# Potential Antidepressants Displayed Combined α<sub>2</sub>-Adrenoceptor Antagonist and Monoamine Uptake Inhibitor Properties

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Received July 21, 2000

Classical antidepressants are thought to act by raising monoamine (serotonin and noradrenaline) levels in the brain. This action is generally accomplished either by inhibition of monoamine metabolism (MAO inhibitors) or by blockade of monoamine uptake (tricyclic antidepressants and selective serotonin or noradrenaline reuptake inhibitors). However, all such agents suffer from a time lag (3-6 weeks) before robust clinical efficacy can be demonstrated. This delay may reflect inhibitory actions of noradrenaline at presynaptic  $\alpha_{2A}$ -adrenergic auto- or heteroreceptors which gradually down-regulate upon prolonged exposure. Blockade of presynaptic  $\alpha_{2A}$ -adrenoceptors by an antagonist endowed with monoamine uptake inhibition properties could lead to new antidepressants with greater efficacy and a shorter time lag. In the literature, only two molecules have been described with such a pharmacological profile. Of these, napamezole (2) was chosen as a point of departure for the design of 4(5)-[(3,4-dihydro-2naphthalenyl)methyl]-4,5-dihydroimidazole (**4a**), which displayed the desired profile:  $\alpha_{2A}$ adrenoceptor antagonist properties and serotonin/noradrenaline uptake inhibition. From this original molecule, a series of derivatives was designed and synthesized, encompassing substituted as well as rigid analogues. Structure-activity relationships permitted the selection of **14c** (4(5)-[(5-fluoroindan-2-yl)methyl]-4,5-dihydroimidazole) as a development candidate.

### Introduction

The monoaminergic hypothesis of depression assumes that the principle symptoms of depression reflect an insufficient concentration of noradrenaline (NA) and serotonin (SER) in corticolimbic synaptic clefts. Classical antidepressants are thought to act by raising monoamine levels in the brain. This is accomplished either by inhibition of monoamine metabolism (MAO inhibitors) or by blockade of monoamine uptake (tricyclic antidepressants: TCAs; selective SER reuptake inhibitors: SSRIs; and selective NA reuptake inhibitors: SNRIs). Historically, the monoaminergic hypothesis initially emphasized the role of NA,<sup>1</sup> but over the past decade, following the demonstration of the efficacy and safety of SSRIs,<sup>2</sup> as exemplified by the success of fluoxetine (1; Figure 1), the importance of serotoninergic mechanism has been underlined.

Currently, the major handicap of used antidepressant agents, irrespective of their mechanism of action, is the 4-6 week delay required to establish therapeutic efficacy.<sup>3</sup> This time lag may reflect monoaminergic mechanisms. Thus inhibition of NA uptake by antidepressants increases levels of NA in the synaptic cleft, which reinforces postsynaptically transmission, and also activates presynaptic  $\alpha_{2A}$ -adrenergic autoreceptors,<sup>4</sup> which decreases the release of NA as well as the release of SER through  $\alpha_{2A}$ -adrenergic heteroreceptors located on serotoninergic terminals. The immediate consequence of these two opposite processes, inhibition of uptake and



Figure 1. Reference compound structures.

release, could be a status quo or even an overall decrease in the neurotransmission. The same consideration may be applied to the action of SSRIs which activate presynaptic 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> serotoninergic autoreceptors. These presynaptic receptors also slowly desensitize leading to a gradual increase of therapeutically effective monoamine concentration in the presence of antidepressant agents. This hypothesis may be tested either by coadministration of a TCA, a SSRI, or a SNRI with an antagonist of these auto- or heteroreceptors or by administration of a drug endowed with both properties.<sup>5–10</sup>

A second strategy implying the discovery of molecules acting both as NA<sup>11,12</sup> and/or SER<sup>13</sup> uptake inhibitors and as antagonists at presynaptic auto- or heteroreceptors has been little exploited. Our research effort aimed to identify a molecule endowed with NA and/or SER uptake inhibitor properties and antagonist activity at presynaptic  $\alpha_2$ -adrenergic autoreceptors. We considered napamezole from Sterling Laboratories (**2**; Figure 1)<sup>14</sup>

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<sup>*a*</sup> Reagents: (a)  $(EtO)_2P(O)CH_2CO_2Et$ , NaH, THF; (b) DIBAL-H,  $CH_2Cl_2$  or (1)  $LiAlH_4$ , THF, (2) IBX, THF; (c) TMSCN,  $ZnI_2$ ; (d) NH<sub>3</sub>, MeOH; (e) NaCN, NH<sub>4</sub>Cl, MeOH, H<sub>2</sub>O; (f) Raney Ni, NH<sub>3</sub>, MeOH or  $LiAlH_4$ , THF or AlH<sub>3</sub>, ether; (g)  $HC(=NH)NH_2$ ·AcOH, EtOH or BrCN,  $CH_2Cl_2$ ; (h) (1)  $HCO_2H$ , HCl, (2) HCl,  $H_2O$ ; (i) (1)  $LiAlH_4$ , THF, (2) BrCN,  $CH_3CN$ ,  $K_2CO_3$ ; (j)  $H_2/Pd/C$ , EtOH.

to be a prototype for this novel class of compounds and a source of inspiration for our design. Although claimed as a SER uptake blocker displaying  $\alpha_2$ -adrenoceptor antagonist properties, this compound manifests far higher affinity for the latter site than for the former site (see Table 1). Atipamezole (3; Figure 1),<sup>15</sup> a potent  $\alpha_2$ adrenoceptor antagonist, displays an imidazole moiety substituted in the 4(5)-position, encouraging exploration of various substitutions of the imidazoline in the napamezole skeleton (4). This change permitted a differentiation of the two nitrogen atoms and revealed their potential ability to afford contrasting pharmacological profiles. In addition, we have evaluated the importance of the imidazole nucleus by replacing it with different heterocycles (5-8), examined the importance of the dihydronaphthalene skeleton by undertaking diverse modifications (9-15), and, finally, rigidified the molecule (16-24) in order to define the active conformation required for pharmacological efficacy.

# Chemistry

Most of the compounds were obtained following general synthetic routes described in Scheme 1 (method A). The key intermediates were ethylenediamines **28a**–**j** 

which cyclized to imidazolines by reaction with formamidine acetate in EtOH. The imidazolines were usually isolated as fumarate salts affording highly crystalline salts from mixtures of *i*-PrOH and acetone.

Various ethylenediamines were obtained by reduction of aminonitriles produced by Strecker reaction or one of its variations, as observed in our previous work on spiroimidazolines.<sup>16</sup> Another method that allowed access to some aminonitriles was the substitution of a halide or any other leaving group by the anion of the synthon N-(diphenylmethylene)aminoacetonitrile developed by O'Donnell (method B, Scheme 2).<sup>17</sup>

Substrates of the Strecker reaction were aldehydes **26a**–**j**, **69** and ketone **67** obtained mainly through Wadsworth–Emmons reaction of triethyl phosphonoacetate on various 2-indanones and 2- tetralones. Esters were either reduced directly in aldehydes using DIBAL-H or reduced first to alcohol by LiAlH<sub>4</sub> and further oxidized using pyridinium chromate or iodoxybenzoic acid (IBX)<sup>18</sup> to aldehydes.

Synthesis of aminoimidazolines and oxazolines was accomplished via reaction of cyanogen bromide with the corresponding ethylenediamines or 2-aminoethanols (Scheme 1). These last intermediates were prepared

### Scheme 2. Method B<sup>a</sup>



<sup>*a*</sup> Reagents: (a) MeMgCl, TiCl<sub>4</sub>; (b) CF<sub>3</sub>CO<sub>2</sub>H, trityl-OH; (c) NBS, AlBN; (d) (i) (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>C=NCH<sub>2</sub>CN, KOH, TBAB, (ii) 1 N HCl, ether; (e) LiAlH<sub>4</sub>, THF; (f) HC(=NH)NH<sub>2</sub>·AcOH, EtOH.





<sup>a</sup> Reagents: (a) KO-t-Bu, toluene; (b) NaBH<sub>4</sub>, MeOH; (c) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>.

either by hydrolysis followed by reduction of the aminonitrile **27a** or by reduction of the cyanohydrin **29a**, respectively.

In the synthesis of the imidazole derivative **5**, another method (Scheme 3) was used. Alkylation of the 1-te-tralone with 1-trityl-4-chloromethylimidazole<sup>11</sup> led to **39** which was submitted to the reduction of the keto group affording the alcohol which was deprotected and dehydrated at the same time, by trifluoroacetic acid.

In the case of rigid molecules, synthesis of corresponding aldehydes **41**, **43**, **45a**,**b**, **53a**,**b** and ketone **59** required additional steps. For instance, the different tetrahydrocyclopropanaphthalenyl aldehydes **41**, **43**, and **45a**,**b** were prepared by carbene addition to the corresponding olefins (Scheme 4) and transformation of the esters into the aldehydes by reduction followed by oxidation. As described (Scheme 5

) for molecules **20a,b**, analogues of **19a,b**,<sup>19,20</sup> the spiro cyclopropylic ester was formed from interaction of 1-indanone **47** with ethyl 2-methylenephosphonoacetate in alkaline conditions.<sup>21</sup> The ketone functionality of the indanone was reduced using NaBH<sub>3</sub>CN in the presence of ZnI<sub>2</sub>,<sup>22</sup> and the ester group was reduced by LiAlH<sub>4</sub> into the corresponding alcohol, which was further oxidized to the aldehyde **53b** using pyridinium chromate. The Strecker reaction was accomplished via a two-

step procedure, where the aldehyde was first condensed with di(*p*-methoxyphenyl)methylamine<sup>23</sup> in the presence of 4 Å molecular sieves and then reacted with TMSCN. High-yield reduction of the aminonitrile with LiAlH<sub>4</sub> afforded two diastereoisomeric ethylenediamines which were easily separated by column chromatography on silica gel eluting with a gradient (0-5%) of MeOH/NH<sub>4</sub>-OH (9/1) in CH<sub>2</sub>Cl<sub>2</sub>. The ethylenediamines were deprotected in a mixture of AcOH/ $H_2O$  (9/1), and the resulting diamines were cyclized classically by reaction with formamidine acetate. The use of di(p-methoxyphenyl)methylamine in the Strecker reaction brought two advantages to the synthetic practice: (1) there was no hydride substitution during the LiAlH<sub>4</sub> reduction of the aminonitrile and (2) the chromatographic separation of the diastereoisomers was made easier, the introduction of bulky groups close to the stereogenic position amplifying the difference between the two isomers.

On the basis of the work of Ghatak,<sup>24</sup> the ketone intermediate **59** in the synthesis of **21a,b** was obtained by 6-*endo*-aryl cyclization leading to the desired *trans* ring junction (Scheme 6). The precursor of this cyclization was prepared by successive condensation of (2-bromophenyl)methyl bromide with the monoacetal of 1,4-cyclohexanedione and tranformation of the keto group in an *exo*-methylene group by Wittig reaction.<sup>25</sup>

Scheme 4<sup>a</sup>



<sup>*a*</sup> Reagents: (a) ZnEt<sub>2</sub>, ICH<sub>2</sub>Cl, C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>; (b) Rh<sub>2</sub>(Acac)<sub>4</sub>, N<sub>2</sub>CHCO<sub>2</sub>Et, ether; (c) (i) LiAlH<sub>4</sub>, THF, (ii) CrO<sub>3</sub>·pyridine; (d) NaCN, NH<sub>4</sub>Cl, MeOH, H<sub>2</sub>O; (e) LiAlH<sub>4</sub>, THF; (f) HC(=NH)NH<sub>2</sub>·AcOH, EtOH, SiO<sub>2</sub> chromatography: CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH.

