Tetrahedron 66 (2010) 9327–9331

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The selective mono and difunctionalization of carbocyclic cleft molecules with pyridyl groups and X-ray crystallographic analysis

Priti Jilka [a], Claire Millington [a], Mark R.J. Elsegood [a], Josef W.A. Frese [a], Simon Teat [b], Marc C. Kimber [a,*]

[a] The Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK
[b] ALS, Berkeley Laboratory, 1 Cyclotron Road, MS2-400, Berkeley, CA 94720, USA

A R T I C L E I N F O

Article history:
Received 26 July 2010
Received in revised form 22 September 2010
Accepted 11 October 2010
Available online 15 October 2010

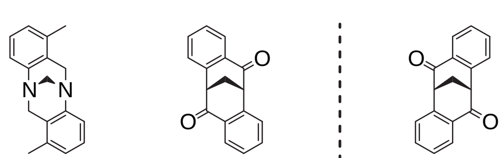
Keywords:
Carbocyclic cleft
Chiral cavity
Alkylation
Esterification
Recognition

A B S T R A C T

The diesterification and selective mono and dialkylation of carbocyclic analogues of Tröger's base with pyridyl groups has been achieved in high yield and good selectivity giving access to a novel range of cleft molecules capable of binding events. Reaction conditions for the selective functionalization of this carbocyclic cleft molecule are discussed as well as the solid state structures of these newly synthesized ligands.

1. Introduction

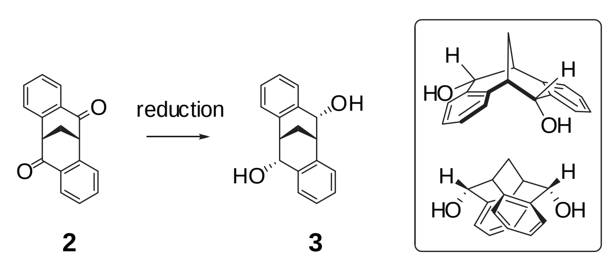
Molecular recognition relies on the ability to design and synthesize appropriate substrates with predictable geometries and binding sites.[1] Towards this end Tröger's base[2] **1** has been used to great effect by a number groups within the context of molecular recognition because it contains a rigid predictable structure, heteroatoms capable of binding events and importantly a chiral cavity.[3,4] While Tröger's base has proved effective as a chiral cleft molecule, a number of carbocyclic and heterocyclic analogues have also been also investigated as possible surrogates.[5] The carbocyclic cleft molecule **2** was initially reported in 1960 by Stetter and Reischl[6] but was fully characterized and resolved in 1975 by Tatemitsu et al.[7] Significant advances in the functionalization of **2** have been developed by the Harding group[8] and an excellent review on its development/uses has been published (Fig. 1).[9]



(±)-1 (-)-2 (+)-2

Fig. 1. Racemic Tröger's base (±)-**1**, and (+)-**2** and (−)-**2**.

Of particular interest to our group is the reduced version of **2**. Treatment of **2** with excess reducing agent results in the formation of the bis-hydroxyl carbocycle **3**, where both hydroxyl groups are directed into the chiral cavity. This potentially gives a ligand, which can bind substrates via metal or Brønsted base/acid binding interactions within a chiral cavity (Scheme 1).



Scheme 1. Reduction of **2** to give diol **3**.

To date the only reported functionalization of these hydroxyl groups has been the attachment of simple esters (bromobenzoate, acetate and menthoxy acetyl) and the synthesis of cyclic ethers.[7,10] The dibromobenzoate and diacetate derivatives were synthesized for characterization reasons, the dimenthoxy acetate was synthesized for separation purposes and the cyclic ethers were synthesized for a study on the use of **3** as a resolution agent in chiral-HPLC.

* Corresponding author. Tel.: +44 (0) 150 922 2570; fax: +44 (0) 150 922 3925; e-mail address: M.C.Kimber@lboro.ac.uk (M.C. Kimber).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.10.027

However, the synthesis of **3** containing tethered heterocyclic groups capable of metal binding or containing Brønsted base/acid binding sites has yet to be reported. Indeed, the incorporation of tethered heterocycles on to **3** could allow for molecular recognition processes. An ideal heterocycle to be attached to these hydroxyl groups contained in **3** would be the pyridyl motif. During a research programme aimed at utilizing **3** in catalysis and molecular recognition events we required methods for simple diesterification and mono/dialkyation of **3** with 2-, 3- and 4-pyridyl subunits (Fig. 2). Diesterification and dietherification would give the diesters **4a**–**c** and diethers **6a**–**c**, both of which would contain pyridyl units capable of metal and Brønsted base interactions. Alternatively, synthesis of **5a**–**c** would potentially give ligands containing both a Brønsted base (the pyridyl unit) and the Brønsted acid site within the same framework. We would now like to report our efforts in developing methods for the synthesis of carbocyclic cleft molecules containing metal binding and Brønsted base/acid sites related to carbocycle **3** and the solid state X-ray analysis of the synthesized ligands.

