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Syntheses of Octahydroquinoline-*N*-oxides: Haptens Designed to Elicit Catalytic Antibodies that Control a Terpenoid-like Cascade Cyclisation[1]

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Dedicated to Professor Christian Birr on the occasion of his 60th birthday

Abstract: An efficient synthetic route to both *cis*- and *trans*-fused racemic *4a,6*-dimethyloctahydroquinoline-*N*-oxides has been developed. These species were employed as haptens to elicit catalytic antibodies capable of controlling the corresponding bicyclic hydrocarbon formation from linear quasi-triisoprenoid substrates. Temperature dependent NMR studies of *cis*-fused compounds proved the existence of two conformational states. Hapten **20b** has elicited an antibody that efficiently catalyses a tandem cationic cyclisation leading to bridge-methylated decalins. © 1997 Elsevier Science Ltd.

Introduction

Catalytic antibodies[2] have been shown to be capable of accelerating a variety of carbon-carbon bond forming reactions. The most recent advance was the finding of an antibody catalyzing the cationic cyclisation of a monoolefinic substrate to form monoterpenoid-like products regioselectively.[3] A major challenge in the field of catalytic antibodies is the generation of an antibody that controls and accelerates a consecutive multiple bond forming reaction (cascade reaction) such as a cationic polyene cyclisation.[4] Such a catalytic antibody may provide valuable information on how natural cyclisation enzymes achieve the astonishing performance in controlling such cascade reactions.[5] The first step was therefore to design and synthesise a haptenic structure utilizing the present knowledge about terpenoid cyclases for raising a catalytically active antibody combining site.[6] In this study we focused on bicyclisation of a quasi-triisoprenoid substrate (Figure 1). The assumed chair-chair transition state can be mimicked by a decalin-like molecule. Incorporation of an *N*-oxide functionality should elicit amino acid residues to initiate carbocation formation. *N*-Oxides have already been proven to be suitable candidates for this purpose.[7] Because of their strongly polarised bond, they may not

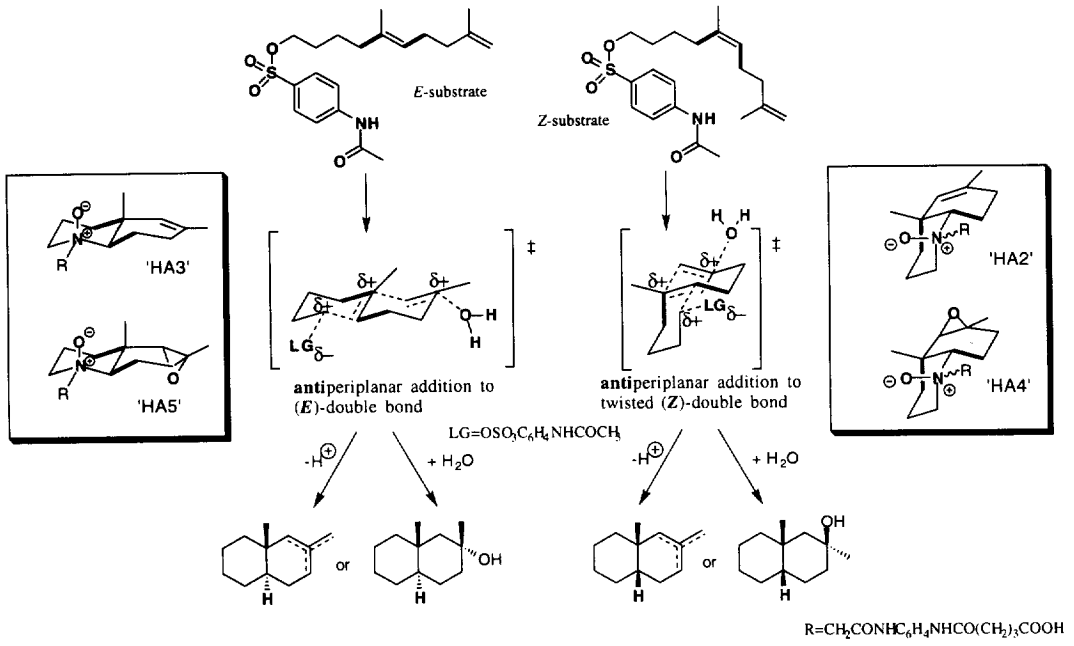


Figure 1. Assumed transition states of envisaged reaction pathway and structural resemblance to hapten designs.

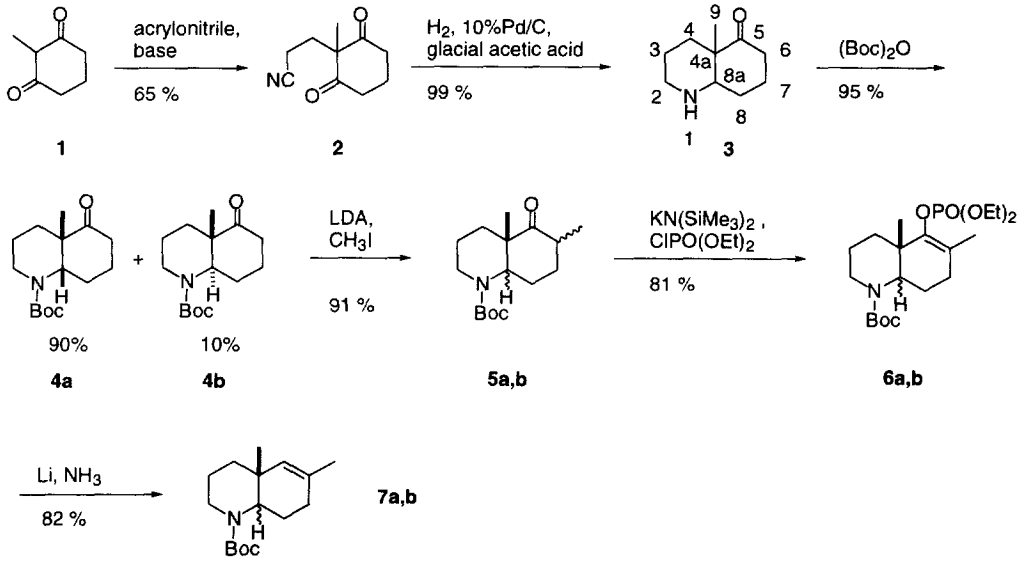
only give rise to cation-stabilizing determinants but may mimic the polarisation of the carbon-oxygen bond between the hydrocarbon portion and the leaving group in the substrate during initiation of cyclisation. The sulfonate group is represented by the methylenecarboxaminophenyl substituent on the ring nitrogen. The propagation of the cyclisation process, especially closure of ring B is mimicked by a 6-membered carbocycle. This design takes into account the fact that the cyclisation is an exergonic process that occurs spontaneously, providing that the activation energy for forming the first carbocation has been overcome and that the appropriate conformation of the polyene chain has been enforced. Two hapten categories were chosen, differing in their stereochemical fusion of both rings. The *trans*-fused hydroquinoline system (HA3 and HA5) should elicit antibodies capable of cyclizing a substrate with an internal *E*-double bond in an antiperiplanar fashion.[8] By contrast, the *cis*-fused species (HA2 and HA4) may give rise to catalysts controlling the cyclisation of a substrate with an internal *Z*-double bond[9] to give *cis*-fused decalin products, a phenomenon not observed in steroid biosynthesis. The C6-site in the hapten, representing the termination of cyclisation, incorporates either a 5,6-double bond or an epoxide moiety. These functionalities were chosen to represent either outcome of the termination, namely olefins (elimination) or alcohols (addition), and should provide an

environment with appropriate polarity in the combining sites. The α-configuration of the epoxide at C5 and C6 of the *trans*-fused system (HA5) was chosen to fit the Stork-Eschenmoser requirement of antiperiplanar attack of a water molecule on the terminal double bond. In the *cis*-fused hydroquinoline series, both possible stereoconfigurations (HA4 and HA6; Figure 4) have been included into the list of target haptens; it is not clear which one represents the water-addition process more appropriately due to conformational exchange of the bicyclic ring system (vide infra).

Results and Discussion

The synthesis of all haptens starts with cyanoethylation of the common precursor 2-methyl-cyclohexane-1,3-dione (**1**) (commercially available) to give **2**[10] in 65% yield (Scheme 1).