The dioxolane moiety was mildly cleaved using pyridinium tosylate.  $^{26}\,$ 

The synthesis of **22** (Scheme 7) took advantage of the symmetry of the molecule which exists as a single stereoisomer. Starting from 1,2-di(bromomethyl)benzene, a double alkylation of dimethyl malonate led to the five-membered ring **63**. Transformation of the ester groups into dibromide derivative **64** through reduction and formation of the ditosylate derivative<sup>27</sup> allowed the formation of the four-membered ring **65** through dialkylation of the synthon *N*-(diphenylmethylene)amino-acetonitrile. Straightforward reduction and cyclization afforded the desired product **22**.

The synthesis of compound **23** (Scheme 8) started with preparation of the corresponding ketone **67** through a modified Wittig–Horner reaction.<sup>28</sup> Application of classical conditions for the Strecker reaction, followed by reduction and cyclization, led to **23** in moderate yields.

Finally, the diastereoisomers **24a,b** (Scheme 9) are further examples of successful use of the di(*p*-methoxyphenyl)methylamine as an ammonia substitute in the Strecker reaction leading to easier separation of the diastereoisomers at the diamine level and more efficient reduction of the nitrile group, avoiding nucleophilic hydride substitution. The key aldehyde **69** was obtained by alkylation of 2-methyl-1-tetralone by ethyl 2-bromoacetate, followed by reduction and oxidation.

# **Biology**

Molecules were evaluated in in vitro assays to define their affinity at  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors and SER and NA reuptake sites. The results of this primary evaluation allowed elaboration of structure–activity relationships (SARs) discussed in this paper. In addition, certain compounds were further evaluated in vivo to define their **Table 1.** Binding Affinities  $(pK_i)$  at Native Rat Receptors and Uptake Sites for Compounds with Substitution of the Aromatic Moiety

Compd #	R	Adrenoceptor		Upt	ake	
		$\alpha_1^a$	$\alpha_2^{a}$	SER <sup>a</sup>	NAª	
1	Fluoxetine	5.4	5.3	8.0	6.1	
2	Napamezole	7.0	8.5	6.7	<6	
3	Atipamezole	5.7	9.9	< 5.5	< 5	
4a	Н	6.4	7.1	7.4	7.3	
4b	8-Cl	6.4	7.6	7.7	7.3	
4c	8-F	6.3	7.4	7.1	6.9	
4d	8-OCH <sub>3</sub>	6.8	7.6	7.8	6.0	
4e	8-CH <sub>3</sub>	6.2	6.8	7.9	6.0	
4f	7 <b>-</b> F	6.6	6.7	8.8	7.3	
4g	7-CF <sub>3</sub>	5.9	6.4	6.8	< 5	
4h	7-OCH₃	5.6	6.3	6.7	< 6	
4i	7-CH <sub>3</sub>	6.4	6.8	7.2	6.0	
4j	6-CH <sub>3</sub>	nt	6.4	7.8	< 6	

<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit. nt: not tested.

bioavailability (ip and po) and antidepressant properties. Detailed reports of the pharmacological profiles of selected compounds will appear elsewhere.

The primary evaluation consisted in determination of affinity at rat  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors by competition with [<sup>3</sup>H]prazosin and [<sup>3</sup>H]RX 821,002, respectively, on membranes prepared from rat cerebral cortex. In addition, affinities at SER and NA reuptake sites were determined by competition experiments employing [<sup>3</sup>H]-paroxetine and [<sup>3</sup>H]nisoxetine, respectively, and membranes prepared from rat frontal cortex (Tables 1–6).

#### Scheme 5<sup>a</sup>



<sup>*a*</sup> Reagents: (a) LDA, ClP(O)(OEt)<sub>2</sub>, THF; (b) DHP, PPTS, CH<sub>2</sub>Cl<sub>2</sub>; (c) NaH, toluene; (d) NaBH<sub>3</sub>CN, ZnI<sub>2</sub>, DCE; (e) KOtBu, CH<sub>2</sub>=C(OPO<sub>3</sub>Et<sub>2</sub>)CO<sub>2</sub>Et, DMSO; (f) LiAlH<sub>4</sub>, THF; (g) CrO<sub>3</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; (h) KCN, NH<sub>4</sub>Cl, MeOH/H<sub>2</sub>O and MeOH/NH<sub>3</sub>, or (*p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CHNH<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> and TMSCN; (i) AcOH/H<sub>2</sub>O; (j) HC(=NH)NH<sub>2</sub>·AcOH, EtOH.

Antagonist actions at  $\alpha_2$ -adrenoceptors were demonstrated for selected compounds by modulation of [<sup>35</sup>S]-GTP $\gamma$ S binding at  $h\alpha_{2A}$ -adrenoceptors expressed in CHO cells, as previously reported<sup>29</sup> (Table 7).

#### Discussion

Compound **4a** demonstrates how a small displacement of one atom (nitrogen) can profoundly affect the pharmacological profile of a molecule. Comparing napamezole (**2**) with its isomer **4a** (Table 1), affinity at  $\alpha_2$ -adrenoceptors is lowered by 1.4 log units, while affinities at SER and NA uptake sites are increased by 0.7 and >1.3 log units, respectively, leading to a molecule with an equilibrated receptorial profile. In this new series of molecules, regarding substitution of the

aromatic moiety, the most striking effect lies with the chloro substitution at position 8, which increases affinity at  $\alpha_2$ -adrenoceptors (0.5 log unit), whereas affinities at SER and NA uptake sites are only marginally affected (0.3 and 0 log unit, respectively). The other substituents at position 8 show less favorable profiles with the fluorine being less potent, the methoxy group being selective for the  $\alpha_2$ -adrenoceptor and SER uptake sites but losing efficacy at NA uptake sites, and the methyl substitution leading to a specific SER uptake effect. Among substituents at position 7, only fluorine manifests an interesting profile with a substantial increase in affinity at SER uptake sites (1.4 log units), accompanied, however, with a loss of affinity at  $\alpha_2$ -adrenoceptors (0.4 log unit). All other substituents in

Scheme 6<sup>a</sup>



<sup>*a*</sup> Reagents: (a) LDA, THF; (b)  $Ph_3P^+MeI^-$ ,  $t-C_5H_{11}O^-Na^+$ , toluene; (c)  $Bu_3SnH$ , AlBN, toluene; (d) PPTS,  $CH_2Cl_2$ ; (e) KCN,  $NH_4Cl$ , MeOH/H<sub>2</sub>O, MeOH/NH<sub>3</sub>; (f) LiAlH<sub>4</sub>, THF; (g) HC(=NH)NH<sub>2</sub>·AcOH, MeOH.

Scheme 7<sup>a</sup>



<sup>*a*</sup> Reagents: (a)  $K_2CO_3$ , butanone; (b) LiAlH<sub>4</sub>, THF/Et<sub>2</sub>O; (c) TsCl, pyridine; (d) LiBr, DMF; (e) NaH, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>C=NCH<sub>2</sub>CN, THF, HCl/Et<sub>2</sub>O; (f) H<sub>2</sub>, Ni, MeOH/NH<sub>3</sub>; (g) HC(=NH)NH<sub>2</sub>·AcOH, MeOH.

this position induce a modest selectivity for SER uptake sites compared to affinity at NA uptake sites and  $\alpha_{2}$ -adrenoceptors, with a lower overall level of activity. The same trend can be found in the only example of substitution at position 6.

Scheme 8<sup>a</sup>



 $^a$  Reagents: (a) (EtO)\_2P(O)CH\_2COCH\_3, K\_2CO\_3, H\_2O; (b) KCN, NH\_4Cl, MeOH, H\_2O; (c) LiAlH\_4, THF; (d) HC(=NH)NH\_2·AcOH, EtOH.

Replacement of 4(5)-imidazoline by 4(5)-imidazole, as in 5 (Table 2), significantly abolishes affinities at uptake sites (-1.2 log units for both SER and NA uptake) but enhances affinity at  $\alpha_2$ -adrenoceptors by 1.9 log units. This result supports the selectivity of the imidazole molety for  $\alpha_2$ -adrenoceptors as exemplified by the structures of atipamezole  $(3)^{15}$  and MPV 1743<sup>30</sup> which are potent and selective  $\alpha_2$ -adrenoceptors antagonists. It implies that affinity at  $\alpha_2$ -adrenoceptors is more tolerant than affinities at bioamine uptake sites to the  $pK_a$  of the critical nitrogen. Addition of an amino group at position 2 of the 4(5)-imidazoline, as in **6**, induces a loss of affinity at  $\alpha_2$ -adrenoceptors (-0.5 log unit) accompanied by an increase of affinity at  $\alpha_1$ -adrenoceptors (0.8 log unit) leading to a  $\alpha_1$ -adrenergic selective molecule, whereas affinities at SER and NA uptake sites are not modified. Replacement of one nitrogen by

### Scheme 9<sup>a</sup>



<sup>*a*</sup> Reagents: (a)  $ICH_2CO_2Et$ , KO-t-Bu, THF; (b) (i)  $NaBH_3CN$ ,  $ZnI_2$ ,  $C_2H_4Cl_2$ , (ii)  $LiAlH_4$ , THF, (iii) IBX, THF; (c) (i) (4- $MeOC_6H_4$ )<sub>2</sub>CHNH<sub>2</sub>, molecular sieves,  $CH_2Cl_2$ , (ii) TMSCN; (d)  $LiAlH_4$ , THF; (e)  $SiO_2$  chromatography:  $CH_2Cl_2/EtOH/NH_4OH$ ; (f) AcOH,  $H_2O$ ; (g) HC(=NH) $NH_2$ ·AcOH, EtOH.

Table 2. Binding Affinities (pKi) at Native Rat Receptors and	ł
Uptake Sites for Compounds with Replacement of the	
4(5)-Imidazoline Residue by Other Heterocycles	

		R	x			
Compd #	R	Х	Adrenoceptor Uptake		take	
			$\alpha_1^a$	$\alpha_2^{a}$	SER <sup>a</sup>	NAª
4a	Н	× ≻_	6.4	7.0	7.4	7.3
5	Н	N N	7.3	8.9	6.2	6.1
6	Н		7.2	6.5	7.4	7.1
7	Н		nt	7.3	6.8	6.3
8a	Н		nt	6.0	7.2	6.0
8b	8-C1		6.5	6.2	nt	< 6
8c	7-CH <sub>3</sub>		6.6	5.8	6.6	< 6
8d	6-CH <sub>3</sub>		nt	5.8	7.1	< 6.0

 $^a$  Mean of at least two independent determinations made in triplicate; the dispersion on  $p\mathit{K}_i$  values is only about 0.2 log unit. nt: not tested.

oxygen, in this specific heterocycle, leads either to the 5-(2-aminooxazoline) or to the 4-(2-aminooxazoline) derivative, **7** and **8** respectively. In the former case, affinity at  $\alpha_2$ -adrenoceptors is preserved, and in the latter case, affinity at SER uptake sites is maintained, indicating that the two intracyclic nitrogen atoms might contribute differently to affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites, respectively. An additional element supporting this analysis lies in the observation that, in **2**, both nitrogens are equivalent and lie in the optimal position for high affinity at  $\alpha_2$ -adrenoceptors, while there is no nitrogen in the position responsible for affinity at SER uptake sites, resulting in a pharmacological profile favoring affinity at  $\alpha_2$ -adrenoceptors.