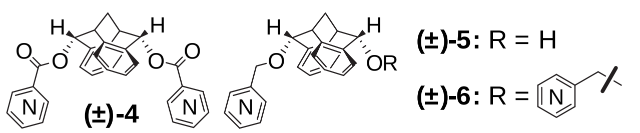
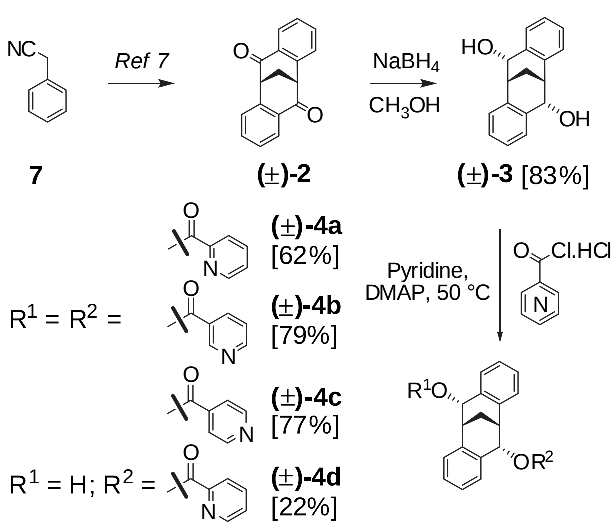


Fig. 2. Ligands containing pyridyl units.

2. Results and discussion

2.1. Synthesis

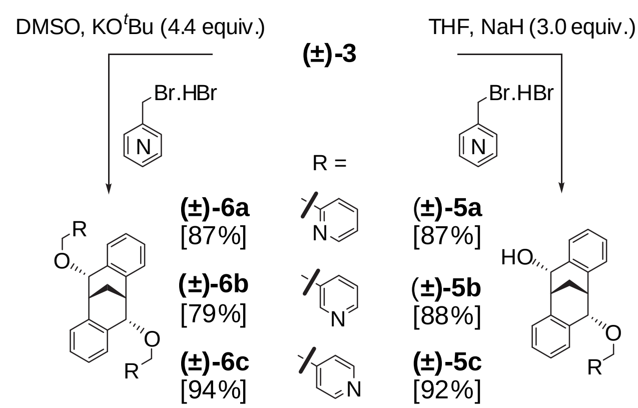
Our synthesis began with racemic carbocycle (±)-**2**, which could be obtained in multigram amounts using an adapted literature method (Scheme 2).[7]



Scheme 2. Diesterification of (±)-**3**.

Reduction of the dione (±)-**2** with an excess of $NaBH_4$ occurs stereo-specifically to give the diol (±)-**3**, where the hydroxyl groups are orientated into the cavity of the bicycle. Initial attempts at formation of the diester using only 2.0 equiv of 4-pyridyl acid chloride hydrochloride salt relative to the (±)-**3** in CH_2Cl_2 with excess NEt_3 at room temperature for 24 h resulted in a mixture of the mono and diesters. Moreover, heating of this mixture proved ineffective as did the addition of DMAP. However, treatment of the diol with 3.0 equiv of the 4-pyridyl acid chloride hydrochloride salt and exchanging the solvent for pyridine with catalytic DMAP at 50 °C for 16 h did yield the desired dipyridyl ester (±)-**4c** in moderate to good yields. Repeating this procedure with the 2- and 3-pyridyl acid chloride hydrochlorides gave their respective dipyridyl esters, (±)-**4a** and (±)-**4b** in good yield. However, the yield of the (±)-**4a** remained a disappointing 62% with the remaining mass balance being accounted for by the isolation of the mono 2-pyridyl ester (±)-**4d** in 22% yield.

Initial attempts at dietherification of (±)-**3**, using 2-, 3- and 4-bromomethylpyridyl hydrobromide salt as the alkylating agent and using NaH as the base, gave unexpectedly the monoalkylated product (±)-**5a** in 87% yield (Scheme 3). Even when the reaction was undertaken with excess base and excess alkylating agent the monoalkyated product predominated. While this result was initially disappointing it did give us a facile entry into the monoalkylated ligands. Accordingly, (±)-**3** was treated with 3- and 4-bromomethylpyridyl hydrobromide salt under these conditions giving the monoalkylated products (±)-**5b** and (±)-**5c** in 88% and 92% yield, respectively. In an attempt to access the dialkylated substrates the solvent was switched from THF to DMF with a concomitant increase in reaction temperature, but this led to an unsatisfactory mixture of the mono and diethers whose separation proved problematic. However, dialkylation of (±)-**3** was achieved using an adapted method of Ley and Heaney.[11] Hence, treatment of (±)-**3** with the desired 2-bromomethylpyridyl hydrobromide salt (2.2 equiv) in DMSO and excess KO^{t}Bu (4.4 equiv) gave the dialkyated carbocycles (±)-**6a** in excellent yield of 87% (Scheme 3). This procedure was then repeated for the 3- and 4-bromomethylpyridyl hydrobromide salts giving excellent yields of the dialkylated products (±)-**6b** and (±)-**6c** in 79% and 94% yield, respectively.



