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Synthesis of enantiomerically pure 2-amino alcohols from amino acids mediated by sulfoxides

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Abstract

Enantiomerically pure (R_1,S_2)- and (S_1,S_2)-2-amino alcohols can be easily synthesized by stereodivergent reduction of α′-(*N*-Boc)amino β-keto sulfoxides (easily synthesized from readily available *N*-Boc amino ester hydrochlorides) with DIBAH (*de* 82–92%) and DIBAH/$ZnBr_2$ (*de* 80%), followed by hydrogenolysis of the C–S bond of the resulting hydroxy sulfoxides and final hydrolysis of the *N*-Boc protecting group.

1. Introduction

The importance of enantiopure 2-amino alcohols is well recognized due to their significance as building blocks in the synthesis of drugs and natural products, ligands for asymmetric catalysis, and chiral auxiliaries.[1] These compounds are usually obtained by resolution of racemates,[2] synthesis from optically pure precursors,[3a] and asymmetric synthesis.[1a,b,4] The more general synthetic routes to chiral 2-amino alcohols include reduction of α-amino acids or α-amino carbonyl compounds,[1,5] ring opening of epoxides,[1,6] cyclic carbonates,[7] sulfates[8a] or sulfites[8b] with amines[1,6] or amine precursors,[1,6c,7,8] diasteroselective formation of the central C–C bond by several procedures,[9] asymmetric aminohydroxylation of olefins[10] and oxa Michael addition to nitro alkenes.[11]

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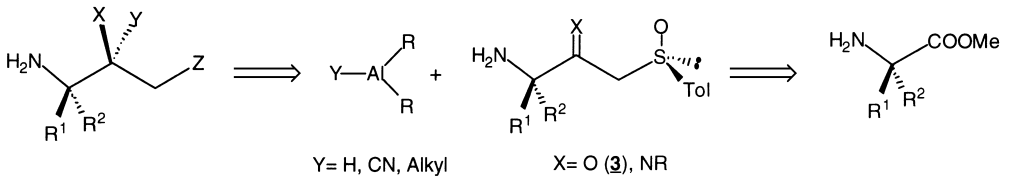
Concerning the use of natural amino acids as readily available starting materials, primary 2-amino alcohols containing one stereogenic center have been obtained by reduction of the parent amino acid or amino ester salts.[1b,5a] The preparation of secondary 2-amino alcohols with two stereogenic centers has been restricted essentially to the steroselective reduction of α-amino ketones[1,5] and the stereoselective addition of organometallic reagents to *N*-protected α-amino aldehydes,[1,3] which in turn are accessible from the corresponding amino acids. These two approaches often provide complementary product stereochemistries but the preparation of both diastereoisomers requires the synthesis of different precursors as starting materials. On the other hand, the generation of high levels of diastereoselectivity and the stability of the α-amino carbonyl compounds have sometimes been problems inherent to these methods.[1a] They have been minimized by using *N*,*N*-dibenzyl α-amino aldehydes[3] but the removal of the benzyl groups may be troublesome under some conditions.[1a] Concerning reduction reactions[5] stereodivergent reduction of α-*N*-phenylfluorenyl ketone to either the *syn*- or *anti*-amino alcohols have been reported[5c] but it is not clear to what an extent the scope of this particular reaction is general (other examples of similar reductions provide the *anti*-isomer).[5d,e]

Nucleophilic additions to enantiomerically pure β-keto sulfoxides have been widely used in asymmetric synthesis of carbinols.[12] Alkylation[13] and hydrocyanation[14] reactions of these compounds with aluminium reagents have been reported to synthesize tertiary alcohols and cyanohydrins respectively, but the most used reaction has been the stereoselective reduction of β-keto sulfoxides[15] with DIBAH and DIBAH/ZnX_2 to yield secondary alcohols.[16] These reagents can also be used on β-imino sulfoxides (easily obtained from β-keto sulfoxides)[17] affording enantiomerically pure amines.[18] Other functional groups such as epoxides, can be obtained by conversion of the hydroxy sulfoxides resulting from these reactions,[19] which can be subsequently opened with nucleophiles.[5,20] As β-keto sulfoxides are easily obtained by reaction of esters with enantiomerically pure methyl *p*-tolyl sulfoxide,[21] we envisioned the synthesis of a large variety of 1,2-amino alcohols (and occasionally 1,2-diamino derivatives) making use of the above-mentioned reactions on the α-sulfinyl-α′-amino ketones **3** (or their imino derivatives), derived from commercial amino ester hydrochlorides (Scheme 1).

Herein we report the synthesis and DIBAH and DIBAH/ZnX_2 reductions of β-keto sulfoxides **3**, derived from readily available (*S*)-alanine, (*R*)-phenylglycine and (*S*)-proline methyl ester hydrochlorides. The obtained results suggest this method can be used as a general stereodivergent procedure to synthesize (*S*,*R*)- and (*S*,*S*)-1,2-amino alcohols starting from (*S*)-*N*-Boc amino esters, the desired configuration at the hydroxylic carbon being obtained by choosing the suitable reducing system. The transformation of the resulting hydroxy sulfoxides into the corresponding enantiomerically pure 3-amino-2-alkanols without significant racemization is also described.

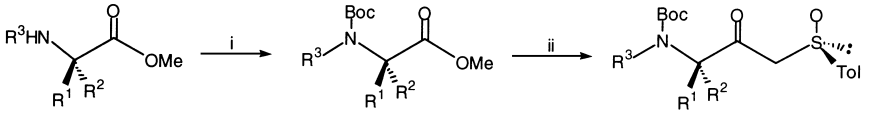


Scheme 1.

