Synthesis of Substituted 10,11-Dihydro-5*H*-dibenz[*b,f*]azepines; Key Synthons in Syntheses of Pharmaceutically Active Compounds

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Substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepines are key synthons in the syntheses of a number of pharmaceutically active compounds such as imipramine, chlorimipramine, and desimipramine analogues. A facile synthesis of substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepines is described, starting out from commercially available 2-bromotoluenes or 2-nitrotoluenes. Initial α-bromination with *N*-bromosuccinimide and subsequent reaction with triethylphosphite afforded the corresponding benzyl phosphonic ester derivatives. After reaction with benzaldehyde derivatives, the expected Horner- Emmons reaction products were obtained. Hydrogenation gave the amino derivatives which were transformed into the corresponding formamides. Under Goldberg conditions [1], the final ring closing step was performed to give the substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepines in 46-75% yield.

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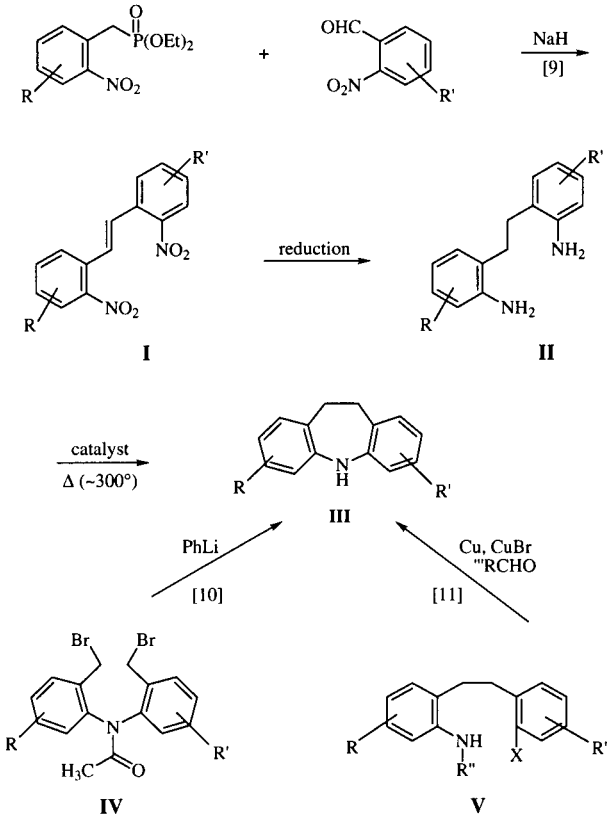
Introduction.

10,11-Dihydro-5*H*-dibenz[*b,f*]azepine derivatives have been used successfully in a number of biologically active compounds and drugs; *e.g.* the antidepressants imipramine, chlorimipramine, desimipramine are among the most commonly known. But in general 10,11-dihydro-5*H*-dibenz[*b,f*]azepine derivatives have been variously reported as having as well antiallergic activity, specifically antihistaminic activity, as also spasmolytic, serotonin antagonistic, antiemetic, antiepileptic, antiinflammatory, sedative and even fungal action [2].

The parent 10,11-dihydro-5*H*-dibenz[*b,f*]azepine was first synthesised in 1899 by Thiele and Holzinger [3] and since then many substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepines have been prepared [4]. The derivatives have been made either directly by substitution reactions on the parent unsubstituted tricycle or they have been made by ring synthesis starting out from substituted synthons. Most direct substitution reactions, *e.g.* nitration [5], formylation [6], bromination [7] and Friedel-Crafts acylations [8] are possible, but they do in general proceed in low yields and do either give mixtures of regioisomers or are limited to only one accessible position on the ring system. Ring synthesis of 10,11-dihydro-5*H*-dibenz[*b,f*]azepines has been approached in a few different ways (Scheme 1). Kitamura and coworkers [9] have described one approach in which a substituted 2-nitrobenzaldehyde was allowed to react with substituted 2-nitrobenzylphosphonic acid esters to give dinitrosystems, **I**, which were subsequently reduced to afford the diamino-derivatives, **II**. Ring closure and formation of the substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepine derivatives, **III** were performed by heating to around 300° in the presence of a number of different catalysts. Alternatively, Bergman and coworkers [10] have reported the successful intramolecular coupling of *N*-acetyl-2,2'-di(bromomethyl)diphenylamine,