Scheme 1

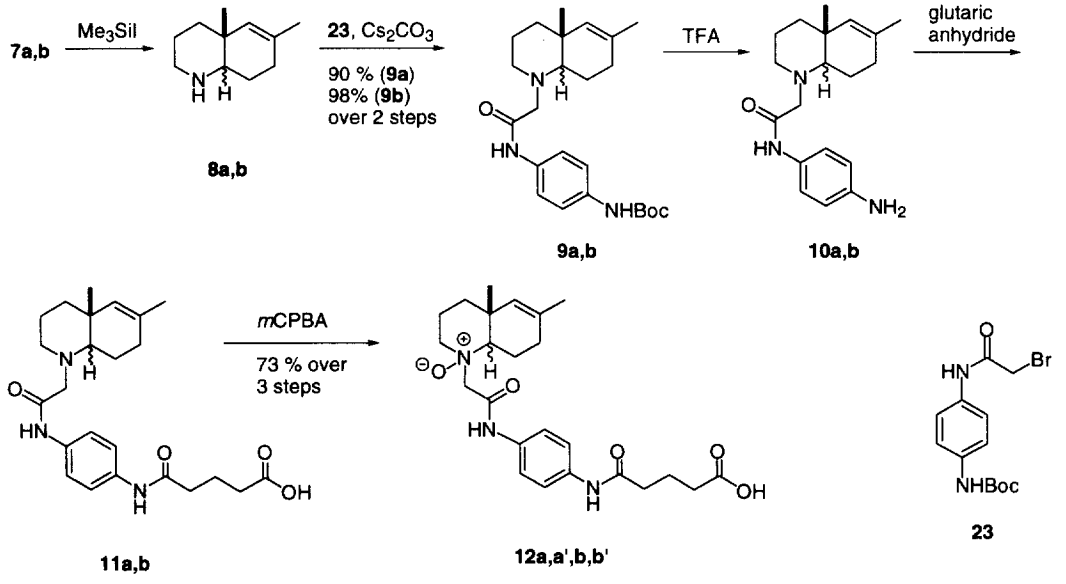


The transformation of **2** into 4a-methyl-decahydro-5-quinolinone (**3**) by catalytic hydrogenation has already been investigated by Litvinenko and co-workers.[11] They used rather harsh conditions (autoclave/60 atm./70 °C/4-5h) and a fresh preparation of very expensive 5% $Rh/BaSO_4$ catalyst.[12] In our low-pressure-room-temperature experiments only 10% Pd/C in glacial acetic acid with 2.5 atm H_2 for five hours quantitatively transforms the monocyclic compound into the bicyclic derivative without any side products.[13] Complete separation of the 9:1 mixture of *cis/trans* -isomers was achieved by Boc-protection[14] of N1 and subsequent silicagel chromatography. Thus this convenient access to such a bridge-methylated heterobicyclic

system is complementary to the Robinson-Annulation sequence, and represents a useful starting point for the synthesis of inhibitors for oxidosqualene cyclases and terpene cyclases in general. The Robinson-Annulation furnishes only *trans*-fused species whereas the former leads to the *cis*-fused compound as the predominant product. Any attempts to alter the outcome of the catalytic hydrogenation to favor the *trans*-isomer by use of other solvents such as dioxane, ethyl acetate and CCl_4 at elevated temperatures around 70 °C only resulted in diminished yields and side product formation.

After chromatographic separation of **4a** and **4b**, these two isomers were taken through the rest of the synthesis separately.[15] Methylation by means of LDA/MeI gave **5a** and **5b** in excellent yields. Introduction of the *5,6*-double bond was carried out employing the Ireland procedure[16] by first forming the enol phosphates **6a,b** and subsequently reducing them to the key intermediates **7a,b** in a clean conversion. Deprotection with trimethylsilyl iodide gave **8a,b** quantitatively and nitrogen alkylation with bromide **23**[7] led to **9a,b** in over 90% yield (Scheme 2).

Scheme 2

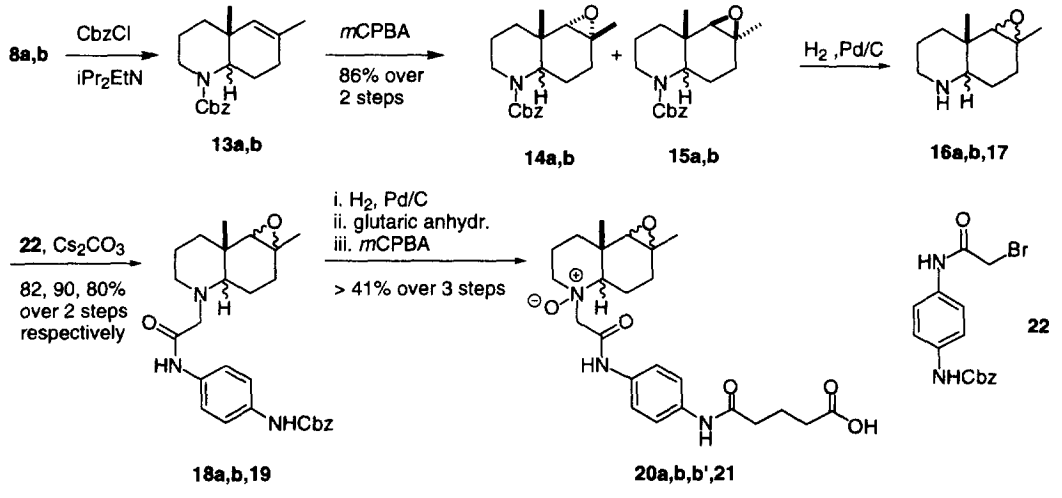


Amines **10a,b** were obtained by deprotection with TFA and transformed to acids **11a,b** by reaction with glutaric anhydride. Attempts to form target haptens 'HA2' (**12a,a'**) and 'HA3' (**12b,b'**) by means of basic 30% hydrogen peroxide without affecting the double bond were unsuccessful; oxidation of the ring nitrogen was too slow and decomposition was predominant. Instead using exactly one equivalent of *m*CPBA at 0 °C worked unexpectedly well and thin layer chromatography revealed a clean conversion. HPLC indicated ratios of

diastereomers to be 63:37 for **12a,a'** and 70:30 for **12b,b'**. **12a** and **12a'** were purified without separation by preparative HPLC and linked as a mixture to the carrier protein,[17] to furnish the complete antigen for immunisation. **12b** and **12b'**, in contrast, were separated by HPLC, characterised independently and reunited in a 1:1 ratio prior to immunisation. Coimmunisation in a 1:1 ratio was chosen because reliable predictions of the better epimeric candidate for eliciting a catalytic antibody was not possible. Assignment of the relative configuration at the *N*-oxide centers of **12b** and **12b'** was carried out by comparison of the ^{1}H NMR spectra and HPLC retention times with those of the already established configurations of **20b** and **20b'**.

In order to synthesise the target epoxides **20a,b,b'** and **21** (Figure 4), the N-protecting group had to be altered to Cbz because the epoxide moiety later would not have survived either strong acidic or nucleophilic deprotection conditions. Therefore amines **8a,b** were Cbz-protected and epoxidised to yield two diastereomers resulting from peracid attack from both sides of the double bond (Scheme 3). As was hoped from steric accessibility considerations, in the *trans* series the attack occurred predominantly from below the molecule leading to the desired α-isomer[18] **14b** in a 79:21 ratio to **15b**. In the *cis* series a 66:33 ratio in favor of the β-isomer **15a** was observed, presumably because of better access by *m*CPBA from the top of the molecule.

Scheme 3



The decahydroquinoline derivatives with a *cis*-fusion between both rings were observed to exist in two preferred conformational states of comparable energy (most likely of chair or halfchair nature); the ratio was dependent on the functionalisation and choice of solvent. The coexistence of both presumed conformers I and II in solution was most strikingly demonstrated by a Dynamic 600 MHz-^{1}H NMR experiment with **16a** in CD_2Cl_2 which shows two resolved signal sets in a 3:2 ratio, emerging at - 60 °C to - 80 °C (Figure 2). Note, for

