

Synthesis of Novel 3-Hydroxy-3-pyridylcamphor Derivatives

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Received 19 February 2009, revised 29 April 2009, accepted 13 May 2009.

ABSTRACT

The synthesis of a series of five novel precursor compounds derived from (*R*)-(+)-camphor is reported. From these precursors, a further four novel pyridyl alcohol ligands were synthesized. The molecules represent the first reported examples where the pyridyl and hydroxyl moieties are pendant on the C3 position of the camphor skeleton. The regioselective synthesis was investigated and an efficient method was identified. The final ligands were obtained in moderate yield with absolute *regio*- and stereoselective control. The molecules were screened as catalysts in the alkylation of aldehydes with diethylzinc in order to compare the new arrangement of donor groups with previously reported results obtained with C2 pendant ligands. The results demonstrated a significant improvement for the synthesized C3 pendant ligands over previous C2 examples with moderate yields and up to 85 % *ee* being obtained.

KEY WORDS

Chiral, camphor ligands, pyridyl alcohols, asymmetric alkylation reactions.

1. Introduction

This is the second paper in a series of research results from our group in the field of asymmetric synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels–Alder reaction.¹ In the search for new ligands for asymmetric catalysis, the natural world has proven to be an invaluable source.^{2,3} A range of very effective homogeneous catalytic systems has been reported based on naturally-occurring molecules.^{4,5} Chiral monoterpenes such as camphor have been widely used in the development of asymmetric catalysts with varying degrees of success in reactions such as the addition of diethylzinc to aldehydes,⁶ hydrogenation and allylic substitution.⁷ They afford a simple, inexpensive and inherently chiral scaffold around which to build the catalyst. The synthesis of pyridyl *N*-donor ligands derived from camphor has been extensively studied.^{8–14} Several of these ligands have proven to be moderately to highly successful chiral catalysts for applications such as allylic oxidations,¹¹ addition of organozinc reagents to aldehydes^{8,10,12,13} and hydrogenation reactions.¹⁴ Previously reported pyridyl alcohol ligands typically fall into one of two categories. In the first the pyridyl and hydroxyl groups are pendant at the C2 position of the camphor skeleton such as in **1**.^{8,13} This category has been much more prevalent with numerous examples in the literature^{8–11,13} and they have generally been used as catalysts in the addition of alkylzinc reagents to aldehydes. The results of these applications have varied from moderate⁸ to good^{10,13} in terms of enantioselectivity. The second category is that in which the hydroxy group is at C2 and the pyridyl moiety is pendant at C3, such as in **2**.¹² This example (**2**), synthesised by Nevalainen *et al.*,¹² was also used as a catalyst for alkylzinc reactions with good results in terms of enantioselectivity. It thus appeared that there was a significant opportunity for investigation into ligands which are derivatized at the C3 position of camphor.

The reasons for this apparent lack of C3 pendant ligands could

be due to the fact that camphor, which has a C2 ketone, is used as a convenient starting material. For analogous ligands pendant on C3, epicamphor, which is not easily synthesized, would have to be used as the starting material. This presents additional undesirable synthetic complications.¹⁵ In order to expand the potential of camphor, however, the synthesis of ligands **3–6**, where both the pyridyl and hydroxyl groups are pendant on C3 of the skeleton was undertaken (see Fig. 1).

To the best of our knowledge, the molecules (**3–6**) represent the first examples of ligands with this arrangement of the donor groups. These compounds were compared directly with ligands such as **1** and **2** in the reaction of diethylzinc to aldehydes.⁸

2. Results and Discussion

In the construction of these ligands, two approaches using similar methodologies were investigated in order to obtain the common precursor to the final target molecules. In both approaches, the (*R*)-(+)-camphor **7** starting material was converted to camphorquinone **8**, followed by ketalization with different diols. The synthesis of camphorquinone was carried out according to literature procedures to yield the yellow semi-crystalline product in good yields.¹⁶ Method A (Scheme 1) involved the reaction of camphorquinone **8** with *meso*-2,3-butanediol *as per* the method adopted by Evans *et al.*^{17–19} This particular diol was chosen for its steric bulk. The two methyl groups on the diol are sufficiently large as to minimize reaction of the diol with the more sterically hindered C2 ketone (Fig. 1). The selective protection of the C3 ketone should thus result. Method B (Scheme 2) utilized ethylene glycol as the protecting group. It is known from the literature that this method consistently results in a protection ratio of approximately 3:1 for the C3:C2 protected product.²⁰ Method A was attempted first.

The reaction of the quinone with the *meso*-2,3-butanediol using the methodology reported by Evans *et al.* yielded what appeared to be the monoprotected ketal **9**.¹⁹ Although Evans *et al.* reported that the 3-substituted product **9** was obtained exclusively, we discovered that after reduction with sodium borohydride to obtain the hydroxy ketal **10**, we did in fact observe a

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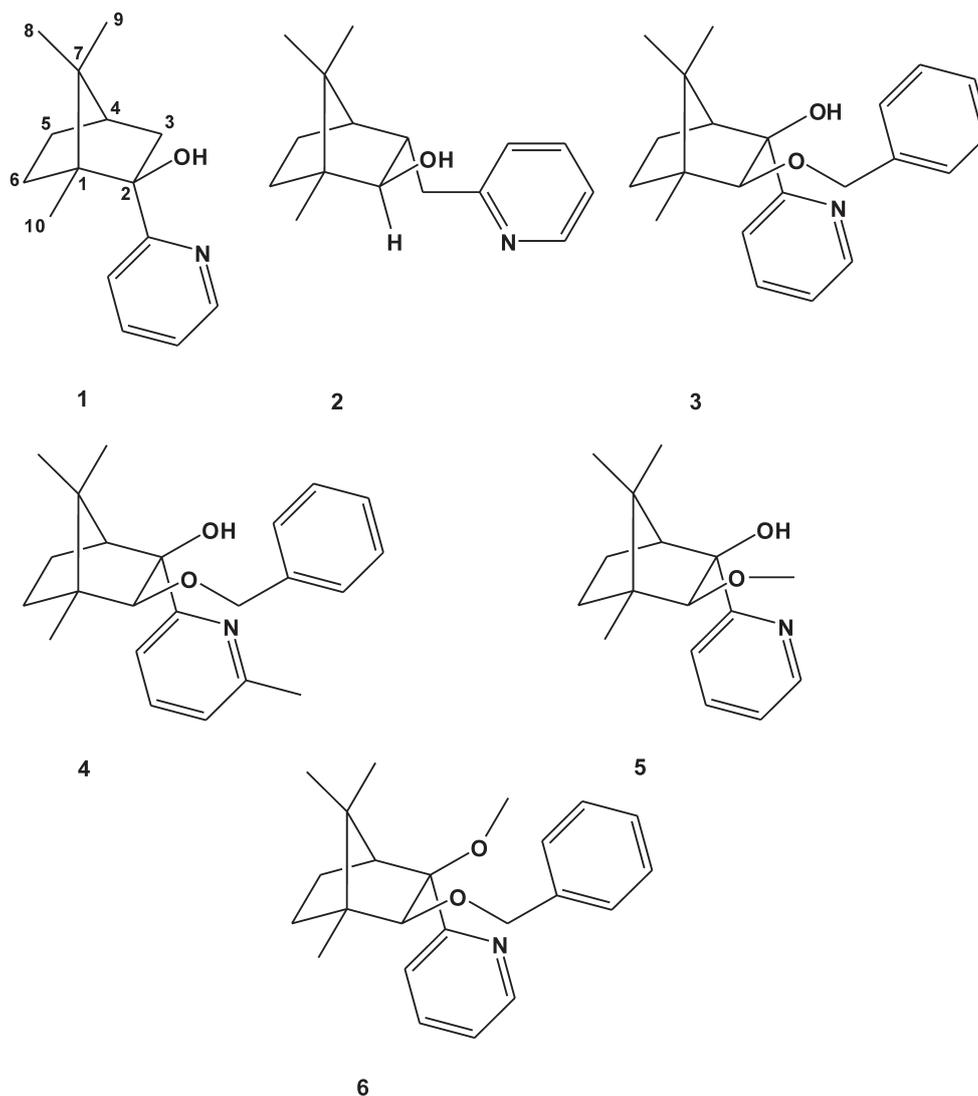


Figure 1 Camphor-derived pyridyl alcohol ligands.

small amount of the 2-substituted product **10b**. The approximate diastereomeric ratio obtained was 9:1 for **10a**:**10b** (Fig. 2). This ratio was determined by integration of the ^1H signal for the H atom attached to C2 (δ 3.34 ppm) or C3 (δ 3.38 ppm). In our case it was not possible to determine this ratio before reduction, nor was it possible to separate these regioisomers before the reduction point.

