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Synthesis of enantiopure norbornane derivatives. Effect of bridgehead substituent on the π-facial selectivity of the reduction of 2-norbornanones and their oximes

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Abstract

One of the most important features of the synthesis of camphor-derived compounds is the control of the stereochemistry at the C2 position. According to this, reduction of bridgehead-substituted 2-norbornanones **1** and 2-norbornanoximes **3** has been considered by us as a very convenient method for the preparation of different classes of enantiomerically pure 1,2- and 1,3-difunctionalised norbornane derivatives. Factors controlling the stereoselectivity in these reductions, as well as the role played by the nature of the bridgehead functional groups are discussed.

1. Introduction

Enantiomerically pure 1,2- and 1,3-amino alcohols, diols, diamines and related compounds are very important in pharmacological research due to their noticeable biological activities. Furthermore, these substances have been widely used in the asymmetric synthesis of many interesting compounds.[1–7] Since some of the most interesting chiral ligands for asymmetric synthesis are molecules with bicyclic structures,[8–11] it is very convenient to have new series of skeleton isomers of these chiral bicyclic ligands, not only as chiral synthetic tools, but also for the study of the mechanisms of asymmetric reactions.[12–15] For these reasons, the development of new synthetic routes to obtain enantiopure bicyclic compounds, mainly when amino and hydroxy groups are present, is of great interest.

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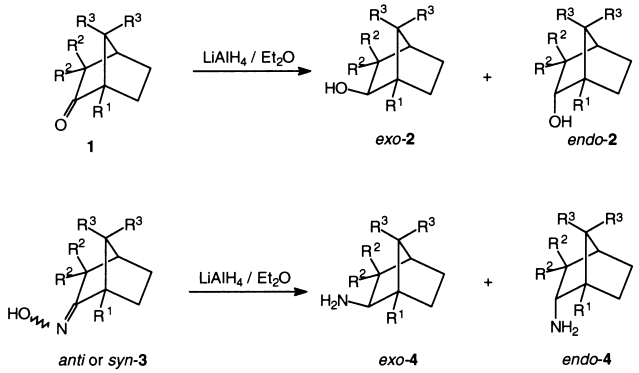
In previous communications we have described the reduction of some bridgehead-substituted 2-norbornanones **1** and 2-norbornanoximes **3** with $LiAlH_4$.[16–21] In the present paper we report new examples of these reductions to yield 2-hydroxynorbornanes **2** and 2-aminonorbornanes **3** (Scheme 1). An explanation of the observed π-facial diastereoselectivity is also given.



	R^1	R^2	R^3
a	H	H	H
b	OTf	H	H
c	OH	H	H
d	CH_3	CH_3	H
e	CH_3	H	CH_3
f	OTf	H	CH_3
g	NH_2	H	CH_3
h	$NHCOCH_3$	H	CH_3
i	NHEt	H	CH_3
j	CO_2CH_3	H	CH_3
k	CN	H	CH_3
l	CH_2OH	H	CH_3
m	OH	H	CH_3
n	CH_2NH_2	H	CH_3
o	H	CH_3	H
p	$OCOCH_3$	CH_3	H
q	OTf	CH_3	H
r	NH_2	CH_3	H
s	$NHCOCH_3$	CH_3	H
t	NHEt	CH_3	H
u	CO_2CH_3	CH_3	H
v	CN	CH_3	H
w	CH_2OH	CH_3	H
x	OH	CH_3	H
y	CH_2NH_2	CH_3	H

Scheme 1. AlH_4Li/ether reduction of 2-norbornanones **1** and 2-nobornanoximes **3**

2. Results and discussion

Both intermediates **1** and **3** are stereospecifically obtained starting from the naturally occurring 1-methyl-2-norbornanones (+)-camphor and (−)-fenchone using synthetic methods developed in our research group.[16–21] The key step of these methods is the preparation of 2-methylidene-1-norbornyl

triflates and 2-methylidene-1-norbornanecarbonitriles via a Wagner–Meerwein rearrangement of the norbornane framework.[22] This methodology allows the enantiospecific synthesis of a wide range of enantiopure bridgehead derivatives such as amides, amines, carboxylic acids, esters, etc., with a C=C double bond (methylidene) located at the C2 position of the norbornane framework. The methylidene unit is a strategic site for the introduction of heteroatomic functions at that position of the norbornane skeleton, through the corresponding 2-norbornanones **1** (obtained by ozonolysis of the methylidene unit)[16–18,20] and oximes **3**.[21]

