Fully Stereoselective Nucleophilic Addition to a Novel Chiral Pyrroline *N*-Oxide: Total Syntheses of (2*S*,3*R*)-3-Hydroxy-3-methylproline and Its (2*R*)-Epimer

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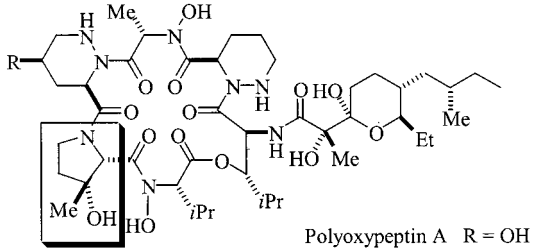
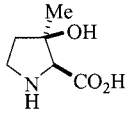
A new total synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline has been performed via a key intermediate chiral pyrroline *N*-oxide, obtained from (*R*)-citramalic acid. This nitrone underwent nucleophilic addition of furyllithium with complete stereoselectivity through a preferential attack *anti* to the methoxymethoxy group. The correct stereochemistry was established through an oxidation–reduction sequence, which allowed inversion of configuration at C-2.

Introduction

Naturally occurring substituted prolines have received much attention in recent years[1,2] due to their presence in a variety of more complex compounds with important and promising biological activities.[3,4] In particular, (2*S*,3*R*)-3-hydroxy-3-methylproline (**1**) has been identified as a novel non-proteinogenic amino acid, an essential component of the recently discovered cyclic hexadepsipeptide antibiotic polyoxypeptins,[5,6] which act as promoters of apoptosis in human pancreatic carcinoma AsPC-1 cells.[7] The recent surge of activity relating to the synthetic chemistry of **1** is indicative of its importance.[8–11]

In this paper we describe the total synthesis of **1** and its (2*R*)-epimer by way of a diastereoselective nucleophilic addition to a cyclic chiral nitrone. This type of reaction has in the past been successfully applied for the synthesis of optically active pyrrolidines.[12] In this context we have recently reported a study on the cyanation of enantiomerically pure cyclic nitrones to give the corresponding 2-cyano-1-hydroxypyrrolidines.[13]





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Results and Discussion

The retrosynthetic analysis for **1** according to this strategy is depicted in Scheme 1. Proline **1** would be prepared from cyclic nitrone **2** by a nucleophilic addition of a suitable carboxylic acid surrogate. Two main points appeared critical for the success of this strategy: *i.* the stereoselectivity of the addition of the carboxylate synthon, and *ii.* the accessibility of the key intermediate nitrone **2**. Indeed, although several methodologies for the synthesis of chiral pyrroline *N*-oxides have been reported by Firenze's team[14–20] and others,[21–24] there is no reported procedure for the preparation of **2**. Nevertheless, the existing methodologies developed for the preparation of suitably protected 3-hydroxypyrroline *N*-oxides from (*S*)-malic acid[14] allowed us to anticipate that (*R*)-(+)-citramalic acid might serve as an appropriate starting material.

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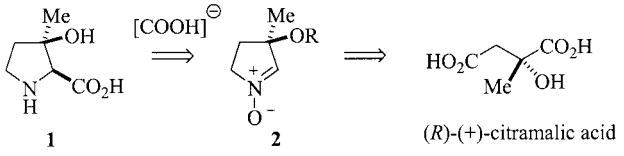
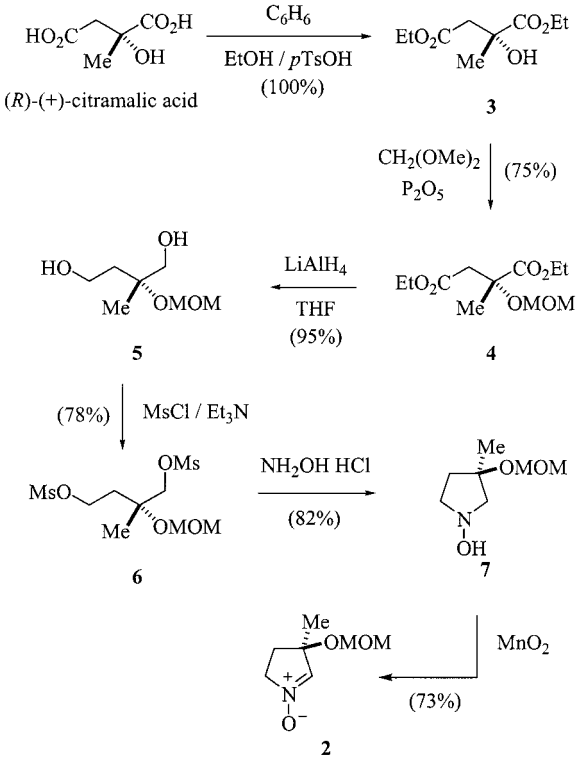


