation of the enol ether functionality of *syn*-**22** or the carbonyl group of pyrrolidinone **26** for the introduction of other or additional substituents. In addition, epimers of this γ-amino acid may be prepared by selective inversion of configuration at one of the stereogenic centers.

Conclusion

In this report we have demonstrated that lithiated alkoxyallenes add with high to outstanding *syn* diastereoselectivities to chiral *N*-phenyl and *N*-benzyl imines derived from (*R*)-glyceraldehyde or an aldehyde prepared from (*S*)-malic acid. The resulting primary adducts were either cyclized under appropriate conditions, or they underwent direct ring-formation, leading to enantiopure *syn*-dihydropyrrole derivatives *syn*-**8**, *syn*-**12**, *syn*-**17**, *syn*-**20**, and *syn*-**22**. With compound *syn*-**22** as crucial intermediate we were able to complete a fairly short and efficient synthesis of the uncommon γ-amino acid (−)-detoxinine. From (*S*)-malic acid, as a chiral pool compound, we required ten steps (with eight isolated intermediates) to arrive at this natural product, with an overall yield of 10%. Several of these steps have not been optimized. The most intriguing feature of our synthetic plan—the reductive transformation of dihydropyrrole derivative *syn*-**22** into triol **29**—could not be achieved directly, but the problem could be solved by the introduction of two additional steps.

Our results again demonstrate the versatility and high synthetic value of lithiated alkoxyallenes for serving as C_3 building blocks, allowing the stereoselective preparation of highly functionalized enantiopure heterocycles such as furans, pyrroles, and 1,2-oxazines, suitable for many further transformations, including syntheses of natural products and their analogues.[22] Our (−)-detoxinine synthesis emphasizes that the combination of lithiated alkoxyallenes with chiral imines allows smooth, flexible, and stereoselective synthesis of substituted pyrrolidin-3-ol derivatives, a structural motif quite frequently found in many biologically active natural products.[23]

Experimental Section

General methods: Unless otherwise stated, all reactions were performed under argon atmosphere in flame-dried flasks by addition of the components by syringe. All solvents were dried by standard procedures. IR spectra were measured with Perkin–Elmer Nicolet 5 SXC or Nicolet 205 FT-IR spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (AC 300, WH 270, AC 250, AC 200, AC 500). Proton chemical shifts are reported in ppm relative to TMS ($\delta = 0.00$ ppm) or to $CHCl_3$ ($\delta = 7.26$ ppm). Higher order NMR spectra were approximately interpreted as first-order spectra if possible. ^{13}C chemical shifts are reported relative to $CDCl_3$ ($\delta = 77.0$ ppm). Neutral aluminium oxide (activity III, Fluka/Merck) or silica gel (0.040–0.063 mm, Fluka) were used for column chromatography. Nucleosil 50–5 (Macherey & Nagel) was used for HPLC. Melting points are uncorrected. Optical rotations were determined with Perkin–Elmer 141 or Perkin–Elmer 241 polarimeters. Starting materials **1**,[24] **6**,[25] **10**,[26] and **23**[16] were prepared by literature procedures. All other chemicals were commercially available and were used as received.

(1*R*,4′*S*)- and (1*S*,4′*S*)-[1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methoxybuta-2,3-dienyl]phenylamine (*syn*-7, *anti*-7): *n*BuLi (2.1M in *n*-hexane, 6.60 mL, 13.8 mmol) was added at −40 °C to a solution of methoxyallene **1** (1.08 g, 15.4 mmol) in absolute THF (30 mL). After the mixture had been stirred at −40 °C for 5 min, **6** (1.44 g, 7.03 mmol) in absolute THF (7 mL) was added, and the reaction mixture was allowed to warm up to −20 °C over 2 h and then quenched with water (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 40 mL). The organic extracts were combined and dried (Na_2SO_4). After removal of the solvents, a brown oil (1.76 g, 91%, purity > 90%) was isolated as a mixture of two diastereomers (*syn*-**7**/*anti*-**7** 89:11, calculated from ^{1}H NMR spectroscopy).

Major diastereomer *syn*-7: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.16$ (dd, $J =$ 7.3, 7.8 Hz, 2H; Ph), 6.72 (t, $J = 7.3$ Hz, 1H; Ph), 6.65 (d, $J = 7.8$ Hz, 2H; Ph), 5.58–5.51, 5.47–5.42 (2 × m, 2H; 4-H), 4.42 (q, $J = 6.3$ Hz, 1H; 4′-H), 4.17 (d_{br}, $J = 8.0$ Hz, 1H; N−H), 4.10–4.05 (m, 1H; 1-H), 3.93–3.88 (m, 2H; 5′-H), 3.41 (s, 3H; OMe), 1.45, 1.39 ppm (2 × s, each 3H, 2 × Me); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 198.5$ (s; C-3), 147.3, 129.1, 117.9, 114.1 (s, 3 × d; Ph), 132.9 (s; C-2), 109.8 (s; C-2′), 92.5 (t; C-4), 76.6 (d; C-4′), 66.9 (t; C-5′), 57.3 (d; C-1), 56.5 (q; OMe), 26.6, 25.4 ppm (2 × q; 2 × Me).

Minor diastereomer *anti*-7: ^{1}H NMR signals are hidden by those of the major diastereomer; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 198.9$ (s; C-3), 147.1, 129.2, 118.1, 114.2 (s, 3 × d; Ph), 131.5 (s; C-2), 110.5 (s; C-2′), 91.4 (t; C-4), 77.2 (d; C-4′), 66.4 (t; C-5′), 58.0 (d; C-1), 56.5 (q; OMe), 26.6, 25.4 ppm (2 × q; 2 × Me).

(2R,4′S)- and (2S,4′S)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methoxy-1-phenyl-2,5-dihydro-1*H*-pyrrole (*syn*-8, *anti*-8): Silver nitrate (618 mg, 3.60 mmol) was added to a mixture of crude **7** (3.64 g, *syn*/*anti* 89:11) dissolved in acetone (106 mL), and the resulting mixture was stirred under argon with exclusion of light at room temperature for 3 h. The mixture was filtered through Celite with ethyl acetate (84 mL) and the filtrate was evaporated. After column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 9:1), dihydropyrrole **8** was isolated as a yellow oil (1.97 g, 54%, two diastereomers). The mixture was treated with *n*-hexane and the major diastereomer *syn*-**8** was isolated as a yellow solid (916 mg, 25%). After removal of *n*-hexane from the remaining solution, a yellow oil was isolated as a mixture of both diastereomers (*syn*-**8**/*anti*-**8** 43:57, 1.05 g, 29%).

Major diastereomer *syn*-8: M.p. 83–84 °C; $[\alpha]_D^{32} = +165.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.25–7.22$ (m, 2H; Ph), 6.74–6.68 (m, 3H; Ph), 4.78 (s_{br}, 1H; 4-H), 4.65 (m_c, 1H; 2-H), 4.43 (dt, $J = 4.0$, 6.6 Hz, 1H; 4′-H), 4.21 (ddd, $J = 1.6$, 5.4, 12.0 Hz, 1H; 5-H_A), 3.97–3.93 (m, 2H; 5-H_B, 5′-H_A), 3.82 (dd, $J = 6.6$, 8.3 Hz, 1H; 5′-H_B), 3.68 (s, 3H; OMe), 1.45, 1.32 ppm (2 × s, each 3H; 2 × Me); ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta =$ 155.6 (s; C-3), 147.4, 129.1, 116.7, 111.8 (s, 3 × d; Ph), 109.1 (s; C-2′), 91.4 (d; C-4), 75.9 (d; C-4′), 65.4 (t; C-5′), 63.0 (d; C-2), 56.8 (q; OMe), 53.9 (t; C-5), 25.8, 24.9 ppm (2 × q; 2 × Me); IR (KBr): $\tilde{\nu} = 3100–3000$ (=C−H), 2990–2800 (C−H), 1660 (C=C), 1240 (C−O), 1060 cm^{-1} (C−N); elemental analysis calcd (%) for $C_{16}H_{21}NO_3$ (275.3): C 69.79, H 7.69, N 5.09; found: C 70.05, H 8.05, N 5.06.