Table 1
Reduction of ketones **1** and their oximes **3** with $LiAlH_4$ in ether[a)]

Entry	Substrate [Lit.][b)]	Product [Lit.][b)]	Yield (%)[c)]	*exo*/*endo*
1	**1a**	**2a** [23]	100	9/91[d)]
2	**1b** [16]	**2c**	98	30/70[e)]
3	**1b** [16]	**2b**[f)]	87	30/70[e)]
4	**1d**	**2d** [24]	100	90/10[d)]
5	**1e**	**2e** [25]	91	90/10[e)]
6	**1f** [16]	**2m** [17]	89	98/2[d)]
7	**1f** [16]	**2f**[f)] [17]	85	98/2[e)]
8	**3f** [21]	**4m** [20]	88	98/2[e)]
9	**1g** [20]	**2g** [20]	70	98/2[e)]
10	**1h** [20]	**2i** [20]	72	90/10[e)]
11	**1j** [36]	**2l** [26]	93	72/28[d)]
12	**3j**	**4l** [27][28]	72	67/33[d)]
13	**1k** [18]	**2n**	70	95/5[e)]
14	**3k**	**4n**	86	60/40[e)]
15	**3º** [29]	**4º** [29]	72	39/61[d)]
16	**1p** [17]	**2x** [17]	86	2/98[e)]
17	**1q** [16]	**Ring Contraction** [16]	91	—
18	**1q** [16]	**2q**[f)] [16]	75	2/98[e)]
19	**3q** [21]	**4x** [20]	82	2/98[e)]
20	**1r** [20]	**2r** [20]	88	2/98[e)]
21	**1s** [20]	**2t** [20]	88	5/95[e)]
22	**1u** [30]	**2w**	95	2/98[e)]
23	**3u**	**4w**	81	5/95
24	**1v** [18]	**2y**	79	2/98[e)]
25	**3v** [21]	**4y**	74	2/98[e)]

a) The reductions were performed as described in the experimental section, unless otherwise stated.
b) Reference corresponding to a previous compound description.
c) Yield in isolated product.
d) Determined by GLC.
e) Determined by ^{1}H-NMR.
f) The reaction was performed at -70 °C for 15 min.

Reduction of the carbonyl and hydroxyimino groups is carried out by reaction with $LiAlH_4$ in ether for 6 h at 25°C (rt). The reaction gives the expected 2-hydroxynorbornanes **2** or 2-aminonorbornanes **4** in good yields (see Table 1). All substrates having R^2=H or Me and R^3=H undergo *exo* hydride attack giving the corresponding *endo*-**2** or *endo*-**4** substituted products in high diastereomeric excess (d.e.). This result

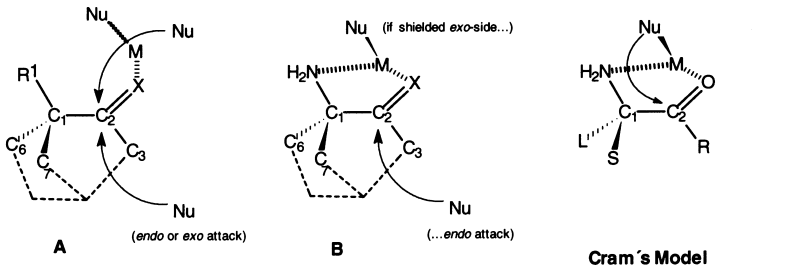


Fig. 1. Hydride reduction models

can be easily explained by both steric approach control and torsional strain theories.[31] With compounds having R^2=H and R^3=Me, the *exo* side is too hindered for the hydride attack due to the presence of a *syn*-7 methyl group. In this case, the steric approach control overrides other factors, and *endo* hydride attack is mainly observed.[31] Since *exo*/*endo* ratios are similar for both ketones **1** and oximes **3**, polar and orbital effects[32] do not seem to play any significant role in the stereochemical course of these reductions, although the reduction rate is higher for the carbonyl than for the hydroxyimino group.[33]