Scheme 1

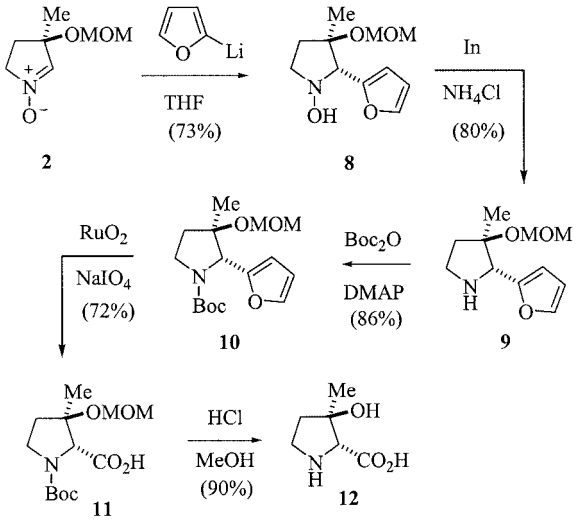
The required protected nitrone **2** was prepared from commercially available (*R*)-(+)-citramalic acid by the reaction sequence shown in Scheme 2. Esterification of the dicarboxylic acid and subsequent protection of the hydroxy group as a MOM derivative furnished the diester **4** (75% overall yield from citramalic acid). Reduction of **4** with $LiAlH_4$ afforded an excellent yield (95%) of the diol **5**, which was subjected to mesylation and subsequent treatment with hydroxylamine to afford *N*-hydroxypyrrolidine **7**. A clean cyclization was observed, affording compound **7** in 60.8% overall yield from **4**. Finally, manganese(IV) oxide-promoted oxidation[25] of **7** gave rise to the nitrone **2** with total regioselectivity (overall yield from (*R*)-citramalic acid: 33.3%, six steps). The observed regioselectivity is in agreement with that found for 3-alkoxy-substituted hydroxypyrrolidines, ascribed to a stereoelectronic effect of the substituent.[14,15] The further enhancement (cf. 9:1 selectivity from the corresponding hydroxypyrrolidine lacking the methyl group[13]) is a consequence of the disubstitution at C-3.



Scheme 2

MOM protection was chosen for its superior chelating capability towards organometallic reagents.[26] In principle, it might be expected that, in the absence of effective steric discrimination, chelation by the alkoxy substituent might direct the attack to the desired diastereotopic face.

The furan ring was chosen as a synthetic equivalent for the carboxylic function, since it is well documented in the literature[27] that such a heterocyclic ring can easily be oxidized to the corresponding carboxylic acid.[28] In addition, we have also demonstrated that furyllithium adds stereoselectively to α-alkoxy nitrones to give furfurylhydroxylamines, which can be further converted into the corresponding α-amino acids.[29,30] Addition of furyllithium to the nitrone **2** (Scheme 3) in THF at 0 °C afforded only one product (by HPLC and NMR analyses), in 73% chemical yield and with total stereoselectivity. Although it displayed spectral and analytical data in agreement with those of an addition product as desired, its relative stereochemistry was not easily identifiable. Several NOE experiments were carried out in an attempt to obtain information on the absolute configuration of the new stereocenter. These studies were inconclusive, however, due to extensive overlapping of meaningful signals in the ^1H NMR spectrum. The planned synthesis was therefore carried out, in order to compare the characteristics of the final synthetic compound with those of our target. Hydroxylamine **8** was deoxygenated by use of indium, following the procedure recently described by some of us.[31] The resulting pyrrolidine **9** was protected in situ as its Boc derivative **10**, which was subjected to RuO_2-mediated oxidation (RuO_2/$NaIO_4$) to afford the crude acid **11**. Acidic hydrolysis (HCl/MeOH) of **11** gave compound **12**, which showed physical and spectroscopic properties clearly different to **1**, thus establishing that the addition of the furan ring had taken place from the wrong face. All attempts to add the furan ring with *cis* stereochemistry with respect to the OMOM group (under several sets of conditions, in-



Scheme 3

cluding in the presence of Lewis acids[32]) were completely unsuccessful.

It was apparent from this result that the addition of furyllithium was occurring exclusively *cis* to the methyl group. This finding was contrary to our initial expectations and even more surprising in view of the total selectivity of the reaction. Control of the addition through chelation of the organolithium derivative by the MOM group (Figure 1, TS model **A**) was then disregarded. Instead, the obtained stereochemistry of adduct **8** suggests that a Felkin−Anh TS model **B** (Figure 1),[33,34] in which the more electronegative OMOM group is antiperiplanar to the incoming organometal nucleophile for electronic reasons,[35] is operative. This arrangement would be greatly favored through stabilization of the negative charge by $\Psi_{3(LUMO)}-\sigma^*_{C-O}$ overlapping. In light of this result, stereoelectronic effects rather than steric ones appear likely to play a predominant role in determining the preference for the observed *anti* attack of nucleophiles to 3-alkoxy-substituted pyrroline *N*-oxides.[12,13]

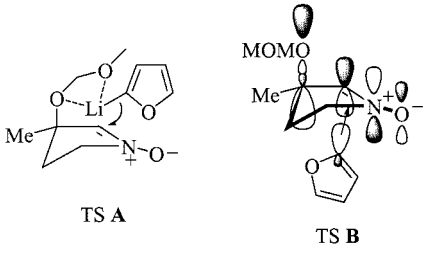
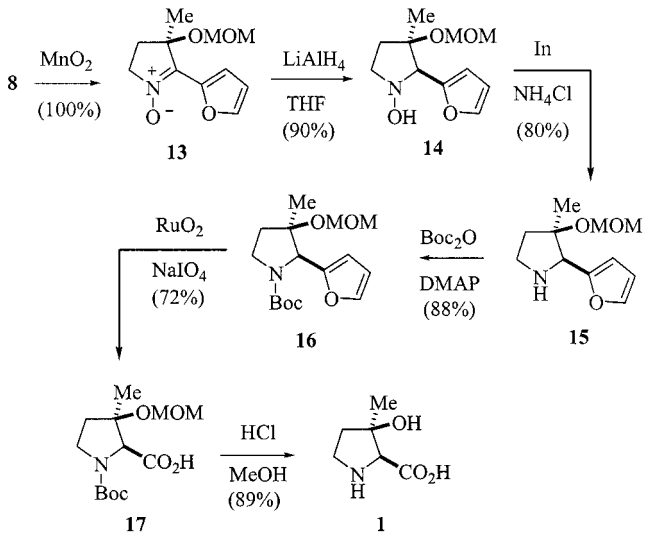