Scheme 1



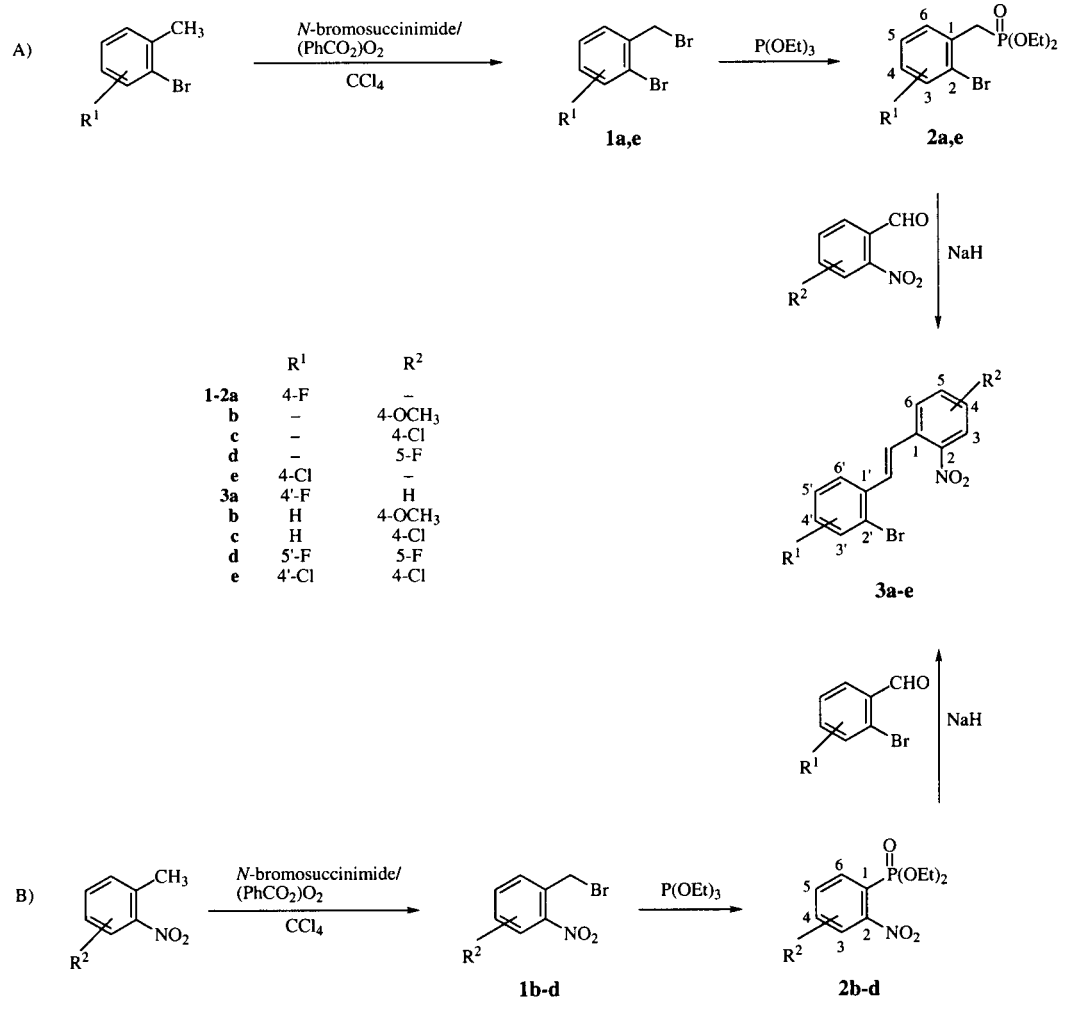
IV using phenyllithium. As both methods require relatively harsh conditions, they are however only useful for a limited set of substituents. Finally, Gailliot and Roberts have suggested the possibility of ring closing *N*-substituted *o*-amino-*o'*-chlorodibenzyls, **V** under Goldberg conditions using copper powder as a catalyst [11]. The apparent lack of one general facile, flexible and easily accessible synthetic route

towards substituted 10,11-dihydro-5*H*-dibenz[*b,f*]azepines of use in our research programs have therefore prompted us to develop the synthesis described herein. The synthesis used in the preparation of five 10,11-dihydro-5*H*-dibenz[*b,f*]azepine compounds, **7a-e** is described.

Results and Discussion.

In Scheme 2, the synthesis of the Horner-Emmons (Wittig) type [12] reaction products, **3a-e** is outlined, showing either a substituted 2-bromotoluene or a substituted 2-nitrotoluene derivative employed as starting material in the first step. The substituted toluenes were brominated in the benzylic position with *N*-bromosuccinimide in carbon tetrachloride using dibenzoyl peroxide in catalytic amounts to promote the radical reaction. The resulting benzyl bromides were prepared in almost quantitative yield in the case of **1a**, **1b** and **1e**. However, in the reactions affording **1c** and **1d**, the two 2-nitro-substituted derivatives which contain a strong electron withdrawing group -a halogen- respectively *meta* or *para* to the methyl group, the starting material was only converted about 50% to the desired bromomethyl derivative. Addition of further amounts of *N*-bromosuccinimide or prolonged reaction time did not lead to completion of the reaction. The bromomethyl derivatives, **1a-e** were transformed quantitatively into the corresponding benzylphosphonic acid diethyl esters, **2a-e** by reaction with triethyl phosphite. When it was possible, the benzyl phosphonic acid diethyl esters, **2a-e** were purified by destillation. In general, this resulted in far better yields in the following step, though the crude compounds by ^{1}H-nmr inspection appeared pure. The substituted benzyl phosphonic acid diethyl esters were allowed to react with substituted benzaldehydes in a Horner-Emmons type variation of the Wittig reaction. As demonstrated by the outcome of the two possible routes shown in Scheme 2, it was possible to make the benzylphosphonic acid diethyl esters react with the benzaldehydes regardless of the respective orientation of their substituents, *i.e.* in reaction with the applied benzaldehydes, 2-bromo- as well as 2-nitrosubstituted benzylphosphonic acid diethyl esters afforded the corresponding