The results obtained for the $LiAlH_4$ reduction of 2-norbornanones **1** and 2-norbornanoximes **3** can be explained assuming an intermolecular hydride attack through the transition state model **A** (Fig. 1). The MMX modelling[34] of this transition state (realised for the case in which X is oxygen) gives a value of 22° for the R1–C1–C2–X torsion angle. The Nu–M–X–C2 torsion angle is not defined and values near 0° are allowed. In the case of bridgehead functional groups (R^1) able to coordinate the metal atom, the intermolecular hydride reduction takes place through the more rigid transition state model **B** (Fig. 1). Model **B** is similar to the one proposed by Cram to explain the high d.e. observed in the nucleophilic addition to α-amino- and α-hydroxy-carbonylic systems, but in Cram's model the attacking group Nu proceeds from the complex itself, via an intramolecular attack[35] (see Fig. 1). In agreement with this, the d.e. obtained in a reaction according to the *loose* model **A** should be lower than that obtained with the *tight* model **B**.[36] This prediction agrees with the experimental results; thus, the d.e.s of the reduction of substrates where R^1=H or Me (**1d**, **1e** and **3o**, entries 4, 5 and 15) are smaller than the d.e.s obtained with substrates having other functional bridgehead groups (see Table 1).

Reductions of methyl ketopinate **1j** and oximes **3j** and **3k** afford surprisingly lower *exo*/*endo* ratios for corresponding alcohol and amines than expected (see entries 11, 12 and 14). On the other hand, ketone **1b** yields a higher proportion of 2-*exo* isomers for alcohols **2c** and **2b** respectively (see entries 2 and 3). These results cannot be attributed to a partial epimerisation,[36] since the *exo*/*endo* ratio is independent of the reaction time. Thus, in the reduction of ketoester **1j** (−78°C, 1.0 mmol $LiAlH_4$), the *exo*/*endo* ratio for intermediate hydroxyester **2j** (not isolated but characterised by ^{1}H-NMR and GLC–MS) remains constant at all percentages of conversion. This ratio of epimers for **2j** is very similar to the measured one for diol **2l** (entry 11). Diol **2l** was obtained when starting ketone **1j** was reduced under the usual conditions (rt, 5.0 mmol $LiAlH_4$). Therefore, the anomalously favoured *exo* attack to substrates **1j**, **3j** and **3k** must be explained by formation of *endo*-lithium complexes (see **C** in Fig. 2) that hinder the intermolecular *endo*-hydride attack. On the other hand, the favoured formation of an *exo*-lithium complex in the case of **1b** (see **D** in Fig. 2) must produce a higher *exo*/*endo* ratio than observed in the case of substrate **1a** (compare entries 1, 2 and 3).

In summary, reduction of bridgehead-substituted 2-norbornanones and 2-norbornanoximes, easily obtained from (+)-camphor and (−)-fenchone by simple procedures, takes place with good yields and with a high degree of asymmetric induction. This feature constitutes an effective and convenient synthetic

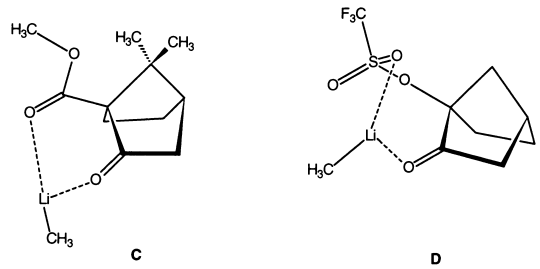


Fig. 2. *endo*- and *exo*-Methyllithium-complex models **C** and **D**, for **1j** and **1b** respectively. Methyllithium has been chosen for matters of simplification

approach for the preparation of a wide range of enantiopure norbornane derivatives. The stereochemical outcome of both ketones **1** and oximes **3** reduction can be explained by an intermolecular hydride attack to lithium complexes (see Fig. 2). In a few cases, the conformation of these complexes causes a decrease in the usually high d.e.

3. Experimental section

3.1. General

Melting points (°C) were measured on a Gallenkamp melting point apparatus and are uncorrected. Solvents were dried by distillation over the following drying agents: diethyl ether (Na/benzophenone), methylene chloride (phosphorous pentoxide). Starting materials and reagents obtained from commercial sources were used without further purification. Flash chromatography was performed over Merck silica gel 60 (230–400 mesh).

