Improved Synthesis of C_2-Symmetrical Pyridinediols and Synthesis of C_s-Symmetrical Pyridinediols

Bartjan Koning,[a] Jan Buter,[a] Ron Hulst,[a][+] Roelof Stroetinga,[a] and Richard M. Kellogg*[a]

Keywords: Pyridine / Alcohols / Asymmetric synthesis / Ketones / Retro reactions / Synthetic methods

Base-induced reaction of 2,6-dimethylpyridine (2,6-lutidine) (**1**) with two equivalents of various ketones has been reported to provide C_2-symmetrical pyridine diols **3**. Closer examination reveals that competitive di-addition to a single methyl group can occur providing C_s-symmetrical pyridine diols **7**. By varying the lithiation times, the formation of this side product could be maximized or minimized on the basis of a mechanistic proposal for the competing pathways. The formation of the C_s-diol **7** could be excluded completely by using potassium diisopropylamide as base; high yields of C_2-symmetrical pyridine diols **3** are obtained. Regioselective additions of **1** to (*R*)-fenchone and (–)-menthone were also achieved.

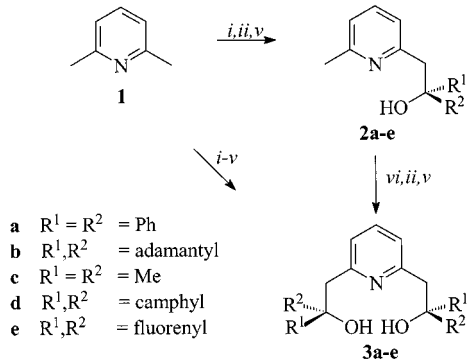
Introduction

The achievements over the past few decades in developing new chiral non-racemic reagents[1] and asymmetric synthetic methodologies[2] have been remarkable. For example, the synthesis of many chiral non-racemic receptor molecules is now a relatively simple matter. In the past, we have developed a synthetic approach to chiral non-racemic pyridine thiols and dithiols,[3] and have, for example, applied the thioethers thereof in palladium-catalyzed allylic substitution.[4]

Sterically bulky C_2-symmetrical pyridine diol ligands like **3** obtained by condensation of ketones with lutidine **1** are of special interest as complexing agents for the development of new homogeneous catalysts. The combination of two hydroxy groups and the pyridine nitrogen atom leads to ligands capable, for example, of stabilizing high-valent osmium alkoxide complexes.[5] With Zr and W good polymerization catalysts are formed.[6] Biomimetic studies of enzymes have been conducted with some Mo complexes.[7] Well-defined complexes with Ti,[8] Zn,[9] Co,[9] Si,[10] and Ru[11] have also been reported in the literature.

The synthesis of this class of compounds was first reported by Tilford and Van Campen[12] and further explored by Berg and Holm[7b] in the synthesis of pyridine diol **3a**. These compounds have been of interest in our group as model systems for zinc-alcohol dehydrogenase,[9b] carboxypeptidase,[13] and for preparation of silicon alkoxides.[10a]

Several derivatives have been prepared making use of the described methodology for the synthesis of pyridine diols **3a** (Scheme 1).[7b,9b] This approach consists of a one-pot, two-step synthesis. Yields are moderate; the benzophenone-based pyridine diol **3a** is obtained in 35% yield, whereas C_2-symmetrical derivatives **3b**, **3c, 3d**, and **3e** (based on adamantanone,[14] acetone,[9b] camphor, and fluorenone,[9b] respectively) are obtained in yields of 51, 34, 45, and 13%, respectively. We shall discuss some additional factors that can have a major effect on the synthetic outcome.



Scheme 1. Reagents and conditions: *i*) *n*BuLi (1.1 equiv.), THF, −60 °C; *ii*) $R^1R^2C{=}O$; *iii*) *n*BuLi (1.1 equiv.), −80 °C; *iv*) $R^1R^2C{=}O$; *v*) 2 N HCl; *vi*) *n*BuLi (2.1 equiv.), THF, room temp.

Synthesis

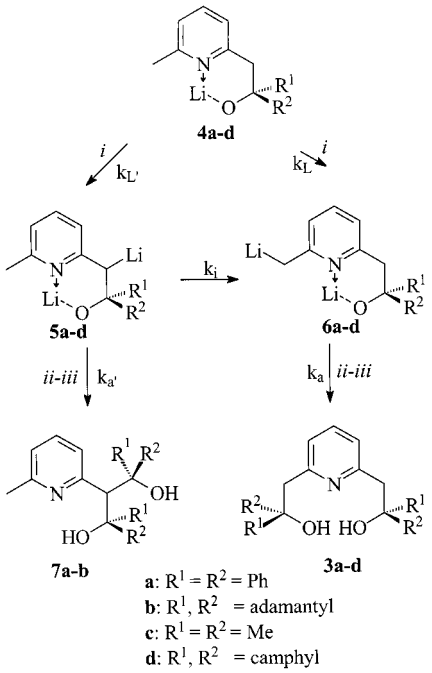
Yields could be improved substantially by applying a two-pot reaction in which the monoadduct **2** is first isolated, and then converted into the C_2-symmetrical di-adduct **3** by adding slightly more than two equivalents of base, followed by the addition of the ketone (Scheme 1). Mixed combinations can be prepared as shown by Nakayama et. al.[6a] However, there is more to this than meets the eye, as will be discussed in the following paragraphs.

The monoadducts **2** formed by addition of monolithiated lutidine to benzophenone, adamantanone, and camphor can be isolated in 85, 88, and 89% yields, respectively. The second reaction step, however, is less straightforward. The time that the mixture is stirred after lithiation and before

[a] Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen,
Nijenborgh 4, 9747 AG Groningen, The Netherlands
Fax: (internat.) + 31-50/363-4296,
E-mail: R.M.Kellogg@chem.rug.nl
[+] Biomade Institute, University of Groningen
Nijenborgh 4, 9747 AG Groningen, The Netherlands

  1434−193X/00/0815−2735 $ 17.50+.50/0

addition of the ketone (lithiation time) strongly influences the yield of the desired C_2-symmetrical product. Using this two-pot synthetic approach, it was found that if a lithiation time of 4 h was applied for the adamantanone derivative **2b**, after which one equivalent of adamantanone was added, followed by work up with 2 N HCl, the adamantanone-based C_2-symmetrical pyridine diol **3b** could be isolated in 70% yield (overall yield 62%). However, when adamantanone was added after a lithiation time of only 30 min, a second product, C_s-symmetrical pyridine diol **7b**, was also isolated. The formation of **7b** must involve deprotonation of the CH_2 group forming the dilithiated intermediate **5b** instead of deprotonation at the presumably sterically less hindered methyl group, which gives rise to the intermediate **6b** (Scheme 2).



Scheme 2. Reagents and conditions: *i*) *n*BuLi (1.1 equiv.), THF; *ii*) ketone; *iii*) 2 N HCl

Experiments at different temperatures and with different lithiation times were conducted in order to obtain further mechanistic insight. In these experiments, monosubstitution product **2b** was treated with two equivalents of *n*-butyllithium under the given conditions. The ratios of the C_s-symmetrical adduct **7b** to C_2-symmetrical adduct **3b** were determined, after quenching the reaction with adamantanone and workup with 2 N HCl, by means of ^{1}H-NMR spectroscopy. The results are given in Table 1; t_1 is the time between the addition of *n*-butyllithium and the addition of the adamantanone, and t_2 is the time the mixture is stirred after the addition of the ketone and before it is quenched with HCl.

At −80 °C lithiation is slow (Entries 1, 2) and even at −40 °C complete lithiation requires several hours (Entries 3−5). Lithiation is far more rapid at 0 °C, and there is a clear tendency with short lithiation times for **7b** to predominate over **3b**, although the ratio tends towards the latter at longer lithiation times (Entries 6−9). This trend is even clearer at room temperature; fairly long lithiation times lead to a striking reversal of the ratio **7b** over **3b** (Entries 10−14). From these results it seems justified to conclude that the lithium alkoxide **4b** first formed is deprotonated at the CH_2 group to form **5b** more rapidly than at the methyl group to form **6b**. In other words, $k_{L'} > k_L$ (Scheme 2). This effect is assumed to arise from coordination of the second equivalent of *n*-butyllithium to the electron-rich oxygen atom in the (presumed) chelate ring of **4b**, followed by facile intermolecular deprotonation at the CH_2 group as shown in Figure 1. A second conclusion is that **6b** is thermodynamically more stable than **5b**. Whether the slow conversion of **5b** to **6b** is due to inter- or intramolecular processes cannot be concluded from the data of Table 1.

