Enantioselective Preparation of a Novel Chiral 1,2-Diamine

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Received 6 February 2001; revised 21 February 2001

Abstract: A short enantioselective preparation of (1S,2S)-trans-1,2-diamino-3-cyclohexene using a double [3,3]-sigmatropic rearrangement of an allylic bis(imidate) is described (Overman rearrangement). The starting chiral diol is conveniently obtained by enzymatic resolution. Chiral diamines are an important class of ligands for asymmetric catalysis. Their preparation is always a challenge and only a few practical solutions have been reported. Recently, we have developed a new method based on a [2,3]-sigmatropic rearrangement starting from allylic alcohols of type 1 and allowing the preparation of a chiral phosphate of type 2 after reduction (Scheme 1). This reaction proceeds with complete transfer of the chirality from the alcohol to the phosphate. Herein, we wish to report a related double Overman-rearrangement allowing the practical preparation of (1S,2S)-1,2-diamino-3-cyclohexene using a double [3,3]-sigmatropic rearrangement of an allylic bis(imidate) (Overman rearrangement). The starting chiral diol is conveniently obtained by enzymatic resolution.

Key words: 1,2-diamines, enzymes, rearrangements, chiral resolution

Chiral diamines are an important class of ligands for asymmetric catalysis. Their preparation is always a challenge and only a few practical solutions have been reported. Recently, we have developed a new method based on a [2,3]-sigmatropic rearrangement starting from allylic alcohols of type 1 and allowing the preparation of a chiral phosphate of type 2 after reduction (Scheme 1). This reaction proceeds with complete transfer of the chirality from the alcohol to the phosphate. Herein, we wish to report a related double Overman-rearrangement allowing the practical preparation of (1S,2S)-1,2-diamino-3-cyclohexene (4) in 9% ee starting from (1R,2R)-1,2-cyclohex-3-enediol (3) (Scheme 1).

Scheme 1

The starting 1,2-diol 3 can be prepared in optically pure form using two methods. In the first approach, we have used an asymmetric reduction of 2-bromo-2-cyclohexen-1-one (5) as a key step for introducing the chirality. The CBS-reduction of 5 (BH$_3$SMe$_2$, Me-CBS (15 mol%), THF, −10 °C, 1 hour) provided the chiral allylic alcohol (R)-6 in 96% yield and 96–97% ee. The debromination of 6 with tert-BuLi (3.2 equivalents, −78 °C, 1 hour) and epoxidation with m-chloroperbenzoic acid (m-CPBA; 1.4 equivalents) in CH$_2$Cl$_2$ at 20 °C for 6 hours furnished a 70:30 mixture of the two diastereoisomeric epoxides 7a and 7b as already described in the literature.

Scheme 2

These two epoxides were readily separated by chromatography (pentane-ether) and the major epoxide 7a was isolated in 50% overall yield from the allylic alcohol 6. By treatment with lithium diethylamide (3.5 equivalents) in a mixture of ether and hexane at reflux for 17 hours, the epoxide 7a underwent a smooth ring opening, affording the selectively protected diol 8, which was directly used in the next step. After desilylation with tetrabutylammonium fluoride (TBAF) in THF and recrystallization in ethyl acetate, the optically pure diol (1R,2R)-3 was obtained in 60% yield and 99% ee (Scheme 2).

Alternatively, diol 3 can be prepared using enzymatic resolution. The racemic diacetate 9 was obtained in three steps from cyclohexadiene in 49% overall yield (Scheme 3). By using Pseudomonas Fluorescens Lipase (PFL) in a buffered aqueous solution at pH 7, a selective hydrolysis of the racemic diacetate 9 occurred leading to
a mixture of the two \((R,R)\)-monoaacetate 10a and 10b (45% yield, 94% ee) as well as unreacted \((S,S)\)-diacetate 9 (43% yield; 97% ee). The monoaacetates \((R,R)\)-10 and the unreacted \((S,S)\)-9 were readily separated by chromatography (using pentane-ether mixtures; see experimental section). After saponification of 9 and 10 with sodium methoxide in methanol and recrystallization in ethyl acetate, the two chiral diols (1S,2S)-3 and (1R,2R)-3 were obtained in > 9% ee (31% yield) and 98.6% ee (29% yield), respectively as determined by HPLC analysis using a Chiralsil-Dex CP column.