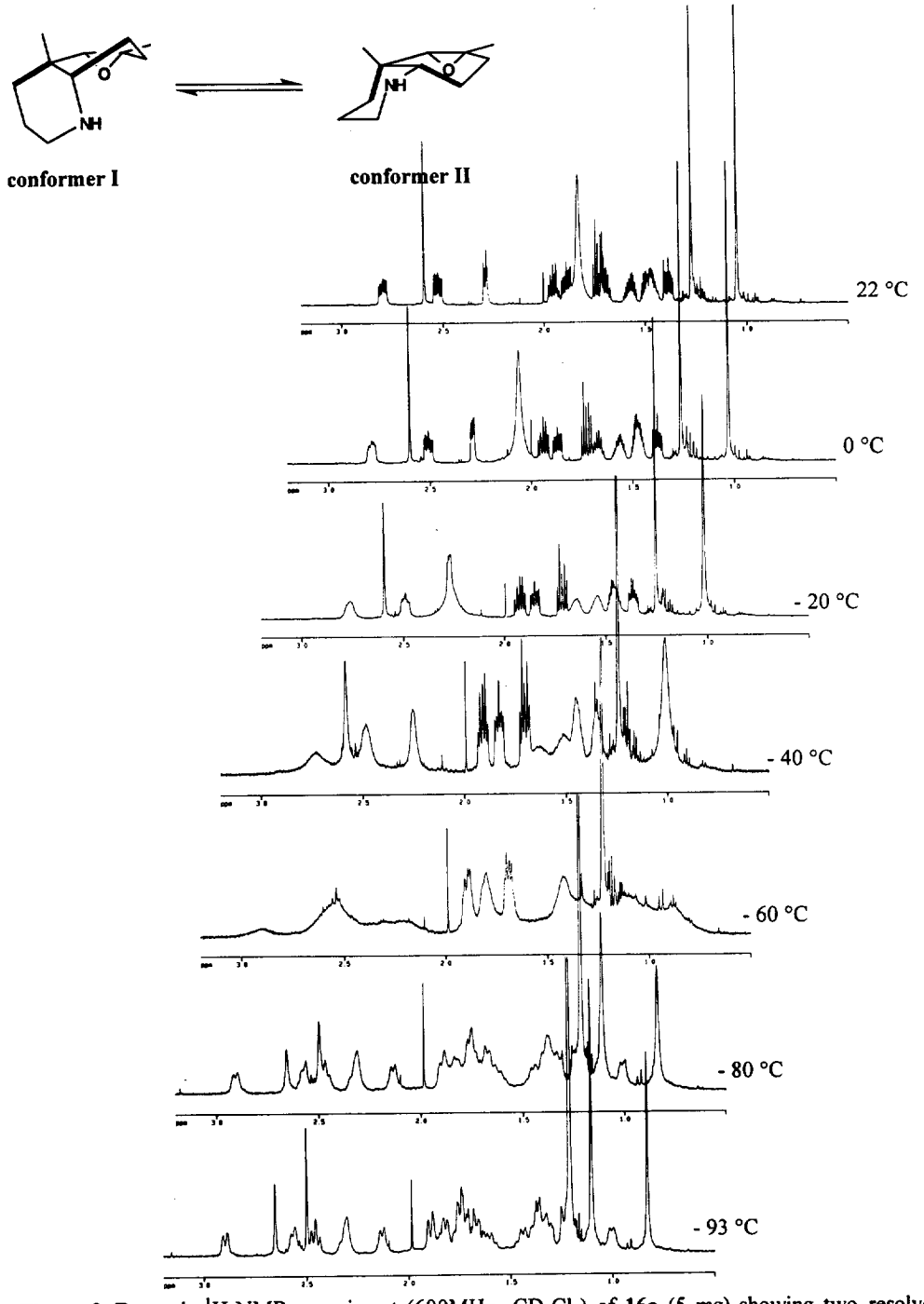


Figure 2. Dynamic ^{1}H NMR experiment (600MHz, CD_2Cl_2) of **16a** (5 mg) showing two resolved sets of signals emerging at - 80 °C for the presumed conformational states I and II.

example, the two separate singlets for the 'epoxide' proton H5 (2.50 and 2.65 ppm), the two singlets for the 4a-methyl group (1.13 and 0.80 ppm) and the separate characteristic signals for all three Nitrogen-neighbouring protons (interval of 1.9 to 2.9 ppm). The presence of conformational interchange is also supported by the Dynamic ^{13}C NMR (two signal sets emerging at - 80 °C). This dynamic behaviour is in accord with observations for *cis*-4a-(methyl)-decalin.[19]

Remarkably, ^{1}H NMR and ^{13}C NMR spectra of the whole series of compounds with a suffix '**a**' (*cis*-fusion of rings A and B) show various degrees of line broadening for specific ring protons and carbons at *room temperature*. In the most extreme case, the spectra of compound **14a** display two completely resolved signal sets. The conformational interchange is slow in relation to the NMR time scale, perhaps because of constraints imposed on the ring framework by the epoxide and carbamate functionalities. The epoxide isomer **15a**, which only differs from **14a** by the β -configuration of the epoxide, gives a 500 MHz-^{1}H NMR spectrum showing broad signals for all ring protons. This indicates a slightly faster exchange between both conformational states. The phenomenon of signal broadening was, as expected, completely absent in the series of *trans*-fused compounds (suffix **b**).

Conformer I of **14a** and **15a** can be considered a loose mimic for non-periplanar *syn*-attack to the internal *(E)*-double bond whereas conformer II is a mimic for the periplanar *anti*-addition to a twisted internal *(Z)*-double bond (Figures 1 and 2). A single-crystal X-ray structure determination of α-epoxide **14a** revealed that, in the solid state, conformer II is energetically favoured (Figure 3). If this can be taken as evidence for the

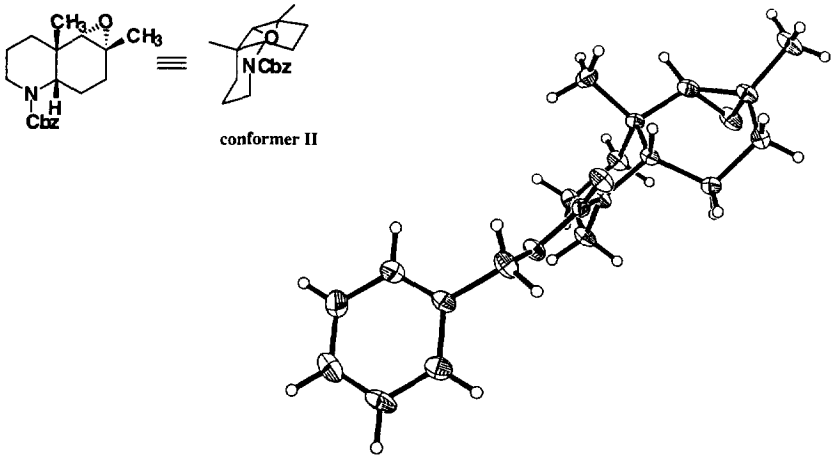


Figure 3. ORTEP view of **14a**; the atoms are drawn with 30% probability ellipsoids. $C_{19}H_{25}NO_3$ (315.4); triclinic; P1 (No. 2, c_i^2); colourless; a = 8.147(2), b = 10.097(2), c = 10.829(4) Å; a = 95.80 (2), b = 106.79(3), g = 90.04(2)°; Z = 2; R = 5.47%; GOF = 1.66.

preferred conformation in solution it would support the purpose of hapten designs HA2 (**12a,a'**) and HA6 (**20a**) (Figure 4) which is to elicit antibodies catalyzing the cyclisation of *(Z)*-configured substrates to *cis*-fused multiring systems. Both isomers **14a** and **15a** were processed to the complete haptens **20a** and **21**, respectively.

Clean removal of the Cbz-group by Pd-catalyzed hydrogenation and alkylation of the free amines **16a,b** and **17** with Cbz-protected bromide **22** gave **18a,b** and **19** in at least 80% yield. Another clean Cbz-deprotection, followed by linker attachment with glutaric anhydride and, finally, N-oxidation resulted in materials that were purified by preparative reversed-phase HPLC to give haptens **20a,b,b'** and **21** (Figure 4).

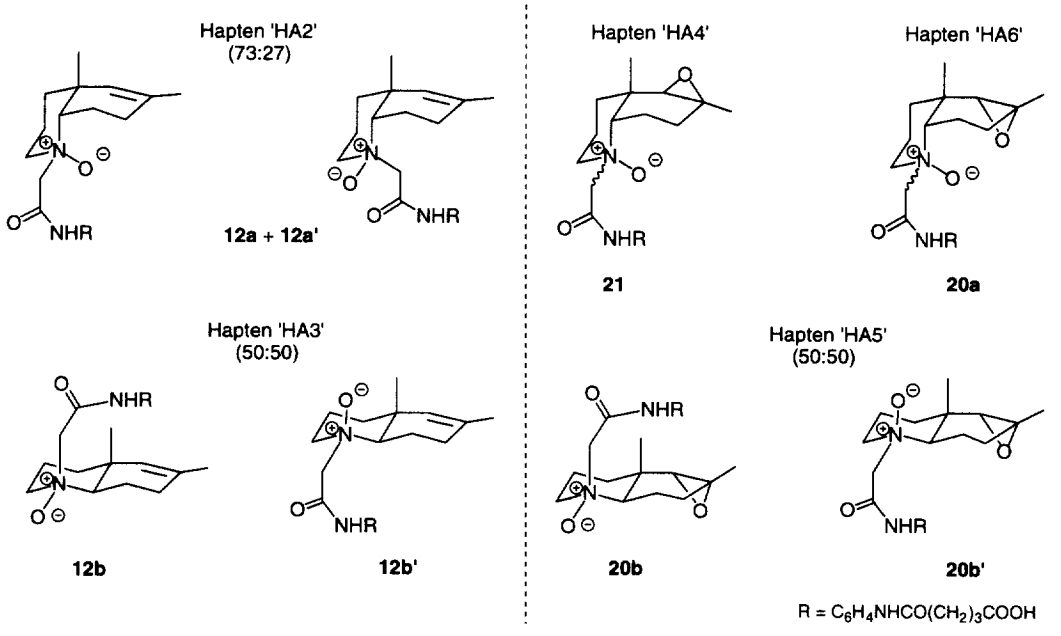


Figure 4. Structures of sets of haptens with double bond representing termination site (left) and epoxide moiety representing termination site (right).

Interestingly, in the epoxidised *cis*-hydroquinoline series, N-oxidation of both epoxide stereoisomers gave only one diastereomer, **20a** and **21**, respectively. This is in contrast to N-oxidation of the *cis*-configured olefin **11a** under the same conditions, leading to the two *N*-oxide isomers **12a** and **12a'**. The observed diastereoselectivity is a well known phenomenon in the case of epoxidation of allylic alcohols.[20] In our case, the epoxide oxygen may complex with the attacking perbenzoic acid and direct it to the ring nitrogen. Reliable assignment of the relative configuration at the *N*-oxide center of *cis*-fused haptens **20a** and **21** on the basis of

^{1}H NMR spectra comparison with the *trans*-fused haptens **20b** and **20b'** has been impossible due to uncertainty of conformational status in solution. The diastereomeric 38:62 mixture of **20b** and **20b'** was separated by preparative HPLC and reunited as a 1:1 mixture before being linked to carrier proteins and used for coimmunisation. Because an antibody catalyst was discovered[9] resulting from immunisation of this diastereomeric hapten mixture, elucidation of the relative stereoconfiguration at the *N*-oxide center of each isomer was carried out by means of comparative ROESY-NMR experiments (Figure 5). The distinctive signals for **20b** at the intersections 1.27ppm/3.9ppm and 1.27ppm/4.0ppm reflect the magnetic through-space interaction of the 4a-methyl group (singlet) with the side-chain methylene substituent at N1 (the latter an A/B system due to hindered rotation, giving rise to a pseudo-doublet). As was expected, the other isomer **20b'** did not show any signal in the area 1.50ppm-1.25ppm/3.50ppm-3.90ppm, even when analyzing cross-sections of lowest intensity. The signal at 1.28/2.78 ppm for **20b** (partial overlap of two independent NOE's) as well as the two signals at 1.45/2.72 and 1.27/2.72 ppm for **20b'** were caused by interaction of the proton at C5 with both methyl substitutents confirming the stereochemistry at the epoxide moiety. Therefore the relative stereoconfiguration *rac*-1*S*,4a*S*,5*S*,6*R*,8a*R* could unambiguously be assigned to compound **20b** (Figure 5).