NMR spectra were recorded on a Varian XL 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer and a Brucker-AC 250 (250 MHz for ^{1}H and 62.5 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in hertz. IR spectra were recorded on a Perkin–Elmer 781 spectrometer. Wavenumbers are in cm^{-1}. Mass spectra were recorded on a GC–MS Shimadzu QP5000 (60 eV) mass spectrometer. For gas chromatography, a Perkin–Elmer Sigma 300 chromatograph equipped with capillary OV 101 column was used. Molecular rotation data ($[\alpha]_D^{20}$) were recorded on a Perkin–Elmer 241 polarimeter. Concentrations are given as g/100 mL of solvent.

3.2. General procedure for the synthesis of 2-norbornanoximes[21] from 2-norbornanones

A solution of ketone **1** (5.0 mmol), pyridine (15.0 mmol) and $NH_2OH{\cdot}HCl$ (25.0 mmol) in 96% ethanol (25 mL) was stirred under reflux for 24 h (the reaction was monitored by GLC). After completion of the reaction, the ethanol was evaporated under reduced pressure and 10% HCl (50 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (4×25 mL), washed with brine (2×25 mL) and dried over $MgSO_4$. The organic solvent was evaporated under reduced pressure and the oximes were purified by crystallisation from ethanol.

*3.3. (*E*)- and (*Z*)-(1*R*)-7,7-Dimethyl-2-hydroxyimine-1-norbornanecarbonitrile **3k***

According to the procedure described above, reaction of ketone **1k** gave oxime **3k** in 85% yield. Analysis (300 MHz ^{1}H-NMR integration of methyl group protons) of the unpurified crude material

revealed the presence of two isomers *Z*-**3k** and *E*-**3k** in a ratio of *Z*:*E*=4:1. Purification by crystallisation (ethanol, −20°C) gave a mixture of *E*-**3k** and *Z*-**3k** as a colourless, crystalline solid. IR (KBr) ν 3450, 3080, 2240, 1490, 1420, 1390, 1100 cm^{-1}. MS *m/z* 178 (10), 161 (12), 145 (10), 136 (40), 118 (12), 106 (15), 91 (30), 79 (25), 69 (45), 67 (32), 53 (30), 43 (70), 41 (100). *E*-**3k**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 2.70 (md, *J*=18.1 Hz, 1H), 2.40–1.90 (m, 5H), 1.45 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.9, 119.0, 52.2, 48.0, 42.6, 35.6, 31.2, 27.2, 20.2, 18.4. *Z*-**3k**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 2.70 (dm, *J*=18.1 Hz, 1H), 2.40–1.90 (m, 5H), 1.45 (m, 1H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.5, 117.8, 52.1, 50.2, 43.1, 32.9, 31.3, 27.3, 19.7, 19.2.

*3.4. (*E*)- and (*Z*)-(1*R*)-3,3-Dimethyl-2-hydroxyimine-1-norbornanecarboxylic acid methyl ester **3u***

According to the procedure described above, reaction of ketone **1u** gave oxime **3u** in 93% yield. Analysis (300 MHz ^{1}H-NMR integration of methyl group protons) of the unpurified crude revealed the presence of two isomers *Z*-**3u** and *E*-**3u** in a ratio of *Z*:*E*=1:2. Purification by crystallisation (ethanol, −20°C) gave a mixture of *E*-**3u** and *Z*-**3u** as a colourless, crystalline solid. IR (KBr) ν 3300, 2980, 2950, 1750, 1440, 1340, 1285, 1160. MS *m/z* 211 (1), 196 (5), 179 (35), 164 (15), 151 (11), 134 (32), 120 (10), 107 (21), 93 (39), 79 (23), 67 (37), 41 (100). *E*-**3u**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 3.71 (s, 3H), 2.30–1.55 (m, 7H), 1.35 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.2, 168.4, 58.5, 51.94, 48.4, 44.1, 39.8, 30.0, 24.3, 22.9, 22.0. *Z*-**3u**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 3.71 (s, 3H), 2.30–1.55 (m, 7H), 1.23 (s, 3H), 1.16 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.2, 168.5, 56.4, 51.95, 47.6, 44.2, 41.6, 27.8, 26.7, 24.2, 24.0.

