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New 1,3-amino alcohols derived from ketopinic acid and their application in catalytic enantioselective reduction of prochiral ketones

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Abstract

New 1,3-amino alcohols, (1*S*,2*S*)- and (1*S*,2*R*)-1-hydroxylmethyl-2-amino-7,7-dimethyl bicyclo[2,2,1]heptane (*endo*-**4** and *exo*-**4**), were prepared from ketopinic acid via oximation and reduction. The enantioselective borane reduction of prochiral ketones catalyzed by the borane complex of *exo*-**4** was examined.

1. Introduction

Chiral amino alcohols, usually prepared from natural homochiral amino acids, are important ligands in asymmetric synthesis including the enantioselective catalytic borane reduction of prochiral ketones,[1–5] enantioselective addition of dialkylzinc,[6,7] asymmetric hydrogen transfer from alcohols to ketones[8,9] and other asymmetric reactions.[10,11] From an economic standpoint, it is desirable to develop new chiral ligands from inexpensive materials and examine their application in asymmetric synthesis. Our study of the synthesis of new amino alcohols involved the use of ketopinic acid which was easily derived from camphor. In this paper, we wish to report the synthesis of new 1,3-amino alcohols, (1*S*,2*S*)- and (1*S*,2*R*)-1-hydroxylmethyl-2-amino-7,7-dimethyl bicyclo[2,2,1]heptane *endo*-**4** and *exo*-**4** and their application in the catalytic enantioselective reduction of alkyl aryl ketones.

2. Results and discussion

The synthetic route for compound **4** is summarized in Scheme 1. The reaction of ketopinic acid with thionyl chloride and methanol produced the methyl ester of **1** in an almost quantitative yield. The ester of

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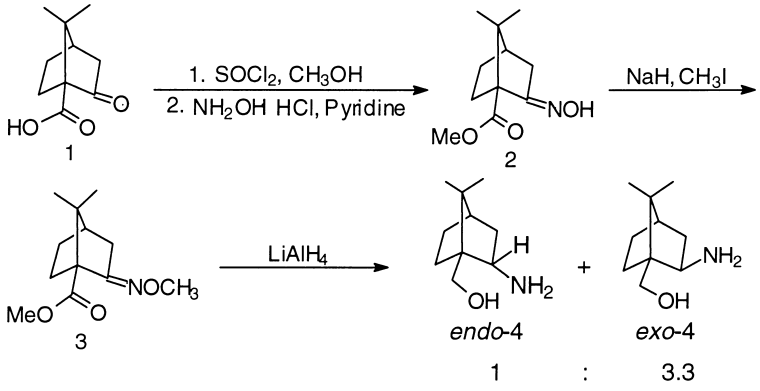
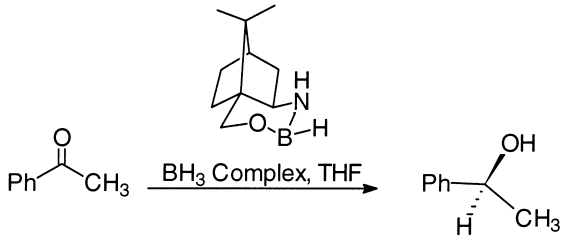
1 was oximated to give methyl ketopinate oxime **2** and the latter reacted with CH_3I to give an intermediate product **3** which was reduced with $LiAlH_4$ to give amino alcohol **4** in an overall yield of about 50%.



Scheme 1.

An oxazaborolidine catalyst was prepared by treating *exo*-**4** with a borane complex according to a procedure published by Itsuno et al.[1] and was used in situ for the homogenous catalytic reduction of prochiral ketones.



The results of the catalytic reduction of acetophenone are listed in Table 1. It was quite clear from Table 1 that the enantiomeric excess (e.e.) of the resulting alcohol was significantly influenced by the

Table 1
The enantioselective reduction of acetophenone with borane catalyzed by oxazaborolidine[a,b,c]

Entry	Molar ratio of 1 to substrate(%)	Borane complex used	Temperature(°C)	E.e.(%) of product
1	3	BH_3.THF	50	49
2	5	BH_3.THF	50	66
3	10	BH_3.THF	0	15
4	10	BH_3.THF	10	68
5	10	BH_3.THF	20	76
6	10	BH_3.THF	30	86
7	10	BH_3.THF	50	87
8	5	BH_3.Me_2S	50	63
9	10	BH_3.Me_2S	30	88
10	10	BH_3.Me_2S	50	89
11	20	BH_3.Me_2S	50	91

a) The e.e. values were determined by chiral GLC analysis with a Chrompack Chirasil-Dex CB column. b) all products were of the *S* configuration as determined by comparison with authentic samples. c) The chemical yields were 90~100%.

