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PAPER

Atroposelective formation of dibenz[*c*,*e*]azepines *via* intramolecular direct arylation with centre-axis chirality transfer†

Caroline A. Cheetham, Richard S. Massey, Silvain L. Pira, Robin G. Pritchard and Timothy W. Wallace*

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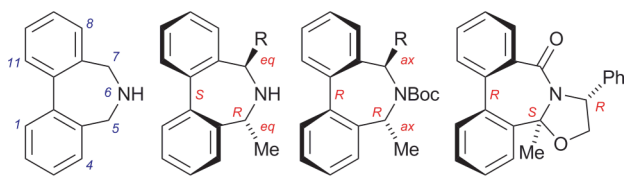
5-Substituted 6,7-dihydrodibenz[*c*,*e*]azepines, a class of secondary amine incorporating a centre-axis chirality relay, are accessible from 1-substituted *N*-(2-bromobenzyl)-1-phenylmethanamines *via* *N*-acylation and ring-closing intramolecular direct arylation. The ring closure proceeds with high atropodiastereoselectivity due to strain effects that are induced by trigonalisation of the nitrogen atom, as predicted using molecular mechanics calculations.

Introduction

Three-atom bridged biaryls have unique conformational features arising from their connectivity, which obliges the Ar–bridge and Ar–Ar bonds to twist in concert. In 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines **1** this has the effect of transforming conformational bias at the benzylic carbon atoms into torque at the biaryl axis and *vice versa*, so that in the presence of a substituent at C(5) or C(7) the system operates as a centre-axis chirality relay that can be controlled through substitution at N(6). This is illustrated by the behavior of the amines (–)-**2** and (–)-**3**, whose respective Boc derivatives (+)-**4** and (+)-**5** have inverted, conformationally stable, biaryl axes, as predicted on the basis of molecular mechanics calculations.[1] As a corollary it can be suggested that the dynamics of the biaryl axis in derivatives of **1**, which are potential tropos ligands,[2] will be subject to the integrated effect of all pairwise interactions between adjacent substituents on C(4), C(5), N(6), C(7) and C(8), in addition to those at the usual biaryl control sites, C(1) and C(11). To facilitate a broad study of this phenomenon we required a more flexible synthetic route to amines such as (–)-**2**, which we first prepared from the lactam **6** and used as the precursor to **3**–**5**.[1]



1 (–)-**2** R = H, (–)-**3** R = Me, (+)-**4** R = H, (+)-**5** R = Me, **6**

School of Chemistry, The University of Manchester, Oxford Road, Manchester, UK, M13 9PL. E-mail: tim.wallace@manchester.ac.uk; Fax: +44 (0) 161 275 4939

† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C and ^{19}F NMR spectra; structures generated *via* molecular mechanics calculations. CCDC reference number 793197. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00889c

The importance of biaryls in biological, synthetic and materials chemistry has inspired the development of numerous methods for their assembly with control of axial chirality,[3,4] a common strategy being to link a pair of functionalised aryl units through a centrally chiral tether prior to aryl–aryl coupling, which may then proceed atroposelectively. With this in mind, we were attracted by the retrosynthesis shown in Fig. 1, as it allows the centre-axis relay to direct its own atroposelective formation and exploits the availability of numerous amines of the form **7** in enantiopure form.[5]

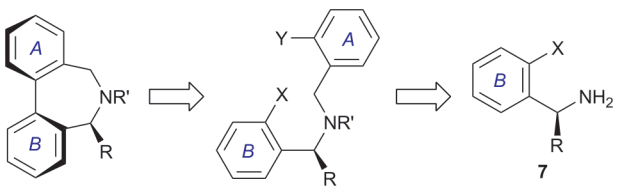
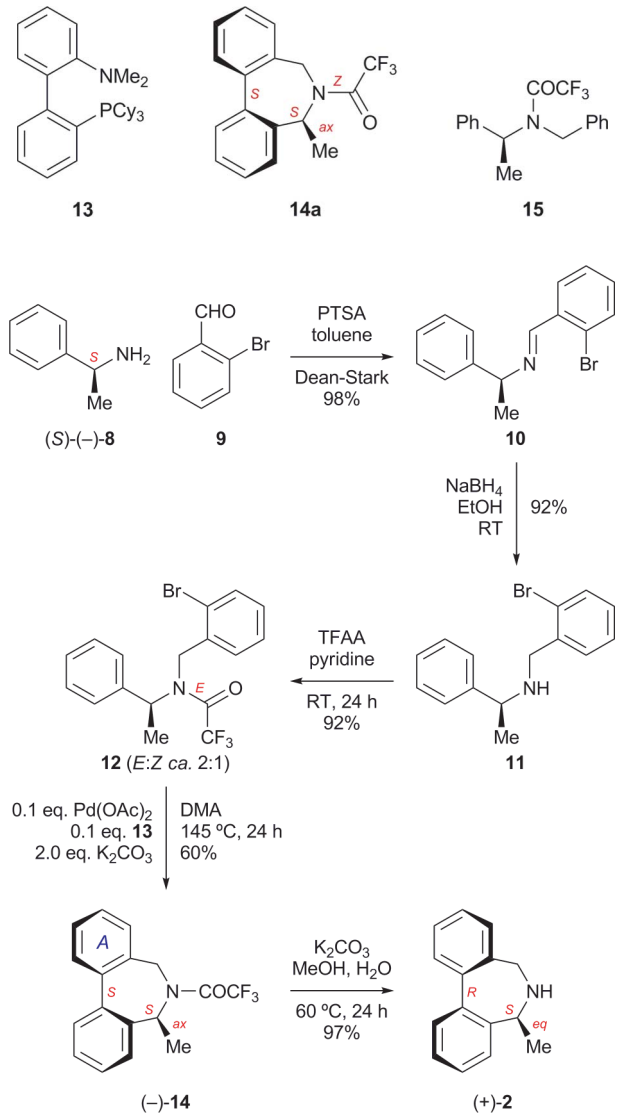


Fig. 1 Proposed atroposelective route to dibenz[*c*,*e*]azepines.

A literature search revealed that the existing Ar–Ar coupling routes to dibenz[*c*,*e*]azepines lack generality,[6,7] involve toxic reagents[6,8,9] or use activating substituents in both coupling partners (X, Y = I, Br, OTf, *etc.*).[8–10] However, a potential solution to this problem was offered by intramolecular direct arylation, which Fagnou and coworkers had shown to be capable of closing seven-membered rings.[11–13] We now report the successful use of this methodology[14] in concise atroposelective routes to 5-substituted 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines.

Synthesis of Materials

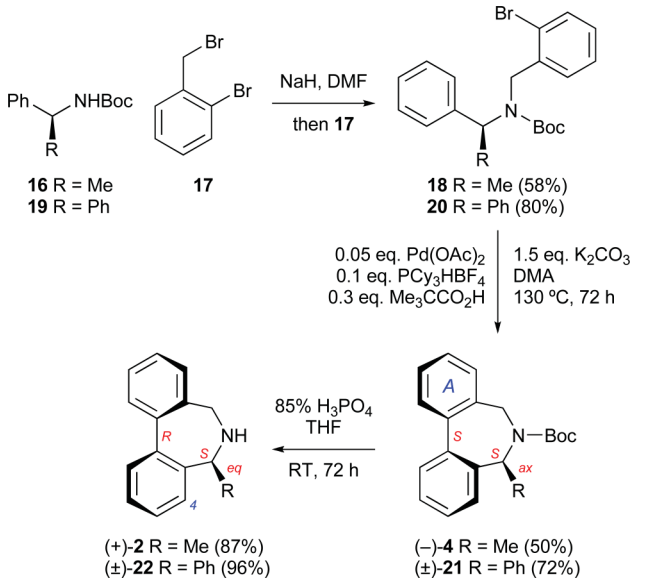
We initially targeted the amine (+)-**2**, preparing the substituted dibenzylamine required for the cyclisation step in a reductive amination sequence (Scheme 1). The condensation of (*S*)-1-phenylethylamine (–)-**8** with *o*-bromobenzaldehyde **9** gave the imine **10**, which was reduced to the amine **11** in good yield. Trifluoroacetylation gave the corresponding amide **12** as a mixture of *E*- and *Z*-rotamers (ratio *ca.* 2 : 1).[15]



Scheme 1 Preparation of amine **2** *via* reductive amination.