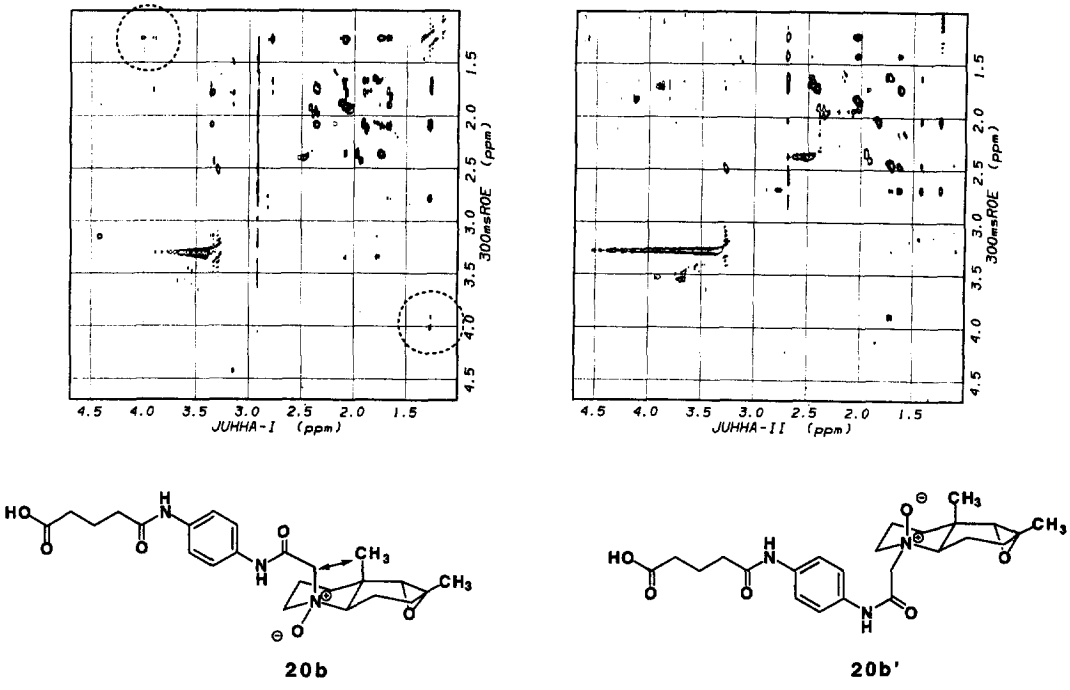
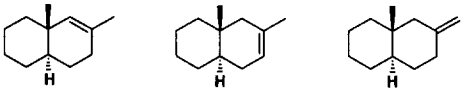


Figure 5. Assignment of relative configuration at N1 of **20b** and **20b'** by ROESY experiments.

Inhibition studies[9] indicated that **20b** elicited the catalytic antibody. This catalyst (HA5-19A4) transformed the *E*-substrate (Figure 1) into the *trans*-configured, regioisomeric decalins **22a,b,c** (ratio 2:3:1) under biphasic assay conditions.[21] Michaelis-Menten parameters were determined by following leaving group release (sulfonic acid production). K_{cat}, k_{uncat} and K_M for solvolysis were found to be 0.021 min^{-1}, 9.2×10^{-6} min^{-1} and 320 μM, respectively, leading to a rate enhancement of 2.3×10^3. The rate acceleration for formation of the decalin products must be greater than the observed k_{cat}/k_{uncat} for solvolysis since **22a,b,c** cannot be detected in the uncatalyzed reaction under our assay conditions.



22a **22b** **22c**

Conclusion

A straightforward high-yield access to bridge-substituted octahydroquinoline-*N*-oxides has been developed which facilitated the introduction of further functionalities such as double bonds and epoxide moieties.[22] Intermediates **3**, **4** and **5** represent attractive starting points for the synthesis of multiring systems incorporating a nitrogen adjacent to the bridge carbon in ring A, that are potential inhibitors for terpene cyclases. Examples for overall yields are 21.8% over 11 steps for **12a**,**a'** and 9.6% over 13 steps for **20a**. In the *cis*-series there is a potential for the existence of two low-energy chair-like conformations. NMR studies revealed that the degree of exchange between these conformations decreases most dramatically with the introduction of an epoxide moiety. All described hapten structures have been used for immunisation and sets of monoclonal antibodies for each have been produced and screened for cyclase activity. Hapten **20b** has elicited a catalyst with striking rate enhancement for bicyclisation.[9] All monoclonal antibodies are being studied for acceptance of alternate substrate structures.

EXPERIMENTAL SECTION

General Procedures: 300 MHz ^{1}H NMR, 500 MHz ^{1}H NMR and 600 MHz ^{1}H NMR spectra were recorded on a Bruker AMX-300, AMX-500 or DRX-600 instrument, respectively. All ^{13}C NMR spectra were recorded at 125 MHz (Bruker AMX-500). Chemical shifts (δ) are given in parts per million (ppm) relative to $CHCl_3$ in $CDCl_3$ (7.27 ppm, ^{1}H; 77.00 ppm, ^{13}C). Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and ψ (pseudo-coupling pattern). High-resolution mass spectra (HRMS) were recorded

at THE SCRIPPS RESEARCH INSTITUTE on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) or electrospray conditions.

All reactions were monitored by thin layer chromatography (TLC), using 0.25 mm Merck silicagel glass plates (60F-254), fractions being visualised by UV light or staining with *p*-anisaldehyde or phosphomolybdic acid solutions with subsequent heat application. Column chromatography was carried out with Mallinckrodt SilicAR 60 silicagel (40-63 μm). Reagent grade solvents for chromatography were obtained from Fisher Scientific. Reagents and anhydrous solvents were obtained from Aldrich Chemical Co. and used as is. All reactions were carried out under anhydrous conditions and an atmosphere of argon, unless otherwise noted. Reported yields were determined after purification to homogenous material.

2-(Cyanoethyl)-2-methyl-cyclohexane-1,3-dione (2). (Complementary NMR spectra to previously published synthesis, see reference 10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, s), 1.78-1.90 (1H, m), 2.02-2.37 (3H, m), 2.53-2.66 (2H, m), 2.72-2.85 (2H, m). ^{13}C NMR ($CDCl_3$): δ 12.0, 16.5, 22.6, 28.1, 36.6, 63.5, 118.8, 208.3.

Mixture of (4a-*trans*)- and (4a-*cis*)-3,4,4a,5,6,7,8,8a-Octahydro-4a-methyl-5-oxo-1(2H)-quinoline, [1:9], (3). To a solution of **2** (8.60 g, 48.0 mmol) in 62 mL of glacial acetic acid in a 400 mL glass bottle 2.80 g Pd/C (10%) were added. The bottle was flushed with hydrogen and then connected to a Parr Hydrogenator. The mixture was shaken under a hydrogen pressure of 50 p.s.i. for approx. 5 h. After neutralisation of an aliquot of the mixture a TLC analysis was carried out (R_f = 0.18, MeOH/CH_2Cl_2 (9:1), ninhydrine). Filtration over celite and extensive evaporation *in vacuo* yielded **3**·HOAc as a light brown crystalline solid (10.90 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (1H, m), 1.15 (3H, s), 1.32-1.49 (2H, m), 1.51-1.65 (2H, m), 1.80 (1H, m), 2.13-2.31 (3H, m), 2.48-2.55 (1H, m), 2.60 (1H, m), 2.85 (1H, m), 3.01-3.09 (1H, m). ^{13}C NMR ($CDCl_3$): δ 20.8, 22.8, 24.6, 26.7, 33.0, 37.0, 46.7, 48.0, 63.5, 214.0; minor isomer δ 15.2, 21.5, 22.5, 26.9, 30.8, 36.3, 48.0, 63.2, 214.5.