Scheme 2



stilbenes in moderate to good yields. The 4-fluoro- and the 4,4'-dichloro-substituted stilbenes, **3a** and **3e**, (prepared *via* route A) were obtained in respectively 70% and 51% yields in the last step, and the 4-methoxy, the 4-chloro and the 5,5'-difluoro-substituted stilbenes, **3b**, **3c** and **3d**, (prepared *via* route B) were obtained in respectively 47%, 83% and 75% yield in the last step.

In Scheme 3, the next sequence of steps leading to ring closure and formation of the desired substituted 10, 11-dihydro-5*H*-dibenz[*b,f*]azepine derivatives, is outlined. In the first step, the nitro and the vinyl groups are reduced by catalytic hydrogenation. Compound **4d** was prepared by hydrogenation using 5% Pt on charcoal in dioxane at 300 psi (Method C). Some debromination was observed and the product could therefore only be obtained in 51% yield. Compounds **4a**, **4b**, **4c** and **4e** were prepared using the milder catalyst 5% Rh on charcoal in a mixture of ethanol and methanol at 350 psi (Method D). When applying this method, the bromo-substituents were largely preserved and the products could be obtained in 80-98% yield. However, in the case of **4c**, some debromination was observed, and the reported yield of 82% is an estimated yield after correction of the amount of debrominated product as measured by nmr. It was not possible to separate the debrominated product from **4c** and the crude product was used directly in the next step. Morpholine was applied as a catalyst