We managed to separate the predominant *regio*-isomer (**10a**) from the minor *regio*-isomer (**10b**) by simple column chromatography.

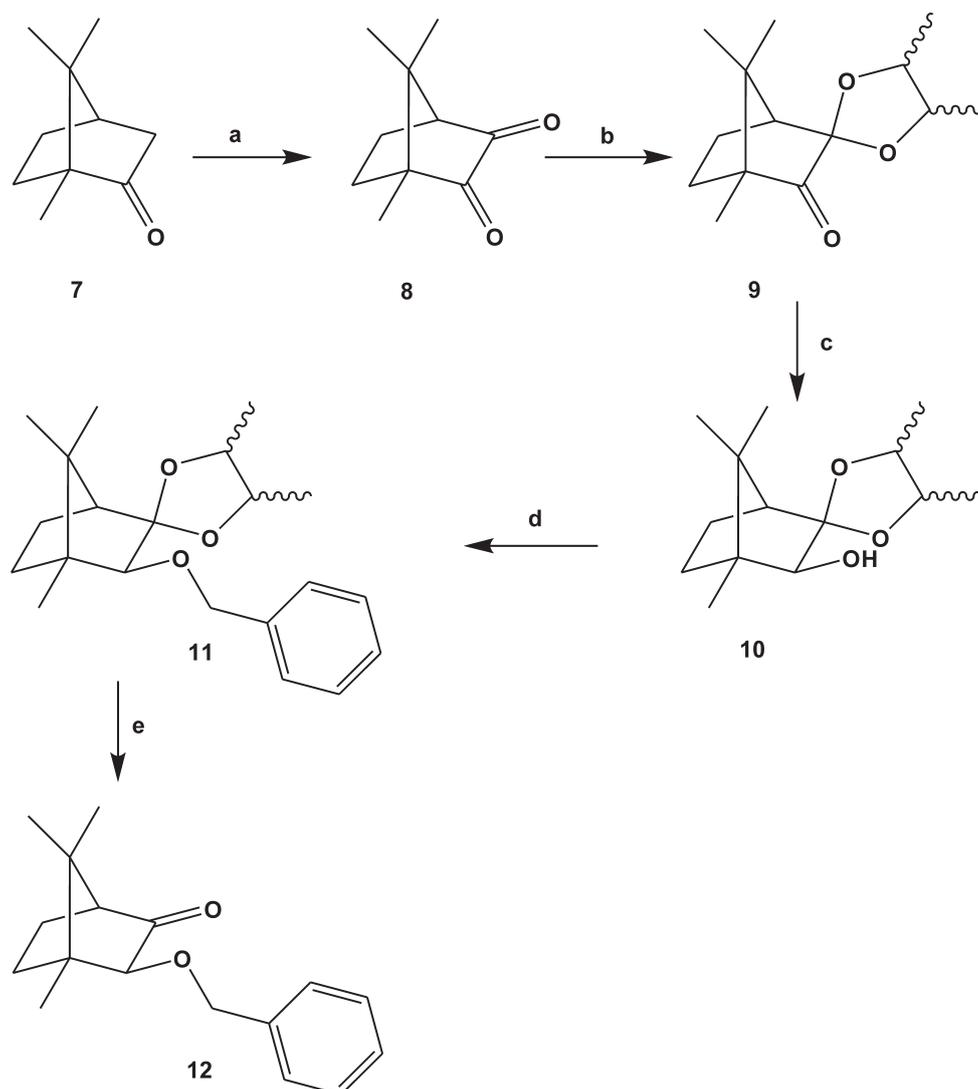
At this stage it was found that a small amount of the *endo*-OH product (**10a-2**) was present. This phenomenon was also observed and reported by Evans *et al.*¹⁹ The diastereomeric ratio of the hydroxyl products **10a-1** and **10a-2** present (Fig. 3) was also determined by ^1H NMR spectroscopy *via* the integration of the respective proton signals. The desired product (**10a-1**) has an *endo*-H at δ 3.34 ppm whilst the *exo*-H of **10a-2** appears at δ 3.67 ppm. The ratio was determined to be 9:1 *exo*:*endo*-OH.

Separation of these diastereomers was not achieved. Further investigation of the isolated mixture of diastereomers **10a-1** and **10a-2** revealed a further two diastereomers **10a-3** and **10a-4** (Fig. 4). The orientation of the butanediol methyl groups resulted in diastereomers which could be assigned by NMR. The isolated material consisted of a mixture of *exo*- and *endo*-OH diastereomers for each diastereomer (**10a-3** or **10a-4**) although

the *exo*-OH diastereomer (as shown in Fig. 4) was the predominant form with the *endo*-OH isomer present only in trace amounts (~5 %).

NMR elucidation of the two diastereomers (**10a-3** and **10a-4**) was carried out. Reasonable separation was obtained, but the spectra still indicated the presence of a mixture. The minor isomer **10a-3** showed no NOESy interactions between the methyl groups (δ 1.11–1.15 ppm) on the butanediol with either the hydroxy proton (δ 2.50 ppm) or the bridge methyl of the camphor (C9 – δ 1.03 ppm). The major product **10a-4** did in fact show through-space correlations with both of these groups. The orientation of these groups also resulted in a significant shift in the signal for the C2 *endo*-H proton. The signal appeared at either δ 3.34 ppm (**10a-3**) or δ 3.19 ppm (**10a-4**) depending on the configuration. The orientation of these butane diol groups was not considered to be important due to the fact that the ketal was to be removed later on in the synthesis.

Protection of the hydroxyl group with benzyl bromide to yield **11** (Scheme 1) as well as the subsequent removal of the ketal to obtain **12** was carried out without difficulty. Although the yields obtained in the various steps of method A were reasonable, the mixtures of diastereomers made this approach problematic. Indeed, even the final C3 ketone (**12**) exhibited significant doubling of the signals in the ^{13}C NMR spectrum. Thus, it was clear that an alternative method was necessary.



Scheme 1

Method A (reaction, reagents and conditions). Key: (a) SeO_2 , Ac_2O , reflux 16 h, 86 %; (b) meso-2,3-butanediol, PTSA, benzene, reflux 12 h, 80 %; (c) NaBH_4 , diethyl ether/MeOH (1:1), RT 2 h, 85 %; (d) benzyl bromide, NaH, dry THF, 12 h, 75 %; (e) conc. HCl/THF (1:3), 2 h, 80 %.

As such, method B, involving a more traditional approach, was explored. The ratio of approximately 3:1 for the C3 to C2 protected ketones was obtained, as expected from the literature. However, a literature survey revealed a synthesis of hydroxy epicamphor by Fleming *et al.*²¹ in which the desired product 13 was crystallized from the crude reaction mixture with ethanol.

Application of this procedure proved very successful in obtaining the desired C3 protected product 13. Although the total yield of this reaction in terms of product isolated in the first step was not as high as in the butanediol method, an average diastereomeric ratio of better than 100:1 was achieved for the alcohol 14 (according to NMR integration as described below). This makes method B much more attractive in terms of *regio*-selectivity. The relative configuration of 13 was confirmed by X-ray crystallography of the product obtained after recrystallization (Fig. 5).