(4a-*cis*)- and (4a-*trans*)-3,4,4a,5,6,7,8,8a-Octahydro-4a-methyl-5-oxo-1(2H)-quinolinecarboxylic Acid, 1,1-Dimethylethyl Ester, (4a,b). A stirred solution of the free base of **3** (4.66 g, 27.88 mmol) in 65 mL of anhydrous 1,4-dioxane was treated with $(Boc)_2O$ (6.39 g, 29.27 mmol, 1.05 equiv) and 3 mL of NEt_3. After stirring overnight, TLC analysis showed reaction to be complete (R_f = 0.34 [**4a**] stains deep purple, 0.43 [**4b**] grey-brown after long heating with ninhydrine, hexanes/EtOAc (2:1)). Evaporation of solvent followed by silicagel-chromatography (hexanes/EtOAc, 10:1 → 2:1) gave **4a** (6.44 g, 24.09 mmol) and **4b** (0.64 g, 2.38 mmol) as colourless oils with an overall yield of 95%. **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, s), 1.31 (1H, dd, J = 15.6, 2.5 Hz), 1.45 (9H, s), 1.56 (2H, dt, J = 13.5, 3.6 Hz), 1.71 (2H, dq, J = 13.4, 4.8 Hz), 2.93 (1H, td, J = 13.4, 3.4 Hz), 4.08 (2H, m, bd). ^{13}C NMR ($CDCl_3$): δ 18.8, 20.1, 21.7, 24.4, 28.3, 29.3, 37.2,

38.0 (br), 49.5, 57.6 (br), 79.7, 155.1, 213.8. **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, s), 1.39 (1H, m), 1.46 (9H, s), 1.49 (1H, m), 1.63 (2H, m), 1.84 (1H, dt, J = 9.5 , 1.6 Hz), 2.03 (1H, m), 2.09 (1H, dm, J = 15.7 Hz), 2.25 (1H, dqnt, J = 14.7, 2.0 Hz), 2.54 (1H, m), 2.58 (1H, td, J = 14.4, 6.3 Hz), 2.76 (1H, qd, J = 13.3, 3.4 Hz), 3.07 (1H, dd, J = 12.5, 3.2 Hz), 4.18 (1H, dm, J = 11.7 Hz). ^{13}C NMR ($CDCl_3$): δ 16.7, 21.6, 24.0, 27.2, 28.4, 32.6, 37.8, 48.9, 50.7, 66.5, 79.5, 155.3, 214.1.

(4a-*cis*)-3,4,4a,5,6,7,8,8a-Octahydro-4a,6-dimethyl-5-oxo-1(2H)-quinolinecarboxylic Acid, 1,1-Dimethylethyl Ester, Mixture of Diastereomers, (5a). A solution of LDA, prepared by the addition of 2.5 M *n*-butyllithium in THF (10.7 mL, 26.74 mmol) to a stirred solution of anhydrous diisopropylamine (2.73 g, 27.00 mmol) at - 78 °C, is shortly warmed to room temperature and cooled down again to - 78 °C before being treated with a solution of **4a** (6.81 g, 25.47 mmol) in 21 mL of anhydrous THF. The temperature is raised to - 20 °C and warming up is continued over 35 min. to - 10 °C. Addition of iodomethane (26.3 g, 185.27 mmol) at - 10 °C in one portion and immediate removal of the cooling bath is followed by warming to room temperature with the aid of a water bath after further 5 min. After 20 min. stirring, the reaction is quenched with saturated $NaHCO_3$, the aqueous phase extracted with Et_2O, the combined organic phases washed with brine and dried over $MgSO_4$. The crude product, obtained after evaporation, is purified using silica gel chromatography (hexanes/EtOAc, 10:1 → 3:1) to yield **5a** as a mixture of diastereomers (6.52 g, 23.19 mmol, 91 %, R_f = 0.51, hexanes/EtOAc (2:1)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, d, J = 6.5 Hz), 1.08 (3H, d, J = 6.7 Hz), 1.15 (3H, s), 1.18 (3H, s), 1.23-1.37 (m), 1.45 (3H, s), 1.47 (9H, s), 1.60-1.76 (m), 1.91-2.11 (m), 2.18-2.33 (m), 2.58-2.78 (m), 2.88-3.03 (m), 3.88-4.06 (m), 4.10-4.20 (m), 4.30-4.39 (m).

(4a-*trans*)-3,4,4a,5,6,7,8,8a-Octahydro-4a,6-dimethyl-5-oxo-1(2H)-quinolinecarboxylic Acid, 1,1-Dimethyl-ethyl Ester, (5b). The same procedure as for **5a** is employed with the following exceptions: After addition of **4b** the mixture is stirred for 15 min. at 0 °C, then for 20 min. at room temperature before adding iodomethane in one portion, which results in a short heat evolution. After 25 min. stirring the reaction mixture is quenched. Yield of **5b** (R_f = 0.54, hexanes/EtOAc (2:1)) containing mainly one diastereomer after silicagel-chromatography: 81%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, d, J = 6.5 Hz), 1.17 (3H, s), 1.51 (9H, s), 1.51-1.56 (2H, m), 1.62-1.70 (2H, m), 1.82-1.86 (1H, m), 2.01-2.13 (2H, m), 2.50-2.61 (1H, m), 2.69 (1H, sept, J = 6.5 Hz), 2.89 (1H, qd, J = 12.9, 3.1 Hz), 3.05 (1H, dd, J = 12.7, 3.1 Hz), 4.20 (1H, dm, J = 13.3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.6, 17.0, 21.5, 27.5, 28.5, 32.9, 33.0, 40.0, 48.9, 50.4, 66.9, 79.5, 155.3, 215.1.

(4a-*cis*)-5-[(Diethoxyphosphinyl)oxy]-3,4,4a,7,8,8a-hexahydro-4a,6-dimethyl-1(2H)-quinoline-carboxylic Acid, 1,1-Dimethylethyl Ester, (6a). A solution of **5a** (6.41 g, 22.78 mmol) in 20 mL of anhydrous THF is added to a stirred solution of $KN(SiMe_3)_2$ (7.16 g, 34.17 mmol) at - 30 °C. After 2 h at - 20 °C the mixture is stirred at room temperature for 30 min. before diethylchlorophosphate (6.29 g, 36.45 mmol) is added in one portion under slight heat evolution. After 30 min. the reaction is quenched with pH 7

phosphate buffer (100 mM), extracted with Et_2O and the combined organic phases are washed with brine and dried over $MgSO_4$. After evaporation of the solvent the crude product is purified using silica gel chromatography (hexanes/EtOAc, 3:2 → 1:2) to yield **6a** (R_f = 0.13, hexanes/EtOAc (2:1)) as colourless crystals (7.73 g, 18.51 mmol, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, s), 1.35 (6H, t, J = 6.9 Hz), 1.45 (9H, s), 1.50-1.80 (4H, m), 1.70 (3H, s), 1.89 (1H, d, J = 11.7 Hz), 1.98-2.10 (2H, m), 2.12-2.28 (1H, m), 2,70-2.83 (1H, m), 3.81-4.10 (2H, m, bd), 4.16 (4H, qntd, J = 7.2, 2.6 Hz). ^{13}C NMR ($CDCl_3$): δ 16.1 (d, $^3J_{CP}$ = 6.2 Hz), 17.2, 20.7 (br), 21.0, 22.7 (br), 28.5, 29.2, 30.3, 38.1, 38.8 (dm, bd), 56.8 (dm, bd), 63.78 (d, J = 5.0 Hz), 63.92 (d, J = 6.2 Hz), 79.3, 118.8, 148.5, 156.0.

(4a-*trans*)-5-[(Diethoxyphosphinyl)oxy]-3,4,4a,7,8,8a-hexahydro-4a,6-dimethyl-1(2H)-quinoline-carboxylic Acid, 1,1-Dimethylethyl Ester, (6b). Same procedure as for **6a**. R_f = 0.15, hexanes/EtOAc (2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, s), 1.27 (6H, td, J = 6.2, 1.0 Hz), 1.31-1.44 (3H, m), 1.36 (9H, s), 1.55-1.69 (1H, m), 1.60 (3H, d, J = 2.0 Hz), 1.88-2.03 (3H, m), 2.18-2.32 (1H, m), 2.55 (1H, td, J = 13.0, 2.5 Hz), 2.94 (1H, dd, J = 12.9, 2.1 Hz), 4.08 (4H, qnt, J = 7.1 Hz), 4.17 (1H, dd, J = 13.5, 4.0 Hz). ^{13}C NMR ($CDCl_3$): δ 15.9 (d, J = 6.7 Hz), 16.3, 16.9, 21.1, 24.6, 28.2, 30.6, 34.9, 40.4, 48.2, 63.65 (d, J = 5.6 Hz), 63.75 (d, J = 5.9 Hz), 64.9, 79.2, 117.6 (d, J = 4.8 Hz), 146.9 (d, J = 10.7 Hz), 155.0.

(4a-*cis*)-3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinecarboxylic Acid, 1,1-Dimethyl-ethyl Ester, (7a). A stirred solution of lithium (90 mg, 13.0 mmol) in approx. 40 mL of liquid NH_3 at - 78 °C under argon is treated with a solution of **6a** (1.01 g, 2.42 mmol) in 20 mL of anhydrous THF. After 1 h the reaction is quenched cautiously with saturated NH_4Cl and Et_2O is added. After evaporation of NH_3, the mixture is extracted with Et_2O, the combined organic phases washed with brine, dried over $MgSO_4$ and purified using silica gel chromatography (hexanes/EtOAc (6:1)) to yield **7a** as a colourless oil (523 mg, 1.97 mmol, 82 %, R_f = 0.67, hexanes/EtOAc (2:1)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, s), 1.28-1.68 (5H, m), 1.45 (9H, s), 1.63 (3H, s), 1.90-2.21 (3H, m), 2.73 (1H, t, bd, J = 11.9 Hz), 3.91 (2H, d, bd), 5.09 (1H, s).