Figure 1. Proposed transition state models for addition of furyllithium to nitrone **2**

The complete stereoselectivity of the nucleophilic addition, besides allowing easy access to the previously unknown 2-epimer of the target proline derivative **12**, shed light on a possible alternative route to **1** by a slight variation of the strategy: an oxidation-reduction sequence on the precursor hydroxylamine **8** might allow the correct configuration to be placed at C-2. Oxidation of hydroxylamine **8** with manganese(IV) dioxide[25] yielded the nitrone **13** in a totally regioselective way and quantitative yield. Attempts with sodium borohydride failed to reduce the nitrone **13**. On the other hand, the use of lithium aluminium hydride quantitatively gave a 9:1 mixture of hydroxylamines **14** and **8**, from which the hydroxylamine **14** was isolated in 90% yield. The physical and spectroscopic properties of **14** were different from those of its epimer **8**, confirming the opposite configuration at C-2. Furthermore, strong NOEs between the MOM group and the furan ring were detected, consistently with a *cis* relative configuration between the two groups. In a fashion similar to that illustrated in Scheme 3 for the hydroxylamine **8**, compound **14** was transformed into the acid **17** (overall yield: 50.7%, 3 steps) (Scheme 4). Acidic deprotection of **17** (HCl/MeOH) gave **1**, the ^{1}H and ^{13}C NMR spectroscopic data for which were identical with those previously reported.[8−11] The optical rotation was also in good agreement with that reported in the literature.[8−11]



Scheme 4

Conclusion

(2*S*,3*R*)-3-Hydroxy-3-methylproline has been prepared in 13 steps and in 9.9% overall yield (83.7% average yield per step) from commercially available (*R*)-(+)-citramalic acid. A major disadvantage of the route is that the undesired diastereomer is obtained upon the direct addition of furyllithium, a problem solved by regioselective oxidation and subsequent reduction. Moreover, several findings worth noting have also been made during this synthesis:

− the scope and generality of the methodology for the synthesis of pyrroline *N*-oxides, previously applied to tartaric and malic acids,[14] has been enlarged to include a new α,α-disubstituted cyclic nitrone, which can be prepared on a multigram scale from citramalic acid,

− the complete regioselectivity in the oxidation of hydroxypyrrolidine **7** to give exclusively the α-substituted nitrone **8**, due to disubstitution at C-3,

− the complete stereoselectivity of the nucleophilic addition of furyllithium to nitrone **2**, affording only the diastereoisomer deriving from an *anti* attack to the OMOM group, which can be interpreted on the basis of a Felkin−Anh TS model, and

− the potential to invert the configuration at C-2, thus allowing formal stereocontrol in the synthesis of the intermediate 2-furyl-*N*-hydroxypyrrolidines, through an oxidation-reduction strategy.

In conclusion, the attractive feature of our synthetic method is the stereocontrolled introduction of the carboxyl moiety. This approach offers greater flexibility than the previously reported synthesis of **1** and lends itself well to the syntheses of other substituted prolines from the D- and L-series.

Experimental Section

General Remarks: The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were determined with 254 nm UV light or by spraying with 5% ethanolic phosphomolybdic acid and iodine. Preparative flash column chromatography was performed on columns of silica gel (40−60 microns). Melting points were not corrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 55 °C with Varian Unity or Bruker 300 instruments. Chemical shifts are reported in ppm (δ) relative to the solvent used. Optical rotations were measured at 25 °C with a Perkin−Elmer 241 polarimeter. Elemental analysis was performed with a Perkin−Elmer 240B microanalyzer.

Diethyl (2*R*)-2-Hydroxy-2-methylsuccinate(3): A mixture of (*R*)-citramalic acid (39 g, 263.5 mmol), *p*-toluenesulfonic acid (1.0 g, 5.25 mmol), absolute ethanol (80 mL), and anhydrous benzene (160 mL) was heated at reflux temperature in a Dean−Stark apparatus for 72 h. Evaporation of the solvent afforded crude **3** (53.7 g, 100%) as an oil, pure enough to be used for the next step. An analytical sample for measurement of the optical rotation and combustion analysis was obtained by elution (Et_2O) through a short pad of silica gel. $[\alpha]_D^{20} = -19$ (c = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, J = 7.3 Hz, 3 H, $-OCH_2CH_3$), 1.07 (t, J = 7.3 Hz, 3 H, $-OCH_2CH_3$), 1.21 (s, 3 H, $-CH_3$), 2.45 and 2.73 (AB system, J = 16.1 Hz, 2 H, $-CH_2-$), 3.90 (q, J = 7.3 Hz, 2 H, $-OCH_2CH_3$), 4.02 (q, J = 7.3 Hz, 2 H, $-OCH_2CH_3$), 5.50 (br. s, 1 H, $-OH$) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.5, 13.9, 26.1, 44.1, 60.6, 61.7, 72.3, 170.7, 175.4 ppm. $C_9H_{16}O_5$ (204.22): calcd. C 52.93, H 7.90; found C 52.71, H 8.27.