The cyclisation of **12** under Fagnou's original conditions,[11b] using 0.1 mol equivalents each of $Pd(OAc)_2$ and the phosphine **13**, provided the product **14** in 60% yield as a 9 : 1 mixture of rotamers (mainly **14a**). The by-product **15**, expected to arise through reductive debromination of **12**, was detected in the product mixture but its formation was observed to be minimal when the ligand:Pd ratio did not exceed 1 : 1. The pseudoaxial orientation of the methyl groups in each of the rotamers of **14** is apparent from their upfield chemical shifts [δ_H (400 MHz, $CDCl_3$) 0.92 and 0.97 respectively], which confirm their proximity to the A-ring, and that the biaryl axis is therefore (*S*)-configured. Hydrolysis of **14** gave the amine (+)-**2** (97%), whose structure and configuration were confirmed by comparison with a sample of (–)-**2**.[1]

As an alternative route to the amine **2**, we established that a cyclisation substrate can also be assembled using *N*-alkylation as the key step (Scheme 2).[16] Treatment of the Boc derivative **16**, derived from (*S*)-**8**, with base and then **17** gave the alkylation product **18** in moderate yield. The cyclisation of **18** was attempted using Fagnou's later conditions,[12] in which the reaction temperature is 130 °C and acetate is supplanted with pivalate. This provided the



Scheme 2 Preparation of amines **2** and **22** *via* *N*-alkylation.

Boc azepine (–)-**4** (50%) which was confirmed as the pure (5*S*,a*S*)-diastereoisomer by NMR [δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, d, J = 7 Hz, 5-Me)] and polarimetry {$[\alpha]_D^{24}$ –322 ± 9 (*c* 0.61, $CHCl_3$); lit.[1] for (5*R*)-**4** $[\alpha]_D^{25}$ +321 ± 10 (*c* 0.82, $CHCl_3$)}. The conversion of (–)-**4** into (+)-**2** (87%) was effected with phosphoric acid in THF.[17] The *N*-alkylation route was also used to assemble the amine **22** *via* a short sequence in which the intramolecular direct arylation also effects the desymmetrisation of a diphenylmethyl group. Thus, treating the Boc derivative **19** of diphenylmethylamine with base and **17** gave the alkylation product **20** in 80% yield. The Pd-mediated cyclisation of **20** gave the carbamate (±)-**21** (72%), which was shown to be the 5-axial diastereoisomer by X-ray crystallography (Fig. 2). Hydrolysis of (±)-**21** with phosphoric acid gave the amine (±)-**22** (96%) as colorless crystals, m.p. 117–118 °C.

Discussion

The distinctive features of **21** and **22** serve to illustrate how the axial configuration, and associated properties, of a 5-substituted dibenz[*c*,*e*]azepine can be induced to 'switch' by changing the *N*-substituent. The ^{1}H NMR spectra of both of these compounds display resonances attributable to upfield-shifted aromatic protons, two at 6.6 ppm for **21** (Fig. 2b) and one at 6.8 ppm for **22** (Fig. 2c). On the basis of the X-ray data, the upfield signal from the carbamate **21** can be assigned to H(2′) and H(6′), which pass within 3 Å of the face of the biaryl A-ring as the phenyl group rotates and thus experience a shielding effect. In contrast, it is clear from molecular mechanics calculations that the phenyl group in the parent amine **22** prefers a pseudoequatorial orientation, from where it exerts a local shielding effect on H(4), the upfield-shifted proton in this case. The switchable features of amines such as **22** should provide new opportunities for probing the edge-to-face interactions of aromatic rings.[18]

The key step in this approach to dibenz[*c*,*e*]azepines is an intramolecular direct arylation that proceeds with high atropodiastereoselectivity. The detailed mechanism of Pd-mediated arylation remains the subject of speculation, but the generally

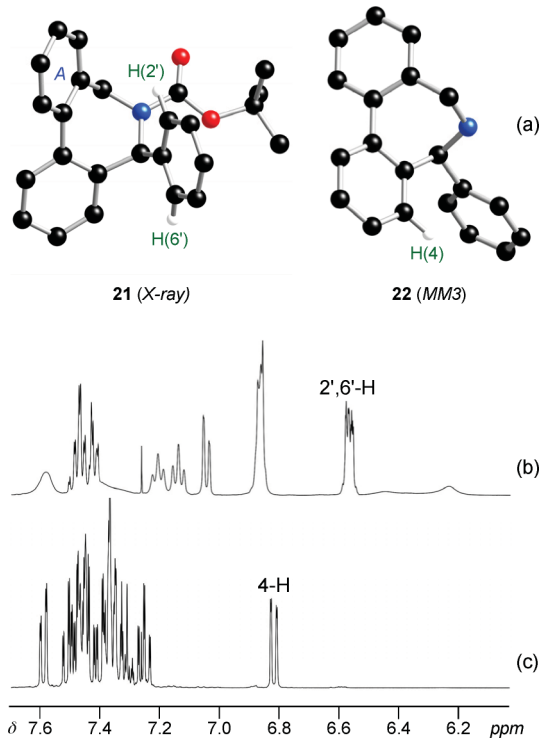
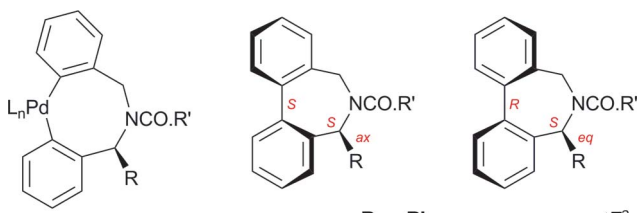


Fig. 2 (a) Structures of **21** and **22** showing the edge-to-face interactions of the aromatic rings; (b), (c) Aromatic regions of 400 MHz ^{1}H NMR spectra of **21** and **22** respectively.

accepted sequence[13] would start with the oxidative addition of a Pd(0) species to the bromoaryl subunit of the substrate, and proceed to a palladacycle **23** *via* an electrophilic substitution (under the conditions used in Scheme 2, this may feature pivalate in a proton-transfer role[12]). The final product is formed when the palladacycle **23** undergoes reductive elimination of the Pd moiety, which returns to the catalytic cycle (Fig. 3). The stereoselectivity of this final step is essentially complete, with the (*S*)-configured precursor **23** being transformed into an (a*S*)-configured biaryl. The origin of this selectivity is ultimately the carbonyl substituent on N(6), whose presence causes the 5-substituent to favour an axial orientation. Molecular mechanics calculations were used to quantify this preference in the form of the difference in steric energy (ΔE) between the respective (5*S*,a*S*) and (5*S*,a*R*)



	R	R'		ΔE^a
(5*S*,a*S*)-**4**	Me	OBu^t	(5*S*,a*R*)-**4**	+19.2
(5*S*,a*S*)-**14**	Me	CF_3	(5*S*,a*R*)-**14**	+20.1
(5*S*,a*S*)-**21**	Ph	OBu^t	(5*S*,a*R*)-**21**	+12.0

[a] Calculated difference in steric energy $E_{aR} - E_{aS}$ (kJ mol^{-1}) of the respective global conformational minima in the (5*S*,a*R*) and (5*S*,a*S*) manifolds. For details see ESI.