Table 1. Effect of lithiation conditions on the yield of **3b** and **7b**

Entry	Reaction temp. [°C]	t_1	t_2	Yield of **7b**	Yield of **3b**
1	−80	5 min	4 h	–	–
2	−80	4 h	4 h	34.4	35.6
3	−40	10 min	90 min	18.5	20.4
4	−40	30 min	90 min	19.1	23.9
5	−40	60 min	90 min	20.6	34.3
6	0	0.75 min	60 min	61.7	16.3
7	0	5 min	60 min	61.0	29.5
8	0	30 min	60 min	60.4	38.5
9	0	60 min	60 min	58.3	41.5
10	room temp.	0.5 min	60 min	66.4	14.5
11	room temp.	5 min	60 min	63.0	37.0
12	room temp.	30 min	60 min	54.5	45.5
13	room temp.	60 min	60 min	28.6	71.4
14	room temp.	4 h	60 min	4.8	95.2

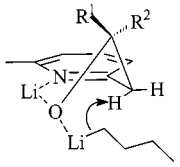
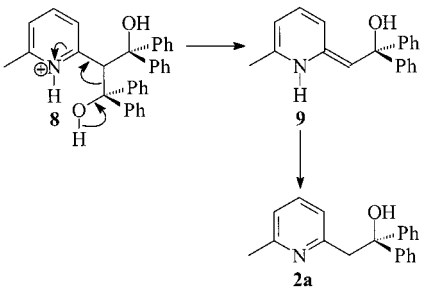


Figure 1. Six-membered intermediate

Using the data of Table 1 as guide, the reaction conditions were optimized for formation of the C_s-diol **7b**. This entailed lithiation and quenching at room temperature after a lithiation time of 30 s.

When similar temperature- and time-dependent lithiation experiments were carried out with the diphenylcarbinol **2a,** only C_2-symmetrical diol **3a** and some starting materials in the reaction mixture were detected. However, when longer lithiation times were used at room temperature, starting material was still recovered, despite the fact that lithiation at this temperature and with these reaction times should be complete. It was also observed that the yield of the C_2-symmetrical diol **3a** increased with prolonged lithiation times. These observations can be explained by the formation of intermediate **5a**, although no trace of the C_s-adduct **7a** was detected. Only on modification of the workup procedure was the C_s-symmetrical diol **7a** obtained. When 2 N NH_4Cl was used in the workup, C_s-symmetrical diol **7a** could be isolated in moderate to low yield (5−35%) de-

pending on the reaction conditions applied (−80 °C to room temp.). The usual workup with 2 N HCl is, apparently, too acidic to keep the diol **7a** intact. Experiments with various lithiation times and at different temperatures followed by workup with 2 N NH_4Cl showed the same phenomenon as observed for the adamantanone adduct. Initially, lithiation of the alkoxide **4a** is preferred at the CH_2 group forming dilithio species **5a**, which is converted into **6a** at prolonged lithiation times. When the C_s-diol **7a** was stirred with 2 N HCl it indeed reverted to the benzophenone monoadduct **2a** and benzophenone (Scheme 3).

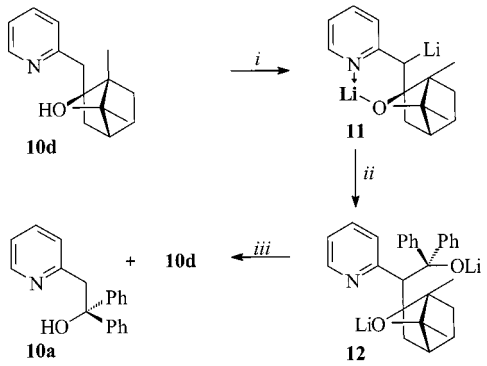


Scheme 3. Retro aldol reaction

This retro aldol reaction is probably initiated by protonation of the pyridine nitrogen atom of **8**, after which the benzophenone is expelled, affording intermediate **9**, which tautomerizes to the pyridine. The retro aldol reaction can also be induced by sonication or heat,[15] and also occurs upon purification of the product by means of column chromatography on silica. This reaction is also observed for the C_s-diol **7b** under acidic conditions at higher temperatures.

The best conditions for the formation of the C_s-diol **7a** (35% yield) were found to be 0 °C with a lithiation time of 1 min. The optimal conditions for the formation of the C_2-diol **3a** involve a lithiation time of 4 h at room temp. to afford **3a** in 67% yield.

When the time- and temperature-dependent lithiation was carried out for the camphor adduct **2d**, again an increase in the formation of the camphor-based C_2-diol **3d** upon longer lithiation times was observed. Recovery of starting material at room temperature was substantial. The C_s-diol **7d**, however, could not be detected, even when a mild workup procedure was applied. The best preparative results for the C_2-diol **3d** were at −40 °C; at higher temperatures more side products are obtained. This diol adduct probably is too unstable to be isolated. The fact that double addition can take place at one methyl group is established in an experiment where the 2-picoline-based camphor alcohol **10d** is dilithiated to afford **11**, which is quenched with benzophenone leading to the mixed diol **12**. This product, however, is also very unstable and upon workup the starting camphor-based alcohol **10d** was isolated together with a reasonable quantity of benzophenone-based alcohol **10a**. Addition at the CH_2 group does take place, but the mixed adduct formed is too unstable to be isolated and a retro aldol reaction takes place providing either the starting material **10d** or the benzophenone adduct **10a** (Scheme 4).



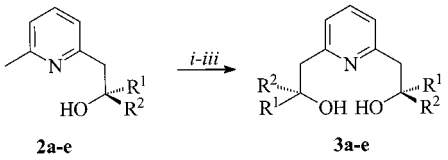
Scheme 4. Reagents and conditions: *i*) BuLi (2.1 equiv.), THF, −60 °C; *ii*) benzophenone; *iii*) 2 N NH_4Cl

In previous investigations of addition of the CH_2 group of this type of compounds to a carbonyl functionality the C_s-diols were never reported.[7a][9b][10a,16] The observation that in most of these cases only low to moderate yields of the C_2-diol **3** are obtained, and the observation that starting materials are recovered, are consistent with lithiation and addition having occurred at the CH_2 group. We conclude that addition reaction at this position can and does take place, and that in some cases the C_s-symmetrical diols **7** can be isolated, provided that they are sufficiently stable to survive retro aldol reaction.

The almost exclusive synthesis of the C_2-diols **3** as single product is possible, although long lithiation times (lithiation time of at least 4 h) are required to ensure that all the kinetic product is converted into the thermodynamic product. Another possibility is to make use of the understanding that was gained in conducting the time-dependent lithiations, of the intermediates. If a base is used that less readily leads to the six-membered intermediate chelate (Figure 1), the deprotonation at the CH_2 group should not be kinetically favored, and deprotonation should only take place at the less hindered methyl group. When the adamantanone-based alcohol **2b** was deprotonated with 2.1 equivalents of potassium diisopropylamide (KDA) and quenched with adamantanone after only 15 min of stirring, the C_2-diol **3b** was obtained as sole product in 95% yield (Scheme 5). KDA is a very strong base, and the potassium does not strongly coordinate with the nitrogen and oxygen atoms. After deprotonation of the hydroxy group, the second attack apparently occurs at the sterically less hindered methyl group, and no reaction at the CH_2 group is observed. This approach is very selective and provides the C_2-diols exclusively after stirring for a short time. Sterically more hindered lithium bases such as *s*BuLi and *t*BuLi were not investigated to see whether they would lead to increased selectivity.

When this new approach was applied in the synthesis of the benzophenone- and camphor-based C_2-diols **3a** and **3d**, the products were isolated in high yields (Table 2).