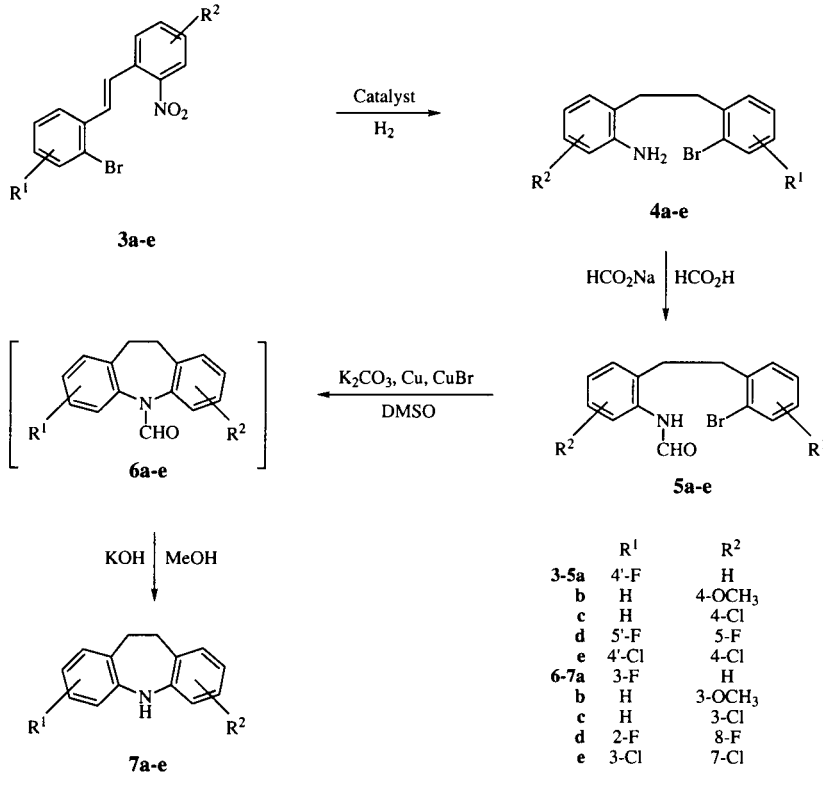
Table 1

^{1}H NMR Spectral Data of Compounds **1a-e** and **2a-e**

Compound	^{1}H NMR (δ ppm)
1a	4.58 (s, 2H, CH_2Br), 7.02 (m, 1H, arom), 7.32 (dd, 1H, arom), 7.42 (q, 1H, arom) [a]
1b	3.88 (s, 3H, CH_3O), 4.80 (s, 2H, CH_2Br), 7.13 (dd, 1H, arom), 7.45 (d, 1H, arom), 7.55 (d, 1H, arom) [a]
1c	4.78 (s, 2H, CH_2Br), 7.52 (d, 1H, arom), 7.58 (dd, 1H, arom), 8.03 (s, 1H, arom) [a]
1d	4.82 (s, 2H, CH_2Br), 7.18 (m, 1H, arom), 7.32 (dd, 1H, arom), 8.14 (q, 1H, arom) [a]
1e	4.55 (s, 2H, CH_2Br), 7.27 (dd, 1H, arom), 7.38 (d, 1H, arom), 7.60 (d, 1H, arom) [a]
2a	1.26 (t, 6H, CH_3), 3.32 (s, 1H, CH_2P=O), 3.38 (s, 1H, CH_2P=O), 4.07 (q, 4H, CH_2O), 7.00 (td, 1H, arom), 7.41 (dd, 1H, arom), 7.45 (m, 1H, arom) [a]
2b	1.24 (t, 6H, CHO, 3.60 (s, 1H, CH_2P=O), 3.65 (s, 1H, CH_2P=O), 3.88 (s, 3H, CH_3O), 4.02 (q, 4H, CH_2O), 7.10 (dd, 1H, arom), 7.37 (dd, 1H, arom), 7.47 (m, 1H, arom) [a]
2c	1.26 (t, 6H, CH_3), 3.64 (s, 1H, CH_2P=O), 3.69 (s, 1H, CH_2P=O), 4.04 (q, 4H, CH_2O), 7.43 (dd, 1H, arom), 7.54 (dd, 1H, arom), 7.96 (d, 1H, arom) [a]
2d	1.28 (t, 6H, CH_3), 3.69 (s, 1H, CH_2P=O), 3.75 (s, 1H, CH_2P=O), 4.08 (q, 4H, CH_2O), 7.10 (m, 1H, arom), 7.19 (m, 1H, arom), 8.04 (q, 1H, arom) [a]
2e	1.28 (t, 6H, CH_3), 3.34 (d, 2H, CH_2P=O), 4.07 (q, 4H, CH_2O), 7.25 (d, 1H, arom), 7.49 (d, 1H, arom), 7.59 (s, 1H, arom) [a]

[a] Recorded in deuteriochloroform.

Scheme 3



	R^1	R^2
3-5a	4'-F	H
b	H	4-OCH_3
c	H	4-Cl
d	5'-F	5-F
e	4'-Cl	4-Cl
6-7a	3-F	H
b	H	3-OCH_3
c	H	3-Cl
d	2-F	8-F
e	3-Cl	7-Cl

Table 2

Reaction Conditions and Physical Data of Compounds **3a-e**, **4a-e** and **5a-e**

Compound	Method	Yield	Mp (°) (recrystallization solvent)	Molelcular Formula	Analysis Calcd. Found		
					%C	%H	%N
3a		70%	121-123	$C_{14}H_9NBrFO_2$	52.17	2.80	4.35
			EtOH		51.76	2.74	4.18
3b	-	47%	88-90	$C_{15}H_{12}NBrO_3$	53.89	3.59	4.19
			EtOH		53.82	3.60	4.06
3c	-	83%	126-129	$C_{14}H_9NBrClO_2$	49.66	2.68	4.14
			EtOH		49.86	2.67	3.91
3d	-	75%	157-160	$C_{14}H_8NBrF_2O_2$	49.44	2.37	4.12
			iPrOH		49.43	2.34	3.93
3e	-	51%	208-209	$C_{14}H_8NBrCl_2O_2$	45.08	2.16	3.75
			Acetone		45.17	2.10	3.66
4a	B	80%	[a]				
4b	D	98%	82-84	$C_{15}H_{16}NBrO$	58.84	5.27	4.57
			[b]		58.72	5.34	4.46
4c	D	82%	[a]				
4d	C	51%	88-91	$C_{14}H_{12}NBrF_2$	53.87	3.88	4.49
			[b]		54.15	3.95	4.38
4e	D	94%	79-80	$C_{14}H_{12}NBrCl_2$	48.73	3.51	4.06
			EtOH		48.78	3.51	3.98
5a	-	92%	152-153	$C_{15}H_{13}NBrFO$	55.90	4.04	4.35
			EtOH		56.11	4.15	4.21
5b	-	86%	108-109	$C_{16}H_{16}NBrO_2$	57.49	4.79	4.19
			EtOH		57.88	4.93	4.10
5c	-	81%	152-154	$C_{15}H_{13}NBrClO$	53.20	3.87	4.14
			EtOH		53.56	3.89	3.96
5d	-	92%	164-165	$C_{15}H_{12}NBrF_2O$	52.97	3.56	4.11
			[c]		53.07	3.56	3.94
5e	-	79%	164-166	$C_{15}H_{12}NBrCl_2O$	48.29	3.24	3.75
			EtOH		48.48	3.27	3.67

[a] Isolated as an oil. [b] Obtained as a solid after evaporation of chromatography fractions. [c] Precipitated after addition of water to the reaction mixture.

modifier and dehalogenation inhibitor in both methods C and D and its presence was crucial if dehalogenation were to be lessened. In the following step, the amino groups were formylated in high yields (79-92%) to the corresponding formamides **5a-e** in order to activate and prepare the compounds for nucleophilic attack in the final, ring closing step. The formylation led to the formation of a mixture of rotamers as evidenced by ^{1}H-nmr. Two separate CHO signals are observed (Table 3). The final, ring closing reaction is in principle a two-step reaction. In the first step a Goldberg type nucleophilic substitution leads to the ring closed and formylated intermediate products, **6a-e**. The reaction is catalysed by copper and copper bromide, but the full mechanism behind the catalysis is not yet fully understood. The final step is a simple hydrolysis of the amides leading to the substituted 10,11-dihydro-5*H*-dibenz[*b,f*]-azepines, **7a-e** in a 46-75% overall yield calculated from the amines, **5a-e**. The intermediate formamide was only isolated in the case of **6b**.