Crystals of *syn*-**8** suitable for X-ray analysis were obtained by recrystallization from *n*-hexane/ethyl acetate. $C_{16}H_{21}NO_3$, $M_r = 275.3$; $T = 302(2)$ K; crystal size: 1.20 × 0.60 × 0.50 mm; orthorhombic, space group $P2_12_12_1$, $a =$ 7.9028(8), $b = 8.6153(7)$, $c = 21.862(2)$ Å; $V = 1488.5(2)$ Å^3; $Z = 4$; $\rho_{calcd} =$ 1.229 Mg m^{-3}; $F(000) = 592$; $\mu(Mo_{K\alpha}) = 0.084$ mm^{-1}. Φ range for data collection: 1.86–27.98°; index ranges: $-8 \le h \le 8$, $-13 \le k \le 13$, $-42 \le l \le 42$; reflections collected/unique: 4062/3592 ($R_{int} = 0.0085$); final R [$I > 2\sigma(I)$]: $R_1 = 0.0358$, $wR_2 = 0.0931$; R (all data): $R_1 = 0.0439$, $wR_2 = 0.1012$.

The programs SHELXS97 and SHELXL97 were used for structure solution and refinement.[27]

Minor diastereomer *anti*-8: ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 155.4$ (s; C-3), 148.1 (s; *i*-Ph), 128.7, 116.5, 112.6 (3 × d; Ph), 109.7 (s; C-2′), 91.0 (d;

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C-4), 77.4 (d; C-4′), 64.9 (t; C-5′), 62.6 (d; C-2), 56.9 (q; OMe), 54.6 (t; C-5), 25.9, 25.5 ppm (2 × q; 2 × Me).

(3*S*,3a*S*,6a*S*)-6a-Methoxy-4-phenyl-3,3a,4,5,6,6a-hexahydrofuro[3,2-*b*]-2*H*-pyrrol-3-ol (9): Compound *syn*-**8** (100 mg, 0.36 mmol) in absolute methanol (2 mL) was added to *p*-TsCl (35 mg, 0.18 mmol) in absolute methanol (2 mL). After the mixture had been stirred at room temperature for one day, $NaHCO_3$ solution (10 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic phases were washed with water and dried (Na_2SO_4), and the solvents were removed. After column chromatography on aluminum oxide (*n*-hexane/ethyl acetate 6:4), **9** (61 mg, 71 %) was isolated as a colorless oil. $[\alpha]_D^{31} = +93$ ($c = 0.55$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.28-7.23$ (m, 2H; Ph), 6.74 (t, $J = 7.3$ Hz, 1H; Ph), 6.66–6.63 (m, 2H; Ph), 4.30–4.27 (m, 1H; 3-H), 4.17–4.10 (m, 1H; 2-H), 4.08–3.97 (m, 2H; 2-H, 3a-H), 3.52–3.32 (m, 2H; 5-H), 3.42 (s, 3H; OMe), 2.49 (s_{br}, 1H; OH), 2.39–2.32, 2.10–2.05 ppm (2 × m, each 1H; 6-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 146.1$, 129.3, 116.8, 112.4 (s, 3 × d; Ph), 117.2 (s; C-6a), 76.3, 47.3, 32.1 (3 × t; C-2, C-5, C-6), 74.1 (d; C-3), 73.4 (d; C-3a), 51.1 ppm (q; OMe); IR (neat): $\tilde{\nu} =$ 3600–3400 (O–H), 3100–3000 (=C–H), 2940–2800 (C–H), 1200 (C–N), 1130 cm^{-1} (C–O); elemental analysis calcd (%) for $C_{13}H_{17}NO_3$ (235.3): C 66.36, H 7.28, N 5.95; found: C 66.44, H 7.56, N 6.23.

(1*S*,4′*S*)-Benzyl[1-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methoxybuta-2,3-dienyl]amine (*syn*-11): *n*BuLi (2.3 M in *n*-hexane, 9.00 mL, 20.7 mmol) was added at −40 °C to a solution of methoxyallene **1** (1.61 g, 23.0 mmol) in absolute THF (46 mL). After the mixture had been stirred at −40 °C for 5 min, **10** (2.45 g, 11.2 mmol) in absolute THF (12 mL) was added, and the reaction mixture was allowed to warm up to −20 °C over 2 h and then quenched with water (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 40 mL). The organic extracts were combined and dried (Na_2SO_4). After removal of the solvents, 3.04 g (94 %) of an orange oil was isolated as a mixture of allene *syn*-**11** and dihydropyrrole *syn*-**12** (ratio 52:48). The cyclization of the mixture was completed in the next step.

Allene *syn*-11: ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 198.9$ (s; C-3), 140.2, 128.3, 128.2, 127.9 (s, 3 × d; Ph), 130.7 (s; C-2), 109.5 (s; C-2′), 91.1 (t; C-4), 77.2 (d; C-4′), 67.0 (t; C-5′), 62.2 (d; C-1), 56.3 (q; OMe), 51.1 (t; CH_2Ph), 27.7, 26.7 ppm (2 × q; 2 × Me).

(2*S*,4′*S*)-1-Benzyl-2-(2,2-dimethyl-1,3-dioxan-4-yl)-3-methoxy-2,5-dihydro-1*H*-pyrrole (*syn*-12): The mixture of *syn*-**11** and *syn*-**12** (2.98 g) was dissolved in acetone (42 mL) under argon atmosphere, silver nitrate (245 mg, 1.44 mmol) was then added, and the resulting mixture was stirred at room temperature with exclusion of light for 3 h. The mixture was filtered through Celite with ethyl acetate (84 mL) and the filtrate was evaporated. After column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 19:1), *syn*-**12** was isolated as a yellow oil (1.69 g, 57 %), which crystallized during storage. M.p. 58–60 °C; $[\alpha]_D^{20} = +50.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.40-7.19$ (m, 5H; Ph), 4.56 (dd, $J = 1.5$, 1.9 Hz, 1H; 4-H), 4.30 (d, $J = 13.2$ Hz, 1H; NCH_2Ph), 4.14 (ddd, $J = 6.7$, 7.8, 8.3 Hz, 1H; 4′-H), 4.07 (dd, $J = 6.7$, 8.3 Hz, 1H; 5′-H_A), 3.80 (dd, $J = 7.8$, 8.3 Hz, 1H; 5′-H_B), 3.70–3.65 (m, 1H; 2-H), 3.64 (d, $J = 13.2$ Hz, 1H; NCH_2Ph), 3.61–3.57 (m, 1H; 5-H_A), 3.58 (s, 3H; OMe), 3.17 (ddd, $J = 1.9$, 3.5, 12.0 Hz, 1H; 5-H_B), 1.41, 1.36 ppm (2 × s, each 3H; 2 × Me); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 155.9$ (s; C-3), 139.7, 128.8, 128.2, 126.8 (s, 3 × d; Ph), 108.5 (s; C-2′), 92.4 (d; C-4), 79.7 (d; C-4′), 69.4 (d; C-2), 66.8 (t; C-5′), 60.3 (t; NCH_2Ph), 56.8 (q; OMe), 56.7 (t; C-5), 26.5, 25.5 ppm (2 × q; 2 × Me); IR (KBr): $\tilde{\nu} = 3130-2780$ (=C–H, C–H), 1660 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{17}H_{23}NO_3$ (289.4): C 70.56, H 8.01, N 4.84; found: C 70.84, H 8.18, N 4.65.

One-pot synthesis of *syn*-12 from 10: *n*BuLi (2.3 M in *n*-hexane, 2.90 mL, 6.54 mmol) was added at −40 °C to a solution of methoxyallene **1** (509 mg, 7.26 mmol) in absolute THF (15 mL). After the mixture had been stirred for 5 min at −40 °C, **10** (717 mg, 11.2 mmol) in absolute THF (12 mL) was added, the reaction mixture was allowed to warm up to −20 °C over 2 h, the cooling bath was removed, and the reaction mixture was stirred for 22 h at room temperature. After addition of water (20 mL) the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvents were removed. After column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 19:1) *syn*-**12** was isolated as a yellow oil (614 mg, 63 %), which crystallized during storage.

