1,3-Amino Alcohols from 4-Amino-1-aza Dienes. Diastereo- and Enantioselective Approach to the Four Diastereoisomers of the N-Terminal Amino Acid Component of Nikkomycins B and B_X

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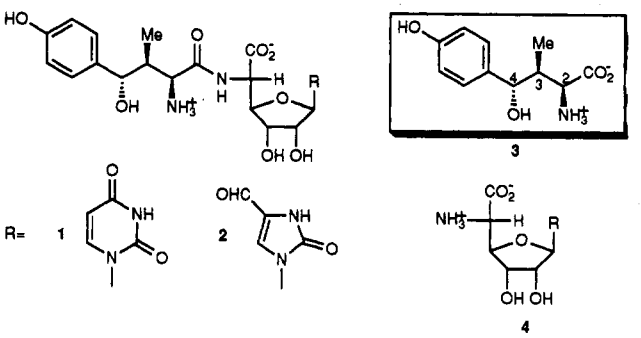
A strategy that entails the preparation of 1,3-amino alcohols from 4-amino-1-aza dienes is used to synthesize the four diastereoisomeric lactones of the N-terminal amino acid moiety of nikkomycins B and B_X in a diastereo- and enantioselective manner. Thus, enantiomerically pure β-amino ketones *anti*-**13** and *syn*-**13** were synthesized starting from the 4-amino-1-aza diene **10** and (*R*)-*O*-benzyllactic aldehyde via the corresponding dihydro- and tetrahydropyrimidines. These β-amino ketones were further converted into the lactones **22–25** with high diastereoselectivity through their 1,3-amino alcohol derivatives.

Introduction

4-Amino-1-aza dienes have been used in our group as starting material for the preparation of several 1,3-difunctionalized compounds,[1] including 1,3-amino alcohols.[1b-e] The 1,3-amino alcohol unit is quite common in natural products, and a good example of this is the nikkomycins or neopolyoxins, a group of nucleoside peptide antibiotics produced by *Streptomyces tendae* and *Streptomyces cacaoi* subsp. *asoensis*.[2] These compounds have been the subject of intensive study in recent years, primarily by König's and Isono's groups, focusing on their isolation, structural assignment, and pharmacological activity.[2,3] Important members of this group of antibiotics are nikkomycins B (**1**) and B_X (**2**), whose syntheses can be achieved by the coupling of two structural units, the N-terminal amino acid **3** and the C-terminal nucleoside amino acid **4**. Compound **3** represents the greater synthetic challenge due to the necessary generation of three stereogenic centers. In this context, König achieved the first synthesis of **3** and its C-2 epimer[3b,d,4] as well as the total synthesis of **2**.[5] Barrett[6] performed an enantio- and diastereoselective synthesis of **3** as well as the total synthesis of **1**. Other routes to **3** and/or its lactone derivative have been published by Barrett,[7] Jäger,[8] and Weinreb.[9] Nevertheless, to our knowledge, nothing has been reported about the preparation of the other two diastereoisomers of **3** and the nikkomycins derived therefrom.



We report here an approach to the synthesis of the four diastereoisomers of the N-terminal amino acid **3** using the strategy previously described by us[1c] for the diastereo- and enantioselective preparation of 1,3-amino alcohols with three chiral centers, such as **9**, from 4-amino-1-aza dienes **5**, via the intermediates **6–8** as outlined in Scheme I.

Results and Discussion

For the synthesis of **3**, a carboxy group precursor R^4 is required.[10] In this sense, the 2-furyl group has been shown to be an effective equivalent of a carboxylic acid.[11] On the other hand, our previous results[1c] showed that the use of (*S*)-*O*-benzyl lactic aldehyde as a chiral auxiliary leads to