2. Results and discussion

Taking into account that the stereoselectivity of the β-keto sulfoxides reduction with DIBAH and DIBAH/ZnX_2 seems to be related to the ability of the sulfinyl oxygen to become associated with metals,[16b] as a previous step of the attack of the hydride, presumably the presence of any basic center at the substrate could interfere in the stereochemical course of these reactions. This assumption was evidenced for β-keto sulfoxides bearing oxygenated functions able to compete with the sulfinyl one for their association with the metal, which evolve with lower stereoselectivity.[22] In order to avoid this problem in the case of β-keto sulfoxides derived from natural amino acids, the protection of the amino group as *N*-Boc derivative, which decreases the ability of the nitrogen to become associated to the metal thus minimizing its ability to compete with the sulfinyl group for the aluminum, seemed to be reasonable.

The synthetic sequence to obtain α-sulfinyl-α′-amino ketone derivatives, **3**, is depicted in Scheme 2. The amino acid methyl ester hydrochlorides **1** reacted with di-*tert*-butyl dicarbonate in methanol in the presence of triethylamine, resulting in the carbamates **2**. The synthesis of the β-keto sulfoxides **3** was performed by reaction of **2** with (*R*)-(+)-methyl *p*-tolyl sulfoxide and LDA at –78°C (–25°C, in the case of **3a**), according to the procedure reported by Solladié.[21] Diastereoisomeric excesses of β-keto sulfoxides were determined by 300 MHz ^{1}H NMR. Crude **3a** was obtained as a 95:5 diasteroisomeric mixture, epimers at the stereogenic carbon vicinal to the nitrogen moiety probably due to the excess of base and/or anion used in its preparation. The purification of the major epimer was carried out by crystallization of the crude product to provide diasteroisomerically pure **3a** (*de* >97%) in 61% yield. On the other hand, the keto sulfoxides **3b** and **3c** were obtained with high diasteroisomeric excesses (>97%) and satisfactory chemical yields (75 and 78%, respectively) and their absolute configuration was unequivocally established as (1*R*,R_S) for **3b** (Fig. 1) and (2*S*,R_S) for **3c**[23] by X-ray diffraction studies.

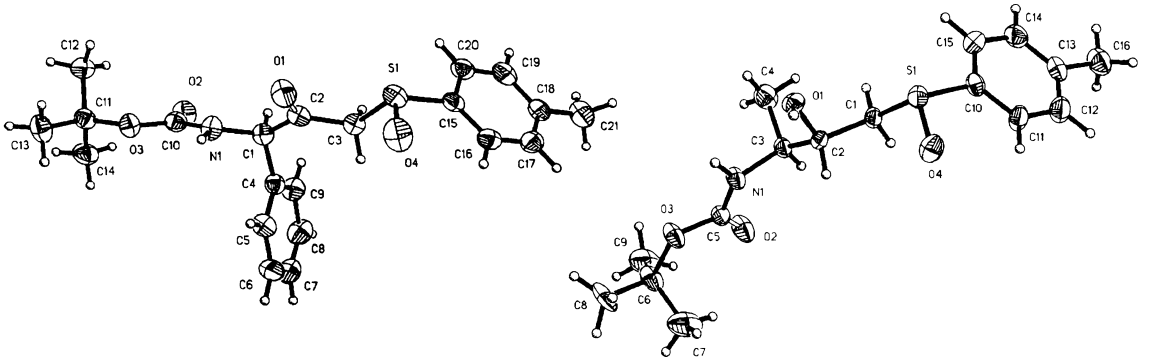


1a [R^1=R^3=H, R^2=Me] **2a** (91%) **3a** (61%)
1b [R^2=R^3=H, R^1=Ph] **2b** (98%) **3b** (75%)
1c [R^1=H, R^2-R^3=$(CH_2)_3$] **2c** (54%) **3c** (78%)

Scheme 2. (i) Et_3N, Boc_2O, MeOH, rt, 24 h; (ii) *p*-Tol-SO-Me, LDA, THF, –78°C (or –25°C), 3–4 h

The reduction of β-keto sulfoxides **3** with DIBAH[15] at –78°C gave the β-hydroxy sulfoxides **4** and **4′** (Table 1) with high stereoselectivity (*de* 82–92%). An excess of DIBAH (5 equiv.) was required to achieve the complete transformation of the starting products and to get high yields. The major β-hydroxy sulfoxides were purified by crystallization (**4a**) or by chromatography (**4b** and **4c**) to give diasteroisomerically pure products (*de* >97%) in yields ranging between 64 and 75%. Configurational assignment of the obtained diastereoisomers was deduced from their ^{1}H NMR, taking into account the well-known behavior of diastereoisomeric β-sulfinyl carbinols,[24] which agrees with the predictions made on the basis of the stereochemical model proposed to explain the DIBAH reduction of β-keto sulfoxides.[15b] The absolute configuration of **4a** was confirmed by a X-ray diffraction study (Fig. 1). The observed stereoselectivity is not complete (*de* 82% for **4a**, 86% for **4b**, and 92% for **4c**) suggesting some interferences of the nitrogen

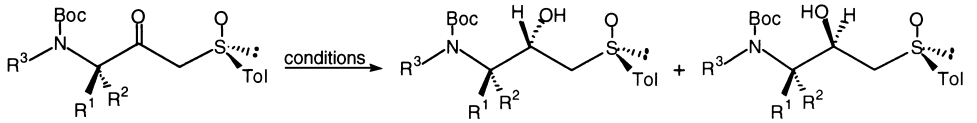
function in the stereochemical course of the reaction, which became less important by increasing the steric hindrance of the nitrogenated carbon or the substitution at the nitrogen. Nevertheless, the stereoselectivity of the reduction is high enough for synthetic purposes, which demonstrates the efficiency of the *N*-Boc group to avoid the competing of the amino and sulfinyl groups for the aluminum. Additionally, we must remark the fact that the same configuration at the hydroxylic carbon is obtained from compounds **3a** and **3b**, both differing in configuration at the nitrogenated carbon, which suggests that the stereochemical course of these reductions is exclusively controlled by the sulfinyl group.