This breakthrough made it possible to proceed with the synthesis of the precursor ketone 12. The ketal 13 was reduced using sodium borohydride to yield the hydroxy ketal 14 in quantitative yield. This also constitutes a vast improvement compared with the butanediol method, where the yield of the isolated hydroxyl ketal 10a was quite poor (~50 %). We determined the diastereomeric ratio by integration of the signal of the *endo*-H proton on C2. Once again it was discovered that a small amount of

endo-OH was present (14b), the ratio being about 10:1 for 14a:14b (determined by NMR – *exo*-H at δ 3.64 ppm and *endo*-H at δ 3.30 ppm).

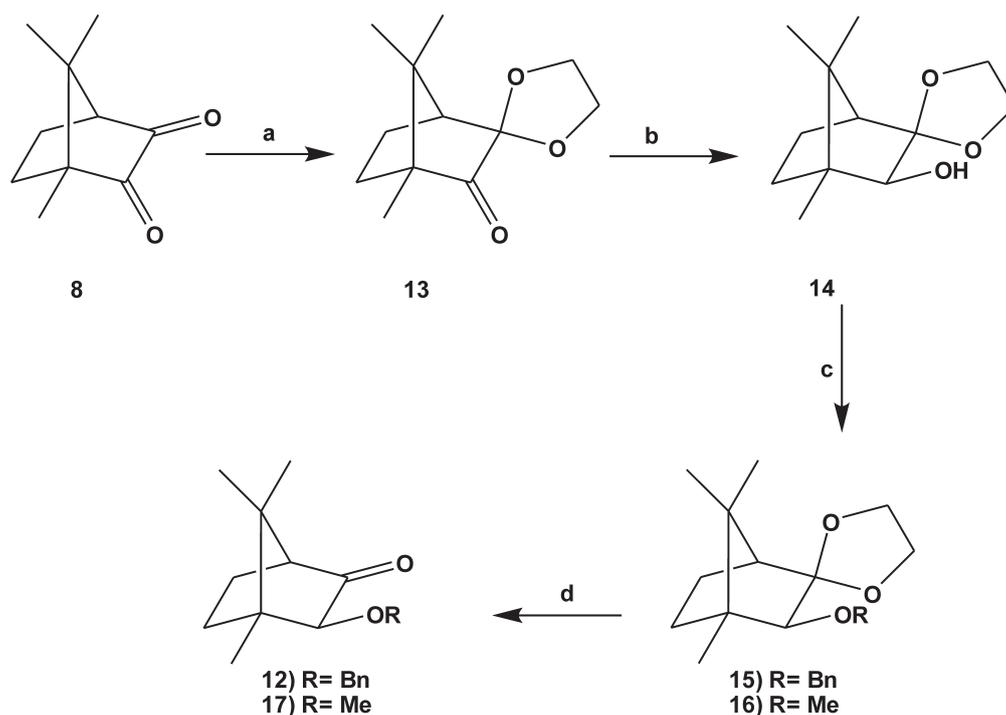
We were unable to separate these diastereomers (Fig. 6). Protection of the hydroxyl groups with benzyl bromide proceeded with good yields at room temperature to give the novel ketal ethers 15a and 15b (Fig. 7).

It was discovered that the separation of the diastereomers improved significantly with each subsequent step. Removal of the ketal group was easily achieved using standard acid techniques to yield the precursor ketone 12 as almost exclusively the *exo* product in good yield.

Reaction of the same hydroxy ketal 14 with iodomethane afforded the methoxy derivative 16 in essentially quantitative yield (Scheme 2). In isolating the product using simple column chromatography, it was discovered that the *exo*-OMe (16a) product could be easily separated from the *endo*-OMe product (16b) (Fig. 8). The concentration of the latter isomer 16b was so low that it could not be isolated.

Removal of the ketal was carried out in the same way as before, using hydrochloric acid in THF at room temperature to yield the methoxy ketone 17 in reasonable yield.

These precursor ketones 12 and 17 were to be reacted with



Scheme 2

Proposed reactions, reagents and conditions for Method B. Key: (a) ethylene glycol, PTSA, benzene, reflux 12 h, 65 %; (b) NaBH₄, diethyl ether/MeOH (1:1), RT 2 h, quant.; (c) benzyl bromide (15), MeI (16), NaH, dry THF, 12 h, 81 % (15), quant. (16); (d) conc. HCl/THF (1:3), 2 h, 80 % (12), 70 % (17).

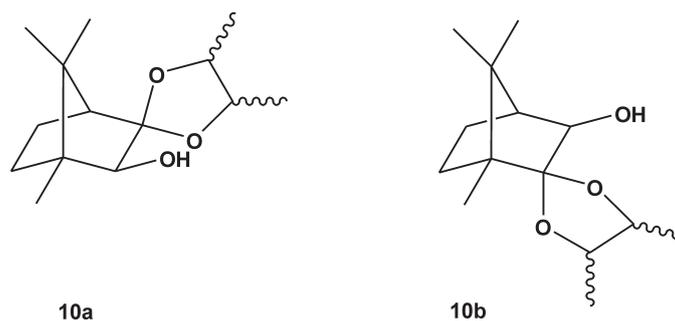
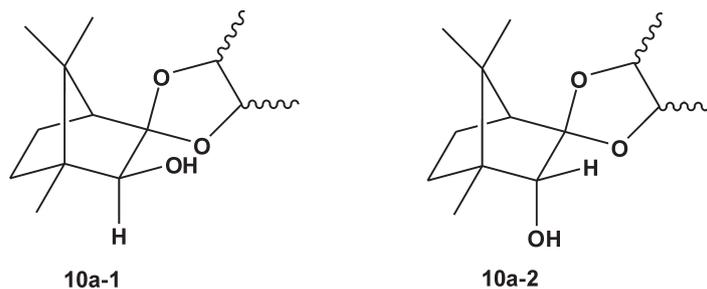


Figure 2 Regio-isomers 10a and 10b.

pyridyllithium in order to afford the final ligands 3–5. From the literature, it is well documented that ketones derived from camphor are very unreactive and give poor yields unless activated by an additive such as CeCl₃.^{7,9,20,23} The commercially available cerium (III) chloride heptahydrate was dried using the method developed by Dimitrov *et al.*²⁴

The lithiation reactions used to afford ligands 3 and 4 were carried out using the technique reported by Dimitrov *et al.*^{9,24} (Scheme 3). It was discovered upon isolation of the products that only the *exo*-ether ketone 12a had reacted and that there was no indication of any *endo* product. It was assumed that the ketones with the ether group *endo* were too sterically hindered to allow

nucleophilic attack by the pyridyllithium from the *endo* side, which is the only side from which it can attack since the steric bulk of the bridge methyl groups prevents *exo* attack. It is widely reported in the literature that nucleophilic attack on ketones attached to the camphor skeleton is only possible from the *endo* side for this reason.^{9,20,25} However, it was discovered that this final reaction step was extremely temperature sensitive. If the lithiation reaction was carried out at a temperature even slightly higher than –78 °C, conformational isomers were obtained when the functionalized pyridines were used. Distinct doubling of several peaks in the ¹³C NMR spectra was clearly observed. With the 6-methyl pyridine derivative 4 this problem was solved by

Figure 3 The *exo*-OH and *endo*-OH diastereomers of compound 10a.

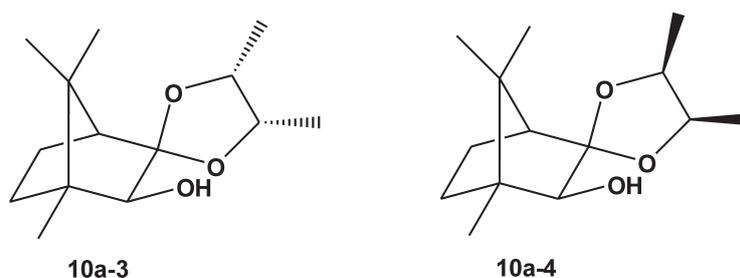


Figure 4 Diastereomers of compound **10a** where the OH group is in the *exo*-position.