Figure 2. Imidazoline and imidazole tautomerism.

This mode of analysis is complicated, however, by the tautomerism exhibited by imidazoline and imidazole residues (Figure 2), each nitrogen in both heterocycles being alternatively a basic sp<sup>2</sup> nitrogen with its lone pair of electrons lying in the plane of the five-membered ring (N<sup>3</sup>) or a less basic more sp<sup>3</sup> nitrogen with its lone pair of electrons either conjugated with a  $\pi$ -system or involved in an aromatic ring current (N<sup>1</sup>). In addition, at physiological pH, imidazoline residues are protonated inducing a degeneracy of the electronic properties of the two nitrogens but not of their spatial attributes.

Modification of the 3,4-dihydronaphthalene skeleton, initially by oxidation, leading to the aromatic naphthalenyl derivative 9 (Table 3), results in an increase of the affinity at NA uptake sites only, with no sensible change of affinity at either  $\alpha_2$ -adrenoceptors or SER uptake sites. Reduction of the 3,4-dihydronaphthalenyl group affords **10a** as a mixture of diastereoisomers ( $\approx$ 50/ 50) which exhibits enhanced affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites without any influence on affinity at NA uptake sites. As previously demonstrated for the parent molecule 4a, addition of a 8-chloro substitution to this structure (10b) further increases this effect. In contrast, replacement of the CH<sub>2</sub> group in position 4 by an oxygen atom (**11a**) or a *gem*-dimethyl moiety (12) reduces affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites while keeping affinity at NA uptake sites constant. Replacement of 3,4-dihydronaphthalenyl skeleton by an indene ring (13) increases affinity at  $\alpha_2$ adrenoceptors. In this structure, reduction of the double

**Table 3.** Binding Affinities  $(pK_i)$  at Native Rat Receptors and Uptake Sites for Compounds with Modification of the 3,4-Dihydronaphthalene Moiety

Compd	Structure	Adrenoceptor		Uptake	
#					
		$\alpha_1^a$	$\alpha_2^a$	SER <sup>a</sup>	NAª
4a	N N	6.4	7.0	7.4	7.3
9a		6.0	6.9	7.3	7.8
9b		6.4	7.5	7.5	7.7
10a		6.1	7.8	8.0	7.0
10b		6.5	8.8	8.3	7.0
<b>11</b> a	N N N N N N N N N N N N N N N N N N N	5.8	6.9	6.6	7.2
11b		6.2	7.5	5.9	6.0
11c	N N	6.5	7.3	6.3	6.1
12		6.1	6.0	< 5	7.4
13		5.9	7.8	7.1	7.5
14a		6.3	8.7	7.2	7.4
15a		5.6	7.9	6.0	7.2
15b	F C C N	nt	7.0	6.8	6.1
15c		< 5.5	< 5	< 5	6.8

<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit. nt: not tested.

bond (14a) leads to a selective  $\alpha_2$ -adrenergic ligand by increasing affinity at  $\alpha_2$ -adrenoceptors (1.7 log units compared to 4a) without changing the other interactions. Replacement of the 3-methylene group by oxygen (15a) decreases affinity at SER uptake sites by 1.1 log units compared to 13.

Aromatic substitution of the indan derivatives 14a-e (Table 4) reinforces the SARs discovered in the dihydronaphthalene skeleton (4a-j). Substitution by a fluorine at position 4 (14b equivalent to position 8 in 4c) increases slightly affinity at  $\alpha_2$ -adrenoceptors while depressing slightly affinity at uptake sites and confers overall a selective  $\alpha_2$ -adrenoceptor antagonist profile to the molecule. The same substitution at position 5 (14c equivalent to position 7 in 4f) increases slightly affinity at  $\alpha_2$ -adrenoceptors affinity at SER uptake sites while depressing slightly affinity at  $\alpha_2$ -adrenoceptors and significantly at NA uptake

**Table 4.** Binding Affinities  $(pK_i)$  at Native Rat Receptors and Uptake Sites for Derivatives of Dihydroindans



<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit.

**Table 5.** Binding Affinities  $(pK_i)$  at Native Rat Receptors and Uptake Sites for Compounds with Partial Rigidification of the Skeleton

Compd #	Structure	Adrenoceptor		Uptake	
		$\alpha_1^{a}$	$\alpha_2^a$	SER <sup>a</sup>	NAª
16a		5.9	7.3	7.3	6.1
16b	H N	5.9	7.2	7.7	6.5
17	H H	nt	6.4	< 5.5	6.6
18a		6.3	6.3	6.2	nt
18b	H H N H H N	6.1	5.5	< 6	7.3
19a	C C C C C C C C C C C C C C C C C C C	6.3	8.2	8.7	7.0
19b	<b>H</b> NN	6.0	6.6	7.6	6.4
20a	H N	5.2	7.1	6.4	6.5
20b	H H N N	6.9	9.1	7.3	7.5

<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit. nt: not tested.

sites, conferring an equilibrated  $\alpha_2$ -adrenoceptor antagonist and SER uptake inhibitor profile to the molecule. In an attempt to avoid the new chiral center in position 2 of the indan moiety created by these substitution patterns, symmetrical disubstitution in position 5,6 was investigated. Molecule **14d** demonstrates a profound decreased affinity at  $\alpha_2$ -adrenoceptors and a slight decreased affinity at NA uptake sites, with a significant increased affinity for the SER uptake sites.

In an attempt to clarify the active conformation of these compounds at their different sites of action, the

**Table 6.** Binding Affinities  $(pK_i)$  at Native Rat Receptors and Uptake Sites for Compounds with Complete Rigidification and Methyl Substitution of the Skeleton

Compd	Structure	Adrenoceptor		Uptake	
#					
		$\alpha_1^{a}$	$\alpha_2^{a}$	SER <sup>a</sup>	NA <sup>a</sup>
21a	H NH	6.1	8.0	7.8	6.7
21b	H N NH	6.2	6.1	7.6	< 6
22		5.3	6.2	5.2	< 5
23	H <sub>3</sub> C N H	5.9	6.1	7.2	6.5
24a	N H	6.0	7.1	8.0	6.7
24b	N H	5.7	6.6	7.5	7.2

<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit.

**Table 7.** Binding Affinities ( $pK_i$ ) and Antagonist Potency ( $pK_B$ ) at  $h\alpha_{2A}$ -Receptors Expressed in CHO Cells



<sup>*a*</sup> Mean of at least two independent determinations made in triplicate; the dispersion on  $pK_i$  values is only about 0.2 log unit. skeleton was rigidified by means of cyclopropyl rings (Figure 3). New bonds (1–4) bridging unbonded carbons



Figure 3. Cyclopropyl rigidifications of molecule 4a.

can be added to structure 10, thereby reducing the number of freely rotating bonds to one. These transformations also confine the imidazoline ring to a specific part of the configurational space available to the parent molecule. The 1,2-methano compounds 16a,b demonstrate a decreased affinity at NA uptake sites while affinities at  $\alpha_2$  adrenergic and SER uptake sites are modulated by specific configuration of the diastereoisomer (Table 5). The cyclopropyl derivative obtained when bonds 1 and 3 were reduced to a unique bond (17) loses affinity at all three sites. In contrast, one of the diastereoisomers of the 4-cyclopropyl derivative (18b) retains affinity at NA uptake sites. The most interesting pair of diastereoisomers is obtained when 2 and 3 become the bonds of a cyclopropyl ring leading to 19a,b. Potentiation occurs at  $\alpha_2$ -adrenergic sites (1.1 log units) and SER uptake sites (1.3 log units) without affecting NA uptake sites in one diastereoisomer (19a), while decreased affinity for  $\alpha_2$ -adrenergic sites and NA uptake sites accompanied with a slight increase in affinity at SER uptake sites is obtained in the other diastereoisomer (19b). This trend is not observed when the identical cyclopropyl rigidification is carried out on the indan skeleton. The more potent diastereoisomer (20b) is a selective  $\alpha_2$ -adrenoceptor antagonist.

Total rigidification of the parent molecule (4a) was accomplished in compounds 21a,b where the two diastereoisomers differ only by the spatial position of one of the nitrogen atoms (N<sup>3</sup> in the tautomer drawn, Table 6). In **21a**, this nitrogen is equatorial with its lone pair of electrons projecting perpendicularly to the main plane of the molecule, and in **21b**, this nitrogen is axial with its lone pair of electrons oriented toward the aromatic ring. The other nitrogen atom (N<sup>1</sup> in the tautomer drawn) occupies more or less the same position in the two diastereoisomers. This difference has a profound effect on affinity at  $\alpha_2$ -adrenoceptors (Table 6), **21a** being more potent than **21b** by nearly 2 orders of magnitude. On the other hand, it has a minimal effect regarding affinity at SER uptake sites, 21a being more potent than **21b** by only 0.2 log unit. This result confirms our previous analysis that N<sup>3</sup> is the critical nitrogen atom for  $\alpha_2$ -adrenergic affinity while N<sup>1</sup> controls affinity at SER uptake sites. Recent work by Kozikowski's group on tropane analogues<sup>31</sup> also emphasizes the importance of geometry between aromatic moieties and the basic nitrogen, as Z and E isomers of the phenylmethylene-7-azatricyclo[4.3.1.0<sup>3,7</sup>]decane derivative displayed contrasting activities at NA, SER, and DA uptake sites.

Since neither of our totally rigid compounds is particularly potent at NA uptake sites, we synthesized **21** as an alternative strategy to rigidify the parent molecule **4a** with, in this case, the lone pair of the nitrogen lying in the plane of the aromatic ring. Results from the



**Figure 4.** Critical structural and conformational features for interaction with the  $\alpha_2$  adrenoceptor site and the SER and NA uptake sites.

biological evaluation (Table 6) demonstrate that this orientation is inappropriate as the molecule loses all activity.

The last change envisaged was the introduction of a methyl substituent on the parent molecule (**4a**) either at position 4(5) of the imidazoline (**23**) or at position 2 of the naphthalene moiety (**24a**,**b**). In the former case, this modification has a deleterious effect on affinities at  $\alpha_2$ -adrenoceptors and NA uptake sites whereas affinity at SER uptake sites remained unchanged. In the latter case, one diastereoisomer (**24a**) displays enhancement affinity at SER uptake sites while the other (**24b**) exhibits decreased affinity at  $\alpha_2$ -adrenoceptors.

To sum up, analysis of this series of napamezole (2) analogues reveals several critical features modulating affinities at  $\alpha_2$ -adrenoceptors and SER and NA uptake sites. Notably,  $\alpha_2$ -adrenergic affinity is favored by the presence of a sp<sup>2</sup> nitrogen atom, at a distance from an aromatic ring which is best accommodated by a fouratom chain in extended conformation. This nitrogen must be able to attain a conformation in which its lone pair of electrons points perpendicularly to the plane of the aromatic ring and it is intolerant to steric crowding in its close vicinity. Further, a broad range of  $pK_{as}$ encompassing imidazole (p $K_a \approx 7$ ) and 2-aminoimidazoline (p $K_a > 10$ ) is acceptable for this nitrogen atom. In addition, substituents in position 8 of the dihydronaphthalene, in particular chlorine, selectively enhance this property (structure I, Figure 4).