Compound **3b** Compound **4a**

Figure 1. X-Ray structures for compounds **3b** and **4a**

Table 1
Results obtained in DIBAH and DIBAH/$ZnBr_2$ reduction of β-keto sulfoxides **3**



3 **4** **4'**

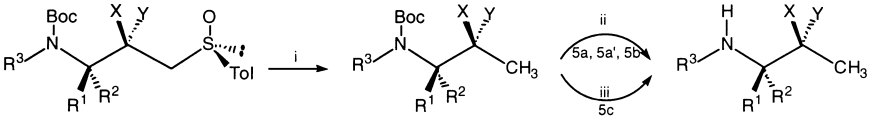
Entry	Starting material	Conditions[a]	Total Yield (%)	**4/4'** ratio[b]	Isolated Yield[c] (%)
1	**3a**	A	99	**4a**(91):**4'a** (9)	64
2	**3b**	A	90	**4b**(93):**4'b** (7)	71
3	**3c**	A	89	**4c**(96):**4'c** (4)	75
4	**3a**	B	98	**4a**(10):**4'a** (90)	71

[a] A: DIBAH, -78ºC. B: DIBAH/$ZnBr_2$, -78ºC. [b] Determined by 300 MHz ^{1}H-NMR. [c] Diastereomerically pure major alcohol.

The synthesis of the carbinols with the opposite configuration at the hydroxylic carbon could be achieved by reduction of the β-keto sulfoxides **3** with DIBAH in the presence of $ZnBr_2$.[15] In these reactions, the inversion of the stereoselection has been justified by assuming the formation of a chelated species between the sulfinyl and the carbonyl oxygens with $ZnBr_2$ previous to the

hydride attack.[15b,c] As the nitrogen in compounds **3** could compete with the oxygens for the metal, thus affecting the usual stereochemical pathway, it was necessary to check whether its protection as *N*-Boc derivative was enough to eliminate such possible competitiveness. In this sense, we have investigated the evolution of **3a** with DIBAH/$ZnBr_2$ (Table 1), because this is the substrate presumably more prone to form such a chelate due to its lower steric hindrance around the nitrogen atom. As expected, the reduction proceeds with high stereoselectivity but the hydroxy sulfoxide **4′a** was now obtained as the major compound. The obtained *de* (80%, entry 4) is similar to that observed in the reduction of $(MeO)_2CH\text{-}CO\text{-}CH_2SOTol$,[21b] which suggests that the ability of the NHBoc group to form chelates is not significant and equivalent to that of the acetal group at C-α′. These results show the efficiency of the *N*-Boc to minimize the ability of the amino group to compete with the sulfinyl one in both DIBAH and DIBAH/$ZnBr_2$ reductions of compounds **3**,[25] thus allowing the synthesis of the epimeric carbinols by stereodivergent reduction of compounds **3**.

The cleavage of the C–S bond of β-hydroxy sulfoxides **4** with Raney nickel yields the corresponding *N*-Boc protected 2-amino alkanols **5** in high yields (Scheme 3). Partial racemization of the hydroxylated chiral carbon, observed in some desulfinylations of hydroxy sulfoxides with Raney nickel,[26] was not detected in these reactions. Finally, acidic hydrolysis of the *N*-Boc protecting group proceeded in good yields by treatment of **5a**, **5′a** and **5b** with a saturated solution of hydrochloric acid in ethyl acetate at room temperature for 2 h producing the hydrochlorides **6a**, **6′a**, and **6b**. Efficient deprotection of the amino group of **5c** required its reaction with trifluoroacetic acid, affording **6c** after basification with ammonium hydroxide and extractive work-up.



4a (X=H, Y=OH) **5a** (92%) **6a** · HCl (81%)
4b (X=H, Y=OH) **5b** (82%) **6b** · HCl (75%)
4c (X=H, Y=OH) **5c** (81%) **6c** (75%)
4′a (X=OH, Y=H) **5′a** (92%) **6d** · HCl (89%)

Scheme 3. (i) Raney nickel, MeOH, rt, 1 h; (ii) HCl–EtOAc, rt, 2 h; (iii) (1) CF_3CO_2H, rt, 0.5 h; (2) NH_4OH, rt, 5 min

The absolute configuration and optical purity of the 2-amino alcohols **6b** and **6c** were determined by comparison of the specific optical rotation of the samples obtained here with those previously reported,[27,28] whereas **6a** and **6′a** had to be transformed into their *N*-acetyl derivatives[29] for their chemical correlation.

In summary, we have shown that both diastereoisomers of chiral 2-amino alcohols can be easily synthesized in high optical purity from the readily available *N*-Boc-protected amino ester hydrochlorides **2** by a four-step sequence involving formation of the β-keto sulfoxides **3** by reaction of **2** with (+)-Me-SOTol/LDA, followed by stereodivergent reduction of **3** with DIBAH or DIBAH/$ZnBr_2$ (yielding the hydroxy sulfoxides **4** and **4′**, respectively), hydrogenolysis of the C–S bond to produce the *N*-Boc protected amino alcohols **5**, and final acid hydrolysis of the protecting group.