Scheme 3. Selective mono and dietherification of (±)-**3**.

2.2. X-ray crystallographic analysis

Crystals suitable for X-ray analysis were obtained for compounds (±)-**4b**, (±)-**4c**, (±)-**4d** and (±)-**5c**.[12] While (±)-**4c**, (±)-**4d** and (±)-**5c** crystallized as racemates, (±)-**4b** resolved on crystallization and the (+)-**4b** was studied crystallographically as the mono-dichloromethane solvate for which the absolute structure was reliably determined (see Table 1, Supplementary data). Due to small crystal dimensions two data sets, (±)-**4c** and (±)-**5c** were collected using synchrotron radiation at the ALS. Fig. 3 shows the molecular structure of (+)-**4b** and clearly indicates that the orientation of the complexing pyridyl units is directed into the cavity of the cleft bicycle as expected. The molecule lies on a crystallographic two-fold axis. The dichloromethane solvate molecule resides in the cleft and is bound via a pair of C–H⋯π interactions; H⋯ring—centroid=2.58 Å.

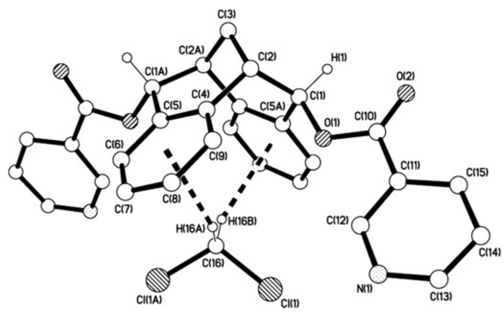


Fig. 3. Molecular structure of (+)-**4b**·$\mathbf{CH_2Cl_2}$ showing pyridyl groups pointing 'downwards' into the cleft and the C–H···π binding of the dichloromethane solvate.

Packing plots shown in Fig. 4(a) and (b) show the way in which the pyridyl groups hydrogen bond to neighbouring molecules via relatively weak C–H···N and C–H···O interactions (H···N/O=2.50/2.60 Å, respectively) forming a micro-porous 3D structure.

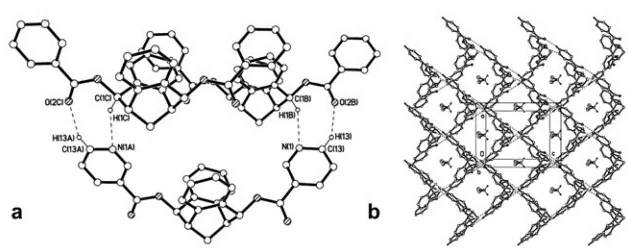


Fig. 4. (a) Detail of hydrogen bonding between molecules in (+)-**4b**, (b) 3D micro-porous packing with dichloromethane encapsulated within clefts.

In (±)-**4c** the pyridyl groups also point towards the cleft. Molecules stack on top of each other, each twisted 90° relative to its neighbours 'above/below' (Fig. 5). The C–H···π interactions are ca. 3.14 Å. Pairs of pyridyl rings π···π stack with a closest C···C separation of ca. 3.36 Å, and there are further weak H-bonds of the C–H···N and C–H···O types in the range 2.54–2.74 Å linking molecules into a weakly-bound 3D network (Fig. 6).

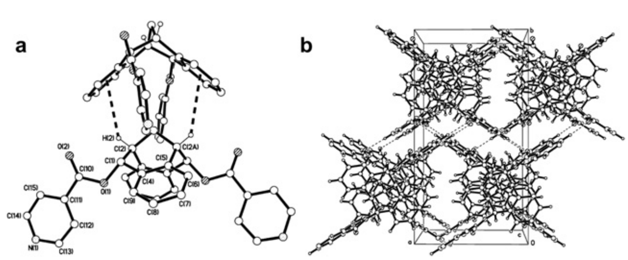


Fig. 5. (a) A pair of stacked molecules of (±)-**4c**, (b) packing in (±)-**4c** showing weak H-bond contacts and overall 3D network. Viewed parallel to the stacking direction.

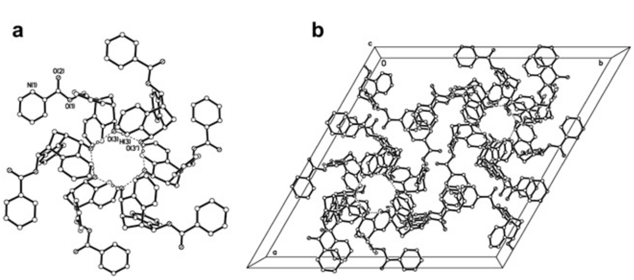


Fig. 6. (a) Groups of six molecules of (±)-**4d** stacked into a ring and H-bonded, (b) π···π Stacking of pyridyl groups of neighbouring rings of (±)-**4d** molecules.