In contrast, affinity at SER uptake sites is dependent on the presence of a protonated nitrogen atom located at a slightly higher distance from an aromatic ring with a much broader tolerance in terms of the precise orientation of the lone pair of electrons. Potentiation occurs selectively when the aromatic ring is substituted by a fluorine at position 7. On the other hand, systematic replacement of a CH<sub>2</sub> group by an oxygen atom at position 4 of dihydronaphthalene or at position 3 of indene leads to a decreased potency. Both affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites are incompatible with the presence of additional bulky substituents at position 4 of the dihydronaphthalene (structure II, Figure 4).

Finally, affinity at NA uptake sites is more difficult to improve. The only change achieving a significant increase was aromatization of the dihydronaphthalene. This can be understood as a shortening of the distance between a protonated nitrogen atom and an aromatic ring (2 or 3 atoms apart versus 4 or 5 atoms). The most striking effect emerged from the analysis of different means for rigidification of the molecule. Indeed, each rigidification which improved affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites decreased affinity at NA uptake sites and vice versa. This observation reinforces the conviction that a fundamental difference, such as the distance between a critical nitrogen atom and an aromatic ring, exists between these two sets of properties: on the one hand, affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites and, on the other hand, affinity at NA uptake sites. As long as enough flexibility is preserved in the molecule the two conditions are compatible, but as rigidity increases to improve affinities at  $\alpha_2$ -adrenoceptors and SER uptake sites, a conformation necessary to accommodate the NA uptake site becomes inaccessible and, in parallel, potency at this site diminishes. In addition, affinity at NA uptake sites is very sensitive to steric crowding as potency decreases when substitution is implemented at position 4(5) of the imidazoline or position 1 of the tetrahydronaphthalenyl skeleton.

In addition to the results discussed above, we also determined the affinities of specific compounds at  $\alpha_1$ adrenoceptors. In most of cases, these affinities were lower than for  $\alpha_2$ -adrenoceptors with a difference close to 2 log units for the most interesting compounds. Finally, according to the hypothesis stated in the Introduction, these SARs are based on the principle that the interaction at  $\alpha_2$ -adrenoceptors is antagonistic in nature. We verified this by  $[^{35}S]GTP\gamma S$  binding (Table 7). In the absence of the NA, no compound manifested intrinsic activity, whereas the increase of  $[^{35}S]GTP\gamma S$ binding elicited by NA was dose-dependently inhibited by all compounds tested. The  $pK_bs$  were, generally, in good agreement with the  $pK_i$ s determined in the same cell line (Table 7) as the regression curve appears as a straight line with a correlation coefficient and slope close to unity: 0.916 and 0.986, respectively.

On the basis of this analysis, compound **14c** (S 34324) was chosen for further pharmacological characterization of the functionnal properties of  $\alpha_2$ -adrenoceptor antagonist and SER uptake inhibitor endowed with NE uptake inhibition potency. The separation and stereospecific synthesis of the four isomers of **14c** will be reported later. Today, in vivo experiments indicate that compound **14c** is active in behavioral and neurochemical models predictive of antidepressant activity (data not shown).

# **Experimental Section**

Biology. 1. Determination of Affinity for  $r\alpha_1$ -Adrenoceptors. Binding affinity was determined as described<sup>32</sup> by competition with [<sup>3</sup>H]prazosin (Amersham, Les Ulis, France). Rat cerebral cortex was homogenized using a polytron in 20 volumes (w/v) of buffer (50 mM Tris-HCl pH 7.4, 4 mM CaCl<sub>2</sub>, 0.1% w/v ascorbic acid and 10  $\mu$ M). The homogenate was centrifuged (35000*g*, 20 min, 4 °C) and the pellet was resuspended in the same volume of buffer for a second centrifugation. The final pellet was resuspended in 80 volumes of buffer and used for binding (final concentration 1/100 w/v). Membranes were incubated in triplicate with 0.2 nM [<sup>3</sup>H]prazosin

Table 8. Preparation Methods for the Imidazolines 4a-j, 9a, 11a-c, 12, 13, 14a-e, and 15a-c

compd	method	last step yield (%)	formula	elemental analysis	mp (°C)
4b	А	83	$C_{14}H_{15}ClN_2 \cdot C_4H_4O_4$	C, H, N, Cl	191-195
<b>4</b> c	Α	55	$C_{14}H_{15}FN_2 \cdot C_4H_4O_4$	C, H, N	183 - 185
<b>4d</b>	Α	88	$C_{15}H_{16}N_2O \cdot C_4H_4O_4$	H, N; C: calcd, 63.68; found, 63.00	206 - 208
<b>4e</b>	Α	90	$C_{15}H_{16}N_2 \cdot C_4H_4O_4$	H, N; C: calcd, 66.65; found, 66.08	182 - 184
<b>4f</b>	Α	62	$C_{14}H_{15}FN_2 \cdot C_4H_4O_4$	C, N; H: calcd, 4.83; found, 5.25	155 - 157
4g	Α	75	$C_{15}H_{15}F_{3}N_{2}$ · $C_{4}H_{4}O_{4}$	C, H, N	169 - 171
4 <b>h</b>	А	57	$C_{15}H_{18}N_2O \cdot C_4H_4O_4$	C, H, N	136 - 138
<b>4i</b>	А	45	$C_{15}H_{18}N_2 \cdot C_4H_4O_4$	C, H, N	137 - 139
<b>4</b> j	А	48	$C_{15}H_{18}N_2 \cdot C_4H_4O_4$	C, H, N	177 - 178
9a	В	77	$C_{14}H_{14}N_2 \cdot C_4H_4O_4$	C, H, N	149 - 150
11a	А	52	$C_{13}H_{14}N_2O \cdot C_4H_4O_4$	C, H, N	148 - 150
11b	В	73	$C_{12}H_{14}N_2O_2 \cdot C_4H_4O_4$	C, H, N	145 - 146
11c	В	60	$C_{13}H_{16}N_2O \cdot C_4H_4O_4$	C, H, N	137 - 139
12	А	58	$C_{16}H_{20}N_2 \cdot 0.5C_4H_4O_4$	C, H, N	178 - 179
13	А	28	$C_{13}H_{14}N_2 \cdot C_4H_4O_4$	C, H, N	161 - 162
14a	В	64	$C_{13}H_{16}N_2 \cdot 0.5C_4H_4O_4$	C, H, N	208 - 210
14b	В	71	$C_{13}H_{15}FN_2 \cdot 0.5C_4H_4O_4$	H, N; C: calcd, 65.20; found, 64.34	212 - 215
14c	В	59	$C_{13}H_{15}FN_2 \cdot 0.5C_4H_4O_4$	C, H, N	187 - 190
14d	В	78	$C_{13}H_{14}F_2N_2 \cdot 0.5C_4H_4O_4$	C, H, N	201 - 202
14e	В	73	$C_{15}H_{20}N_2 \cdot C_4H_4O_4$	C, H, N	198 - 200
15a	В	66	$C_{12}H_{12}N_2O \cdot C_4H_4O_4$	C, H, N	154 - 156
15b	В	61	$C_{12}H_{11}FN_2O \cdot C_4H_4O_4$	C, H, N	148 - 151
15c	В	57	$C_{18}H_{16}N_2O{\boldsymbol{\cdot}}C_4H_4O_4$	C, H, N	152-153

and competing ligand in a final volume of 0.5 mL, for 1 h at 22 °C. Nonspecific binding was defined with 10  $\mu M$  phentolamine.

**2.** Determination of Affinity for  $r\alpha_2$ -Adrenoceptors. Binding affinity was determined as described<sup>33</sup> by competition with [<sup>3</sup>H]RX 821002 (Amersham, Les Ulis, France). Rat cerebral cortex was homogenized using a polytron in 20 volumes (w/v) of buffer (Tris-HCl 50 mM, pH 7.5 at 25 °C, EDTA 1 mM and guanylyl imidodiphosphate, GppNHp, 100  $\mu$ M). The homogenate was centrifuged (35000*g*, 20 min, 4 °C) and the pellet was resuspended in the same volume of buffer for a second centrifugation. The final pellet was resuspended in 300 volumes of buffer and used for binding (final concentration 1/400 w/v). For binding experiments membranes were incubated with [<sup>3</sup>H]RX 821002 (0.4 nM final) and competing ligand for 1 h at 22 °C. Nonspecific binding was defined with phentolamine (10  $\mu$ M).

**3.** Determination of Affinity for CHO-h $\alpha_{2A}$ -Adrenoceptors. Binding affinity was determined as described<sup>32</sup> by competition with [<sup>3</sup>H]RX 821002 (Amersham, Les Ulis, France). Membranes were prepared from CHO-h $\alpha_{2A}$  cells stably expressing the human adrenergic  $\alpha_{2A}$ -receptor (provided by Prof. A. D. Strosberg, Inst. Cochin, Paris, France). Cells grown in adherent culture were harvested by centrifugation and homogenized using a polytron. The homogenate was centrifuged (43000*g*, 30 min, 4 °C) and the membrane pellet resuspended in buffer (Tris-HCl 33 mM, pH 7.5, EDTA 1 mM) with 10 strokes in a Potter homogenizer sonicated for 15 s and stored at -80 °C until use. For binding experiments, ~10 µg membranes were incubated with [<sup>3</sup>H]RX 821002 (0.8 nM final) and competing ligand, for 1 h at 22 °C. Nonspecific binding was defined with phentolamine (10  $\mu$ M).

4. [<sup>35</sup>S]GTP $\gamma$ S Binding Assay. Efficacy at CHO-h $\alpha_{2A}$  receptors was determined by the binding of [<sup>35</sup>S]GTP $\gamma$ S (Amersham, Les Ulis, France) as described.<sup>29</sup> Membranes (40  $\mu$ g/mL) were preincubated 30 min at room temperature in the presence of drugs or GTP $\gamma$ S diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3  $\mu$ M GDP and 3mM MgCl<sub>2</sub>). Incubation was started by the addition of 0.2 nM [<sup>35</sup>S]GTP $\gamma$ S and further followed 60 min at room temperature. Nonspecific binding was defined using nonradiolabeled GTP $\gamma$ S (10  $\mu$ M).

**5. Ligand Binding at Native Rat SER Reuptake Sites.** Binding affinity was determined as described<sup>34</sup> by competition with [<sup>3</sup>H]paroxetine (NEN, Les Ulis, France). Membranes were prepared from rat frontal cortex by homogenization with a polytron followed by two centrifugations at 20000*g*. The pellet was resuspended each time in incubation buffer. The final resuspension was made in 40 volumes of buffer. For binding experiments, freshly prepared membranes (final concentration 1/80 w/v) were incubated in triplicate with 2nM [<sup>3</sup>H]paroxetine and competing ligand in a final volume of 0.4 mL for 2 h at 25 °C. The high concentration of [<sup>3</sup>H]paroxetine was necessary due to its low specific activity (<20 Ci/mmol). The incubation buffer contained 50 nM Tris-HCl (pH 7.4), 120 nM NaCl and 5 mM KCl. Nonspecific binding was defined with 10  $\mu$ M citalopram.

**6. Ligand Binding at Native Rat NA Reuptake Sites.** Binding affinity was determined as described<sup>35</sup> by competition with [<sup>3</sup>H]nisoxetine (Amersham, Les Ulis, France). Membranes were prepared from rat frontal cortex by homogenization with a polytron followed by two centrifugations at 20000*g*. The pellet was resuspended each time in 60 volumes of incubation buffer. For binding experiments, freshly prepared membranes (final concentration 1/100 w/v) were incubated in triplicate with 2 nM [<sup>3</sup>H]nisoxetine and competing ligand in a final volume of 0.5 mL for 4 h at 4 °C. The incubation buffer contained 50 mM Tris-HCl (pH 7.4), 120 mM NaCl and 5 mM KCl. Nonspecific binding was defined with 10 µM desipramine.