The C_s-diols also have interesting features, as they are known to coordinate several metals.[17] It would thus be de-



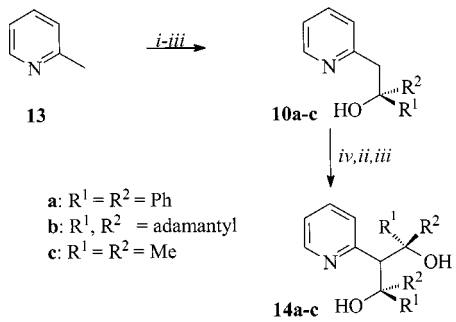
Scheme 5. Reagents and conditions: *i*) KDA (2.1 equiv.), THF, −50 °C; *ii*) $R^1R^2C{=}O$ (2.1 equiv.); *iii*) 2 N NH_4Cl

Table 2. Summary of optimized yields for the synthesis of C_2-diols **3**

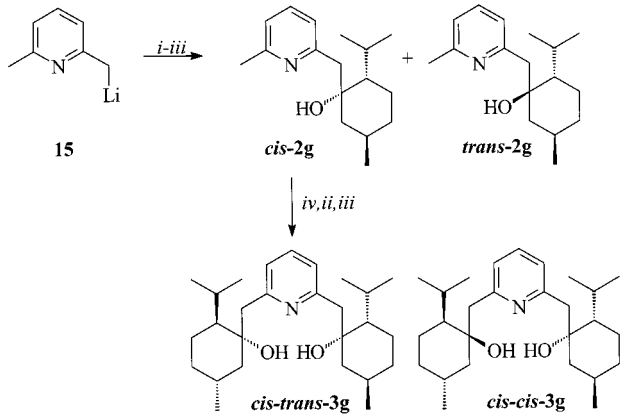
Used ketone	Mono-adduct **2** (yield using *n*BuLi)	Di-adduct **3** (yield using KDA)	Overall yield of **3**
Benzophenone	**2a** (85%)	**3a** (90%)	77%
Adamantanone	**2b** (88%)	**3b** (95%)	84%
(*R*)-(+)-Camphor	**2d** (90%)	**3d** (95%)	86%

sirable to have a synthetic approach that would selectively afford these materials. In our hands it was not possible to synthesize the lutidine-based C_s-diols as single products, free of the formation of the thermodynamically more stable C_2-diols. Since lithiation at the methyl group is thermodynamically favored over lithiation at the CH_2 position, and since the conversion of the kinetic product to the thermodynamically product occurs, it will be very difficult to synthesize the C_s-diols selectively using this approach. This problem is readily circumvented by use of 2-picoline (**13**), which when deprotonated with *n*-butyllithium and quenched with benzophenone, adamantanone, acetone, or camphor provides pyridine alcohols **10** in good yields. The isolated pyridine alcohols **10** were subsequently lithiated with two equivalents of *n*-butyllithium and allowed to react with a second ketone in order to give the desired C_s-diol **14**. For the benzophenone, adamantanone, and acetone adducts, the C_s-diols **14a**, **14b**, and **14c** were found in 33, 26, and 30% isolated yields, respectively (Scheme 6). The diols **14a** and **14b** undergo retro aldol reaction to the pyridine alcohol **10** and the ketones under acidic conditions and elevated temperatures, therefore making purification of the compounds very difficult. The diol **14c** is more stable, and retro aldol reaction occurs only above 100 °C or under acidic conditions. When camphor was used no C_s-diol could be isolated and only starting materials were recovered.

Efforts to add, facially selective if possible, the monolithiated lutidine **15** to other chiral ketones like (*R*)-fenchone and (−)-menthone were less successful. Addition to (*R*)-fenchone afforded inseparable *exo* and *endo* adducts in equal amounts. Addition of the lithio species **15** to (−)-menthone gave the *cis* and *trans* isomers **2g** in a ratio of 16:5 in favor of the *cis* adduct (Scheme 7). These isomers could be separated by means of column chromatography. The configurations of the isomers were deduced from the HETCOR, COSY, and NOESY NMR spectral data (not shown). An NOE interaction of the equatorial benzylic CH_2 protons (Figure 2a) with proton H_f and the axial proton H_a for the *cis* isomer was observed, whereas for the *trans* isomer interaction of the axial benzylic proton (Figure 2b) with either one of these protons is absent.



Scheme 6. Reagents and conditions: *i*) *n*BuLi (1.1 equiv.), THF, −60 °C; *ii*) $R^1R^2C{=}O$; *iii*) 2 N NH_4Cl; *iv*) *n*BuLi (2.1 equiv.), THF



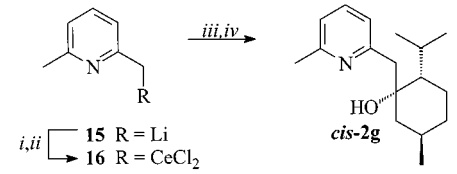
Scheme 7. Reagents and conditions: *i*) *n*BuLi (1.1 equiv.), THF, −60 °C; *ii*) (−)-menthone; *iii*) 2 N NH_4Cl; *iv*) *n*BuLi (2.1 equiv.), THF, 0 °C

Figure 2. a) (left): *cis* adduct; b) (right): *trans* adduct

When the *cis*-**2g** isomer was lithiated with two equivalents of *n*-butyllithium and allowed to react with (−)-menthone, the bis-product was formed as a mixture of the isomers *cis-cis*-**3g** and *cis-trans*-**3g** in a ratio of 6:1. The *cis-cis*-**3g** isomer could be selectively crystallized from a mixture of water/ethanol.

Better facial selectivity for the (*R*)-fenchone derivative was obtained when the lithium in the monolithio species **15** was replaced by $CeCl_3$, followed by the addition of (*R*)-fenchone. Alkylcerium reagents are known to give clean 1,2-addition to "difficult" ketones.[18] This is presumed to be due to the reduced basicity and the oxaphilicity of the alkylcerium reagent.[19] Furthermore, complexation of the cerium to the carbonyl functionality, and subsequent attack

of the alkyl group to the carbon atom enhances selectivity. We thought that complexation of the alkyl reagent to the carbonyl group could improve the regioselectivity of the addition reaction to (*R*)-fenchone and (−)-menthone. Indeed, some improvement was found when the cerium species **16** was synthesized from the lithio species **15** and allowed to react with (*R*)-fenchone. However, although the *endo*/*exo* isomer ratio for this reaction improved to 1:2 at −50 °C in THF, a mixture of the two isomers was obtained. When the reaction temperature was lowered to −80 °C, a small improvement of the ratio to 1:4 was found. Addition of the cerium species **16** to (−)-menthone, however, led to far better results. When (−)-menthone was allowed to react with **16** at −80 °C only the *cis* isomer **2g** was formed (Scheme 8).



Scheme 8. Reagents and conditions: *i*) *n*BuLi (1.1 equiv.), THF, −70 °C; *ii*) $CeCl_3$THF; *iii*) (−)-menthone; *iv*) 2 N NH_4Cl

Conclusions

Aided by the understanding of the lithiation process, an approach has been developed that allows the preparation of chiral as well as achiral C_2-symmetrical pyridine diols in high yields. The synthetic approach to C_s-symmetrical pyridine diols opens up a route to interesting new ligands the complexation behavior of which is currently under investigation. The use of $CeCl_3$ in the addition reaction of 2,6-lutidine to (−)-menthone gave a regiospecific addition to the *cis*-pyridine diol. The application of $CeCl_3$ in the addition reactions opens up a new perspective for regioselective addition to chiral ketones, as shown for (−)-menthone.

Experimental Section

General Remarks: All reactions were carried out under Ar. The following solvents were distilled prior to use: THF was distilled from Na wire, acetonitrile and dichloromethane were distilled from CaH_2, and diethyl ether, ethyl acetate, and hexane were distilled from P_2O_5. − Column chromatography was performed on alumina (Merck 90, II/III, 0.063−0.200 mm) or silica gel (Aldrich 60, 230−400 mesh). − Elemental microanalyses were carried out in the analytical department of this laboratory. − ^{1}H- and ^{13}C-NMR spectra were recorded using a Varian Unity Plus 500, a Varian VXR 300 instrument or a Genuine 200 instrument. The chemical shifts are expressed relative to $CDCl_3$ for ^{1}H-NMR (at δ = 7.26) and ^{13}C-NMR (at δ = 76.91). NOESY,[20] and COSY[21] spectra were performed using standard Varian pulse programs. − Deuterated solvents were dried with an Al_2O_3 (activity 1) column just prior to use. All other reagents were obtained from Aldrich or Acros Chimica and used as received, unless otherwise noted.

2-(6-Methyl-2-pyridinyl)-1,1-diphenyl-1-ethanol (2a): 2,6-Lutidine (**1**) (10.0 g, 93.3 mmol) was dissolved in 200 mL of THF and cooled to −60 °C. *n*-Butyllithium (1.6 M in hexane, 59.4 mL, 95.0 mmol) was added under stirring. The mixture was warmed to −50 °C and stirring was continued for 1 h before benzophenone (17.3 g, 95.0 mmol) in 25 mL of THF was added by means of a canula. The mixture was allowed to reach ambient temperature overnight, and was acidified to pH = 1 with 2 N HCl. After stirring for 1 h, the mixture was neutralized with 2 N NaOH. The aqueous layer was extracted with ethyl acetate twice and the organic layers were dried with $MgSO_4$. After concentration in vacuo, the product was recrystallized from methanol yielding a colorless solid (23.0 g, 79.5 mmol, 85%) with m.p. 124−125 °C. − IR (KBr): $\tilde{\nu}$ = 3250, 2900, 1610, 1600, 1450, 1100, 800, 700, 550 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 3.67 (s, 2 H), 6.90 (m, 2 H), 7.15 (m, 2 H), 7.23 (m, 4 H), 7.40 (m, 1 H), 7.49 (m, 4 H), 8.17 (br, OH), − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 24.1 (q), 46.7 (t), 78.2 (s), 120.9 (d), 121.4 (d), 126.1 (d), 126.2 (d), 127.7 (d), 137.0 (d), 147.3 (s), 156.7 (s), 158.4 (s). − HRMS: calcd. 289.147; found 289.147. − $C_{20}H_{19}NO$ (289.4): calcd. C 83.03, H 6.62, N 4.84; found C 83.13, H 6.47, N 4.87.