Table 3

MS (EI) and ^{1}H NMR Spectral Data of Compounds **3a-e**, **4a-e** and **5a-e**

Compound	MS (m/z)	^{1}H NMR (δ ppm)
3a	321 (M^+, 9%), 119 ($NOPhCH^+$, 100%)	7.08 (td, 1H, arom), 7.35 (m, 1H, arom), 7.35 (d, 1H, CH=CH), 7.45 (m, 1H, arom), 7.48 (d, 1H, CH=CH), 7.60-7.73 (m, 2H, arom), 7.79 (d, 1H, arom), 8.00 (d, 1H, arom) [a]
3b	333 (M^+, 52%), 149 (M-$BrPhCH^+$, 100%)	3.89 (s, 3H, CH_3O), 7.12-7.21 (m, 2H, arom), 7.34 (d, 1H, CH=CH), 7.31-7.35 (m, 1H, arom), 7.49 (d, 1H, CH=CH), 7.48-7.51 (m, 1H, arom), 7.59 (d, 1H, arom), 7.69 (d, 1H, arom), 7.73 (d, 1H, arom) [a]

Table 3 (continued)

Compound	MS (m/z)	^{1}H NMR (δ ppm)
3c	339 (M^+, 12%), 153 ($NOClPhCH^+$, 100%)	7.18 (td, 1H, arom), 7.35 (m, 1H, arom), 7.46 (q, 2H, CH=CH), 7.60 (m, 2H, arom), 7.69 (d, 1H, arom), 7.76 (d, 1H, arom), 8.00 (d, 1H, arom) [a]
3d	339 (M^+, 8%), 137 ($FNOPhCH^+$, 100%)	6.95 (m, 1H, arom), 7.16 (m, 1H, arom), 7.35 (d, 1H, CH=C), 7.41 (m, 2H, arom), 7.53 (d, 1H, CH=C), 7.52-7.61 (m, 1H, arom), 8.11 (m, 1H, arom) [a]
3e	373 (M^+, 53%), 205 ($BrClPhCH^+$, 100%)	7.34 (d, 1H, arom), 7.35 (d, 1H, CH=CH), 7.47 (d, 1H, CH=CH), 7.52 (m, 3H, arom), 7.74 (d, 1H, arom), 8.01 (d, 1H, arom) [a]
4a	293 (M^+, 8%), 106 ($M\text{-}FBrPhCH_2^+$, 100%)	2.73 (m, 2H, CH_2Ph), 2.98 (m, 2H, CH_2Ph), 3.67 (bs, 1H, NH_2), 6.63-6.67 (m, 2H, arom), 6.90-6.96 (m, 1H, arom), 6.99-7.08 (m, 2H, arom), 7.09-7.16 (m, 1H, arom), 7.29 (dd, 1H, arom) [a]
4b	305 (M^+, 7%), 136 ($M\text{-}BrPhCH_2^+$, 100%)	2.73 (t, 2H, CH_2Ph), 2.98 (t, 2H, CH_2Ph), 3.75 (s, 3H, CH_3O), 3.75 (bs, 2H, NH_2), 6.27 (d, 1H, arom), 6.32 (dd, 1H, arom), 6.98 (d, 1H, arom), 7.09 (m, 1H, arom), 7.21 (m, 2H, arom), 7.55 (d, 1H, arom) [a]
4c	309 (M^+, 4%), 140 ($M\text{-}BrPhCH_2^+$, 100%)	2.75 (m, 2H, CH_2Ph), 2.98 (m, 2H, CH_2Ph), 3.30 (bs, 1H, NH_2), 6.68-6.76 (m, 2H, arom), 6.94 (m, 1H, arom), 7.09 (m, 1H, arom), 7.15-7.30 (m, 1H, arom), 7.55 (dd, 1H, arom) [a]
4d	311 (M^+, 6%), 124 ($M\text{-}BrFPhCH_2^+$, 100%)	2.73 (m, 2H, CH_2Ph), 2.98 (m, 2H, CH_2Ph), 3.56 (bs, 1H, NH_2), 6.61 (m, 1H, arom), 6.73-6.80 (m, 2H, arom), 6.83 (m, 1H, arom), 6.93 (dd, 1H, arom), 7.49 (m, 1H, arom) [a]
4e	345 (M^+, 8%), 140 ($M\text{-}BrClPhCH_2^+$, 100%)	2.70 (m, 2H, CH_2Ph), 2.95 (m, 2H, CH_2Ph), 3.74 (bs, 2H, NH_2), 6.68 (m, 2H, arom), 6.89 (d, 1H, arom), 7.07 (d, 1H, arom), 7.20 (dd, 1H, arom), 7.57 (d, 1H, arom) [a]
5a	321 (M^+, 18%), 134 ($M\text{-}FBrPhCH_2^+$, 100%)	2.86 and 2.97 (2 x m, 2 x 4H, CH_2Ph), 6.94 (2 x m, 2 x 1H, arom), 7.03-7.38 (m, 5H + 6H, arom + 1H, NH), 7.54 (d, 1H, NH), 7.88 (d, 1H, arom), 8.42 (s, 1H, CHO), 8.45 (d, 1H, CHO) [a] - rotamer ratio = 1.5:1
5b	333 (M^+, 5%), 164 ($M\text{-}BrPhCH_2^+$, 100%)	2.81 and 2.95 (2 x m, 2 x 4H, CH_2Ph), 3.81 (s, 2 x 3H, CH_3O), 6.65 (d, 1H, arom), 6.72 (ddd, 2H, arom), 7.06-7.27 (m, 2 x 4H, arom + 2 x 1H, NH), 7.55 (m, 2H, arom), 7.66 (d, 1H, arom), 8.35 (s, 1H, CHO), 8.43 (d, 1H, CHO) [a] - rotamer ratio = 1.3:1
5c	339 (M^+, 17%), 168 ($M\text{-}BrPhCH_3^+$, 100%)	2.87 and 2.98 (2 x m, 2 x 4H, CH_2Ph), 7.04-7.23 (m, 5H + 6H, arom + 1H, NH), 7.45 (d, 1H, NH), 7.55 (2 x d, 2 x 1H, arom), 8.05 (s, 1H, arom), (s, 1H, CHO), 8.41 (d, 1H, CHO) [a] - rotamer ratio = 1:1
5d	339 (M^+, 18%), 152 ($M\text{-}BrFPhCH_2^+$, 100%)	2.89 (m, 2 x 4H, CH_2Ph), 7.08 (m, 2 x 3H, arom), 7.27 (m, 1H + 2H, arom), 7.63 (m, 2H + 1H, arom), 8.23 (d, 1H, CHO), 8.29 (s, 1H, CHO), 9.65 (s, 1H, NH), 9.80 (d, 1H, NH) [b] - rotamer ratio = 2.6:1
5e	373 (M^+, 10%), 168 $M\text{-}BrClPhCH_2^+$, 100%)	2.83 and 2.95 (2 x m, 2 x 4H, CH_2Ph), 7.03-7.22 (m, 4H + 5H, arom + 1H, NH), 7.59 (2 x d, 2 x 1H, arom), 7.71 (d, 1H, NH), 8.02 (s, 1H, arom), 8.39 (s, 1H, CHO), 8.45 (d, 1H, CHO) [a] - rotamer ratio = 1:1

