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Structure–selectivity studies on catalysts for the phase-transfer catalysed asymmetric alkylation of glycine imine esters

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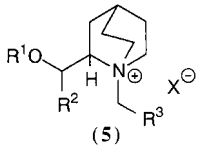
Abstract—In this paper, we describe the synthesis of a series of chiral quaternary ammonium salts with core structures that are closely related to the cinchona alkaloid, cinchonine. By employing these salts as asymmetric phase-transfer agents in the benzylation of a glycine imine, an optimal catalyst structure is identified.

The use of cinchona alkaloid derived phase-transfer catalysts to effect the asymmetric alkylation of amino acid imine esters such as **3** was first reported by O'Donnell in 1989.[1] Initially, *N*-benzyl derivatives **1** and **2** of the cinchona alkaloids were employed for this process typically leading to enantioselectivities in the range 42–66% e.e.[2] It was also shown that diastereoisomeric catalysts **1** and **2**, derived from cinchonidine and cinchonine, respectively, were enantiocomplimentary in the sense that they led to selectivity for opposite enantiomers of the product imine **4** (Scheme 1).[3] It was later demonstrated that careful optimisation of the reaction conditions could lead to significantly higher enantioselectivities (up to 81% e.e.),[4] and more recently it has been established by us[5] and others[6] that the corresponding *N*-anthracenylmethyl cinchona alkaloid salts lead to significantly increased enantioselectivities, typically in the range 80–99% e.e.[7]

In this paper, we present some of our studies that were aimed at identifying the optimal structure for catalysts of the type shown in Scheme 1. At the start of this study, we chose to probe the role of key structural elements present in catalysts **1** and **2** by investigating a range of quaternary ammonium ions of type **5**.[8] We considered that variation of substituents R^1, R^2 and R^3 would allow us to determine the optimal groups in these parts of the quaternary ammonium structure.[9] It was hoped that knowledge gained from this study would allow the design of novel catalysts, which would give improved enantioselectivity over salts such as **1** and **2**. We chose initially to investigate structures that lacked the C-5 vinyl substituent present in the alkaloid-derived catalysts since this substituent was known to have relatively little influence on the enantioselectivity of the imine alkylation reactions, and its omission eliminated any stereochemical ambiguities arising from the consequent chiral centres at N-1, C-4 and C-5.



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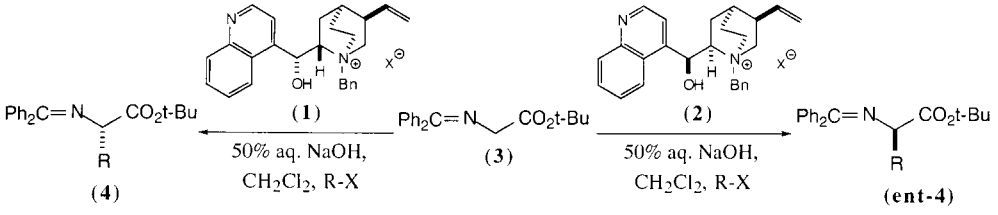

Scheme 1.

Keywords: cinchona alkaloid; phase-transfer; asymmetric catalysis; amino acid.
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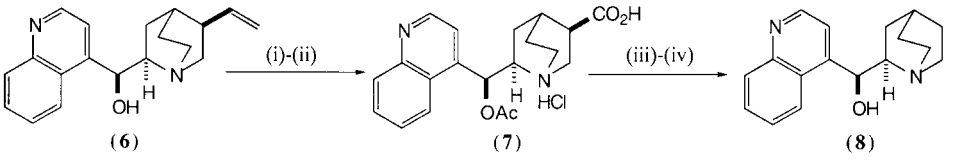
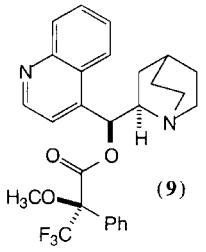


Scheme 2. *Reagents*: (i) Ac_2O (99%); (ii) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH–H_2O; HCl (29%); (iii) *i*-BuOCOCl, NMM; *N*-hydroxy-2-thiopyridine, Et_3N; 2-methyl-2-propanethiol, $h\nu$ (52%); (iv) LiOH, THF–H_2O (87%).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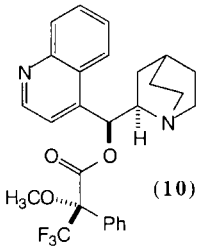

(10)

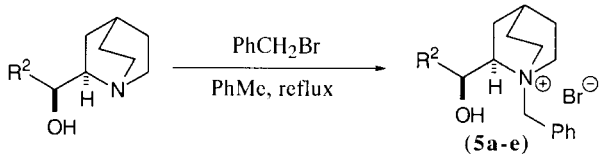
A range of R^1, R^2 and R^3 groups were selected in order to gain more insight into the steric and electronic requirements at these positions. In most instances, the precursor quinuclidines were available from work in our laboratories,[10] however it was necessary to prepare amine **8** and this was achieved as outlined in Scheme 2.

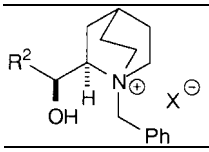
In this sequence, it was found that *O*-acetylation of cinchonine **6** facilitated purification of the intermediates and led to improved overall yields. The stereochemical integrity of quinuclidine **8** was confirmed by conversion into the corresponding Mosher's esters **9** and **10** (using both (*R*)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, respectively, and analysis by ^{1}H NMR.

1. Variation of R^2

The first series of quaternary ammonium salts investigated, **5a**–**e**, were ones in which the substituent R^2 was varied. In this case, we chose to incorporate an *N*-benzyl substituent in order to allow direct comparison with catalysts **1** and **2**, consequently, the salts **5a**–**e** were prepared from the corresponding quinuclidines via *N*-alkylation with benzyl bromide (Table 1).

Table 1.

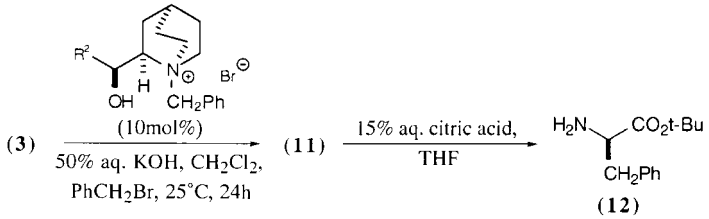


Product		R^2	Yield (%)
	**5a**	Cyclohexyl	77
	5b	CH_3OCH_2	100
	5c	Ph	78
	5d	Naphth-1-yl	89
	5e	Quinolin-4-yl	76

The resulting salts **5a**–**e** were then employed as phase-transfer catalysts in the alkylation of glycine imine **3** with benzyl bromide (Table 2). This particular assay reaction was chosen because it was known that the enantioselectivity of the crude imine **11** could be readily assessed by HPLC,[2a] and because the absolute stereochemistry of this product was already known.

For the purposes of this study, all reactions were run at 25°C with magnetic stirring (ca. 1000 rpm) in 10 ml

Table 2.



Catalyst	e.e. of **11** (%)	Yield of **12** (%)
5a	23	64
5b	10	66
5c	48	52
5d	36	76
5e	56	76

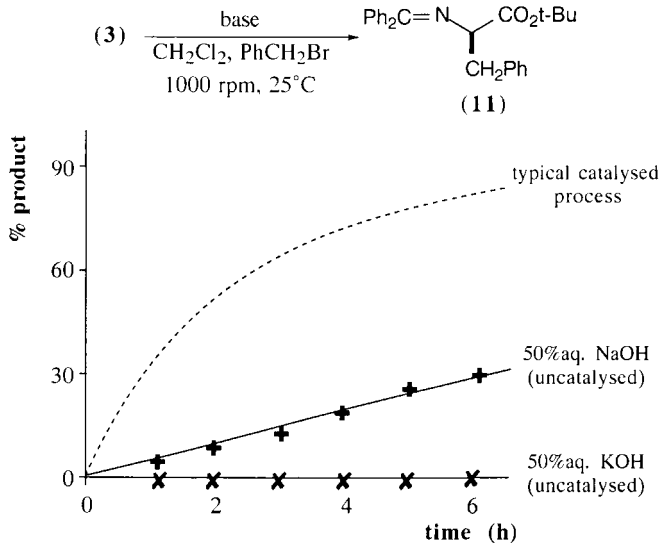


Figure 1.

round-bottomed flasks.[11] Initially we had planned to use previously reported conditions (Scheme 1)[2a] in which 50% aqueous sodium hydroxide was utilised as the base, however it was found that this lead to a significant rate of background reaction (Fig. 1). This problem was easily overcome by switching to 50% aqueous potassium hydroxide, which gave no background reaction on the timescales involved.

As the resulting imine **11** proved moderately sensitive to hydrolysis on chromatographic media, it was routinely hydrolysed to phenylalanine *tert*-butyl ester **12** before purification by chromatography.

It was found that the quaternary ammonium salts **5a–e** were all able to catalyse the alkylation of glycine imine **3**, giving complete consumption of starting material within 24 h at 25°C, and in all cases the (*R*)-isomer of the imine **11** was formed in excess. The level of enantioselectivity obtained, varied significantly (10–56% e.e.) and from this limited study it appears that a planar (aryl) substituent in position R^2 (e.g. catalysts **5c–e**) is preferable. The nature of the aryl group also appears to be important with the quinolin-4-yl substituent (catalyst **5e**) giving the highest selectivity amongst the groups examined.

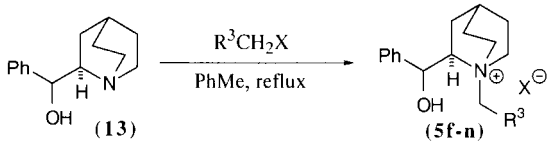
2. Variation of R^3

We next examined variation of the *N*-substituent, R^3. For this study, a series of salts **5f–n** were prepared via quaternisation of quinuclidine **13** with the appropriate alkylating agent (Table 3).