Diethyl (2*R*)-2-Methoxymethoxy-2-methylsuccinate(4): Dimethoxymethane (183 g, 2.41 mol) and P_2O_5 (106.3 g, 749 mmol) were added to a solution of the diester **3** (22.2 g, 108.6 mmol) in $CHCl_3$ (500 mL). After having been stirred at room temperature for 45 min (no starting product was observed by TLC), the reaction mixture was diluted with $CHCl_3$ (500 mL). The resulting solution was cooled to 0 °C and a saturated aqueous solution of Na_2CO_3 was added dropwise until pH = 8. The two layers were separated, and the aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was rotary evaporated to give the crude product as a yellow oil. Purification by column chromatography (hexane/ethyl acetate, 95:5) afforded pure **4** (20.2 g, 75%) as an oil. $[\alpha]_D^{20} = +5$ (c = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.07 (t, J = 7.3 Hz, 3 H, $-OCH_2CH_3$), 1.12 (t, J = 7.3 Hz, 3 H, $-OCH_2CH_3$), 1.38 (s, 3 H, $-CH_3$), 2.70 (s, 2 H, $-CH_2-$), 3.18 (s, 3 H, $-OCH_2OCH_3$), 3.95 (q, J = 7.3 Hz, 2 H, $-OCH_2CH_3$), 4.04 (q, J = 7.3 Hz, 2 H, $-OCH_2CH_3$), 4.63 (s, 2 H, $-OCH_2OCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 13.9, 22.3, 43.5, 55.4, 60.2, 61.0, 77.2, 92.2, 169.3, 172.2 ppm. $C_{11}H_{20}O_6$ (248.27): calcd. C 53.21, H 8.12; found C 53.15, H 8.20.

(2*R*)-2-Methoxymethoxy-2-methylbutane-1,4-diol (5): A solution of **4** (17.3 g, 69.7 mmol) in dry THF (300 mL) was added dropwise to a well stirred, cooled (0 °C) suspension of $LiAlH_4$ (5.3 g, 139.5 mmol) in dry THF (250 mL). The reaction mixture was heated at reflux for 2 h, after which it was cooled to 0 °C and a 10% aqueous solution of KOH (30 mL) was added dropwise. After 1 h of additional stirring at ambient temperature the resulting mixture was filtered through a pad of Celite. The precipitated salts were washed with Et_2O and the combined filtrates were dried ($MgSO_4$) and rotary evaporated to give essentially pure diol **5** (10.87 g, 95%) as an oil. An analytical sample for measurement of the optical rotation and combustion analysis was obtained by elution (EtOAc) through a short pad of silica gel. $[\alpha]_D^{20} = -24$ (c = 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 3 H, $-CH_3$), 1.77 (ddd, J = 4.4, 5.9, 15.4 Hz, 1 H, H^{3a}), 1.86 (ddd, J = 4.4, 8.1, 15.4 Hz, 1 H, H^{3b}), 3.41 (s, 3 H, $-OCH_2OCH_3$), 3.51 (s, 2 H, H^{1a} and H^{1b}), 3.70 (dt, J = 5.1, 11.0 Hz, 1 H, H^{4a}), 3.84 (ddd, J = 4.4, 8.1, 11.7 Hz, 1 H, H^{4b}), 4.65 and 4.80 (AB system, J = 7.5 Hz, 2 H, $-OCH_2OCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.6, 40.0, 55.6, 58.4, 68.1, 79.4, 90.7 ppm. $C_7H_{16}O_4$ (164.20): calcd. C 51.20, H 9.82; found C 51.09, H 9.96.

(2*R*)-2-Methoxymethoxy-2-methyl-1,4-bis[(methylsulfonyloxy)]-butane (6): Et_3N (31.7 g, 313.9 mmol) was added to a well stirred solution of the diol **5** (9.3 g, 56.7 mmol) in CH_2Cl_2 (120 mL). The resulting solution was cooled to 0 °C, and mesyl chloride (18.5 mL, 228 mmol) was added dropwise. The solution was stirred at room temperature for 1 h; ice was then added, and the organic phase was washed with 1 N HCl solution, saturated aq. Na_2CO_3, and brine. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was rotary evaporated to give crude **6** (14.15 g, 78%), sufficiently pure to be used for the next reaction. An analytical sample for measurement of the optical rotation and combustion analysis was obtained by elution (EtOAc) through a short pad of silica gel. $[\alpha]_D^{20} = -7.8$ (c = 0.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, $-CH_3$), 2.01 (dt, J = 6.6, 18.7 Hz, 1 H, H_{3a}), 2.12 (dt, J = 6.6, 18.7 Hz, 1 H, H^{3b}), 3.00 (s, 3 H, $-SO_2CH_3$), 3.03 (s, 3 H, $-SO_2CH_3$), 3.36 (s, 3 H, $-OCH_2OCH_3$), 4.08 and 4.19 (AB system, J = 10.2 Hz, 2 H, H^{1a} and H^{1b}), 4.33−4.45 (m, 2 H, H^{4a} and H^{4b}), 4.72 (AB system, J = 7.8 Hz, 2 H, $-OCH_2OCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.7, 36.5, 37.4, 37.5, 55.7, 65.3, 73.1, 75.2, 91.7 ppm. $C_9H_{20}O_8S_2$ (320.38): calcd. C 33.74, H 6.29; found C 33.65, H 6.41.