2-[(6-Methyl-2-pyridinyl)methyl]-2-adamantanol (2b): 2,6-Lutidine (**1**) (3.84 g, 35.8 mmol) was dissolved in 100 mL of THF and cooled to −50 °C. Subsequently, *n*-butyllithium (1.6 M in hexane, 22.6 mL, 36.2 mmol) was added and stirring was continued for 30 min. A solution of adamantanone (5.4 g, 36 mmol) in 10 mL of THF was added slowly and stirring was continued overnight allowing the mixture to reach room temp. slowly. The solution was quenched with 2 N HCl and stirred for 15 min before it was neutralized with 2 N NaOH. The solution was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with Na_2SO_4. After being taken to dryness, the product was recrystallized from hexane yielding a colorless solid (8.1 g, 31.5 mmol, 88%) with m.p. 131−132 °C. − IR (KBr): $\tilde{\nu}$ = 3250, 2900, 1610, 1600, 1450, 1000, 700 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.4−2.0 (m, 12 H), 2.28 (m, 2 H), 2.50 (s, 3 H), 3.08 (s, 2 H), 6.48 (s, OH), 6.94 (d, *J* = 11.7 Hz, 1 H), 6.98 (d, *J* = 11.7 Hz, 1 H), 7.49 (dd, *J* = 11.7 Hz, *J* = 11.7 Hz, 1 H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.1 (q), 27.2 (d), 32.6 (t), 34.4 (t), 37.1 (d), 38.3 (t), 43.2 (t), 75.2 (s), 120.8 (d), 121.2 (d), 136.8 (d), 157.2 (s), 158.8 (s). − HRMS: calcd. 257.178; found 257.179. − $C_{17}H_{23}NO$ (257.4): calcd. C 79.33, H 9.01, N 5.44. found C 78.96, H 9.05, N 5.45.

(1*R*,2*S*)-1,7,7-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo-[2.2.1]heptan-2-ol (2d): To a solution of 2,6-lutidine (**1**) (6.0 g, 56 mmol) in 250 mL of THF at −60 °C was added *n*-butyllithium (1.6 M in hexane, 38.5 mL, 61.6 mmol). The mixture was stirred at −60 °C for 30 min and (*R*)-(+)-camphor (8.5 g, 56 mmol) in 20 mL of THF was added. Stirring was continued for 1 h at −60 °C. The mixture was quenched with 1 N HCl, stirred for 30 min and neutralized with 2 N NaOH. The solution was extracted with ethyl acetate twice and the combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvents in vacuo, the product was purified by means of kugelrohr distillation (75 °C, 0.4 Torr) yielding **2d** as a colorless solid (13.0 g, 50.1 mmol, 90%) with m.p. 38−39 °C. − $[\alpha]_D^{23}$ = −28.7 (*c* = 1.5, acetone). − IR (KBr): $\tilde{\nu}$ = 3300, 3000, 1610, 1600, 1450, 1100, 830, 800 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.45 (s, 3 H), 0.76 (s, 3 H), 1.05 (m, 1 H), 1.07 (s, 3 H), 1.30 (m, 1 H), 1.41 (m, 2 H), 1.63 (m, 2 H), 1.98 (m, 1 H), 2.44 (s, 3 H), 2.88 (s, 2 H), 6.65 (br, OH), 6.91 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 7.45 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 11.1 (q), 20.9 (q), 21.3 (q), 24.2 (q), 27.1 (t), 30.7 (t), 44.9 (t), 47.4 (d), 49.5 (s), 52.2 (s), 81.1 (s), 120.8 (d), 121.1 (d), 136.9 (d), 156.8 (s), 159.7 (s). − HRMS: calcd. 259.194; found 259.194 −

$C_{17}H_{25}NO$ (259.4): calcd. C 78.72, H 9.71, N 5.40; found C 78.75, H 9.78, N 5.54.

2-({6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanol (3b) with *n*-Butyllithium: The mono-adduct **2b** (1.1 g, 4.3 mmol) was dissolved in 50 mL of THF and *n*-butyllithium (1.6 M in hexane, 5.6 mL, 9.0 mmol) was added to deprotonate the starting material. The mixture was stirred for 4 h before adamantanone (0.7 g, 4.3 mmol) in 5 mL of THF was added. After stirring for 1 h 1 N HCl was added and after stirring for 30 min it was neutralized with 2 N NaOH. The solution was extracted with dichloromethane twice and the combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvent, the product was recrystallized from ethanol yielding **3b** as colorless needles (1.2 g, 3.0 mmol, 70%) with m.p. 199−200 °C. − IR (KBr): $\tilde{\nu}$ = 3500, 2850, 1610, 1600, 1450, 700 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.4−1.9 (m, 20 H), 2.00 (m, 4 H), 2.24 (m, 4 H), 3.13 (s, 4 H), 4.21 (s, 2 OH), 7.07 (d, *J* = 7.7 Hz, 2 H), 7.55 (t, *J* = 7.7 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 27.3 (d), 32.7 (t), 34.6 (t), 37.2 (d), 38.3 (t), 44.6 (t), 75.4 (s), 122.5 (d), 136.8 (d), 158.3 (s). − HRMS: calcd. 407.282; found 407.282. − $C_{27}H_{37}NO_2$ (407.6): calcd. C 79.56, H 9.15, N 3.44; found C 79.44, H 9.10, N 3.48.

Time-Dependent Lithiations for 2b: The mono-adduct **2b** (2.5 mmol) was dissolved in 50 mL of THF and cooled to the temperature given in Table 1, *n*-butyllithium (1.6 M in hexane, 5.5 mmol) was added and the mixture was stirred for the given time t_1 (see Table 1). Subsequently, adamantanone (2.5 mmol) in 5 mL of THF was added. Stirring was continued for the given time t_2 at the given temperature. The mixture was quenched with 2 N HCl, stirred for 30 min and neutralized with 2 N NaOH. The solution was extracted twice with dichloromethane and dried with $MgSO_4$. The product distribution given in Table 1 was determined by means of ^1H NMR.

2-[(2-Hydroxy-2-adamantyl)(6-methyl-2-pyridinyl)methyl]-2-adamantanol (7b): The mono-adduct **2b** (0.5 g, 2.0 mmol) was dissolved in 50 mL of THF and cooled to 0 °C. *n*-Butyllithium (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added by syringe and the mixture was stirred for 45 s. A solution of adamantanone (0.3 g, 2.1 mmol) in 2 mL of THF was added at once. Stirring was continued for 1 h at 0 °C and the mixture was quenched with 2 N HCl, stirred for 30 min at room temp. and neutralized with 2 N NaOH. The solution was extracted twice with dichloromethane and dried with $MgSO_4$ .The product was purified by means of column chromatography [silica, hexane/diethyl ether (9:1)] affording a colorless solid (0.4 g, 1.0 mmol, 52%) with m.p. 194−195 °C. − IR (KBr): $\tilde{\nu}$ = 3372, 2931, 2898, 1594, 1572, 1456, 1057, 978 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 2 H), 1.21 (d, *J* = 12.2 Hz, 2 H), 1.39 (d, *J* = 12.2 Hz, 2 H) 1.48 (d, *J* = 9.3 Hz, 2 H), 1.60 (m, 2 H), 1.67 (m, 4 H), 1.77−1.84 (m, 6 H), 2.04 (d, *J* = 12.7 Hz, 2 H), 2.23 (d, *J* = 12.7 Hz, 2 H), 2.40 (m, 4 H), 2.55 (s, 3 H), 3.93 (s, 1 H), 7.02 (d, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 7.10 (s, 2 OH), 7.48 (dd, *J* = 7.8 Hz, *J* = 7.8 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 26.5 (q), 27.0 (d), 32.9 (t), 33.0 (t), 34.2 (t), 35.1 (t), 36.8 (d), 37.6 (d), 38.0 (t), 47.9 (q), 80.2 (s), 121.0 (d), 123.6 (d), 136.0 (d), 157.3 (s), 160.8 (s). − HRMS: calcd. 407.282; found 256 (− $C_{10}H_{15}O$), 238 (− $C_{10}H_{17}O_2$). − CI (NH_3) gave a molecular ion at *m*/*z* 408. − $C_{27}H_{37}NO_2$ (407.6): calcd. C 79.37, H 9.37, N 3.43; found C 79.46, H 9.28, N 3.43.