In (±)-**4d** groups of six molecules form into finite rings, rather than infinite stacks as in (±)-**4c**, yet still have the internal clefts filled by the external surface of the neighbouring molecule. The hydroxyl groups form a chair shaped H-bonded 12-membered ring about the crystallographic three axis Fig. 6(a). Neighbouring six-membered rings overlap pyridyl groups resulting in π···π stacking parallel to the crystallographic *c* axis with C···C and C···N separations in the range 3.26–3.53 Å Fig. 6(b).

In (±)-**5a** the packing is rather simpler, with 1D chains formed parallel to the crystallographic *b* axis via strong O–H···N H-bond interactions with H···N=1.95 Å Fig. 7(a). As in the above examples the cleft is again filled, this time with a molecule from the chain 'above/below' via C–H···π interactions of 2.82 and 3.15 Å Fig. 7(b). Compared with (±)-**4c** one interaction is similar in length and one is significantly shorter.

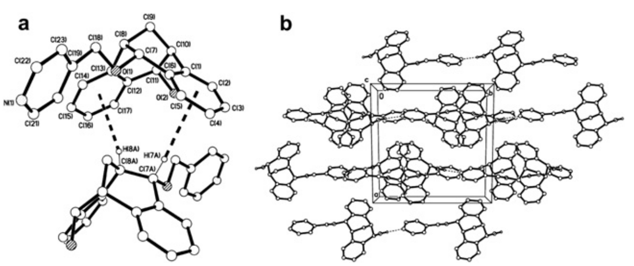


Fig. 7. (a) Packing in (±)-**5a** showing 1D H-bonded chains parallel to *b*, (b) C–H···π interactions between H-bonded chains in (±)-**5a**.

3. Conclusions

In conclusion, we have disclosed a convenient method for the selective functionalization of the carbocyclic cleft molecule (±)-**3** and, for the first time, with heterocyclic groups capable of metal binding and containing both Brønsted base/acid sites. Single crystal X-ray analysis of (+)-**4b**·$\mathbf{CH_2Cl_2}$, (±)-**4c**, (±)-**4d** and (±)-**5c** all indicate the orientation of the complexing pyridyl groups are directed into the cavity. The clefts are filled with either solvent molecules or external surfaces of other cleft molecules via C–H···π interactions, demonstrating their ability to take up molecules with the appropriate shape and, potentially, chirality. With the ability to access optically pure **3** these new heterocyclic cleft molecules provide us with a new family of chiral ligands capable of molecular recognition and catalysis processes as well as in the development of novel chiral scaffolds. The use of these ligands in these areas is currently under investigation within our group and will be reported on in due course.

4. Experimental procedures

4.1. General

Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran (benzophenone/Na) and dichloromethane (CaH), which were freshly distilled. Light petroleum refers to the fraction with bp 40–60 °C. Thin layer chromatography was carried out on GF_{254} aluminium foil backed plates. The plates were visualized under UV light and/or anisaldehyde stain. Flash chromatography was carried out using 60H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using FTIR Spectrometer as solutions using chloroform as solvent. ^{1}H and ^{13}C NMR spectra were recorded using 400 MHz NMR machine (^{1}H 400 MHz and ^{13}C 100 MHz, respectively); chemical shifts are quoted in parts per miilion and coupling constants, *J*, are quoted in hertz; *d*-Chloroform was used throughout unless otherwise stated. In the ^{13}C spectra, signals corresponding to C, CH, CH_2 or CH_3 groups, as assigned from DEPT, are noted. Spectra were calibrated to residual solvent peaks. High and low resolution mass spectra were carried out on an orbi-trap high resolution mass spectrometer. Optical rotation measurements were recorded using chloroform as solvent. Melting points are uncorrected. Compound **2** was synthesized using known literature procedures.[7,8b]

4.2. General diesterification method

To a solution of the diol (±)-**3** (0.100 g, 0.397 mmol) in pyridine (1.00 mL) was added the pyridyl acid chloride HCl salt (0.211 g, 1.190 mmol) followed by DMAP (catalytic, 0.01 g) and the resultant reaction mixture heated at 50 °C overnight under an N_2 atmosphere. The reaction mixture was then cooled, diluted with CH_2Cl_2 and washed sequentially with satd $NaHCO_3$ and brine. The organic layers were then dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude solid was then either recrystallized or purified by column chromatography. This gave the following compounds;

*4.2.1. (±)-4,8-Di(2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene)picolinate, (±)-**4a**.* Colourless crystals (0.90 g, 62%) mp 283–285.5 °C decomp.; R_f (3:1, ethyl acetate/petroleum ether) 0.4; ν_{max} (solution, $CHCl_3$) 3013, 1733, 1304, 1382, 1242, 1139 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.18 (m, 2H), 8.77 (dd, *J*=1.7, 4.8 Hz, 2H), 8.26–8.24 (m, 2H), 7.37–7.34 (m, 2H), 7.14–7.13 (m, 4H), 7.04–7.02 (m, 2H), 6.92 (d, *J*=7.6 Hz, 2H), 6.55 (d, *J*=5.7 Hz, 2H), 3.67–3.65 (m, 2H), 2.56–2.55 (m, 2H); δ_C (100 MHz; $CDCl_3$) 165.43 (C), 153.88 (CH), 151.33 (CH), 137.42 (CH), 134.78 (C), 134.16 (C), 131.10 (CH), 127.80 (CH), 127.12 (CH), 126.87 (CH), 125.88 (C), 123.47 (CH), 75.27 (CH), 35.96 (CH), 29.00 (CH_2); HRMS MH^+, $C_{29}H_{23}N_2O_4$, found 463.1636, requires MH^+ 463.1658.