(3*R*)-*N*-Hydroxy-3-methoxymethoxy-3-methylpyrrolidine (7): A suspension of the dimesylate **6** (13.92 g, 43.5 mmol) and hydroxylamine hydrochloride (13.6 g, 195.7 mmol) in Et_3N (130 mL) was heated at reflux for 4 h. The solvent was then evaporated and the remaining solid was washed with Et_2O (4 × 25 mL). The ethereal extracts were concentrated under reduced pressure to give crude **7** (5.75 g, 82%) sufficiently pure to be used in the next reaction. An analytical sample for measurement of the optical rotation and combustion analysis was obtained by elution (Et_2O) through a short pad of silica gel. $[\alpha]_D^{20} = -3$ (c = 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 325 K): δ = 1.40 (s, 3 H, $-CH_3$), 1.82 (dt, J = 7.3, 13.1 Hz, 1 H, H^{4a}), 2.12 (dt, J = 6.3, 13.1 Hz, 1 H, H^{4b}), 2.90 (d, J = 11.7 Hz, 1 H, H^{2a}), 2.96−3.09 (m, 1 H, H^{5a}), 3.20 (td, J = 7.3, 10.2 Hz, 1 H, H^{5b}), 3.30 (d, J = 11.7 Hz, 1 H, H^{2b}), 3.34 (s, 3 H, $-OCH_2OCH_3$), 4.69 (s, 2 H, $-OCH_2OCH_3$), 5.53 (br. s, 1 H, $-NOH$) ppm. ^{13}C NMR ($CDCl_3$, 325 K): δ = 25.6, 36.9, 55.1, 58.0, 70.3, 82.2, 92.0 ppm. $C_7H_{15}NO_3$ (161.20): calcd. C 52.16, H 9.38, N 8.69; found C 52.09, H 9.46, N 8.52.

(3*R*)-3-Methoxymethoxy-3-methyl-1-pyrroline *N*-Oxide (2): Manganese(IV) oxide (3.94 g, 45.3 mmol) was added in portions to an ice-cooled solution of *N*-hydroxypyrrolidine **7** (4.86 g, 30.2 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred for an additional 30 minutes. The solution was then filtered through Na_2SO_4 and concentrated under reduced pressure, and the crude product was purified by column chromatography (gradient from EtOAc to EtOAc/MeOH, 4:1) to give pure nitrone **2** (3.51 g, 73%) as a viscous oil. $[\alpha]_D^{20} = +10$ (c = 0.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H, $-CH_3$), 2.02 (ddd, J = 6.8, 9.3, 13.2 Hz, 1 H, H^{4a}), 2.26 (ddd, J = 4.4, 8.8, 13.2 Hz, 1 H, H^{4b}), 3.14 (s, 3 H, $-OCH_3$), 3.69 (dddd, J = 1.0, 4.4, 8.8, 13.7 Hz, 1 H, H^{5a}), 3.95 (dddd, J = 1.5,

6.8, 8.3, 13.7 Hz, 1 H, H^{5b}), 4.43 and 4.45 (AB system, J = 7.8 Hz, 2 H, $-OCH_2OCH_3$), 6.70 (s, 1 H, H^2) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.8, 34.4, 55.0, 61.3, 82.9, 91.9, 138.0 ppm. $C_7H_{13}NO_3$ (159.18): calcd. C 52.82, H 8.23, N 8.80; found C 52.93, H 8.15, N 8.98.

(2*R*,3*R*)-2-(2-Furyl)-*N*-hydroxy-3-methoxymethoxy-3-methylpyrrolidine (8): Butyllithium (20 mL of a 1.6 M solution in hexanes, 32 mmol) was added at −80 °C to a well stirred solution of furan (2.04 g, 2.18 mL, 30 mmol) in THF (100 mL), and the resulting solution was stirred at 0 °C for 2 h. The solution was then cooled to −90 °C and treated with a solution of the nitrone **2** (2.39 g, 15 mmol) in THF (80 mL), added drop by drop. The rate of addition was adjusted so as to keep the internal temperature below −80 °C. After the addition was complete the reaction mixture was warmed to room temperature over 1 h and stirring was then maintained for an additional 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl (60 mL). Stirring was continued for 10 min at ambient temperature, and Et_2O (80 mL) was then added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 75 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure (*ds* > 95% by ^1H NMR analysis). Column chromatography (hexane/EtOAc, 90:10) afforded pure **8** (2.49 g, 73%) as an oil. $[\alpha]_D^{20}$ = +35 (*c* = 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.06 (s, 3 H, $-CH_3$), 1.82 (ddd, J = 7.8, 11.7, 13.6 Hz, 1 H, H^{4a}), 2.21 (ddd, J = 1.9, 7.8, 13.6 Hz, 1 H, H^{4b}), 3.11 (ddd, J = 7.8, 11.7, 16.6 Hz, 1 H, H^{5a}), 3.33 (m, 1 H, H^{5b}), 3.38 (s, 3 H, $-OCH_2OCH_3$), 4.13 (s, 1 H, H^2), 4.71 and 4.78 (AB system, J = 7.3 Hz, 2 H, $-OCH_2OOCH_3$), 6.29 (br. d, J = 2.93 Hz, 1 H, furyl-H^3), 6.33 (dd, J = 1.9, 3.4 Hz, 1 H, furyl-H^4), 7.37 (br. s, 1 H, furyl-H^5) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.5, 35.6, 38.0, 55.3, 76.0, 83.4, 91.7, 108.5, 110.2, 142.1, 152.4 ppm. $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 57.90, H 7.35, N 6.30.