These materials were then tested in our standard assay reaction and the results are shown in Table 4.

Again, all the salts **5f–n** were able to catalyse the alkylation of glycine imine **3**, and wide variation of enantioselectivity

Table 3.



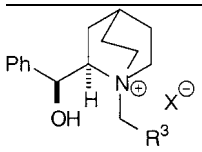
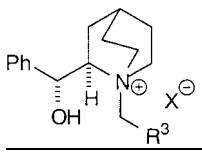
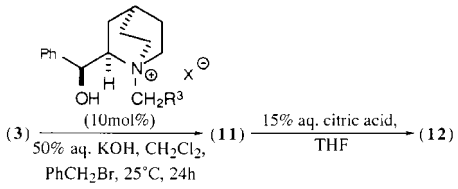
Product		R^3	X	Yield (%)
	**5f**	H	I	79
	5g	*n*-Propyl	I	27
	5h	Cyclohexyl	Br	30
	5i	4-Nitrophenyl	Br	69
	5j	4-Methoxyphenyl	Cl	69
	5k	Naphth-1-yl	Cl	60
	5l	Naphth-2-yl	Br	95
	5m	Anthracen-9-yl	Cl	51
	**5n**	Ph	Br	75

Table 4.



Catalyst	e.e. of **11** (%)	Yield of **12** (%)
5c	48	52
5f	8	67
5g	2	76
5h	4	56
5i	38	66
5j	38	59
5k	52	67
5l	40	67
5m	75	57
5n	2	73

was observed (2–75% e.e.). It was found that in general simple arylmethyl *N*-substituents (catalysts **5c**, **i**,**j**) gave substantially better levels of enantioselectivity than alkyl *N*-substituents (catalysts **5f**–**h**), and that the correct relative stereochemistry at C-2 and C-1′ was essential for enantioselectivity (compare catalysts **5c** and **n**). Both these observations are no great surprise as similar results have been reported for related phase-transfer catalysed processes.[9] More surprising was the observation that extending the aromatic π-system in the *N*-arylmethyl substituent led to dramatic changes in the level of enantioselectivity. It was found that a *N*-naphth-1-ylmethyl substituent (catalyst **5k**) lead to a slight increase in enantioselectivity relative to *N*-benzyl (catalyst **5c**), whereas the corresponding *N*-naphth-2-ylmethyl substituent (catalyst **5l**) lead to a decrease in selectivity. This would seem to suggest that the extent and orientation of the π-plane in the *N*-arylmethyl substituents is important in determining the level of enantioselectivity, an observation that is dramatically illustrated by the *N*-anthracen-9-ylmethyl substituted system **5m** which gave substantially higher levels of enantioselectivity than any of the other catalysts investigated.

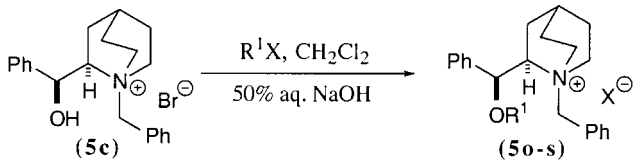
3. Variation of R^1

In all the above alkylation reactions, the quaternary ammonium salt undergoes rapid *O*-alkylation to give the corresponding *O*-benzyl derivative,[2a] and it is this species that is the active catalyst. In order to investigate variation of this *O*-substituent (R^1), we prepared a range of derivatives **5o**–**s** via alkylation under two-phase conditions[2a] (Table 5). Attempts to introduce more bulky R^1-substituents via alkylation were not successful.

These salts were then subjected to the standard assay reaction and the results are shown in Table 6.

In this case, less variation in enantioselectivity was observed (26–50% e.e.) with *n*-butyl (**5p**) and benzyl (**5q**) R^1-substituents giving highest selectivity. It should also be noted that the pre-prepared *O*-benzyl catalyst **5q** gave essentially the same enantioselectivity as that generated via *O*-benzylation in situ (**5c**, Table 2).

Table 5.



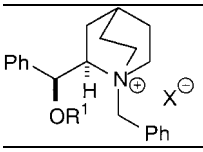
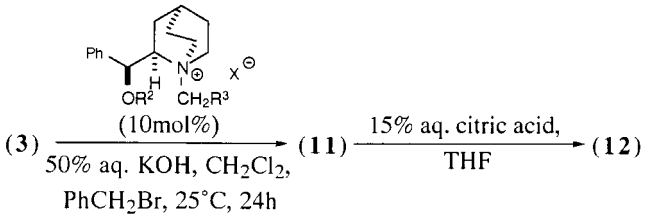
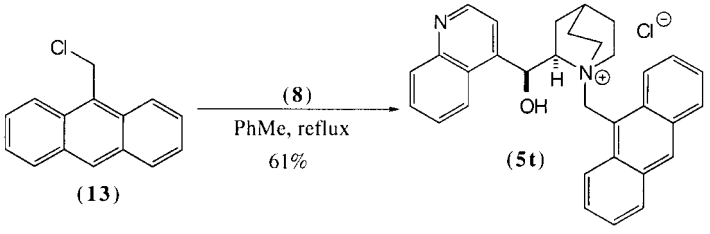
Product		R^1	X	Yield (%)
	**5o**	CH_3	I	92
	5p	*n*-Butyl	I	76
	5q	$PhCH_2$	Br	83
	5r	CH_3OCH_2	Br	82
	5s	$PhCH_2OCH_2$	Br	94

Table 6.

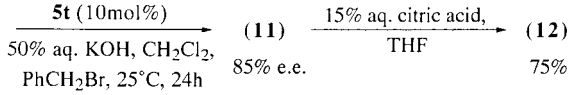


Catalyst	e.e. of **11** (%)	Yield of **12** (%)
5o	36	59
5p	50	57
5q	48	64
5r	26	60
5s	30	50

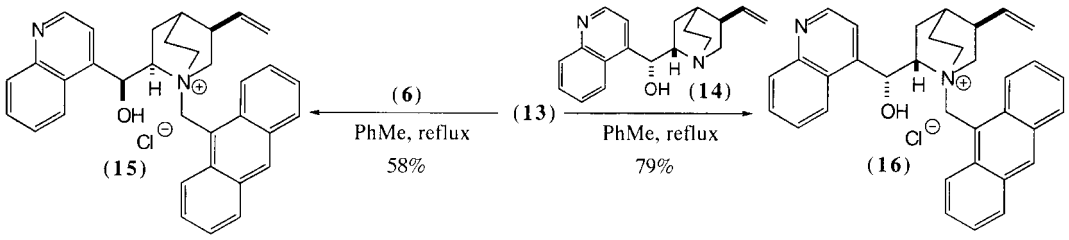
If the effects of the various substituents tested in catalyst **5** are additive, the combination of R^1=Bn or *n*-Bu, R^2=quinolin-4-yl and R^3=9-anthracenylmethyl should lead to the highest levels of enantioselectivity in the assay reaction. In order to test this, we prepared quaternary ammonium salt **5t** via simple quaternisation of the quinuclidine **8** (Scheme 3).



Scheme 3.



Scheme 4.



Scheme 5.

We chose not to pre-alkylate the hydroxyl function in **5t** since this would undergo rapid benzylation during the assay reaction (Scheme 4).

Using the pre-catalyst **5t**, it was found that the alkylation proceeded smoothly to give **11** in 85% e.e. and after hydrolysis of the imine function (*R*)-phenylalanine *tert*-butyl ester **12** could be isolated in 75% overall yield. The level of enantioselectivity obtained in this case was significantly higher than that found with the other catalysts investigated and the similarity between the precursor quinuclidine **8** and the alkaloids cinchonine **6** and cinchonidine **14** prompted us to investigate the naturally occurring alkaloids as direct catalyst precursors. Thus 9-chloromethylanthracene **13** was reacted with the alkaloids to give quaternary ammonium salts **15** and **16** (Scheme 5).

The salts **15** and **16** were then subjected to the standard assay (Scheme 6). As anticipated, the resulting catalysts were enantio-complimentary, the cinchonine-derived salt **15** leading to the formation of (*R*)-**12** in excess and the cinchonidine derived-catalyst **16** leading to selectivity for (*S*)-**12**. In both the cases, the active catalyst is the corresponding *O*-benzyl derivative, generated in situ via alkylation of the pre-catalyst, and the level of enantiomeric excess was similar to that obtained using pre-catalyst **5t**, confirming the assumption that the C-5 vinyl substituent present in the alkaloids had relatively little effect in this type of reaction process. It is however interesting to note that the cinchonidine-derived catalyst **16** gave slightly higher enantioselectivitiy than catalyst **5t**.

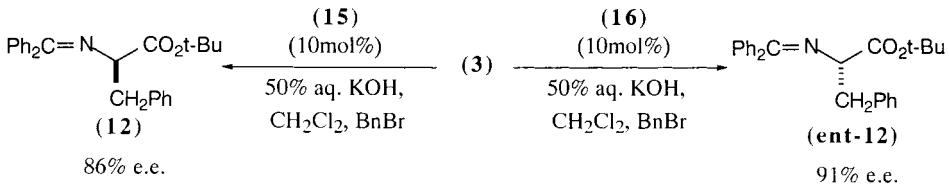
The ease with which salts **15** and **16** can be made, coupled with the high level of enantioselectivity obtained in the alkylation of imine **3**, suggests that pre-catalysts of this type may have considerable potential in the asymmetric synthesis of α-amino acids and details of our work in this area is presented in the following paper.

In conclusion, by preparing a series of quaternary ammonium salts **5** and investigating the enantioselectivity obtained in the alkylation of imine **3**, we have been able to show that the *N*-anthracenylmethyl substituent is a key structural element which leads to substantially enhanced enantioselectivity over smaller *N*-alkyl substituents. This investigation also suggests that the 1-quinolyl group present in the parent alkaloid plays a key role in enantioselectivity.