3. Experimental

3.1. General methods

Melting points were determined in a Culatti melting point apparatus. All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of argon and monitored by TLC. Solvents were dried according to literature procedures. Optical rotations were measured on a Jasco DIP-360 digital polarimeter at 20°C (concentration in g/100 ml). The IR spectra were recorded on a Nicolet-5SX spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained either on a Varian Gemini-200 or Unity-300 spectrometer at room temperature in deuteriochloroform using TMS as internal standard. Mass spectra were measured on a Jeol AX-505 mass spectrometer at 70 eV and 190°C. The diastereoisomeric excesses were determined by 300 MHz ^{1}H NMR spectroscopy. The two different sets of signals in the NMR spectra (assigned as *Z* and *E*) in compounds **2c** and **3c** resulted by the observable rotamers of the *N*-Boc group.

3.2. Preparation of N-(tert-butoxycarbonyl)methyl esters 2

To a solution of the corresponding methyl ester hydrochloride **1** (24 mmol) in 30 ml of dry methanol, triethylamine (36 mmol) and di-*tert*-butyl dicarbonate (36 mmol) were added. The mixture was stirred at room temperature for 24 h. The volatiles were removed under vacuum and the residue was dissolved in 30 ml of $CHCl_3$. The organic phase was washed with 10% aqueous citric acid (2×20 ml), dried and concentrated.

3.2.1. (S)-N-(tert-Butoxycarbonyl)alanine methyl ester 2a

Obtained from L-alanine methyl ester hydrochloride. White crystals, mp 30°C, 91% yield; $[\alpha]_D$ –44 (*c* 1, MeOH). IR ($CHCl_3$) ν_{max}: 3443, 2983, 1741, 1710, 1504, and 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 3.75 (s, 3H), 4.33 (m, 1H), 5.15 (bd, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.5, 28.2, 49.1, 52.2, 80.0, 155.0, 173.8; EIMS *m*/*z* 203 (1%, M^+), 144 (55), 88 (40), 57 (100), 44 (68).

3.2.2. (R)-N-(tert-Butoxycarbonyl)phenylglycine methyl ester 2b

Obtained from D-phenylglycine methyl ester hydrochloride. White crystals, mp 104°C, 98% yield; $[\alpha]_D$ –130 (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3439, 2984, 1743, 1712, 1494, 1367 and 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43 (s, 9H), 3.71 (s, 3H), 5.32 (d, J = 7.5 Hz, 1H), 5.55 (m, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.2, 52.6, 57.6, 80.1, 127.1, 128.4, 128.9, 136.9, 154.8, 171.6; EIMS *m*/*z* 265 (1%, M^+), 206 (71), 150 (100), 106 (88), 104 (15), 57 (83).

3.2.3. (S)-N-(tert-Butoxycarbonyl)proline methyl ester 2c

Obtained from L-proline methyl ester hydrochloride. Oil, pb 135°C/16 mm, 54% yield; $[\alpha]_D$ –61.5 (*c* 0.34, MeOH). IR ($CHCl_3$) ν_{max}: 3394, 2981, 1746, 1689, 1406 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) (*Z*, 60%): δ 1.46 (s, 9H), 1.80–2.05 (m, 3H), 2.15–2.30 (m, 1H), 3.35–3.60 (m, 2H), 3.72 (s, 3H), 4.34 (dd, J = 7.9 and 3.4 Hz, 1H); (*E*, 40%): δ 1.41 (s, 9H), 1.80–2.05 (m, 3H), 2.15–2.30 (m, 1H), 3.35–3.60 (m, 2H), 3.72 (s, 3H), 4.22 (dd, J = 8.3 and 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) (*Z*): δ 24.2, 28.3, 29.8, 46.4, 51.9, 58.6, 79.7, 153.7, 173.6; (*E*): δ 3.5, 28.1, 30.7, 46.2, 51.8, 58.9, 79.7, 154.3, 173.6; EIMS *m*/*z* 230 (5%, M^+), 229 (4), 170 (65), 128 (65), 114 (93), 70 (100), 57 (96), 41(54).

3.3. Preparation of β-keto sulfoxides **3**

3.3.1. (3S,R_S)-N-(tert-Butoxycarbonyl)-3-amino-1-(p-tolylsulfinyl)-2-butanone **3a**

A solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (6.16 g, 40 mmol) in 10 ml of THF was added dropwise to a solution of LDA (40 mmol) in 100 ml of THF at –78°C. The mixture was stirred at –78°C for 1.5 h. Then a solution of **2a** (4.06 g, 20 mmol) in 10 ml of THF was added and the resulting mixture was stirred at –25°C for 3.5 h. The reaction mixture was decomposed with 100 ml of saturated ammonium chloride solution and extracted with CH_2Cl_2 (2×50 ml). The organic phase was washed with brine, dried and evaporated. The crystalline residue (*de* 90%) was recrystallized from CH_2Cl_2–hexane to give 2.74 g (42%) of **3a** as white crystals, mp 106°C; $[\alpha]_D$ +189 (*c* 1, $CHCl_3$), *de* >97%. The mother liqueurs were purified by silica gel column chromatography eluting with hexane:EtOAc, 35:65, to produce, additionally, 1.23 g (19% yield) of **3a**, mp 106°C, *de* >97%; IR ($CHCl_3$) ν_{max}: 3437, 2984, 2931, 1706, 1496, 1370, and 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), major diasteroisomer: δ 1.24 (d, J = 7.2 Hz, 3H), 1.43 (s, 9H), 2.42 (s, 3H), 3.78 and 4.13 (AB system, J = 13.8 Hz, 2H), 4.20 (m, 1H), 5.25 (m, 1H, interchangeable with D_2O), 7.34–7.57 (AA′BB′ system, 4H); minor diasteroisomer: δ 1.27 (d, J = 7.2 Hz, 3H), 1.43 (s, 9H), 2.42 (s, 3H), 3.86 and 4.01 (AB system, J = 13.8 Hz, 2H), 4.20 (m, 1H), 5.25 (m, 1H, interchangeable with D_2O), 7.34–7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz), major diasteroisomer: δ 16.1, 21.4, 28.3, 56.0, 65.5, 80.3, 124.1, 130.1, 140.2, 142.4 155.0, 201.5; EIMS *m*/*z* 326 (2%, M^++1), 144 (100), 140 (74), 88 (36), 57 (98), 44 (84); CIMS *m*/*z* 326 (50%, M^++1), 270 (100), 226 (18), 130 (45), 86 (95).