(4a-*trans*)-3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinecarboxylic Acid, 1,1-Dimethyl-ethyl Ester, (7b). Same procedure as for **7a**. Yield of **7b** (R_f = 0.70, hexanes/EtOAc (2:1)): 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, s), 1.21 (1H, dt, J = 17.4, 4.4 Hz), 1.31 (1H, m), 1.35 (9H, s), 1.43 (1H, dm), 1.52 (3H, s), 1.67 (1H, qt, J = 13.3, 4.5 Hz), 1.88-1.98 (3H, m), 2.18-2.32 (1H, m), 2.55 (1H, td, J = 13.1, 2.8 Hz), 2.85 (1H, dd, J = 12.5, 1.9 Hz), 4.17 (1H, dd, J = 13.2, 4.3 Hz), 4.93 (1H, s). ^{13}C NMR ($CDCl_3$): δ 18.7, 21.7, 23.0, 25.0, 28.3, 32.0, 36.7, 38.8, 48.6, 65.1, 78.7, 130.9, 131.4, 155.0.

(4a-*cis*)-3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinoline, (8a). A stirred solution of **7a** (92 mg, 0.347 mmol) in 2.5 mL of anhydrous CH_2Cl_2 is treated with iodotrimethylsilane (83 mg, 0.416 mmol) for 10 min. The solution is quenched with MeOH and the solvent is completely removed *in vacuo*. The remaining colourless crystals of **8a**·HI are essentially pure and suitable for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ

1.09 (3H, s), 1.43 (1H, td, J = 13.0, 3.1 Hz), 1.64-1.81 (2H, m), 1.77 (3H, s), 1.89 (1H, dq), 2.01-2.22 (2H, m), 2.26-2.52 (2H, m), 2.80 (1H, td, J = 12.2, 3.2 Hz), 3.19 (1H, m), 3.52 (1H, dm, J = 12.2 Hz), 5.06 (1H, s). ^{13}C NMR ($CDCl_3$): δ 19.2, 21.4, 23.8, 25.2, 28.7, 34.0, 35.9, 43.6, 58.0, 126.2, 135.2.

(4a-*cis*)-[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]phenyl]-carbamic Acid, 1,1-Dimethylethyl Ester (9a). A stirred solution of crude **8a**·HI from the previous step in 1 mL of CH_2Cl_2, 1 mL of EtOH and 0.32 mL of H_2O is treated with **8c** (171 mg, 0.520 mmol) and subsequently with Cs_2CO_3 (347 mg, 1.065 mmol). The mixture is heated to 55 °C for 2.5 h. Water is added and the mixture is extracted with CH_2Cl_2. The combined organic phases are washed with brine, dried over $MgSO_4$ and after evaporation the residue is purified using silica gel chromatography (hexanes/EtOAc, 6:1 → 3:1). **9a** is obtained as a colourless oil (130 mg, 0.314 mmol, 90% over 2 steps, R_f = 0.34, hexanes/EtOAc (2:1), stains dark-brown with ninhydrine). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, s), 1.33-1.40 (1H, m), 1.49-1.57 (2H, m), 1.52 (9H, s), 1.63-1.75 (2H, m), 1.65 (3H, s), 1.83-1.91 (1H, m), 1.92-2.01 (2H, m), 2.42-2.50 (2H, m), 2.67 (1H, t, J = 10.0 Hz), 3.12 (1H, d, J = 16.5 Hz), 3.24 (1H, d, J = 16.5 Hz), 5.11 (1H, s), 6.47 (1H, s, bd), 7.33 (2H, d, J = 8.0 Hz), 7.47 (2H, d, J = 8.0 Hz), 9.47 (1H, s, bd). ^{13}C NMR ($CDCl_3$): δ 17.9 (br), 22.6, 23.1, 27.1 (br), 28.1, 28.9 (br), 33.7 (br), 35.3, 49.2 (br), 58.3, 63.6, 80.1 (br), 119.1, 119.5, 131.4, 131.5, 132.9, 134.5, 152.8, 169.4.

(4a-*trans*)-[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]phenyl]-carbamic Acid, 1,1-Dimethylethyl Ester, (9b). Same procedure as for **7a** → **9a**. Yield of **9b** after silicagel-chromatography: 98% over 2 steps (R_f = 0.33, hexanes/EtOAc (2:1), stains grey-brown with ninhydrine). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (3H, s), 1.26 (1H, td, J = 13.2, 4.0 Hz), 1.44-1.58 (3H, m), 1.51 (9H, s), 1.59 (3H, s), 1.65-1.71 (1H, m), 1.88-2.02 (3H, m), 2.08 (1H, dd, J = 12.7, 2.4 Hz), 2.45 (1H, td, J = 11.9, 3.0 Hz), 2.99 (1H, m), 3.01 (1H, d, J = 17.1 Hz), 3.21 (1H, d, J = 17.1 Hz), 5.09 (1H, s), 6.52 (1H, s, bd), 7.34 (2H, d, J = 8.1 Hz), 7.47 (2H, d, J = 8.1 Hz), 9.33 (1H, s, bd). ^{13}C NMR ($CDCl_3$): δ 20.4, 21.9, 22.0, 22.8, 28.2, 30.5, 35.5, 37.4, 57.8, 59.2, 69.0, 80.2, 11.92, 119.5, 130.9, 131.4, 132.8, 134.5, 152.8, 170.0.

(4a-*cis*)-5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]-phenyl]amino]-5-oxo-pentanoic Acid, (11a). A stirred solution of **9a** (100 mg, 0.242 mmol) in 0.5 mL of CH_2Cl_2 is treated with 0.39 mL of TFA for 2.5 h. After evaporation of the solvent and TFA, the residue is redissolved in CH_2Cl_2 and washed with saturated Na_2CO_3, brine and dried over $MgSO_4$ to give ca. 70 mg (90%) of **10a** as a colourless oil. Redissolution of **10a** in 1.2 mL of anhydrous CH_2Cl_2 and treatment with 28 mg glutaric anhydride while stirring for 2 h yields a solution of **11a** which is, according to TLC (R_f = 0.58, CH_3CN/H_2O (5:2), stains green-brown with ninhydrine), sufficiently pure to be introduced into the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (3H, s) 1.39 (1H, m), 1.50-1.60 (2H, m), 1.65 (3H, s), 1.68-1.78 (2H, m), 1.83-1.91 (1H, m), 1.92-1.97 (2H, m), 1.99 (2H, qnt), 2.42 (4H, 2 overlapping t), 2.53-2.63 (2H, m), 2.74

(1H, t, J = 10.0 Hz), 3.30 (1H, d, bd, J = 16.5 Hz), 3.36 (1H, d, bd, J = 16.5 Hz), 5.09 (1H, s), 7.47 (2H, d, J = 9 Hz), 7.50 (2H, d, J = 9 Hz), 8.22 (1H, s, bd), 9.71 (1H, s, bd).

(4a-*trans*)-5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]-phenyl]amino]-5-oxo-pentanoic Acid, (11b). Same procedure as for **11a**. R_f = 0.65, CH_3CN/H_2O (5:2), stains green-brown with ninhydrine. ^1H NMR (500 MHz, $CDCl_3$): δ 1.16 (3H, s), 1.22-1.30 (1H, m), 1.48-1.58 (3H, m), 1.60 (3H, s), 1.68 (1H, m), 1.91-2.01 (3H, m), 2.04 (2H, qnt), 2.18 (1H, d, J = 10 Hz), 2.44 (4H, 2 overlapping t), 2.52 (1H, t, J = 10 Hz), 3.03 (1H, d, J = 10 Hz), 3.10 (1H, d, J = 17.5 Hz), 3.30 (1H, d, J = 17.5 Hz), 5.09 (1H, s), 7.49 (4H, m), 7.90 (1H, s, bd), 9.48 (1H, s, bd).

(4a-*cis*)-5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]-phenyl]amino]-5-oxo-pentanoic Acid, *N*-oxide, (63:37 mixture of diastereomers), (12a,a'). The solution of **11a** in CH_2Cl_2 from the previous step is cooled to 0 °C and treated with *m*CPBA (>57%, 60 mg, >0.348 mmol). A few drops of MeOH are added to maintain a clear solution. Stirring is continued for 2.5 h while warming up to room temperature. TLC analysis (R_f = 0.47, CH_3CN/H_2O (5:2), stains purple with ninhydrine) may reveal the need for some additional *m*CPBA. Otherwise the solvent is removed *in vacuo*, the residue is redissolved in CH_3CN/H_2O (2:1), filtered through a Sep-Pak C_{18} cartridge and purified by preparative HPLC [Vydac 218TP1022, 300 Å silica, 10μ, C_{18}, 250 x 22mm, isocratic elution of CH_3CN/H_2O(0.1% TFA) 27:73, flow rate 10 mL/min]. ^1H NMR (500 MHz, CD_3OD): δ 1.09 (3H, s, II), 1.39 (3H, s, I), 1.57-1.62 (m), 1.63-1.72 (m), 1.68 (3H, s, I+II), 1.77-1.85 (m), 1.95 (2H, q, I+II), 2.00-2.07 (m), 2.07-2.18 (m), 2.21-2.27 (m), 2.27-2.33 (m), 2.38 (2H, t, I+II), 2.42 (2H, t, I+II), 3.80 (1H, t, J = 10 Hz, I), 3.94-4.06 (2H for II, 1H for I, m), 4.10 (1H, d, I+II), 4.53 (1H, d, J = 15 Hz, I), 4.65 (1H, d, J = 15 Hz, II), 4.66 (1H, d, J = 15 Hz, I), 4.76 (1H, d, J = 15 Hz, II), 5.06 (1H, s, I), 5.16 (1H, s, II), 7.56 (4H, m, I+II). HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_5$ ($M + H^+$) 444.2498; found 444.2510.