(3*S*,3a*S*,6a*S*)-4-Benzyl-6a-methoxy-3,3a,4,5,6,6a-hexahydrofuro[3,2-*b*]-2*H*-pyrrol-3-ol (13): Compound *syn*-**12** (168 mg, 0.58 mmol) in absolute methanol (10 mL) was added to 6 N HCl (10 mL). After stirring for 18 h at room temperature the solution was neutralized by addition of 2 N NaOH solution. After addition of Et_2O (10 mL) the aqueous phase was separated and extracted with ethyl acetate (5 × 15 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvents were removed. After column chromatography on aluminium oxide (100 % *n*-hexane to 100 % ethyl acetate), **13** (63 mg, 44 %) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.33-7.23$ (m, 5H; Ph), 4.24 (dd, $J = 4.4$, 9.0 Hz, 1H; 3-H), 3.96–3.92 (m, 2H; 2-H), 3.84, 3.61 (2 × d, $J = 13.0$ Hz, each 1H; CH_2-Ph), 3.35 (s, 3H; OMe), 2.99 (ddd, $J = 2.0$, 7.5, 9.0 Hz, 1H; 5-H), 2.91 (s, 1H; 3a-H), 2.51 (td, $J = 7.5$, 9.0 Hz, 1H; 5H), 2.12–2.04 (m, 1H; 6-H), 2.00–1.90 (m, 1H; 6-H), 1.88 ppm (s_{br}, 1H; OH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 138.4$, 128.9, 128.4, 127.3 (s, 3 × d; Ph), 118.7 (s; C-6a), 79.4 (d; C-3), 75.7 (t; C-2), 74.7 (d; C-3a), 59.0 (t; C-5), 53.4 (t; CH_2Ph), 50.5 (q; OMe), 33.4 ppm (t; C-6); IR (neat): $\tilde{\nu} = 3440$ (O–H), 3090–3030 (=C–H), 2940–2800 (C–H), 1100 (C–N), 1130 cm^{-1} (C–O); elemental analysis calcd (%) for $C_{13}H_{17}NO_3$ (235.3): C 67.45, H 7.68, N 5.62; found: C 66.96, H 7.25, N 5.62.

(*S*)-1,2,4-Butanetriol:[10] (*S*)-Malic acid (2.00 g, 14.9 mmol) in dry THF (10 mL) was added dropwise at 0 °C to a stirred solution of borane–dimethylsulfide complex (24.0 mL, 48.0 mmol, 2 M in THF) and trimethylborate (5.00 mL, 4.55 g, 43.8 mmol). After the mixture had been stirred for 15 min at 0 °C, the cooling bath was removed. After the mixture had been stirred for 16 h, methanol (12 mL) was carefully added and the resulting solution was evaporated to dryness. A further three co-evaporations with methanol (3 × 20 mL) and subsequent flash chromatography (dichloromethane/methanol 85:15) afforded the triol as a colorless oil (1.58 g, quant.). ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 4.46$ (t, $J = 5.7$ Hz, 1H), 3.97–3.90 (m, 2H), 3.17–3.02 (m, 3H; OH), 2.91–2.76 (m, 2H), 1.58 (dtd, $J = 3.9$, 7.1, 13.9 Hz, 1H), 1.03–0.89 ppm (m, 1H).

(2*S*,4*S*)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane (14):[11] (*S*)-1,2,4-Butanetriol (1.58 g, 14.9 mmol) and benzaldehyde dimethylacetal (2.64 g, 15.9 mmol) in dry dichloromethane (50 mL) were stirred at room temperature in the presence of camphorsulfonic acid (174 mg, 0.75 mmol). After the mixture had been stirred for 16 h, triethylamine (144 mg, 1.57 mmol) was added and the solvents were removed under reduced pressure. The product **14** (2.45 g, 84 %, purity 90–95 %, ca. 5–10 % stereoisomers and constitutional isomers) was obtained after column chromatography on silica gel (*n*-hexane/ethyl acetate 2:1 to 1:1) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.51-7.30$ (m, 5H; Ph), 5.49 (s, 1H; 2-H), 4.24 (dd, $J = 5.2$, 11.4 Hz, 1H; 4-H_A), 3.94–3.87 (m, 2H; 4-H_B, 2-H), 3.60–3.55 (m, 2H; CH_2OH), 2.69–2.56 (s_{br}, 1H; OH), 1.88–1.77 (m, 1H; 5-H_A), 1.36 ppm (d_{br}, $J = 13.4$ Hz, 1H; 5-H_B); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 138.2$, 128.8, 128.1, 126.0 (s, 3 × d; Ph), 101.1 (d; C-2), 77.4 (d; C-4), 66.4 (t; C-6), 65.3 (t; CH_2OH), 26.7 ppm (t; C-5); IR (neat): $\tilde{\nu} = 3430$ (O–H), 3070–3035 (=C–H), 2955—2860 cm^{-1} (C–H); MS (80 eV, EI): m/z (%): 194 (85) $[M]^+$, 163 (96) $[M - CH_2OH]^+$, 105 (100) $[M - C_7H_5]^+$, 91 (36) $[Bn]^+$; elemental analysis calcd (%) for $C_{11}H_{14}O_3$ (194.2): C 68.02, H 7.27; found: C 67.93, H 7.21.

(2*S*,4*S*)-4-Formyl-2-phenyl-1,3-dioxane:[11] A solution of dry DMSO (0.70 mL, 771 mg, 9.86 mmol) in dichloromethane (5 mL) was added dropwise, at −60 °C under argon, to a solution of oxalyl chloride (0.40 mL, 582 mg, 4.59 mmol) in dichloromethane (10 mL). After the mixture had been stirred for 12 min, a solution of alcohol **14** (826 mg, 4.25 mmol) in dichloromethane (5 mL) was added dropwise. The mixture was stirred at −60 °C for 30 min and was then treated with triethylamine (2.80 mL, 2.03 g, 20.1 mmol). After a further 5 min the cooling bath was removed, water (20 mL) was added, and the mixture was allowed to warm up to room temperature. The phases were separated, the aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with saturated ammonium chloride solution (60 mL) and water (60 mL) and dried (Na_2SO_4). Evaporation of the solvents afforded crude aldehyde (800 mg, 98 %). The product was used in the next step without purification. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.73$ (s, 1H; CHO), 7.56–7.35 (m, 5H; Ph), 5.61 (s, 1H; 2-H), 4.41–4.33 (m, 2H; 4-H, 6-H_A), 4.03 (td, $J =$ 2.8, 11.9 Hz, 1H; 6-H_B), 2.06–1.76 ppm (m, 2H; 5-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 200.1$ (s; CHO), 137.6, 129.0, 128.1, 126.0 (s, 3 × d; Ph), 100.9 (d; C-2), 80.1 (d; C-4), 66.2 (t; C-6), 25.7 ppm (t; C-5).

(2*S*,4*S*)-Benzyl[2-phenyl-(1,3-dioxan-4-yl)methylen]amine (15): Magnesium sulfate (501 mg, 4.16 mmol) and benzylamine (446 mg, 4.16 mmol) in dichloromethane (5 mL) were added to a solution of freshly prepared (2*S*,4*S*)-4-formyl-2-phenyl-1,3-dioxane (800 mg, 4.16 mmol) in dichloromethane (15 mL). The mixture was stirred for 3 h at room temperature and then filtered, and the filtrate was evaporated to produce a yellowish oil (1.03 g, 88 %). Product **15** was used in the next step without purification. $[\alpha]_D^{20} = -13.8$ ($c = 0.96$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 3.7$ Hz, 1H; N=CH), 7.53 – 7.15 (m, 10H; Ph), 5.52 (s, 1H; 2-H), 4.55 (s, 2H; PhCH_2), 4.47 (d_{br}, $J = 11.5$ Hz, 1H; 4-H), 4.23 (ddd, $J = 1.3$, 5.0, 11.6 Hz, 1H; 6-H_A), 3.91 (ddd, $J = 2.6$, 11.6, 12.3 Hz, 1H; 6-H_B), 2.02 (dddd, $J = 5.0$, 11.5, 12.3, 13.3 Hz, 1H; 5-H_A), 1.68 ppm (dtd, $J = 1.3$, 2.6, 13.3 Hz, 1H; 5-H_B); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 164.3$ (s; C=N), 138.3, 138.0, 128.6, 128.2, 128.0, 127.7, 126.8, 125.9 (2 × s, 6 × d; Ph), 100.9 (d; C-2), 77.8 (d; C-4), 66.3 (t; C-6), 64.3 (t; CH_2Ph), 28.3 ppm (t; C-5).