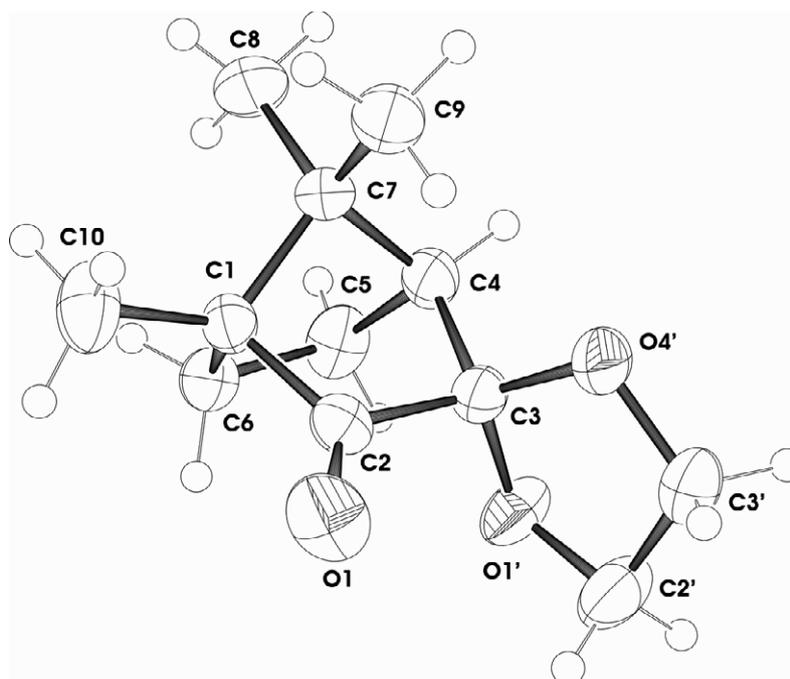


Figure 5 ORTEP diagram of compound **13** showing displacement ellipsoids at the 50 % probability level.²²

carrying out the lithiation at $-78\text{ }^{\circ}\text{C}$ or lower. The same procedure was used in the synthesis of ligand **5** (Scheme 4).

Attempts were also made to synthesize the 6-methylpyridine derivative from the methyl ether ketone **17**, but we could not resolve the isomers. This particular derivative formed conformational isomers **18a** and **18b** regardless of the temperature (Fig. 9).

A variable temperature NMR study of this compound clearly showed that as the temperature of the sample was increased, the ^{13}C NMR signals for the conformers shifted closer together. However, even at a temperature of $100\text{ }^{\circ}\text{C}$ the signals were still distinct, indicating that the pyridyl group was not free to rotate. It therefore seemed that for the signals of the conformers to be merged completely in order to yield only a single form, the mixture would have to be heated to a point at which decomposition

of the sample would be possible. As a result, it was decided that further efforts with this derivative were not worth pursuing for our applications.

The final derivative **6** was synthesized in acceptable yield by simply reacting ligand **3** with excess iodomethane in the presence of NaH in dry THF at room temperature (Scheme 5). The product was easily isolated using column chromatography.

As mentioned previously, most C2 analogous ligands have been applied as catalysts in the addition of diethylzinc to various aldehydes. Previous results for the C2 pendant example **1** were mediocre for this reaction (44 % *ee*). In order to determine the efficacy of the synthesized ligands it was necessary to compare them in the same application used for close C2 pendant analogues. As such, the ligands were screened as catalysts in the reaction of diethylzinc with some selected aromatic aldehydes (see Table 1).

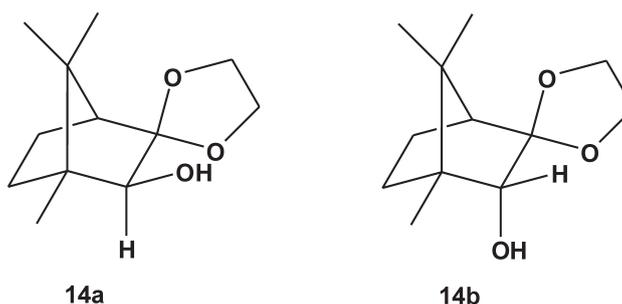


Figure 6 Diastereomers **14a** and **14b**.

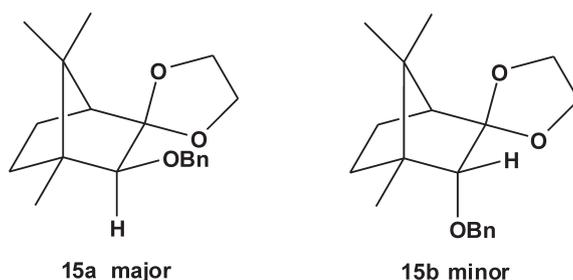
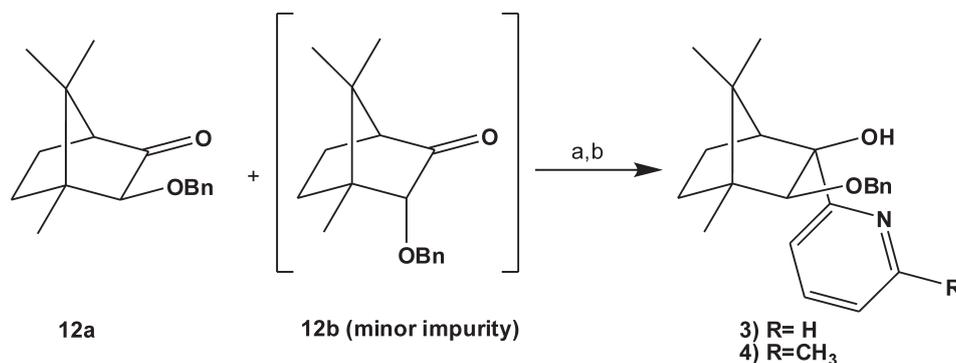


Figure 7 Diastereomers 15a and 15b.



Scheme 3

Synthesis of ligands 3 and 4. Key: (a) ketone 12, CeCl₃, dry THF, RT; (b) pyridyllithium, -78 °C 1 h, RT overnight.

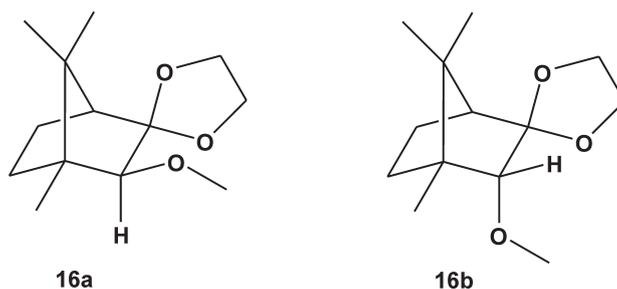


Figure 8 Diastereomers 16a and 16b.

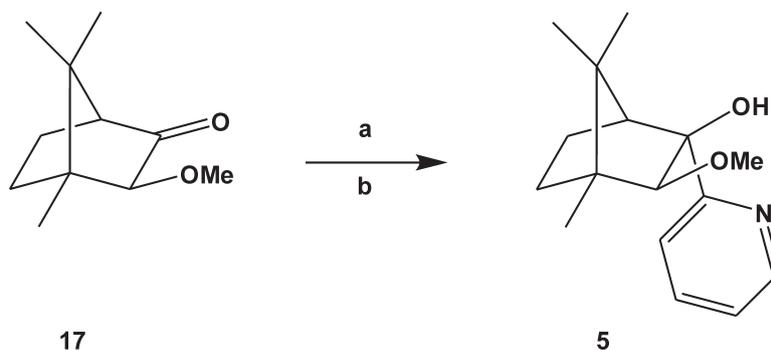
The reactions were carried out at room temperature with toluene as the solvent.

On screening the ligands against benzaldehyde it was determined that ligand 4 was the most effective agent in terms of selectivity (72 % *ee*). This ligand was then applied in the reaction of a series of *para*-functionalized aldehydes. The selectivity obtained for the addition of diethylzinc to *p*-anisaldehyde proved to be the best with 85 % *ee* obtained. It was decided that as a result of the extended reaction times it would not be viable to attempt the reactions at low temperature.

These results compare very favourably with those obtained for the C2 pendant examples. If compared directly with the C2 analogue 1, our equivalent C3 derivative 3 showed an improvement of more than 20 % (44 % *ee*^b vs. 68 % *ee*). These ligands perform better for the selected reaction than any other camphor pyridine β -amino alcohol derivatives in the literature.