3.3.2. (1R,R_S)-N-(tert-Butoxycarbonyl)-1-amino-1-phenyl-3-(p-tolylsulfinyl)-2-propanone **3b**

A solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (0.308 g, 2 mmol) in 5 ml of THF was added dropwise to a solution of LDA (4 mmol) in 20 ml of THF at –78°C. The mixture was stirred at –78°C for 1 h. Then a solution of **2b** (0.530 g, 2 mmol) in 10 ml of THF was added and the resulting mixture was stirred at –78°C for 3 h. The reaction mixture was decomposed with 20 ml of saturated ammonium chloride solution and extracted with Et_2O (2×25 ml). The organic phase was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography eluting with hexane:EtOAc, 30:70. White crystals, mp 177°C (petroleum ether), 75% yield; $[\alpha]_D$ –67 (*c* 1, $CHCl_3$), *de* >97%; IR ($CHCl_3$) ν_{max}: 3427, 2984, 2930, 1708, 1491, 1369 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 9H), 2.41 (s, 3H), 3.71 and 3.92 (AB system, J = 13.8 Hz, 2H), 5.19 (d, J = 6 Hz, 1H), 5.75 (s, 1H, interchangeable with D_2O), 7.23–7.48 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 28.2, 64.9, 65.4, 80.1, 124.1, 128.2, 128.9, 129.4, 130.1, 137.0, 139.0, 142.4, 154.6, 197.0; CIMS *m*/*z* 388 (72%, M^++1), 332 (83), 288 (10), 248 (20), 192 (86), 174 (19), 148 (100).

3.3.3. (2S,R_S)-1-(tert-Butoxycarbonyl)-2-(2′-p-tolylsulfinyl)acetylpyrrolidine **3c**

A solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (1.30 g, 8.5 mmol) in 5 ml of THF was added dropwise to a solution of LDA (17 mmol) in 50 ml of THF at –78°C. The mixture was stirred at –78°C for 1 h. Then a solution of **2c** (1.3 g, 5.7 mmol) in 5 ml of THF was added and the resulting mixture was stirred at –78°C for 4 h. The reaction mixture was decomposed with 100 ml of saturated ammonium chloride solution and extracted with Et_2O (3×20 ml). The organic phase was washed with brine, dried and concentrated. The oily residue was purified by silica gel column chromatography eluting with hexane:EtOAc, 30:70. White crystals, mp 92–93°C (ether–hexane), 78% yield; $[\alpha]_D$ +80 (*c* 1, MeOH), *de* >97%; IR ($CHCl_3$) ν_{max}: 2981, 2883, 1722, 1683, 1396, 1163

and 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (*Z*): δ 1.37 (s, 9H), 1.80 (m, 3H), 2.15 (m, 1H), 2.41 (s, 3H), 3.42 (m, 1H), 3.58 (m, 1H), 3.63–4.04 (AB system, J = 14.4 Hz, 2H), 4.27 (m, 1H), 7.35 and 7.57 (AA′BB′ system, 4H); (*E*): δ 1.42 (s, 9H), 1.80 (m, 3H), 2.15 (m, 1H), 2.42 (s, 3H), 3.42 (m, 1H), 3.58 (m, 1H), 3.85–3.99 (AB system, J = 15 Hz, 2H), 4.36 (m, 1H), 7.31 and 7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) (*Z*): δ 21.4, 23.8, 27.7, 28.4, 46.9, 65.4, 66.1, 80.4, 124.1, 130.0, 140.6, 142.0, 153.7, 201.9; (*E*): δ 21.4, 24.6, 28.4, 28.6, 47.0, 66.1, 66.6, 80.9, 124.2, 130.2, 140.6, 142.3, 154.4, 201.9; EIMS *m*/*z* 352 (5%, M^++1), 170 (60), 140 (25), 114 (100), 70 (98), 57 (60).

3.4. *Preparation of β-hydroxy sulfoxides* **4**

DIBAH reduction: To a solution of β-keto sulfoxide **3** (1 equiv.) in THF (5 ml/mmol) at –78°C a 1.5 M solution of DIBAH in toluene (5 equiv.) was added dropwise. The reaction mixture was stirred for 10–15 min to completion and the excess of DIBAH was decomposed by adding MeOH (2 ml/mmol). The solvents were removed under vacuum and the residue was treated with a 5% HCl solution (10 ml/mmol) and extracted with Et_2O (3×10 ml/mmol). The organic phase was washed with brine, dried and evaporated.

