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Enantioselective synthesis of both enantiomers of 2-amino-2-(2-furyl)ethan-1-ol as a flexible building block for the preparation of serine and azasugars

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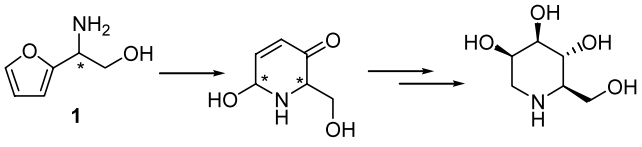
Abstract—The selective conversion of 1-(2-furyl)-2-hydroxyethan-1-one and ethyl 2-(2-furyl)-2-oxo acetate into (*E*)- and (*Z*)-oximes and oxime ethers followed by oxazaborolidine-catalyzed enantioselective reduction using different amino alcohols furnished both enantiomers of the important chiral building block 2-amino-2-(2-furyl)ethan-1-ol with an ee of up to 96%.

1. Introduction

Optically active α-furylamine derivatives have received much attention due to their importance as useful building blocks for the synthesis of a considerable number of nitrogen-containing natural products, such as α-amino acids,[1] β-lactams,[2] indolizidines,[3] quinolizidines[4] and piperidine alkaloids.[5] Among these, chiral 2-amino-2-(2-furyl)ethan-1-ol **1** is a very useful starting material for the synthesis of polyhydroxylated piperidines (azasugars) via chiral dihydropyridones (Scheme 1).[5a] Polyhydroxylated piperidines have attracted considerable attention due to their importance as glycosidase inhibitors.[6] Zhou[5c,d] and Altenbach[5b] have applied this building block to the total synthesis of 1-deoxyazasugars and desoxoprosophylline.[7]

Zhou et al. obtained non-racemic 2-amino-2-(2-furyl)ethan-1-ol **1** from the kinetic resolution of *rac*-**1**, which was prepared by the addition of an organometallic reagent to α-furfuryl imine, in low yield. The same authors reported the asymmetric synthesis of **1** in 5 steps employing a Sharpless asymmetric dihydroxylation starting from α-furyl ethylene.[5a,8] Altenbach et al. used furyl glycine and obtained the furylamine **1** via the reduction of the carboxyl group.[5b]



Scheme 1.

As we reported earlier, furyl alkyl ketones can be used as starting materials for the enantioselective synthesis of both enantiomers of α-amino acids. Oxime ether formation and oxazaborolidine-catalyzed enantioselective reduction followed by oxidation of the furan ring furnished α-amino acids in good yields and high enantiomeric purities.[9,10]

In connection with our preliminary results reported previously, we describe herein the enantioselective synthesis of both enantiomers of 2-amino-2-(2-furyl)ethan-1-ol **1** starting from 1-(2-furyl)-2-hydroxyethan-1-one **2**, and ethyl 2-(2-furyl)-2-oxo acetate **3**, respectively.

2. Results and discussion

As illustrated in Scheme 2, 1-(2-furyl)-2-hydroxyethan-1-one **2** was converted to oxime **4** using $H_2NOH{\cdot}HCl$/NaOAc in EtOH. Oxime **4** was obtained in 97% yield as a mixture of diastereomers ((*E*)/(*Z*):ratio:77:23). The chromatographic separation of these gave pure the (*E*)-isomer (mp 132–133°C, 73%) and the (*Z*)-isomer (mp 126–127°C, 21%) as colorless solids. The reaction