Fig. 3 Generalised precursor and product isomers in the catalytic cycles leading to **4**, **14** and **21**, with the difference in steric energy (ΔE) between the isolated product and the alternative least-strained axial invertomer (Macromodel 8.0, MM3).

conformational minima (Fig. 3). The ΔE values (12–20 kJ mol^{-1}) are consistent with conformational equilibria dominated (>99% at 25 °C) by the respective (5*S*,a*S*)-diastereoisomers, which behave as 'fixed axis' systems despite lacking the usual axis-restraining features, *viz.* substituents at C(1) and C(11) or the fusion of a 5-membered ring to the C(5)–N(6) bond.[19]

Conclusions

We have described two variants of a new route to 5-substituted 6,7-dihydrodibenz[*c*,*e*]azepines, a unique class of secondary amine incorporating a centre-axis chirality relay. In both variants the pivotal step is the ring closure of an *N*-acylated 1-substituted *N*-(2-bromobenzyl)-1-phenylmethanamine *via* Pd-mediated intramolecular direct arylation, which proceeds with high atropodiastereoselectivity due to strain effects that can be predicted using molecular mechanics calculations. We are currently exploring the scope of these reactions in various synthetic contexts, and evaluating the potential of the dibenzazepine centre-axis relay as a mechanistic and structural tool.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage or Stuart Scientific SMP10 apparatus and are uncorrected. IR spectra were recorded for neat thin films using Perkin–Elmer FT-IR Spectrum RX1 or BX spectrometers. NMR spectra were recorded on Bruker DPX300 or Avance 400 spectrometers and calibrated internally by reference to signals from the solvent ($CDCl_3$ at 77.16 ppm for ^{13}C spectra; $CHCl_3$ at 7.26 ppm for ^{1}H spectra)[20] or externally (referenced to $CFCl_3$ at 0 ppm for ^{19}F spectra). Coupling constants (*J* values) are given in Hz; multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn) or multiplet (m). NMR spectra were assigned with the aid of COSY, HMBC, HMQC and DEPT spectra where appropriate. Low-resolution mass spectra were recorded on a Micromass Trio 2000 instrument using the electrospray ionisation method; data for most of the peaks of intensity <20% of that of the base peak are omitted. High-resolution (accurate mass) data were recorded using a Thermo Finnigan MAT95XP instrument. HPLC analyses were carried out using a PE Series 200 system with Gemini ODS column (25 cm × 4.6 mm, 5 #x3bc;m) and the following parameters: column temperature ambient; mobile phase A methanol, mobile phase B water, A : B 70 : 30; flow rate 1 mL min^{-1}; injection volume 1 μL, detection at 254 nm. Elemental analyses were carried out by the University of Manchester microanalytical services using Carlo Erba EA1108 equipment. Optical rotations were measured at 589 nm using an AA-100 polarimeter (Optical Activity Ltd.).

Reactions were routinely carried out under nitrogen. Most reagents and solvents were used as supplied commercially, including anhydrous *N*,*N*-dimethylacetamide (DMA; Sigma Aldrich 271012). Anhydrous THF was distilled from sodium/benzophenone ketyl immediately before use.[21] Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. TLC was carried out using Macherey–Nagel Polygram SIL G/UV_{254} plates and the chromatograms were routinely visualised using UV light (254 nm) and alkaline aq. $KMnO_4$. Preparative column (flash) chromatography was carried out on 60H silica gel (Merck 9385) using the flash

technique.[22] Compositions of solvent mixtures are quoted as ratios of volume. 'Ether' refers to diethyl ether. 'Petrol' refers to a fraction of light petroleum, b.p. 60–80 °C, unless indicated otherwise.

(*S*)-*N*-(2-Bromobenzylidene)-1-phenylethanamine 10

To a solution of (–)-1-phenylethylamine (*S*)-**8** (6.45 mL, 6.14 g, 50 mmol) in toluene (50 mL) was added 2-bromobenzaldehyde **9** (5.84 mL, 9.26 g, 50 mmol) followed by *p*-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol). The mixture was heated to 145 °C (bath temperature) under Dean–Stark conditions for 5 h, allowed to cool to room temperature and concentrated under reduced pressure to afford the imine **10** (14.2 g, 98%) as a pale yellow oil. The crude product, which was used directly in the next step, had δ_H (400 MHz, $CDCl_3$) 8.75 (1 H, s, N=CH), 8.12 (1 H, dd, *J* 2.0, 8.0 Hz, ArH), 7.56 (1 H, dd, *J* 1.5, 8.0 Hz, ArH), 7.45 (2 H, d, *J* 7.5 Hz, ArH), 7.38–7.31 (3 H, m, ArH), 7.28–7.26 (2 H, m, ArH), 4.63 (1 H, q, *J* 6.5 Hz, NC*H*CH_3), 1.61 (3 H, d, *J* 6.5 Hz, NCHC*H*$_3$); *m*/*z* (ES^+) 290 (*M*H$^+$, 100%), 288 (*M*H$^+$, 90) (Found: *M*H$^+$ 288.0383; $C_{15}H_{15}BrN$ requires 288.0383); R_f 0.76 (hexane–EtOAc, 3 : 1).

(*S*)-*N*-(2-Bromobenzyl)-1-phenylethanamine 11

A solution of the crude imine (*S*)-**10** (13.9 g, 48 mmol) in EtOH (24 mL) was cooled to 0 °C and $NaBH_4$ (2.01 g, 53 mmol) was added in five equal portions. On completion of the addition the solution was allowed to warm to room temperature and stirred for 18 h. The solution was concentrated under reduced pressure and the residue taken up in ether (100 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and sat. aq. NaCl (50 mL), dried and concentrated under reduced pressure. Chromatography of the residue (hexane–EtOAc, 9 : 1) gave the *title compound* **11** (12.9 g, 92%) as a colourless oil (Found: C, 61.8; H, 5.6; N, 4.8. $C_{15}H_{16}BrN$ requires C, 62.08; H, 5.56; N, 4.83%); $[\alpha]_D^{24}$ –51 ± 4 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 3058, 3020, 2963, 2924, 2863, 2840, 1491, 1465, 1450, 1440, 1121, 1025; δ_H (400 MHz, $CDCl_3$) 7.54 (1 H, dd, *J* 1.0, 8.0 Hz, ArH), 7.41–7.24 (7 H, m, ArH), 7.12 (1 H, td, *J* 1.8, 7.6 Hz, ArH), 3.83 (1 H, q, *J* 6.6 Hz, NHC*H*CH_3), 3.74 (1 H, d, *J* 13.7 Hz, NHC*H*$_A$H$_B$), 3.69 (1 H, d, *J* 13.7 Hz, NHCH$_A$*H*$_B$), 1.82 (1 H, br s, NH) 1.38 (3 H, d, *J* 6.6 Hz, NHCHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 145.4 (C), 139.6 (C), 132.9 (CH), 130.7 (CH), 128.7 (CH), 128.6 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 124.1 (C), 57.5 (CH), 51.8 (CH_2), 24.7 (CH_3); *m*/*z* (ES^+) 292 (*M*H$^+$, 100%), 290 (*M*H$^+$, 92) (Found: *M*H$^+$ 290.0537; $C_{15}H_{17}BrN$ requires 290.0539); R_f 0.55 (hexane–EtOAc, 3 : 1).