3. Conclusion

In summary, novel chiral ligands 3–6 were successfully synthesized in moderate yield and absolute *stereo*- and *regio*-selectivity



Scheme 4

Synthesis of ligand 5. Key: (a) CeCl₃, dry THF, RT; (b) pyridyllithium, -78 °C 1 h, RT overnight.

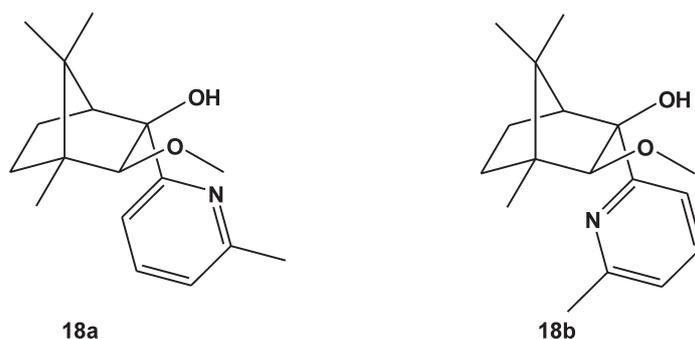
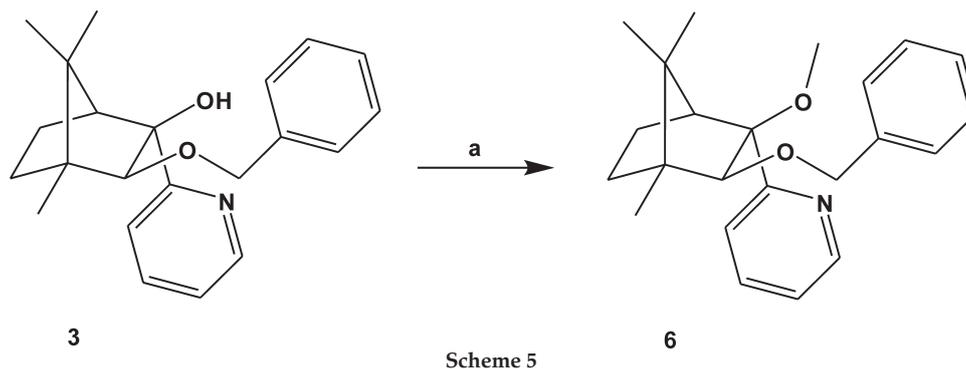


Figure 9 Depiction of the proposed conformational isomers of compound 18.



Scheme 5
Synthesis of ligand 6. Key: (a) MeI, NaH, THF, room temperature, 12 h.

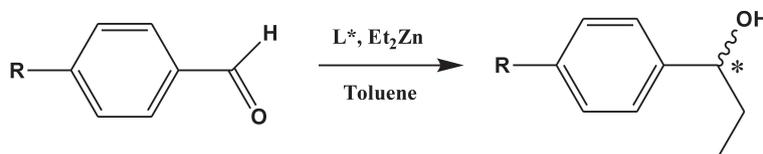
using method B, which proved superior to method A in terms of selectivity. In addition, several potentially useful novel precursors were also synthesized, some in good yield. The ligands reported are unique in that they are the first reported examples of pyridyl alcohols derived from camphor which are pendant on the C3 position of the camphor skeleton. In establishing the procedure to synthesize the ligands, it was found that it is possible using an established recrystallization technique to isolate the mono-protected ketal **13** as a single diastereomer in acceptable yield. This opens up many possibilities for *regio*-selective synthesis using camphorquinone as a starting material. The ligands (**3–6**) were screened as catalysts in the alkylation of aldehydes with diethylzinc. The results obtained indicated that the ligands were significantly better than the analogous C2 pendant ligands previously reported in the literature with a best selectivity of

85% *ee* obtained with ligand **4**. This demonstrates that the arrangement of the donor groups on the camphor skeleton can have a significant effect on their efficacy as chiral catalysts.

4. Experimental

All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments (Bruker, Karlsruhe, Germany) with CDCl_3 as solvent unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 instrument (Perkin-Elmer, Waltham, MA, USA) equipped with a Universal ATR attachment. Optical rotation data was acquired on a Perkin-Elmer Model 341 polarimeter using a 1 mL cell with a pathlength of 100 mm. Accurate mass measurements were obtained on a Bruker MicroTOF Q2 instrument using APCI and ESI ionization methods. All solvents were dried using standard

Table 1 Reaction of diethylzinc with various aldehydes at room temperature.



Ligand	Substrate	Time/h	Yield/% ^a	<i>ee</i> /° ^b	Configuration ^c
3	Benzaldehyde	48	65	68	<i>R</i>
4	Benzaldehyde	48	59	72	<i>R</i>
5	Benzaldehyde	48	76	50	<i>R</i>
6	Benzaldehyde	48	0	N/A	–
4	<i>p</i> -Nitrobenzaldehyde	48	73	25	<i>R</i>
4	<i>p</i> -Anisaldehyde	48	67	85	<i>R</i>
4	<i>p</i> -Tolualdehyde	48	71	58	<i>R</i>
4	<i>p</i> -Chlorobenzaldehyde	48	74	30	<i>R</i>

^a Isolated yield after flash chromatography.

^b Determined by HPLC (Diacel Chiralpak IB column).

^c Determined by optical rotation and comparison with literature values.

procedures prior to use. All reagents were purchased and used without further purification. Column chromatography was carried out on Silicagel 60 particle size 0.063–0.200 mm (230–400 mesh). All HPLC analysis was carried out on a Shimadzu Prominence system (Shimadzu, Tokyo, Japan) using a Diacel Chiralpak IB column with hexane:isopropanol (97.5:2.5) as eluent.

(1R)-(-)-Camphorquinone (8)

Synthesis was carried out as per the method used by Lu *et al.*¹⁶ (1R)-(+)-Camphor (30.42 g, 200 mmol) and selenium dioxide (51.05 g, 460 mmol) in acetic anhydride (50.0 mL) were refluxed overnight. The black selenium residue was filtered off and the dark yellow filtrate was diluted with 50 mL of ice cold water. The resulting yellow precipitate was filtered and washed with ice cold water (3 × 20 mL). The yellow solid was dried on the filter paper under vacuum. NMR spectroscopy of the crude material indicated it was pure enough for further use without any additional purification (28.55 g, 86 %). M. p. 201–205 °C. Analytical data were identical to those of an authentic sample.

(1R, 4S)-(-)-3,3-(*meso*-2,3-butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (9)¹⁹

A stirred solution of camphorquinone (5.00 g, 30.1 mmol), *p*-toluenesulphonic acid (1.00 g, 5.25 mmol) and *meso*-2,3-butanediol (2.70 g, 29.9 mmol) in benzene (350 mL) was heated under reflux using a Dean-Stark trap. The reaction was monitored using TLC (EtOAc:hexane 25:75, $R_f = 0.56$). On completion, the solution was neutralized with aqueous sodium bicarbonate and washed with brine (2 × 100 mL), and water (3 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified using column chromatography (EtOAc:hexane 5:95, $R_f = 0.56$) to yield the product as a pale yellow oil (6.07 g, 85 %). ¹H NMR [CDCl_3 , 400 MHz]: δ_{H} 0.7–1.05 (m, 9H); 1.08–1.20 (m, 2H); 1.24–1.30 (m, 6H); 1.45–1.80 (m, 2H); 1.85–1.90 (m, 2H); 4.10–4.24 (m, 2H); 4.46–4.64 ppm (m, 1H); ¹³C NMR [CDCl_3 , 100 MHz]: δ_{C} 9.42 (q), 14.8 (q), 14.9 (q), 20.8 (t), 21.5 (q), 30.5 (t), 43.4 (s), 52.3 (d), 57.6 (s), 75.5 (d), 75.6 (d), 106.7 (s), 216.0 ppm (s).