In all the experiments, at the end of the incubation period, membranes were filtered through Whatman GF/B filters pretreated with 0.1% de polyethylenimine followed by three successive washes with ice-cold buffer. Radioactivity retained on the filters was determined by scintillation counting.

**7. Data Analysis.** Binding isotherms were analyzed by nonlinear regression using the program Prism (GraphPad Software Inc., San Diego, CA) to determine  $IC_{50}$  values. These were converted to inhibition constants ( $K_i$ ) via the Cheng–Prusoff equation:<sup>36</sup>  $K_i = IC_{50}/\{(L/K_D) - 1\}$ , where L is the concentration of [<sup>3</sup>H]ligand and  $K_D$  is its dissociation constant. In practice, the amount of free [<sup>3</sup>H]ligand varies minimally (<10%) from the total [<sup>3</sup>H]ligand. The  $K_D$  values were: 0.4 nM for [<sup>3</sup>H]RX 821002 at rat  $\alpha_2$ -receptors and 0.4 nM at h $\alpha_{2A}$ -receptors, 0.1 nM for [<sup>3</sup>H]paroxetine.

In the GTP $\gamma$ S binding experiment, antagonist potencies are expressed as  $pK_B = -\log K_B$ , with  $K_B = IC_{50}/1 + ([ago]/EC_{50}-ago)$ , where  $IC_{50}$  is the inhibitory concentration of antagonist that gives 50% inhibition of [<sup>35</sup>S]GTP $\gamma$ S binding in the presence of a fixed concentration of agonist ([ago], NA 10  $\mu$ M) and  $EC_{50}$ ago is the EC<sub>50</sub> of the agonist when tested alone.

**Chemistry.** Reagents were commercially available and of synthetic grade. <sup>1</sup>H NMR spectra relative to TMS were recorded on Bruker 200 or 400 MHz spectrometers. Infrared spectra were obtained as Nujol emulsion, on a Bruker Fourier transform spectrometer. All new substances were homo-

geneous in TLC and exhibited spectroscopic data consistent with the assigned structures. Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 instrument and are in agreement with the calculated values within the  $\pm 0.4\%$  range unless otherwise stated. Melting points were obtained on a Reichert hot stage microscope and are uncorrected. Silica gel 60, Merck 230–400 mesh, was used for both flash and medium-pressure chromatography. TLC were performed on precoated 5-  $\times$  10-cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm).

Method A: 4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (4a). Ethyl (3,4-Dihydronaphthalen-2-yl)acetate (25a). A solution of triethyl phosphonoacetate (56 g, 0.25 mol) in anhydrous THF (70 mL) was added dropwise to a suspension of NaH (6 g, 0.25 mol) in anhydrous THF maintained at 0 °C under an N<sub>2</sub> atmosphere. The reaction mixture was stirred at 10 °C for 30 min, cooled at 0 °C and a solution of  $\beta$ -tetralone **24a** (36.5 g, 0.25 mol) in anhydrous THF (50 mL) was added dropwise. The solution was stirred for 3 h at 20 °C, hydrolyzed at 0 °C by the addition of water (200 mL). The organic solvents were evaporated under reduced pressure and the residue extracted with  $CH_2Cl_2$  (3  $\times$ 200 mL). The combined organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford 25a as a brown oil which was purified through vacuum distillation as a colorless oil (46.5 g, 86%), bp 88-91 °C/0.03 mmHg. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.20-6.95 (m, 4H), 6.35 (s, 1H), 4.20 (q, 2H), 3.20 (s, 2H), 2.85 (t, 2H), 2.35 (t, 2H), 1.25 (t, 3H).

(3,4-Dihydronaphthalen-2-yl)acetaldehyde (26a). A solution of DIBAL-H in CH<sub>2</sub>Cl<sub>2</sub> (1 M, 170 mL) was added dropwise to a solution, cooled at -60 °C, of 25a (18.6 g, 0.086 mol) in CH<sub>2</sub>Cl<sub>2</sub> (360 mL). After 2 h stirring at -60 °C, the reaction mixture was hydrolyzed by successive additions of NH<sub>4</sub>Cl (10%, 35 mL) and HCl (1 N, 42 mL). The temperature was brought to 20 °C in 1 h and the solid was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The pooled filtrates were washed with water (100 mL) and brine, dried (MgSO<sub>4</sub>) and concentrated. The crude product was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 95/5) to yield **26a** as a colorless oil (9.2 g, 62%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.75 (t, 1H), 7.15–6.95 (m, 4H), 6.40 (s, 1H), 3.30 (s, 2H), 2.85 (t, 2H), 2.30 (t, 2H).

**2-Amino-3-(3,4-dihydronaphthalen-2-yl)propionitrile (27a).** A solution of **26a** (3.44 g, 20 mmol) and  $ZnI_2$  (0.25 g, 0.8 mmol) in  $CH_2Cl_2$  (100 mL) was treated dropwise with TMSCN (2.18 g, 22 mmol). After 20 h stirring, the solution was evaporated under reduced pressure and the residue poured into a solution of  $NH_3$  in MeOH (7 N, 200 mL). The reaction mixture was kept in a sealed vessel for 4 h and concentrated. The residue was taken up in HCl (1 N, 100 mL), washed with ether (50 mL), the aqueous phase was basified by addition of NaOH (6 N) and extracted with  $CH_2Cl_2$  (3 × 50 mL). The pooled organic phases were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford **27a** as an oil (2.8 g, 71%) used without purification.

**3-(3,4-Dihydronaphthalen-2-yl)propane-1,2-diamine** (**28a**). A mixture of **27a** (2.57 g, 13 mmol), Raney Ni (2 g) in MeOH (120 mL) and a solution of NH<sub>3</sub> in MeOH (7 N, 50 mL) was hydrogenated under 1 atm for 16 h. The reaction mixture was filtered over Celite, concentrated and purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH = 90/9/1) to yield **28a** as a colorless oil (1.45 g, 55%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.10 (m, 3H), 6.95 (d, 1H), 6.25 (s, 1H), 3.20 (m, 1H), 2.85 (dd, 1H), 2.70 (m, 3H), 2.25 (d, 2H), 2.10 (t, 2H).

**4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (4a).** A mixture of **28a** (0.50 g, 2.5 mmol) and formamidine acetate (0.29 g, 2.75 mmol) in EtOH (20 mL) was stirred for 20 h. The solvent was evaporated under reduced pressure and the residue was taken up in  $CH_2Cl_2$  (10 mL). After treatment with NaOH (2 N, 5 mL), the aqueous phase was extracted with  $CH_2Cl_2$  (3 × 20 mL). The pooled organic phases were dried (MgSO<sub>4</sub>) and concentrated. The remaining oil was dissolved in EtOH (10 mL) and treated with a solution of fumaric acid (290 mg, 2.5 mmol) in EtOH (5 mL); **4a** was obtained as a white powder (0.53 g, 65%), mp 165–166 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.20 (m, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 6.30 (s, 1H), 4.40 (m, 1H), 3.85 (t, 1H), 3.45 (dd, 1H), 2.75 (t, 2H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

Following the typical procedure described above, part of the imidazolines listed in Table 8 were prepared, starting from the appropriate tetralones.

**2-Amino-4(5)-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Bromhydrate (6).** A solution of BrCN (0.12 g, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise to a solution of **28a** (0.21 g, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), cooled at 0 °C. After 2 h stirring, the solid was collected by filtration and dried to afford **6** as a white powder (0.23 g, 75%), mp 143 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  7.10 (m, 3H), 7.05 (d, 1H), 6.30 (d, 1H), 4.20 (m, 1H), 3.70 (t, 1H), 3.30 (dd, 1H), 2.75 (t, 2H), 2.40 (m, 2H), 2.20 (t, 2H). Anal. (C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>·HBr) C, H, N, Br.

2-Amino-4-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5dihydrooxazole, Hydrochloride (7). 2-Amino-3-(3,4-dihydronaphthalen-2-yl)propionic Acid, Hydrochloride (30). A solution of 27a (4.14 g, 21 mmol) in formic acid (20 mL) was saturated at 0 °C with anhydrous HCl. When the gas evolution subsided, the acid was evaporated under reduced pressure and the waxy residue was dissolved in HCl (6 N, 30 mL) and brought to reflux overnight. The solvent was evaporated under reduced pressure and the residue crystallized from EtOH to afford **30**-HCl as a white powder (4.88 g, 92%). <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  9.50–8.20 (bd, 4H), 7.20–7.00 (m, 4H), 6.35 (s, 1H), 4.05 (m, 2H), 3.00–2.70 (m, 4H), 2.40–2.00 (m, 2H).

2-Amino-4-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5dihydrooxazole, Hydrochloride (7). A suspension of 30. HCI (5.32 g, 21 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at -10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive careful addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred for 45 min, filtered and the filtrate concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>4</sub>OH = 90/9/1) to afford 2-amino-3-(3,4-dihydronaphthalen-2-yl)propanol as a colorless oil (1.49 g, 35%). A solution of BrCN (0.90 g, 8.6 mmol) in THF (20 mL) was added dropwise at 0 °C, to a solution of the amino alcohol in THF (12 mL) in the presence of K<sub>2</sub>CO<sub>3</sub> (1.20 g, 8.6 mmol). After 1 h stirring at room temperature, the solid was filtered and the THF was evaporated under reduced pressure. The residue was taken up in EtOH (25 mL) and treated with ethereal HCl. The precipitate was then filtered and recrystallized from a *i*-PrOH (10 mL)/diethyl ether (30 mL) mixture to give 7 as a white powder (0.45 g, 16%), mp 168-170 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  9.50–8.50 (bd, 3H), 7.20–6.95 (m, 4H), 6.35 (s, 1H), 4.85 (m, 1H), 4.60-4.35 (m, 2H), 2.90-2.65 (m, 3H), 2.60 (m, 1H), 2.25 (m, 2H). Anal. (C14H16N2O·HCl) C, H, N.

2-Amino-5-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5dihydrooxazole, Fumarate (8a). 2-Hydroxy-3-(3,4-dihydronaphthalen-2-yl)propionitrile (29a). A solution of 26a (3.44 g, 20 mmol) and  $ZnI_2$  (0.25 g, 0.8 mmol) in  $CH_2Cl_2$  (100 mL) was treated dropwise with TMSCN (2.18 g, 22 mmol). After 20 h stirring, the solution was evaporated under reduced pressure and the residue was used without further purification.