3.4.1. (2S,3S,R_S)-N-(tert-*Butoxycarbonyl*)-3-amino-1-(p-*tolylsulfinyl*)-2-butanol **4a**

Obtained from 1.97 g (6.06 mmol) of **3a** (*de* >97%). The crystalline crude product (1.93 g, *de* 82%) was purified by crystallization from CH_2Cl_2/hexane to give 1.27 g (64% yield) of **4a** as white crystals, mp 116–118°C; $[\alpha]_D$ +160.4 (*c* 1, $CHCl_3$), *de* >97%; IR ($CHCl_3$) ν_{max}: 3440, 3003, 2983, 2933, 1704, 1500, 1165, and 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13 (d, J = 6.9 Hz, 3H), 1.40 (s, 9H), 2.43 (s, 3H), 2.64 (dd, J = 1.8 and 13.5 Hz, 1H), 3.06 (dd, J = 10.2 and 13.5 Hz, 1H), 3.62 (bs, 1H), 4.08 (ddd, J = 1.8, 4.5 and 10.5 Hz), 4.42 (s, 1H, interchangeable with D_2O), 4.71 (s, 1H, interchangeable with D_2O), 7.35 and 7.51 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.7, 21.4, 28.3, 50.5, 58.5, 69.7, 79.7, 124.0, 130.1, 139.5, 141.7, 155.5; EIMS *m*/*z* 327 (5%, M^+), 254 (15), 205 (20), 183 (45), 139 (95), 132 (80), 88 (35), 71 (20), 57 (100), 44 (57), 43 (28).

3.4.2. (1R,2S,R_S)-N-(tert-*Butoxycarbonyl*)-1-amino-1-phenyl-3-(p-*tolylsulfinyl*)-2-propanol **4b**

Obtained from 0.774 g (2 mmol) of **3b** (*de* >97%). The crude product (0.701 g, *de* 86%) was purified by silica gel column chromatography eluting with hexane:EtOAc, 35:65, to produce 0.552 g (71% yield) of **4b** as white crystals, mp 180°C (acetone/hexane); $[\alpha]_D$ +203.5 (*c* 1, $CHCl_3$), *de* >97%; IR ($CHCl_3$) ν_{max}: 3440, 2931, 1711, 1494 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 9H), 2.42 (s, 3H), 2.69 (dd, J = 1.8 and 13.5 Hz, 1H), 3.22 (dd, J = 10.2 and 13.8 Hz, 1H), 4.10 (m, 1H, interchangeable with D_2O), 4.40 (m, 1H), 4.53 (m, 1H), 5.52 (m, 1H, interchangeable with D_2O), 7.18–7.50 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.3, 58.5, 59.2, 69.6, 79.9, 124.0, 126.7, 127.6, 128.6, 130.1, 139.2, 139.9, 141.7, 155.8; EIMS *m*/*z* 389 (1%, M^+), 206 (28), 183 (60), 150 (95), 139 (75), 106 (100), 91 (15), 57 (72).

3.4.3. (1′S,2S,R_S)-1-(tert-*Butoxycarbonyl*)-2-(2′-p-*tolylsulfinyl*-1′-*hydroxy*)*ethylpyrrolidine* **4c**

Obtained from 0.704 g (2 mmol) of **3c** (*de* >97%). The crude product (0.630 g, *de* 92%) was purified by silica gel column chromatography eluting with hexane:EtOAc, 35:65, to produce 0.528 g (75% yield) of **4c** as white crystals, mp 123–124°C (acetone/hexane); $[\alpha]_D$ +23 (*c* 0.4, MeOH), *de* >97%; IR ($CHCl_3$) ν_{max}: 3394, 2979, 1661, 1408, 1323, 1121 and 1033 cm^{-1}; ^1H

NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H), 1.75 (m, 3H), 2.00 (m, 1H), 2.42 (s, 3H), 2.75 (m, 2H), 3.11 (m, 1H), 3.42 (m, 1H), 4.02 (m, 1H), 4.21 (m, 1H), 7.33 and 7.53 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 23.8, 28.3, 29.7, 47.8, 61.6, 62.5, 68.8, 80.4, 124.0, 130.0, 141.3, 156.3; EIMS *m/z* 354 (3%, M^++1), 170 (43), 158 (36), 139 (35), 114 (100), 70 (97), 57 (55); CIMS *m/z* 354 (30%, M^++1), 298 (8), 282 (11), 255 (25), 254 (100), 158 (15), 114 (10).

*3.4.4. (2*R*,3*S*,*R_S*)*-N-*(*tert-*Butoxycarbonyl)-3-amino-1-(*p-*tolylsulfinyl)-2-butanol* ***4′a***