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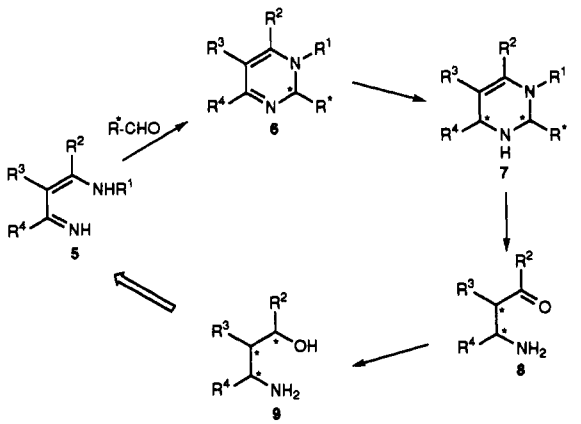
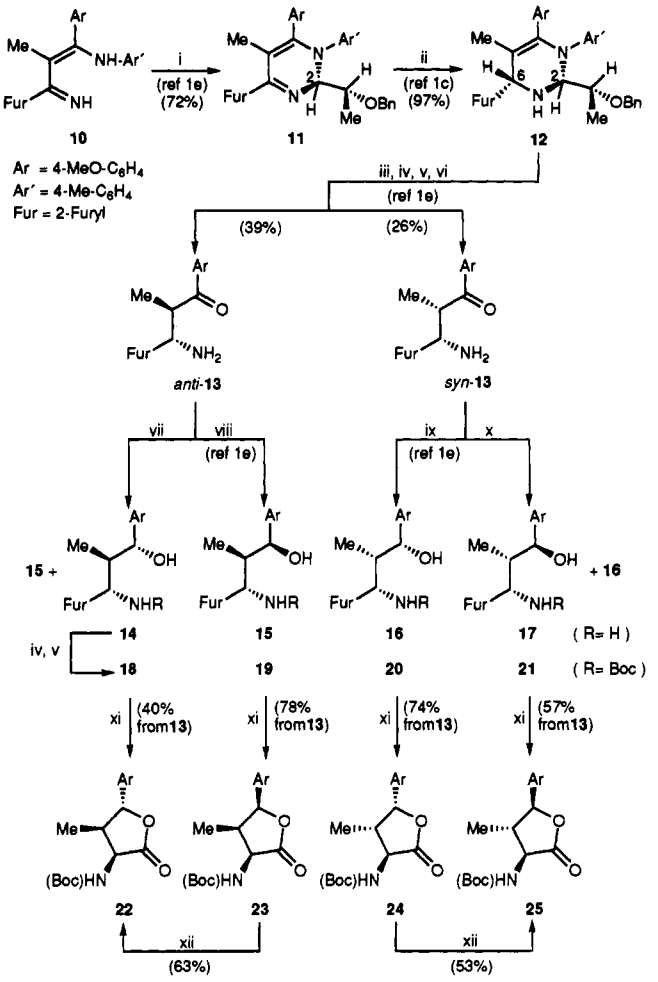
Scheme I



Scheme II[a]



[a] Reagents: (i) (*R*)-CH(Me)(OBn)CHO/$ZnCl_2$(1 equiv)/THF/60 °C; (ii) $NaBH_4$/MeOH/rt; (iii) 2N H_2SO_4/40 °C; (iv) $(Boc)_2O$/NaOH/H_2O/*t*-BuOH; (v) flash chromatography; (vi) TFA/CH_2Cl_2/rt; (vii) $NaBH(s\text{-}Bu)_3$/THF/−78 °C to rt; (viii) $NaAlH_2(OCH_2CH_2OCH_3)_2$/toluene/−78 °C; (ix) DIBALH/$ZnCl_2$/−78 °C; (x) $KBH(s\text{-}Bu)_3$/THF/−78 °C to rt; (xi) O_3/NaOH/CH_2Cl_2/MeOH/H_2O_2/−78 °C; (xii) BBr_3(1 equiv)/CH_2Cl_2/−78 °C.

amino alcohols **9** with the *R* configuration at the carbon that bears the amino group (C-2 in **3**). This would provide the unnatural enantiomer of **3** and its diastereoisomers. Thus, as a chiral auxiliary, we employed the (*R*)-*O*-benzyl lactic aldehyde, since our goal was to obtain the natural component **3** (*2S,3S,4S*) as well as its three other diastereoisomers in an enantiomerically pure form. In this way, condensation of the aza diene **10** with the aldehyde in the presence of $ZnCl_2$ led to the corresponding dihydropyrimidine as a mixture of the two C-2 epimers, whose major component **11** (**11**/C-2 epimer ratio 86/14) was reduced with $NaBH_4$ to give the tetrahydropyrimidine **12** as single diastereoisomer (de > 99%) (Scheme II). The assignment of the relative and absolute stereochemistry at the inner-ring chiral centers in **11** (C-2) and **12** (C-2 and C-6) was made by comparison of their ^{1}H-NMR data with those of their analogs **6** and **7**[1c] and by the X-ray crystallographic analysis[1c] of **7** [$R^1 = R^2$ = Ph, R^3 = Me, R^4 = 4-MeC_6H_4, R^* = (*S*)-CH(Me)(OBn)]. The X-ray study clearly shows the *anti*-configuration of the tetrahydropyrimidine at C-2 and C-6 and the absolute stereochemistry. Thus, it is apparent that the absolute configuration of **12** is (*2S,6S*), consistent with our earlier report.[1c] At this stage, the first stereogenic center of **3** (C-6 in **12**, which becomes C-2 in **3**) has been established with the *S* configuration.