(1R, 2S, 4S)-(-)-3,3-(*meso*-2,3-butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (10a)¹⁹

To a stirred solution of 9 (5.00 g, 20.9 mmol) in diethyl ether/MeOH (1:1, 150 mL) was added NaBH_4 (3.78 g, 100 mmol) portionwise at ca. 0 °C. The solution was allowed to warm gradually to room temperature and left to stir for 2 h. The solvent was removed *in vacuo* and the white solid residue redissolved in water. The solution was extracted with dichloromethane (3 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (EtOAc:hexane 10:90, $R_f = 0.45$ on TLC EtOAc:hexane 25:75) to yield the pure product as a clear oil (2.51 g, 49 %). ¹H NMR [CDCl_3 , 400 MHz]: δ_{H} 0.79–0.88 (m, 6H); 1.03 (s, 3H); 1.11–1.15 (m, 8H); 1.47–1.67 (m, 3H); 2.61 (br s, OH); 3.30 (s, 1H); 4.06–4.08 (q, 1H); 4.18–4.20 ppm (q, 1H); ¹³C NMR [CDCl_3 , 100 MHz]: δ_{C} 10.9 (q), 14.6 (q), 15.2 (q), 20.5 (t), 21.1 (q), 21.6 (q), 33.4 (t), 47.6 (s), 49.3 (s), 52.8 (d), 73.7 (d), 74.8 (d), 85.2 (d), 113.7 ppm (s).

(1R, 2S, 4S)-(-)-2-Benzyloxy-3,3-(*meso*-2,3-butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan (11)

To a stirred suspension of NaH (1.92 g, 80 mmol) in dry THF (50 mL) was added a solution of 10 (4.0 g, 16.6 mmol) in dry THF (50 mL). The resulting solution was stirred at room temperature for 1 h before benzyl bromide (2.40 mL, 20.1 mmol) was added

quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane 5:95, $R_f = 0.75$ on TLC EtOAc:hexane 25:75) to yield the novel product as a clear oil (4.11 g, 75 %). $[\alpha]_{\text{D}}^{20} -35.4^\circ$ ($c = 1$, CHCl_3); ¹H NMR [CDCl_3 , 400 MHz]: (NB: due to mixture of isomers, integration values may not be accurate) δ_{H} 0.80 (s, 3H); 0.88 (s, 3H); 1.07–1.26 (m, 9H); 1.45–1.74 (m, 4H); 3.29 (s, 1H); 4.07–4.24 (m, 2H); 4.42–4.45 (d, 1H); 4.84–4.87 (d, 1H), 7.21–7.38 ppm (m, 5H); ¹³C NMR [CDCl_3 , 100 MHz]: δ_{C} 11.7 (q), 15.6 (q), 15.8 (q), 20.4 (t), 21.3 (q), 34.3 (t), 47.9 (s), 49.5 (s), 51.9 (d), 72.6 (d), 73.1 (d), 73.5 (t), 92.1 (d), 114.3 (s), 127.0 (d), 127.3 (d), 128.1 (d), 139.6 ppm (s) (NB: only major product peaks reported); IR (ATR): ν_{max} 2937 (m), 2875 (m), 1454 (m), 1091 (vs), 1029 (m) cm^{-1} ; HRMS calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_3$ ($[\text{M}+\text{H}]^+$) 331.227320, found 331.223351.

(1R, 2S, 4S)-(-)-2-Benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (12)

To a stirred solution of THF:HCl (3:1, 100 mL) was added 11 (5.00 g, 15.1 mmol) in THF (30 mL). The solution was stirred at room temperature for 2 h. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralized with solid sodium bicarbonate. The neutralized solution was extracted with diethyl ether (3 × 30 mL). The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane 10:90, $R_f = 0.65$ on TLC EtOAc:hexane 25:75) to yield the pure product as a pale yellow oil (3.13 g, 80 %). $[\alpha]_{\text{D}}^{20} -120.7^\circ$ ($c = 2$, CHCl_3); ¹H NMR [CDCl_3 , 400 MHz]: (NB: due to mixture of isomers, integration values may not be accurate) δ_{H} 0.90 (s, 3H); 1.02 (s, 3H); 1.08 (s, 3H); 1.24–1.44 (m, 3H); 1.65 (m, 1H); 1.77–1.93 (m, 3H); 2.12 (m, 1H); 3.24 (s, 1H), 4.67–4.70 (d, 1H), 5.00–5.03 (d, 1H), 7.25–7.34 ppm (m, 5H); ¹³C NMR [CDCl_3 , 100 MHz]: δ_{C} 10.9 (q), 18.6 (q), 20.8 (t), 21.5 (q), 33.9 (t), 46.3 (s), 49.9 (s), 59.3 (d), 73.6 (t), 85.1 (d), 127.4 (d), 127.5 (d), 128.2 (d), 138.5 ppm (s); IR (ATR): ν_{max} 2956 (m), 2878 (m), 1748 (vs), 1110 (s), 1094 (s) cm^{-1} . HRMS calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_2$ ($[\text{M}+\text{H}]^+$) 259.169805, found 259.164749.

(1R, 4S)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (13)^{15,16,21}

A stirred solution of camphorquinone (5.00 g, 30.1 mmol), *p*-toluenesulphonic acid (1.00 g, 5.25 mmol) and ethylene glycol (1.90 g, 30.6 mmol) in benzene (100 mL) was heated under reflux using a Dean-Stark trap. The reaction was monitored using TLC. On completion, the solution was neutralized with aqueous sodium bicarbonate and washed with brine (2 × 100 mL) and water (3 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified using column chromatography (EtOAc:hexane 5:95, $R_f = 0.55$ on TLC EtOAc:hexane 25:75) to yield the product as a pale yellow oil. This oil solidified on standing and was recrystallized from ethanol to yield the pure product as a white crystalline material (4.11 g, 65 %). ¹H NMR [CDCl_3 , 400 MHz]: δ_{H} 0.91 (s, 3H); 0.98–1.02 (d, 6H); 1.45–1.70 (m, 2H); 1.75–1.82 (m, 1H); 1.85–2.02 (m, 2H); 3.85–4.02 (m, 2H); 4.20–4.32 (m, 1H); 4.35–4.45 ppm (m, 1H); ¹³C NMR [CDCl_3 , 100 MHz]: δ_{C} 9.18 (q), 19.0 (q), 21.4 (t), 21.5 (q), 30.9 (t), 43.6 (s), 51.5 (d), 58.2 (s), 64.5 (t), 66.1 (t), 106.9 (s), 217.4 ppm (s).

(1R, 2S, 4S)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (14)^{15,16,21}

To a stirred solution of **13** (5.00 g, 23.8 mmol) in diethyl ether/MeOH (1:1, 100 mL) was added NaBH₄ (3.78 g, 100 mmol) portionwise at ca. 0 °C over a period of 10 min. The solution was allowed to warm gradually to room temperature and left to stir for 2 h. The solvent was removed *in vacuo* and the white solid residue redissolved in water. The solution was extracted with dichloromethane (3 × 20 mL). The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo*. The product was obtained as a clear oil (5.04 g, 100 %). NMR spectroscopy showed the product to be pure enough for further use without additional purification. ¹H NMR [CDCl₃, 400 MHz]: δ_H 0.75–0.86 (m, 6H); 1.10 (s, 3H); 1.20–1.28 (m, 2H); 1.45–1.82 (m, 4H); 2.42 (d, OH); 3.31 (d, 1H); 3.76–4.12 ppm (m, 4H); ¹³C NMR [CDCl₃, 100 MHz]: δ_C 10.3 (q), 20.1 (q), 20.4 (t), 20.6 (q), 32.8 (t), 46.8 (s), 48.9 (s), 51.9 (d), 62.9 (t), 64.9 (t), 84.8 (d), 114.6 ppm (s).