(2*R*,3*R*)-2-(2-Furyl)-3-methoxymethoxy-3-methylpyrrolidine (9): The hydroxylamine **8** (2.27 g, 10 mmol) was dissolved in a 2:1 solution of EtOH and saturated aqueous NH_4Cl (60 mL) in a 250 mL round-bottomed flask fitted with a Claisen condenser and a magnetic stirring bar. Powdered indium (1.38 g, 12 mmol) was then added, and the mixture was heated under reflux. After 4 h the reaction mixture was cooled, filtered through Celite, and concentrated under reduced pressure. A saturated aqueous Na_2CO_3 solution (15 mL) was then added, and the product was extracted with EtOAc (3 × 15 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to afford the crude amine **9** (1.69 g, 80%) sufficiently pure to be used for the next reaction. ^1H NMR ($CDCl_3$): δ = 1.06 (s, 3 H, $-CH_3$), 1.85 (dt, J = 8.3, 13.2 Hz, 1 H, H^{4a}), 2.08 (ddd, J = 4.3, 10.7, 13.2 Hz, 1 H, H^{4a}), 3.07−3.20 (m, 2 H, H^{5a} + H^{5a}), 3.45 (s, 3 H, $-OCH_2OCH_3$), 4.20 (s, 1 H, H^2), 4.71 and 4.75 (AB system, J = 7.3 Hz, 2 H, $-OCH_2OCH_3$), 6.15 (br. d, J = 2.93 Hz, 1 H, furyl-H^3), 6.26 (dd, J = 1.9, 3.4 Hz, 1 H, furyl-H^4), 7.29 (d, J = 1.9 Hz, 1 H, furyl-H^5) ppm.

(2*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-2-(2-furyl)-3-methoxymethoxy-3-methylpyrrolidine (10): DMAP (8.3 mg, 0.054 mmol) and Boc_2O (2.35 g, 10.8 mmol) were added sequentially to a well stirred solution of the amine **9** (1.14 g, 5.4 mmol) in CH_3CN (50 mL). The resulting solution was stirred at ambient temperature for 2 h, after which the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give pure **10** (1.45 g, 86%) as an oil. $[\alpha]_D^{20}$ = −2.3 (*c* = 0.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 325 K): δ = 1.01 (s, 3 H, $-CH_3$), 1.24 (s, 9 H, $-OC(CH_3)_3$], 1.98−2.10 (m, 2 H, H^{4a} and H^{4b}), 3.35 (s, 3 H, $-OCH_2OCH_3$), 3.48−3.68 (m, 2 H, H^{5a} and H^{5b}), 4.69−4.82 (m, 3 H, H^2 and $-OCH_2OCH_3$), 6.09 (br. s, 1 H, furyl-H^3), 6.27 (br. t, J = 2.4, 1 H, furyl-H^4), 7.28 (br. s, 1 H, furyl-H^5) ppm. ^{13}C NMR ($CDCl_3$, 325 K): δ = 19.5, 28.1, 34.7, 44.2, 55.2, 64.4, 79.1, 86.3, 91.3, 106.8, 110.2, 141.8, 154.3, 157.6 ppm. $C_{16}H_{25}NO_5$ (311.37): calcd. C 61.72, H 8.09, N 4.50; found C 61.85, H 7.95, N 4.40.

(2*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-3-methoxymethoxy-3-methylproline (11): Ruthenium(IV) oxide (80 mg, 0.60 mmol) was added to a well stirred solution of $NaIO_4$ (3.92 g, 17.6 mmol) in $H_2O/CCl_4/CH_3CN$ (3:2:3, 80 mL). After 15 min stirring, the 2-furyl derivative **10** (0.96 g, 3 mmol) in CH_3CN (10 mL) was added. The solution instantaneously turned from yellowish to black. Enough $NaIO_4$ to restore the yellowish color was then added. After 5 min, the mixture was diluted with water (15 mL) and extracted with EtOAc (4 × 30 mL). The organic combined extracts were washed successively with 20% aq. $NaHSO_3$ (until colorless) and brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure. This residue was taken up in satd. aq. K_2CO_3 (10 mL), and the solution was stirred for 10 min and then washed with EtOAc (2 × 25 mL). Acidification (pH = 2) of the aqueous layer by addition of 2 N HCl, extraction with CH_2Cl_2 (3 × 40 mL), drying ($MgSO_4$) of the combined organic extracts over magnesium sulfate, and evaporation of the solvent under reduced pressure gave acid **11** (0.625 g, 72%) sufficiently pure to be used for the next deprotection step. ^1H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, $-CH_3$), 1.38 [s, 9 H, $-OC(CH_3)_3$], 1.92 (dt, J = 9.9, 13.2 Hz, 1 H, H^{4a}), 1.99−2.10 (m, 1 H, H^{4b}), 3.34 (s, 3 H, $-OCH_2OCH_3$), 3.50 (ddd, J = 6.2, 9.5, 14.3 Hz, 1 H, H^{5a}), 3.63 (t, J = 9.5 Hz, 1 H, H^{5b}), 4.65−4.80 (m, 3 H, $-OCH_2OCH_3$ and H^2) ppm.