*4.2.2. (±)-4,8-Di(2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene)nicotinate, (±)-**4b**.* Colourless crystals (0.145 g, 79%) mp 227–228.5 °C decomp.; R_f (3:1, ethyl acetate/petroleum ether) 0.6; ν_{max} (solution, $CHCl_3$) 3014, 1733, 1304, 1243, 1139 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.80 (d, *J*=0.8 Hz, 2H), 7.92 (d, *J*=7.6 Hz, 2H), 7.75–7.74 (m, 2H), 7.46 (dd, *J*=4.8, 5.6 Hz, 2H), 7.20–7.12 (m, 4H), 7.00–6.98 (m, 2H), 6.95 (d, *J*=7.6 Hz, 2H), 6.60 (d, *J*=5.6 Hz, 2H), 3.72–3.71 (m, 2H), 2.56–2.55 (m, 2H); δ_C (100 MHz; $CDCl_3$) 164.85 (C), 150.43 (CH), 147.83 (C), 137.10 (CH), 134.89 (C), 134.32 (CH), 131.21 (CH), 127.14 (CH), 127.13 (CH), 127.00 (CH), 126.96 (CH), 125.35 (CH), 75.70 (CH), 35.74 (CH), 28.97 (CH_2); HRMS MNa^+, $C_{29}H_{22}N_2O_4Na$, found 485.1455, requires MNa^+485.1477.

*4.2.3. (±)-4,8-Di(2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene)isonicotinate, (±)-**4c**.* Colourless crystals (0.142 g, 77%) mp 281–285 °C decomp.; R_f (3:1, ethyl acetate/petroleum ether) 0.68; ν_{max} (solution, $CHCl_3$) 3011, 1738, 1304, 1282, 1242, 1139 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.83–8.81 (m, 4H), 7.89–7.85 (m, 4H), 7.18–7.11 (m, 4H), 7.10–7.06 (m, 2H), 6.97 (d, *J*=7.6 Hz, 2H), 6.62 (d, *J*=5.6 Hz, 2H), 3.76–3.74 (m, 2H), 2.66–2.64 (m, 2H); δ_C (100 MHz; $CDCl_3$) 165.26 (C), 150.84 (CH), 137.11 (C), 134.71 (C), 133.98 (C), 131.13 (CH), 127.86 (CH), 127.16 (CH), 129.88 (CH), 123.09 (CH), 75.60 (CH), 35.80 (CH), 28.93 (CH_2); HRMS MH^+, $C_{29}H_{23}N_2O_4$, found 463.1638, requires MH^+ 463.1658.

*4.2.4. (±)-{(4-Hydroxy)-8-picolinate}-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene, (±)-**4d**.* Colourless crystals (0.032 g, 22%) mp 157–159 °C; R_f (3:1, ethyl acetate/petroleum ether) 0.4; ν_{max} (solution, $CHCl_3$) 3566, 2936, 1736, 1584, 1489, 1243 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.83–8.82 (m, 1H), 7.96 (d, *J*=7.6 Hz, 1H), 7.82–7.80 (m, 1H), 7.53–7.49 (m, 2H), 7.36–7.35 (m, 1H), 7.36–7.33 (m, 4H), 7.09–7.06 (m, 1H), 7.05–7.04 (m, 1H), 6.60 (d, *J*=5.2 Hz, 1H), 5.11–5.08 (m, 1H), 3.65 (s, 1H), 3.37 (s, 1H), 2.61–2.56 (m, 1H), 2.47–2.43 (m, 1H), 1.59 (d, *J*=11.6 Hz, 1H); δ_H (100 MHz; $CDCl_3$) 164.85 (C), 150.41 (CH), 147.86 (C), 139.16 (C), 137.04 (CH), 134.79 (C), 134.63 (C), 134.16 (C), 130.79 (CH), 130.58 (CH), 127.81 (CH), 127.76 (CH), 127.42 (CH), 127.27 (CH), 127.16 (CH), 127.08 (CH), 126.66 (CH), 125.32 (CH), 75.91 (CH), 72.51 (CH), 39.08 (CH), 36.11 (CH), 29.16 (CH_2); HRMS MH^-, $C_{23}H_{19}NO_3$, found 356.1296, requires MH^- 356.1287.