4. Experimental

4.1. General

Infra-red absorption spectra were recorded on Perkin–Elmer 1600 and 1710 Fourier-transform spectrometers. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC300 spectrometer. All chemical shifts (δ) were referenced to the deuterium lock and are reported in parts per million (ppm). The following abbreviations have been used to describe the signal multiplicity: br (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), and *J* (coupling constant in Hz). Mass spectra (MS) were recorded at low resolution on a Finnigan 4500 instrument with chemical ionisation (CI) using ammonia. Accurate mass measurement (high resolution) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1-S instrument. Optical rotations ($[\alpha]_D$) are quoted to ±10% accuracy and were measured on an AA-10 monochromatic 589 nm (Optical Activity) polarimeter at room temperature. Melting points (mp) were determined using an electrothermal apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed using Gilson apparatus with the columns and conditions outlined in the relevant experimental procedures. Enantiomeric excesses determined by HPLC as described in the experimental section were reproducible to ±2%. Thin layer chromatography (TLC) was performed either on plates pre-coated (0.25 mm) with CAMLAB DC-Fertigplatten SIL G-25 UV254 (silica) or plates pre-coated (0.2 mm) with CAMLAB DC-Fertigfolien ALOX N UV254 (neutral alumina). The plates were



Scheme 6.

visualised by the use of a combination of ultraviolet light, iodine, ethanolic vanillin, or aqueous potassium permanganate. Silica gel 60 (particle sizes 40–60 μ) or aluminium oxide 90 active neutral (1077) both supplied by Merck were employed for flash chromatography. Where necessary, solvents and reagents were dried and purified according to recommended procedures.[12]

4.1.1. Preparation of (2*R*,5*R*,1′*S*)-2-[1-acetoxy-1-(quinolin-4-yl)]methyl-5-carboxy-1-azabicyclo[2.2.2]octane hydrochloride (7). Potassium carbonate (14.0 g) was added to a solution of (2*R*,5*R*,1′*S*)-2-[1-acetoxy-1-(quinolin-4-yl)]methyl-5-ethylene-1-azabicyclo[2.2.2]octane[13] (11.0 g, 30.0 mol) in *tert*-butanol (1300 ml) and the resulting mixture was warmed to 85°C. A prewarmed (60°C) solution of potassium permanganate (2.0 g, 10.0 mmol) and sodium periodate (33.6 g, 160.0 mmol) in water (1100 ml) was then added and the mixture was stirred at room temperature for 2 h. Sodium sulfite (20.0 g) was next added and the mixture was stirred for a further 20 min. The resulting two layers were separated and the upper layer was concentrated to a volume of ca. 500 ml. This was washed with ethyl acetate (2×250 ml) then combined with the lower layer. The combined aqueous solutions were acidified to pH 5 with 3 M HCl, washed with chloroform (2×250 ml) (to remove the liberated iodine) and then concentrated under reduced pressure. The solid residue was continuously extracted for 24 h with hot chloroform and the extracts were dried over magnesium sulfate, then concentrated under reduced pressure to give the crude product **7** (3.6 g, 28%) as an orange semi-solid, suitable for use in subsequent reactions. $[\alpha]_D$=+39 (*c*=0.4, $CHCl_3$). ν_{max} (neat) 3419, 2959, 1750 cm^{-1}. ^1H NMR δ (300 MHz, D_2O) 10.49 (1H, brs, CO_2H), 8.73 (1H, d, *J*=4.0 Hz, H-2″), 8.49 (1H, d, *J*=8.0 Hz, H-8″), 8.09 (1H, d, *J*=8.0 Hz, H-5″), 7.75–7.52 (2H, m, H-6″, H-7″), 7.41 (1H, d, *J*=4.0 Hz, H-3″), 7.20–7.05 (1H, m, H-1′), 4.32–4.15 (1H, m, H-5), 3.53–3.18 (3H, m), 3.15–2.91 (1H, m), 2.75–2.62 (1H, m, H-7b), 2.62–2.50 (1H, m), 2.39–1.47 (3H, m), 2.14 (3H, s, $COCH_3$), 1.47–1.22 (1H, m). *m/z* (NH_3, Cl) 355 ($M+H^+$, 100%), 297 (90%). Found $[M+H]^+$ 355.1676, $C_{20}H_{22}N_2O_4$ requires 355.1658.

4.1.2. Preparation of (2*R*,1′*S*)-2-[1-acetoxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane. A solution of (2*R*,5*R*,1′*S*)-2-[1-acetoxy-1-(quinolin-4-yl)]methyl-5-carboxy-1-azabicyclo[2.2.2]octane hydrochloride **7** (1.50 g, 3.84 mmol) in THF (30 ml) was cooled to −15°C under argon. Isobutylchloroformate (0.56 ml, 4.32 mmol) was added followed by *N*-methylmorpholine (0.43 ml, 3.84 mmol) and the mixture was stirred at room temperature for 2 h. The solution was then re-cooled to −15°C and a mixture of *N*-hydroxy-2-thiopyridine (0.50 g, 4.48 mmol) and triethylamine (0.68 ml, 4.85 mmol) in THF (15 ml) was added. The solution was then stirred at −15°C in the dark for 1 h, then 2-methyl-2-propanethiol (4.50 ml, 44.80 mmol) was added. The reaction flask was then placed in a water-bath, irradiated with a 100 W sun-lamp for 30 min, then poured into saturated aqueous sodium hydrogen carbonate (30 ml). The aqueous layer was extracted with diethyl ether (2×50 ml) and the combined organics were dried over magnesium sulfate, then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (4:1, ethyl acetate/methanol) to give the product (615 mg, 52%) as a white foam. R_f (silica gel) 0.2 (4:1, ethyl acetate/methanol). $[\alpha]_D$=+45 (*c*=2.6, $CHCl_3$). ν_{max} (neat) 2940, 1744 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.85 (1H, d, *J*=4.5 Hz, H-2″), 8.21 (1H, d, *J*=8.5 Hz, H-8″), 8.09 (1H, d, *J*=8.5 Hz, H-5″), 7.71–7.66 (1H, m, H-7″), 7.59–7.54 (1H, m, H-6″), 7.36 (1H, d, *J*=4.5 Hz, H-3″), 6.55 (1H, d, *J*=7.0 Hz, H-1′), 3.42–3.34 (1H, m, H-2), 3.21–3.05 (1H, m, H-6a), 2.83–2.62 (3H, m, H-6, H_2-7), 2.09 (1H, s, $COCH_3$), 1.91–1.85 (1H, m), 1.75–1.38 (6H, m). *m/z* (NH_3, Cl) 31 ($M+H^+$, 100%). Found $[M+H]^+$ 311.1768, $C_{19}H_{23}N_2O_2$ requires 311.1759.

4.1.3. Preparation of (2*R*,1′*S*)-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane (8). Lithium hydroxide (1.45 g) in water (4.5 ml) was added to a solution of (2*R*,1′*S*)-2-[1-acetoxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane (600 mg, 1.94 mmol) in THF (9 ml) and methanol (4.5 ml). The resulting mixture was stirred at room temperature for 1 h, then concentrated to a volume of ca. 5 ml under reduced pressure. The mixture was then diluted with water (20 ml) and extracted with ethyl acetate (3×20 ml). The organic extracts were dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by recrystallisation from ethyl acetate to give the product **8** (462 mg, 87%) as a white solid. $[\alpha]_D$=+120 (*c*=1.0, $CHCl_3$) [lit. $[\alpha]_D$=+133 (*c*=0.8, EtOH)].[14] Mp 224–225°C [lit. mp 230°C].[14] ν_{max} (neat) 3050, 2937 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.80 (1H, d, *J*=4.5 Hz, H-2″), 8.06 (1H, d, *J*=7.5 Hz, H-8″), 7.85 (1H, d, *J*=8.5 Hz, H-5″), 7.63–7.56 (2H, m, H-3″, H-7″), 7.26–7.20 (1H, m, H-6″), 5.70 (1H, d, *J*=3.5 Hz, H-1′), 4.83 (1H, brs, OH), 3.57–3.45 (1H, m, H-2), 3.18–3.06 (1H, m, H-6a), 2.91–2.59 (3H, m, H-6b, H_2-7), 1.92–1.74 (2H, m), 1.68–1.16 (5H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 150.1, 149.6, 148.0, 130.0, 128.9, 126.4, 125.5, 122.9, 118.3, 71.6, 59.9, 50.7, 43.9, 26.3, 25.8, 25.4, 21.9. *m/z* (NH_3, Cl) 269 ($M+H^+$, 100%). 246 (62%). Found $[M+H]^+$ 269.1660, $C_{17}H_{21}N_2O$ requires 269.1654.

4.2. General method for the preparation of Mosher's ester derivatives

The appropriate alcohol (0.06 mmol) was dissolved in dry dichloromethane (3 ml), placed under an argon atmosphere, and three drops of triethylamine was added. DMAP (13 mg, 0.10 mmol) was then added followed by (*R*)-(−)- or (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20 μl, 0.14 mmol). The resulting mixture was stirred for 90 min, and then all volatiles were removed in vacuo. The residue was dissolved in chloroform (2 ml), washed with saturated aqueous potassium carbonate (2×2 ml), dried over magnesium sulfate and concentrated under reduced pressure to give the crude product.