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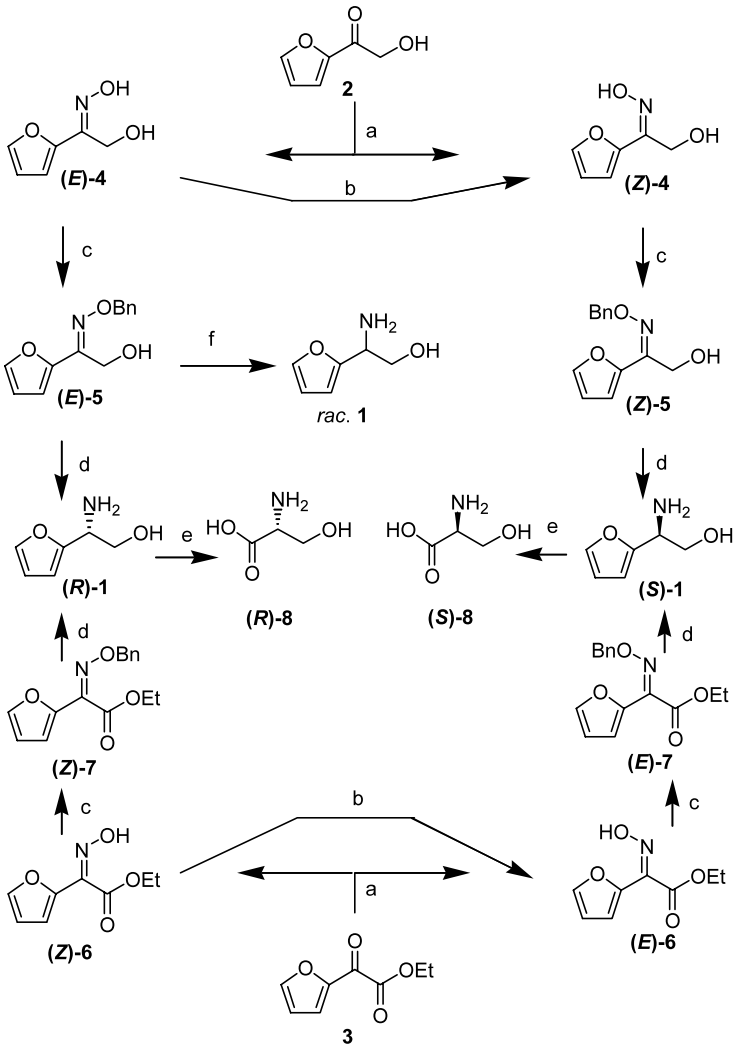


Scheme 2. *Reagents and conditions*: (a) $H_2NOH{\cdot}HCl$, NaOAc, EtOH; (b) HCl/Et_2O; (c) NaH, BnBr, DMF; (d) $BH_3{\cdot}THF$, cat.; (e) O_3, DCM, −78°C; (f) $BH_3{\cdot}SMe_2{\cdot}THF$.

of **4** ((*E*)/(*Z*) mixture) with hydrogen chloride in ether furnished oxime **4** with an (*E*)/(*Z*) ratio of 1:6, which was purified by recrystallization [75% (*Z*)-**4**]). The (*E*)- and (*Z*)-isomers were identified by their ^1H and ^{13}C NMR spectra. (The (*E*)-isomer displays a multiplet for C-3H of furan at 6.64 ppm, whereas the same proton appears at 7.34 ppm in the (*Z*)-isomer. A similar observation can be seen in ^{13}C NMR shifts: C-3 of the (*E*)-isomer appears at 112.7 ppm, and at 119.8 ppm for the (*Z*)-isomer. Oximes were converted to *O*-benzyl oximes (*E*)-**5** and (*Z*)-**5** using NaH and benzyl bromide in DMF in 94–96% yields. No isomerization was observed during this conversion. The *O*-benzyl oximes were purified by flash column chromatography and isolated as viscous oils.

The second approach starts from ethyl 2-(2-furyl)-2-oxo acetate **3**; it is converted selectively to its (*E*)- and (*Z*)-oximes, which are separated carefully either by chromatography or recrystallization (71–74% yields).[9,10a] The (*E*)- and (*Z*)-isomers were identified by their ^1H and ^{13}C NMR spectra. Additionally the structure of (*E*)-**6** was determined by X-ray crystallographic analysis.[11] Since the two geometric isomers give opposite enantiomers,[9,10] in other words the configuration of the product is fully controlled by the appropriate choice of the geometric isomer of the oxime, it is essential to have pure oximes. Oximes were converted to oxime ethers (*E*)-**7** and (*Z*)-**7** using NaH and benzyl bromide in 88–92% yields. The *O*-benzyl oximes were purified by flash column chromatography and isolated as viscous oils.