4.3. General method for monoalkylation

To a solution of the diol (±)-**3** (0.100 g, 0.397 mmol) in dry THF (5.00 mL) was added the pyridylmethyl bromide (0.221 g, 0.872 mmol, (note that the HBr salt was neutralized with NEt_3 (0.121 mL, 0.872 mmol)) in THF (1.00 mL) prior to addition and therefore added as a solution) and the reaction mixture stirred at 0 °C under N_2. To this mixture was added NaH (3.0 equiv) and the subsequent reaction mixture was then allowed to warm to room temperature and stirred overnight. After this period the reaction mixture was cooled to 0 °C, satd NH_4Cl added and the mixture warmed to room temperature. The reaction mixture then diluted with CH_2Cl_2 and the combined organic layers were then washed with brine, dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude solid was then purified by column chromatography. This gave the following compounds;

*4.3.1. (±)-{(4-Hydroxy)-8-(pyridin-2-yl)methoxy}-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene, (±)-**5a**.* Oil (0.119 g, 87%) R_f (3:1 ethyl acetate/petroleum ether) 0.35; ν_{max} (solution, $CHCl_3$) 3567, 3015, 2925, 1604, 1102, 1037 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.59 (d, *J*=4.4 Hz, 1H), 7.72 (dt, *J*=2.0, 8.0 Hz, 1H), 7.60 (d, *J*=10.0 Hz, 1H), 7.52–7.49 (m, 2H), 7.29–7.27 (m, 3H), 7.23–7.08 (m, 4H), 5.27 (d, *J*=13.2 Hz, 1H), 5.06–5.04 (m, 1H), 4.97–4.94 (m, 2H), 3.61–3.60 (m, 1H), 3.34–3.33 (m, 1H), 2.46–2.38 (m, 1H), 1.75 (br s, 1H); δ_H (100 MHz; $CDCl_3$) 158.39 (CH), 148.92 (CH), 139.03 (C), 137.54 (C), 136.90 (C), 134.77 (C), 133.83 (C), 130.75 (CH), 130.01 (CH), 127.56 (CH), 127.42 (CH), 127.32 (CH), 129.91 (CH), 126.73 (CH), 126.70 (CH), 122.58 (CH), 121.88 (CH), 80.92 (CH), 72.84 (CH), 72.50 (CH_2), 39.38 (CH), 34.78 (CH), 29.20 (CH_2); HRMS MH^+, $C_{23}H_{22}NO_2$, found 344.1638, requires MH^+ 344.1651.

*4.3.2. (±)-{(4-Hydroxy)-8-(pyridin-3-yl)methoxy}-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene, (±)-**5b**.* Colourless crystals (0.121 g, 88%) mp 150–151.5 °C decomp.; R_f (3:1 ethyl acetate/petroleum ether) 0.3; ν_{max} (solution, $CHCl_3$) 3567, 3014, 2928, 1102, 1038 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.74 (s, 1H), 8.58 (d, *J*=4.0 Hz, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.45–7.43 (m, 1H), 7.34 (dd, *J*=4.8, 7.6 Hz, 1H), 7.28–7.26 (m, 2H), 7.20–7.13 (m, 4H), 5.21 (d, *J*=12.0 Hz, 1H), 5.05 (d, *J*=5.6 Hz, 1H), 4.90 (d, *J*=4.8 Hz, 1H), 4.87 (d, *J*=12.0 Hz, 1H), 3.58–3.56 (m, 1H), 3.35–3.33 (m, 1H), 2.48–2.36 (m, 2H), 1.62 (br s, 1H); δ_H (100 MHz; $CDCl_3$) 149.36 (CH), 149.25 (CH), 139.01 (C), 137.25 (C), 135.63 (CH), 134.54 (C), 133.72 (C), 133.51 (C), 130.49 (CH), 129.99 (CH), 127.66 (CH), 127.49 (CH), 127.31 (CH), 127.04 (CH), 126.87 (CH), 126.82 (CH), 123.62 (CH), 80.78 (CH), 72.78 (CH), 69.24 (CH_2), 39.32 (CH), 34.91 (CH), 29.23 (CH_2); HRMS MH^+, $C_{23}H_{22}NO_2$, found 344.1633, requires MH^+ 344.1651.

*4.3.3. (±)-{(4-Hydroxy)-8-(pyridin-4-yl)methoxy}-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene, (±)-**5c**.* Colourless crystals (0.126 g, 92%) mp 215–218 °C decomp.; R_f (3:1 ethyl acetate/petroleum ether) 0.3; ν_{max} (solution, $CHCl_3$) 3566, 3015, 2928, 1605, 1101, 1036 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.61 (m, 2H), 7.53–7.48 (m, 2H), 7.41 (d, *J*=5.2 Hz, 2H), 7.30–7.28 (m, 1H), 7.22–7.18 (m, 3H), 7.13–7.09 (m, 1H), 7.05 (dd, *J*=1.2, 8.8 Hz, 1H), 5.23 (d, *J*=13.6 Hz, 1H), 5.06 (d, *J*=5.2 Hz, 1H), 4.90 (d, *J*=4.8 Hz, 1H), 4.87 (d, *J*=13.6 Hz, 1H), 3.57–3.55 (m, 1H), 3.35–3.34 (m, 1H), 2.49–2.41 (m, 2H), 1.76 (br s, 1H); δ_C (100 MHz; $CDCl_3$) 149.67 (CH), 147.59 (C), 139.05 (C), 137.13 (C), 134.47 (C), 133.76 (C), 130.52 (CH), 130.08 (CH), 127.67