In summary, we have reported an enantioselective synthesis to a new chiral diamine. The evaluation of \((S,S)\)-4 or simple derivatives of it as ligands for asymmetric metal catalysis is currently underway in our laboratories.

Mps were measured on a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded on a Bruker ARX 200 or ACX 300 instruments. IR spectra were recorded on a Nicolet 510 or a Perkin-Elmer 281 spectrometer. Electron impact (EI) mass spectra were recorded on a Varian MAT CH 7A. All reagents were of commercial quality. *Pseudomonas Fluorescens* Lipase was purchased from FLUKA.

**Optically Pure trans-1,2-Dihydroxy-3-cyclohexene (3)**

**Method A: Enzymatic Resolution**

**Racemic trans-1,2-Diacetoxy-3-cyclohexene (9)**

A solution of bromine (42 g, 14.5 mL) in *CHCl₃* (150 mL) was added dropwise to a solution of cyclohexadiene (27 mL, 280 mmol) in *CHCl₃* (200 mL) at 0 °C. After evaporation of the solvent, the residue was filtered through a short plug of silica with pentane. Following the removal of pentane, the residual oil was treated with 2 N KOH (400 mL) and vigorously stirred for 4 days. After neutralization with concd HCl and solid NaHCO₃, to set the pH to 7, all the volatiles were removed in vacuum. The resulting solid was extracted with *CH₄Cl₂* and evaporated. Without any further purification, the diol was dissolved in pyridine (300 mL) and treated with acetic anhydride (51 mL, 540 mmol). After stirring at r.t. overnight, the solution was poured onto ice/water (600 g), extracted with Et₂O and dried (MgSO₄). Removal of the solvent and distillation at reduced pressure gave 25.4 g (49% yield) of the racemic diacetae 9 as a colorless oil. Bp 126–129 °C (9 mbar).

\begin{align*}
\text{Bp} & 126–129 \text{ °C (9 mbar).} \\
\text{H NMR} & (300 MHz, CDCl₃): \delta = 5.90 (m, 1H, H-4), 5.58 (dd, 1H, J = 9.9, 2.1 Hz, H-3), 5.38 (m, 1H), 5.03 (m, 1H), 2.22 (m, 2H, CH₂), 2.08 (s, 6H, CH₂), 1.99 (m, 1H, CH₂), 1.83 (m, 1H, CH₂).
\end{align*}
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**Method B**

(R)-2-Bromo-2-cyclohexen-1-ol (6)

2-Bromo-2-cyclohexen-1-one (5) was prepared according to the method of Kowalski.6 The CBS-reduction of the enone 5 was performed as follows: A solution of the enone 5 (25 g, 143 mmol) in dry THF (150 mL) and a solution of BH₃·SMe₂ (8.6 mL, 86 mmol, 0.6 equiv) in dry THF (100 mL) were simultaneously added dropwise within 1 h to a solution of Me₂CBS catalyst (6.0 g, 21 mmol, 0.15 equiv) in dry THF at −10°C to −15°C. After the addition, the reaction mixture was stirred at −15°C for 45 min and quenched with MeOH (50 mL). After evaporating THF and MeOH under vacuum, the residue was dissolved in Et₂O and washed with brine. The organic layer was dried (MgSO₄) and Et₂O was evaporated. The crude yellow oil obtained was purified by chromatography on silica gel (Et₂O-pentane, 1:1). (R)-2-Bromo-2-cyclohexen-1-ol (6) was isolated as a colorless liquid (23.9 g, 95% yield) with an optical purity of 96%−98% ee.

**IR (KBr):** ν = 3371, 1641 cm⁻¹.

[α]D²⁰ +22.4 (c 1.8, CHCl₃) (99.5% ee) for the (1S,2S) enantiomer.

1H NMR (200 MHz, CDCl₃); δ = 6.23−6.10 (m, 1H, H-3), 4.25−4.18 (m, 1H, H-1), 3.11 (br s, 1H, OH), 2.12−1.65 (m, 6H).