2-[6-(2-Hydroxy-2,2-diphenylethyl)-2-pyridinyl]-1,1-diphenyl-1-ethanol (3a) with *n*-Butyllithium:[22] A solution of mono-adduct **2a** (1.0 g, 3.5 mmol) was stirred at 0 °C and *n*-butyllithium (1.6 M in hexane, 4.6 mL, 7.4 mmol) was added. The mixture was stirred for 4 h and quenched by the addition of benzophenone (0.6 g, 3.5 mmol). After stirring for 1 h, 2 N NH_4Cl was added and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with brine and dried with Mg_2SO_4. After removal of the solvent, the C_2-diol was recrystallized from water/ethanol affording **3a** as colorless crystals (1.1 g, 2.3 mmol, 67%). − ^1H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 4 H), 5.17 (br, 2 OH), 6.61 (d, *J* = 8.1 Hz, 2 H), 7.2 (m, 21 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 48.0 (t), 78.0 (s), 122.8 (d), 126.0 (d), 126.5 (d), 127.9 (d), 136.8 (s), 146.5 (d), 157.3 (s).

2-(6-Methyl-2-pyridinyl)-1,1,3,3-tetraphenyl-1,3-propanediol (7a): The mono-adduct **2a** (0.95 g, 3.29 mmol) was dissolved in 75 mL of dry THF and cooled to 0 °C. Subsequently, *n*-butyllithium (1.6 M in hexane, 4.5 mL, 7.2 mmol) was added. The red mixture was stirred for 1 min and a solution of benzophenone (0.60 g, 3.31 mmol) in 5 mL of THF was added. Stirring was continued for another hour and the mixture was quenched with 2 N NH_4Cl and extracted twice with dichloromethane. The organic layers were combined and dried with Na_2SO_4. After removal of the solvents by means of rotary evaporation, the solid mixture of C_2 and C_s product was washed with hot diethyl ether to leave the C_2 product after filtration. The ether was removed affording the C_s product, which was recrystallized from ethyl acetate/hexane (1:4) yielding a colorless solid (0.30 g, 0.64 mmol, 35%), m.p.146−147 °C. − ^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.90 (s, 1 H), 6.23 (d, *J* = 6.7 Hz,1 H), 6.56 (d, *J* = 6.7 Hz, 1 H), 6.7−6.8 (m, 9 H), 6.9−7.0 (m, 4 H), 7.2−7.3 (m, 8 H), 8.48 (br, 2 OH). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 23.9 (q), 56.8 (d), 82.4 (s), 120.1 (d), 125.6 (d), 125.9 (d), 126.1 (d), 126.6 (d),127.1 (d), 127.3 (d), 127.8 (d), 135.2 (d), 144.5 (s), 148.1 (d), 155.0 (s),159.9 (s). − HRMS: calcd. 471.220; no proper HRMS could be obtained CI (NH_3) gave a molecular ion at *m*/*z* 472. − $C_{33}H_{29}NO_2$ (471.6): calcd. C 84.05, H 6.20, N 2.97; found C 83.36, H 6.21, N 2.98.

(1*R*,2*S*)-2-[(6-{[(1*R*,2*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl]methyl}-2-pyridinyl)methyl]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol (3d) with *n*-Butyllithium: The mono-adduct **2d** (1.0 g, 3.9 mmol) was dissolved in 50 mL of THF and cooled to −40 °C. *n*-Butyllithium (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added and the mixture was stirred for 3 h at −40 °C. After cooling to −60 °C, (*R*)-(+)-camphor (0.6 g, 3.9 mmol) in 5 mL of THF was added and stirring was continued for ca. 12 h, allowing the mixture to reach ambient temperature. The mixture was quenched with 2 N NH_4Cl and extracted twice with dichloromethane. The combined organic layers were washed with brine and dried with $MgSO_4$. The product was purified by means of column chromatography [SiO_2, hexane/diethyl ether (9:1)] yielding **3d** as a colorless solid, which was recrystallized from ethanol/water (2:1) (1.0 g, 2.3 mmol, 60%), m.p. 124−125 °C. − $[\alpha]_D^{23}$ = −98.8 (*c* = 2.5, acetone). − IR (KBr): $\tilde{\nu}$ = 3450, 3000, 1630, 1620, 1500, 1060, 850 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.51 (s, 6 H), 0.77 (s, 6 H), 1.04 (s, 6 H), 1.10 (m, 2 H), 1.44 (m, 6 H), 1.68 (m, 4 H), 1.94 (m, 2 H), 2.91 (s, 4 H), 4.44 (br, 2 OH), 7.04 (d, *J* = 7.7 Hz, 2 H), 7.49 (t, *J* = 7.7 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 10.8 (q), 20.9 (q), 21.4 (q), 27.1 (t), 30.6 (t), 44.9 (t), 45.8 (t), 46.8 (d), 49.4 (s), 52.5 (s), 80.8 (s), 122.5 (d), 137.2 (d), 159.1 (s). − HRMS: calcd. 411.314; found 411.314. − $C_{27}H_{41}NO_2$ (411.6): calcd. C 78.78, H 10.04, N 3.40; found C 78.64, H 9.82, N 3.42.

(1*R*,2*S*)-1,7,7-Trimethyl-2-(2-pyridinylmethyl)bicyclo[2.2.1]heptan-2-ol (10d): *n*-Butyllithium (1.6 M in hexane, 21.8 mL, 34.9 mmol) was added to a stirred solution of 2-methylpyridine (3.2 g, 34.8 mmol) in 75 mL of THF at −60 °C. After stirring for 30 min, a solution of (*R*)-(+)-camphor (5.4 g, 35 mmol) in 5 mL of THF

was added by syringe. Stirring was continued for 3 h allowing the mixture to reach room temp. The mixture was quenched with 2 N NH_4Cl and extracted twice with ethyl acetate, after which the combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvent, the product was purified by kugelrohr distillation (120 °C, 0.1 Torr) yielding **10d** as a colorless oil (6.2 g, 25 mmol, 72%): $[\alpha]_D^{23} = -15.9$ (c = 0.6, acetone). − IR (KBr): $\tilde{\nu}$ = 3300, 2950, 1650, 1630, 1450, 1050, 800, 500 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.48 (s, 3 H), 0.81 (s, 3 H), 0.98 (d, J = 13.2 Hz, 1 H), 1.09 (m, 1 H), 1.11 (s, 3 H), 1.41 (m, 3 H), 1.70 (m, 2 H), 2.06 (d, J = 13.2 Hz, 1 H), 2.91 (s, 2 H), 6.31 (br, OH), 7.17 (m, 2 H), 7.61 (t, J = 7.7 Hz, 1 H), 8.45 (d, J = 4.0 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 11.0 (q), 20.9 (q), 21.3 (q), 27.1 (t), 30.6 (t), 44.9 (d), 45.1 (t), 47.3 (t), 49.4 (s), 52.8 (s), 81.1 (s), 121.3 (d), 124.2 (d), 136.7 (d), 147.8 (d), 160.4 (s). − HRMS: calcd. 245.178; found 245.178 − $C_{16}H_{23}NO$ (245.4): calcd. C 78.32, H 9.45, N 5.71; found C 78.33, H 9.54, N 5.44.

Reaction of (10d) with *n*-Butyllithium and Benzophenone to Obtain 10a: To a stirred solution of **10d** (0.7 g, 2.7 mmol) in 50 mL of THF at −60 °C was added *n*-butyllithium (1.6 M in hexane, 3.5 mL, 5.6 mmol) followed after 5 min by the addition of benzophenone (0.5 g, 2.7 mmol). The mixture was stirred for 1 h, allowing it to reach ambient temperature, and was quenched with 2 N NH_4Cl. The solution was extracted with dichloromethane twice and the organic layers were washed with brine and dried with Na_2SO_4. After removal of the solvent, the product **10a** and the starting material **10d** were separated by means of crystallization from hexane, from which the benzophenone adduct **10a** crystallized as colorless needles (0.3 g, 1.1 mmol, 40%) with m.p. 155−156 °C. − IR (KBr): $\tilde{\nu}$ = 3200, 3000, 1600, 1580, 1450, 1100, 850, 800, 700 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 2 H), 7.05 (m, 2 H), 7.14 (m, 2 H), 7.24 (t, J = 8.1 Hz, 4 H), 7.47 (m, 5 H), 7.74 (br, OH), 8.37 (d, J = 4.4 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ 0 46.9 (t), 78.3 (s), 121.4 (d), 124.5 (d), 126.1 (d), 126.3 (d), 127.8 (d), 136.8 (d), 147.1 (s), 147.8 (d), 159.2 (s). − HRMS: calcd. 275.131; found 275.132 − $C_{19}H_{17}NO$ (275.4): calcd. C 82.88, H 6.22, N 5.09; found C 82.37, H 6.23, N 5.05.