Hydrolysis of **12** with 2 N H_2SO_4 at 40 °C for 1 h gave the corresponding β-amino ketones **13** as a 60:40 mixture of the *anti*-**13** and *syn*-**13** isomers.[12] Separation was achieved by chromatography of their *N*-Boc derivatives. Deprotection with TFA led to the enantiomerically pure amines *anti*-**13** and *syn*-**13** (*ee* > 99%),[13] thus creating the second required stereocenter of the skeleton of **3** and its diastereoisomers. The third stereogenic center was created by reduction of the carbonyl group of **13** to give the complete set of 1,3-amino alcohols **14**–**17**. The reduction occurred, as expected,[1b-e] with very high stereoselectivity in the generation of the carbinolic center, with the syn relative stereochemistry. Thus, the reduction of *anti*-**13** and *syn*-**13** with Red-Al and DIBALH/$ZnCl_2$, respectively, led to **15** and **16** as the only diastereoisomers (de > 99%) in each case. The anti reduction did not take place with high diastereoselectivity, although improvement was achieved.[1e] In this case, the highest diastereoselectivity was obtained when more bulky reducing agents were used; thus, the reduction of *anti*-**13** and *syn*-**13** with N- and K-selectride (Aldrich), respectively, gave **14** and **17** as the major components mixed with **15** (**14**/**15** ratio 67/33) and **16** (**17**/**16** ratio 87/13).

Conversion of the 2-furyl substituent into a carboxylic group was then accomplished by first transforming amino alcohols **14**–**17** into their *N*-Boc derivatives **18**–**21**. In the case of **14** and **17** the reaction was performed with the crude mixtures of diastereoisomers, and then a chromatographic separation was performed. The ozonolysis of **18**–**21** yielded the corresponding lactones **22**–**25** without apparent diastereoisomer contamination. These results confirm once more[4,7b,8,9] the tendency of the corresponding amino hydroxy acids to undergo cyclization to the amino lactones, which can be opened under suitable conditions.[4,6b,8] Attempted removal of the *O*-methyl group present in the 4-$MeOC_6H_4$ moiety of **22**–**24** with 3 equiv of BBr_3[4,7b] was unsuccessful.[14] However, in the case of **23** and **24**, we observed the epimerization of C-4 albeit in low yield. Treatment of **23** and **24** with 1 equiv of BBr_3 gave the most stable *trans*-lactones **22** and **25**, respectively, as

(12) An *anti*-**13** enriched mixture (*anti*-**13**/*syn*-**13** ratio 95/5) could be achieved by hydrolysis of **12** with HCl/aq EtOH/−10 °C/1 h; nevertheless, to date we have not been able to obtain a better diastereoselectivity for *syn*-**13**.

(13) Upon Mosher's test (see ref 1c).

(14) Experiments to de-O-methylate at an earlier stage are currently underway. Furthermore, we are also trying to perform the previous sequence starting from an aza diene with Ar = 4-[(*t*-Bu)Ph_2Si]OC_6H_4.

single diastereoisomers (de > 99%). A similar isomerization from the cis to the trans configuration has been observed before[4] but in that case led to a mixture of isomers. This epimerization method improves the stereochemical outcome in the preparation of lactones **22** and **25** from the corresponding amino ketones (only moderate via **14** and **17**) and completes a highly diastereoselective synthesis of the enantiomerically pure lactones **22–25** with the absolute configuration of the N-terminal amino acid **3** (**25**) and its three possible unnatural diastereoisomers. Presumably, the use of (*S*)-*O*-benzyl lactic aldehyde would provide access to the enantiomers of **22–25**, which would complete this approach to the eight stereoisomers of **3**. Additional work continues in our laboratory to complete the route to nikkomycins B and B_X.

Experimental Section

General. All reagents were of commercial quality (Aldrich). Solvents used in reactions were dried and distilled according to standard procedures before use. Solvents used in extractions were distilled prior to use. Flash column chromatography was performed on silica gel (grade 60, Merck). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Mass spectra were obtained by EI (70 eV). Melting points were determined in open capillaries and are uncorrected.

2-(2-Furyl)-4-(*p*-methoxyphenyl)-3-methyl-4-(*p*-tolylamino)-1-aza-1,3-butadiene (10). To a stirred solution of LDA (88 mmol) in anhydrous THF (200 mL) was added a solution of [1-(*p*-methoxyphenyl)propylidene]-*p*-tolylamine (20.25 g, 80 mmol) in anhydrous THF (150 mL) in a ice bath. After 2 h, $ZnCl_2$ (140 mL, 1 M in ether) was added dropwise and kept for 15 min at 0 °C; then, 2-furonitrile (7 mL, 80 mmol) was added at 0 °C. The mixture was stirred overnight at rt and heated for an additional 6 h at 60 °C. After the mixture was cooled, a saturated aqueous solution of $NaHCO_3$ was poured into the mixture and the organic layer was extracted with ether, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a crude solid which was washed with *n*-hexane and filtered providing 24.47 g (88%) of spectroscopically pure **10** as a yellow solid. Mp: 137–9 °C (*n*-hexane/ether (3:1)). ^1H NMR: δ 1.88 (s, 3H), 2.23 (s, 3H), 3.82 (s, 3H), 6.43–7.56 (m, 11 H_{arom}). ^{13}C NMR: δ 16.43 (q), 20.74 (q), 55.18 (q), 103.94 (s), 108.92 (d), 111.87 (d), 113.87 (d), 123.41 (d), 126.26 (s), 129.25 (d), 130.42 (d), 133.62 (d), 137.34 (s), 143.12 (d), 145.53 (s), 150.10 (s), 159.76 (s), 161.71 (s). MS: *m/e* 346 (M^+, 10) 329 (20), 224 (100). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.34; H, 6.51; N, 7.88.