5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-1(2H)-quinolinyl)acetyl]amino]-phenyl]amino]-5-oxo-pentanoic Acid, *N*-oxide, (12b,b'). Same procedure as for **12a,a'**. R_f = 0.52, CH_3CN/H_2O (5:2), stains brown with ninhydrine after prolonged heating. Purification and separation of both *N*-oxide diastereomers (70:30 ratio) by preparative HPLC [Vydac 218TP1022, 300 Å silica, 10μ, C_{18}, 250 x 22mm, isocratic elution of CH_3CN/H_2O(0.1% TFA) 30:70, flow rate 10 mL/min]. **rac-(1*S*,4a*R*,8a*R*)-, (12b, major isomer)**: ^1H NMR (500 MHz, DMF-d_7): δ 1.26 (3H, s), 1.53-1.67 (1H, m), 1.62 (3H, s), 1.67-1.71 (1H, m), 1.91 (2H, qnt, J = 7.5 Hz), 2.00-2.10 (2H, m), 2.24 (2H, s, bd), 2.37 (2H, t, J = 7.5 Hz), 2.40 (1H, m), 2.44 (2H, t, J = 7.5 Hz), 2.50-2.55 (1H, m), 3.87 (1H, t, J = 12.5 Hz), 4.03 (1H, d, J = 10 Hz), 4.36 (1H, d, J = 15 Hz), 4.57 (1H, d, J = 15 Hz), 5.16 (1H, s), 5.20 (1H, d, J = 10 Hz), 7.64 (2H, d, J = 10 Hz), 7.70 (2H, d, J = 10 Hz), 10.05 (1H, s), 10.90 (1H, s). HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_5$ ($M + H^+$) 444.2498; found 444.2513. **rac-(1*R*,4a*R*,8a*R*)-, (12b', minor isomer)**: ^1H NMR (500 MHz, DMF-d_7): δ 1.28 (3H. s), 1.52-1.63 (1H, m),

1.60 (3H, s), 1.68 (1H, d, J = 10 Hz), 1.90 (3H, m), 2.13-2.26 (3H, m), 2.37 (2H, t, J = 7.5 Hz), 2.40 (2H, m), 2.45 (2H, t, J = 7.5 Hz), 4.12 (1H, d, J = 10 Hz), 4.17 (1H, d, J = 15 Hz), 4.34 (1H, t, J = 15 Hz), 4.87 (1H, d, J = 15 Hz), 5.00 (1H, d, J = 15 Hz), 5.14 (1H, s), 7.61 (2H, d, J = 7.5 Hz), 7.70 (2H, d, J = 7.5 Hz), 10.08 (1H, s), 11.07 (1H, s). HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_5$ (M + H^+) 444.2498; found 444.2514.

rac-(4a*S*,5*R*,6*S*,8a*S*)-[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]carbamic Acid, Benzyl Ester, (19). **8a** is produced from **7a** (129 mg, 0.486 mmol) as described earlier. **8a**·HI in 2 mL of anhydrous CH_2Cl_2 is then treated under stirring with diisopropylethylamine (NEt_iPr_2) (140 mg, 1.083 mmol) and benzylchloroformate (95%, 94 mg, 0.551 mmol, 1.13 equiv) for 1 h. The mixture is washed with 1 N HCl and brine and dried over $MgSO_4$. After evaporation of the solvent the remaining colourless oil of **13a** is redissolved in 4 mL of CH_2Cl_2, cooled to 0 °C and treated with *m*CPBA (>57%, 160 mg) under stirring. After 1 h the cooling bath is removed and after further 1 h an additional 20 mg *m*CPBA is added and stirred for another 1 h. TLC shows 2 spots for **14a** (R_f = 0.37, hexanes/EtOAc (2:1)) and **15a** (R_f = 0.34). The mixture is washed with saturated Na_2CO_3 and brine, dried over $MgSO_4$ and finally purified and separated using silica gel chromatography (hexanes/EtOAc, 6:1 → 4:1) to yield **14a** (44.3 mg, 0.140mmol, colourless crystals) and **15a** (88.0 mg, 0.279 mmol, colourless oil) in an overall yield of 86%. A stirred solution of **15a** (98 mg, 0.311 mmol) in 4.9 mL of anhydrous EtOH is treated with Pd/C (10%, 33 mg) and is hydrogenated for 2 h upon which the suspension is filtered and the filtrate, after evaporation of the solvent, is dissolved in 2.2 mL of anhydrous DMF. Treatment with Cs_2CO_3 (101 mg, 0.311 mmol) and **22** (170 mg, 0.466 mmol, 1.5 equiv) under stirring for 17 h and subsequent washing with H_2O, extraction with CH_2Cl_2, drying over $MgSO_4$ and evaporation gives a brownish residue which is purified on two preparative TLC plates (20 x 20 cm, 1 mm) (R_f = 0.54, CH_2Cl_2/EtOAc (3:1)) followed by extraction with acetone to give **19** as a colourless oil (115 mg, 0.247 mmol, 80% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, s), 1.35 (1H, m), 1.39 (3H, s), 1.41 (1H, m), 1.55-1.60 (1H, m), 1.64-1.74 (2H, m), 1.80-1.91 (3H, m), 2.40 (1H, d, J = 10.9 Hz), 2.43 (1H, m), 2.62 (1H, td, J = 11.5, 3.0 Hz), 2.62 (s) + 2.63 (s)(together 1H, due to 2 conformers), 3.06 (1H, d, J = 16.5 Hz), 3.09 (1H, d, J = 16.5 Hz), 5.18 (2H, s), 7.07 (1H, s, bd), 7.30-7.40 (7H, m), 7.49 (2H, d, J = 7 Hz), 9.25 (1H, s). ^{13}C NMR ($CDCl_3$): δ 15.8, 21.6, 22.9, 24.3, 28.1, 28.7 (br), 29.2, 31.7, 34.3, 47.7, 53.7, 59.0, 59.1, 60.2, 66.8, 69.8, 119.3 (br), 119.8, 120.8, 128.2 (split), 128.5, 133.2, 134.0, 136.0, 153.4, 169.0. HRMS (FAB, NBA) calcd for $C_{27}H_{33}N_3O_4$ (M + H^+) 464.2549; found 464.2526.

rac-(4a*S*,5*S*,6*R*,8a*S*)-[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]carbamic Acid, Benzyl Ester, (18a). **14a** from the previous step is processed to **18a** (R_f = 0.49, CH_2Cl_2/EtOAc (3:1)) with a yield over 2 steps of 82%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (1H, m), 1.32 (3H, s), 1.37 (3H, s), 1.39 (1H, m) 1.53-1.66 (3H, m), 1.69-1.78 (1H, m), 1.87 (1H, td, J = 13.5, 4.6 Hz), 2.04 (1H, d, J = 10.4 Hz), 2.15 (1H, d, J = 12.6 Hz), 2.40-2.50 (2H, m), 2.62(s) + 2.64 (s) (together 1H, due to

2 conformers), 3.04 (1H, d, J = 17.0 Hz), 3.09 (1H, d, J = 17.0 Hz), 5.18 (2H, s), 7.16 (1H, s, bd), 7.30-7.40 (7H, m), 7.49 (2H, d, J = 8.9 Hz), 9.40 (1H s, bd). ^{13}C NMR ($CDCl_3$): δ 14.8, 21.7, 22.9, 25.3, 27.0, 29.1, 30.3, 31.7, 33.2, 47.5, 53.7, 58.7, 64.3, 66.8, 67.8, 119.3, 119.7, 121.0, 128.1, 128.2, 128.5, 128.6, 133.3, 134.1, 136.0, 153.4, 169.2.

rac-(4a*S*,5*S*,6*R*,8a*R*)-[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]carbamic Acid, Benzyl Ester, (18b). Same procedure as for the preparation of **19**. Yields over 3 steps of separated **14b** (R_f = 0.44, hexanes/EtOAc (2:1)) and **15b** (R_f = 0.37, (2:1)) in a ratio of 79:21: 86%. **14b** is processed as described for second part of synthesis of **19** to produce **18b** (R_f = 0.48, CH_2Cl_2/EtOAc (3:1)), after preparative TLC purification, in a yield of 90% over 2 steps. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, s), 1.27 (3H, s), 1.31 (1H, m), 1.37 (1H, m), 1.56 (2H, t, bd, J = 13.1 Hz), 1.65 (1H, td, J = 12.4, 4.6 Hz), 1.78 + 1.81 (1H, 2 dubletts, J = 6.7 Hz), 1.90 (2H, m), 2.26 (1H, dd, J = 12.6, 3.0 Hz), 2.40 (1H, t, J = 12.0 Hz), 2.61 + 2.67 (1H, 2 singletts), 2.87 (1H, m), 2.94 (1H, d, J = 17.2 Hz), 3.08 (1H, d, J = 17.2 Hz), 5.17 (2H, s), 7.31-7.38 (7H, m), 7.47 (2H, d, J = 6.9 Hz), 9.22 (1H, s). ^{13}C NMR ($CDCl_3$): δ 16.9, 20.5, 21.4, 24.1, 27.8, 29.1, 31.6, 34.4, 34.9, 53.7, 57.3, 57.8, 59.5, 62.8, 66.7, 69.7, 119.3, 119.6, 128.2, 128.4, 133.0, 134.1, 136.0, 153.5, 169.9. HRMS (FAB, NBA) calcd for $C_{27}H_{33}N_3O_4$ ($M + H^+$) 464.2549; found 464.2541.