13C NMR (50 MHz, CDCl₃); δ = 135.1, 128.3, 34.6, 34.0, 20.1

MS (El): m/z (%) = 176.0 (1) [M⁺], 97.0 (100) [M⁻−Br], 79.0 (23), 41.0 (50).


Enantioemic excess was determined by HPLC with a Chiracel OJ column. Flow rate: 0.7 mL min⁻¹. Temp: 20°C. Eluent: n-heptane-propan-2-ol (99.5:0.5). Retention times of (R)- and (S)-enantomers are 31.39 min and 36.94 min, respectively.

**1(R,2R)-1,2-Dihydroxy-3-cyclohexene (3)**

A solution of tert-BuLi in pentane (1.2 M, 350 mL, 420.0 mmol, 3.2 equiv) was added dropwise to a solution of (R)-2-bromo-2-cyclohexen-1-ol (6, 23.0 g, 130 mmol) in Et₂O (200 mL) at −78°C. After the addition, the mixture was stirred for further 10 min at −78°C and slowly warmed up to −20°C. Quenching was carefully carried out by addition sat. NaHCO₃ (50 mL) and warming up to r.t. After drying the organic layer (MgSO₄), the solvents were evaporated under vacuum. The crude 2-cyclohexenol (13.5 g) and imidazole (19.5 g, 286 mmol, 2.2 equiv) were dissolved in DMF (100 mL) and TBDPS-Cl (36.6 mL, 143 mmol, 1.1 equiv) was added dropwise at r.t. After stirring overnight, the crude reaction mixture was poured on water (200 mL) and extracted three times with Et₂O (200 mL). The organic layers were washed successively with 10% HCl, H₂O, and brine. After drying (MgSO₄), the solvents were evaporated. The crude protected 2-cyclohexenol was dissolved in CH₂Cl₂ (500 mL) and cooled to 0°C. Solid m-CBPA moistened with 30% H₂O (45 g, 180 mmol, 1.4 equiv) was added over 15 min. The reaction mixture was allowed to warm up to r.t. and was stirred overnight. After filtration of the white precipitate of m-CBPA, the organic layer was washed successively with sat. NaHCO₃, sat. NaHCO₃, and brine. After drying (MgSO₄), the crude reaction mixture of epoxides 7a and 7b (ratio 7:3) was purified by chromatography on silica gel (pentane-Et₂O, 99:1 to 95:5). The epoxide 7a (23.0 g, 50% yield from 6) was isolated as a colorless oil, which was used without any further purification in the following step.

A solution of Et₂NLi was prepared by adding BuLi (1.55 M in hexanes, 150 mL, 232 mmol) to a solution of Et₂NH (28.0 mL, 275 mmol) in Et₂O (100 mL) at 0°C. This solution of Et₂NLi was added to a solution of epoxide 7a (23.0 g, 65.0 mmol) in Et₂O (150 mL) at r.t. and the reaction mixture was heated to reflux for 17 h. After cooling to 0°C, the reaction was carefully quenched with H₂O (30 mL). The organic phase was washed successively with 10% HCl, sat. NaHCO₃, and brine. After drying (MgSO₄), the crude reaction mixture was dissolved in THF (30 mL) and TBAF (1 M solution in THF, 65 mL, 1 equiv) was added at r.t. After stirring for 14 h, THF was evaporated and the crude mixture was directly purified by chromatography on silica gel (Et₂O-MeOH, 100:0 to 96:4). After recrystallization from Et₂OAc, the diol (1R,2R)-3 (4.45 g, 60% yield from 7a) was obtained in optical pure form (> 9% ee) as a colorless crystalline solid.

**IR (KBr):** ν = 3306 cm⁻¹.

[α]D²⁰ +22.4 (c 1.21, CHCl₃) (99.5% ee) for the (1S,2S) enantiomer.

1H NMR (300 MHz, CDCl₃); δ = 5.54 (m, 1H, H-3), 4.12 (m, 1H, H-1), 3.59 (m, 1H, H-3), 3.11 (br s, 1H, OH), 2.12−1.65 (m, 6H).