(2*R*)-2-[(1*R*)-1-(Benzyloxy)ethyl]-6-(2-furyl)-4-(*p*-methoxyphenyl)-5-methyl-3-*p*-tolyl-2,3-dihydropyrimidine (11). Obtained from **10** (6.92 g, 20 mmol) and (*R*)-*O*-benzyl lactic aldehyde (3.61 g, 22 mmol) following a previously described procedure[1e] by heating the reaction mixture at 60 °C. After workup, the corresponding dihydropyrimidine was obtained as a mixture of two isomers (11/C-2 epimer ratio 86/14). From the crude residue 7.10 g (72%) of **11** was isolated as a dark yellow syrup by column chromatography (*n*-hexane/ether (1:1)). ^1H NMR: δ 1.46 (d, 3 H, *J* = 6.0 Hz), 2.14 (s, 3 H), 2.15 (s, 3 H), 3.73 (s, 3 H), 3.86 (m, 1 H), 4.52, 4.77 (ABq, 2 H, *J* = 11.5 Hz), 5.52 (d, 1 H, *J* = 8.6 Hz), 6.49–7.55 (m, 16 H_{arom}). ^{13}C NMR: δ 15.64 (q), 16.52 (q), 20.51 (q), 54.86 (q), 71.11 (t), 71.22 (d), 80.12 (d), 108.78 (s), 111.28 (d), 113.22 (d), 120.12 (d), 124.54 (d), 127.18 (s), 127.29 (d), 127.39 (d), 128.15 (d), 128.59 (d), 132.33 (d), 132.54 (s), 138.43 (s), 143.38 (s), 143.57 (d), 145.71 (s), 151.87 (s), 154.99 (s), 159.44 (s). $[\alpha]^{23}_D$: +563.8° (*c* 0.34, $CHCl_3$). Anal. Calcd for $C_{32}H_{32}N_2O_3$: C, 78.02; H, 6.55; N, 5.69. Found: C, 77.86; H, 6.32; N, 5.87.

(2*S*,6*S*)-2-[(1*R*)-1-(Benzyloxy)ethyl]-6-(2-furyl)-4-(*p*-methoxyphenyl)-5-methyl-3-*p*-tolyl-1,2,3,6-tetrahydropyrimidine (12). Obtained (7.19 g, 97%) as a pale yellow solid by reduction of **11** (7.41 g, 15 mmol) with $NaBH_4$ (105 mmol) in MeOH (40 mL) following a previously described procedure.[1c] Mp: 92–4 °C (*n*-hexane/ether (2:1)). ^1H NMR: δ 1.46 (d, 3 H, *J* = 6.4 Hz), 1.63 (s, 3 H), 2.17 (s, 3H), 2.37 (dd, 1 H, *J* = 4.3, 10.5 Hz, NH), 3.70 (s, 3 H), 4.09 (dq, 1 H, *J* = 9.0, 6.4 Hz), 4.36 (dd, 1 H, *J* = 9.0, 4.3 Hz), 4.40 (d, 1 H, *J* = 10.5 Hz), 4.71, 4.80 (ABq, 2 H, *J* = 11.2 Hz), 6.32–7.49 (m, 16 H_{arom}). ^{13}C NMR: δ 16.95 (q), 20.51 (q), 53.20 (d), 54.87 (q), 72.11 (t), 73.73 (d), 79.31 (d), 107.15 (d), 110.08 (d), 112.86 (d), 115.15 (s), 123.52 (d), 127.34 (d), 127.48 (d), 128.26 (d), 128.97 (d), 130.26 (s), 130.85 (s), 131.05 (d), 135.88 (s), 138.84 (s), 141.82 (s), 146.14 (d), 154.35 (s), 158.28 (s). $[\alpha]^{23}_D$: +413.6° (*c* 0.42, $CHCl_3$). Anal. Calcd for $C_{32}H_{34}N_2O_3$: C, 77.71; H, 6.93; N, 5.66. Found: C, 77.92; H, 6.82; N, 5.73.

Preparation of Both Diastereoisomers of the β-Amino Ketone 13.[1e] Compound **12** (1.09 g, 2.2 mmol) was hydrolyzed with 2 N H_2SO_4 (10 mL) at 40 °C for 1 h to give 0.42 g of **13** as a mixture of diastereoisomers (*anti*-**13**/*syn*-**13** ratio 60/40, by ^1H-NMR(300 MHz)). The crude mixture was treated with $(Boc)_2O$ (0.35 g, 1.6 mmol) and NaOH(0.06 g) in H_2O/*t*-BuOH (8 mL, 1:1). After usual workup,[1e] the crude residue was chromatographed (*n*-hexane/ether (3:1)) to give 0.33 g (41%) of ***N*-Boc *anti*-13** as a solid and 0.22 g (27%) of ***N*-Boc *syn*-13** as a syrup. The separated diastereoisomer *N*-Boc derivatives of **13** were treated with TFA (10 equiv) in CH_2Cl_2 at rt for 1 h to give 0.22 g (39% from **12**) of *anti*-**13** and 0.15 g (26% from **12**) of *syn*-**13**, respectively, as dark colored syrups which decompose by chromatographic purification or distillation.