(*S*)-*N*-(2-Bromobenzyl)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide 12

A solution of the amine (*S*)-**11** (6.20 g, 21.4 mmol) in pyridine (40 mL) under nitrogen was treated with trifluoroacetic anhydride (3.0 mL, 4.53 g, 21.6 mmol) and the solution was stirred at room temperature for 24 h. The mixture was diluted with water (100 mL) and CH_2Cl_2 (100 mL) and the layers separated. The organic layer was washed with water (3 × 100 mL), dried and concentrated under reduced pressure. Chromatography of the residue (hexane–EtOAc, 9 : 1) gave the *title compound* **12** (7.58 g, 92%) as a yellow crystalline solid, m.p. 52–54 °C (Found: C, 52.8; H, 3.9; N, 3.5. $C_{17}H_{15}BrF_3NO$ requires C, 52.87; H, 3.91; N, 3.63%); $[\alpha]_D^{24}$ –49 ± 2 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 1681, 1448, 1197, 1183, 1133, 1078, 1027, 748, 728, 694, 670; δ_H (400 MHz, $CDCl_3$) (2 : 1 mixture of rotamers a and b) 7.49 (0.33 H, dd, *J* 1.0, 8.0 Hz, ArH, rotamer b), 7.44 (0.66 H, dd, *J* 1.0, 8.0 Hz, ArH, rotamer a), 7.37–7.22 (5.33 H, m, ArH, rotamers a and b), 7.18 (0.66 H, dt, *J* 1.0, 7.5 Hz, ArH, rotamer a), 7.13–7.09 (0.66 H, m, ArH, rotamer a), 7.04 (0.66 H, dt, *J* 1.5, 7.5 Hz, ArH, rotamer a), 6.92 (0.66 H, d, *J* 8.0 Hz, ArH, rotamer a), 5.73 (0.33 H, q, *J* 7.1 Hz, NC*H*CH_3, rotamer b), 5.48 (0.66 H, q, *J* 6.9 Hz, NC*H*CH_3, rotamer a), 4.67 (0.66 H, d, *J* 16.5 Hz, NC*H*$_A$H$_B$, rotamer a), 4.62 (0.33 H, d, *J* 18.2 Hz, NC*H*$_A$H$_B$, rotamer b), 4.53 (0.33 H, d, *J* 18.2 Hz, NCH$_A$*H*$_B$, rotamer b), 4.28 (0.66 H, d, *J* 16.5 Hz, NCH$_A$*H*$_B$, rotamer a), 1.59 (2 H, d, *J* 6.9 Hz, NCHC*H*$_3$, rotamer a), 1.51 (1 H, d, *J* 7.1 Hz, NCHC*H*$_3$, rotamer b); δ_C (100 MHz, $CDCl_3$) (2 : 1 mixture of rotamers) 158.2 (C, q, *J* 35.5 Hz, rotamer b), 157.5 (C, q, *J* 35.5 Hz, rotamer a), 138.6 (C, rotamer a), 137.7 (C, rotamer b), 135.6 (C, rotamer a), 135.1 (C, rotamer b), 132.7 (CH, rotamer b), 132.6 (CH, rotamer a), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.45 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 127.29 (CH), 122.2 (C), 121.9 (C), 117.0 (C, q, *J* 288 Hz, rotamer a), 116.5 (C, q, *J* 289 Hz, rotamer b), 56.0 (CH, q, *J* 3 Hz, rotamer a), 55.9 (CH, rotamer b), 48.2 (CH_2, q, *J* 3 Hz, rotamer b), 46.8 (CH_2, rotamer a), 18.0 (CH_3, rotamer a), 17.2 (CH_3, rotamer b); δ_F (376.5 MHz, $CDCl_3$) (2 : 1 mixture of rotamers) –67.5 (2 F, s, rotamer a), –68.8 (1 F, s, rotamer b); *m*/*z* (ES^+) 410 (*M*Na$^+$, 43%), 408 (*M*Na$^+$, 45) (Found: *M*Na$^+$ 408.0181; $C_{17}H_{15}BrF_3NONa$ requires 408.0182); R_f 0.74 (hexane–EtOAc, 3 : 1); HPLC t_R 40.0 min.

1-[(a*S*,5*S*)-5,7-Dihydro-5-methyl-6*H*-dibenz[*c*,*e*]azepin-6-yl]-2,2,2-trifluoroethanone (–)-14

To a solution of (*S*)-**12** (1.43 g, 3.7 mmol) in DMA (25 mL) under nitrogen was added anhydrous K_2CO_3 (1.03 g, 7.4 mmol) followed by $Pd(OAc)_2$ (83 mg, 0.37 mmol) and *DavePhos* **13** (146 mg, 0.37 mmol), and the mixture was heated to 145 °C (bath temperature) for 24 h. The mixture was allowed to cool to room temperature, diluted with ether (25 mL) and sat. aq. NaCl (65 mL) and the layers separated. The organic layer was washed with sat. aq. NaCl (5 × 65 mL), dried and concentrated under reduced pressure. The residual brown oil was chromatogaphed over silica gel (hexane–EtOAc, 19 : 1), affording the *title compound* **14** (679 mg, 60%) as an off-white solid, m.p. 114–116 °C; $[\alpha]_D^{25}$ –301 ± 10 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3011, 1711, 1679, 1443, 1188, 1159; δ_H (400 MHz, $CDCl_3$) (9 : 1 mixture of rotamers) 7.61–7.50 (4 H, m, ArH, rotamers a and b), 7.46–7.28 (4 H, m, ArH, rotamers a and b), 5.44 (0.9 H, q, *J* 7.0 Hz, 5-H, rotamer a), 5.26 (0.1 H, d, *J* 14.0 Hz, 7-H$_{eq}$, rotamer b), 5.16 (0.1 H, br q, *J* 7.0 Hz, 5-H, rotamer b), 4.76 (0.9 H, dd, *J* 1.0, 14.0 Hz, 7-H$_{eq}$, rotamer a), 4.12 (0.9 H, d, *J* 14.0 Hz, 7-H$_{ax}$, rotamer a), 3.83 (0.1 H, d, *J* 14.0 Hz, 7-H$_{ax}$, rotamer b), 0.97 (0.3 H, d, *J* 7.0 Hz, 5-Me, rotamer b), 0.92 (2.7 H, d, *J* 7.0 Hz, 5-Me, rotamer a); δ_C (100 MHz, $CDCl_3$) (9 : 1 mixture of rotamers, quoted signals for rotamer a only) 154.2 (C, q, *J* 35.5 Hz), 140.9 (C), 138.9 (C), 137.3 (C), 132.4 (C), 130.6 (CH), 129.8 (CH), 129.6 (CH), 129.1 (CH), 128.8 (CH), 128.68 (CH), 128.67 (CH), 127.8 (CH), 116.8 (C, q, *J* 287.5 Hz), 58.5 (CH), 48.1 (CH_2, q, *J* 3.5 Hz), 19.9 (CH_3); *m*/*z* (ES^+) 328

(MNa$^+$, 100%) (Found: MNa$^+$ 328.0920; $C_{17}H_{14}F_3NONa$ requires 328.0920); R_f 0.72 (hexane–EtOAc, 3 : 1); HPLC t_R 29.0 min.