Preparation of KDA:[23] To a stirred solution of potassium *tert*-butoxide (0.9 g, 8.0 mmol) in 50 mL of THF was added diisopropylamine (0.8 g, 8.0 mmol), and the mixture was cooled to −100 °C. *n*-Butyllithium (1.6 M in hexane, 5.0 mL, 8.0 mmol) was added over a period of 10 min and the solution was stirred for 30 min before use.

2-({6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanol (3b) with KDA: The mono-adduct **2b** (0.5 g, 1.9 mmol) was dissolved in 25 mL of THF and cooled to −50 °C. A freshly prepared potassium diisopropylamide solution (0.16 M in THF, 4.0 mmol, 25 mL) was added by canula. Stirring was continued for 15 min before adamantanone (0.3 g, 2.0 mmol) in 5 mL of THF was added. After 1 h, the mixture was quenched with 2 N NH_4Cl, extracted twice with dichloromethane, and dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure to obtain **3b** as a solid that was recrystallized from ethanol yielding colorless needles (0.8 g, 1.8 mmol, 95%). Experimental data were in full accordance with those described in previous paragraphs.

2-[6-(2-Hydroxy-2,2-diphenylethyl)-2-pyridinyl]-1,1-diphenyl-1-ethanol (3a) with KDA: To a stirred solution of the mono-adduct **2a** (0.52 g, 1.80 mmol) in 50 mL of THF at −70 °C was added a freshly prepared solution of KDA (0.25 M in THF, 14.8 mL, 3.7 mmol). The red solution was stirred for 15 min and benzophenone (1.81 g, 0.33 mmol) in 5 mL of THF was added. Stirring was continued for 1 h, allowing the reaction mixture to reach −10 °C, and subsequently quenched with 2 N NH_4Cl. The product was isolated by two-fold extraction with dichloromethane. The organic layers were washed with brine and dried with Na_2SO_4. After removal of the solvents, the product was recrystallized from water/ethanol affording **3a** as colorless crystals (0.76 g, 1.62 mmol, 90%). Experimental data were in full accordance with those described in previous paragraphs.

(1*R*,2*S*)-2-[(6-{[(1*R*,2*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl]methyl}-2-pyridinyl)methyl]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol (3d) with KDA: Mono-adduct **2d** (0.5 g, 1.9 mmol) was dissolved in 50 mL of THF and a solution of KDA (0.16 M in THF, 25 mL, 4.0 mmol) was added at −50 °C. After stirring for 15 min, a solution of (*R*)-(+)-camphor (0.3 g, 2.0 mmol) in 5 mL of THF was added. Stirring was continued for 2 h while the solution was allowed to reach ambient temperature. The mixture was quenched with 2 N NH_4Cl and extracted twice with dichloromethane. The combined organic layers were washed with brine and dried with $MgSO_4$. The product was recrystallized from ethanol/water (2:1) (0.8 g, 1.8 mmol, 95%). All experimental data are in full accordance with those described in previous paragraphs.

1,1-Diphenyl-2-(2-pyridinyl)-1-ethanol (10a): To a solution of 2-picoline (**13**) (3.9 g, 42 mmol) in 100 mL of THF at −60 °C was added *n*-butyllithium (1.6 M in hexane, 26.3 mL, 42.1 mmol) and the mixture was stirred for 30 min. A solution of benzophenone (7.6 g, 42 mmol) in 10 mL of THF was added. Stirring was continued for 1 h allowing the mixture to reach ambient temperature. The mixture was quenched with 2 N NH_4Cl, extracted twice with ethyl acetate and the combined organic layers were dried with $MgSO_4$. The product was recrystallized from ethanol yielding a colorless solid (10.8 g, 39.4 mmol, 94%). All spectroscopic data are in accordance with those described in previous paragraphs.

2-(2-Pyridinylmethyl)-2-adamantanol (10b): 2-Picoline (**13**) (0.9 g, 9.7 mmol) was dissolved in 75 mL of THF and cooled to −60 °C. Subsequently, *n*-butyllithium (1.6 M in hexane, 6.9 mL, 11 mmol) was added and stirring was continued for 30 min. Adamantanone (1.65 g, 10.9 mmol) in 5 mL of THF was slowly added and the reaction mixture was stirred for 1 h. After the reaction was quenched with 2 N NH_4Cl, the solution was extracted twice with ethyl acetate and the combined organic layers were dried with $MgSO_4$. The product was purified by means of column chromatography [silica, hexane/diethyl ether (3:1)] yielding **10b** as a colorless solid (1.8 g, 7.4 mmol, 74%) with m.p. 87−88 °C. − IR (KBr): $\tilde{\nu}$ = 3300, 2900, 1600, 1590, 1400, 950, 800 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.4−2.0 (m, 12 H), 2.33 (d, J =11.0 Hz, 2 H), 3.14 (s, 2 H), 6.05 (br, OH), 7.15 (m, 2 H), 7.61 (t, J = 7.7 Hz, 1 H), 8.50 (d, J = 5.5 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 27.3 (d), 27.4 (d), 32.7 (t), 34.6 (t), 37.2 (d), 38.4 (t), 43.6 (t), 75.4 (s), 121.3 (d), 124.4 (d), 136.6 (d), 148.3 (d), 159.6 (s). − HRMS: calcd. 243.162; found 243.163. − $C_{16}H_{21}NO$ (243.4): calcd. C 78.97, H 8.70, N 5.76. found C 78.95, H 8.79, N 5.81.

2-Methyl-1-(2-pyridinyl)-2-propanol (10c):[24] To a stirred solution of 2-picoline (**13**) (0.7 g, 7.4 mmol) in 50 mL of THF at −50 °C was added *n*-butyllithium (1.6 M in hexane, 5.0 mL, 8.1 mmol) followed by the addition of acetone (0.6 g, 10 mmol) after stirring for 15 min. Stirring was continued for another 15 min, and the solution was quenched with NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with $MgSO_4$. The product was obtained after distillation by means of kugelrohr (60 °C, 0.05 Torr) affording **10c** (0.6 g, 3.8 mmol, 51%). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 6 H), 2.84 (s,

2 H), 5.6 (br, OH), 7.05 (d, J = 8.1 Hz, 1 H), 7.10 (m, 1 H), 7.55 (t, J = 8.1 Hz, 1 H), 8.42 (d, J = 4.4 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.3 (q), 48.5 (t), 70.6 (s), 121.3 (d), 124.2 (d), 136.6 (d), 148.2 (d), 159.8 (s).

1,1,3,3-Tetraphenyl-2-(2-pyridinyl)-1,3-propanediol (14a): To a solution of the mono-adduct **10a** (1.0 g, 3.6 mmol) in 50 mL of THF at room temp. was added *n*-butyllithium (1.6 M in hexane, 4.8 mL, 7.7 mmol). The mixture was stirred for 15 min and benzophenone (0.7 g, 3.6 mmol) in 5 mL of THF was added. The mixture was stirred overnight. The mixture was quenched with 2 N NH_4Cl and extracted with dichloromethane, and the organic layer dried with $MgSO_4$. The mixture was concentrated and the solid was washed with hot methanol and recrystallized from ethyl acetate/hexane yielding a colorless solid (0.6 g, 1.2 mmol, 33%) with m.p. 143−144 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (s, 1 H), 6.53 (d, J = 7.7 Hz,1 H), 6.8−7.1 (m, 14 H), 7.3 (m, 8 H), 8.21 (d, J = 4.8 Hz, 1 H), 8.27 (br, 2 OH). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 57.0 (d), 82.4 (s), 120.7 (d), 125.7 (d), 125.8 (d), 126.0 (d), 126.6 (d), 127.1 (d), 127.3 (d), 127.9 (d), 134.9 (d), 144.5 (s), 146.3 (d), 148.1 (s),160.9 (s). − HRMS: calcd. 457.204; no proper HRMS could be obtained. CI (NH_3) gave molecular ions at *m*/*z* 183 and 276. − $C_{32}H_{27}NO_2$ (457.6): calcd. C 84.00, H 5.95, N 3.06; found C 83.87, H 5.99, N 3.11.