(2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanone (*N*-Boc *anti*-13). Mp: 82–3 °C (*n*-hexane/ether (4:1)). ^1H NMR: δ 1.29 (d, 3 H, *J* = 7.0 Hz), 1.44 (s, 9 H), 3.82 (s, 3 H), 4.14 (dq, 1 H, *J* = 7.0, 9.2 Hz), 5.08 (dd, 1 H, *J* = 4.1, 9.2 Hz), 6.16 (d, 1 H), 6.17 (br s, 1 H, NH), 6.18 (br s, 1 H), 6.95, 7.89 (ABq, 4 H), 7.20 (br s, 1 H). ^{13}C NMR: δ 15.21 (q), 28.11 (q), 41.79 (d), 51.59 (d), 55.18 (q), 76.58 (s), 105.80 (d), 110.01 (d), 113.61 (d), 128.99 (s), 130.41 (d), 141.21 (d), 154.06 (s), 155.06 (s), 163.50 (s), 201.81 (s). $[\alpha]^{23}_D$: +1.8° (*c* 0.56, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.68; H, 7.12; N, 3.98.

(2*S*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanone (*N*-Boc *syn*-13). ^1H NMR: δ 1.24 (d, 3 H, *J* = 6.9 Hz), 1.42 (s, 9 H), 3.83 (s, 3 H), 4.02 (dq, 1 H, *J* = 6.9, 7.6 Hz), 5.05 (br d, 1 H, *J* = 7.3, NH), 5.22 (dd, 1 H, *J* = 7.6, 7.3 Hz), 6.12 (d, 1 H), 6.19 (dd, 1 H), 6.90, 7.90 (ABq, 4 H), 7.24 (d, 1 H). ^{13}C NMR: δ 13.70 (q), 28.15 (q), 43.85 (d), 50.73 (d), 55.32 (q), 79.62 (s), 106.56 (d), 110.13 (d), 113.70 (d), 129.06 (s), 130.41 (d), 141.49 (d), 153.28 (s), 155.06 (s), 163.38 (s), 199.71 (s). $[\alpha]^{23}_D$: −22.2° (*c* 0.65, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.57; H, 6.81; N, 4.11.

(2*R*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanone (*anti*-13). ^1H NMR: δ 1.02 (d, 3 H, *J* = 6.6 Hz), 1.74 (br s, 2 H, NH_2), 3.85 (s, 3 H), 3.86 (m, 1 H), 4.35 (d, 1 H, *J* = 9.0 Hz), 6.22 (d, 1 H), 6.30 (m, 1 H), 6.94, 7.98 (ABq, 4 H), 7.36 (br s, 1 H). ^{13}C NMR: δ 15.69 (q), 45.55 (d), 52.04 (d), 54.90 (q), 106.02 (d), 109.61 (d), 113.30 (d), 129.08 (s), 130.26 (d), 141.20 (d), 155.80 (s), 163.10 (s), 201.42 (s).

(2*S*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanone (*syn*-13). ^1H NMR: δ 1.20 (d, 3 H, *J* = 7.0 Hz), 1.75 (br s, 2 H, NH_2), 3.83 (s, 3 H), 3.91 (m, 1 H), 4.41 (d, 1 H, *J* = 5.2 Hz), 6.16 (d, 1 H), 6.24 (m, 1 H), 6.92, 7.95 (ABq, 4 H), 7.29 (m, 1 H). ^{13}C NMR: δ 11.38 (q), 43.95 (d), 50.84 (d), 54.54 (q), 104.74 (d), 109.41 (d), 113.04 (d), 128.21 (s), 129.79 (d), 140.50 (d), 156.32 (s), 162.66 (s), 200.53 (s).

(1*R*,2*R*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (14). To a solution of *anti*-**13** (0.50 g, 1.9 mmol) in anydrous THF (15 mL) was added N-Selectride (11.6 mL, 1 M in THF) at −78 °C, and the solution was stirred at rt overnight. EtOH was added into the reaction flask, and when the evolution of gas was complete 3 N NaOH and H_2O_2 (2 mL, 30%) were poured into the mixture. The organic layer was extracted with ether, dried, and evaporated to give 0.43 g of a viscous oil which contained the two epimers (14/15 ratio 67/33). ^1H NMR: δ 0.33 (d, 3 H, *J* = 6.7 Hz), 2.08 (m, 1 H), 3.60 (br s, 3 H, OH and NH_2), 3.81 (s, 3 H), 3.90 (d, 1 H, *J* = 9.9 Hz), 4.48 (d, 1 H, *J* = 9.2 Hz), 6.08 (d, 1 H), 6.31 (dd, 1 H), 6.85, 7.26 (ABq, 4 H), 7.33 (m, 1 H).