DIBAH/$ZnBr_2$ reduction of ***3a***: A solution of β-keto sulfoxide **3a** (0.163 g, 0.5 mmol) in 3 ml of THF was added to a cooled solution of $ZnBr_2$ (0.124 g, 0.55 mmol) in 10 ml of THF at 0°C under argon and the resulting mixture was stirred at this temperature for 1.5 h. Then the solution was cooled at –78°C and a 1.5 M solution of DIBAH in toluene (1.5 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 1 h and the excess of DIBAH was decomposed by adding 2 ml of MeOH. Once the solution reached room temperature, the volatiles were removed under vacuum and the residue was treated with 15 ml of saturated ammonium chloride and extracted with CH_2Cl_2 (3×10 ml). The organic phase was washed with brine, dried and evaporated. The crystalline crude product (0.16 g, *de* 80%) was purified by crystallization from CH_2Cl_2/hexane to give 0.116 g (71% yield) of **4′a** as white crystals, mp 126°C; $[\alpha]_D$ +138 (*c* 1, $CHCl_3$), *de* >97%; IR ($CHCl_3$) ν_{max}: 3440, 2997, 2982, 2933, 1703, 1499, 1165, and 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 (d, J = 6.9 Hz, 3H), 1.39 (s, 9H), 2.42 (s, 3H), 2.85 (dd, J = 2.7 and 13.5 Hz, 1H), 2.99 (dd, J = 9.3 and 13.5 Hz, 1H), 3.54 (s, 1H, interchangeable with D_2O), 3.77 (bs, 1H), 4.27 (ddd, J = 2.1, 2.7 and 9.3 Hz, 1H), 4.87 (s, 1H, interchangeable with D_2O), 7.34 and 7.53 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.1, 21.4, 28.3, 50.4, 60.6, 71.1, 79.4, 123.9, 130.1, 140.3, 142.0, 155.9; EIMS *m/z* 327 (5%, M^+), 254 (13), 183 (37), 139 (65), 132 (100), 88 (39), 57 (83), 44 (64).

3.5. Desulfurization of sulfinyl alcohols

To a suspension of Raney nickel (ca. 300 mg) in 5 ml of MeOH a solution of sulfinyl hydroxy compound **4** (1 mmol) in 5 ml of MeOH was added. The mixture was stirred at room temperature for 1 h. The catalyst was removed by filtration over Celite and washed with MeOH. The evaporation of the solvent produced the corresponding *N*-(*tert*-butoxycarbonyl)amino alcohol **5**.

*3.5.1. (2*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-amino-2-butanol* ***5a***

White crystals, mp 73–74°C, 92% yield; $[\alpha]_D$ –3.8 (*c* 1, MeOH); IR ($CHCl_3$) ν_{max}: 3624, 3445, 2982, 1704, 1504, 1367 and 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 1.75 (bs, 1H, interchangeable with D_2O), 3.70 (bs, 1H), 3.85 (qd, J = 3.0 and 6.6 Hz, 1H), 4.63 (bs, 1H, interchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.0, 18.5, 28.4, 51.7, 70.6, 80.1, 155.2; CIMS *m/z* 190 (90%, M^++1), 134 (100), 116 (24), 90 (83).

*3.5.2. (1*R*,2*R*)-*N*-(*tert*-Butoxycarbonyl)-1-amino-1-phenyl-2-propanol* ***5b***

White solid, mp 93°C, 82% yield; $[\alpha]_D$ –36.5 (*c* 1, MeOH); IR ($CHCl_3$) ν_{max}: 3591, 3444, 2982, 2932, 1709, 1496 and 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, J = 6.3 Hz, 3H), 1.41 (s, 9H), 2.19 (s, 1H, interchangeable with D_2O), 4.00 (bs, 1H), 4.54 (bs, 1H), 5.38 (bd, 1H, interchangeable with D_2O), 7.22–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.2, 28.3, 60.3, 71.1, 79.7, 126.5, 127.4, 128.6, 140.7, 156.2; EIMS *m/z* 252 (1%, M^++1), 206 (27), 150 (100), 135

(10), 106 (87), 57 (68); CIMS *m*/*z* 252 (15%, M^++1), 206 (20), 196 (84), 178 (49), 152 (44), 135 (100), 106 (18).

*3.5.3. (1′*R*,2*S*)-1-(*tert*-Butoxycarbonyl)-2-(1′-hydroxy)ethylpyrrolidine* ***5c***

Oil, 81% yield; $[\alpha]_D$ –59.8 (*c* 1, MeOH); IR ($CHCl_3$) ν_{max}: 3365, 2978, 1668, 1409, 1166 and 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H), 1.60–2.10 (m, 4H), 3.18–3.32 (m, 1H), 3.43–3.60 (m, 1H), 3.80–4.10 (m, 2H), 4.50 (bs, 1H, interchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.7, 24.1, 28.5, 29.7, 48.0, 63.5, 69.7, 80.0, 156.5; EIMS *m*/*z* 216 (3%, M^++1), 215 (2), 170 (25), 114 (90), 70 (100), 57 (75).

*3.5.4. (2*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-amino-2-butanol* ***5′a***

Oil, 92% yield; $[\alpha]_D$ –3.7 (*c* 1.08, MeOH); IR (film) ν_{max}: 3356, 2976, 2933, 1689, 1519, 1367 and 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.3 Hz, 3H), 1.45 (s, 9H), 2.47 (bs, 1H, interchangeable with D_2O), 3.56 (bs, 1H), 3.69 (qd, J = 4.5 and 6.3 Hz, 1H), 4.78 (bs, 1H, interchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.0, 20.2, 28.3, 51.9, 71.0, 79.4, 156.3; CIMS *m*/*z* 190 (100%, M^++1), 134 (49), 116 (9), 90 (42), 88 (8).

3.6. Hydrolysis of N-*(*tert*-butoxycarbonyl)amino alcohols*

A saturated hydrogen chloride solution in ethyl acetate (5 ml) was added to *N*-(*tert*-Boc)amino alcohols **5a**, **5′a** or **5b** (0.5 mmol). The resulting solution was stirred at room temperature for 2 h. The volatiles were removed under vacuum and the solid residue was triturated with ethyl acetate.

