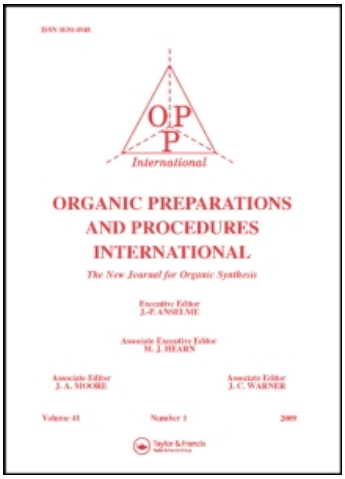

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A CONVENIENT SYNTHESIS OF *cis*-(1R)-N-BENZYL-(2S)-(HYDROXYMETHYL)CYCLOHEXYLAMINE

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A CONVENIENT SYNTHESIS OF *cis*-(1R)-N-BENZYL-(2S)-(HYDROXYMETHYL)CYCLOHEXYLAMINE

Submitted by (05/26/92) B. Vanderplas*, C. W. Murtiashaw, T. Sinay, and F. J. Urban

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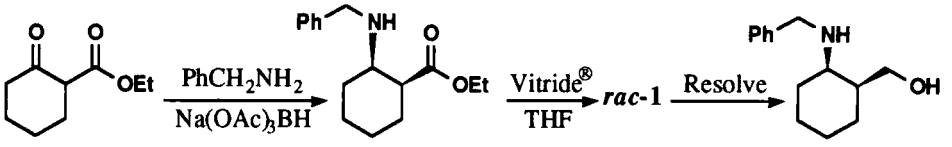
cis-(1R)-N-Benzyl-(2S)-(hydroxymethyl)cyclohexylamine (**1**), first reported in 1979,[1] has been utilized both as a resolving agent[1,2] and as the precursor to an optically active phase transfer catalyst.[3] Compound **1** was found to be particularly effective in recent attempts to resolve an important pharmaceutical intermediate. Unfortunately, large amounts of **1** are difficult to obtain either commercially or by published procedures. We have accordingly developed the following three-step route to **1**.



Beginning with commercially available ethyl 2-cyclohexanonecarboxylate **2**, reductive amination with benzylamine/sodium triacetoxyborohydride provided the racemic amino ester (***rac*-3**) with exclusive *cis*-orientation (within NMR detection limits). Reduction of the ester with Vitride®,[4] followed by resolution with (+)-mandelic acid gave the desired optically active amino alcohol **1** in 55% overall yield (based on available enantiomer). Since the absolute configuration of **1** was not clear from the earlier literature, a single crystal X-ray analysis of its dibenzoyl-L-tartaric acid salt was carried out and revealed **1** to be the *cis* -(1R,2S)-diastereomer.

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used as received. Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR were obtained on a Bruker AM-250 spectrometer. IR spectra were recorded with a Perkin Elmer Model 1620 FTIR spectrophotometer. Mass spectra were obtained with a Hewlett-Packard 5890 GC (HP-1 12m capillary column) in tandem with a Hewlett Packard Model 5971A Mass Selective Detector. X-ray data were collected on a Nicolet R3m/μ diffractometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

(±)-*cis*-N-Benzyl-2-(carboethoxy)cyclohexylamine (*rac*-3).- In a 5 L flask, glacial HOAc (677 mL, 11.8 mol) was added slowly over a period of 2 hrs to a mixture of $NaBH_4$ (145 g, 3.80 mol) in CH_2Cl_2 (2.2 L) The resulting thick slurry was mechanically stirred 18 hrs under N_2, then slowly added *via* positive N_2 pressure to a solution of ethyl 2-cyclohexanonecarboxylate (**2**) (262 g, 1.54 mol), benzy-

lamine (165 g, 1.54 mol), and glacial HOAc (91 mL, 1.59 mol) in CH_2Cl_2 (1.6L). After stirring the thick slurry for 18 hrs, the reaction was quenched by the careful addition of H_2O (1.6L). The pH was adjusted to 10 with 25% aq. NaOH (1.3L) and the layers were separated. The CH_2Cl_2 layer was washed once with H_2O (1L), dried with $MgSO_4$, and concentrated to yield ***rac*-3** as a yellow oil: 397 g (99%); ^1H NMR ($CDCl_3$): δ 7.38-7.13 (m, 5H), 4.22-4.02 (m, 2H), 3.79 (ab q, 2H), 3.06-2.94 (m, 1H), 2.75-2.62 (m, 1H), 2.08-1.25 (m, 9H), 1.23 (apparent t, 3H); ^{13}C NMR ($CDCl_3$): δ 174.6, 140.8, 128.3, 128.1, 126.8, 60.0, 54.5, 51.0, 45.8, 28.5, 25.0, 23.9, 21.8, 14.3; FT-IR (neat): 3335, 2978, 2932, 2855, 1726,1452,1373, 1308,1177, 1127, 1038 cm^{-1}; MS: 261 (M^+), 218, 146, 106, 91 (base).