(2*R*,3*R*)-3-Hydroxy-3-methylproline (12): The crude acid **11** (0.50 g, 1.73 mmol) was dissolved in MeOH (40 mL), and HCl solution (2 N, 5 mL) was added. The resulting mixture was heated at reflux for 2 h, after which the solvent was eliminated under reduced pressure. The crude material was purified by ion-exchange chromatography (Dowex 50 W) by elution with water and then with a 2 N solution of NH_4OH. After evaporation of the ammonia fraction under reduced pressure, pure **12** (0.226 g, 90%) was obtained as a white, sticky foam. $[\alpha]_D^{20}$ = −30 (*c* = 0.2, D_2O). ^1H NMR (D_2O): δ = 1.35 (s, 3 H, $-CH_3$), 1.86−2.03 (m, 2 H, H^{4a} and H^{4b}), 3.34 (dt, J = 7.0, 11.7 Hz, 1 H, H^{5a}), 3.46 (ddd, J = 4.0, 8.8, 11.7 Hz, 1 H, H^{5b}), 3.74 (s, 1 H, H^2) ppm. ^{13}C NMR (D_2O): δ = 21.9, 37.2, 44.1, 70.2, 79.1, 177.0 ppm. $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.83, H 7.25., N 9.30.

(3*R*)-2-(2-Furyl)-3-methoxymethoxy-3-methyl-1-pyrroline *N*-Oxide (13): Treatment of **8** (2.27 g, 10 mmol) with manganese(IV) oxide (1.30 g, 15 mmol) under the conditions as described above for the preparation of **2** quantitatively gave nitrone **13** (2.25 g, 100%) as an oil sufficiently pure to be used in the next reaction. ^1H NMR ($CDCl_3$): δ = 1.23 (s, 3 H, $-CH_3$), 2.21 (ddd, J = 7.3, 9.3, 13.7 Hz, 1 H, H^{4a}), 2.61 (ddd, J = 4.4, 8.8, 13.6 Hz, 1 H, H^{4b}), 3.30 (s, 3 H, $-OCH_2OCH_3$), 4.00 (ddd, J = 4.4, 9.3, 13.7 Hz, 1 H, H^{5a}), 4.28 (dt, J = 8.8, 13.7 Hz, 1 H, H^{5b}), 4.63 and 4.66 (AB system, J = 7.8 Hz, 2 H, $-OCH_2OCH_3$), 6.56 (dd, J = 1.9, 3.4 Hz, 1 H, furyl-H^4), 7.50 (br. s, 1 H, furyl-H^5), 7.90 (d, J = 3.4 Hz, 1 H, furyl-H^3) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.0, 33.1, 55.7, 60.9, 85.3, 92.5, 98.8, 111.8, 115.9, 139.8, 143.4 ppm.

(2*S*,3*R*)-2-(2-Furyl)-*N*-hydroxy-3-methoxymethoxy-3-methylpyrrolidine (14): A solution of **13** (1.92 g, 8.48 mmol) in dry THF (25 mL) was added dropwise to a well stirred, cooled (0 °C) suspension of $LiAlH_4$ (0.64 g, 16.96 mmol) in dry THF (20 mL). The reac-

tion mixture was stirred at ambient temperature for 30 min, after which it was cooled to 0 °C and a 10% aqueous solution of KOH (5 mL) was added dropwise. After 1 h of additional stirring at ambient temperature the resulting mixture was filtered through a pad of Celite. The precipitated salts were washed with Et_2O and the combined filtrates were dried ($MgSO_4$) and rotary evaporated to give the crude mixture of hydroxylamines **8** and **14** in a 1:9 ratio (measured by ^1H NMR). Purification by column chromatography (hexane/EtOAc, 2:3) gave pure **14** (1.73 g, 90%) as an oil. $[\alpha]_D^{20} = -146$ (c = 0.28, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.41 (s, 3 H, $-CH_3$), 2.00 (ddd, J = 3.3, 9.4, 13.6 Hz, 1 H, H^{4a}), 2.25 (dt, J = 8.5, 13.6 Hz, 1 H, H^{4b}), 2.87 (pseudo q, J = 9.6 Hz, 1 H, H^{5a}), 3.18 (s, 3 H, $-OCH_2OCH_3$), 3.52 (td, J = 3.7, 9.6 Hz, 1 H, H^{5b}), 3.68 (s, 1 H, H^2), 4.37 and 4.58 (AB system, J = 7.7 Hz, 2 H), 5.51 (br. s, 1 H, −NO*H*), 6.31 (br. d, J = 2.9 Hz, 1 H, furyl-H^3), 6.36 (dd, J = 1.8, 3.3 Hz, 1 H, furyl-H^4), 7.39 (br. s, 1 H, furyl-H^5) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.1, 33.3, 35.2, 54.6, 55.0, 81.5, 91.8, 108.6, 110.3, 142.1, 151.2 ppm. $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 57.95, H 7.40, N 6.30.