Variation of conditions for Pd-catalysed ring closure

Five experiments were run using the procedure described for the preparation of **14** (above), using the amide **12** (1 mol equiv.) and K_2CO_3 (2 mol equiv.) and one of five different catalytic conditions (Table 1). Each solution was heated for 24 h at 145 °C, allowed to cool, diluted with ether (5 mL) and quenched with sat. aq. NaCl (15 mL). The ether layer was washed with sat. aq. NaCl (5 × 15 mL), dried, filtered and evaporated under reduced pressure. The residue was then diluted with MeOH (*ca.* 5 mL) and analysed by HPLC.

Table 1 Effect of variation in Pd : ligand ratio on the formation of by-product **15**

Entry	$Pd(OAc)_2$ mol%	phosphine **13** mol%	relative yield of **15**[a]
1	10	40	8.00
2	10	20	1.73
3	10	10	1.76
4	5	10	1.91
5	5	5	1.00

[a] based on raw UV detector integrals.

(a*R*,5*S*)-6,7-Dihydro-5-methyl-5*H*-dibenz[*c*,*e*]azepine (+)-2

A solution of the amide **14** (679 mg, 2.22 mmol) in MeOH (40 mL) under argon was treated with K_2CO_3 (1.34 g, 9.70 mmol) followed by water (100 mL), and the mixture was stirred at 60 °C for 24 h. After cooling to room temperature, the mixture was diluted with water (200 mL) and CH_2Cl_2 (200 mL). The layers were then separated, the aqueous layer was extracted with more CH_2Cl_2 (3 × 100 mL) and the combined organic phase was dried and evaporated. The residual yellow oil was purified by chromatography over silica gel (CH_2Cl_2–MeOH, 9 : 1), giving the amine **2** (450 mg, 97%) as a colourless oil, $[\alpha]_D^{22}$ +27.0 (*c* 0.8, $CHCl_3$) {lit.[1] for (5*R*)-**2** $[\alpha]_D^{25}$ −23.5 ± 1 (*c* 0.65, $CHCl_3$)}; ν_{max}/cm^{-1} ($CHCl_3$) 3068, 3009, 2965, 2926, 1481, 1451, 1379, 1112; δ_H (400 MHz, $CDCl_3$) 7.50–7.34 (8 H, m, ArH), 3.75 (1 H, d, *J* 12.5 Hz, 7-H), 3.73 (1 H, q, *J* 6.5 Hz, 5-H), 3.51 (1 H, d, *J* 12.5 Hz, 7-H), 2.23 (1 H, br s, NH), 1.49 (3 H, d, *J* 6.5 Hz, 5-Me); δ_C (100 MHz, $CDCl_3$) 141.33 (C), 141.29 (C), 139.3 (C), 137.0 (C), 128.5 (CH), 128.25 (CH), 128.2 (CH), 128.1 (CH), 128.08 (CH), 127.8 (CH), 127.6 (CH), 125.0 (CH), 50.3 (CH), 49.5 (CH_2), 19.0 (CH_3); *m*/*z* (ES$^+$) 210 (MH$^+$, 100%) (Found: MH$^+$ 210.1277; $C_{15}H_{16}N$ requires 210.1278); R_f 0.01 (hexane–EtOAc, 3 : 1), 0.73 (EtOAc–MeOH/Et_3N, 80 : 20 : 1), 0.27 (CH_2Cl_2–MeOH, 9 : 1). The sample of (+)-**2** was identical (TLC, ^{1}H- and ^{13}C-NMR) to an authentic sample of (−)-**2** obtained as described.[1]

(*S*)-*N*-(2-Bromobenzyl)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide 15

To a solution of 1-phenylethylamine (±)-**8** (0.15 mL, 143 mg, 1.2 mmol) in toluene (15 mL) was added benzaldehyde (0.12 mL, 125 mg, 1.2 mmol) followed by *p*-toluenesulfonic acid monohydrate (20 mg, 0.11 mmol) and powdered 4 Å molecular sieves (2 g). The mixture was heated to 145 °C (bath temperature) for 5 h, allowed to cool to room temperature and filtered through Celite. Concentration of the filtrate under reduced pressure gave the imine (±)-*N*-benzylidene-1-phenylethanamine **A** as a pale yellow oil, δ_H (300 MHz, $CDCl_3$) 8.38 (1 H, s, N=CH), 7.81–7.76 (2 H, m, ArH), 7.46–7.25 (8 H, m, ArH), 4.55 (1 H, q, *J* 6.5 Hz, C*H*CH_3), 1.60 (3 H, d, *J* 6.5 Hz, Me) {lit.[23] δ_H (500 MHz, $CDCl_3$) 8.38 (1 H, s), 4.56 (1 H, q, *J* 6.6 Hz), 1.60 (3 H, d, *J* 6.7 Hz)}; R_f 0.73 (hexane–EtOAc, 3 : 1). A solution of the crude **A** in EtOH (5 mL) was treated with $NaBH_4$ (62 mg, 1.6 mmol) and stirred at room temperature for 18 h. The solution was concentrated and the residue taken up in ether (20 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (3 × 15 mL), dried and concentrated. Chromatography of the residue (hexane–EtOAc, 9 : 1) gave the amine (±)-*N*-benzyl-1-phenylethanamine **B** (164 mg, 66%) as a colourless oil, ν_{max}/cm^{-1} (film) 3083, 3060, 3024, 2962, 2923, 1492, 1452, 1369, 1126, 1028, 761, 735, 699; δ_H (400 MHz, $CDCl_3$) 7.38–7.22 (10 H, m, Ar*H*), 3.82 (1 H, q, *J* 6.6 Hz, NHC*H*CH_3), 3.66 (1 H, d, *J* 13.1 Hz, NHC$H_A$$H_B$), 3.60 (1 H, d, *J* 13.1 Hz, NHC$H_A$$H_B$), 1.59 (1 H, br s, NH) 1.37 (3 H, d, *J* 6.6 Hz, NHCHCH_3); δ_C (100 MHz, $CDCl_3$) 145.7 (C), 140.8 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 57.6 (CH), 51.8 (CH_2), 24.7 (CH_3); *m*/*z* (ES$^+$) 212 (MH$^+$, 100%); R_f 0.29 (hexane–EtOAc, 3 : 1). The above ^{1}H- and ^{13}C-NMR spectra of **B** are in accord with published data.[24] A solution of the amine (±)-**B** (164 mg, 0.78 mmol) in pyridine (1 mL) under nitrogen was treated with trifluoroacetic anhydride (0.12 mL, 181 mg, 0.86 mmol) and the solution was stirred at room temperature for 24 h. The mixture was diluted with water (10 mL) and CH_2Cl_2 (15 mL) and the layers separated. The organic layer was washed with water (3 × 15 mL), dried and concentrated under reduced pressure. Chromatography of the residue (hexane–EtOAc, 9 : 1) gave the *title compound* **15** (153 mg, 64%) as a colourless oil, ν_{max}/cm^{-1} ($CHCl_3$) 1688, 1496, 1451, 1202, 1140, 753, 697; δ_H (400 MHz, $CDCl_3$) (2 : 1 mixture of rotamers) 7.3–6.9 (10 H, m, ArH), 5.49 (0.33 H, q, *J* 7.2 Hz, NC*H*CH_3, rotamer b), 5.34 (0.66 H, q, *J* 6.9 Hz, NC*H*CH_3, rotamer a), 4.57 (0.66 H, d, *J* 15.3 Hz, NC$H_A$$H_B$, rotamer a), 4.55 (0.33 H, d, *J* 17.0 Hz, NC$H_A$$H_B$, rotamer b), 4.22 (0.33 H, d, *J* 17.0 Hz, NCH$_A$$H_B$, rotamer b), 3.93 (0.66 H, d, *J* 15.3 Hz, NCH$_A$$H_B$, rotamer a), 1.47 (2 H, d, *J* 6.9 Hz, NCHCH_3, rotamer a), 1.33 (1 H, d, *J* 7.2 Hz, NCHCH_3, rotamer b); δ_C (100 MHz, $CDCl_3$) (2 : 1 mixture of rotamers) 158.2 (C, q, *J* 35.5 Hz, rotamer b), 157.7 (C, q, *J* 35.5 Hz, rotamer a), 138.7 (C, rotamer b), 138.0 (C, rotamer a), 136.9 (C, rotamer a), 136.3 (C, rotamer b), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.45 (CH), 128.2 (CH), 127.9 (CH), 127.85 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (C), 117.1 (C, q, *J* 288 Hz, rotamer a), 116.7 (C, q, *J* 289 Hz, rotamer b), 56.1 (CH, rotamer b), 55.9 (CH, q, *J* 3 Hz, rotamer a), 48.8 (CH_2, q, *J* 3 Hz, rotamer b), 47.0 (CH_2, rotamer a), 18.3 (CH_3, rotamer a), 17.2 (CH_3, rotamer b); δ_F (376.5 MHz, $CDCl_3$) (2 : 1 mixture of rotamers) −67.5 (2 F, s, rotamer a), −68.0 (1 F, s, rotamer b); *m*/*z* (ES$^+$) 330 (MNa$^+$, 100%), 308 (MH$^+$, 11) (Found: MNa$^+$ 308.1250; $C_{17}H_{17}F_3NO$ requires 308.1257); R_f 0.65 (hexane–EtOAc, 3 : 1); HPLC t_R 25.5 min.