2-[(2-Hydroxy-2-adamantyl)(2-pyridinyl)methyl]-2-adamantanol (14b): A solution of *n*-butyllithium (1.6 M in hexane, 6.3 mL, 10 mmol) was added to a stirred solution of mono-adduct **10b** (1.2 g, 5.0 mmol) in 75 mL of THF at 0 °C. Stirring was continued for 30 min and adamantanone (0.8 g, 5.1 mmol) in 5 mL of THF was added. The mixture was stirred for another hour and quenched with 2 N NH_4Cl. The solution was extracted twice with dichloromethane, the combined organic layers were dried with $MgSO_4$. After concentration of the solution, the solid was washed with hot hexane leaving **14b** as a white solid (0.5 g, 1.3 mmol, 26%) with m.p. 183−184 °C. − IR (KBr): $\tilde{\nu}$ = 3400, 2950, 1650, 1630, 1450, 1100, 750 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (s, 2 H), 1.21 (m, 3 H), 1.46 (m, 4 H) 1.6−1.9 (m, 13 H), 2.05 (d, J = 12.1 Hz, 2 H), 2.23 (d, J = 12.1 Hz, 2 H), 2.44 (m, 4 H), 3.98 (s, 1 H), 6.82 (s, 2 OH), 7.19 (m, 1 H), 7.28 (d, J = 8.1 Hz, 1 H), 7.59 (m, 1 H), 8.59 (d., J = 5.1 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 26.6 (d), 27.0 (d), 32.9 (t), 33.0 (t), 34.3 (t), 35.2 (t), 36.9 (d), 37.7 (d), 38.1 (t), 48.0 (d), 80.3 (s), 121.5 (d), 126.5 (d), 136.1 (d), 148.7 (d), 161.9 (s). − HRMS: calcd. 393.267; no proper HRMS could be obtained. CI (NH_3) gave a molecular ion at *m*/*z* 394. − $C_{26}H_{35}NO_2$ (393.6): calcd. C 79.35, H 8.96, N 3.56; found C 78.60, H 9.09, N 3.64.

2,4-Dimethyl-3-(2-pyridinyl)-2,4-pentanediol (14c): To a stirred solution of **10c** (0.4 g, 2.4 mmol) in 50 mL of THF at −30 °C was added *n*-butyllithium (1.6 M in hexane, 3.0 mL, 4.9 mmol). The solution was stirred for 30 min and acetone (0.2 g, 3.0 mmol) was added. After stirring for 1 h, the mixture was quenched with 2 N NH_4Cl. The solution was extracted twice with ethyl acetate and the combined organic layers were dried with $MgSO_4$. The starting material was removed by means of kugelrohr distillation (80 °C, 0.05 Torr) and the residue was purified by means of column chromatography [silica, hexane/ethyl acetate (1:1)] affording **14c** as a colorless oil (0.2 g, 0.7 mmol, 30%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 6 H), 1.37 (s, 6 H), 2.74 (s, 1 H) 5.11 (br, 2 OH), 7.05 (d, J = 7.7 Hz, 1 H), 7.13 (m, 1 H), 7.58 (dd, J = 7.7 Hz, J = 7.7 Hz, 1 H), 8.45 (d., J = 4.0 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.4 (q), 31.6 (q), 62.2 (d), 74.2 (s), 121.6 (d), 126.3 (d), 136.5 (d), 147.9 (d), 162.7 (s). − HRMS: calcd. 209.141; no proper HRMS could be obtained. CI(NH_3) gave a molecular ion at *m*/*z* 152. − $C_{12}H_{19}NO_2$ (209.3): calcd. C 68.85, H 9.16, N 6.70; found C 68.63, H 9.00, N 6.47.

(1*R*,2*RS*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]-bicyclo[2.2.1]heptan-2-ol (2f): 2,6-Lutidine (**1**) (1.0 g, 0.9 mmol) in 50 mL of THF was lithiated with *n*-butyllithium (1.6 M in hexane, 6.2 mL, 9.9 mmol) at −60 °C. After stirring for 10 min (*R*)-(−)-fenchone (1.4 g, 9.2 mmol) in 5 mL of THF was added and stirring was continued for 1 h. NH_4Cl was added and the mixture was extracted with ethyl acetate yielding **2f** as a mixture of the *exo* and *endo* isomers (1.9 g, 7.3 mmol, 79%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67 (s, 3 H), 0.76 (s, 3 H), 0.86 (s, 3 H), 0.90(s, 3 H), 0.99 (s, 3 H), 1.05 (s, 3 H), 1.1−1.8 (m, 12 H), 2.1−2.3 (m, 2 H), 2.47 (s, 6 H), 2.85 (d, J = 15.6, 2 H), 2.95 (s, 2 H), 3.03 (d, J = 15.6, 2 H), 6.95 (m, 4 H), 7.5 (m, 4 H).

(1*RS*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)-methyl]cyclohexanol (2g): To a solution of 2,6-lutidine (**1**) (0.7 g, 6.5 mmol) in 50 mL of THF at −60 °C was added *n*-butyllithium (1.6 M in hexane, 4.1 mL, 6.5 mmol). After stirring for 10 min, (−)-menthone (1.0 g, 6.5 mmol) in 5 mL of THF was added. Stirring was continued for 1 h at −60 °C before the mixture was quenched with NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried with $MgSO_4$. The *cis* and *trans* products in the mixture with a ratio of 2:1 were separated by means of column chromatography (silica, hexane/diethyl ether 10:1) yielding the pure isomers.

***trans*-2g:** (0.5 g, 2.0 mmol, 30%), m.p. 60−62 °C. − $[\alpha]_D^{23}$ = +67 (c = 0.8, acetone). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 1 H), 0.91 (m, 2 H), 1.03 (d, J = 7.0 Hz, 3 H), 1.33 (m, 2 H), 1.37 (m, 2 H), 1.67 (m, 1 H), 1.73 (m, 1 H), 2.44 (dq, J = 7.0 Hz, J = 7.0 Hz, 1 H), 2.52 (s, 3 H), 2.94 (dd, J = 14.0 Hz, J = 14.0 Hz, 2 H), 6.91 (d, J = 7.5 Hz, 1 H), 7.01 (d, J = 7.8 Hz, 1 H), 7.51 (dd, J = 7.0 Hz, J = 7.8 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 19.2 (q), 22.3 (q), 23.4 (t), 24.86 (q), 24.78 (q), 30.3 (d), 35.0 (t), 38.9 (t), 47.8 (t), 51.9 (d), 75.6 (s), 120.8 (d), 121.2 (d), 136.9 (d), 157.3 (s), 159.4 (s). − HRMS: calcd. 261.209; found 261.209. − $C_{17}H_{27}NO$ (261.4): calcd. C 78.11 H 10.41, N 5.36; found C 78.12, H 10.57, N 5.12.

***cis*-2g:** (1.0 g, 3.8 mmol, 59%), m.p. 64−66 °C. − $[\alpha]_D^{23}$ = −121 (c = 0.6, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67 (d, J = 6.2 Hz, 3 H), 0.75 (m, 2 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 1.05 (m, 1 H), 1.15 (m, 1 H), 1.52 (m, 2 H), 1.67 (m, 2 H), 2.19 (dq, J = 6.9 Hz, J = 6.9 Hz, 1 H), 2.44 (d, J = 3.9, 1 H), 2.45 (s, 3 H), 3.31 (d, J = 13.9 Hz, 1 H), 6.84 (d, J = 7.3 Hz, 1 H), 6.93 (d, J = 7.7 Hz, 1 H), 7.44 (dd, J = 6.9 Hz, J = 7.7 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 18.0 (q), 20.8 (t), 22.4 (q), 23.8 (q), 24.2 (q), 26.2 (d), 27.7 (d), 35.4 (t), 46.1 (t), 47.4 (t), 51.1 (d), 74.7 (s), 120.6 (d), 121.5 (d), 136.8 (d), 157.1 (s), 159.9 (s). − HRMS: calcd. 261.209; found 261.209. − $C_{17}H_{27}NO$ (261.4): calcd. C 78.11 H 10.41, N 5.36; found C 78.04, H 10.39, N 5.49.