4.2.1. Preparation of (2*R*,1′*S*,1″′*R*)-2-{1-[(2-methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-(quinolin-4-yl)}methyl-1-azabicyclo[2.2.2]octane (9). (2*R*,1′*S*)-2-[1-Hydroxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane **8** (30 mg, 0.11 mmol) was reacted with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (70 μl, 0.37 mmol) according to the general method above. The crude product

was purified by chromatography on silica gel (19:1, dichloromethane/methanol) to give the product **9** (45 mg, 79%) as a colourless oil. R_f (silica gel) 0.5 (19:1, dichloromethane/methanol). $[\alpha]_D$=+100 (c=0.6, $CHCl_3$). ν_{max} (neat) 2946, 1751 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.80 (1H, d, J=4.5 Hz, H-2″), 8.45–8.29 (2H, m, Ar–H), 7.54–7.41 (2H, m, Ar–H), 7.48–7.10 (5H, m, Ar–H), 7.05–6.88 (3H, m, Ar–H, H-1′), 3.42–3.13 (1H, m, H-2), 3.35 (3H, s, OCH_3), 2.98–2.81 (1H, m, H-6a), 2.49–2.12 (3H, m, H-6b, H_2-7), 1.48–1.30 (3H, m), 1.29–1.15 (1H, m), 1.07–0.85 (3H, m). ^1H NMR δ (300 MHz, C_6D_6) 8.81 (1H, d, J=4.5 Hz, H-2″), 8.44–8.28 (2H, m, Ar–H), 7.52–7.41 (2H, m, Ar–H), 7.35–7.10 (2H, m, Ar–H), 7.09–6.85 (1H, m, Ar–H), 7.03–6.73 (4H, m, Ar–H, H-1′), 3.31–3.16 (1H, m, H-2), 3.22 (3H, s, OCH_3), 2.98–2.80 (1H, m, H-6a), 2.49–2.13 (3H, m, H-6b, H_2-7), 1.52–1.31 (3H, m), 1.30–1.17 (1H, m), 1.08–0.83 (3H, m). m/z (NH_3, Cl) 485 ($M+H^+$, 40%), 251 (100%). Found $[M+H]^+$ 485.2057, $C_{27}H_{28}N_2O_3F_3$ 485.2052.

4.2.2. Preparation of (2*R*,1′*S*,1‴*S*)-2-{1-[(2-methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-(quinolin-4-yl)}methyl-1-azabicyclo[2.2.2]octane (10). (2*R*,1′*S*)-2-[1-Hydroxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane **8** (30 mg, 0.11 mmol) was reacted with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (70 μl, 0.37 mmol) according to the general method above. The crude product was purified by chromatography on silica gel (19:1, dichloromethane/methanol) to give the product **10** (56 mg, 99%) as a colourless oil. R_f (silica gel) 0.5 (19:1, dichloromethane/methanol). $[\alpha]_D$=+35 (c=1.02, $CHCl_3$). ν_{max} (neat) 2947, 1751 cm^{-1}. ^1H NMR δ (300 MHz, C_6D_6) 8.74 (1H, d, J=4.5 Hz, H-2″), 8.38–8.22 (2H, m, Ar–H), 7.47–7.37 (2H, m, Ar–H), 7.34–7.21 (2H, m, Ar–H), 7.18–7.11 (1H, m, Ar–H), 7.03–6.73 (4H, m, Ar–H, H-1′), 3.34 (3H, s, OCH_3), 3.22–3.09 (1H, m, H-2), 3.02–2.86 (1H, m, H-6a), 2.47–2.13 (3H, m, H-6b, H_2-7), 1.49–1.27 (3H, m), 1.26–1.12 (1H, m), 1.08–0.83 (3H, m). m/z (NH_3, Cl) 484 ($M+H^+$, 50%), 316 (60%), 252 (100%). Found $[M+H]^+$ 485.2069, $C_{27}H_{28}N_2O_3F_3$ requires 485.2052.

4.2.3. Preparation of (2*R*,1′*S*)-2-(1-cyclohexyl-1-hydroxy)-methyl-1-azabicyclo[2.2.2]octane. 5% Rhodium-on-alumina (0.50 g) was added to a solution of (2*R*,1′*S*)-2-(1-phenyl-1-hydroxy)methyl-1-azabicyclo[2.2.2]octane (0.50 g, 2.30 mmol) in methanol (30 ml), the mixture was then placed under a hydrogen atmosphere at 45 psi and left to stir at room temperature for one week. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (gradient elution: 4:1, ethyl acetate/methanol to methanol) to give the product (138 mg, 27%) as a white solid. $[\alpha]_D$=+69 (c=0.52, $CDCl_3$). Mp 124–125°C. ν_{max} (neat) 3378, 2924 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 3.48–3.42 (1H, m, H-1′), 3.05–2.58 (5H, m, H-2, H_2-6, H_2-7), 2.45–2.15 (1H, brs, OH), 1.88–0.96 (18H, m). ^{13}C NMR δ (75 MHz $CDCl_3$) 78.7, 56.8, 50.1, 42.8, 39.7, 30.7, 30.5, 26.7, 26.6, 26.5, 26.0, 25.8, 25.2, 21.6. m/z (NH_3, Cl) 224 ($M+H^+$, 100%). Found $[M+H]^+$ 224.2012, $C_{14}H_{25}NO$ requires 224.2014.

4.2.4. Preparation of (2*R*,1′*S*)-2-(1-cyclohexyl-1-hydroxy)-methyl-1-phenylmethyl-azoniabicyclo[2.2.2]octane bromide (5a). A solution of (2*R*,1′*S*)-2-(1-cyclohexyl-1-hydroxy)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.22 mmol) and benzyl bromide (30 μl, 0.22 mmol) in toluene (2 ml) under argon was heated at reflux for 2 h. The mixture was then cooled to room temperature, the resulting precipitate was collected by filtration and washed with diethyl ether (2×3 ml) to give the product **5a** (62 mg, 71%) as a white solid. $[\alpha]_D$=+49 (c=1.0, $CHCl_3$). Mp 245–246°C. ν_{max} (neat) 3271, 2927 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.71–7.65 (2H, m, Ar–H), 7.34–7.28 (3H, m, Ar–H), 5.35–5.20 (2H, m, H-1a″, OH), 5.06 (1H, d, J=12.5 Hz, H-1b″), 4.55–4.35 (2H, m, H-1′, H-6a), 3.72–3.55 (2H, m, H_2-7), 3.39–3.20 (2H, m, H-2, H-6b), 2.30–0.70 (18H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 133.7 (2C), 130.0, 128.9 (2C), 127.6, 70.1, 66.5, 62.4, 56.8, 52.2, 41.0, 29.4, 29.3, 26.0, 25.9, 25.8, 25.5, 24.1, 23.8, 20.6. m/z (FAB) 314 (M^+−Br, 100%). Found $[M-Br]^+$ 314.2473, $C_{21}H_{32}NO$ requires 314.2484.

4.2.5. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-2-methoxy)-ethyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide (5b). A solution of (2*R*,1′*S*)-2-(1-hydroxy-2-methoxy)-ethyl-1-azabicyclo[2.2.2]octane (100 mg, 0.54 mmol) and benzyl bromide (60 μl, 0.54 mmol) in toluene (2 ml) under argon was heated at reflux for 45 min. The mixture was then cooled to room temperature and concentrated under reduced pressure to give the product **5b** (193 mg, 100%) as a brown soild. $[\alpha]_D$=+38 (c=0.64, $CHCl_3$). Mp 174–175°C. ν_{max} (neat) 3387, 2947 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.68–7.57 (2H, m, Ar–H), 7.45–7.29 (3H, m, Ar–H), 5.36 (1H, d, J=6.0 Hz, OH), 5.18 (1H, d, J=12.5 Hz, H-1″), 5.14–5.03 (1H, m, H-1′), 4.85 (1H, d, J=12.5 Hz, H-1″), 4.55–4.40 (1H, m, H-6a), 3.90–3.78 (1H, m, H-7a), 3.56–3.22 (5H, m, H-2, H-6b, H-7b, H_2-2′), 3.26 (3H, s, OCH_3), 2.41–2.25 (1H, m, H-8a), 2.22–2.13 (1H, m, H-4), 2.12–1.98 (1H, m, H-5a), 1.97–1.77 (3H, m, H_2-3, H-8b), 1.68–1.47 (1H, m, H-5b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 133.5, 130.2, 129.0 (2C), 127.2, 72.7, 66.0, 64.1, 63.3, 59.1, 56.8, 52.2, 24.6, 24.1, 23.9, 20.4. m/z (FAB) 276(M^+−Br, 100%). Found $[M-Br]^+$ 276.1981, $C_{29}H_{30}NO$ requires 276.1963.

4.2.6. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide (5c). A mixture of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (100 mg, 0.46 mmol) and benzyl bromide (50 μl, 0.46 mmol) in toluene (5 ml) was heated at 90°C for 2 h. The mixture was then cooled to room temperature and the resulting precipitate was filtered to give the product **5c** (140 mg, 78%) as a white solid. $[\alpha]_D$=+72 (c=2.0, ethanol). Mp 250–251°C. ν_{max} (neat) 3237, 2950 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.64–7.38 (4H, m, Ar–H), 7.24–7.14 (4H, m, Ar–H), 6.98–6.83 (2H, m, Ar–H), 6.05–5.95 (1H, m, H-1′), 5.76 (1H, brs, OH), 5.62 (1H, d, J=12.0 Hz, C*Ha*HbPh), 5.00 (1H, d, J=12.0 Hz, CHa*Hb*Ph), 4.46–4.43 (1H, m, H-6a), 4.35–4.29 (1H, m, H-2), 4.05–3.90 (1H, m, H-7a), 3.25–3.11 (1H, m, H-6b), 2.81–2.67 (1H, m, H-7b), 2.01–1.81 (3H, m, H-3a, H-8a, H-4), 1.81–1.70 (1H, m), 1.68–1.58 (1H, m), 1.49–1.46 (1H, m), 1.21–1.08 (1H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 139.2, 133.7 (2C), 129.8, 128.7 (2C), 128.0 (2C), 127.6, 127.04, 126.0 (2C), 68.6, 67.5, 61.9,

56.1, 50.6, 25.4, 24.2, 23.5, 20.8. *m/z* (NH_3, Cl) 308 (M^+-Br, 5%), 218 (100%). Found $[M-Br]^+$ 308.2010, $C_{21}H_{26}NO$ requires 308.2014.