(CH), 127.51 (CH), 127.26 (CH), 127.10 (CH), 126.87 (CH), 126.74 (CH), 121.96 (CH), 81.17 (CH), 72.78 (CH), 69.92 (CH_2), 39.34 (CH), 34.88 (CH), 29.21 (CH_2); HRMS MH^+, $C_{23}H_{22}NO_2$, found 344.1634, requires MH^+ 344.1651.

4.4. General method for dialkylation

To a solution of the diol (±)-**3** (0.100 g, 0.397 mmol) in dry DMSO (2.00 mL) was added the pyridylmethyl bromide HBr salt (0.221 g, 0.872 mmol) and the reaction mixture stirred at 0 °C under N_2. To this mixture was added powdered KO^tBu (0.200 g, 1.783 mmol) and the subsequent black reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured into H_2O and extracted with ethyl acetate (×3). The combined organic layers were then washed with brine, dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude solid was then recrystallized (CH_2Cl_2/petroleum ether) giving the following compounds.

*4.4.1. (±)-4,8-{(Dipyridin-2-yl)methoxy}-2,3:6,7-dibenzobicyclo [3.3.1]nona-2,6-diene, (±)-**6a**.* Colourless crystals (0.152 g, 88%) mp 237–238.5 °C; ν_{max} (solution, $CHCl_3$) 3014, 2928, 2860, 1086 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.59 (dd, J=0.8, 4.8 Hz, 4H), 7.73 (dt, J=1.6, 7.6 Hz, 2H), 7.61 (d, J=7.6 Hz, 2H), 7.48–7.46 (m, 2H), 7.25–7.22 (m, 2H), 7.15–7.07 (m, 6H), 5.28 (d, J=13.2 Hz, 2H), 4.98 (d, J=13.2 Hz, 2H), 4.96 (d, J=13.6 Hz, 2H), 4.96 (d, J=4.8 Hz, 2H), 3.63–3.61 (m, 2H), 2.44–2.42 (m, 2H); δ_C (100 MHz; $CDCl_3$) 158.61 (C), 148.98 (CH), 136.97 (C), 136.84 (CH), 134.56 (C), 130.70 (CH), 127.00 (CH), 126.50 (CH), 126.46 (CH), 122.51 (CH), 121.86 (CH), 81.09 (CH), 73.37 (CH_2), 34.69 (CH), 29.16 (CH_2); HRMS MNa^+, $C_{29}H_{26}N_2O_2Na$, found 457.1872, requires MNa^+ 457.1892.

*4.4.2. (±)-4,8-Di{(pyridin-3-yl)methoxy}-2,3:6,7-dibenzobicyclo [3.3.1]nona-2,6-diene, (±)-**6b**.* Colourless crystals (0.136 g, 79%) mp 203–205 °C; ν_{max} (solution, $CHCl_3$) 3014, 2928, 2860, 1085 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.74 (s, 2H), 8.60 (d, J=4.0 Hz, 2H), 7.88 (d, J=8.0 Hz, 2H), 7.36 (dd, J=4.8, 7.2 Hz, 4H), 7.26 (2, 2H), 7.13–7.11 (m, 6H), 5.20 (d, J=12.0 Hz, 2H), 4.87–4.86 (m, 2H), 4.86 (d, J=12.0 Hz, 2H), 3.56–3.54 (m, 2H), 2.42–2.40 (m, 2H); δ_C (100 MHz; $CDCl_3$) 148.99 (CH), 148.85 (CH), 136.68 (C), 135.97 (CH), 135.25 (C), 133.95 (C), 130.48 (CH), 127.21 (CH), 126.68 (CH), 126.41 (CH), 123.79 (CH), 80.94 (CH), 69.91 (CH_2), 34.83 (CH), 29.22 (CH_2); HRMS MH^+, $C_{29}H_{27}N_2O_2$, found 435.2054, requires MH^+ 435.2073.