A small sample was purified by flash chromatography (3:1 Hexanes:EtOAc) for combustion analysis.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.42; H, 8.76; N, 5.41

(±)-*cis*-N-Benzyl-2-(hydroxymethyl)cyclohexylamine (*rac*-1).- 70% Vitride® (1.28 L) in THF (2.6 L) was cooled to 10°. To this was added ***rac*-3** (395 g, 1.51 mol) dissolved in THF (800 mL), maintaining a temperature of <20°. The resulting yellow solution was stirred for 2 hrs at 20°, then quenched by the slow addition of EtOAc (500 mL) at 10°. After stirring for 1hr, 1N NaOH (800 mL), followed by H_2O (1 L), was added. The aqueous phase was removed and the organic phase was washed once with brine and concentrated under reduced pressure to a volume of one liter. Water (2.5L) was added and the volume was concentrated to 2.5 L. The oily mixture was cooled to 20°, seeded, stirred for 2 hrs at ambient temperature, and then collected. The solid was washed with water to yield 294.8 g (90%) of ***rac*-1**, mp. 62-65°. ^1H NMR ($CDCl_3$): δ 7.40-7.20 (m, 5H), 4.10-3.52 (m, 6H), 3.04-2.93 (m, 2.93), 2.02-1.78 (m, 2H), 1.75-1.26 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 139.6, 128.6, 128.3, 127.3, 66.4, 58.6, 51.7, 39.0, 27.8, 25.9, 23.4, 22.6; FTIR (CH_2Cl_2): 3245 (br), 3051, 2930, 2856, 1452, 1265, 1093 cm^{-1}; MS: 219 (M^+), 176, 146, 91 (base).

A small sample was purified by flash chromatography (2:1 EtOAc:Hexanes) for combustion analysis, mp. 65-67° (softened 62°).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65 N, 6.39. Found: C, 76.75; H, 9.73; N, 6.43

cis-(1R)-N-Benzyl-(2S)-(hydroxymethyl)cyclohexylamine (1).- Racemic amino alcohol (***rac*-1**) (200 g, 0.912 mol) and (+)-mandelic acid (140 g, 0.919 mol) were heated in THF (3.4 L) and MeOH (0.2 L) to 50°. The resulting hazy solution was allowed to cool to 25°, and the precipitated solids were filtered and washed with THF (100 mL) to yield 169.4 g of the mandelate salt as a white fluffy solid (65% based on available enantiomer): $[\alpha]_D^{22}$ = +39.9° (c = 1, MeOH). The mandelate salt (110.4 g, 0.297 mol) was dissolved in H_2O (1.66 L) and the pH was adjusted to 11.5 with 25% aq. NaOH. The precipitated solid was stirred for 2 hrs, collected and washed with H_2O to yield: 61.0 g (61.2% from racemic free amine, based on available enantiomer) of the title compound **1**, mp. 66.5-68°, lit.[3] 68-69°; $[\alpha]_D^{22}$ = -23.2° (c = 1, MeOH), lit.[3] $[\alpha]_D^{24}$ = -40.6° (c =1, Et_2O); ^1H and ^{13}C NMR identical to ***rac*-1**; Optical purity: 96% ee as measured by chiral HPLC (Chiralcel OD column, 90/10 hexanes/2-propanol, 2 mL/min., 230 nm).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65 N, 6.39. Found: C, 76.76; H, 9.47; N, 6.39

A sample was crystallized from 2-propanol as its dibenzoyl-L-tartaric acid salt, from which single

crystal X-ray analysis determined the absolute configuration to be *cis*-(1R,2S).

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4. Lithium aluminum hydride has also been used with equal success.

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STUDY IN CROSSOVER FRIES MIGRATION

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The Fries rearrangement may proceed *via* an intramolecular,[1] intermolecular[2] or partially inter- and intramolecular mechanism.[3] Crossover experiments support multiple mechanistic pathways.[4] The acetyl group migrates to *ortho* and *para* positions, while the benzoyl group moves predominantly to the *para* position.[5] It is difficult to prepare 2-benzoyl-1-napthanol[6] and 2-acetyl- and 2-benzoyl-1,5-dihydroxynapthalene. The present communication describes suitable conditions which give crossover products, exclusively. We have successfully synthesized 2-benzoyl-1-napthanol- and 2-acetyl-1,5-dihydroxynaphthalene in less time and good yields. Aromatic esters such as phenyl benzoate do not undergo rearrangements with BF_3•etherate; however, when an active phenolic compound such as phenol, hydroquinone, resorcinol, phloroglucinol, 1-naphthol, 2-naphthol and 1,5-dihydroxynaphthalene is added, the acetyl or benzoyl group migrates from the corresponding esters to the more active aromatic *ortho* position of the phenolic compound to give the corresponding crossover products.