**2-Amino-5-[(3,4-dihydronaphthalen-2-yl)methyl]-4,5dihydrooxazole, Fumarate (8a).** A solution of **29a** (15.6 g, 79 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at -10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive careful addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred for 45 min, filtered and the filtrate concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>4</sub>OH = 90/9/1) to afford 2-amino-3-(3,4-dihydronaphthalen-2-yl)propanol as a colorless oil (5.90 g, 37%). To a solution of the amino alcohol (1 g, 5 mmol) in THF (30 mL) in the presence of  $K_2CO_3$  (0.75 g, 5.4 mmol), a solution of BrCN (0.57 g, 5.4 mmol) in  $CH_2Cl_2$  (5 mL) was added dropwise at 0 °C. After 1 h stirring at room temperature, the solid was filtered and the THF was evaporated under reduced pressure. The oily residue was dissolved in EtOH (25 mL) and treated with fumaric acid (0.25 g, 2.15 mmol). The mixture was refluxed for 30 min and stirred at 20 °C for 3 h. The solid **8a** was collected by filtration and dried under vacuum as a white powder (0.43 g, 30%), mp 213 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.20–7.00 (m, 4H), 7.75 (d, 1H), 6.45 (s, 1H), 6.35 (s, 1H), 5.00 (m, 1H), 3.80 (dd, 1H), 3.40 (dd, 1H), 2.80 (t, 2H), 2.60 (m, 2H), 2.25 (t, 2H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

**2-Amino-5-[(8-chloro-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8b).** The compound was obtained as described for **8a**, as a white powder (32%), mp 186–188 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  7.25 (m, 1H), 7.15 (m, 2H), 6.70 (s, 1H), 6.45 (s, 2H), 5.25 (m, 1H), 3.90 (t, 1H), 3.50 (dd, 1H), 2.80 (t, 2H), 2.75 (m, 2H), 2.30 (t, 2H). Anal. (C<sub>14</sub>H<sub>15</sub>ClN<sub>2</sub>O·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

**2-Amino-5-[(7-methyl-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Fumarate (8c).** The compound was obtained as described for **8a**, as a white powder (24%), mp 190–192 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  7.00 (m, 1H), 6.90 (d, 1H), 6.85 (s, 1H), 6.45 (s, 2H), 6.30 (s, 1H), 5.20 (m, 1H), 3.85 (t, 1H), 3.45 (m, 1H), 2.65 (m, 4H), 2.20 (m, 5H). Anal. (C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

**2-Amino-5-[(6-methyl-3,4-dihydronaphthalen-2-yl)methyl]-4,5-dihydrooxazole, Hemifumarate (8d).** The compound was obtained as described for **8a**, as a white powder (31%), mp 214–215 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  6.95 (d, 3H), 6.40 (s, 2H), 6.30 (s, 1H), 5.05 (m, 1H), 3.80 (t, 1H), 3.35 (dd, 1H), 2.70 (t, 2H), 2.55 (t, 2H), 2.25 (m, 5H). Anal. (C<sub>15</sub>H<sub>18</sub>-ClN<sub>2</sub>O·0.5C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

**4(5)-[(1,2,3,4-Tetrahydronaphthalen-2-yl)methyl]-4,5dihydroimidazole, Succinate (10a).** A solution of **4a** (1 g, 3 mmol) in EtOH (20 mL) was hydrogenated in the presence of Pd/C (10%, 100 mg) under 1 atm. After 2 h, the catalyst was filtered through glass fibers and the solvent evaporated under reduced pressure. The waxy residue was concentrated through scratching in acetone (10 mL); compound **10a** was obtained as a white powder (0.99 mg, 98%), mixture (45/55) of the two diastereoisomers, mp 158–159 °C. <sup>1</sup>H NMR (DMSO $d_6$ ):  $\delta$  8.15 (s, 1H), 7.05 (m, 4H), 4.30 (m, 1H), 3.90–3.40 (m, 2H), 2.80 (dd, 3H), 2.40 (dd, 1H), 2.25 (s, 4H), 1.85 (m, 2H), 1.70–1.40 (m, 3H). Anal. (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>) C, H, N.

Method B: 4(5)-(8-Chloro-2-naphthylmethyl)-4,5-dihydroimidazole, Fumarate (9b). 8-Chloro-2-methyl-1,2,3,4tetrahydronaphthalen-2-ol (32). To a cooled (-40 °C) solution of TiCl<sub>4</sub> (1 M, 90 mL) in CH<sub>2</sub>Cl<sub>2</sub>, MeMgBr (3 M, 30 mL) in THF was added over 30 min. To the resulting mixture, 8-chloro-2-tetralone (31; 13.5 g, 74.8 mmol) dissolved in CH<sub>2</sub>-Cl<sub>2</sub> (60 mL) was added over 30 min. The resulting mixture was then warmed to 0 °C. After 3 h, the suspension was poured over ice (300 g), the layers were separated, the organic phase was washed with HCl (2 N, 100 mL) and brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated to afford **32** as a brown solid (14.1 g, 96%) used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.30–7.00 (m, 3H), 3.15–2.70 (m, 4H), 2.00–1.65 (m, 2H), 1.60 (m, 1H), 1.40 (s, 3H).

**1-Chloro-7-methylnaphthalene (33).** A mixture of **32** (14.2 g, 72 mmol), trityl-OH (21.9 g, 84 mmol) and CF<sub>3</sub>CO<sub>2</sub>H (54 mL) was stirred at room temperature for 2 days. The mixture was then extracted with cyclohexane ( $3 \times 100$  mL), the pooled organic phases were washed with H<sub>2</sub>O (100 mL), NaHCO<sub>3</sub> (5%, 100 mL) and brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated to give a brown oil which was purified by flash column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 95/5) to afford **33** as a colorless oil (10.5 g, 85%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.05 (d, 1H), 7.75 (d, 1H), 7.70 (dd, 1H), 7.55 (m, 1H), 7.35 (dd, 1H), 7.25 (m, 1H), 2.55 (s, 3H).

1-Chloro-7-bromomethylnaphthalene (34). A solution of 33 (10.8 g, 61.2 mmol), NBS (11.4 g, 64 mmol) and AIBN (0.8

g, 5.1 mmol) in CCl<sub>4</sub> (175 mL) was heated under reflux for 1 h. The suspension was then cooled to 10 °C, filtered and the filtrate concentrated to afford **34** (10.5 g, 76%) as a white solid, mp 123–124 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.15 (d, 1H), 7.95 (d, 1H), 7.70 (d + dd, 2H), 7.85 (d, 1H), 7.75 (d, 1H), 7.35 (t, 1H), 4.70 (s, 2H).

**2-Amino-3-(8-chloro-2-naphthyl)propionitrile (35).** A solution of **34** (5 g, 19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) was added dropwise under an N<sub>2</sub> atmosphere, to a cooled (0 °C) suspension of *N*-(diphenylmethylene)aminoacetonitrile (4.5 g, 20.4 mmol), tetrabutylamonium bromide (0.6 g, 1.86 mmol) and powdered KOH (85%, 1.3 g, 19.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL). After stirring for 1 night at room temperature, the suspension was filtered and the filtrate concentrated. The resulting oily residue was taken up in ether (200 mL) and HCl (1 N, 200 mL) and stirred vigorously overnight. The aqueous phase was separated, basified with NaOH (6 N), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 80 mL), dried (MgSO<sub>4</sub>) and concentrated to afford compound **35** as a brown oil (3.3 g, 73%) which was used without further purification.

**4(5)-(8-Chloro-2-naphthylmethyl)-4,5-dihydroimidazole, Fumarate (9b).** Starting from **35**, the compound **9b** was obtained as described for **4a**, as a white powder (86%), mp 172-175 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.05 (s, 1H), 8.00 (d, 1H), 7.95 (d, 1H), 7.90 (dd, 1H), 7.65 (dd, 1H), 7.45 (t, 1H), 6.45 (s, 2H), 4.50 (m, 1H), 3.75 (m, 1H), 3.50 (m, 1H), 3.10 (m, 2H). Anal. (C<sub>14</sub>H<sub>13</sub>ClN<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N, Cl.

Following the typical procedures described above, some of the imidazolines listed in Table 8 were prepared, starting from the appropriate bromides.

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]imidazole, Fumarate (5). 4-[(1,2,3,4-Tetrahydronaphthalen-1-on-2yl)methyl]-1-tritylimidazole (38). A mixture of 1-tetralone (0.73 g, 5 mmol), potassium *tert*-butylate (0.56 g, 5 mmol) and 4-chloromethyl-1-tritylimidazole (37; 1.8 g, 5 mmol) in toluene (30 mL), was brought to reflux for 5 h. The solvents were then evaporated, the residue taken up in a mixture of  $CH_2Cl_2/H_2O$ (50 mL/50 mL), the organic phase separated, dried (MgSO<sub>4</sub>) and concentrated. The residual solid was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 3/1) to afford **38** as a white solid (0.59 g, 25%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.90 (d, 1H), 7.50 (t, 1H), 7.40–7.10 (m, 11H), 7.05 (m, 6H), 6.50 (s, 2H), 3.00 (t, 2H), 2.90 (AB system, 4H), 2.15 (t, 2H).

**4-[(1,2,3,4-Tetrahydronaphthalen-1-ol-2-yl)methyl]-1tritylimidazole (39).** A mixture of **38** (0.12 g, 0.25 mmol) and NaBH<sub>4</sub> (0.04 g, 1 mmol) in MeOH (12 mL) was stirred overnight. Solvent was then evaporated, the residue taken up in a mixture of Ether/H<sub>2</sub>O (20 mL/20 mL), the organic phase separated, dried (MgSO<sub>4</sub>) and concentrated to afford **39** as a mixture of two diastereoisomers (0.10 g, 93%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.65 (d, 1H), 7.35 (m, 11H), 7.15 (m, 8H), 6.60 (2s, 1H), 4.60 (2d, 1H), 2.90–2.70 (m, 4H), 2.05 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H).

4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]imidazole, Fumarate (5). To a solution of 39 (0.61 g, 1.3 mmol) in CH<sub>2</sub>-Cl<sub>2</sub> (30 mL), CF<sub>3</sub>CO<sub>2</sub>H (1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise at 0 °C. The solution was stirred overnight, solvent was then evaporated, the residue taken up in HCl (0.5 N, 100 mL), the aqueous phase washed with ether (2  $\times$  100 mL), basified with NaOH (38%) up to pH 14, extracted with CH2- $Cl_2$  (2  $\times$  100 mL), dried (MgSO<sub>4</sub>) and concentrated. The residual solid was purified by column chromatography (SiO<sub>2</sub>,  $CH_2Cl_2/EtOH/NH_4OH = 95/4.5/0.5$ ), dissolved in acetone (15) mL) and fumaric acid (0.12 g) in *i*-PrOH (2.5 mL) was added and 5 was obtained by filtration as an off-white solid (0.24 g, 56%), mp 138.5–140.5 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.70 (s, 1H), 7.10 (m, 3H), 6.95 (d, 1H), 6.85 (s, 1H), 6.60 (s, 2H), 6.25 (s, 1H), 4.00-3.00 (m, 2H), 3.40 (s, 2H), 2.70 (t, 2H), 2.20 (t, 2H). Anal. (C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) H, N; C: calcd, 66.25; found, 65.73.

**4(5)-(1,2,3,7b-Tetrahydrocyclopropa**[*a*]**naphthalen-1***a***ylmethyl)-4,5-dihydroimidazole, Fumarate (16a). Ethyl 1-(1,2,3,7b-Tetrahydrocyclopropa**[*a*]**naphthalen-1***a***-yl)-acetate (40).** A solution of Et<sub>2</sub>Zn in hexane (1 M, 200 mL) and a solution of ICH<sub>2</sub>Cl (71 g, 400 mmol) in 1,2-dichloroethane

(125 mL) were added successively dropwise to a solution of **25a** (7.2 g, 33 mmol) in 1,2-dichloroethane (75 mL) cooled at -25 °C. The temperature of the reaction mixture was brought to 10 °C and maintained at that temperature under stirring for 4 h. After cooling to 0 °C, the mixture was treated with saturated NH<sub>4</sub>Cl (50 mL) then water (100 mL) and extracted with ether (3 × 200 mL). The pooled organic phases were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford **40** as an oil (7.4 g, 98%) which was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20 (m, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 7.00 (m, 1H), 4.45 (q, 2H), 2.75–2.45 (m, 2H), 2.60 (d, 1H), 2.35 (d, 1H), 2.20 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.25 (t, 3H), 1.15 (m, 1H), 0.90 (m, 1H).