(1*S*,2*R*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (15). Obtained (0.50 g, 91%, de > 99%) by reduction of *anti*-**13** (0.55 g, 2.1 mmol) with Red-Al (4 mL, 3.4 M in toluene) in toluene at −78 °C.[1e] Mp: 85–6 °C (*n*-hexane/AcOEt (1:1)). ^1H NMR: δ 0.72 (d, 3 H, *J* = 7.1 Hz), 2.29 (m, 1 H), 2.60 (br, s, 3 H, OH and NH_2), 3.81 (s, 3 H), 3.96 (d, 1 H, *J*

= 7.2 Hz), 4.88 (d, 1 H, J = 2.8 Hz), 6.13 (d, 1 H), 6.31 (dd, 1 H), 6.87, 7.24 (ABq, 4 H), 7.37 (d, 1 H). ^{13}C NMR: δ 12.35 (q), 42.85 (d), 53.06 (d), 55.13 (a), 75.07 (d), 105.19 (d), 110.01 (d), 113.20 (d), 127.32 (d), 134.91 (s), 141.41 (d), 157.00 (s), 158.33 (s). [α]^{23}D: +40.0° (c 0.86, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.70; H, 7.47; N, 5.52.

(1*R*,2*S*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (16). Obtained (0.26 g, 87%, de > 99%) by reduction of *syn*-**13** (0.30 g, 1.1 mmol) with DIBALH (6.95 mL, 1 M in THF)/$ZnCl_2$ (3.50 mL, 1 M in ether) at −78 °C.[1e] ^{1}H NMR: δ 0.60 (d, 3 H, J = 7.1 Hz), 2.23 (m, 1 H), 2.50 (br s, 3 H, OH and NH_2), 3.83 (s, 3 H), 4.39 (d, 1 H, J = 1.3 Hz), 5.16 (d, 1 H, J = 1.3 Hz), 6.14 (d, 1 H), 6.32 (m, 1 H), 6.95, 7.30 (ABq, 4 H), 7.35 (m, 1 H).

(1*S*,2*S*,3*S*)-3-Amino-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (17). Obtained (0.57 g) as a crude mixture of diastereoisomers (17/16 ratio 87/13, by ^{1}H-NMR (300 MHz)) by reduction of *syn*-**13** (0.65 g, 2.5 mmol) with K-Selectride (12 mL, 1 M in THF) following the method described for the preparation of **14**. After chromatographic purification of the crude residue (*n*-hexane/AcOEt (1:1)) and recrystallization (*n*-hexane/AcOEt (1:1)) a sample of pure **17** was isolated. Mp: 121–3 °C. ^{1}H NMR: δ 0.94 (d, 3 H, J = 7.3 Hz), 2.22 (m, 1 H), 2.80 (br s, 3 H, OH and NH_2), 3.80 (s, 3 H), 4.19 (d, 1 H, J = 2.2 Hz), 4.67 (d, 1 H, J = 5.2 Hz), 6.13 (d, 1 H), 6.31 (dd, 1 H), 6.88, 7.31 (ABq, 4 H), 7.32 (d, 1 H). ^{13}C NMR: δ 12.04 (q), 42.56 (d), 50.63 (d), 55.19 (q), 77.61 (d), 105.03 (d), 110.03 (d), 113.55 (d), 127.12 (d), 136.77 (s), 141.34 (d), 157.44 (s), 158.53 (s). [α]^{23}D: +4.1° (c 0.90, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.81; H, 7.39; N, 5.27.

(1*R*,2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (18). Obtained (0.30 g, 43% from *anti*-**13**) as a viscous oil by reaction of crude **14** (0.43 g, 1.7 mmol, 14/15 ratio 67/33) with $(Boc)_2O$ (1 equiv) following the procedure described for the preparation of the *N*-Boc derivatives of **13**.[1e] ^{1}H NMR: δ 0.59 (d, 3 H, J = 7.0 Hz), 1.44 (s, 9H), 2.37 (m, 1 H), 3.80 (s, 3 H), 4.32 (d, 1 H, J = 8.4 Hz), 5.19–5.25 (m, 2 H, CHNH), 6.23 (d, 1 H), 6.33 (dd, 1 H), 6.85, 7.24 (ABq, 4 H), 7.36 (d, 1 H). ^{13}C NMR: δ 12.69 (q), 28.29 (q), 44.06 (d), 50.46 (d), 55.17 (q), 56.01 (d), 59.66 (s), 106.84 (d), 110.07 (d), 113.66 (d), 127.88 (d), 135.04 (s), 141.51 (d), 153.32 (s), 155.12 (s), 159.02 (s). [α]^{23}D: +1.5° (c 0.89, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.86. Found: C, 66.52; H, 7.64; N. 3.63.