4.2.7. Preparation of (2*R*,1′*S*)-2-[1-hydroxy-1-(naphth-1-yl)]methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide (5d). A solution of (2*R*,1′*S*)-2-[1-hydroxy-1-(naphth-1-yl)]methyl-1-azabicyclo[2.2.2]octane (0.15 g, 0.62 mmol) and benzyl bromide (70 μl, 0.62 mmol) in toluene (2 ml) under argon was heated at reflux for 1.5 h. The mixture was then cooled to room temperature, the resulting precipitate was collected by filtration and washed with diethyl ether (2×3 ml) to give the product **5d** (0.24 g, 89%) as a white solid. $[\alpha]_D=+100$ (*c*=1.2, $CHCl_3$). Mp 255–256°C. ν_{max} (neat) 3220, 2949 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.02 (1H, d, *J*=8.5 Hz, Ar–H), 7.86 (1H, d, *J*=7.0 Hz, Ar–H), 7.70 (2H, d, *J*=6.5 Hz, Ar–H), 7.54 (1H, d, *J*=8.0 Hz, Ar–H), 7.45 (1H, d, *J*=7.0 Hz, Ar–H), 7.40–7.31 (1H, m, Ar–H), 7.30–7.12 (4H, m, Ar–H), 7.06–6.95 (1H, m, Ar–H), 6.60–6.50 (1H, m, H-1′), 6.15 (1H, d, *J*=6.0 Hz, OH), 5.59 (1H, d, *J*=12.0 Hz, H-1a″), 5.48 (1H, d, *J*=12.0 Hz, H-1b″), 4.73–4.57 (1H, m, H-6a), 4.04–3.78 (2H, m, H-2, H-7a), 3.22–3.06 (1H, m, H-6b), 3.02–2.83 (1H, m, H-7b), 2.16–1.86 (3H, m, H-3a, H-8a, H-4), 1.72–1.40 (3H, m, H_2-5, H-8b), 1.01–0.82 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 134.1, 132.9, 129.9, 128.7, 128.2, 128.1, 127.3, 127.0, 125.3, 125.1, 124.8, 122.8, 68.0, 65.2, 62.2, 56.7, 50.5, 26.1, 24.1, 23.3, 20.7. *m/z* (FAB) 358(M^+-Br, 100%). Found $[M-Br]^+$ 358.2152, $C_{25}H_{28}NO$ requires 358.2171.

4.2.8. Preparation of (2*R*,1′*S*)-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide (5e). A solution of (2*R*,1′*S*)-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane **8** (50 mg, 0.19 mmol) and benzyl bromide (20 μl, 0.19 mmol) in toluene (4 ml) under argon was heated at reflux for 1.5 h. The mixture was then cooled to room temperature, the resulting precipitate was collected by filtration and washed with diethyl ether (2×3 ml) to give the product **5e** (63 mg, 76%) as a white solid. $[\alpha]_D=+92$ (*c*=1.0, $CHCl_3$). Mp 240–241°C. ν_{max} (neat) 3196 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.80 (1H, d, *J*=4.5 Hz, Ar–H), 8.23 (1H, dd, *J*=3.0, 6.5 Hz, Ar–H), 7.84 (1H, d, *J*=4.5 Hz, Ar–H), 7.66–7.32 (3H, m, Ar–H), 7.20–7.02 (5H, m, Ar–H), 6.55 (1H, d, *J*=6.0 Hz, OH), 6.52–6.45 (1H, m, H-1′), 5.93 (1H, d, *J*=12.0 Hz, H-1a″), 5.39 (1H, d, *J*=12.0 Hz, H-1b″), 4.59–4.45 (1H, m, H-6a), 4.15–4.05 (1H, m, H-2), 4.05–3.90 (1H, m, H-7a), 3.2–3.08 (1H, m, H-6b), 2.87–2.71 (1H, m, H-7b), 2.0–1.82 (4H, m), 1.71–1.39 (3H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 149.4, 147.0, 144.5, 133.9 (2C), 129.8, 129.5, 128.6 (2C), 128.3, 127.2, 126.9, 123.5, 123.2, 119.8, 66.8, 65.3, 61.7, 56.6, 50.3, 26.3, 24.1, 23.1, 20.7. *m/z* (FAB) 359 (M^+-Br, 100%). Found $[M-Br]^+$ 359.2121, $C_{24}H_{27}N_2O$ requires 359.2132.

4.2.9. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-methyl-1-azoniabicyclo[2.2.2]octane iodide (5f). A solution of (2*R*,1′*S*)-2-[1-hydroxy-1-(quinolin-4-yl)]-methyl-1-azabicyclo[2.2.2]octane (100 mg, 0.46 mmol) and methyl iodide (30 μl, 0.46 mmol) in toluene (2 ml) under argon was stirred at room temperature for 3 h. The resulting precipitate was collected by filtration and washed with ethyl acetate (2×2 ml) to give the product **5f** (130 mg, 79%) as a white solid. $[\alpha]_D=+53$ (*c*=1.52, DMSO). Mp 222–224°C. ν_{max} (neat) 3295, 2947 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.61–7.55 (2H, m, Ar–H), 7.35–7.20 (3H, m, Ar–H), 5.75 (1H, m, H-1′), 4.60–4.45 (2H, m, H-2, H-6a), 4.05–3.90 (1H, m, H-7a), 3.56 (3H, s, NCH_3), 3.55–3.40 (1H, m, H-6b), 3.35–3.22 (1H, m, H-7b), 2.15–1.80 (5H, m, H-3a, H-4, H_2-5, H-8a), 1.35–1.20 (2H, m, H-3b, H-8b). *m/z* (FAB) 232 (M^+-I, 100%). Found $[M-I]^+$ 232.1690, $C_{15}H_{22}NO$ requires 232.1701.

4.2.10. Preparation of (2*R*,1′*S*)-1-*n*-butyl-2-(1-hydroxy-1-phenyl)methyl-1-azoniabicyclo[2.2.2]octane iodide (5g). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and 1-iodobutane (30 μl, 0.23 mmol) in toluene (2 ml) under argon was heated at reflux for 3 h. The mixture was then cooled to room temperature, the resulting precipitate was collected by filtration and washed with diethyl ether (2×3 ml) to give the product **5g** (25 mg, 27%) as a white solid. $[\alpha]_D=+20$ (*c*=1.6, $CHCl_3$). Mp 190–192°C. ν_{max} (neat) 3286 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.55–7.4 (2H, m, Ar–H), 7.4–7.18 (3H, m, Ar–H), 5.69 (1H, m, H-1′), 4.72 (1H, d, *J*=6.0 Hz, OH), 4.51–4.32 (1H, m, H-1a″), 4.32–4.17 (1H, m, H-6a), 3.79–3.55 (3H, m, H-2, H-7a, H-6b), 3.55–3.40 (2H, m, H-1b″, H-7b), 2.2–1.68 (8H, m), 1.68–1.43 (2H, m), 1.43–1.2 (1H, m), 1.01 (3H, t, *J*=7.0 Hz, CH_3). ^{13}C NMR δ (75 MHz, $CDCl_3$) 139.0, 128.6 (2C), 127.9, 126.0 (2C), 67.6, 67.0, 60.5, 56.8, 54.2, 24.9, 24.4, 24.29, 23.7, 20.3, 20.0, 14.2. *m/z* (NH_3, Cl) 274 (M^+-I, 100%). Found $[M-I]^+$ 274.2173, $C_{18}H_{28}NO$ requires 274.2171.

4.2.11. Preparation of (2*R*,1′*S*)-1-(1-cyclohexyl)methyl-2-(1-hydroxy-1-phenyl)methyl-1-azoniabicyclo[2.2.2]-octane bromide (5h). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (100 mg, 0.46 mmol) and cyclohexylmethyl bromide (60 μl, 0.46 mmol) in *m*-xylene (4 ml) under argon was heated at reflux for 18 h. The mixture was then cooled to room temperature, the resulting precipitate was filtered and washed with diethyl ether (2×5 ml) to give the product **5h** (55 mg, 30%) as a white solid. $[\alpha]_D=+44$ (*c*=1.28, DMSO). Mp 160–162°C. ν_{max} (neat) 3467, 2926 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.48–7.20 (5H, m, Ar–H), 5.77–5.62 (2H, m, H-1′, OH), 4.52–4.37 (1H, m, H-6a), 4.18–4.06 (1H, dd, *J*=3.0, 14.0 Hz, H-1a″), 3.85–3.75 (1H, m, H-2), 3.70–3.40 (4H, m, H-6b, H_2-7, H-1b″), 2.19–1.57 (12H, m), 1.40–1.02 (6H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 140.0, 128.4 (2C), 127.5, 126.1 (2C), 68.4, 66.8, 66.6, 57.0, 53.9, 34.2, 33.1, 32.8, 26.3, 26.1, 25.4, 24.6, 24.4, 23.8, 20.3. *m/z* (NH_3, Cl) 314 (M^+-Br, 100%). Found $[M-Br]^+$ 314.2469, $C_{21}H_{32}NO$ requires 314.2484.

4.2.12. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-(4-nitrophenyl)methyl-1-azoniabicyclo[2.2.2]-octane bromide (5i). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and *p*-nitrobenzylbromide (50 mg, 0.23 mmol) in toluene (4 ml) under argon was heated at reflux for 1.5 h. The solution was then cooled to room temperature. The resulting precipitate was collected by filtration and washed with toluene (2×3 ml) to give the product **5i** (69 mg, 69%)

as a white solid. $[\alpha]_D$=+46 (c=1.48, DMSO). Mp 258–260°C. ν_{max} (neat) 3292, 2928 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.87 (2H, d, J=8.0 Hz, Ar–H), 7.80 (2H, d, J=8.0 Hz, Ar–H), 7.38–7.36 (2H, m, Ar–H), 6.99–6.97 (3H, m, Ar–H), 6.25 (1H, d, J=12.0 Hz, H-1a″), 5.82–5.78 (1H, m, H-1′), 5.62 (1H, d, J=12.0 Hz, H-1b″), 5.42 (1H, d, J=6.0 Hz, OH), 4.62–4.50 (1H, m, H-6a), 4.23–4.18 (1H, m, H-2), 4.01–3.90 (1H, m, H-7a), 3.05–2.95 (1H, m, H-6b), 2.80–2.70 (1H, m, H-7b), 2.05–1.40 (5H, m), 1.30–1.10 (2H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 138.3, 134.9 (2C), 129.0, 128.1 (2C), 127.2, 125.6 (2C), 125.3, 123.6 (2C), 69.7, 67.1, 60.4, 56.7, 50.9, 25.4, 24.1, 23.5, 20.5. m/z (FAB) 353(M^+−Br, 100%). Found $[M-Br]^+$ 353.1878, $C_{21}H_{25}N_2O_3$ requires 353.1865.