(*S*)-*t*-Butyl *N*-(1-phenylethyl)carbamate 16

A solution of the amine (*S*)-**8** (4.848 g, 40 mmol) in EtOH (20 mL) was vigorously stirred and cooled in ice-water during

the addition a solution of di-*t*-butyl dicarbonate (9.60 g, 44 mmol) in EtOH (40 mL).[25] Effervescence and warming occurred almost immediately. After the addition the cooling bath was removed and stirring was continued at room temperature for 0.5 h. The mixture was then evaporated *in vacuo* and the residual white solid crystallised from ether (30 mL), giving the known carbamate **16** (5.66 g, 64%) as colourless rhombs, m.p. 88–89 °C (lit.[25] 87–88 °C). Evaporation of the mother liquors and recrystallisation of the residue from ether (12 mL) gave a second crop of **16** (1.74 g, 20%) (total 7.40 g, 84%); ν_{max}/cm^{-1} (film) 3380, 1685; δ_H (400 MHz, $CDCl_3$) 7.36–7.21 (5 H, m, ArH), 4.79 (2 H, br s, MeC*H* and NH), 1.49–1.35 (12 H, br s, Me and CMe_3); δ_C (100 MHz, $CDCl_3$) 155.2 (C), 155.1 (C), 128.7 (CH), 127.2 (CH), 126.0 (CH), 79.6 (C), 50.3 (CH), 28.5 (CH_3), 22.8 (CH_3); *m*/*z* (ES$^+$) 244 (*M*Na$^+$, 100%); R_f 0.49 (hexane–EtOAc, 4 : 1).

(*S*)-*t*-Butyl *N*-(1-phenylethyl)-*N*-[(2-bromophenyl)methyl]carbamate 18

In a 100 mL two-necked flask fitted with a stirrer bar, nitrogen inlet and septum cap, a portion of NaH (60% dispersion in mineral oil, 500 mg, 12.5 mmol) was freed from oil by decantation with hexane (5 mL) and covered with dry DMF (10 mL).[16] With stirring and cooling to 5–10 °C, a solution of the carbamate **16** (2.66 g, 12.0 mmol) in dry DMF (20 mL) was quickly added. The mixture was stirred for 5 min at 5–10 °C followed by 30 min at room temperature, and then treated with a solution of 2-bromobenzyl bromide **17** (3.21 g, 12.8 mmol) in dry DMF (4 mL). A beige solution slowly formed and stirring was continued at room temperature for 20 h. The solution was then evaporated *in vacuo* and the residual oil partitioned between EtOAc (40 mL) and water (40 mL). The layers were separated, the aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phase was washed with sat. aq. NaCl (25 mL), dried and evaporated. The residual oil (4.62 g) was dissolved in hot hexane (20 mL). On cooling, the solution provided a portion of unreacted **16** (250 mg, 5%) as colourless crystals, m.p. 87–89 °C. Evaporation of the mother liquors gave an oil which was purified by flash chromatography (h 10 cm, d 4.5 cm; hexane/CH_2Cl_2, 1 : 2), giving the *title compound* **18** (2.72 g, 58%) as a colourless oil; $[\alpha]_D^{24}$ −50.5 ± 1.5 (*c* 1.28, $CHCl_3$); ν_{max}/cm^{-1} (film) 2973, 1685, 1439, 1395, 1363, 1325, 1274, 1251, 1212, 1160, 1133, 1043, 1024, 992, 861, 745, 697; δ_H (400 MHz, $CDCl_3$) 7.46 (1 H, dd, *J* 1, 8 Hz, ArH), 7.38–7.29 (4 H, m, ArH), 7.27–7.14 (3 H, m, ArH), 7.05 (1 H, dt, *J* 2, 8 Hz, ArH), 5.71 (0.6 H, br s, C*H*Me, rotamer a), 5.30 (0.4 H, br s, C*H*Me, rotamer b), 4.69–4.07 (2 H, br m, CH_2), 1.46 (3 H, d, *J* 7 Hz, Me), 1.38 (9 H, s, CMe_3); δ_C (400 MHz, $CDCl_3$) 156.1 (C), 141.8 (C), 138.6 (C), 132.4 (CH), 128.5 (2 × CH), 128.0 (CH), 127.3 (CH), 127.2 (2 × CH), 122.2 (C), 80.3 (C), 53.5 (CH), 47.2 (CH_2), 28.4 (CH_3), 17.7 (CH_3); *m*/*z* (ES$^+$) 414 (*M*Na$^+$, 100%), 412 (*M*Na$^+$, 92) (Found: *M*Na$^+$ 412.0894; $C_{20}H_{24}BrNNaO_2$ requires 412.0883); R_f 0.40 (hexane–EtOAc, 12 : 1), 0.25 (hexane–CH_2Cl_2, 1 : 2), 0.75 (CH_2Cl_2).