(1*R*,2′*S*,4′*S*)-Benzyl[2-methoxy-1-(2-phenyl-1,3-dioxan-4-yl)buta-2,3-dienyl]-amine (*syn*-16): *n*BuLi (2.5 M in *n*-hexane, 4.00 mL, 10.0 mmol) was added at −40 °C to a solution of methoxyallene **1** (1.00 mL, 840 mg, 12.0 mmol) in absolute THF (20 mL). After the mixture had been stirred at −40 °C for 15 min, crude **15** (1.00 g, from 4.25 mmol **14**) in absolute THF (10 mL) was added, and the reaction mixture was allowed to warm up to −20 °C over 2 h and then quenched with water (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvents were removed. After column chromatography on aluminium oxide (20 % ethyl acetate/*n*-hexane) *syn*-**16** was isolated as a yellowish oil (672 mg, 45 % with respect to **14**). $[\alpha]_D^{20} = +10.3$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.60 – 7.25$ (m, 10H; Ph), 5.60 (s, 1H; 2′-H), 5.56 (s, 2H; 4-H), 4.32 (dd, $J = 4.3$, 11.1 Hz, 1H; 6′-H_A), 4.14 (m_c, 1H; 4′-H), 4.03 – 3.97 (m, 1H; 6′-H_B), 4.00, 3.82 (2 × d, $J = 13.9$ Hz, each 1H; PhCH_2), 3.50 (s, 3H; OMe), 3.39 (d, $J = 8.3$ Hz, 1H; 1-H), 2.43 (s_{br}, 1H; NH), 1.97 (ddt, $J = 4.3$, 11.7, 12.6 Hz, 1H; 5′-H_A), 1.62 ppm (d_{br}, $J = 12.6$ Hz, 1H; 5′-H_B); ^{13}C NMR (125.8 MHz; $CDCl_3$): $\delta = 199.4$ (s; C-3), 139.9, 138.2, 128.3, 127.8*, 127.7, 126.3, 125.6 (2 × s, 5 × d; Ph), 130.8 (s; C-2), 100.6 (d; C-2′), 90.2 (t; C-4), 77.6 (d; C-4′), 66.3 (t; C-6′), 63.8 (d; C-1), 55.8 (q; OMe), 50.8 (t; PhCH_2), 27.7 ppm (t; C-5′),* higher intensity; IR (neat): $\tilde{\nu} = 3340$ (N–H), 3085 – 2850 (C–H), 1955 cm^{-1} (C=C=C); MS (80 eV, EI): *m*/*z* (%): 351 (6) $[M]^+$, 336 (1) $[M - CH_3]^+$, 188 (100) $[M - C_{10}H_{11}O_2]^+$; elemental analysis calcd (%) for $C_{22}H_{25}NO_3$ (351.5): C 75.19, H 7.17, N 3.99; found: C 74.82, H 7.19, N 3.76.

(2*R*,2′*S*,4′*S*)-1-Benzyl-3-methoxy-2-(2-phenyl-1,3-dioxan-4-yl)-2,5-dihydro-1*H*-pyrrole (*syn*-17): Compound *syn*-**16** (657 mg, 1.87 mmol) was dissolved in acetone (20 mL), silver nitrate (63 mg, 0.37 mmol) was added, and the resulting mixture was stirred under argon with exclusion of light at room temperature for 16 h. The mixture was filtered through Celite with ethyl acetate (3 × 20 mL) and the filtrate was evaporated. After column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 8:1), *syn*-**17** was isolated as a colorless oil (579 mg, 88 %). $[\alpha]_D^{20} = -27.6$ ($c = 1.25$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.57 – 7.53$ (m, 2H; Ph), 7.41 – 7.22 (m, 8H; Ph), 5.56 (s, 1H; 2′-H), 4.54 (s_{br}, 1H; 4-H), 4.24 (dd, $J = 4.7$, 11.3 Hz, 1H; 6′-H_A), 4.17 (d, $J = 13.3$ Hz, 1H; NCH_2Ph), 3.95 – 3.87 (m, 2H; 6′-H_B, 4′-H), 3.74 (d_{br}, $J = 4.8$ Hz, 1H; 2-H), 3.64 (d, $J = 13.3$ Hz, 1H; NCH_2Ph), 3.62 (ddd, $J = 2.1$, 4.8, 12.4 Hz, 1H; 5-H_A), 3.56 (s, 3H; OMe), 3.13 (ddd, $J = 2.1$, 3.2, 12.4 Hz, 1H; 5-H_B), 1.94 (ddt, $J = 4.7$, 12.0, 12.9 Hz, 1H; 5′-H_A), 1.78 ppm (d_{br}, $J = 12.9$ Hz, 1H; 5′-H_A); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 156.0$ (s; C-3), 139.5, 138.7, 128.4, 128.3, 128.0, 127.9, 126.6, 125.9 (2 × s, 6 × d; Ph), 101.2 (d; C-2′), 92.2 (d; C-4), 79.8 (d; C-4′), 70.5 (d; C-2), 66.9 (t; C-6′), 60.7 (t; NCH_2Ph), 56.6 (q; OMe), 56.6 (t; C-5), 27.0 ppm (t; C-5′); IR (neat): $\tilde{\nu} = 3090 – 3000$ (=C–H), 2960 – 2850 (C–H), 1660 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 351 (1) $[M]^+$, 246 (3) $[M - NCH_2Ph]^+$, 188 (45) $[M - C_{10}H_{11}O_2]^+$, 91 (100) $[Bn]^+$; HRMS (80 eV): calcd for $C_{22}H_{25}NO_3$: 351.18344; found 351.18731; elemental analysis calcd (%) for $C_{22}H_{25}NO_3$ (351.5): C 75.19, H 7.17, N 3.99; found: C 74.92, H 7.16, N 3.64.

One-pot synthesis of *syn*-17 from 15: *n*BuLi (2.5 M in *n*-hexane, 4.00 mL, 10.0 mmol) was added at −40 °C to a solution of methoxyallene **1** (1.00 mL, 840 mg, 12.0 mmol) in absolute THF (20 mL). After the mixture had been stirred at −40 °C for 15 min, crude **15** (1.00 g, from 4.12 mmol **14**) in absolute THF (10 mL) was added. The reaction mixture was allowed to warm up to room temperature over 16 h and was then quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), the combined organic phases were dried (Na_2SO_4), and the solvents were removed under reduced pressure. After purification by column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 8:1), *syn*-**17** was isolated as a yellowish oil (736 mg, 51 % with respect to **14**).

(2*R*,4′*S*)-1-(1-Benzyl-3-methoxy-2,5-dihydro-1*H*-pyrrol-2-yl)propane-1,3-diol (*syn*-18): *p*-Toluenesulfonic acid monohydrate (571 mg, 3.00 mmol) was added at room temperature to a solution of *syn*-**17** (702 mg, 2.00 mmol) in absolute methanol (40 mL). After stirring for 44 h at room temperature, the reaction mixture was quenched with potassium carbonate solution (10 % in water, 40 mL). The aqueous phase was extracted with dichloromethane (3 × 40 mL), the combined organic phases were dried (Na_2SO_4), and the solvents were removed under reduced pressure. After purification by column chromatography on silica gel (dichloromethane/methanol 20:1), **18** was isolated as a yellowish oil (402 mg, 76 %). $[\alpha]_D^{20} = -49.2$ ($c = 0.25$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.36 – 7.25$ (m, 5H; Ph), 4.59 – 4.56 (m_c, 1H; 4′-H), 4.05 (d, $J = 13.1$ Hz, 1H; NCH_2Ph), 3.86 – 3.60 (m, 6H; 1-H, 3-H_A, 3-H_B, 2′-H, 5′-H_A, OH), 3.72 (d, $J = 13.1$ Hz, 1H; NCH_2Ph), 3.66 (s, 3H; OMe), 3.50 (s_{br}, 1H; OH), 3.23 (ddd, $J = 2.1$, 3.2, 12.4 Hz, 1H; 5′-H_B), 1.84 – 1.78 ppm (m, 2H; 2-H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 155.7$ (s; C-3), 138.0, 128.6, 128.5, 127.4 (s, 3 × d; Ph), 91.6 (d; C-4′), 71.8, 71.6 (2 × d; C-1, C-2′), 61.6, 61.1 (2 × t; NCH_2Ph, C-3), 57.0 (t, q; C-5′, OMe), 36.9 ppm (t; C-2); IR (neat): $\tilde{\nu} = 3405$ (O–H), 3085 – 3005 (=C–H), 2935 – 2835 (C–H), 1665 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 263 (2) $[M]^+$, 220 (6) $[M - C_2H_3O]^+$, 188 (100) $[M - C_3H_7O_2]^+$, 172 (3) $[M - C_7H_7]^+$, 91 (75) $[C_7H_7]^+$; HRMS (80 eV): calcd for $C_{15}H_{21}NO_3$: 263.15214; found 263.15365.