4.2.13. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-[4-methoxyphenyl)methyl-1-azoniabicyclo-[2.2.2] octane chloride (5j). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and *p*-methoxybenzyl chloride (30 μl, 0.23 mmol) in toluene (4 ml) under argon was heated at reflux for 3 h. The mixture was then cooled to room temperature, the resulting precipitate was collected by filtration and washed with toluene (3 ml) and ethyl acetate (3 ml) to give the product **5j** (59 mg, 69%) as a white soild. $[\alpha]_D$=+52 (c=1.0, $CHCl_3$). Mp 249–250°C. ν_{max} (neat) 3197, 2952 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.46 (2H, d, J=7.0 Hz, Ar–H), 7.37 (2H, d, J=8.0 Hz, Ar–H), 7.05–6.85 (3H, m, Ar–H), 6.64 (2H, d, J=7.0 Hz, Ar–H), 6.54 (1H, d, J=6.0 Hz, OH), 5.94 (1H, m, H-1′), 5.64 (1H, d, J=12.0 Hz, H-1a″), 5.11 (1H, d, J=12.0 Hz, H-1b″), 4.55–4.37 (1H, m, H-6a), 4.18–4.05 (1H, m, H-2), 3.90–3.65 (1H, m, H-7a), 3.71 (3H, s, OCH_3), 3.18–3.02 (1H, m, H-6b), 2.80–2.65 (1H, m, H-7b), 2.05–1.08 (3H, m, H-3a, H-8a, H-4), 1.80–1.66 (1H, m), 1.66–1.50 (1H, m), 1.50–1.40 (1H, m, H-8b), 1.20–1.15 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 160.4, 139.5, 135.0 (2C), 127.9 (2C), 126.8, 125.9 (2C), 119.6, 113.9 (2C), 68.8, 67.5, 61.7, 55.9, 55.0, 50.0, 25.3, 24.2, 23.6, 20.9. m/z (FAB) 338 (M^+−Cl, 65%), 218 (100%), 138 (40%), 121 (45%). Found $[M-Cl]^+$ 338.2123, $C_{22}H_{28}NO_2$ requires 338.2120.

4.2.14. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-(naphth-1-yl)methyl-1-azoniabicyclo[2.2.2]-octane chloride (5k). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and 1-naphthylmethyl chloride (35 μl, 0.23 mmol) in toluene (4 ml) under argon was heated at reflux for 24 h. The mixture was then cooled to room temperature and the resulting precipitate was collected by filtration to give the product **5k** (52 mg, 60%) as a rust coloured solid. $[\alpha]_D$=+80 (c=1.0, $CHCl_3$). ν_{max} (neat) 3184, 2950 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 8.36 (1H, d, J=9.0 Hz, Ar–H), 7.59–7.24 (8H, m, Ar–H), 6.92–6.78 (3H, m, Ar–H), 6.31–6.22 (1H, m, H-1′), 6.22–6.07 (2H, m, OH, H-1a″), 5.69 (1H, d, J=12.5 Hz, H-1b″), 4.62–4.42 (2H, m, H-2, H-6a), 4.09–3.90 (1H, m, H-7a), 2.85–2.72 (1H, m, H-6b), 2.56–2.41 (1H, m, H-7b), 1.97–1.64 (4H, m), 1.58–1.37 (1H, m), 1.37–1.02 (2H, m). m/z (FAB) 358 (M^+−Br, 100%). Found $[M-Br]^+$ 358.2177, $C_{25}H_{28}NO$ requires 358.2171.

4.2.15. Preparation of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)-methyl-1-(naphth-2-yl)methyl-1-azoniabicyclo[2.2.2]-octane bromide (5l). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and 2-naphthylmethyl bromide (51 mg, 0.23 mmol) in toluene (4 ml) under argon was heated at reflux for 4 h. The mixture was then cooled to room temperature and the resulting precipitate was collected by filtration to give the product **5l** (96 mg, 95%) as a white solid. $[\alpha]_D$=+48 (c=1.0, $CHCl_3$). Mp 254–255°C. ν_{max} (neat) 3233, 2951 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.80 (1H, s, Ar–H), 7.68–7.08 (9H, m, Ar–H), 6.95–6.80 (2H, m, Ar–H), 6.11 (1H, m, H-1′), 6.02 (1H, d, J=12.0 Hz, H-1a″), 5.83 (1H, d, J=5.5 Hz, OH), 5.33 (1H, d, J=12.0 Hz, H-1b″), 4.64–4.45 (1H, m, H-6a), 4.45–4.31 (1H, m, H-2), 4.15–4.00 (1H, m, H-7a), 3.23–3.09 (1H, m, H-6b), 2.75–2.60 (1H, m, H-7a), 2.05–1.52 (6H, m), 1.25–1.10 (1H, m). ^{13}C NMR δ (75 MHz, $CDCl_3$) 139.0, 133.6, 132.9, 132.2, 129.6, 128.0, 127.9, 127.3, 126.9, 126.2, 125.8, 125.6, 124.7, 68.4, 67.6, 61.7, 56.0, 50.3, 25.5, 24.2, 23.5, 20.8. m/z (FAB) 358 (M^+−Br, 100%). Found $[M-Br]^+$ 358.2188, $C_{25}H_{28}NO$ requires 358.2171.

4.2.16. Preparation of (2*R*,1′*S*)-1-(anthracen-9-yl)-methyl-2-(1-hydroxy-1-phenyl)methyl-1-azoniabicyclo-[2.2.2]octane chloride (5m). A solution of (2*R*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (50 mg, 0.23 mmol) and 9-chloromethylanthracene (52 mg, 0.23 mmol) in toluene (2 ml) under argon was heated at reflux for 24 h. The mixture was then cooled to room temperature and petroleum ether was (2 ml) added. The resulting precipitate was collected by filtration, then recrystallised from chloroform/petroleum ether to give the product **5m** (52 mg, 51%) as a yellow solid. R_f (silica gel) 0.3 (93:7, dichloromethane/methanol). $[\alpha]_D$=+107 (c=0.82, $CHCl_3$). Mp 189–190°C. ν_{max} (neat) 3173 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 9.05–8.90 (1H, m, Ar–H), 8.48–8.29 (1H, m, Ar–H), 7.88 (1H, s, Ar–H), 7.73–7.69 (3H, m, Ar–H), 7.60–7.45 (2H, m, Ar–H), 7.32–7.08 (5H, m, Ar–H, OH), 6.90–6.75 (2H, m, Ar–H), 6.72–6.59 (2H, m, H-1′, H-1a″), 6.17 (1H, d, J=13.0 Hz, H-1b″), 4.90–4.81 (1H, m, H-2), 4.62–4.49 (1H, m, H-6a), 4.15–3.98 (1H, m, H-7a), 2.49–2.38 (1H, m, H-6b), 2.21–2.04 (1H, m, H-7b), 1.92–1.55 (4H, m, H-3a, H-5a, H_2-8), 1.32–1.20 (1H, m, H-4), 1.20–1.07 (1H, m, H-3b), 1.07–0.90 (1H, m, H-5b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 139.0, 132.9, 130.5, 128.5, 128.0, 127.5, 127.4, 127.2, 126.4, 126.1, 125.3, 124.7, 124.5, 118.6, 68.7, 68.6, 56.5, 53.7, 50.5, 26.2, 24.7, 23.8, 20.1. m/z (FAB) 408 (M^+−Cl, 25%), 191 (100%). Found $[M-Cl]^+$ 408.2313, $C_{29}H_{30}NO$ requires 408.2327.

4.2.17. Preparation of (2*S*,1′*S*)-2-(1-hydroxy1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo-[2.2.2] octane bromide (5n). A solution of (2*S*,1′*S*)-2-(1-hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane (43 mg, 0.20 mmol) and benzylbromide (23 μl, 0.20 mmol) in toluene (4 ml) under argon was heated at reflux for 2 h. The mixture was then cooled to room temperature and the resulting precipitate was collected by filtration to give the product **5n** (58 mg, 75%) as a white solid. $[\alpha]_D$=+47 (c=0.68, ethanol). Mp 248–250°C. ν_{max} (neat) 3245, 2928 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.70–7.67 (2H, m, Ar–H), 7.49–7.13 (8H, m, Ar–H), 6.05 (1H, brs, OH), 5.52 (1H,

d, J=9.5 Hz, H-1′), 5.39 (1H, d, J=13.0 Hz, H-1a″), 5.06 (1H, d, J=13.0 Hz, H-1b″), 4.47–4.29 (2H, m, H-2, H-6a), 3.65–3.41 (3H, m, H-6b, H_2-7), 2.06–1.62 (5H, m, H-4, H_2-5, H_2-8), 1.52–1.05 (2H, m, H_2-3). ^{13}C NMR δ (75 MHz, $CDCl_3$) 140.6, 133.9 (2C), 130.0, 128.9, 128.3, 128.0, 74.1, 67.4, 66.5, 56.4, 50.2, 30.1, 24.3, 23.7, 20.7. m/z (NH_3, Cl) 308 (M^+−Br, 100%). Found $[M-Br]^+$ 308.2017, $C_{21}H_{26}NO$ requires 308.2014.