(a*S*,5*S*)-*t*-Butyl 5-phenyl-5*H*-dibenz[*c*,*e*]azepine-6(7*H*)-carboxylate (−)-4

A 100 mL round-bottomed flask was charged with (−)-**18** (814 mg, 2.09 mmol), anhydrous K_2CO_3 (432 mg, 3.13 mmol), tricyclohexylphosphonium tetrafluoroborate (77 mg, 0.21 mmol), pivalic acid (64 mg, 0.63 mmol) and $Pd(OAc)_2$ (24 mg, 0.107 mmol) and a stirrer bar. The flask was purged with nitrogen for 20 min, DMA (20 mL) was added, and the stirred mixture was heated to 130 °C (bath temperature). After 72 h at 130 °C the DMA was evaporated *in vacuo* and the black residue was digested with CH_2Cl_2 (30 mL) and filtered. The filtrate was concentrated and the residual oil purified by chromatography (h 5 cm, d 4.5 cm; CH_2Cl_2), giving the *title compound* **4** (321 mg, 50%) as a colourless oil; $[\alpha]_D^{24}$ −322 ± 9 (*c* 0.61, $CHCl_3$) {lit.[1] for 5*R*-**4** $[\alpha]_D^{25}$ +321 ± 10 (*c* 0.82, $CHCl_3$)}; ν_{max}/cm^{-1} (film) 2972, 1681, 1397, 1361, 1156, 1117, 1038, 868, 761, 752, 736; δ_H (400 MHz, $CDCl_3$) 7.55–7.33 (8 H, m, ArH), 5.12[a] (1 H, br s, 5-H), *ca.* 5.0[a] (1 H, br s, 7-H), 3.73 (2 H, br d, *J* 11.9 Hz, 7-H), 1.55 (9 H, s, CMe_3), 0.88 (3 H, d, *J* 6.9 Hz, Me); δ_C (100 MHz, $CDCl_3$) 153.7 (C), 141.0 (C), 139.2 (2 × C), 135.3 (C), 130.2 (CH), 129.7 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 128.2 (2 × CH), 127.6 (CH), 79.8 (C), 57.7 (CH), 47.3 and 46.6 (both br, 7-CH_2, rotamers), 28.7 (CH_3), 21.5 (br, CH_3); R_f 0.50 (CH_2Cl_2).

[a] Broad overlapping signals.

(a*R*,5*S*)-6,7-Dihydro-5-methyl-5*H*-dibenz[*c*,*e*]azepine (+)-2

To a solution of (−)-**4** (309 mg, 1.0 mmol) in THF (3 mL) was added 85% aq. phosphoric acid[17] (2.0 mL, 29 mmol) at room temperature. The mixture was vigorously stirred at room temperature for 72 h, then diluted with water (10 mL), cooled to 0 °C and basified to pH 11 by the dropwise addition of 10 M aq. KOH (≥ 9 mL). After warming to room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was washed with brine (15 mL), dried and concentrated under reduced pressure to give the *title compound* (+)-**2** (181 mg, 87%) as a colourless oil; $[\alpha]_D^{24}$ +30.3 ± 1.4 (*c* 1.05, $CHCl_3$). The material was identical (TLC, ^{1}H- and ^{13}C-NMR) to that obtained from (−)-**14** as described above.

t-Butyl *N*-(diphenylmethyl)carbamate 19

A solution of diphenylmethylamine (7.34 g, 40 mmol) in EtOH (20 mL)[25] was vigorously stirred and cooled in ice-water during the addition a solution of di-*t*-butyl dicarbonate (9.60 g, 44 mmol) in EtOH (40 mL). A white precipitate formed almost immediately, accompanied by effervescence and warming. After the addition the cooling bath was removed and stirring was continued at room temperature for 0.5 h. The mixture was then heated to dissolve the precipitate and left to cool. The resulting crystalline mass was collected on a Buchner funnel, rinsed with a small amount of ice-cold EtOH and dried, first by suction and then *in vacuo*, giving the carbamate **19** (8.11 g, 72%) as colourless needles, m.p. 122–124 °C (lit.[26] 120.5–121.5 °C). Evaporation of the mother liquors and recrystallisation of the residue from EtOH (15 mL) gave a second crop of **19** (2.17 g, 19%) (total 10.28 g, 91%); ν_{max}/cm^{-1} (film) 3370, 1686; δ_H (400 MHz, $CDCl_3$) 7.35–7.30 (4 H, m, ArH), 7.28–7.23 (6 H, m, ArH), 5.92 (1 H, br s, CH), 5.17 (1 H, br s, NH), 1.45 (9 H, br s, CMe_3) (in accord with published data[26]); δ_C (100 MHz, $CDCl_3$) 155.2 (C), 142.2 (C), 128.7 (CH), 127.5 (CH), 127.4 (CH), 80.0 (C), 58.6 (CH), 28.5 (CH_3); *m*/*z* (ES$^+$) 306 (*M*Na$^+$, 100%); R_f 0.45 (hexane–EtOAc, 4 : 1), 0.24 (hexane–CH_2Cl_2, 1 : 2).

t-Butyl *N*-(diphenylmethyl)-*N*-[(2-bromophenyl)methyl]carbamate 20

In a 100 mL two-necked flask fitted with a stirrer bar, nitrogen inlet and septum cap, a portion of NaH (60% dispersion in mineral oil, 515 mg, 12.9 mmol) was freed from oil by decantation with hexane (5 mL) and covered with dry DMF (10 mL).[16] With stirring and cooling to 5–10 °C, a solution of the carbamate **19** (3.40 g, 12.0 mmol) in dry DMF (20 mL) was quickly added. The mixture was stirred for 5 min at 5–10 °C followed by 30 min at room temperature, and then treated with a solution of 2-bromobenzyl bromide **17** (3.08 g, 12.3 mmol) in dry DMF (4 mL). A pale yellow solution slowly formed and stirring was continued at room temperature for 20 h. The solution was then evaporated *in vacuo* and the residual oil partitioned between EtOAc (40 mL) and water (40 mL). The layers were separated, the aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phase was washed with sat. aq. NaCl (25 mL), dried and evaporated. The residual oil (5.62 g) was dissolved in hot EtOAc (5 mL) and the solution diluted with hot hexane (15 mL). On cooling, the solution provided a portion of unreacted **19** (460 mg, 12%) as colourless needles, m.p. 121–123 °C. Evaporation of the mother liquors gave a pale yellow oil which was purified by flash chromatography (h 10 cm, d 4.5 cm; hexane/CH_2Cl_2, 1 : 2), giving the *title compound* **20** (4.32 g, 80%) as a colourless viscous oil; ν_{max}/cm^{-1} (film) 2973, 1690, 1439, 1390, 1364, 1272, 1250, 1155, 1103, 1024, 892, 745, 696; δ_H (400 MHz, $CDCl_3$) 7.31 (1 H, dd, *J* 1, 8 Hz, ArH), 7.28–7.17 (10 H, m, ArH), 7.04 (1 H, br t, *J* 7 Hz, ArH), 6.92 (1 H, dd, *J* 1.5, 8 Hz, ArH), 6.87 (1 H, br s, ArH), 6.66 (1 H, br s, $CHPh_2$), 4.57 (2 H, s, CH_2), 1.35 (9 H, s, CMe_3); δ_C (400 MHz, $CDCl_3$) 156.2 (C), 139.8 (C), 137.5 (C), 132.0 (CH), 128.9 (CH), 128.4 (CH), 128.1 (CH), 127.7 (CH), 127.4 (CH), 126.7 (CH), 122.0 (C), 80.6 (C), 64.0 (CH), 49.0 (CH_2), 28.3 (CH_3); *m*/*z* (ES$^+$) 476 (*M*Na$^+$, 100%), 474 (*M* H$^+$, 95) (Found: *M*Na$^+$ 474.1054; $C_{25}H_{26}BrNNaO_2$ requires 474.1040); R_f 0.40 (hexane–EtOAc, 12 : 1), 0.35 (hexane–CH_2Cl_2, 1 : 2).