(1*S*,2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (19). Obtained (0.64 g, 92%) from **15** (0.50 g, 1.9 mmol) and $(Boc)_2O$ (1 equiv) following the procedure described above. Mp: 104–5 °C (*n*-hexane/ether (5:1)). ^{1}H NMR: δ 0.60 (d, 3 H, J = 6.8 Hz), 1.45 (s, 9 H), 2.14 (m, 1 H), 3.75 (br s, 1 H, OH), 3.79 (s, 3 H), 4.75 (t, 1 H, J = 9.0 Hz), 4.93 (br s, 1 H), 5.45 (br d, 1 H, J = 8.2 Hz, NH), 6.22 (d, 1H), 6.32 (dd, 1 H), 6.87, 7.25 (ABq, 4 H), 7.36 (m, 1 H). ^{13}C NMR: δ 9.28 (q), 28.09 (q), 43.82 (d), 52.15 (d), 54.94 (q), 71.05 (d), 79.98 (s), 106.74 (d), 109.98 (d), 113.14 (d), 126.39 (d), 135.02 (s), 141.55 (d), 153.58 (s), 155.55 (s), 157.96 (s). [α]^{23}D: −66.2° (c 0.77, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.86. Found: C, 66.60; H, 7.65; N, 3.57.

(1*R*,2*S*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (20). Obtained (0.32 g, 90%) as a syrup from **16** (0.26 g, 1 mmol) and $(Boc)_2O$ (1 equiv) following the procedure described above. ^{1}H NMR: δ 0.90 (d, 3 H, J = 6.9 Hz), 1.43 (s, 9 H), 2.26 (m, 1 H), 2.53 (br s, 1 H, OH), 3.78 (s, 3 H), 4.60 (br d, 1 H, J = 3.4 Hz), 4.84 (dd, 1 H, J = 9.3, 4.8 Hz), 4.95 (br d, 1 H, J = 9.3 Hz, NH), 6.17 (br s, 1 H), 6.29 (dd, 1 H), 6.85, 7.25 (ABq, 4 H), 7.34 (d, 1 H). ^{13}C NMR: δ 8.63 (q), 28.21 (q), 44.19 (d), 51.68 (d), 55.10 (q), 74.24 (d), 79.70 (s), 106.23 (d), 110.10 (d), 113.48 (d), 126.98 (d), 135.45 (s), 141.51 (d), 154.29 (s), 155.44 (s), 158.57 (s). [α]^{23}D: −4.7° (c 0.56, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.86. Found: C, 66.28; H, 7.57; N, 3.75.

(1*S*,2*S*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(2-furyl)-1-(*p*-methoxyphenyl)-2-methyl-1-propanol (21). Obtained (0.25 g, 58% from *syn*-**13**) as a viscous oil by reaction of crude **17** (0.24 g, 0.9 mmol, 17/16 ratio 87/13) and $(Boc)_2O$ (1 equiv) following the procedure described above. ^{1}H NMR: δ 0.55 (d, 3 H, J = 6.9 Hz), 1.49 (s, 9 H), 2.26 (m, 1 H), 3.79 (s, 3 H), 4.19 (d, 1 H, J = 9.5 Hz), 5.38 (dd, 1 H, J = 9.5, 0.9 Hz), 5.43 (d, 1 H, J = 9.5 Hz, NH), 6.20 (d, 1 H), 6.34 (dd, 1 H), 6.85, 7.26 (ABq, 4 H), 7.36 (m, 1 H). ^{13}C NMR: δ 11.67 (q), 28.16 (q), 45.05 (d), 50.16 (d), 55.05 (q), 75.75 (d), 80.18 (s), 105.87 (d), 110.11 (d), 113.51 (d), 128.03 (d), 134.73 (s), 141.49 (d), 153.82 (s), 156.50 (s), 158.83 (s). [α]^{23}D: +21.8° (c 0.80, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.86. Found: C, 66.26; H, 7.64; N, 3.71.

Preparation of Lactones 22–25 (General Procedure). A O_3/O_2 gas stream (300 L/h with 2.5 g of O_3) was bubbled through a solution of the *N*-Boc amino alcohol **18–21** (0.11 g, 0.3 mmol) and NaOH (0.1 g) in CH_2Cl_2 (15 mL), MeOH (2.5 mL), and H_2O_2 (1 mL, 30%) at −78 °C until total consumption of the starting material (TLC). The mixture was stirred to rt and then 1 additional hour at that temperature. The organic layer was extracted, dried, and evaporated to give a crude residue which provided the lactones **22–25**, respectively, by column chromatography (*n*-hexane/AcOEt (3:1)).