(2*S*,3*R*)-2-(2-Furyl)-3-methoxymethoxy-3-methylpyrrolidine (15): Treatment of **14** (1.8 g, 8.2 mmol) with In powder (1.15 g, 10 mmol) under the conditions described above for the preparation of **9** gave pyrrolidine **15** (1.3 g, 80%) as an oil sufficiently pure to be used in the next reaction. ^1H NMR ($CDCl_3$): δ = 1.23 (s, 3 H, $-CH_3$), 2.01−2.13 (m, 2 H, H^{4a} and −N*H*), 2.25 (ddd, J = 5.5, 8.4, 13.5 Hz, 1 H, H^{4b}), 3.01 (dt, J = 4.4, 10.6 Hz, 1 H, H^{5a}), 3.14−3.27 (m, 1 H, H^{5b}), 3.20 (s, 3 H, $-OCH_2OCH_3$), 3.79 (s, 1 H, H^2), 4.50 and 4.54 (AB system, J = 7.3 Hz, 2 H, $-OCH_2OCH_3$), 6.20 (br. d, J = 2.8 Hz, 1 H, furyl-H^3), 6.38 (dd, J = 1.9, 3.4 Hz, 1 H, furyl-H^4), 7.36 (br. s, 1 H, furyl-H^5) ppm.

(2*S*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-2-(2-furyl)-3-methoxymethoxy-3-methylpyrrolidine (16): Treatment of **15** (1.3 g, 6 mmol) with Boc_2O (2.61 g, 12 mmol) under the conditions described above for the preparation of **10** afforded pure pyrrolidine **16** (1.64 g, 88%) as an oil after column chromatography (hexane/EtOAc, 1:1). $[\alpha]_D^{20} = +5$ (c = 0.79, $CHCl_3$). ^1H NMR ([D$_6$]DMSO, 373 K): δ = 1.29 (s, 3 H, $-CH_3$), 1.38 [s, 9 H, $-OC(CH_3)_3$], 1.88 (ddd, J = 4.0, 7.7, 12.1 Hz, 1 H, H^{4a}), 2.26 (dt, J = 8.5, 12.1 Hz, 1 H, H^{4b}), 2.94 (s, 3 H, $-OCH_2OCH_3$), 3.36 (dt, J = 7.7, 10.3 Hz, 1 H, H^{5a}), 3.54 (ddd, J = 4.0, 8.5, 10.3 Hz, 1 H), H^{5b}), 4.41 and 4.58 (AB system, J = 7.0 Hz, 2 H, $-OCH_2OCH_3$), 4.55 (s, 1 H, H^2), 6.12 (br. d, J = 3.3 Hz, 1 H, furyl-H^3), 6.38 (dd, J = 1.8, 2.9 Hz, 1 H, furyl-H^4), 7.50 (br. s, 1 H, furyl-H^5) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.3, 28.1, 34.8, 44.2, 55.2, 63.9, 79.3, 82.5, 91.9, 107.1, 110.7, 141.2 (2 C), 157.4 ppm. $C_{16}H_{25}NO_5$ (311.37): calcd. C 61.72, H 8.09, N 4.50; found C 61.83, H 7.95, N 4.40.

(2*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-3-methoxymethoxy-3-methylproline (17): Treatment of **16** (0.48 g, 1.54 mmol) with ruthenium(IV) oxide (40 mg, 0.3 mmol) under the conditions described above for the preparation of **11** gave acid **17** (0.321 g, 72%) as an oil sufficiently pure to be used in the next reaction. ^1H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, $-CH_3$), 1.40 (s, 9 H, $-OC(CH_3)_3$], 1.82 (ddd, J = 3.9, 6.8, 11.7 Hz, 1 H, H^{4a}), 2.09 (dt, J = 8.3, 11.7 Hz, 1 H, H^{4b}), 3.41 (ddd, J = 4.4, 10.0, 14.6 Hz, 1 H, H^{5a}), 3.62 (dt, J = 9.8, 14.6 Hz, 1 H, H^{5b}), 3.31 (s, 3 H, $-OCH_2OCH_3$), 4.60 and 4.62 (AB system, J = 7.3 Hz, 2 H, $-OCH_2OCH_3$), 4.07 (s, 1 H, H^2) ppm.

(2*R*,3*R*)-3-Hydroxy-3-methylproline (1): Treatment of **17** (1.168 g, 0.58 mmol) with MeOH (15 mL) and 2 N HCl (1.7 mL) under the conditions described above for the preparation of **12** afforded a crude product, which was purified by ion-exchange chromatography (Dowex 50 W) by elution with water and then with a 2 N solution of NH_4OH. After evaporation of the ammonia fraction under reduced pressure, pure **1** (75 mg, 89%) was obtained as a white solid. m.p. 195−197 °C. [ref.[3] m.p. 195−197 °C]. $[\alpha]_D^{20} = -39$ (c = 0.40, H_2O). {ref.[4] $[\alpha]_D = -42.0$ (c = 1.30, H_2O)}. ^1H NMR (D_2O): δ = 1.59 (s, 3 H, $-CH_3$), 2.10−2.18 (m, 2 H, H^{4a} and H^{4b}), 3.40 (ddd, J = 4.5, 7.3, 11.2 Hz, 1 H, H^{5a}), 3.52 (dt, J = 7.5, 11.2 Hz, 1 H, H^{5b}), 3.85 (s, 1 H, H^2) ppm. ^{13}C NMR (D_2O): δ = 24.3, 39.9, 43.7, 70.1, 78.8, 171.2 ppm. $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.72, H 7.43, N 9.56.

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