t-Butyl 5-phenyl-5*H*-dibenz[*c*,*e*]azepine-6(7*H*)-carboxylate 21

A 100 mL round-bottomed flask was charged with **20** (1.415 g, 3.13 mmol), anhydrous K_2CO_3 (648 mg, 4.69 mmol), tricyclohexylphosphonium tetrafluoroborate (115 mg, 0.31 mmol), pivalic acid (96 mg, 0.94 mmol) and $Pd(OAc)_2$ (35 mg, 0.155 mmol) and a stirrer bar. The flask was purged with nitrogen for 20 min, DMA (30 mL) was added, and the stirred mixture was heated to 130 °C (bath temperature). The reaction mixture became yellow–orange as the bath temperature approached 130 °C. After 72 h at 130 °C the DMA was evaporated *in vacuo* and the black residue was digested with CH_2Cl_2 (40 mL) and filtered. The filtrate was concentrated and the residual oil purified by chromatography (h 6 cm, d 4.5 cm; CH_2Cl_2), which gave the *title compound* **21** (833 mg, 72%) as a pale yellow solid after trituration with ether/hexane (1 : 1). Crystallisation from ethanol gave the analytical sample as colourless cubes, m.p. 169–171 °C (Found: C, 80.95; H, 6.84; N, 3.78. $C_{25}H_{25}NO_2$ requires C, 80.83; H, 6.78; N, 3.77%); ν_{max}/cm^{-1} (film) 2973, 1684, 1397, 1361, 1168, 1157, 1129, 1117, 903, 870, 745, 735, 697, 637, 599; δ_H (400 MHz, $CDCl_3$) (mixture of rotamers a and b, ratio = *ca.* 3 : 2) 7.58 (1 H, br s, ArH), 7.51–7.30 (4 H, m, ArH), 7.21 (1 H, t, *J* 7.3 Hz, ArH), 7.14 (1 H, t, *J* 7.3 Hz, ArH), 7.05 (1 H, dd, *J* 1.0, 7.5 Hz, ArH), 6.89–6.83 (3 H, m, ArH), 6.54–6.59 (2 H, m, ArH), 6.44 (0.4 H, br s, 5-H, rotamer b), 6.24 (0.6 H, br s, 5-H, rotamer a), 5.21 (0.6 H, br s, 7-H, rotamer a), 5.04 (0.4 H, br s, 7-H, rotamer b), 3.91 (0.6 H, br s, 7-H, rotamer a), 3.89 (0.4 H, br s, 7-H, rotamer b), 1.58 (3.5 H, br s, CMe_3, rotamer b), 1.38 (5.5 H, br s, CMe_3, rotamer a); δ_C (100 MHz, $CDCl_3$) (major and minor rotamers, pairings tentative) 154.5 (C), 142.5 (br, C, major), 141.8 (br, C, minor), 140.8 (br, C), 140.0 (C), 138.3 (C), 134.7 (br, C, major), 134.5 (br, C, minor), 131.1 (br, CH), 129.9 (br, CH), 129.3 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 125.5 (CH), 125.4 (CH), 80.3 (C), 64.5 (br, CH, major), 62.9 (br, CH, minor), 48.0 (br, CH_2, minor), 47.0 (br, CH_2, major), 28.5 (CH_3); *m*/*z* (ES$^+$) 394 (*M*Na$^+$, 100%); R_f 0.27 (hexane–CH_2Cl_2, 1 : 2).

6,7-Dihydro-5-phenyl-5*H*-dibenz[*c*,*e*]azepine 22

To a solution of (±)-**21** (371.5 mg, 1.0 mmol) in THF (3 mL) was added 85% aq. phosphoric acid[17] (2.0 mL, 29 mmol) at room temperature. The mixture was vigorously stirred at room temperature for 72 h, then diluted with water (10 mL), cooled to 0 °C and basified to pH 11 by the dropwise addition of 10 M aq. KOH (≥ 9 mL). After warming to room temperature, the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extract was washed with brine (20 mL), dried and concentrated under reduced pressure to give the *title compound* (±)-**22** (261 mg, 96%) as a cream solid which formed white needles, m.p. 117–118 °C (EtOH) (Found: C, 88.47; H, 6.39; N, 5.13. $C_{20}H_{17}N$ requires C, 88.52; H, 6.31; N, 5.16%); ν_{max}/cm^{-1} (film) 3313w, 3055, 1492, 1476, 1442, 1291, 1265, 1216, 1190, 1103, 1071, 1029, 1006, 926, 877, 846, 749, 711, 697, 633; δ_H (400 MHz, $CDCl_3$) 7.59 (1 H, dd, *J* 1.5, 7.5 Hz, ArH), 7.53–7.28 (10 H, m, ArH), 7.25 (1 H, dt, *J* 1.5, 7.5 Hz, ArH), 6.83–6.80 (1 H, m, ArH), 4.87 (1 H, s, 5-H), 3.89 (1 H, d, *J* 13.6, 7-H), 3.66 (1 H, d, *J* 13.6, 7-H), 2.43 (1 H, br s, NH); δ_C (100 MHz, $CDCl_3$) 141.9 (C), 141.1 (C), 141.0 (C), 139.5 (C), 137.4 (C), 128.6 (CH), 128.4 (CH), 128.30 (CH), 128.28 (CH), 128.1 (CH), 128.01 (CH), 127.96 (CH), 127.85 (CH), 127.82 (CH), 127.6 (CH), 127.4 (CH), 60.2 (CH), 49.7 (CH_2); *m*/*z* (ES$^+$) 272 (*M*H$^+$, 100%); R_f 0.01 (hexane–EtOAc, 3 : 1), 0.73 (EtOAc–MeOH/Et_3N, 80 : 20 : 1).

Crystal data and structure refinement

***t*-Butyl 5-phenyl-5*H*-dibenz[*c*,*e*]azepine-6(7*H*)-carboxylate 21.** CCDC deposition number 793197; Empirical formula $C_{25}H_{25}NO_2$; Formula weight 371.46; Temperature 100(2) K; Radiation wavelength 0.71073 Å; Crystal system monoclinic, space group $P2_1/c$; Unit cell dimensions a = 9.4053(3) Å; α = 90°; b = 9.7021(4) Å; β = 92.978(2)°; c = 21.9587(10) A° ; γ = 90°; Cell volume 2001.05(14) Å^3; Z 4; Calculated density 1.233 Mg m^{-3}; Absorption coefficient 0.077 mm^{-1}; F(000) 792; Crystal size 0.10 × 0.15 × 0.25 mm^3; Data collection method Enraf Nonius FR 590 CCD diffractometer; Theta range for data collection 3.02 to 25.50°; Index ranges 0 ⩽ h ⩽ 11, 0 ⩽ k ⩽11, –26 ⩽ l ⩽ 26; Reflections collected 14457; Independent reflections 3710 [R(int) = 0.096]; Completeness to theta = 25.50° 99.7%; Refinement method Full-matrix least-squares on F^2; Data/restraints/parameters 3710/0/354; Goodness-of-fit on F^2 1.056; Final R indices [$I > 2\sigma(I)$] R_1 = 0.0861, wR_2 = 0.1660; R indices (all data) R_1 = 0.1888,

wR_2 = 0.2154; Extinction coefficient 0.0046(12); Largest diff. peak and hole 0.411 and −0.405 e.Å^{-3}.

Molecular mechanics calculations (Fig. 3)

Minimised steric energy (MSE) structures for the 5*S* stereoisomers of compounds **4**, **14**, **21** and **22** were calculated on a Mac Mini 2.6 GHz Intel Core 2 Duo running Linux (Fedora Core 12, x86 64-bit), using *MacroModel* v. 8.0 (*Maestro* v. 9.0.211 interface) with the MM3 force field and Monte Carlo conformational search (*csearch*) method (1000 iterations). The *csearch* parameters were: no solvent; PRCG method; convergence on gradient; max. number of iterations 3000; convergence threshold 0.0200. For structure graphics see ESI.†

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