1-(1,2,3,7b-Tetrahydrocyclopropa[a]naphthalen-1ayl)acetaldehyde (41). A solution of compound 40 (5 g, 21.5 mmol) in anhydrous THF (75 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (0.97 g, 25 mmol) in anhydrous THF (75 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 7 mL), followed by ether (250 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (18.5 mL, 226.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (360 mL) at 0 °C under a N<sub>2</sub> atmosphere, was added CrO<sub>3</sub> (11.60 g, 116.2 mmol). After stirring for 1 h at room temperature, alcohol obtained from 40 (3.64 g, 19.4 mmol) in solution in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated The residue was diluted with Et<sub>2</sub>O, washed with 1 N NaOH, 1 N HCl and brine, dried (MgSO<sub>4</sub>) and concentrated to give the pure aldehyde  ${\bf 41}$ (3.05 g, 79%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.85 (s, 1H), 7.30– 6.95 (m, 4H), 2.80-2.35 (m, 4H), 2.15 (m, 1H), 1.85 (dd, 1H), 1.65 (m, 1H), 1.25 (m, 1H), 0.90 (m, 1H).

4(5)-(1,2,3,7b-Tetrahydrocyclopropa[a]naphthalen-1aylmethyl)-4,5-dihydroimidazole, Fumarate (16a,b). Starting from the aldehyde **41**, the compound was obtained as described for 4a, as a mixture of diastereoisomers (50/50) which were separated by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>- $Cl_2/MeOH/NH_4OH = 95/4.5/0.5$ ). Each diastereoisomer was salified as the fumarate and crystallized from a mixture of i-PrOH/acetone as a white powder. Diastereoisomer 1, 16a (12%), mp 192 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.20 (s, 1H), 7.20 (dd, 1H), 7.15-7.00 (m, 3H), 6.45 (s, 2H), 4.35 (m, 1H), 2.60 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.80-1.65 (m, 2H), 1.50 (m, 1H), 1.05 (m, 1H), 0.80 (m, 1H). Anal. (C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N. Diastereoisomer 2, **16b** (10%), mp 204 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  7.95 (s, 1H), 7.20 (m, 1H), 7.15-6.95 (m, 3H), 6.40 (s, 2H), 4.25 (m, 1H), 3.85 (m, 1H), 3.40 (m, 1H), 2.70-2.35 (m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.05 (m, 1H), 0.85 (m, 1H). Anal.  $(C_{15}H_{18}N_2 \cdot C_4H_4O_4)$  C, H, N.

**4(5)-(1a,2,3,7b-Tetrahydro-1***H*-cyclopropa[*a*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (17). 1a,2,3,7b-Tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylic Acid, Ethyl Ester (42). To a solution of 1,2-dihydronaphthalene (6.5 g, 50 mmol) and Rh<sub>2</sub>(AcO)<sub>4</sub> (51 mg, 0.11 mmol) in ether (30 mL), N<sub>2</sub>CHCO<sub>2</sub>Et (5.7 g, 50 mmol) dissolved in ether (15 mL) was added, at room temperature, at the rate of 2.5 mL/h. The reaction mixture was filtered over Al<sub>2</sub>O<sub>3</sub> (10 g), the solids rinsed with ether (100 mL) and the pooled filtrates concentrated. The oily residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 1.25%) to afford the isomers *syn* (2.7 g, 25%) and *anti* (42; 3.68 g, 34%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.35–6.90 (m, 4H), 6.15 (q, 2H), 2.80–2.30 (m, 3H), 2.30–2.10 (m, 2H), 2.05 (m, 1H), 1.90–1.60 (m, 1H), 1.25 (t, 3H).

**1a,2,3,7b-Tetrahydro-1***H***-cyclopropa[a]naphthalene-1carboxaldehyde (43).** A solution of compound **42** (2.6 g, 12 mmol) in anhydrous THF (75 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (0.7 g, 18 mmol) in anhydrous THF (75 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 7 mL), followed by ether (250 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (11.4 mL, 140 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) at 0 °C under a N<sub>2</sub> atmosphere was added CrO<sub>3</sub> (7.25 g, 72.7 mmol). After stirring for 1 h at room temperature, alcohol prepared from **42** dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated. The residue was diluted with Et<sub>2</sub>O, washed with 1 N NaOH, 1 N HCl and brine, dried (MgSO<sub>4</sub>) and concentrated to give the pure aldehyde **43** (1.63 g, 79%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.35 (d, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 7.00 (m, 1H), 2.75–2.60 (m, 2H), 2.50 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H).

**4(5)-(1a,2,3,7b-Tetrahydro-1***H***-cyclopropa**[*a*]**naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (17).** Starting from the aldehyde **43**, the compound was obtained as described for **4a**, as a mixture of diastereoisomers (55/45) which was salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (61%), mp 95 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.30 (s, 1H), 7.30–7.25 (2d, 1H), 7.15–6.95 (m, 3H), 6.45 (s, 2H), 3.90 (m, 2H), 3.55–3.45 (2m, 1H), 2.65–2.35 (m, 2H), 2.10–2.00 (2m, 2H), 1.65–1.55 (m, 3H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

4(5)-(1a,2,7,7a-Tetrahydro-1*H*-cyclopropa[*b*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (18a,b). 1a,2,7,-7a-Tetrahydro-1H-cyclopropa[b]naphthalene-1-carboxylic Acid, Ethyl Ester (44a,b). To a solution of 1,4dihydronaphthalene (4.32 g, 33 mmol) and Rh(AcO)<sub>4</sub> (73 mg, 0.17 mmol) in ether (100 mL), N2CHCO2Et (3.8 g, 33 mmol) dissolved in ether (21.5 mL) was added, at room temperature, at the rate of 4 mL/h. The reaction mixture was filtered over  $\mathrm{Al}_2\mathrm{O}_3$  (10 g), the solids rinsed with ether (100 mL) and the pooled filtrates concentrated. The oily residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt: 1%) to afford the isomers anti (44a; 1.4 g, 20%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 7.10 (m, 2H), 7.00 (m, 2H), 4.10 (q, 2H), 3.20-3.00 (m, 4H), 2.00 (m, 2H), 1.50 (m, 1H), 1.25 (m, 3H). And syn (44b; 1.97 g, 28%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.05 (m, 4H), 3.75 (q, 4H), 3.20-3.00 (m, 4H), 1.85-1.65 (m, 3H), 1.10 (t, 3H).

1a,2,3,7b-Tetrahydro-1H-cyclopropa[a]naphthalene-1carbaldehyde (45a). A solution of compound 44a (1.4 g, 6.5 mmol) in anhydrous THF (50 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (0.37 g, 9.8 mmol) in anhydrous THF (50 mL) cooled at 0 °C. After 2 h stirring at room temperature, the reaction mixture was hydrolyzed by the cautious addition of NaOH (1 N, 0.4 mL), followed by ether (100 mL). The suspension was stirred for 2 h, filtered and the filtrate concentrated. To a solution of pyridine (6.15 mL, 75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C under a N<sub>2</sub> atmosphere was added CrO<sub>3</sub> (3.92 g, 39 mmol). After stirring for 1 h at room temperature, alcohol prepared from **44a** dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered and the filtrate evaporated The residue was diluted with Et<sub>2</sub>O, washed with 1 N NaOH, 1 N HCl and brine, dried (MgSO<sub>4</sub>) and concentrated to give the pure aldehyde 45a (0.62 g, 55%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.15–7.00 (m, 4H), 3.50 (d, 2H), 3.05 (m, 4H), 1.25 (bd, 1H), 1.20 (m, 2H), 0.90 (m, 1H).

**4(5)-(1a,2,7,7a-Tetrahydro-1***H***-cyclopropa**[*b*]**naphtha-len-1-yl)-4,5-dihydroimidazole, Fumarate (18a).** Starting from the aldehyde **45a**, the compound was obtained as described for **4a**, salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (61%), mp 194 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  7.70 (s, 1H), 7.15–7.00 (m, 4H), 6.35 (s, 2H), 3.80–3.60 (m, 2H), 3.30 (m, 1H), 3.10–2.85 (m, 4H), 1.30 (m, 2H), 0.60 (m, 1H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) H, N; C: calcd 69.86; found 69.41.

**4(5)-(1a,2,7,7a-Tetrahydro-1***H*-cyclopropa[*b*]naphthalen-1-yl)-4,5-dihydroimidazole, Fumarate (18b). Starting from the ester **44b**, the compound was obtained as described for **18a**, salified as the fumarate and crystallized from a mixture of *i*-PrOH/acetone as a white powder (41%), mp 185– 187 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.10 (s, 1H), 7.05 (m, 4H), 6.45 (s, 1H), 3.70 (m, 1H), 3.55–3.30 (m, 2H), 3.25–2.65 (m, 4H), 1.45 (m, 2H), 1.15 (m, 1H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

4(5)-{Spiro[cyclopropane-2':2"-(1",2",3",4"-tetrahydronaphthalene)]-1'-yl}-4,5-dihydroimidazole, Fumarate (19a). (1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)phosphonic Acid, Diethyl Ester (48). A solution of 1-tetralone (10 g, 68 mmol) in anhydrous THF (120 mL) was added dropwise to a stirred 1 M solution of lithium diisopropylamide (75 mmol, 75 mL) at -65 °C under N<sub>2</sub>. After stirring for 45 min, the resulting enolate was treated with diethyl chlorophosphate (12.90 g, 75 mmol) and the mixture was allowed to warm to 0 °C over the course of 50 min. After this mixture was cooled to -70 °C, it was transferred to a 2 M solution of lithium diisopropylamide (150 mmol, 75 mL). The resulting solution was allowed to warm to 10 °C over 2 h and was treated with a solution of acetic acid (272 mmol, 15.5 mL) in Et<sub>2</sub>O (250 mL). The resulting mixture was filtered and the filtrate concentrated. The oily residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 60/40) to give the phosphonate 48 (13.5 g, 70%) as a brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.05 (d, 1H), 7.50 (td, 1H), 7.40–7.20 (m, 2H), 4.30– 4.00 (m, 4H), 3.40-3.10 (m, 2H), 3.00-2.60 (m, 1H), 2.60-2.30 (m, 2H), 1.40-1.10 (2t, 6H).

**2-Oxiranylmethoxytetrahydropyran (46).** A solution of glycidol (5 g, 67.5 mmol), dihydropyran (28.4 g, 337.5 mmol) and pyridinium tosylate (1.70 g, 6.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was stirred for 4 h at 20 °C. The solution was then washed once with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 50/50) to give the epoxyde **46** (3.78 g, 35%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.65 (m, 1H), 3.85 and 3.50 (2m, 2H), 3.95, 3.70 and 3.40 (3m, 2H), 3.20 (m, 1H), 2.80, 2.70 and 2.60 (3m, 2H), 2.00–1.40 (m, 6H).