4.3. General method for the *O*-alkylation of quaternary ammonium salts

A solution of quaternary ammonium halide (1.0 mmol) in dicholoromethane (8 ml) was treated sequentially with the appropriate alkyl halide (3.0 mmol) and 50% aqueous sodium hydroxide solution (0.18 ml, 2.3 mmol), and the resulting mixture was stirred at room temperature for 4 h. The aqueous layer was extracted with dichloromethane (2×8 ml) and the combined organic layers were washed with water (2×3 ml), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was then stirred as a suspension in diethyl ether (15 ml) for 3 h, then filtered and washed with diethyl ether (2×20 ml) to give the product.

4.3.1. Preparation of (2*R*,1′*S*)-2-(1-methoxy-1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane iodide (5o). (2*R*,1′*S*)-2-(1-Hydroxy-1-phenyl)methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide **5c** (100 mg, 0.28 mmol) was reacted with methyl iodide (0.05 ml, 0.78 mmol) according to the general procedure above to give the product **5o** (81 mg, 92%) as a white solid. $[\alpha]_D$=+55 (c=0.36, $CHCl_3$). ν_{max} (neat) 3435, 2948 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.81–7.60 (4H, m, Ar–H), 7.50–7.20 (6H, m, Ar–H), 6.10 (1H, d, J=12.0 Hz, H-1a″), 5.34 (1H, d, J=3.0 Hz, H-1′), 4.85–4.70 (2H, m, H-6a, H-2), 4.20 (1H, d, J=12.0 Hz, H-1b″), 4.15–4.05 (1H, m, H-7a), 3.45–3.30 (1H, m, H-6b), 3.41 (3H, s, OCH_3), 2.80–2.65 (1H, m, H-7b), 2.15–1.95 (2H, m), 1.95–1.75 (2H, m), 1.75–1.55 (2H, m), 1.38–1.25 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 134.0, 133.6 (2C), 130.4, 129.1 (2C), 128.7 (2C), 128.4, 127.3 (2C), 127.1, 79.1, 67.2, 61.6, 56.7, 55.4, 51.2, 25.5, 24.1, 22.9, 20.7. m/z (FAB) 322 (M^+−I, 100%). Found $[M-I]^+$ 322.2177, $C_{22}H_{29}NO_2$ requires 322.2171.

4.3.2. Preparation of (2*R*,1′*S*)-2-(1-phenyl-1-*n*-butoxy)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane iodide (5p). (2*R*,1′*S*)-2-(1-Hydroxy-1-phenyl)methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide **5c** (50 mg, 0.13 mmol) was reacted with 1-iodobutane (0.02 ml, 0.13 mmol) according to the general procedure above to give the product **5o** (38 mg, 76%) as a solid. $[\alpha]_D$=+96 (c=1.7, $CHCl_3$). ν_{max} (neat) 3267 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCl_3$) 8.0–6.90 (10H, m, Ar–H), 6.21–5.71 (2H, m), 5.62–5.35 (1H, m), 5.20–5.05 (1H, m), 4.92–4.65 (2H, m), 4.59–3.92 (4H, m), 3.71–3.55 (1H, m), 3.49–3.03 (2H, m), 2.95–2.52 (2H, m), 2.24–1.10 (6H, m), 0.98 (3H, t, 7.0 Hz, H-4‴). m/z (FAB) 364 (M^+−I, 100%). Found $[M-I]^+$ 364.2460, $C_{25}H_{35}NO_2$ requires 364.2640.

4.3.3. Preparation of (2*R*,1′*S*)-2-(1-benzyloxyl-1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide (5q). (2*R*,1′*S*)-2-(1-Hydroxy-1-phenyl)methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide **5c** (100 mg, 0.26 mmol) was reacted with benzyl bromide (0.09 ml, 0.76 mmol) according to the general procedure above to give the product **5q** (90 mg, 83%) as a white solid. $[\alpha]_D$=+80 (c=2.2, ethanol). Mp 116–117°C. ν_{max} (neat) 3402, 2951 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.82–7.76 (2H, m, Ar–H), 7.49–7.31 (8H, m, Ar–H), 5.99 (1H, d, J=12.0 Hz, H-1a″), 5.59 (1H, d, J=2.5 Hz, H-1′), 4.95–4.78 (3H, m, H-1a‴′, H-2, H-6a), 4.32 (1H, d, J=11.5 Hz, H-1b‴′), 4.12–4.02 (1H, m, H-7a), 3.73 (1H, d, J=12.0 Hz, H-1b″), 3.28–3.15 (1H, m, H-7b), 2.73–2.58 (1H, m, H-6b), 2.20–2.03 (2H, m, H-3a, H-5a), 1.97–1.87 (2H, m, H_2-8), 1.71–1.55 (2H, m, H-4, H-5b), 1.48–1.36 (1H. m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 136.4, 134.6, 133.6 (2C), 130.1, 129.0, 128.8, 128.8, 128.5, 127.4, 76.3, 70.9, 67.3, 61.3, 55.4, 50.5, 25.4, 24.2, 23.0, 20.8. m/z (FAB) 398 (M^+−Br, 100%). Found $[M-Br]^+$ 398.2481, $C_{28}H_{32}NO$ requires 398.2484.

4.3.4. Preparation of (2*R*,1′*S*)-2-(1-phenyl-1-methoxy-methoxy)methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]-octane chloride (5r). (2*R*,1′*S*)-2-(1-Hydroxy-1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide **5c** (50 mg, 0.13 mmol) was reacted with chloromethylmethyl-ether (0.01 ml, 0.13 mmol) according to the general procedure above to give the product **5r** (39 mg, 82%) as a solid. $[\alpha]_D$=+100 (c=1.0, $CHCl_3$). ν_{max} (neat) 3402, 2953 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.78–7.62 (4H, m, Ar–H), 7.48–7.21 (6H, m, Ar–H), 6.21 (1H, d, J=12.0 Hz, H-1a″), 5.87 (1H, m, H-1′), 5.02–4.85 (2H, m, H-2, H-6a), 4.81 (1H, d, J=6.0 Hz, H-1a‴′), 4.66 (1H, d, J=12.0 Hz, H-1b″), 4.56 (1H, d, J=6.0 Hz, H-1b‴′), 4.26–4.10 (1H, m, H-7a), 3.44 (3H, s, OCH_3), 3.43–3.36 (1H, m, H-7b), 2.84–2.69 (1H, m H-6b), 2.16–1.85 (4H, m, H-3a, H-5a, H_2-8), 1.75–1.57 (2H, m, H-4, H-5b), 1.48–1.35 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 134.8, 133.9 (2C), 130.2, 129.1 (2C), 128.9 (2C), 128.5, 128.0, 127.2 (2C), 95.4, 75.2, 67.0, 61.4, 56.7, 55.6, 50.4, 25.5, 24.4, 23.2, 20.9. m/z (FAB) 352 (M^+−Cl, 100%). Found $[M-Cl]^+$ 352.2264, $C_{23}H_{30}NO_2$ requires 352.2276.

4.3.5. Preparation of (2*R*,1′*S*)-2-(1-phenyl-1-benzyloxy-methyloxy)methyl-1-phenylmethyl-1-azabicyclo[2.2.2]-octane chloride (5s). (2*R*,1′*S*)-2-(1-Hydroxy-1-phenyl)-methyl-1-phenylmethyl-1-azoniabicyclo[2.2.2]octane bromide **5c** (50 mg, 0.13 mmol) was reacted with chloromethyl-benzylether (0.02 ml, 0.13 mmol) according to the above general procedure to give the product **5s** (54 mg, 94%) as a solid. $[\alpha]_D$=+103 (c=2.17, $CHCl_3$). ν_{max} (neat) 3392, 2952 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.80–7.72 (2H, m, Ar–H), 7.58–7.18 (9H, m, Ar–H), 6.14 (1H, d, J=12.0 Hz, H-1a″), 5.91 (1H, m, H-1′), 5.02 (1H, d, J=6.0 Hz, H-1a‴′), 4.98–4.85 (2H, m, H-2, H-6a), 4.72–4.57 (4H, m, H-1b″, H-3a‴′, H-3b‴′, H-1b‴′), 4.21–4.05 (1H, m, H-7a), 3.35–3.22 (1H, m, H-7b), 2.83–2.69 (1H, m, H-6b), 2.15–1.87 (4H, m, H-3a, H-5a, H_2-8), 1.78–1.55 (2H, m, H-4, H-5b), 1.53–1.39 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 136.6, 134.9, 133.7 (2C), 129.9, 128.8, 128.6, 128.4, 128.0, 127.6, 127.4, 127.1, 93.7, 75.4, 71.0, 67.1, 61.5, 55.5, 50.3, 25.3, 24.2, 23.1, 20.7. m/z (FAB) 428 (M^+−Cl, 100%). Found $[M-Cl]^+$ 428.2578, $C_{29}H_{34}NO_2$ requires 428.2589.