(1R, 2S, 4S)-(-)-2-Benzyloxy-3,3-ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan (15)

To a stirred suspension of NaH (1.92 g, 80.0 mmol) in dry THF (50 mL) was added a solution of **14** (4.41 g, 20.8 mmol) in dry THF (50 mL). The resulting solution was stirred at room temperature for 1 h before benzyl bromide (2.50 mL, 21.0 mmol) was added quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 × 30 mL). The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane 5:95, R_f = 0.80 on TLC EtOAc:hexane 25:75) to yield the novel product as a clear oil (5.09 g, 81 %). [α]_D²⁰ -35.9 ° (c = 1, CHCl₃); ¹H NMR [CDCl₃, 400 MHz]: δ_H 0.82 (s, 3H); 0.90 (s, 3H); 1.21 (m, 4H); 1.53–1.65 (m, 4H); 3.18 (s, 1H); 3.76–3.97 (m, 4H); 4.44–4.46 (d, 1H); 4.65–4.67 (d, 1H); 7.24–7.34 ppm (m, 5H); ¹³C NMR [CDCl₃, 100 MHz]: δ_C 11.8 (q), 20.6 (t), 20.9 (q), 21.3 (q), 34.3 (t), 47.9 (s), 50.2 (s), 52.9 (d), 63.4 (t), 65.1 (t), 73.5 (t), 92.9 (d), 116.1 (s), 127.2 (d), 127.3 (d), 128.2 (d), 139.3 ppm (s); IR (ATR): ν_{max} 2946 (m), 2875 (m), 1096 (vs), 1027 (s), 1010 (m) cm⁻¹; HRMS calcd. for C₁₉H₂₆O₃ ([M+H]⁺) 303.196020, found 303.196342.

(1R, 2S, 4S)-(-)-2-Benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (12)

To a stirred solution of THF:HCl (3:1, 100 mL) was added **15** (5.00 g, 16.5 mmol) in THF (50 mL). The solution was stirred at room temperature for 2 h. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralized with solid sodium bicarbonate. The neutralized solution was extracted with diethyl ether (3 × 30 mL). The organic layers were combined and dried (Na₂SO₄) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane 10:90, R_f = 0.65 on TLC EtOAc:hexane 25:75) to yield the pure product as a pale yellow oil (3.42 g, 80 %). [α]_D²⁰ -145.7 ° (c = 1, CHCl₃); ¹H NMR [CDCl₃, 400 MHz]: δ_H 0.90 (s, 3H); 1.02 (s, 3H); 1.08 (s, 3H); 1.24–1.44 (m, 2H); 1.77–1.93 (m, 2H); 2.12 (m, 1H); 3.24 (s, 1H); 4.67–4.70 (d, 1H); 5.00–5.03 (d, 1H); 7.25–7.34 ppm (m, 5H); ¹³C NMR [CDCl₃, 100 MHz]: δ_C 10.9 (q), 18.6 (q), 20.8 (t), 21.5 (q), 33.9 (t), 46.3 (s), 49.9 (s), 59.3 (d), 73.6 (t), 85.1 (d), 127.4 (d), 127.5 (d), 128.2 (d), 138.5 (s), 218.3 ppm (s); IR (ATR): ν_{max} 2956 (m), 2878 (m), 1748 (vs), 1110 (s), 1094 (s) cm⁻¹; HRMS calcd. for C₁₇H₂₂O₂ ([M+H]⁺) 259.169805, found 259.164749.

(1R, 2S, 4S)-(-)-2-Methoxy-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan (16)

To a stirred suspension of NaH (1.92 g, 80 mmol) in dry THF (30 mL) under nitrogen was added a solution of **14** (5.00 g, 23.6 mmol) in dry THF (70 mL).

The resulting solution was stirred at room temperature for 1 h before methyl iodide (4.48 mL, 72.0 mmol) was added quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 × 30 mL). The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane 5:95, R_f = 0.65 on TLC EtOAc:hexane 25:75) to yield the novel product as a clear oil (5.42 g, 100 %). [α]_D²⁰ -16.9 ° (c = 1, CHCl₃); ¹H NMR [CDCl₃, 400 MHz]: δ_H 0.77 (s, 3H), 0.84 (s, 3H), 1.09 (s, 3H), 1.16–1.18 (m, 1H), 1.47–1.66 (m, 4H), 2.89 (s, 1H); 3.36 (s, 3H); 3.79–3.81 (m, 2H), 3.87–3.90 (m, 1H), 3.96–3.99 ppm (m, 1H); ¹³C NMR [CDCl₃, 100 MHz]: δ_C 11.5 (q), 20.6 (t), 20.8 (q), 21.1 (q), 34.3 (t), 47.8 (s), 50.1 (s), 52.9 (q), 60.3 (d), 63.2 (t), 65.2 (t), 95.7 (d), 115.9 ppm (s); IR (ATR): ν_{max} 2945 (s), 2287 (s), 1115 (vs), 1094 (vs), 1044 (s) cm⁻¹; HRMS calcd. for C₁₃H₂₂O₃ ([M+H]⁺) 227.164720, found 227.159440.

(1R, 2S, 4S)-(-)-2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (17)

To a stirred solution of THF:HCl (3:1, 100 mL) was added **16** (5.00 g, 22.1 mmol) in THF (50 mL). The solution was stirred at room temperature for 2 h. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralized with solid sodium bicarbonate. The neutralized solution was extracted with diethyl ether (3 × 30 mL). The organic layers were combined and dried (Na₂SO₄) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane 10:90, R_f = 0.60 on TLC EtOAc:hexane 25:75) to yield the pure product as a yellow oil (2.90 g, 72 %). [α]_D²⁰ -155.8 ° (c = 1, CHCl₃); ¹H NMR [CDCl₃, 400 MHz]: δ_H 0.84 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.31–1.38 (m, 2H), 1.75–1.86 (m, 2H), 2.03 (s, 1H), 2.98 (s, 1H), 3.53 ppm (s, 3H); ¹³C NMR [CDCl₃, 100 MHz]: δ_C 10.7 (q), 18.5 (q), 20.7 (t), 21.2 (q), 33.9 (t), 46.2 (s), 49.8 (s), 59.1 (q), 60.6 (d), 88.0 (d), 217.9 ppm (s); IR (ATR): ν_{max} 2956 (s), 2883 (m), 1749 (vs), 1110 (vs), 1014 (m) cm⁻¹; HRMS calcd. for C₁₁H₁₈O₂ ([M+H]⁺) 183.138505, found 183.135218.

General Procedure for Synthesis of Ligands 3–5 and 18

Anhydrous CeCl₃ (1.5 eq) was weighed into a dry two-neck round bottom flask. The appropriate ketone (1 eq) in dry THF (30 mL) was added and the mixture was stirred under nitrogen at room temperature until a homogeneous gel-like mixture was obtained (usually about 30 min). The mixture was cooled to -78 °C and the appropriate pyridyllithium solution (3 eq) in THF (10 mL) was added quantitatively. The solution was stirred for ca. 1 h at -78 °C before being allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and 2 mol L⁻¹ HCl (20 mL) was added. The solution was then extracted with 2 mol L⁻¹ HCl (2 × 30 mL) and the acidic extract retained. The acid layer was neutralized with solid sodium bicarbonate before being extracted with diethyl ether (3 × 30 mL). The organic layers were combined, dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane 5:95) to yield the respective products as yellow oils.

(1R, 2S, 3S, 4S)-(+)-2-Benzyloxy-3-pyridyl-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (3)

Pale yellow oil (46 %): $R_f = 0.57$ on TLC EtOAc:hexane 25:75; $[\alpha]_D^{20} +73.3^\circ$ ($c = 3$, CHCl_3); $^1\text{H NMR}$ [CDCl_3 , 400 MHz]: δ_{H} 0.52–0.57 (m, 1H), 0.85 (s, 3H), 0.99 (s, 3H), 1.18–1.30 (m, 4H), 1.38–1.43 (m, 2H), 1.63 (s, 1H), 2.01 (s, 1H), 3.81 (s, 1H), 4.59–4.68 (q, 2H), 4.79 (s, 1H), 7.11–7.14 (m, 1H), 7.23–7.34 (m, 4H), 7.52–7.55 (m, 1H), 7.64–7.67 (m, 1H), 8.45–8.47 ppm (m, 1H); $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz]: δ_{C} 12.0 (q), 22.2 (q), 22.4 (t), 22.5 (q), 33.1 (t), 49.9 (s), 50.4 (s), 56.3 (d), 74.4 (t), 83.5 (s), 88.1 (d), 121.8 (d), 122.6 (d), 127.6 (d), 127.7 (d), 128.3 (d), 136.4 (d), 138.4 (s), 147.0 (d) 164.8 ppm (s); IR (ATR): ν_{max} 3495 (br, m), 2954 (m), 1590 (m), 1064 (vs), 735 (vs) cm^{-1} ; HRMS calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 338.212004, found 338.219073.