(2*R*,2′*S*,4′*S*)-1-Benzyl-(2-phenyl-1,3-dioxan-4-yl)-3-[2-(trimethylsilyl)ethoxy]-2,5-dihydro-1*H*-pyrrole (*syn*-20): *n*BuLi (2.5 M in *n*-hexane, 5.00 mL, 12.5 mmol) was added at −50 °C to a solution of 1-[2-(trimethylsilyl)-ethoxy]allene[12] (2.24 g, 14.4 mmol) in absolute THF (30 mL). After the mixture had been stirred for 30 min at −40 to −50 °C, crude **15** (1.51 g, from 6.00 mmol **14**) in absolute THF (10 mL) was added, and the reaction mixture was allowed to warm up to room temperature over 16 h and then quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), the combined organic phases were dried ($MgSO_4$), and the solvents were removed under reduced pressure. After purification by column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 10:1) and drying in vacuo (0.02 mbar, 50 °C), *syn*-**20** was isolated as a yellowish oil (1.15 g, 44 % with respect to **14**). $[\alpha]_D^{20} = -13.6$ ($c = 1.38$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.57 – 7.24$ (m, 10H; Ph), 5.58 (s, 1H; 2′-H), 4.69 – 4.58 (m_c, 1H; 4-H), 4.32 (ddd, $J = 1.1$, 4.7, 11.3 Hz, 1H; 6′-H_A), 4.24 (d, $J = 13.4$ Hz, 1H; NCH_2Ph), 4.04 – 3.96 (m, 2H; 4′-H, 6′-H_B), 3.93 – 3.88 [m, 2H; OCH_2CH_2Si(CH_3)$_3$], 3.80 – 3.76 (m, 1H; 2-H), 3.72 (d, $J = 13.4$ Hz, 1H; NCH_2Ph), 3.71 (ddd, $J = 2.0$, 4.9, 12.3 Hz, 1H; 5-H_A), 3.18 (ddd, $J = 2.0$, 3.0, 12.3 Hz, 1H; 5-H_B), 2.11 – 2.01 (m, 1H; 5′-H_A), 1.83 – 1.78 (m, 1H; 5′-H_B), 1.17 – 1.12 (m_c, 2H; CH_2Si(CH_3)$_3$), 0.10 ppm (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 155.0$ (s; C-3), 139.8, 139.0, 128.5, 128.3, 128.0, 127.9, 126.6, 126.1 (2 × s, 6 × d, Ph), 101.2 (d; C-2′), 92.3 (d; C-4), 80.1 (d; C-4′), 70.9 (d; C-2), 67.0, 67.0 (2 × t; C-6′, OCH_2CH_2Si(CH_3)$_3$), 61.2 (t; NCH_2Ph), 57.1 (t; C-5), 27.5 (t; C-5′), 17.4 (t; CH_2Si(CH_3)$_3$), −1.5 ppm (q; Si(CH_3)$_3$); IR (neat): $\tilde{\nu} = 3085 – 3000$ (=C–H), 2960 – 2850 (C–H), 1655 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 437 (6) $[M]^+$, 274 (100) $[M - C_{10}H_{11}O_2]^+$, 91 (48) $[Bn]^+$, 73 (55) $[Si(CH_3)_3]^+$; elemental analysis calcd (%) for $C_{26}H_{35}NO_3Si$ (437.7): C 71.35, H 8.06, N 3.20; found: C 71.15, H 8.18, N 2.99.

(2*R*,2′*S*,4′*S*)-1-Benzyl-3-benzyloxy-2-(2-phenyl-1,3-dioxan-4-yl)-2,5-dihydro-1*H*-pyrrole (*syn*-22): *n*BuLi (2.5 M in *n*-hexane, 10.0 mL, 25.0 mmol) was added at −50 °C to a solution of benzyloxyallene **23** (3.98 g, 27.2 mmol) in absolute THF (50 mL). After the mixture had been stirred for 20 min at −40 to −50 °C, crude **15** (2.65 g, from 10.0 mmol **14**) in absolute THF (20 mL) was added, and the reaction mixture was allowed to warm up to room temperature over 16 h and then quenched with water (50 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL), the combined organic phases were dried ($MgSO_4$), and the solvents were removed under reduced pressure. After purification by column chromatography on aluminium oxide (*n*-hexane/ethyl acetate 10:1), *syn*-**22** was isolated as a yellowish oil (2.15 g, 50 % with respect to **14**). $[\alpha]_D^{20} = -32.9$ ($c = 0.49$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.51 – 7.16$ (m, 15H; Ph), 5.51 (s, 1H; 2′-H), 4.83 (s, 2H; OCH_2Ph), 4.66 (m_c, 1H; 4-H), 4.26 (ddd, $J = 1.2$, 4.9, 11.3 Hz, 1H; 6′-H_A), 4.16 (d, $J = 13.5$ Hz, 1H; NCH_2Ph), 4.00 – 3.88 (m, 2H; 4′-H, 6′-H_B), 3.84 (ddt, $J = 1.4$, 3.3, 4.7 Hz, 1H; 2-H), 3.69 (d, $J = 13.5$ Hz, 1H; NCH_2Ph), 3.67 (ddd, $J = 2.0$, 4.7, 12.4 Hz, 1H; 5-H_A), 3.18 (ddd, $J = 2.0$, 3.3, 12.4 Hz, 1H; 5-H_B), 2.10 – 1.91 (m, 1H; 5′-H_A), 1.80 – 1.69 ppm (m, 1H; 5′-H_B);

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^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 155.0$ (s; C-3), 139.7, 138.9, 136.7, 128.5, 128.5, 128.3, 128.1, 128.0, 127.7, 127.2, 126.7, 126.2 (3 × s, 9 × d; Ph), 101.5 (d; C-2′), 93.6 (d; C-4), 79.6 (d; C-4′), 71.3 (t; O*C*H$_2$Ph), 70.8 (d; C-2), 67.0 (t; C-6′), 60.9 (t; N*C*H$_2$Ph), 57.0 (t; C-5), 27.0 ppm (t; C-5′); IR (neat): $\tilde{\nu} =$ 3100–3000 (=C-H), 2975 (C–H), 1655 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 427 (1) $[M]^+$, 336 (5) $[M - C_7H_7]^+$, 264 (100) $[M - C_{10}H_{11}O_2]^+$, 91 (72) $[Bn]^+$; HRMS (80 eV): calcd for ($C_{28}H_{29}NO_3 - C_{10}H_{11}O_2$; mol peak is too weak): 336.15996; found 336.15756; elemental analysis calcd (%) for $C_{28}H_{29}NO_3$ (427.6): C 78.66, H 6.84, N 3.28; found: C 78.44, H 6.80, N 2.94.