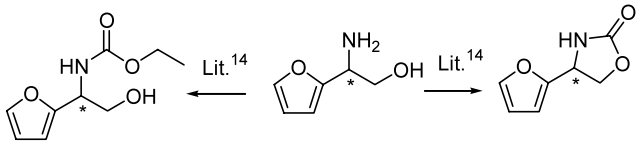
Oxime ethers are a class of readily available compounds for the conversion of carbonyl groups to amines. Some of the most important work in this area was reported by Itsuno et al.,[12] who showed that acetophenone oxime ethers can be converted into amines with high ee's using BH_3–oxazaborolidine complexes. The enantioselective reduction of (*E*)-**5** and (*Z*)-**5** was carried out with BH_3 in the presence of oxazaborolidine complexes[13] prepared from different chiral amino alcohols using the following procedure: A solution of borane in THF was added under argon dropwise to a

solution of (1*R*,2*S*)-norephedrine in THF at −20°C. The resulting mixture was allowed to warm to −5°C and stirring was continued at this temperature for 16 h. A solution of oxime ether (*E*)-**5** in THF was added dropwise. The resulting solution was stirred at 30°C for 48 h (monitored by TLC) and was decomposed by the slow addition of 2 M aqueous HCl. The product amine (*R*)-**1** was obtained in 80% yield and 76% ee after purification of the crude product. Under similar conditions using oxime ether (*Z*)-**5** furnished amine (*S*)-**1** in 75% yield and 73% ee. Different amino alcohols were used in the reduction reaction and, as shown in Table 1, the (*R*)- and (*S*)-amine are obtained in 73–80% yields and 73–87% ee. The highest ee was found with amino alcohol **11**. These results are in accordance with our previous results.[9,10]

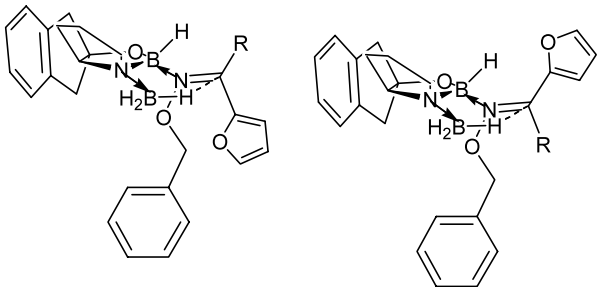
The highest enantiomeric purity was obtained when the ratio of borane:amino alcohol:oxime ether was ca. 2.5:1.25:1.0. An excess of borane relative to amino alcohol led to low enantiomeric excesses. Better results were obtained starting from the reduction of oxime ethers of ethyl 2-(2-furyl)-2-oxo acetate **3**. Enantioselective reductions of (*Z*)-**7** were carried out using the conditions described above. Different amounts of reduction reagents were used and the best enantiomeric purity was obtained when the ratio of borane:amino alcohol:oxime ether was ca. 1:6:3. The amino alcohol (*R*)-**1** was obtained in 94–96% ee and 82–86% chemical yield. Under similar conditions (*E*)-**7** furnished amine (*S*)-**1** in 77–81% yield and 71–91% ee (Table 1).

Amines were characterized by NMR and IR. The enantiomeric purity of the products was determined via analysis of the *N*-acetyl derivative by HPLC on a chiral stationary phase column comparing with a racemic product, which was synthesized from (*Z*)-**7** using $BH_3{\cdot}SMe_2$. As shown in Scheme 2, amines (*S*)- and (*R*)-**1** are converted into (*S*)- and (*R*)-serine ((*S*)-**8**, and (*R*)-**8**) by oxidation of the furan ring with ozone in 91–93% yields. The absolute configurations of (*S*)-**1** and (*R*)-**1** were found by comparison of the specific rotation values with known serine data. It is also possible to predict the absolute configuration of **1** by converting it to oxazolidinone or its carbamic acid ethyl ester by known procedures (Scheme 3).[14] The amino alcohols used for the preparation of oxazaborolidines were recovered in 93–95% yields during the work-up procedure as their HCl salts.

The reduction of oxime ether (*Z*)-**7** under similar conditions with catalytic amounts of oxazaborolidine complexes prepared with amino alcohols (0.1–0.2 equiv.) afforded products with ee's of 16–20%. The effect of the *O*-protecting group on the reduction of oxime ethers was investigated. The reduction was carried out on a (*Z*)-*O*-methyl oxime and determination of the ee's of the product amines showed low selectivity (21% ee).