*3.5. (*E*)-(1*R*)-7,7-Dimethyl-2-hydroxyimine-1-norbornanecarboxylic acid methyl ester **3j***

According to the procedure described above, reaction of ketone **1j** gave oxime **3j** in 95% yield. Purification by crystallisation (ethanol, −20°C) provided pure *E*-**3j** as a colourless, crystalline solid. $[\alpha]_D^{20}$ +13.2 (*c* 1.03, CH_2Cl_2). IR (CCl_4) ν 3300, 2960, 1740, 1440, 1330, 1290, 1250, 1220, 1090. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0–8.0 (br s, 1H), 3.74 (s, 3H), 2.70 (dm, *J*=18.0 Hz, 1H), 2.35 (m, 1H), 2.15 (d, *J*=17.9 Hz, 1H), 2.00–1.75 (m, 3H), 1.30 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2, 165.2, 60.9, 51.8, 50.8, 44.8, 33.6, 29.7, 26.8, 20.8, 29.4. MS *m/z* 211 (5), 194 (7), 179 (35), 163 (22), 152 (29), 146 (27), 134 (26), 120 (20), 107 (24), 93 (47), 79 (41), 67 (66), 54 (39), 43 (56), 41 (100).

*3.6. General procedure for the $LiAlH_4/Et_2O$ reduction of norbornanones **1** and oximes **3***

The corresponding 2-norbornanone or 2-norbornanoxime (1.0 mmol) in absolute diethyl ether (5 mL) was added through a dropping funnel to lithium aluminium hydride in absolute diethyl ether (20 mL) at 0°C. After stirring at rt for 6 h, the mixture was poured into 100 mL of ice–water and extracted with diethyl ether (4×30 mL). Compounds containing amino groups were extracted with 10% aqueous HCl (3×30 mL); the aqueous solution was basified with 30% aqueous NaOH, and the mixture was extracted with diethyl ether (4×30 mL), washed with brine (1×30 mL), and dried (Na_2CO_3). After evaporation of the solvent, amino alcohols and diamines were purified by crystallisation of their hydrochlorides from MeOH/Et_2O. In the case of alcohols and diols, the first organic layer was washed with brine (1×30 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude was purified by column chromatography (silica gel, hexane/Et_2O).

3.7. (±)-1,2-exo/endo-Norbornanediol **2c**

According to the procedure described above, reaction of ketone **1b** gave diol **2c** in 98% yield as a colourless solid. Due to high water solubility, continuous extraction with diethyl ether was necessary. Analysis (300 MHz ^{1}H-NMR integration of C2 methine protons) of the crude product revealed the presence of two isomers *endo*-**2c** and *exo*-**2c** in a ratio of *endo*:*exo*=70:30, that could not be separated by column chromatography. IR (CCl_4) ν 3600, 3390, 2960, 2880, 1140, 1080, 1050. *endo*-**2c**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.20 (br s, 2H), 4.02 (d, *J*=8.5 Hz, 1H), 2.17–1.06 (m, 9H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 85.0, 75.1, 42.4, 38.8, 33.7, 30.4, 26.0. *exo*-**2c**: ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.20 (br s, 2H), 3.52 (d, *J*=6.8 Hz, 1H), 2.17–1.06 (m, 9H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 83.4, 74.0, 41.4, 38.8, 32.2, 30.6, 29.8.

3.8. (±)-2-exo/endo-Hydroxy-1-norbornyl triflate **2b**

According to the procedure described above (−15°C, 15 min), reaction of ketone **1b** gave triflate **2b** in 87% yield as a colourless liquid. Triflate **2b** was used in the next step without further purification (it decomposes under chromatographic conditions).[16,17] Analysis (300 MHz ^{1}H-NMR integration of C2 methine protons) of the unpurified crude revealed the presence of two isomers *endo*-**2b** and *exo*-**2b** in a ratio of *endo*:*exo*=70:30. IR (CCl_4) ν 3560, 3410, 2960, 2870, 1410, 1245, 1210, 1145, 1100, 1030. *endo*-**2b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.46 (d, *J*=10.9 Hz, 1H), 2.60–2.50 (m, 1H), 2.45 (br s, 1H), 2.30–1.55 (m, 7H), 1.25 (dt, *J*=18.0 Hz, 3.4 Hz, 1H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 118.0 (q, *J*=323.4 Hz), 104.6, 72.8, 40.7, 38.4, 31.8, 29.1, 23.9. *exo*-**2b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.98 (d, *J*=6.4 Hz, 1H), 2.60–2.50 (m, 1H), 2.30 (br s, 1H), 2.30–1.55 (m, 7H), 1.35 (m, 1H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 118.0 (q, *J*=323.4 Hz), 101.9, 72.2, 40.1, 36.7, 30.2, 29.2, 28.4.