(1*S*,2′*R*)-1-(1-Benzyl-3-benzyloxy-2,5-dihydro-1*H*-pyrrol-2-yl)-3-benzyloxypropan-1-ol (*syn*-24): Diisobutylaluminum hydride (1.5 M in toluene, 1.30 mL, 1.95 mmol) was added under argon at −78 °C to a solution of *syn*-**22** (270 mg, 0.63 mmol) in dry dichloromethane (5 mL). The mixture was allowed to warm up to room temperature over 16 h and then cooled to 0 °C, and saturated sodium potassium tartrate solution (5 mL) was added. After 1 h, water (20 mL) was added and the solution was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed under reduced pressure. After column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1), **24** (191 mg, 71%) was obtained as colorless oil. $[\alpha]_D^{20} = -39.6$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 7.44-7.18$ (m, 15H; Ph), 4.84 (s, 2H; OC*H*$_2$Ph), 4.70 (s, 1H; 4′-H), 4.44 (s, 2H; OC*H*$_2$Ph), 4.22–4.00 (s_{br}, 1H; OH), 3.99 (d, $J = 13.7$ Hz, 1H; NC*H*$_2$Ph), 3.70 (d_{br}, $J = 9.8$ Hz, 1H; 1-H), 3.73–3.61 (m, 4H; NC*H*$_2$Ph, 2′-H, 3-H), 3.52–3.48 (m, 1H; 5′-H$_A$), 3.05 (d_{br}, $J = 12.2$ Hz, 1H; 5′-H$_B$), 1.98–1.80 (m, 1H; 2-H$_A$), 1.73–1.53 ppm (m, 1H; 2-H$_B$); ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): $\delta = 155.1$ (s; C-3′), 139.6, 138.7, 136.9, 128.3, 128.1, 128.1*, 127.7, 127.3, 127.2, 127.2, 126.7 (3 × s, 8 × d; Ph), 92.7 (d; C-4′), 72.0 (d; C-2′), 71.8 (t; O*C*H$_2$Ph), 70.8 (t; O*C*H$_2$Ph), 68.2 (d; C-1), 67.4 (t; C-3), 60.7 (t; N*C*H$_2$Ph), 57.0 (t; C-5′), 33.5 ppm (t; C-2), * signal with higher intensity; IR (neat): $\tilde{\nu} = 3435$ (O–H), 3085–3030 (=C–H), 2925–2860 (C–H), 1665 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 429 (1) $[M]^+$, 338 (3) $[M - Bn]^+$, 264 (60) $[M - C_{10}H_{11}O_2]^+$, 91 (100) $[Bn]^+$; HRMS (80 eV): calcd for $C_{28}H_{31}NO_3$: 429.23029; found 429.23245.

Reduction of *syn*-22 with Pd(OH)$_2$/H$_2$: A suspension of palladium hydroxide on charcoal (100 mg, 0.19 mmol, pre-dried for 2 h at 60 °C under reduced pressure of 10^{-2} mbar) in dry ethanol (8 mL) was saturated with hydrogen for 1 h. Boc anhydride (0.22 mL, 209 mg, 0.96 mmol) and *syn*-**22** (200 mg, 0.47 mmol) dissolved in dry ethanol (4 mL) were then added. After stirring at room temperature under hydrogen atmosphere for 48 h, the mixture was filtered through Celite with methanol (60 mL). After evaporation of the solvents and purification by column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1), pyrrolidinone **26** (21 mg, 13%) and dihydropyrrole **25** (73 mg, 37%) were obtained as colorless oils.

(2*R*,2′*S*,4′*S*)-1-*tert*-Butoxycarbonyl-2-(2-phenyl-1,3-dioxan-4-yl)pyrrolidin-3-one (26) (two rotamers, ratio ca. 1:1): $[\alpha]_D^{20} = -133.9$ ($c = 0.72$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.43-7.26$ (m, 5H; Ph), 5.45, 5.44 (2 × s, 1H; 2′-H), 4.47–4.23 (m, 1H; 4′-H), 4.25, 4.16 (2 × dt, $J = 2.5$, 10.5 Hz, 1H; 5-H$_A$), 4.15, 4.03 (2 × s_{br}, 1H; 2-H), 4.05–3.92 (m, 1H; 6′-H$_B$), 3.73–3.57 (m, 1H; 5-H$_B$), 2.60–2.35 (m, 2H; 4-H), 2.21–2.02 (m, 1H; 5′-H$_A$), 1.65–1.45 (m, 1H; 5′-H$_B$), 1.51, 1.49 ppm (2 × s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 213.7$, 213.1 (2 × s; C-3), 155.0, 154.4 (2 × s; NCO), 138.2, 138.0, 128.8, 128.7, 128.1, 125.7, 125.6 (2 × s, 5 × d; Ph), 101.3, 101.0 (2 × d; C-2′), 80.6, 80.3 (2 × s; *C*(CH$_3$)$_3$), 79.8, 79.4 (2 × d; C-4′), 66.8, 66.6 (2 × t; C-6′), 65.4, 64.8 (2 × d; C-2), 43.5, 42.8 (2 × t; C-5), 37.1, 36.6 (2 × t; C-4), 28.3 (q; C(*C*H$_3$)$_3$), 27.8 ppm (t; C-5′); IR (neat): $\tilde{\nu} = 3100-3065$ (=C–H), 2975–2860 (C–H), 1760, 1695 cm^{-1} (C=O); MS (80 eV, EI): *m*/*z* (%): 347 (1) $[M]^+$, 290 (1) $[M - C(CH_3)_3]^+$ (1), 274 (4) $[M - OC(CH_3)_3]^+$, 163 (100) $[C_{10}H_{11}O_2]^+$, 91 (42) $[Bn]^+$, 57 (69) $[C(CH_3)_3]^+$; HRMS (80 eV): found 257.12732; $C_{12}H_{19}NO_5$ calcd 257.12632; elemental analysis calcd (%) for $C_{19}H_{25}NO_5$ (347.4): C 65.69, H 7.25, N 4.03; found: C 65.68, H 7.26, N 4.00.

(2*R*,2′*S*,4′*S*)-3-Benzyloxy-1-*tert*-butoxycarbonyl-2-(2-phenyl-1,3-dioxan-4-yl)-2,5-dihydro-1*H*-pyrrole (25) (two rotamers, ratio ca. 1:1): $[\alpha]_D^{20} = -84.6$ ($c = 0.69$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.45-7.25$ (m, 10H; Ph), 5.52, 5.48 (2 × s, 1H; 2′-H), 4.87 (s_{br}, 2H; OC*H*$_2$Ph), 4.75, 4.59 (2 × s_{br}, 1H; 4-H), 4.68 (s_{br}, 1H; 2-H), 4.38–4.15 (m, 3H; 4′-H, 5-H$_A$, 6′-H$_A$), 4.01–3.92 (m, 2H; 5-H$_B$, 6′-H$_B$), 2.06–1.95 (m, 1H; 5′-H$_A$), 1.55–1.42 (m, 1H; 5′-H$_B$), 1.49, 1.48 ppm (2 × s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 154.8$, 154.4, 153.4, 153.3 (4 × s; C=O, C-3), 138.8, 138.6, 136.3, 136.2, 128.6, 128.3*, 128.0, 128.0, 127.9, 127.8, 127.3, 127.2, 126.1, 126.0 (4 × s, 10 × d; Ph), 101.5, 101.0 (2 × d; C-2′), 92.4, 90.0 (2 × d; C-4), 80.0, 79.6 (2 × s; *C*(CH$_3$)$_3$), 76.9, 76.4 (2 × d; C-4′), 71.4 (t; O*C*H$_2$Ph), 66.9, 66.9 (2 × t; C-6′), 64.2, 64.1 (2 × d; C-2), 51.5, 51.0 (2 × t; C-5), 28.4 (q; C(*C*H$_3$)$_3$), 26.9, 26.6 ppm (2 × t; C-5),* higher intensity; IR (neat): $\tilde{\nu} = 3090-3035$ (=C–H), 2975–2860 (C–H), 1700 (C=O), 1660 cm^{-1} (C=C); MS (80 eV, EI): *m*/*z* (%): 437 (2) $[M]^+$, 436 (7) $[M - H]^+$, 380 (2) $[M - C(CH_3)_3]^+$, 163 (16) $[C_{10}H_{11}O_2]^+$, 91 (100) $[Bn]^+$, 57 (80) $[C(CH_3)_3]^+$; HRMS (80 eV): $C_{26}H_{31}NO_5$ calcd 437.22022; found 437.22485.

Reduction of *syn*-22 with Pd/C/H$_2$: A stirred suspension of palladium on charcoal (498 mg, 0.47 mmol) in dry ethanol (15 mL) was saturated with hydrogen for 30 min. A solution of *syn*-**22** (500 mg, 1.17 mmol) in dry ethanol (12 mL) was then added, and the mixture was stirred under hydrogen atmosphere at normal pressure for 20 h at room temperature. The mixture was filtered through Celite with methanol (60 mL). After removal of the solvents under reduced pressure and column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1), pyrrolidinone **26** (204 mg, 50%) and pyrrolidine **27** (54 mg, 11%) were obtained as colorless oils.