Table 2
The enantioselective catalytic reduction of prochiral ketones with borane[a]

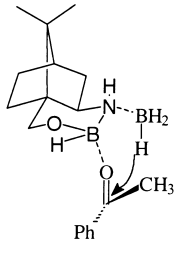
Entry	Ketones	E.e.%	Configuration
1	ethyl phenyl ketone	67[b]	*S*
2	ω-bromo-acetophenone	67[c]	*R*
3	*p*-chloro-acetophenone	73[c]	*S*
4	acetophenone	86	*S*

a) The chemical yields were 80~90%. b) The e.e. values were determined by HPLC analyses with a Daicel OD column and the configurations of the products were determined by comparison with literature values. c) The e.e. values were determined by GLC analyses with a Chrompack Chirasil-Dex CB column.

reaction temperature. (Entry 3 and 7: the e.e. changed from 15% to 87% when the temperature was increased from 0°C to 50°C.) These results are consistent with the results reported by Corey, et al.[2,13,14]

The molar ratio of the amino alcohol to the substrate is also an important factor influencing the enantioselectivity of the reaction. The e.e. value increased with the increase of catalyst concentration and the optimum molar ratio of *exo*-**4** to the substrate was about 20%. Two different types of borane complexes, $BH_3 \cdot THF$ and $BH_3 \cdot Me_2S$, have been tested and have been found to give similar results.

It should be noted that using ligands prepared from natural amino acids in the reduction of acetophenone gives (*R*)-*sec*-phenethyl alcohol, while the *S*-enantiomer is obtained by using *exo*-**4** as a catalyst. Since both enantiomers are often needed in asymmetric synthesis, the use of *exo*-**4** complements the use of the standard amino acid-derived amino alcohol as a chiral ligand in this class of reaction. A possible transition state of the key reaction intermediate is shown below. The attack of the *Re*-face of the ketone by the hydride leads to the *S* alcohol.



Other typical prochiral aromatic ketones were tested in the enantioselective borane reduction using *exo*-**4** as a chiral ligand (Table 2).

3. Experimental

Unless otherwise indicated, all reactions were carried out under an N_2 atmosphere. Melting points were measured using an electrothermal 9100 apparatus in capillaries and the data were uncorrected. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter at 20°C. NMR spectra were recorded on a Bruker DPX-400 spectrometer. Mass analyses were performed on a Finnigan model mat 95 ST mass spectrometer. HPLC analyses were performed using a Hewlett–Packard model HP 1050 LC interfaced to an HP 1050 series computer workstation. GC analyses were performed using a Hewlett–Packard HP 4890A apparatus. The ketopinic acid was prepared from camphorsulfonic chloride according to a procedure in the literature[12] and the other chemicals were purchased from Acros or Aldrich and were used as received.

3.1. Preparation of (1S)-7,7-dimethyl-2-oximino-bicyclo[2,2,1]heptane-1-carboxylic acid methyl ester **2**

To a solution of 1.85 g ketopinic acid (10 mmol) in 20 ml methanol was added dropwise 1.2 g thionyl chloride (10 mmol) at 0°C. The mixture was stirred at the same temperature for 1 h and then at room temperature for 12 h. The methanol was removed under reduced pressure and benzene (2×30 ml) was added to distill off the residual thionyl chloride. The crude product was dissolved in 2 ml pyridine and 10 ml absolute anhydrous ethanol and into the solution were added hydroxylamine hydrochloric acid salt (1.4 g, 20 mmol) and sodium acetate (0.8 g, 10 mmol). The reaction mixture was heated at reflux temperature for 3 h. After the solvents were removed in vacuo, 8 ml water and 20 ml diethyl ether were added to the residue and the mixture was shaken vigorously to extract the product. The organic layer was separated and the water layer was extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate, 1:0.5, v/v) to afford a colorless solid (1.94 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.28–1.33 (m, 1H), 1.73–1.80 (m, 1H), 1.91–1.95 (m, 2H), 2.03–2.07 (d, J=16.4, 1H), 2.34–2.41 (m, 1H), 2.67 (s, 1H), 3.75 (s, 3H, CH_3).