(1R, 2S, 3S, 4S)-(+)-2-benzyloxy-3-(6-methylpyridine)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (4)

Pale yellow waxy solid (57 %): $R_f = 0.56$ on TLC EtOAc:hexane 25:75; $[\alpha]_D^{20} +40.4^\circ$ ($c = 1$, CHCl_3); $^1\text{H NMR}$ [CDCl_3 , 400 MHz]: δ_{H} 0.61–0.66 (m, 1H), 0.86 (s, 3H), 0.97 (s, 3H), 1.14–1.47 (m, 6H), 1.61 (m, 1H), 2.02–2.03 (m, 1H), 2.52 (s, 3H), 3.86 (s, 1H), 4.62–4.70 (q, 2H), 4.77 (s, 1H), 7.00 (m, 1H), 7.26–7.36 (m, 5H), 7.52–7.55 ppm (m, 1H); $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz]: δ_{C} 12.0 (q), 22.2 (q), 22.5 (t), 22.6 (q), 22.4 (q), 33.2 (t), 49.8 (s), 50.3 (s), 55.9 (d), 74.0 (t), 83.6 (d), 88.0 (d), 119.0 (d), 120.8 (d), 127.5 (d), 127.9 (d), 128.2 (d), 136.5 (d), 138.5 (s) 155.7 (s), 163.8 ppm (s); IR (ATR): ν_{max} 3498 (br,m), 2941 (m), 1453 (s), 1063 (vs), 696 (s) cm^{-1} ; HRMS calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 352.227654, found 352.226553.

(1R, 2S, 3S, 4S)-(+)-2-methoxy-3-pyridyl-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (5)

Yellow oil (48 %): $R_f = 0.54$ on TLC EtOAc:hexane 25:75; $[\alpha]_D^{20} +35.3^\circ$ ($c = 1$, CHCl_3); $^1\text{H NMR}$ [CDCl_3 , 400 MHz]: δ_{H} 0.53–0.55 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.23–1.45 (m, 5H), 2.04 (m, 2H), 3.48 (s, 3H), 3.84 (s, 1H), 4.52 (s, 1H), 7.12–7.15 (m, 1H), 7.56–7.58 (m, 1H), 7.65–7.67 (m, 1H), 8.45–8.67 ppm (m, 1H); $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz]: δ_{C} 11.7 (q), 22.2 (q), 22.3 (t), 22.3 (q), 33.1 (t), 49.9 (s), 50.3 (s), 56.2 (d), 60.7 (d), 83.3 (s), 89.9 (d), 121.7 (d), 122.6 (d), 136.4 (d), 146.9 (d), 164.9 ppm (d); IR (ATR): ν_{max} 3491 (br, m), 2938 (s), 1590 (m), 1101 (m), 1073 (m) cm^{-1} ; HRMS calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 262.180704, found 262.187022.

(1R, 2S, 3S, 4S)-(+)-2-methoxy-3-(6-methylpyridyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (18)

Yellow oil (48 %): $R_f = 0.54$ on TLC EtOAc:hexane 25:75; $[\alpha]_D^{20} +39.9^\circ$ ($c = 1$, CHCl_3); $^1\text{H NMR}$ [DMSO , 600 MHz]: δ_{H} 0.43–0.46 (m, 1H), 0.77–0.91 (m, 4H), 1.08–1.64 (m, 7H), 1.86(s, 1H), 2.51 (s, 1H), 3.32 (s, 3H), 4.41 (s, 1H), 7.08–7.09 (m, 1H), 7.16–7.18 (m, 1H), 7.34–7.36 (m, 1H), 7.63–7.66 ppm (m, 1H); $^{13}\text{C NMR}$ [DMSO , 150 MHz]: δ_{C} 11.9 (q), 13.8 (q), 21.8 (q), 22.3 (t), 21.9 (q), 22.1 (q), 22.5 (t), 24.3 (t), 29.3 (t), 32.8 (t), 34.9 (t), 49.1 (s), 49.8 (s), 55.9 (d), 59.8 (d), 84.7 (s), 89.5 (d), 119.2 (d), 120.6 (d), 121.1 (d), 122.6 (d), 127.1 (d), 128.1 (d), 136.0 (d) 136.6 (d), 149.0 (d), 154.8 (s), 164.6 ppm (s); IR (ATR): ν_{max} 3501 (br,m), 2936 (m), 1576 (m), 1100 (s), 1075 (s) cm^{-1} ; HRMS calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 276.196354, found 276.202930.

(1R, 2S, 3S, 4S)-(+)-2-benzyloxy-3-methoxy-1,7,7-trimethyl-3-pyridyl-bicyclo[2.2.1]heptan (6)

Ligand 3 (0.50 g, 1.48 mmol) was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in dry THF (50 mL). The solution was allowed to stir at room temperature under nitrogen for 30 min. MeI (excess) was added quantitatively and the solution was stirred at room temperature overnight. Excess NaH was

quenched by dropwise addition of water and the solvent and excess MeI removed *in vacuo*. The crude residue was diluted with water and extracted with diethyl ether (3 × 30 mL).

The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane 5:95) to yield the pure product as a pale yellow oil (0.50 g, 95.9 %). $R_f = 0.63$ on TLC EtOAc:hexane 25:75; $[\alpha]_D^{20} +53.1^\circ$ ($c = 1$, CHCl_3); $^1\text{H NMR}$ [CDCl_3 , 400 MHz]: δ_{H} 0.52–0.57 (m, 1H), 0.85 (s, 3H), 0.99 (s, 3H), 1.18–1.30 (m, 6H), 1.38–1.43 (m, 2H), 1.63 (s, 1H), 2.01 (s, 1H), 3.81 (s, 1H), 4.59–4.68 (q, 2H), 4.79 (s, 1H), 7.11–7.14 (m, 1H), 7.23–7.34 (m, 4H), 7.52–7.55 (m, 1H), 7.64–7.67 (m, 1H), 8.45–8.47 ppm (m, 1H); $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz]: δ_{C} 12.1 (q), 21.6 (q), 21.9 (q), 22.4 (t), 32.6 (t), 49.6 (s), 51.2 (s), 54.5 (d), 56.9 (q), 74.3 (t), 88.1 (d), 91.3 (s), 121.9 (d), 123.4 (d), 126.9 (d), 127.0 (d), 128.1 (d), 136.3 (d), 139.7 (s) 147.5 (d), 162.6 ppm (s); IR (ATR): ν_{max} 2938 (m), 2870 (m), 1589 (m), 1097 (vs), 731 (vs) cm^{-1} ; HRMS calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) 352.227654, found 352.233176.

General Procedure for the Addition of Diethylzinc to Aldehydes

To a solution of the ligand (20 mol % relative to aldehyde) in dry toluene (2 mL) under a nitrogen atmosphere at ambient temperature, was added a solution of ZnEt_2 in hexane (1.0 mol L^{-1} , 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min, and then benzaldehyde (60 mg, 0.5 mmol) was added. The reaction was stirred at room temperature for 48 h and then quenched by adding 10 % HCl and extracted with Et_2O and the organic phase was washed with brine and dried over anhydrous Na_2SO_4 . After evaporation of the solvent, the crude oil was purified *via* flash chromatography (hexane/ethyl acetate) and its enantiomeric excess determined by chiral HPLC.

Acknowledgements

This work was supported by grants from the National Research Foundation, Gun 2046819 (South Africa), Aspen Pharmacare and the University of KwaZulu-Natal.

Supplementary Material

The proton and carbon NMR spectra of all novel compounds reported are available as supplementary material. The 2D NMR spectra of compounds 10a-3 and 10a-4 and the crystallographic data for structure 13 are also available.

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