(1*R*,2*S*,5*R*)-1-[(6-{[(1*R*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]methyl}-2-pyridinyl)methyl]-2-isopropyl-5-methylcyclohexanol (*cis*-*cis*-3g): The mono-adduct *cis*-**2g** (0.7 g, 2.5 mmol) was dissolved in 50 mL of THF and cooled to 0 °C, *n*-butyllithium (1.6 M in hexane, 3.4 mL, 5.4 mmol) was added and the mixture was stirred for 5 min. (−)-Menthone (0.4 g, 2.5 mmol) in 3 mL of THF was added and the mixture was stirred overnight. The mixture was quenched with NH_4Cl and extracted twice with dichloromethane. The combined organic layers were dried with Na_2SO_4. After concentration in vacuo, the solid was crystallized from water/ethanol affording *cis*-*cis*-**3g** as a colorless solid (0.4 g, 1.0 mmol, 40%), m.p. 125−126 °C. − $[\alpha]_D^{23}$ = −109 (c = 1.3, acetone). − ^{1}H NMR

(300 MHz, $CDCl_3$): δ 0.67 (d, J = 6.4 Hz, 6 H), 0.8 (m, 4 H), 0.89 (d, J = 6.9 Hz, 6 H), 0.94 (d, J = 6.6 Hz, 6 H), 1.05 (m, 2 H), 1.4−1.8 (m, 10 H), 2.20 (m, 2 H), 2.49 (d, J = 13.2 Hz, 2 H), 3.32 (d, J = 13.2 Hz, 2 H), 3.75 (br, 2 OH), 6.99 (d, J = 7.7 Hz, 2 H), 7.50 (t, J = 7.7 Hz, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 18.1 (q), 20.8 (t), 22.3 (q), 23.7 (q), 26.1 (d), 27.6 (d), 35.1 (t), 47.1 (t), 47.4 (t), 51.0 (d), 74.7 (s), 122.3 (d), 136.8 (d), 159.2 (s). − HRMS: calcd. 415.345; found 415.345. − $C_{27}H_{45}NO_2$ (395.5): calcd. C 78.02, H 10.91, N 3.37; found C 77.91, H 10.99, N 3.37.

Dichloro[(6-methyl-2-pyridinyl)methyl]cerium (16): To a stirred solution of 2,6-lutidine (**1**) (0.1 M solution in THF, 10 mL, 1.0 mmol) at −70 °C was added *n*-butyllithium (0.6 mL, 1.0 mmol). After stirring for 15 min, this solution was added to $CeCl_3$·THF[25] (0.1M solution in THF, 10 mL, 1.0 mmol) at −70 °C. The solution was stirred for 1 h at −50 °C and used as such for the addition reactions to ketones.

General Procedure for the Addition of 16 to Ketones: To a stirred solution of **16** (0.05 M solution in THF, 20 mL, 1.0 mmol) at −70 °C was added a solution of the ketone (1.0 mmol) in 2 mL of THF. Stirring was continued for 3 h after which the solution was quenched with NH_4Cl and extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried with $MgSO_4$.

(1*R*,2*RS*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo-[2.2.1]heptan-2-ol (2f) with $CeCl_3$: According to the above general procedure starting from **16** (0.05 M solution in THF, 22 mL, 1.1 mmol) and (*R*)-(−)-fenchone (0.2 g, 1.1 mmol), a mixture of *endo* and *exo* isomers **2f** was obtained in a ratio of 4:1 (0.2 g, 0.6 mmol, 54%). The spectra for these isomers are in accordance with those described in previous paragraphs.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)methyl]-cyclohexanol (*cis*-2g) with $CeCl_3$: According to the above general procedure starting from **16** (0.05 M solution in THF, 36 mL, 1.8 mmol) and (−)-menthone (0.3 g, 1.8 mmol) ***cis*-2g** was obtained as a colorless solid after column chromatography (silica, hexane/diethyl ether 9:1) (0.2 g, 0.8 mmol, 45%). Spectra were in full accordance with those described in previous paragraphs.

Acknowledgments

B. K. has been partially supported by a grant from the Dutch National Science Foundation (NWO) administered through the Office for Chemical Research (CW).

[1] [1a] J. D. Morrison, *Asymmetric Synthesis*, vol. 5; Academic Press, New York, **1985**. − [1b] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley, New York, **1995**.

[2] [2a] G. Proctor, *Asymmetric Synthesis*, Oxford University Press, Oxford, England, **1996**. − [2b] R. S. Atkinson, *Stereoselective Synthesis*, Wiley, Chichester, **1995**. − [2c] R. A. Aitken, S. N. Kilény, *Asymmetric Synthesis*, Blackie Academic & Professional, London, **1992**.

[3] B. Koning, R. Hulst, A. Bouter, J. Buter, A. Meetsma, R. M. Kellogg, *Chem. Commun*. **1997,** 1065−1066.

[4] B. Koning, A. Meetsma, R. M. Kellogg, *J. Org. Chem.* **1998**, *63*, 5533−5540.

[5] Z.-Y. Li, W.-Y. Yu, C.-M. Che, C.-K. Poon, R.-J. Wang, T. C. W. Mak, *J. Chem. Soc., Dalton Trans.* **1992**, 1657−1661.

[6] [6a] S. Igai, I. Imaoka, N. Mitani, Ube Industries, Japan, Patent JP 09012582 A2, **1989** (*Chem. Abstr.* **1997**, *126*, 225669). − [6b] Y. Nakayama, N. Ikushima, A. Nakamura, *Chem. Lett*. **1997**, 861−862.

[7] [7a] V. C. Gibson, E. L. Marshall, C. Redshaw, W. Clegg, M. R. J. Elsegood, *J. Chem. Soc., Dalton Trans.* **1996**, 4197−4199. − [7b] J. M. Berg, R. H. Holm, *J. Am. Chem. Soc*. **1984**, *106*, 3035−3036.

[8] H. Mack, M. S. Eisen, *J. Chem. Soc., Dalton Trans.* **1998**, 917−921.

[9] [9a] R. M. Kellogg, B. Kaptein, J. Buter, *J. Bull. Soc. Chim. Belg*. **1990**, *99*, 703−705. − [9b] B. Kaptein, G. Barf, R. M. Kellogg, F. van Bolhuis, *J. Org. Chem*. **1990**, *55*, 1890−1901.

[10] [10a] J. J. H. Edema, R. Libbers, A. Ridder, R. M. Kellogg, *J. Organomet. Chem*. **1994**, *464*, 127−132. − [10b] T. K. Prakasha, A. Chandrasekaran, R. O. Day, R. R. Holmes, *Inorg. Chem*. **1996**, *35*, 4342−4346.

[11] P.-M. Chan, W.-Y. Yu, C.-M. Che, K.-K. Cheung, *J. Chem. Soc., Dalton Trans.* **1998**, 3183−3190.

[12] C. H. Tilford, M. G. van Camphen, *J. Am. Chem. Soc*. **1954**, *76*, 2431−2441.

[13] A. M. Ridder, R. Libbers, J. J. H. Edema, R. M. Kellogg, unpublished results.

[14] J. J. M. Edema, R. Libbers, A. M. Ridder, R. M. Kellogg, F. van Bolhuis, H. Kooijman, A. L. Spek,. *J. Chem. Soc., Chem. Commun*. **1993**, 625−627.

[15] R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1983**, 809−811.

[16] J. Quick, C. Mondello, M. Humora, T. Brennan, *J. Org. Chem*. **1978**, *43*, 2705−2708.

[17] [17a] K. Nonoyama, M. Nonoyama, *Transition Met. Chem*. **1987**, *12*, 497−500. − [17b] S. Schmidt, L. Omnes, F. W. Heinemann, J. Kuhnigk, C. Krueger, A. Grohmann, *Z. Naturforsch., B: Chem. Sci.* **1998**, *53*, 946−954.

[18] [18a] T. Iamamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc*. **1989**, *111*, 4392−4398. − [18b] H.-J. Liu, N. H. Al-said, *Tetrahedron Lett*. **1991**, *32*, 5473−5476.

[19] T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett*. **1984**, *25*, 4233−4236.

[20] [20a] J. Jeener, B. H. Meier, P. Bachmann, R. R. Ernst, *J. Chem. Phys.* **1979**, 71, 4546−4553. − [20b] D. Neuhaus, M. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH Publishers, Cambridge, **1989**.

[21] A. Bax, R. Freeman, *J. Magn. Reson*. **1981**, 44, 542−561.

[22] J. M. Berg, R. H. Holm, *J. Am. Chem. Soc*. **1985**, *107*, 917−925.

[23] E. Pasquinet, P. Rocca, F. Marsais, A. Godard, G. Queguiner, *Tetrahedron* **1998**, *54*, 8771−8782.

[24] J. Büchi, W. Broger, G. Schmidt. *Helv. Chim. Acta* **1965**, *48*, 275−279.

[25] S. F. Martin, *Org. Synth.* **1998**, *76*, 228.

Received December 10, 1999
[O99668]