3.2. (1S)-7,7-Dimethyl-2-(methoximido)-bicyclo[2,2,1]heptane-1-carboxylic acid methyl ester **3**

To a suspension of 0.15 g sodium hydride (6.25 mmol) in 15 ml dry tetrahydrofuran was added a solution of 1.17 g methyl ketopinate oxime **2** (5.5 mmol) in 5 ml dry THF at 0°C. The reaction mixture was stirred at the same temperature for 1 h followed by the addition of 0.86 g CH_3I (6 mmol). The ice bath was removed and the stirring was continued for another 5 h. After removal of the THF under reduced pressure, the residue was extracted with diethyl ether (3×15 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give a light yellow oil which was purified by column chromatography (hexane:ethyl acetate, 1:0.3, v/v, 1.08 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.28–1.29 (m, 1H), 1.71–1.78 (m, 1H), 1.90–1.93 (m, 2H), 2.05–2.09 (d, J=17.5, 1H), 2.36–2.37 (m, 1H), 2.63 (s, 1H), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

3.3. (1S,2S)- and (1S,2R)-1-(Hydroxylmethyl)-2-amino-7,7-dimethyl bicyclo[2,2,1]heptane **4**

A sample of **3** (0.3 g, 1.33 mmol) in 5 ml dry THF was added dropwise to a solution of 0.15 g $LiAlH_4$ and 25 ml dry THF at 0°C. The mixture was stirred at ambient temperature for 3 h and then at reflux temperature for 12 h. Purification by column chromatography (methanol:ethyl acetate, 4:1) gave the amino alcohols *endo*-**4** (0.034 g, 15% yield) and *exo*-**4** (0.11 g, 49% yield). The analytical data for these products are as follows. (1) *endo*-**4**: m.p.=190–192°C; $[\alpha]_D$=39.8 (*c* 0.47, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): 0.73–0.77 (dd, J=4.16, 4.10 Hz, 1H), 0.90 (s, 3H), 0.91 (s, 3H), 1.22–1.29 (m, 1H), 1.55–1.63 (m, 2H), 1.80–1.87 (m, 1H), 2.01–2.07 (m, 1H), 2.29–2.37 (m, 1H), 3.50–3.51 (t, J=1.80 Hz, 1H), 3.60–3.62 (d, J=10.14 Hz, 1H), 3.84–3.87 (d, J=10.19 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): 19.07, 19.99, 23.49, 28.38, 41.47, 46.28, 47.83, 51.27, 56.31, 66.65; MS (ESI): 170 (M+1, 100), 153 (M−16, 4), 135 (M−35, 6). (2) *exo*-**4**: m.p.=199–201°C; $[\alpha]_D$ −53.3 (*c* 0.57, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (s, 3H, CH_3), 1.05–1.07 (m, 2H), 1.18 (s, 3H, CH_3), 1.40–1.42 (m, 1H), 1.58 (m, 1H), 1.69–1.72 (m, 2H), 1.83 (dd, J=8.84, 8.96 Hz, 1H), 3.05–3.08 (dd, J=5.00, 5.00 Hz, 1H), 3.81–3.87 (dd, J=11.60, 11.60 Hz, 2H); ^{13}C NMR (101 MHz, $CHCl_3$): 20.72, 21.74, 26.68, 32.57, 42.70, 46.13, 46.75, 51.49, 59.47, 64.02; MS (ESI): 170 (M+1, 100), 153 (M−16, 10), 135 (M−34, 8); exact mass calcd for $C_{10}H_{20}ON$: 170.1545; found: 170.1547.

3.4. A general procedure for the catalytic reduction of prochiral ketones

Under a nitrogen atmosphere, 16 mg of *exo*-**4** in 2 ml of dry THF was added to 1 ml of 1 M $BH_3 \cdot THF$ solution (1 mmol) at 0°C. The reaction mixture was stirred for 3 h at ambient temperature to form an oxazaborolidine catalyst and then was warmed to 50°C. A solution of acetophenone (1 mmol) in 2 ml dry THF was added dropwise over 50–60 min at the same temperature. After stirring for another hour the reaction mixture was cooled to 0°C and was quenched with 1 ml of 2 M HCl solution. Ethyl acetate (5 ml) was added to extract the product and the organic layer was separated and concentrated in vacuo. Flash chromatography of the material afforded the chiral alcohol. The e.e. value of the product was determined by GC or HPLC analysis.

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