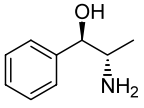
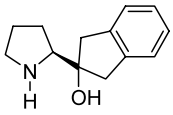
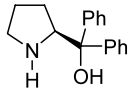


Scheme 3.



Scheme 4.

Table 1. Enantioselective synthesis of (*S*)-**1** and (*R*)-**1** using different amino alcohols

O-benzyloxime	Amino alcohols					
						
	(1*R*,2*S*)-9		**(*S*)-10**[11,13e]		**(*S*)-11**	
	1*					
	yield(%)	ee(%)	yield(%)	ee(%)	yield(%)	ee(%)
***Z*-5**	75	73 (*S*)	76	80 (*S*)	73	87 (*S*)
***E*-5**	80	76 (*R*)	77	78 (*R*)	74	84 (*R*)
***Z*-7**	82	95 (*R*)	85	94 (*R*)	86	96 (*R*)
***E*-7**	77	71 (*S*)	79	80 (*S*)	81	91 (*S*)

* ee's were determined by HPLC from oxazolidinone or carbamic acid ethyl ester derivatives (Chiralcel OD, eluent hexane/2-propanol 90:10, flow rate 0.8 ml/min).

The suggested mechanism outlined in Scheme 4 shows that the formation of low energy *cis*-pentalane is favored because β-binding of BH_3·THF to oxazaborolidine forms very strained *trans*-pentalane, which is disfavored. As shown in Table 1, the geometry of oxime becomes a dominant factor in the stereoselectivity by the formation of amines. It looks like that the prochiral nitrogen moiety is responsible for the high selectivity but not the prochiral carbon.

3. Conclusion

1-(2-Furyl)-2-hydroxyethan-1-one and ethyl 2-(2-furyl)-2-oxo acetate were converted into their (*E*)- and (*Z*)-oximes selectively in good yields, and oxazaborolidine-catalyzed enantioselective reduction of the corresponding *O*-benzyl oxime ethers afforded both enantiomers of 1-(2-furyl)ethylamine in good yields with an ee of up to 96%. Both enantiomers of serine were then obtained in high yields by the oxidation of the furan ring with ozone. The configuration of the amine products is controlled by the appropriate choice of geometrical isomer of the *O*-benzyloxime.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC–LC–MS equipped with an appropriate optically active column, as described in the footnote to Table 1. Optical rotations were measured with a Bellingham & Stanley P20 polarimeter.

4.2. Synthesis of ethyl 2-(2-furyl)-2-oxo acetate, 3

To 1.8 g furyl glyoxalic acid (13 mmol) dissolved in 50 mL $CHCl_3$ was added EtOH (20 mmol) and H_2SO_4. The mixture was refluxed for 10 h, cooled to room temperature and sat. $NaHCO_3$ was added. After separation of the layers the organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Further purification of the crude product by flash column chromatography (1:6 EtOAc:hexane) afforded furylglyoxalic acid ethyl ester in 93% yield. **3**: colorless solid, mp 34–35°C; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, $J=7.2$, 3H), 4.39 (q, $J=7.2$, 2H), 6.61 (dd, $J=1.7$, 3.6, 1H), 7.63 (d, $J=3.6$, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.4, 62.9, 113.3, 124.8, 149.7, 150.2, 161.4, 171.4. Anal. calcd for $C_8H_8O_4$ (168.1): C, 57.14; H, 4.80. Found: C, 57.32; H, 4.66.

4.3. General procedure for oximes

Ethyl 2-(2-furyl)-2-oxo acetate **3** (or **2a**) (1.5 g, 9 mmol), and NH_2OH·HCl (0.8 g, 12 mmol) and CH_3CO_2Na (0.9 g, 12 mmol) were mixed in absolute ethanol (50 mL) and stirred under reflux for 12 h. The reaction was monitored by TLC. After 12 h the hot solution was filtered and the ethanol was evaporated. The remaining solid was dissolved in water and extracted with diethyl ether. The ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product as a mixture of isomers. Separation of the isomers was achieved by flash column chromatography (1:5 ether:toluene) to give the following products.

4.3.1. (*E*)-1-(2-Furyl)-2-hydroxyethan-1-one oxime, (*E*)-4.[15] ^{1}H NMR ($CDCl_3$): δ 3.34 (br.s, 1H), 4.81 (m, 2H), 6.34 (m, 1H), 6.64 (d, $J=3.5$,1H), 7.55 (m, 1H), 11.26 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 61.8, 111.8, 112.7, 140.2, 143.3, 164.2.