3.9. (1S,2R)-3,3-Dimethyl-1-hydroxymethyl-2-norbornanol **2w**

According to the procedure described above, reaction of ketone **1u** gave diol **2w** in 95% yield, as a colourless liquid. $[\alpha]_D^{20}$ −19.8 (*c* 0.77, MeOH). IR (CCl_4) ν 3400, 2960, 2880, 1470, 1370, 1080, 1030. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.76 (d, *J*=10.7 Hz, 1H), 3.72 (d, *J*=10.7 Hz, 1H), 3.61 (s, 1H), 3.20 (br s, 2H), 1.90–1.65 (m, 3H), 1.55–1.05 (m, 4H), 1.01 (s, 3H), 0.88 (s, 3H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 82.5, 66.3, 54.0, 47.9, 39.1, 36.4, 30.5, 25.4, 21.5, 20.0. MS *m/z* 137 (1), 121 (3), 109 (7), 81 (100), 72 (32), 69 (23), 55 (17), 41 (32).

3.10. (1S,2R)-1-Aminomethyl-3,3-dimethyl-2-norbornanol **2y**

According to the procedure described above, reaction of ketone **1v** gave amino alcohol **2y** in 79% yield, as a colourless liquid: mp (hydrochloride) >210°C (decomposition). $[\alpha]_D^{20}$ (hydrochloride) −18.2 (*c* 1.00, MeOH). IR (CCl_4) ν 3400, 2960, 2860, 1460, 1110, 1080. ^{1}H-NMR (hydrochloride) (300 MHz, CD_3OD) δ 3.53 (d, *J*=1.7 Hz, 1H), 3.15 (d, *J*=12.9 Hz, 1H), 3.09 (d, *J*=12.9 Hz, 1H), 2.00–1.40 (m, 5H), 1.30–1.15 (m, 2H), 1.01 (s, 3H), 0.88 (s, 3H). ^{13}C-NMR (hydrochloride) (75 MHz, CD_3OD) δ 83.4, 51.6, 49.4, 45.7, 40.4, 38.1, 30.7, 26.5, 22.4, 20.5. MS *m/z* 152 (2), 137 (2), 123 (3), 109 (14), 89 (10), 81 (100), 72 (23), 69 (24), 55 (12), 41 (35).

3.11. (1S,2S)-1-Aminomethyl-7,7-dimethyl-2-norbornanol **2n**

According to the procedure described above, reaction of ketone **1k** gave amino alcohol **2n** in 70% yield, as a colourless liquid: mp (hydrochloride) >230°C (decomposition). $[\alpha]_D^{20}$ (hydrochloride) +22.7 (*c* 0.93, MeOH). IR (CCl_4) ν (hydrochloride) 3400, 2960, 1600, 1510, 1460, 1080. ^{1}H-NMR (hydrochloride) (300 MHz, CD_3OD) δ 3.87 (dd, *J*=7.3, 4.0 Hz, 1H), 3.21 (d, *J*=12.8 Hz, 1H), 2.85 (d, *J*=12.8 Hz, 1H), 1.80–1.50 (m, 6H), 1.25–1.00 (m, 1H), 1.10 (s, 3H), 0.89 (s, 3H). ^{13}C-NMR (hydrochloride) (75 MHz, CD_3OD) δ 76.8, 51.6, 49.0, 47.5, 42.2, 40.6, 31.2, 28.2, 21.4. MS *m/z* 152 (2), 151 (1), 136 (5), 119 (7), 108 (100), 93 (44), 82 (20), 67 (24), 56 (25), 43 (22).