(3*S*,4*R*,5*R*)-3-[(*tert*-Butoxycarbonyl)amino]-5-(*p*-methoxyphenyl)-4-methyltetrahydrofuranone (22). Obtained (0.089 g, 92%) from **18**. Mp: 140–2 °C (*n*-hexane/ether (4:1)). ^{1}H NMR: δ 1.15 (d, 3 H, J = 7.2 Hz), 1.45 (s, 9 H), 2.96 (m, 1 H), 3.81 (s, 3 H), 4.51 (dd, 1 H, J = 6.8, 5.4 Hz), 5.00 (d, 1 H, J = 5.4 Hz, NH), 5.27 (br s, 1 H), 6.90, 7.23 (ABq, 4 H). ^{13}C NMR: δ 13.50 (q), 28.15 (q), 40.65 (d), 52.75 (d), 55.28 (q), 80.51 (s), 85.51 (d), 114.18 (d), 126.32 (d), 129.86 (s), 155.37 (s), 159.58 (s), 174.87 (s). [α]^{23}D: −22.3° (c 0.56, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21: N, 4.36. Found: C, 63.66; H, 7.06; N, 4.13.

(3*S*,4*R*,5*S*)-3-[(*tert*-Butoxycarbonyl)amino]-5-(*p*-methoxyphenyl)-4-methyltetrahydrofuranone (23). Obtained (0.090 g, 93%) from **19**. Mp: 103–5 °C (*n*-hexane/ether (4:1)). ^{1}H NMR: δ 0.54 (d, 3 H, J = 6.9 Hz), 1.46 (s, 9 H), 3.14 (m, 1 H), 3.82 (s, 3 H), 4.78 (dd, 1 H, J = 6.4, 5.6 Hz), 5.14 (d, 1 H, J = 5.6 Hz, NH), 5.57 (d, 1 H, J = 4.7 Hz), 6.91, 7.18 (ABq, 4 H). ^{13}C NMR: δ 8.27 (q), 28.15 (q), 40.42 (d), 55.18 (q), 56.33 (d), 80.49 (s), 81.30 (d), 113.88 (d), 126.35 (d), 127.03 (s), 155.23 (s), 159.29 (s), 174.65 (s). [α]^{23}D: +26.5° (c 0.82, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.42; H, 7.46; N, 4.51.

(3*S*,4*S*,5*R*)-3-[(*tert*-Butoxycarbonyl)amino]-5-(*p*-methoxyphenyl)-4-methyltetrahydrofuranone (24). Obtained (0.092 g, 95%) from **20**. Mp: 154–6 °C (*n*-hexane/ether (4:1)). ^{1}H NMR: δ 0.84 (d, 3 H, J = 6.9 Hz), 1.45 (s, 9 H), 2.77 (m, 1 H), 3.81 (s, 3 H), 4.25 (dd, 1 H, J = 7.7, 9.7 Hz), 4.96 (d, 1 H, J = 7.7 Hz, NH), 5.54 (d, 1 H, J = 8.2 Hz), 6.90, 7.06 (ABq, 4 H). ^{13}C NMR: δ 13.59 (q), 28.10 (q), 41.28 (d), 54.36 (d), 55.19 (q), 80.48 (s), 81.99 (d), 113.90 (d), 127.09 (d), 130.61 (s), 155.56 (s), 159.54 (s), 175.23 (s). MS *m/e* 321 (M^+, <1), 265 (14), 135 (100). [α]^{23}D: −64.3° (c 0.56, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.72; H, 7.17; N, 4.40.

(3*S*,4*S*,5*S*)-3-[(*tert*-Butoxycarbonyl)amino]-5-(*p*-methoxyphenyl)-4-methyltetrahydrofuranone (25). Obtained (0.094 g, 98%) as a viscous oil from **21**. ^{1}H NMR: δ 1.17 (d, 3 H, J = 6.4 Hz), 1.47 (s, 9 H), 2.34 (m, 1 H), 3.81 (s, 3 H), 4.26 (dd, 1 H, J = 11.5, 7.6 Hz), 4.83 (d, 1 H, J = 10.2 Hz), 5.10 (d, 1 H, J = 7.6 Hz, NH), 6.90, 7.28 (ABq, 4 H). ^{13}C NMR: δ 13.56 (q), 28.18 (q), 46.84 (d), 55.25 (q), 57.85 (d), 80.49 (s), 84.70 (d), 114.07 (d), 128.11 (d), 135.96 (s), 155.48 (s), 160.20 (s), 174.19 (s). MS: *m/e* 321 (M^+, 3), 135 (20), 40 (100). [α]^{23}D: +20.1° (c 0.82, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.39; H, 7.12; N, 4.46.

Epimerization of Lactones 23 and 24. To a solution of **23** or **24** (0.048 g, 0.15 mmol) in anhydrous CH_2Cl_2 (12 mL) was added BBr_3 (0.16 mL, 1 M in CH_2Cl_2) dropwise at −78 °C, and the mixture was stirred for 10 min. H_2O was poured into the mixture at −78 °C, and it was warmed to rt. After usual workup the crude residues were purified by column chromatography (*n*-hexane/AcOEt (3:1)) to give **22** (0.030 g, 63%) and **25** (0.026 g, 53%), respectively.

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