5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]-amino]-5-oxo-pentanoic Acid, *N*-oxide, (21). A stirred solution of **19** (56 mg, 0.121 mmol) in 2 mL of anhydrous EtOH containing Pd/C (10%, 10.5 mg) is hydrogenated for 2 h. After almost quantitative conversion to the free amine, the Pd/C is removed by filtration over celite, the solvent is evaporated and the residue is redissolved in 1 mL of anhydrous CH_2Cl_2 before glutaric anhydride (14.5 mg, 0.127 mmol, 1.05 equiv) is added while stirring for 2 h. The solution of the resulting acid (R_f = 0.64, CH_3CN/H_2O (5:2), stains brown-green with ninhydrine) is treated with *m*CPBA (>57%, 31 mg) and 0.1 mL of MeOH for 2 h. Removal of the solvent, redissolution in CH_3CN/H_2O (1:1) and filtration through a Sep-Pak C_{18} cartridge produces a fairly pure solution of **21** (R_f = 0.37, CH_3CN/H_2O (5:2), stains blue-purple with ninhydrine) which upon standing at 4 °C crystallises overnight to give highly pure **21** as a colourless solid (23 mg, 0.050 mmol, 41% over 3 steps). The mother liquor contains further **21** which can be isolated by preparative HPLC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (3H, s), 1.36 (1H, d, J = 13.2 Hz), 1.56 (1H, d, J = 12.6 Hz), 1.61 (3H, s), 1.68 (3H, d, J = 13.3 Hz), 1.73 (1H, m), 1.79 (2H, qnt, J = 7.3 Hz), 1.90-1.93 (1H, m), 2.24 (2H, t, J = 7.3 Hz), 2.31 (2H, t, J = 7.3 Hz), 2.38 (1H, q, J = 13.3 Hz), 2.53 (1H, s), 3.03-3.15 (2H, m), 3.36 (1H, t, J = 12.5 Hz), 3.87 (1H, m), 4.01 (1H, m), 7.42 (2H, dd, J = 9.0, 2.3 Hz), 7.51 (2H, d, J = 9.0 Hz), 9.86 (1H, s). ^{13}C NMR (DMSO-d_6): δ 16.2, 20.7, 21.0, 23.5, 25.8, 26.4, 28.5, 33.5, 34.9, 35.4, 58.9, 60.6, 69.2, 71.4, 74.4,

119.6, 119.7, 133.5, 135.1, 162.4, 170.5, 175.2. HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_6$ (M + H^+) 460.2448; found 460.2437.

5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]-amino]-5-oxo-pentanoic Acid, *N*-oxide, (20a). Same procedure for the conversion of **18a** to **20a** as described earlier for the synthesis of **21**. R_f of free amine = 0.44, CH_3CN/H_2O (5:2), stains dark-green with ninhydrine, R_f of **20a** = 0.35, purple. Purification of the *N*-oxide could not be achieved by crystallisation but only by preparative HPLC [Vydac 218TP1022, 300 Å silica, 10µ, C_{18}, 250 x 22mm, isocratic elution of CH_3CN/H_2O (no TFA!) 30:70, flow rate 10 mL/min]. Only one diastereomer (**20a**) has been detected. ^{1}H NMR (500 MHz, CD_3OD): δ 1.31 (3H, s), 1.47 (1H, d, *J* = 13.8 Hz), 1.63 (3H, s), 1.61-1.77 (2H, m), 1.80-1.90 (2H, m), 1.97 (2H, qnt, *J* = 7.4 Hz), 2.05 (1H, t, *J* = 14.7 Hz), 2.37 (2H, t, *J* = 7.4 Hz), 2.41 (2H, t, *J* = 7.4 Hz), 2.48 (1H, m), 2.59 (1H, s), 3.38 (2H, m), 3.51 (1H, m), 4.05 (1H, d, *J* = 11 Hz), 4.26 (1H, d, *J* = 11 Hz), 7.53 (4H, m). ^{13}C NMR (CD_3OD): δ 17.3, 21.0, 22.30, 22.35, 27.4, 28.6, 31.4, 34.8, 35.7, 37.0, 60.6, 62.9, 70.1, 70.8, 79.6, 121.6, 121.7, 135.0, 136.6, 163.4, 173.7, 177.7. HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_6$ (M + H^+) 460.2448; found 460.2468.

5-[[4-[[(3,4,4a,7,8,8a-Hexahydro-4a,6-dimethyl-5,6-epoxy-1(2H)-quinolinyl)acetyl]amino]phenyl]-amino]-5-oxo-pentanoic Acid, *N*-oxide (20b,b'). Same procedure as for the synthesis of **21**. (R_f of free amine = 0.58, CH_3CN/H_2O (5:2), stains brown-green with ninhydrine, R_f of **20b,b'** = 0.41, brown-green). Separation of the mixture **20b** : **20b'** (38 : 62) was carried out by preparative HPLC [Vydac 218TP1022, 300 Å silica, 10µ, C_{18}, 250 x 22mm, isocratic elution of CH_3CN/H_2O(no TFA!) 30:70, flow rate 10 mL/min]. **rac-(1*S*,4a*S*,5*S*,6*R*,8a*R*)-, (20b)** (shorter retention time) : ^{1}H NMR (500 MHz, CD_3OD): δ 1.27 (3H, s), 1.29 (3H, s), 1.67 (1H, d, *J* = 12.9 Hz), 1.72-1.83 (2H, m), 1.90 (1H, d, *J* = 15.6 Hz), 1.96 (2H, qnt, *J* = 7.4 Hz), 2.06-2.13 (3H, m), 2.32-2.37 (3H, m), 2.41 (2H, qnt, *J* = 7.4 Hz), 2.79 (1H, s), 3.16 (1H, t, *J* = 9.9 Hz), 3.37 (1H, d, *J* = 12.2 Hz), 3.91 (1H, d, *J* = 13.3 Hz), 4.01 (1H, m), 4.44 (1H, d, *J* = 11.3 Hz), 7.51 (2H, d, *J* = 9.3 Hz), 7.52 (2H, d, *J* = 9.3 Hz). ^{13}C NMR (CD_3OD): δ 17.0, 17.1, 20.4, 22.4, 24.1, 29.0, 33.7, 37.0, 59.8, 64.4, 69.7, 72.4, 73.9, 121.5, 121.6, 135.1, 136.6, 173.7. HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_6$ (M + H^+) 460.2448; found 460.2457. **rac-(1*R*,4a*S*,5*S*,6*R*,8a*S*)-, (20b')** (longer retention time) : ^{1}H NMR (500 MHz, CD_3OD): δ 1.27 (3H, s), 1.46 (3H, s), 1.65 (1H, d, *J* = 13.9 Hz), 1.68-1.75 (2H, m), 1.82-1.86 (1H, m), 1.98 (2H, qnt, *J* = 7.1 Hz), 2.02-2.09 (3H, m), 2.37 (2H, t, *J* = 7.5 Hz), 2.41 (2H, t, *J* = 7.5 Hz), 2.49 (1H, d, *J* = 14.2 Hz), 2.71 (1H, s), 3.46 (1H, d, *J* = 11.9 Hz), 3.73-3.77 (1H, m), 3.90 (1H, t, *J* = 12.5 Hz), 4.07 (1H, d, *J* = 14.6 Hz), 4.09 (1H, d, *J* = 14.6 Hz), 7.52 (4H, s). HRMS (FAB, NBA) calcd for $C_{24}H_{33}N_3O_6$ (M + H^+) 460.2448; found 460.2458.

N-(Bromoacetyl)-N'-(benzyloxycarbonyl)-phenylenediamine (22). A stirred solution of phenylen-diamine (2.00 g, 18.50 mmol) in 200 mL of anhydrous CH_2Cl_2 at 0 °C is treated wih benzylchloroformate (3.15

g, 18.50 mmol) and NEt*i*Pr$_2$ (2.39 g, 18.50 mmol). The mixture is slowly warmed to room temperature and stirred overnight, thereafter concentrated *in vacuo* and washed with water, brine, dried over $MgSO_4$, evaporated and purified using silica gel chromatography (hexanes/EtOAc, 3:1 → 1:2, R_f = 0.21 (1:1)) to yield the mono-Cbz-protected starting material as a colourless solid (3.62 g, 14.95 mmol, 81 %). This pure material (1.80 g, 7.43 mmol) is then dissolved in 70 mL of anhydrous CH_2Cl_2, stirred at 0 °C and treated with bromoacetylbromide (1.57 g, 7.80 mmol, 1.05 equiv) and NEt*i*Pr$_2$ (1.01 g, 7.81 mmol) to result in an instantaneous precipitation of a beige solid, which is insoluble in CH_2Cl_2 and ethylacetate. The solid material is filtered off and dried *in vacuo* to yield **22** as a powder (2.00 g, 5.51 mmol, 74 %), essentially pure according to its proton NMR spectrum. ^{1}H NMR (300 MHz, CD_3CN): δ 3.93 (2H, s), 5.17 (2H, s), 7.36-7.51 (9H, m), 7.83 (1H, s, bd), 8.60 (1H, s, bd).

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