*4.4.3. (±)-4,8-Di{(pyridin-4-yl)methoxy}-2,3:6,7-dibenzobicyclo [3.3.1]nona-2,6-diene, (±)-**6c**.* Colourless crystals (0.162 g, 94%) mp 235–240 °C decomp.; ν_{max} (solution, $CHCl_3$) 3014, 2928, 2860, 1085 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.61 (dd, J=1.2, 4.4 Hz, 4H), 7.44 (d, J=7.6 Hz, 2H), 7.40–7.38 (m, 4H), 7.22–7.05 (m, 6H), 5.21 (d, J=13.2 Hz, 2H), 4.89 (d, J=4.8 Hz, 2H), 4.86 (d, J=13.6 Hz, 2H). 3.58–3.56 (m, 2H), 2.43–2.41 (m, 2H); δ_C (100 MHz; $CDCl_3$) 149.98 (CH), 147.34 (C), 136.63 (C), 134.22 (C), 130.59 (CH), 127.26 (CH), 126.68 (CH), 126.46 (CH), 121.86 (CH), 81.23 (CH), 69.77 (CH_2), 34.80 (CH), 29.16 (CH_2); HRMS MH^+, $C_{29}H_{27}N_2O_2$, found 435.2053, requires MH^+ 435.2073.

4.5. X-ray crystallography

Crystal data were collected on Bruker APEX 2 CCD diffractometers using narrow slice 0.3° ω-scans for (+)-**4b**·**CH_2Cl_2**, (±)-**4c**, (±)-**4d** and (±)-**5c**.[12] Data for (±)-**4c** and (±)-**5c** were collected at the ALS, Station 11.3.1 using silicon 111 monochromated X-radiation.[12] Data were corrected for Lp effects and for absorption, based on repeated and symmetry equivalent reflections, and solved by direct methods.[13,14] Structures were refined by full matrix least squares on F^2.[13,14] H atoms were included in a riding model. Hydrogen atom U_{iso} values were constrained to be 120% of that of the carrier atom except for methyl and hydroxyl-H (150%). The absolute structure for (+)-**4b**·**CH_2Cl_2** was well determined with absolute structure parameter x=0.06(7). Further details are provided in Table 1 in the Supplementary data. CCDC 784572-784575 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

MCK thanks Loughborough University for funding. The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

Supplementary data

Supplementary data including ^{1}H and ^{13}C NMR of (±)-**4a**–**c**, (±)-**5a**–**c** and (±)-**6a**–**c** and the crystallographic data for (+)-**4b**, (±)-**4c**,**d** and (±)-**5c**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.027. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, 1995.
2. Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225.
3. Dolensky, B.; Elguero, J.; Kral, V.; Pardo, C.; Valik, M. *Adv. Heterocycl. Chem.* **2007**, *93*, 1.
4. Sergeyev, S. *Helv. Chim. Acta* **2009**, *92*, 415.
5. (a) Kagan, J.; Chen, S.-Y.; Dalmacio, A.; Agdeppa, J. *Tetrahedron Lett.* **1977**, *18*, 4469; (b) Butkus, E.; Berg, U.; Malinauskieneù, J.; Sandstrom, J. *J. Org. Chem.* **2000**, *65*, 1353; (c) Stoncius, S.; Butkus, E.; Zyilinskas, A.; Larsson, K.; Ohrstrom, L.; Berg, U.; Warnmark, K. *J. Org. Chem.* **2004**, *69*, 5196; (d) Wallentin, C.-J.; Wixe, T.; Wendt, O. F.; Bergquist, K.-E.; Warnmark, K. *Chem.—Eur. J.* **2010**, *16*, 3994.
6. Stetter, H.; Reischl, A. *Chem. Ber.* **1960**, *93*, 791.
7. Tatemitsu, H.; Ogura, F.; Nakagawa, Y.; Nakagawa, M.; Naemura, K.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2473.
8. (a) Try, A. C.; Painter, L.; Harding, M. M. *Tetrahedron Lett.* **1998**, *39*, 9809; (b) Kimber, M. C.; Try, A. C.; Painter, L.; Harding, M. M.; Turner, P. *J. Org. Chem.* **2000**, *65*, 3042; (c) Field, J. D.; Turner, P.; Harding, M. M.; Hatzikominos, T.; Kim, L. *New J. Chem.* **2002**, *26*, 720; (d) Anderberg, P. I.; Turner, J. J.; Evans, K. J.; Hutchins, L. M.; Harding, M. M. *Dalton Trans.* **2004**, 1708; (e) Lee, C. K. Y.; Groneman, J. L.; Turner, P.; Rendina, L. M.; Harding, M. M. *Tetrahedron* **2006**, *62*, 4870.
9. Turner, J. J.; Harding, M. M. *Supramol. Chem.* **2005**, *17*, 369.
10. (a) Naemura, K.; Fukunaga, R. *Chem. Lett.* **1985**, 1651; (b) Naemura, K.; Fukunaga, R.; Yamanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1560; (c) Naemura, K.; Fukunaga, R.; Komatsu, M.; Yamanaka, M.; Chikamatsu, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 83; (d) Thunberg, L.; Allenmark, S.; Friberg, A.; Ek, F.; Frejd, T. *Chirality* **2004**, *16*, 614.
11. Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.
12. SAINT and APEX 2 *Software for CCD Diffractometers*; Bruker AXS: Madison, USA, 2008.
13. Sheldrick, G. M. *SHELXTL User Manual, version 6.10*; Bruker AXS: Madison, WI, USA, 2000.
14. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.