(2*S*,3*R*,2′*S*,4′*S*)-3-Benzyloxy-1-*tert*-butoxycarbonyl-2-(2-phenyl-1,3-dioxan-4-yl)pyrrolidine (27): $[\alpha]_D^{20} = -18.8$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 330 K): $\delta = 7.50-7.25$ (m, 10H; Ph), 5.52 (s, 1H; 2′-H), 4.58 (s, 2H; OC*H*$_2$Ph), 4.25 (ddd, $J = 1.4$, 4.9, 11.3 Hz, 1H; 6′-H$_A$), 4.29–4.25 (m, 1H; 4′-H), 4.09 (td, $J = 7.5$, 9.9 Hz, 1H; 3-H), 4.05–4.00 (m, 1H; 2-H), 3.93 (ddd, $J = 2.5$, 11.3, 12.4 Hz, 1H; 6′-H$_B$), 3.47–3.36 (m, 2H; 5-H), 2.21 (dddd, $J = 4.9$, 12.0, 12.4, 13.4 Hz, 1H; 5′-H$_A$), 2.20–2.06 (m, 2H; 4-H), 1.52–1.47 (m, 1H; 5′-H$_B$), 1.45 ppm (s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$, 330 K): $\delta = 155.3$ (s; C=O), 139.3, 138.5, 128.4*, 128.0, 127.6, 127.4, 126.1 (2 × s, 5 × d; Ph), 101.3 (d; C-2′), 79.5 (s; *C*(CH$_3$)$_3$), 78.0 (d; C-4′), 76.4 (d; C-3), 72.2 (t, O*C*H$_2$Ph), 67.4 (t; C-6′), 59.9 (d; C-2), 44.0 (t; C-5), 29.3 (t; C-4), 29.0 (t; C-5′), 28.5 ppm (q; C(*C*H$_3$)$_3$),* higher intensity; IR (neat): $\tilde{\nu} = 3090-3035$ (=C–H), 2975–2865 (C–H), 1695 cm^{-1} (C=O); MS (80 eV, EI): *m*/*z* (%): 439 (3) $[M]^+$, 382 (1) $[M - C(CH_3)_3]^+$, 366 (9) $[M - OC(CH_3)_3]^+$, 276 (76) $[M - C_{10}H_{11}O_2]^+$, 163 (20) $[C_{10}H_{11}O_2]^+$, 91 (100) $[Bn]^+$, 57 (35) $[C(CH_3)_3]^+$; HRMS (80 eV): $C_{26}H_{33}NO_5$ calcd 439.23587; found 439.23373.

(2*S*,3*R*,2′*S*,4′*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-(2-phenyl-1,3-dioxan-4-yl)-pyrrolidine (28): Pyrrolidinone **26** (728 mg, 2.10 mmol) was dissolved in dry THF (70 mL), and *L*-Selectride (4.20 mL, 4.20 mmol, 1 M in THF) was slowly added at −78 °C under argon. After the mixture had been kept for 4 h at this temperature, water (70 mL) was added and the solution was extracted with dichloromethane (3 × 70 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. Product **28** was obtained as a colorless solid (612 mg, 84%) after column chromatography on silica gel (*n*-hexane/ethyl acetate 2:1). M.p. 55–57 °C; $[\alpha]_D^{20} = -76.1$ ($c = 0.71$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.45-7.41$ (m, 2H; Ph), 7.36–7.28 (m, 3H; Ph), 5.50 (s, 1H; 2′-H), 4.48–4.39 (m, 2H; 4′-H, 3-H), 4.27 (ddd, $J = 1.5$, 5.1, 11.4 Hz, 1H; 6′-H$_A$), 4.02 (dd, $J = 3.7$, 7.1 Hz, 1H; 2-H), 3.93 (ddd, $J = 2.5$, 11.4, 12.5 Hz, 1H; 6′-H$_B$), 3.53–3.46 (m, 1H; 5-H$_A$), 3.43 (ddd, $J = 5.2$, 8.7, 10.8 Hz, 1H; 5-H$_B$), 2.68 (d_{br}, $J = 6.3$ Hz, 1H; OH), 2.21 (dddd, $J = 5.1$, 11.9, 12.5, 13.5 Hz, 1H; 5′-H$_A$), 2.10 (dddd, $J = 5.2$, 7.3, 8.3, 12.4 Hz, 1H; 4-H$_A$), 1.94 (tdd, $J = 7.4$, 8.7, 12.4 Hz, 1H; 4-H$_B$), 1.51 (dtd, $J = 1.5$, 2.5, 13.5 Hz, 1H; 5′-H$_B$), 1.47 ppm (s, 9H; C(CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 155.2$ (s; C=O), 138.3, 128.8, 128.1, 125.8 (s, 3 × d; Ph), 101.4 (d; C-2′), 79.6 (s; *C*(CH$_3$)$_3$), 77.3 (d; C-4′), 72.1 (d; C-3), 67.3 (t; C-6′), 60.6 (d; C-2), 44.3 (t; C-5), 33.1 (t; C-4), 28.3 (q; C(*C*H$_3$)$_3$), 27.5 ppm (t; C-5′); IR (KBr): $\tilde{\nu} = 3435$ (O–H), 3100–3000 (=C–H), 2975–2895 (C–H), 1695, 1670 cm^{-1} (C=O); MS (80 eV, EI): *m*/*z* (%): 349 (5) $[M]^+$, 331 (2) $[M - H_2O]^+$, 292 (10) $[M - C(CH_3)_3]^+$, 276 (14) $[M - OC(CH_3)_3]^+$, 186 (83) $[M - C_{10}H_{11}O_2]^+$, 163 (40) $[C_{10}H_{11}O_2]^+$, 91 (21) $[Bn]^+$, 57 (69) $[C(CH_3)_3]^+$; HRMS (80 eV): $C_{19}H_{27}NO_5$ calcd 349.18588; found 349.18892; elemental analysis calcd (%) for $C_{19}H_{27}NO_5$ (349.4): C 65.31, H 7.79, N 4.01; found: C 65.27, H 7.85, N 3.79.

(2*S*,3*R*,1′*S*)-1-*tert*-Butoxycarbonyl-2-(1,3-dihydroxyprop-1-yl)-3-hydroxypyrrolidine (29): A stirred suspension of palladium on charcoal (174 mg, 0.17 mmol) in dry ethanol (12 mL) was saturated with hydrogen for 30 min. A solution of **28** (555 mg, 1.59 mmol) in dry ethanol (8 mL) was then added, and the mixture was stirred under hydrogen atmosphere at normal pressure and at room temperature for 16 h. The mixture was filtered through Celite with methanol (100 mL), and the filtrate was evaporated to give triol **29** as a colorless solid (408 mg, 98%). M.p. 78–80 °C (with decomposition); $[\alpha]_D^{20} = -61.3$ ($c = 1.02$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 4.39$ (td, $J = 7.1$, 7.8 Hz, 1H; 3-H), 4.14 (td, $J = 3.8$, 9.5 Hz, 1H; 1′-H),

3.79 (dd, $J = 3.8, 7.1$ Hz, 1H; 2-H), 3.77–3.68 (m, 2H; 3′-H), 3.50–3.38 (m, 2H; 5-H), 2.10–1.96 (m, 2H; 4-H), 1.93–1.84 (m, 1H; 2′-H_A), 1.78 (dtd, $J = 5.9, 9.5, 14.1$ Hz, 1H; 2′-H_B), 1.46 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, CD_3OD, 326 K): $\delta = 157.6$ (s; C=O), 81.1 (s; $C(CH_3)_3$), 72.6 (d; C-3), 69.9 (d; C-1′), 64.2 (d; C-2), 60.7 (t; C-3′), 45.6 (t; C-5), 38.4 (t; C-2′), 33.1 (t; C-4), 28.8 ppm (q; $C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 3370$ (O–H), 3000–2890 (C–H), 1695, 1660 cm^{-1} (C=O); MS (FAB, negative-mode): m/z (%): 260 (100) $[M-H]^-$; MS (FAB, positive-mode): m/z (%): 262 (35) $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{23}NO_5$ (261.3): C 55.16, H 8.87, N 5.36; found: C 55.21, H 8.75, N 5.24.