4.3.2. (*Z*)-1-(2-Furyl)-2-hydroxyethan-1-one oxime, (*Z*)-4.[15] ^{1}H NMR ($CDCl_3$): δ 3.37 (br.s, 1H), 4.71 (m, 2H), 6.48 (m, 1H), 7.34 (d, $J=3.5$,1H), 7.64 (m,1H), 10.14 (br.s,1H); ^{13}C NMR ($CDCl_3$): δ 61.3, 112.1, 119.8, 140.4, 143.6, 164.7.

4.3.3. (*E*)-Ethyl 2-(2-furyl)-2-(hydroxyimino)acetate, (*E*)-6. Mp 72–73°C; ^{1}H NMR ($CDCl_3$): δ 1.42 (t, $J=7.1$, 3H), 4.40 (q, $J=7.1$, 2H), 6.55 (dd, $J=1.7$, 3.5, 1H), 7.41 (d, $J=3.5$, 1H), 7.55 (s, 1H), 10.76 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 61.9, 111.6, 119.5, 139.5, 142.4, 143.7, 161.4. Anal. calcd for $C_8H_9NO_4$ (183.1): C, 52.46; H, 4.95; N, 7.65. Found: C, 52.65; H, 4.86.

4.3.4. (*Z*)-Ethyl 2-(2-furyl)-2-(hydroxyimino)acetate, (*Z*)-6. Mp 90–92°C; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, $J=6.7$, 3H), 4.33 (q, $J=6.7$, 2H), 6.35 (dd, $J=1.8$, 3.4, 1H), 6.56 (d, $J=3.4$, 1H), 7.41 (s, 1H), 9.97 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.4, 62.5, 111.9, 112.9, 143.1, 144.9, 145.6, 161.8. Anal. calcd for $C_8H_9NO_4$ (183.1): C, 52.46; H, 4.95; N, 7.65. Found: C, 52.32; H, 4.78.

4.4. Isomerization of oximes

Oxime (10 mmol) ((*E*)/(*Z*) mixture) was suspended in dry ether (50 mL) and HCl gas was bubbled through the solution at 0°C. The reaction was monitored by TLC. Initially a clear solution was observed and then a white precipitate formed. Evaporation of the solvent gave oxime with an (*E*)/(*Z*) ratio of 6:1. Separation of the isomers was achieved by flash column chromatography.

4.5. General procedure for oxime ethers

To the suspension of NaH (washed from oil with hexane, 5.4 mmol) in DMF (20 mL) under argon atmosphere at 0°C was slowly added oxime (5.4 mmol) over 30 min. Benzyl bromide (5.4 mmol) was added and the mixture was stirred for 10 h at rt. After the addition of water (5 mL) the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography (1:3 EtOAc:hexane).

4.5.1. (*E*)-1-(2-Furyl)-2-hydroxyethan-1-one *O*-benzyloxime, (*E*)-5. Viscous oil, ^{1}H NMR ($CDCl_3$): δ 3.51 (br.s, 1H), 4.92 (br.s, 2H), 5.43 (s, 2H), 6.52 (m, 1H), 7.25–7.77 (m,7H); ^{13}C NMR ($CDCl_3$): δ 61.9, 76.4, 110.3, 112.5, 127.3, 127.4, 128.7, 140.9, 143.4, 144.6, 164.6. Anal. calcd for $C_{13}H_{13}NO_3$ (231.3): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.21; H, 5.43.

4.5.2. (*Z*)-1-(2-Furyl)-2-hydroxyethan-1-one *O*-benzyloxime, (*Z*)-5. Viscous oil, ^{1}H NMR ($CDCl_3$): δ 3.55 (br.s, 1H), 4.97 (br.s, 2H), 5.47 (s, 2H), 6.49 (m, 1H), 7.47–7.81 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 62.3, 76.3, 112.4, 116.2, 127.5, 128.6, 130.1, 140.5, 142.9, 144.7, 165.4. Anal. calcd for $C_{13}H_{13}NO_3$ (231.3): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.31; H, 5.37.