[a] Recorded in deuteriochloroform. [b] Recorded in dimethyl sulfoxide.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes with a Büchi melting point apparatus. The structure of all compounds are consistent with spectroscopic data and satisfactory elemental analyses were obtained where stated. The mass spectra were recorded on a Finnigan MAT TSQ70B instrument. The ^{1}H-nmr spectra were obtained on a Bruker WM400 apparatus. Chemical shifts are expressed in δ (ppm) downfield from trimethylsilane as an internal reference. Microanalyses were carried out on a Perkin-Elmer

Table 4

Reaction Conditions and Physical Data of Compounds **6b** and **7a-e**

Compound	Method	Yield [#]	Mp (°) (recrystallization solvent)	Molecular Formula	Analysis Calcd. Found		
					%C	%H	%N
6b	F	47%	130-132 EtOAc/heptane	$C_{16}H_{15}NO_2$	75.89 75.99	5.93 6.07	5.53 5.45
7a	E	46%	60-63 heptane	$C_{14}H_{12}NF$	78.87 79.28	5.63 5.77	6.57 6.30
7b	F	91%	90-92 heptane	$C_{15}H_{15}NO$	80.00 79.91	6.67 6.80	6.22 5.97
7c	E	53%	79-83 heptane	$C_{14}H_{12}NCl$	73.20 73.19	5.27 5.29	6.10 6.00
7d	E	61%	73-74	$C_{14}H_{11}NF_2$	72.72 72.70	4.79 4.86	6.06 5.74
7e	E	75%	111-114 heptane	$C_{14}H_{11}NCl_2$	63.66 63.57	4.20 4.22	5.30 5.10

#) The yields reported for **7a**, **7c**, **7d** and **7e** are calculated from compounds **5a**, **5c**, **5d** and **5e**, respectively. The yield reported for **7b** is calculated from compound **6b**.