(3a*R*,7*S*,7a*R*)-1-*tert*-Butoxycarbonyl-1,2,3,3a,5,6,7,7a-octahydro-7-hydroxypyrano-[3,2-b]pyrrol-5-one (30): A suspension of platinum dioxide (44 mg, 0.19 mmol) in water (1 mL) was first treated with hydrogen for 1 h, and was then saturated with argon (5 min) and then with oxygen (5 min). A solution of triol **29** (49 mg, 0.19 mmol) in water (2 mL) was then added, and oxygen gas was bubbled through this mixture at 40 °C. After 2 h the mixture was stirred under an oxygen atmosphere at room temperature for 17 h, water was then removed under reduced pressure, and column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) furnished lactone **30** as a colorless solid (32 mg, 66%). M.p. 140–141 °C (literature value:[15c] 141–142 °C); $[\alpha]_D^{20} = -35.9$ ($c = 0.73$; $CHCl_3$) (literature value: -6.5 ($c = 1.0$, $CHCl_3$),[15b] -31.7 ($CHCl_3$)[15c]); ^{1}H NMR (500 MHz, C_6D_6, 334 K): $\delta = 5.12$ (s, 1H; OH), 3.74–3.67 (m, 2H; 3a-H, 6-H), 3.38 (t, $J = 5.0$ Hz, 1H; 7a-H), 3.08–3.03 (m, 1H; 2-H_A), 2.91 (dt, $J = 6.1, 11.3$ Hz, 1H; 2-H_B), 2.72 (dd, $J = 4.2, 15.0$ Hz, 1H; 6-H_A), 2.12 (dd, $J = 12.7, 15.0$ Hz, 1H; 6-H_B), 1.51–1.45 (m, 1H; 3-H_A), 1.37 (s, 9H; $C(CH_3)_3$), 0.97 ppm (dddd, $J = 5.1, 8.9, 11.3, 13.9$ Hz, 1H; 3-H_B); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 169.6$ (s; C-5), 156.0 (s; C(O)OC$(CH_3)_3$), 80.6 (s; $C(CH_3)_3$), 78.0 (d; C-3a), 70.4 (d; C-7), 66.2 (d; C-7a), 44.6 (t; C-2), 36.3 (t; C-6), 30.5 (t; C-3), 28.3 ppm (q; $C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 3375$ (O–H), 3000–2885 (C–H), 1715, 1695 cm^{-1} (C=O); MS (80 eV, EI): m/z (%): 257 (1) $[M]^+$, 242 (1) $[M-CH_3]^+$, 57 (100) $[C(CH_3)_3]^+$; HRMS (80 eV): $C_{12}H_{19}NO_5$ calcd 257.12632; found 257.12732; elemental analysis calcd (%) for $C_{12}H_{19}NO_5$ (257.1): C 55.73, H 7.25, N 5.15; found: C 56.02, H 7.44, N 5.44.

Crystals of **30** suitable for X-ray analysis were obtained by recrystallization from *n*-hexane/dichloromethane. $C_{12}H_{19}NO_5$, $M_r = 257.1$; $T = 113(2)$ K; crystal size: $0.09 \times 0.12 \times 0.70$ mm; monoclinic, space group $P2_1$, $a = 6.2068(14)$, $b = 8.725(2)$, $c = 11.671(3)$ Å, $\beta = 96.877(5)°$; $V = 627.5(2)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.362$ Mg m^{-3}; $F(000) = 276$; $\mu(Mo_{K\alpha}) = 0.106$ mm^{-1}. Φ range for data collection: 1.76–30.59°; index ranges: $-8 \le h \le 8$, $-12 \le k \le 12$, $-16 \le l \le 16$; reflections collected/unique: 7864/3702 ($R_{int} = 0.0222$); final R [$I > 2\sigma(I)$]: $R_1 = 0.0317$, $wR_2 = 0.0782$; R (all data): $R_1 = 0.0340$, $wR_2 = 0.0794$.

For structure solution and refinement the programs SHELXS97 and SHELXL97 were used.[27]

(−)-Detoxinine, (3*S*,2′*S*,3′*R*)-3-Hydroxy-3-(3-hydroxypyrrolidin-2-yl)propionic acid: Trifluoroacetic acid (1 mL) was added under argon at 0 °C to lactone **30** (97 mg, 0.39 mmol). After 2 h the cooling bath was removed and the mixture was stirred for 15 min at room temperature. After removal of trifluoroacetic acid under reduced pressure and ion exchange chromatography (Dowex® 50×4–100, 1M aqueous NH_3 solution as eluent), (−)-detoxinine was isolated as a colorless solid (61 mg, 89%). M.p. 224–227 °C (literature value: 224–227 °C,[15f] 225–228 °C[15a]); $[\alpha]_D^{20} = -5.0$ ($c = 0.60$, H_2O) (literature value: -4.8 ($c = 0.5$, H_2O),[15a] -4.4 ($c = 0.5$, H_2O)[15d]); ^{1}H NMR (250 MHz, D_2O): $\delta = 4.51–4.44$ (m, 1H; 3′-H), 4.30 (ddd, $J = 4.5, 7.8, 9.2$ Hz, 1H; 3-H), 3.55–3.33 (m, 3H; 2′-H, 5′-H), 2.61 (dd, $J = 4.5, 15.7$ Hz, 1H; 2-H_A), 2.40 (dd, $J = 7.8, 15.7$ Hz, 1H; 2-H_B), 2.21 (dtd, $J = 4.1, 10.0, 14.2$ Hz, 1H; 4′-H_A), 2.09 ppm (dddd, $J = 1.2, 3.5, 7.8, 14.2$ Hz, 1H; 4′-H_B); ^{13}C NMR (125.8 MHz, D_2O): $\delta = 181.2$ (s; C-1), 72.9 (d; C-3′), 71.9 (d; C-2′), 68.4 (d; C-3), 45.2 (t; C-5′), 44.4 (t; C-2), 35.3 ppm (t; C-4′); IR (KBr): $\tilde{\nu} = 3200$ (br; N–H, O–H), 2915, 2720, 2505 (br; C–H), 1630 (C=O), 1555 cm^{-1} (N–H); MS (FAB, negative-mode): m/z (%): 174 (4) $[M-H]$; MS (FAB, positive-mode): m/z (%): 176 (4) $[M+H]^+$; elemental analysis calcd (%) for $C_7H_{13}NO_4$ (175.2): C 47.99, H 7.48, N 8.00; found: C 47.66, H 7.37, N 7.73.

CCDC-195173 (*syn*-**8**) and CCDC-195174 (**30**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk).

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4.23 (td, $J = 2.4$, 11.2 Hz, 1H; 4′-H), 4.10–3.94 (m, 2H; 6′-H_B, 2-H), 3.58 (d, $J = 13.2$ Hz, 1H; NCH_2Ph), 3.56 (dd, $J = 2.2$, 12.0 Hz, 1H; 5-H_A)**, 3.13 (ddd, $J = 1.8$, 4.0, 12.0 Hz, 1H; 5-H_B), 2.64–2.46 (m, 1H; 5′-H_A), 1.34–1.23 ppm (m, 1H; 5′-H_B), * further fine coupling observed, ** further splitting was not observed due to signal overlapping; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 153.9$ (s; C-3), 140.3, 139.1, 136.6, 128.7, 128.6, 128.5, 128.1, 128.0, 127.4, 126.6, 126.2 (3 × s, 8 × d; Ph), 102.1 (d; C-2′), 93.6 (d; C-4), 79.1 (d; C-4′), 71.4 (t; OCH_2Ph), 70.1 (d; C-2), 67.2 (t; C-6′), 60.5 (t; NCH_2Ph), 56.8 (t; C-5), 24.9 ppm (t; C-5′); IR (neat): $\tilde{\nu} = 3090–3000$ (=C–H), 2960–2800 (C–H), 1660 cm^{-1} (C=C); MS (80 eV, EI): m/z (%): 427 (1) $[M]^+$, 336 (5) $[M - C_7H_7]^+$, 264 (100) $[M - C_{10}H_{11}O_2]^+$, 91 (92) $[Bn]^+$; HRMS (80 eV): $C_{28}H_{29}NO_3$ calcd 427.21474; found 427.21731; NOE-data show that *syn*-**22** and *anti*-**22** differ only in the configuration at C-2.

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