4.5.3. (*E*)-Ethyl 2-[(benzyloxy)imino]-2-(2-furyl)acetate, (*E*)-7. Viscous oil, ^{1}H NMR ($CDCl_3$): δ 1.43 (t, $J=7.1$, 3H), 4.43 (q, $J=7.1$, 2H), 5.37 (s, 2H), 6.50 (dd, $J=1.6$, 3.3, 1H), 7.29 (d, $J=3.3$, 1H), 7.32–7.43 (m, 5H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.6, 62.3, 78.6, 112.2, 119.8, 128.3, 128.6, 128.7, 128.9, 136.7, 140.8, 143.8, 162.5. Anal. calcd for $C_{15}H_{15}NO_4$ (273.2): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.72; H, 5.66.

4.5.4. (*Z*)-Ethyl 2-[(benzyloxy)imino]-2-(2-furyl)acetate, (*Z*)-7. Viscous oil, ^{1}H NMR ($CDCl_3$): δ 1.25 (t, $J=7.1$, 3H), 4.30 (q, $J=7.1$, 2H), 5.16 (s, 2H), 6.34 (dd, $J=1.6$, 3.1, 1H), 6.53 (d, $J=3.1$, 1H), 7.18–7.29 (m, 5H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.5, 62.2, 77.6, 112.1, 112.7, 128.2, 128.3, 128.4, 128.7, 137.4, 144.9, 145.6, 161.8. Anal. calcd for $C_{15}H_{15}NO_4$ (273.2): C, 65.92; H, 5.53; N, 5.13. Found: C, 66.18; H, 5.69.

4.6. Reduction of oxime ethers

A solution of borane (20 mmol) in THF (20 ml) was added under argon dropwise to a solution of amine (10 mmol) in THF (10 ml) at −20°C. The resulting mixture was allowed to warm to −5°C and stirring was continued at this temperature for 16 h. A solution of the oxime ether (8 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred at 30°C for 48 h (monitored by TLC) and was decomposed by the slow addition of 2 M aqueous HCl. After separation of the layers the organic phase was washed with brine, dried over $MgSO_4$ and concentrated to give the crude amine. Further purification of the crude product was achieved by flash column chromatography (1:1:1 EtOAc:hexane:MeOH) to give the desired compounds as follows.

4.6.1. 2-Amino-2-(2-furyl)ethan-1-ol, (*R*)-1 and (*S*)-1.[5] Viscous oils, $[\alpha]_D^{20}=+7.8$ (*c* 0.8, MeOH) for (*R*)-**1**; $[\alpha]_D^{20}=-7.4$ (*c* 0.8, MeOH) for (*S*)-**1**; ^{1}H NMR ($CDCl_3$): δ 2.79 (br.s, 3H), 3.55 (dd, $J=8.0$, 10.6, 1H), 3.71 (dd, $J=4.0$, 10.6, 1H), 3.94 (dd, $J=4.0$, 8.0, 1H), 6.09 (d, $J=3.1$, 1H), 6.21 (dd, $J=1.6$, 3.1, 1H), 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 51.7, 65.3, 105.7, 110.6, 141.9, 156.2.

4.7. Ozonolysis

Ozone gas was passed through a solution of amine (5 mmol) in DCM (50 mL) at −78°C. After 30 min the reaction was stopped and N_2 was passed through the mixture to remove the excess ozone. Evaporation of the solvent gave the product as a white powder.

4.7.1. (*R*)-Serine. $[\alpha]_D^{20}=+1.4$ (*c* 1, 1N HCl) (commercially available compound), mp 217–219°C.

4.7.2. (*S*)-Serine. $[\alpha]_D^{20}=-1.3$ (*c* 1, 1N HCl) (commercially available compound), mp 221–223°C.

4.8. Synthesis of *rac*-1

To a solution of oxime ether (5 mmol) in abs. THF (25 mL) was added $BH_3{\cdot}SMe_2$ (12 mmol) dropwise over 1 h. Then the mixture was stirred for 36 h at rt and hydrolyzed with 2N aqueous HCl. After separation of the layers the organic phase was washed with brine, dried over $MgSO_4$ and concentrated to give the crude amine. Further purification of the crude product was achieved by flash column chromatography (1:1:1 EtOAc:hexane:MeOH) to give the racemic amine.

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