13C NMR (75 MHz, CDCl₃); δ = 135.1, 128.3, 34.6, 34.0, 20.1

MS (El): m/z (%) = 114.1 (0.32) [M⁺], 96.2 (4.6), 70.3 (100), 69.2 (23.4).

Synthesis 2001, No. 6, 863−866

ISSN 0039-7881 © Thieme Stuttgart · New York

(1S,2S)-N,N'-Bis(trichloroacetyl)-trans-1,2-diamino-3-cyclohexene (12)

NaH (200 mg, 60% dispersion in mineral oil) was added in portions to a solution of (1S,2S)-1,2-dihydroxy-3-cyclohexene 3 (2.74 g, 24.0 mmol) in dry THF (20 mL) under Ar. The resulting mixture was stirred for 1 h, then cooled in an ice/water bath and a solution of trichloroacetonitrile (6.93 g, 4.8 mL, 48 mmol) in dry THF (20 mL) was added dropwise within 30 min. The resulting brown solution was stirred at r.t. for 3 h. After evaporation of the volatile components in vacuum, the residue was extracted three times with pentane (30 mL) and the combined extracts were evaporated in vacuum to give the colorless crystalline diimide 11, which was then dissolved in xylene (30 mL) and refluxed for 6 h. After cooling to 0 °C, the resulting white precipitate was filtered and washed with pentane to give the optically pure bis(trichloroacetamide) 12 (5.40 g, 56% yield) as fine colorless needles.

Mp >310 °C (decomposition).

IR (KBr): ν = 2912.5, 1604.9, 1524.0 cm⁻¹.

Anal. Calcd for C_10H_10N_2O_2Cl_6 (402.92): C, 29.81; H, 2.50; N, 6.96. Found: C, 29.55; H, 2.51; N, 6.74.

(1S,2S)-trans-1,2-Diamino-3-cyclohexene Dihydrochloride (4)

A slurry of bis(trichloroacetamide) 12 (1.72 g, 4.2 mmol) in 6 M NaOH (10 mL) was stirred at 85 °C for 6 h leading to a yellow solution. After cooling to r.t., the reaction mixture was extracted with dioxane (3 × 30 mL) and the combined organic extracts were dried (MgSO₄). Evaporation of the solvent gave a yellow oil (550 mg), which was dissolved in a MeOH-benzene mixture (1:1, 20 mL) and treated with concd HCl (1 mL). Evaporation of the solvents and repeating the previous treatment gave a solid that was washed with EtOH. After drying, the dihydrochloride 4 was obtained as a white solid (510 mg, 65% yield).

Mp >310 °C (decomposition).

IR (KBr): ν = 3304, 1686.8, 1528.1 cm⁻¹.

(1S,2S)-trans-1,2-Dihydroxy-3-cyclohexene 3 (2.74 g, 24.0 mmol) in dry THF (20 mL) under Ar. The resulting mixture was stirred for 1 h, then cooled in an ice/water bath and a solution of trichloroacetonitrile (6.93 g, 4.8 mL, 48 mmol) in dry THF (20 mL) was added dropwise within 30 min. The resulting brown solution was stirred at r.t. for 3 h. After evaporation of the volatile components in vacuum, the residue was extracted three times with pentane (30 mL) and the combined extracts were evaporated in vacuum to give the colorless crystalline diimide 11, which was then dissolved in xylene (30 mL) and refluxed for 6 h. After cooling to 0 °C, the resulting white precipitate was filtered and washed with pentane to give the optically pure bis(trichloroacetamide) 12 (5.40 g, 56% yield) as fine colorless needles.

Mp >310 °C (decomposition).

Acknowledgement

We thank the Deutsche Forschungsgemeinschaft (Leibniz program), the Institut de Recherches Servier (Suresnes, France), the Humboldt Foundation for a fellowship to A. K. and PPG-SIPSY for financial support. We also thank the BASF AG (Ludwigshafen), Chemetall GmbH (Frankfurt) and Degussa-Hüls AG (Hanau) for the generous gift of chemicals.

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