*3.6.1. (2*R*,3*S*)-3-Amino-2-butanol hydrochloride* ***6a***

White solid, mp 106–107°C, 81% yield; $[\alpha]_D$ –11.1 (*c* 0.22, MeOH); IR (Nujol) ν_{max}: 3396, 2924, 2854, 1609, 1458, 1216, 1057 and 1026 cm^{-1}; ^1H NMR (D_2O, 300 MHz): δ 1.09 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 3.27 (qd, J = 3.3 and 6.9 Hz, 1H), 3.90 (qd, J = 3.3 and 6.6 Hz, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 12.5, 18.1, 53.0, 67.8 [lit.:[29] ^{13}C NMR (D_2O): δ 12.18, 17.79, 52.57, 67.32]; CIMS *m*/*z* 90 (65%, M^++1–HCl), 73 (15), 72 (100), 55 (5). The (2*R*,3*S*)-3-acetamido-2-acetoxybutane was prepared from **6a** (acetic anhydride, pyridine, 4-(dimethylamino)pyridine, CH_2Cl_2, room temperature, 12 h), mp 61°C, 65% yield; $[\alpha]_D$ –31 (*c* 2.5, 2-butanone) [lit.:[29] mp 62–63°C, $[\alpha]_D$ –33.0 (*c* 0.5, 2-butanone)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13 (d, J = 6.9 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.98 (s, 3H), 2.08 (s, 3H), 4.14 (qd, J = 3.6 and 6.9 Hz, 1H), 4.90 (qd, J = 3.6 and 6.6 Hz, 1H), 5.79 (sa, 1H, interchangeable with D_2O)

*3.6.2. (1*R*,2*R*)-1-Amino-1-phenyl-2-propanol hydrochloride* ***6b***

White solid, mp 195°C, 75% yield; $[\alpha]_D$ –24 (*c* 0.9, H_2O) [lit.:[27] mp 192–193°C, $[\alpha]_D$ +26 (*c* 0.9, H_2O) for (1*S*,2*S*)-enantiomer]; IR (KBr) ν_{max}: 3421, 2993, 2920, 1615, 1526, 1454 and 1096 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ 1.07 (d, J = 6.0 Hz, 3H), 3.93 (d, J = 9.6 Hz, 1H), 4.08–4.20 (m, 1H), 7.44 (s, 5H); ^{13}C NMR ($CDCl_3$+CD_3OD, 75 MHz): δ 20.3, 62.9, 68.7, 128.1, 129.7, 129.9, 134.9; CIMS *m*/*z* 152 (75%, M^++1–HCl), 135 (100), 134 (20), 106 (18).

*3.6.3. (1′*R*,2*S*)-2-(1′-Hydroxy)ethylpyrrolidine* ***6c***

To **5c** (0.2 mmol) trifluoroacetic acid (0.2 ml) was added. The solution was stirred at room temperature for 0.5 h. The volatiles were removed under a nitrogen stream and the residue was evaporated to dryness under vacuum. The residue was treated with 1 ml of concentrated

ammonium hydroxide and stirred at room temperature for 5 min. The aqueous phase was extracted with CH_2Cl_2 (3×2 ml). The organic phase was dried with anhydrous potassium carbonate and the solvent was removed under vacuum to give a white solid: mp 82°C, 75% yield; $[\alpha]_D$ –35.3 (*c* 1, MeOH) [lit.:[28] mp 86°C, $[\alpha]_D$ –36.4 (*c* 1, MeOH)]; IR ($CHCl_3$) ν_{max}: 3351, 2957, 2924, 2853, 2272 and 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (d, J = 6.0 Hz, 3H), 1.50–2.00 (m, 4H), 2.71 (m, 2H), 2.90–3.25 (m, 3H), 3.78 (m, 1H).

3.6.4. (2S,3S)-3-Amino-2-butanol hydrochloride ***6′a***

Oil, 89% yield; $[\alpha]_D$ +15 (*c* 1.46, MeOH); IR (film) ν_{max}: ca. 3600–2200 (b), 1727, 1603, 1505, 1391, and 1104 cm^{-1}; ^1H NMR (D_2O, 300 MHz): δ 1.10 (d, J = 6.3 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H), 3.04 (qd, 1H), 3.61 (qd, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 15.4, 19.6, 54.1, 69.2 [lit.:[30] ^{13}C NMR (D_2O): δ 15.56, 19.47, 53.92, 68.93]. The (2*S*,3*S*)-3-Acetamido-2-acetoxybutane was prepared from **6′a** (acetic anhydride, pyridine, 4-(dimethylamino)pyridine, CH_2Cl_2, room temperature, 12 h), oil, 58% yield; $[\alpha]_D$ –33 (*c* 1.46, 2-butanone) [lit.:[29] mp 15–16°C, $[\alpha]_D$ +35 (*c* 0.503, 2-butanone) for the (2*R*,3*R*)-enantiomer]; IR (film) ν_{max}: 3291, 2982, 2938, 1737, 1652, 1548, 1449, 1374, 1242, and 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.12 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H), 2.01 (s, 3H), 2.08 (s, 3H), 4.15 (qd, 1H), 4.90 (qd, J = 4.2 and 6.6 Hz, 1H), 5.65 (sa, 1H, interchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.3, 18.1, 21.1, 23.3, 48.4, 72.9, 169.6, 170.6; EIMS *m*/*z* 173 (1%,M^+), 129 (10), 113 (17), 86 (76), 72 (13), 44 (100), 43 (43).

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25. Although the herein mentioned results only concern the synthesis of methyl carbinols, the efficiency shown by the *N*-Boc group to minimize the ability of the amino group to compete with the sulfinyl one in DIBAH/$ZnBr_2$ reductions suggests that the evolution of other substituted α-alkylsulfoxides will also be highly stereoselective, thus allowing the synthesis of other alkyl carbinols with the limitations indicated in Ref. 15c.
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