4.3.6. Preparation of (2*R*,1′*S*)-1-(anthracen-9-yl)methyl-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azoniabicyclo-[2.2.2]octane chloride (5t). A solution of (2*R*,1′*S*)-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azabicyclo[2.2.2]octane **8** (50 mg, 0.19 mmol) and 9-chloromethylanthracene (43 mg, 0.19 mmol) in toluene (2 ml) under argon was heated at reflux for 24 h. The mixture was then cooled to room temperature and the resulting precipitate was collected by filtration. The solid was then recrystallised from chloroform/petroleum ether to give the product **5t** (57 mg, 61%) as a yellow solid. R_f (silica gel) 0.3 (93:7, dichloromethane/methanol). $[\alpha]_D$=+288 (c=1.46, $CHCl_3$). Mp 194–195°C. ν_{max} (neat) 3164 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 9.14 (1H, d, J=9.0 Hz, Ar–H), 8.90 (1H, d, J=8.5 Hz, Ar–H), 8.84 (1H, d, J=4.5 Hz, Ar–H), 8.52 (1H, d, J=9.0 Hz, Ar–H), 8.13 (1H, d, J=5.0 Hz, Ar–H), 8.03 (1H, d, J=4.5 Hz, Ar–H), 7.89 (1H, s, Ar–H), 7.61–7.48 (3H, m, Ar–H), 7.30–7.05 (5H, m, Ar–H), 7.04–6.95 (2H, m, H-1′, OH), 6.81 (1H, d, J=13.5 Hz, H-1a″), 6.51 (1H, d, J=13.5 Hz, H-1b″), 4.75–4.65 (1H, m, H-2), 4.65–4.50 (1H, m, H-6a), 4.21–4.08 (1H, m, H-7a), 2.45–2.25 (2H, m, H-6b, H-7b), 1.88–1.55 (5H, m, H-3a, H-4, H-5a, H_2-8), 1.35–1.21 (1H, m, H-3b), 1.05–0.90 (1H, m, H-5b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 150.1, 149.5, 145.5, 133.2, 132.5, 131.0, 130.1, 129.3, 129.0, 128.4, 128.2, 127.7, 127.3, 126.8, 126.3, 125.3, 124.8, 124.7, 124.1, 122.8, 120.1, 118.4, 118.2, 67.4, 66.9, 60.2, 54.6, 50.9, 26.9, 24.6, 23.6, 19.9. m/z (FAB) 459 (M^+-Cl, 50%), 269 (40%), 191 (100%). Found $[M-Cl]^+$ 459.2447, $C_{32}H_{31}N_2O$ requires 459.2436.

4.3.7. Preparation of (2*R*,5*R*,1′*S*)-1-(anthracen-9-yl)-methyl-5-ethylene-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azoniabicyclo[2.2.2]octane chloride (15). A solution of cinchonine **6** (500 mg, 1.70 mmol) was heated at reflux in toluene (20 ml) under argon with 9-chloromethylanthracene (390 mg, 1.70 mmol) for 24 h. The solution was then cooled to room temperature and the resulting precipitate was filtered. The residue was recrystallised from chloroform/petroleum ether to give the product **15** (521 mg, 58%) as a yellow solid. R_f (silica gel) 0.3 (93:7, dichloromethane/methanol). $[\alpha]_D$=+240 (c=1.0, $CHCl_3$). Mp 166–167°C. ν_{max} (neat) 3050 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 9.25 (1H, d, J=9.0 Hz, Ar–H), 8.96 (1H, d, J=8.5 Hz, Ar–H), 8.85 (1H, d, J=4.0 Hz, Ar–H), 8.39 (1H, d, J=9.0 Hz, Ar–H), 8.27 (1H, d, J=4.5 Hz, Ar–H), 8.07 (1H, d, J=4.5 Hz, Ar–H), 7.85 (1H, s, Ar–H), 7.61 (1H, d, J=8.5 Hz, H-3v), 7.54 (1H, d, J=8.0 Hz, Ar–H), 7.44 (1H, d, 8.5 Hz, Ar–H), 7.30–6.91 (7H, m, Ar–H, H-1′, H-1a″), 6.46 (1H, d, J=13.5 Hz, H-1b″), 5.62–5.51 (1H, m, H-1‴), 5.01 (1H, d, J=10.5 Hz, H-2a‴), 4.79 (1H, d, J=12.0 Hz, H-2b‴), 4.77–4.52 (1H, m, H-2). 4.45–4.35 (1H, m, H-7a), 4.32–4.18 (1H, m, H-6a), 2.53–2.39 (1H, m, H-7b), 2.37–2.25 (1H, m, H-6b), 1.90–1.85 (1H, m, H-3a), 1.79–1.60 (2H, m, H-5, H-8a), 1.57–1.45 (1H, m, H-4), 1.41–1.30 (1H, m, H-8b), 0.70–0.55 (1H, m, H-3b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 148.9, 146.3, 146.1, 135.4, 132.9, 132.6, 130.9, 130.2, 129.9, 128.6, 128.4, 128.1, 127.5, 127.2, 126.8, 124.8, 124.5, 124.1, 120.0, 117.9, 117.4, 67.6, 66.6, 57.5, 54.1, 53.8, 38.0, 26.2, 24.0, 22.6. m/z (FAB) 485 (M^+-Cl, 30%), 404 (100%), 398 (45%), 191 (80%). Found $[M-Cl]^+$ 485.2603 $C_{34}H_{33}N_2O$ requires 485.2593.

4.3.8. Preparation of (2*S*,5*R*,1′*R*)-1-(anthracen-9-yl)-methyl-5-ethylene-2-[1-hydroxy-1-(quinolin-4-yl)]methyl-1-azoniabicyclo[2.2.2]octane chloride (16). A solution of cinchonidine **14** (250 mg, 0.85 mmol) in toluene (10 ml) was heated at reflux under argon with 9-chloromethylanthracene (195 mg, 0.85 mmol) for 24 h. The solution was then cooled to room temperature and the resulting precipitate was filtered. The residue was recrystallised from chloroform/petroleum ether to give the product **16** (348 mg, 79%) as a yellow solid. R_f (silica gel) 0.3 (93:7, dichloromethane/methanol). $[\alpha]_D$=−340 (c=1.0, $CHCl_3$) [lit. $[\alpha]_D$=−363 (c=0.8, $CHCl_3$)].[6a] Mp 169–170°C [lit. mp 168°C (dec.)].[6a] ν_{max} (neat) 3000 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 9.05 (1H, d, J=9.0 Hz, Ar–H), 8.84–8.80 (2H, m, Ar–H), 8.67 (1H, d, J=9.0 Hz, Ar–H), 8.18 (1H, d, J=5.0 Hz, Ar–H), 8.00 (1H, d, J=4.5 Hz, Ar–H), 7.93 (1H, s, Ar–H), 7.63–7.52 (3H, m, Ar–H), 7.37–7.32 (1H, m, Ar–H), 7.23–7.13 (3H, m, Ar–H), 7.04–6.99 (2H, m, Ar–H, H-1′), 6.83 (1H, d, J=13.5 Hz, H-1a″), 6.62 (1H, d, J=13.5 Hz, H-1b″), 5.45–5.34 (1H, m, H-1‴), 5.23 (1H, d, J=17.5 Hz, H-2a‴), 4.87 (1H, d, J=10.0 Hz, H-2b‴), 4.80–4.59 (2H, m, H-2, H-7a), 4.14–4.02 (1H, m, H-6a), 2.61–2.48 (1H, m, H-6b), 2.41–2.29 (1H, m, H-7b), 2.16–2.04 (1H, m, H-5), 1.94–1.61 (3H, m, H-3a, H-4, H-8a), 1.16–0.88 (2H, m, H-3b, H-8b). ^{13}C NMR δ (75 MHz, $CDCl_3$) 148.9, 146.4, 136.3, 133.1, 132.6, 131.0, 130.3, 130.1, 128.8, 128.7, 128.6, 128.2, 127.6, 127.3, 126.9, 126.2, 125.5, 124.7, 124.7, 124.1, 120.0, 118.1, 117.7, 67.2, 66.8, 61.2, 54.7, 50.4, 38.4, 25.8, 25.6, 23.4. m/z (FAB) 485 (M^+-Cl, 20%), 193 (100%). Found $[M-Cl]^+$ 485.2598 $C_{34}H_{33}N_2O$ requires 485.2593.

4.4. General procedure for the reaction of *tert*-butyl *N*-(diphenylmethylene)glycinate (3) with benzyl bromide

A mixture of *tert*-butyl *N*-(diphenylmethylene)glycinate **3** (100 mg, 0.34 mmol) and the appropiate catalyst (0.034 mmol) in dichloromethane (3 ml) was treated sequentially with benzyl bromide (0.38 mmol) and 50% aqueous potassium hydroxide (0.76 ml, 6.68 mmol). The mixture was then stirred for 18 h at room temperature, then the two phases were separated and the toluene solution was passed through a short column of magnesium sulfate. The solvent was then removed under reduced pressure to give crude *tert*-butyl *N*-(diphenylmethylene)phenylalaninate **11** as an oil. R_f (silica gel) 0.6 (9:1, hexane/ethyl acetate). ν_{max} (neat) 2929, 1733 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.60–6.50 (15H, Ar–H, m), 4.10 (1H, dd, J=5.0, 9.0 Hz, H-2), 3.25-3.11 (2H, m, H-3), 1.42 (9H, s, $C(CH_3)_3$). m/z (NH_3, Cl) 386 ($M+H^+$, 100%), 182 (30%). Found $[M+H]^+$ 386.2113 $C_{26}H_{28}NO_2$ requires 386.2120. R_t HPLC (DNPG 'Bakerbond', 98.5:1.5, hexane/dioxane, 254nm, 0.5 ml/min) 36.8 min (*R*-isomer), 40.4 min (*S*-isomer).

4.4.1. Hydrolysis of *tert*-butyl *N*-(diphenylmethylene)-phenylalaninate (11). Hydrolysis of crude *tert*-butyl *N*-(diphenylmethylene)phenylalaninate **11** was preformed using the previously reported procedure.[2a] The residue was purified by chromatography on silica gel (ethyl acetate) to give phenylalanine *tert*-butyl ester **12** as a colourless oil. R_f (silica gel) 0.1(1:1, ethyl acetate/petroleum ether). ν_{max} (neat) 3379, 2978, 1729 cm^{-1}. ^1H NMR δ (300 MHz, $CDCl_3$) 7.45–7.18 (5H, m, Ar–H), 3.65–3.55 (1H, m, H-2), 3.05–2.99 (1H, dd, J=6.0, 14.0 Hz, H-3a), 2.86–2.79 (1H, dd, J=6.0, 14.0 Hz, H-3b), 1.61–1.55 (2H, m,

NH_2), 1.40 (9H, s, C $(CH_3)_3$). *m/z* (NH_3, Cl) 239 ($M+NH_4^+$, 75%), 222 ($M+H^+$, 100%), 93 (75%), 76 (60%). Found $[M+H]^+$ 222.1497, $C_{13}H_{20}NO_2$ requires 222.1494.

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