Table 5

MS (EI) and ^{1}H NMR Spectral Data of Compounds **6b** and **7a-e**

Compound	MS (m/z)	^{1}H NMR (δ ppm)
6b	253 (M^+, 100%)	2.83 (2 x m, 2 x 2H, CH_2Ph), 3.33 (2 x m, 2 x 2H, CH_2Ph), 3.79 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 6.75 (d, 1H, arom), 6.80 (m, 2H, arom), 6.90 (d, 1H, arom), 7.12 (q, 2H, arom), 7.19-7.39 (m, 3H + 4H, arom), 7.35 (m, 1H, arom), 8.54 (s, 1H, CHO), 8.59 (s, 1H, CHO) [a] - rotamer ratio = 1:1
7a	213 (M^+, 100%)	3.02 (m, 4H, CH_2Ph), 5.95 (bs, 1H, NH), 6.39-6.48 (m, 2H, arom), 6.70 (d, 1H, arom), 6.80 (t, 1H, arom), 6.94 (t, 1H, arom), 7.00-7.10 (m, 2H, arom) [a]
7b	225 (M^+, 100%)	3.01 (m, 4H, CH_2Ph), 3.77 (s, 3H, CH_3O), 5.95 (bs, 1H, NH), 6.27 (d, 1H, arom), 6.34 (dd, 1H, arom), 6.70 (d, 1H, arom), 6.78 (t, 1H, arom), 6.92 (d, 1H, arom), 7.05 (m, 2H, arom) [a]
7c	229 (M^+, 100%)	3.04 (m, 4H, CH_2Ph), 5.96 (bs, 1H, NH), 6.70 (m, 1H, arom), 6.72 (d, 2H, arom), 6.80 (t, 1H, arom), 6.94 (d, 1H, arom), 7.01-7.10 (m, 2H, arom) [a]
7d	231 (M^+, 100%)	3.04 (m, 4H, CH_2Ph), 5.69 (bs, 1H, NH), 6.63-6.69 (m, 2H, arom), 6.74-6.80 (m, 4H, arom) [a]
7e	263 (M^+, 100%)	3.01 (s, 4H, CH_2Ph), 5.94 (bs, 1H, NH), 6.85 (m, 4H, arom), 6.95 (d, 2H, arom) [a]

[a] Recorded in deuteriochloroform.

Model 240 elemental analyser. Merck Kieselgel 60 F_{254} on glass plates was used for tlc monitoring, detection by UV (254 and 366 nm).

Substituted Bromomethylphenyl Derivatives **1a-e**. General Synthesis of **1b**.

In a 500 ml, round bottom flask, 4-methoxy-2-nitrotoluene (50.0 g, 0.30 mole) was dissolved in tetrachloromethane (200 ml). *N*-Bromosuccinimide (53.4 g, 0.30 mole) was added followed by dibenzoyl peroxide (0.3 g, 0.001 mole). The reaction mixture was heated at reflux temperature for 24 hours. More *N*-bromosuccinimide was added (9.0 g, 0.05 mole) and heating was continued for 4 hours. After cooling, the solution was poured into iced water (350 ml). Using 2 *M* sodium hydroxide, the *p*H was adjusted to 10 and the phases were separated. The aqueous phase was extracted with dichloromethane (150 ml). The combined organic extracts were washed with 5% sodium bicarbonate (aqueous) (2 x 100 ml) and dried over magnesium sulfate. Evaporation of the solvent afforded **1b** as an amorphous product in quantitative yield (76.3 g). This crude 1-bromomethyl-4-methoxy-2-nitrobenzene was used in the next step without further purification. For ^{1}H-nmr spectral data see Table 1.

Substituted Benzylphosphonic Acid Diethyl Ester Derivatives **2a-e**. General Synthesis of **2b**.

A mixture of **1b** (71.0 g, 0.29 mole) and triethyl phosphite (60 ml) was heated on an oilbath at 110° for 5 hours. The mixture was allowed to stir at room temperature overnight. The volatile materials were evaporated *in vacuo*, affording 4-methoxy-2-nitrobenzylphosphonic acid diethyl ester, **2b** in quantitative yield (96.5 g) as a dark oil; for ^{1}H-nmr spectral data see Table 1.

Substituted 2-(2-(2-Bromophenyl)vinyl)nitrobenzenes **3a-e**. General Synthesis of **3b**.

In a 1 l three-necked flask equipped with thermometer, **2b** (96.5 g, 0.32 mole) and 2-bromobenzaldehyde (50.0 g, 0.33 mole) were dissolved in dry dimethoxyethane (350 ml). Sodium hydride (14.0 g, 0.35 mole) was added slowly in portions. A temperature rise to about 50° was observed. When addition was complete, the reaction mixture was heated at reflux temperature for 2 hours and allowed to stir at room temperature overnight. Water (600 ml) was added carefully, the resulting mixture was extracted with ethyl acetate (4 x 200 ml) and the combined organic extracts were dried over magnesium sulfate. The solvent was removed by evaporation and the residue was suspended in ethanol (130 ml). The precipitate was filtered and washed with more ethanol (250 ml) to give 4-(2-(2-bromophenyl)vinyl)-3-nitroanisole, **3b** in 47% yield (49.8 g); for physical data see Table 2; for ms and ^{1}H-nmr spectral data see Table 3.