3.12. (1R,2R)-2-Amino-3,3-dimethyl-1-norbornanemethanol **4w**

According to the procedure described above, reaction of oxime **3u** gave amino alcohol **4w** in 81% yield, as a colourless liquid: mp (hydrochloride) >200°C (decomposition). $[\alpha]_D^{20}$ (hydrochloride) −1.0 (*c* 0.91, MeOH). IR (CCl_4) ν 3400, 2960, 1610, 1470, 1380, 1370, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.93 (d, *J*=10.4 Hz, 1H), 3.70 (d, *J*=10.4 Hz, 1H), 2.80 (br s, 1H), 2.73 (d, *J*=1.6 Hz, 1H), 1.80–1.05 (m, 9H), 0.98 (s, 3H), 0.83 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 69.9, 66.4, 52.5, 48.1, 39.0, 37.9, 30.8, 25.5, 22.4, 20.5. MS *m/z* 169 (5), 152 (13), 134 (9), 121 (16), 108 (12), 82 (38), 71 (100), 56 (42), 41 (73).

3.13. (1S,2R)-1-Aminomethyl-3,3-dimethyl-2-norbornylamine **4y**

According to the procedure described above, reaction of oxime **3v** gave diamine **4y** in 74% yield, as a colourless liquid: mp (dihydrochloride) >240°C (decomposition). $[\alpha]_D^{20}$ (dihydrochloride) −8.4 (*c* 0.92, MeOH). IR (dihydrochloride) (KBr) ν 3400, 2920, 1620, 1530, 1450, 1400. ^{1}H-NMR (dihydrochloride) (300 MHz, CD_3OD) δ 3.34 (d, *J*=13.7 Hz, 1H), 3.20 (s, 1H), 3.19 (d, *J*=13.7 Hz, 1H), 2.00–1.40 (m, 7H), 1.17 (s, 3H), 1.08 (s, 3H). ^{13}C-NMR (dihydrochloride) (75 MHz, CD_3OD) δ 62.6, 51.5, 49.6, 42.1, 39.9, 38.9, 30.7, 25.6, 23.6, 20.4. MS *m/z* 168 (4), 151 (20), 136 (9), 122 (15), 107 (27), 79 (25), 71 (100), 70 (39), 56 (42), 41 (30).

3.14. (1S,2R)- and (1S,2S)-1-Aminomethyl-7,7-dimethyl-2-norbornylamine **4n**

According to the procedure described above, reaction of oxime **3k** gave diamine **4n** in 86% yield, as a colourless liquid. Analysis (300 MHz ^{1}H-NMR integration of methyl group protons) of the unpurified crude revealed the presence of two isomers *endo*-**4n** and *exo*-**4n** in a ratio of *endo*:*exo*=40:60, that could not be separated by crystallisation of the corresponding dihydrochlorides. IR (dihydrochloride) (KBr) ν 3400, 2920, 2020, 1620, 1530, 1450, 1400. *endo*-**4n**: ^{1}H-NMR (dihydrochloride) (300 Hz, CD_3OD) δ 3.70 (dm, *J*=11.1 Hz, 1H), 3.22 (s, 2H), 2.45 (m, 1H), 2.04–1.15 (m, 7H), 1.10 (s, 3H), 1.09 (s, 3H). ^{13}C-NMR (dihydrochloride) (75 MHz, CD_3OD) δ 55.4, 51.7, 50.2, 47.1, 40.4, 35.6, 28.3, 25.1, 20.54, 19.59. MS *m/z* 168 (2), 151 (35), 136 (35), 119 (65), 108 (72), 82 (70), 69 (31), 56 (77), 43 (100), 41 (65). *exo*-**4n**: ^{1}H-NMR (dihydrochloride) (300 Hz, CD_3OD) δ 3.57 (t, *J*=6.9 Hz, 1H), 3.30 (d, *J*=17.1 Hz, 1H), 3.08 (d, *J*=17.1 Hz, 1H), 2.04–1.15 (m, 7H) 1.06 (s, 3H), 1.02 (s, 3H). ^{13}C-NMR (dihydrochloride) (75 MHz, CD_3OD) δ 56.7, 51.5, 50.1, 46.8, 39.1, 37.4, 32.7, 27.5, 21.2, 20.7. MS *m/z* 151 (35), 136 (40), 119 (70), 108 (73), 82 (78), 79 (31), 56 (75), 43 (100), 41 (67).

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