Substituted 2-(2-(2-Bromophenyl)ethyl)phenylamines **4a-e**.

General Method C. Synthesis of **4d**.

Compound **3d** (3.0 g, 8.8 mmoles) was dissolved in dioxane (60 ml). Morpholine (9 drops) was added followed by 5% Pt/C (0.9 g) and the reaction mixture was hydrogenated at room temperature at 300 psi overnight. The mixture was filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (250 g) using a mixture of heptane and ethyl acetate (7:3) as the eluent. This afforded 2-(2-(2-bromo-5-fluorophenyl)ethyl)-4-fluoroaniline, **4d** in 51% yield (2.2 g); for physical data see Table 2, for ms and ^{1}H-nmr spectral data see Table 3.

General Method D. Synthesis of **4b**.

Compound **3b** (3.0 g, 9.0 mmoles) was suspended in a mixture of ethanol (75 ml) and methanol (25 ml). Morpholine (6 drops) was added followed by 5% Rh/C (0.68 g) and the reaction mixture was hydrogenated at room temperature at 350 psi for 4 hours. The mixture was filtered through hyflo® and evaporated to dryness, affording crude 4-(2-(2-bromophenyl)ethyl)-3-aminoanisole, **4b** in 98% yield (2.71 g); for physical data see Table 2, for ms and ^{1}H-nmr spectral data see Table 3.

Substituted *N*-(2-(2-(2-Bromophenyl)ethyl)phenyl)formamides **5a-e**. General Syntesis of **5b**.

In a 50 ml roundbottom flask **4b** (1.5 g, 5.0 mmoles) was dissolved in formic acid (10 ml) and sodium formate (0.75 g, 0.010 mole) was added. The reaction mixture was heated at reflux temperature for 3 hours. After cooling to room temperature, the product precipitated, water (80 ml) was added and the mixture was allowed to stir for 0.5 hour. The white precipitate was filtered, washed with water and dried, affording *N*-(2-(2-(2-bromophenyl)ethyl)-5-methoxyphenyl)formamide in 86% yield (1.4 g); for physical data see Table 2, for ms and ^{1}H-nmr spectral data see Table 3.

Substituted 10,11-Dihydro-5*H*-dibenz[*b,f*]azepines **7a-e**.

General Method E. Synthesis of **7d**.

Formamide **5d** (1.8 g, 5.3 mmoles) was dissolved in dry dimethyl sulfoxide (10 ml) and potassium carbonate (0.9 g, 6.4 mmoles), copper (0.2 g, 3.1 g-atoms) and cuprous bromide (0.25 g, 1.7 mmoles) were added. The reaction mixture was heated at 160° for 3 hours. After cooling to 50°, 5 *N* aqeous sodium hydroxide (1.0 ml) was added and the mixture was stirred at 75° for 30 minutes. The mixture was poured into water (100 ml) and extracted with ethyl acetate (150 ml). The resulting mixture was filtered before the phases were separated. The organic phase was washed with 1 *N* aqueous hydrochloric acid and subsequently with 10% aqueous sodium bicarbonate solution and dried over magnesium sulfate. After evaporation of the solvent, the product was purified by column chromatography on silica gel (75 g) using a mixture of ethyl acetate and heptane (3:7) as eluent. This afforded 2,8-difluoro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine, **7d** in 61% yield (0.75 g).

General Method F. Synthesis of **7b**.

In a 50 ml round bottom flask **5b** (1.0 g, 3.0 mmoles) was dissolved in dimethyl sulfoxide (10 ml), and potassium carbonate (0.54 g, 4.0 mmoles), copper (0.15 g, 2.4 g-atoms) and cuprous bromide (0.21 g, 1.5 mmoles) were added. The reaction mixture was heated at 160° for 24 hours. After cooling to room temperature, water was added (40 ml) and the mixture was extracted with diethyl ether (4 x 50 ml), washed with water (2 x 30 ml) and dried over magnesium sulfate. After evaporation of the solvent, the product was purified by column chromatography on silica gel (50 g) using a mixture of ethyl acetate and heptane (1:4) as eluent. This afforded 3-methoxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carbaldehyde, **6b** in 47% yield (0.36 g).

The formamide, **6b** (1.5 g, 0.06 mole) was suspended in 96% ethanol (20 ml), and 6 *M* aqueous sodium hydroxide (3.5 ml) was added. The mixture was heated at reflux temperature for 1 hour. After cooling, concentrated aqueous hydrochloric acid (0.5 ml) was added to neutralize the solution, and the solvent was subsequently removed by evaporation. Water (50 ml) was added, the precipitate was filtered, washed with water (50 ml) and dried to give 3-methoxy-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine, **7b** in 92% yield (1.2 g).

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