2'-(Tetrahydropyran-2-yloxymethyl)spiro[1'.2]cyclopropane-3,4-dihydro-1-oxonaphthalene (49). A solution of phosphonate 48 (27 g, 95 mmol) in toluene (60 mL) was added to a suspension of NaH (4.40 g, 109.2 mmol) in toluene (160 mL) at 20 °C under N2. The reaction mixture was stirred at ambient temperature for 1 h and epoxyde 46 (30 g, 190 mmol) was added. After refluxing for 4 days, the solution was cooled, hydrolyzed with water and extracted with  $Et_2O$  (3  $\times$  100 mL). The organic layer was then washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ EtOAc = 80/20) to give the compound **49** (19 g, 70%) as a pale red oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.00 (d, 1H), 7.50 (t, 1H), 7.40-7.20 (m, 2H), 4.65 (2m, 1H), 4.05, 3.75, 3.65 and 3.40 (4m, 2H), 3.85 and 3.55 (2m, 2H), 3.30-2.90 (m, 2H), 2.20-2.00 (m, 3H), 1.70-1.40 (m, 7H), 0.70 (m, 1H).

{**Spiro[cyclopropane-2:2'-(1',2',3',4'-tetrahydronaph-thalene)]-1-yl}methanol (52a).** To a solution of compound **49** (2.50 g, 8.7 mmol) in 1,2-dichloroethane (45 mL) at room temperature under N<sub>2</sub> were added solid ZnI<sub>2</sub> (4.16 g, 13 mmol) and NaBH<sub>3</sub>CN (4.10 g, 62.2 mmol). The reaction mixture was heated at 80-85 °C for 3 h. It was then cooled and poured into an ice cold mixture of saturated aqueous NH<sub>4</sub>Cl containing 10 vol % of 5 N HCl (180 mL). The mixture was extracted with EtOAc (3 × 80 mL) and the combined extracts were dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 70/30) to give the alcohol **52a** (760 mg, 46%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.05 (m, 4H), 3.70 (t, 2H), 2.90 (t, 2H), 2.80 and 2.55 (2d, 2H), 1.80 (m, 2H), 1.20 (m, 2H), 0.65 and 0.30 (2dd, 2H).

{**Spiro[cyclopropane-2:2'-(1',2',3',4'-tetrahydronaphthalene)]-1-yl}carboxaldehyde (53a).** To a solution of pyridine (18.5 mL, 226.5 mmol) in  $CH_2Cl_2$  (360 mL) at 0 °C under N<sub>2</sub> was added  $CrO_3$  (11.60 g, 116.2 mmol). After stirring for 1 h at room temperature, alcohol **52** (3.64 g, 19.4 mmol) in solution in  $CH_2Cl_2$  (80 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction was then filtered and the filtrate evaporated in vacuo. The residue was diluted with  $Et_2O$ , washed with 1 N NaOH, 1 N HCl and saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the pure aldehyde **53a** (3.05 g, 85%) as an oil.  $^1H$  NMR (CDCl\_3):  $\delta$  9.50 (d, 1H), 7.05 and 6.95 (2m, 4H), 3.00–2.60 (m, 4H), 2.10–1.80 (m, 3H), 1.20 and 1.50 (2m, 2H).

**1-{Spiro[cyclopropane-2':2"-(1",2",3",4"-tetrahydronaphthalene)]-1'-yl}ethane-1,2-diamine (54a,b).** Starting from the aldehyde **53a**, the compounds were obtained as described for **4a**, as a mixture of two diastereoisomers (50/50) **54a/54b** (0.905 g, 36%) as a brown oil. The two diastereoisomers were separated by HPLC (Kromasil 100.5 C18, 265 nm, CH<sub>3</sub>OH/ H<sub>2</sub>O/CF<sub>3</sub>COOH = 350/650/5). **54a:** <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20– 7.00 (2m, 4H), 3.05 and 2.80 (m, 2H), 2.90 (m, 3H), 2.70 (m, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.65 (m, 1H), 1.60 (m, 4H), 0.75 (m, 1H), 0.60 (m, 1H), 0.25 (m, 1H). **54b:** <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20–7.00 (2m, 4H), 3.00 and 2.20 (m, 2H), 2.90 (m, 3H), 2.65 (m, 1H), 2.45 (m, 1H), 1.90 (m, 1H), 1.60 (m, 1H), 1.60 (m, 4H), 0.75 (m, 1H), 0.65 (m, 1H), 0.30 (m, 1H).

4(5)-{Spiro[cyclopropane-2':2"-(1",2",3",4"-tetrahydronaphthalene)]-1'-yl}-4,5-dihydroimidazole, Fumarate (19a). A mixture of the above diamine 54a (0.17 g, 0.8 mmol) and formamidine acetate (0.094 g, 0.9 mmol) in EtOH (5 mL) was stirred at 20 °C under N<sub>2</sub> for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et<sub>2</sub>O and rendered basic with aqueous NaOH (35%); the mixture was extracted with  $CH_2Cl_2$  and the organic layer washed with brine, dried (MgSO<sub>4</sub>) and evaporated. The solid residue was dissolved in acetone (10 mL) and treated with a solution of fumaric acid (0.082 g, 0.7 mmol) in i-PrOH (4 mL). After evaporation and crystallization of the residue from acetone/i-PrOH, the derivative 19a was obtained as a white powder (0.068 g, 65%), mp 149 °C. <sup>1</sup>H NMR (DMSO $d_6$ ):  $\delta$  8.20 (s, 1H), 7.10 (m, 3H), 7.00 (d, 1H), 3.90 (m, 1H), 3.90 and 3.55 (m, 2H), 2.95 and 2.80 (m, 2H), 2.90 and 2.25 (m, 2H), 2.00 and 1.55 (m, 2H), 1.05 (m, 1H), 0.55 (m, 1H), 0.30 (m, 1H). Anal. (C15H18N2·C4H4O4) C, H, N.

**4(5)**-{**Spiro[cyclopropane-2':2**"-(1",2",3",4"-tetrahy**dronaphthalene)]**-1'-**y**]-4,5-**dihydroimidazole, Fumarate** (**19b).** Compound **19b** was prepared according to the procedure described for **19a** and obtained as a white solid, mp 164 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.25 (s, 1H), 7.10 (m, 3H), 7.05 (d, 1H), 3.95 (m, 1H), 3.95 and 3.35 (m, 2H), 2.80 and 2.45 (m, 2H), 2.80 (m, 2H), 1.75 and 1.65 (m, 2H), 0.97 (m, 1H), 0.65 (m, 1H), 0.55 (m, 1H). Anal. (C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H; N: calcd, 8.18; found, 7.65.

4(5)-[Spiro(cyclopropane-2':2"-indan)-1'-yl]-4,5-dihydroimidazole, Fumarate (20a). {Spiro[cyclopropane-2: 2'-(1'-indanone)]-1-yl}carboxylic Acid, Ethyl Ester (50). Solid NaH (3.43 g, 140 mmol) was added portionwise to a solution of 1-indanone (20 g, 120 mmol) and ethyl 2-[(diethoxyphosphoryl)oxy]acrylate (36 g, 140 mmol) in anhydrous THF (260 mL) in such a way that the temperature did not exceed 35 °C. At the end of the addition the reaction vessel was plunged into an oil bath at 50 °C, the reaction mixture temperature climbed to 60 °C, afterward it was kept stirring at 45 °C for 1 h. The reaction mixture was poured on a mixture of ice (1 L) and HCl (1 N, 1 L), extracted with AcOEt ( $3 \times 600$ mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 93/7) to yield **50** as a colorless oil (3.8 g, 26%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.80 (m, 1H), 7.65 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 4.20 (m, 2H), 3.30 (s, 1H), 2.50 (m, 1H), 1.75 (m, 2H)1.25 (t. 3H)

**[Spiro(cyclopropane-2:2'-indan)-1-yl]carboxylic Acid, Ethyl Ester (51).** Compound **50** (24.2 g, 90 mmol) was added dropwise under mechanical stirring, to a suspension of NaBH<sub>3</sub>-CN (42.7 g, 680 mmol) and ZnI<sub>2</sub> (41.5 g, 130 mmol) in 1,2dichoroethane (500 mL). The suspension was brought to reflux under stirring for 14 h. The inorganic salts were filtered and the filtrate was hydrolyzed by NH<sub>4</sub>Cl (10%, 1 L) and HCl (6 N, 180 mL). The aqueous phase was extracted with AcOEt (2 × 500 mL), the salts were hydrolyzed in the same aqueous phase which was extracted one more time with AcOEt (2 × 300 mL). The pooled organic phases were washed with Na<sub>2</sub>-CO<sub>3</sub> (10%, 500 mL) and brine (500 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt = 95/5) to yield **51** as a colorless oil (3.8 g, 26%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.25–7.10 (m, 4H), 4.15 (m, 2H), 3.25–2.80 (m, 4H), 1.85 (m, 1H), 1.35 (m, 1H), 1.25 (m, 3H), 1.20 (m, 1H).

**[Spiro(cyclopropane-2:2'-indan)-1-yl]carbinol (52b).** A solution of compound **51** (13.9 g, 53 mmol) in anhydrous THF (250 mL)was added dropwise to a suspension of LiAlH<sub>4</sub> (3.1 g, 82 mmol) in anhydrous THF (250 mL) cooled at -18 °C. After 3 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive cautious additions of water (3.1 mL), NaOH (3.1 mL) and water (6.2 mL). The resulting suspension was stirred overnight, filtered and the filtrate concentrated. Compound **52b** was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20 (m, 4H), 3.80–3.50 (m, 2H), 3.20–2.75 (m, 4H), 1.30 (m, 2H), 0.85 (m, 1H), 0.50 (m, 1H).

**[Spiro(cyclopropane-2:2'-indan)-1-yl]carboxaldehyde (53b).** A solution of compound **52b** (14.3 g, 68 mmol) in  $CH_2Cl_2$  (140 mL)was added dropwise to a suspension of pyridinium chromate prepared at 0 °C from pyridine (68 mL, 670 mmol) and  $CrO_3$  (42 g, 420 mmol) in  $CH_2Cl_2$  (1 L). After 5 h stirring, the solids were filtered, washed with ether (100 mL) and the filtrates concentrated. The residue was taken up in ether (1 L), the insoluble material filtered, the filtrate washed successively with NaOH (1 N, 1 L), HCl (1 N, 2 × 750 mL), NaHCO<sub>3</sub> (10%, 2 × 500 mL), brine (500 mL), dried (MgSO<sub>4</sub>) and concentrated to afford compound **53b** which was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.40 (d, 1H), 7.20 (m, 4H), 3.30–2.85 (m, 4H), 2.10 (m, 1H), 1.40 (m, 1H), 0.60 (m, 1H).

2-Di(4-methoxyphenyl)methylamino-2-[spiro(cyclopropane-2':2"-indan)-1'-yl]ethylamine (54c,d). A solution of compound  ${\bf 53b}$  (12 g, 58 mmol) in  $CH_2Cl_2$  (250 mL) was stirred for 2 h in the presence of di(4-methoxyphenyl)methylamine (14 g, 58 mmol) and molecular sieves (4 Å, 18 g). Then, TMSCN (6.3 g, 64 mmol) was added and the suspension stirred for 14 h. The solids were filtered, the filtrate washed with NaOH (0.1 N, 500 mL) and brine (250 mL), dried (MgSO<sub>4</sub>) and concentrated to afford the aminonitrile which was used without further purification. A solution of the aminonitrile (26.7 g, 68 mmol) in anhydrous THF (125 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (3.3 g, 87 mmol) in anhydrous THF (500 mL) cooled at -10 °C. After 1 h stirring at room temperature, the reaction mixture was hydrolyzed by the successive cautious addition of water (3.3 mL), NaOH (3.3 mL) and water (6.6 mL). Ether (300 mL) was added and the suspension was stirred 45 min, filtered and the filtrate concentrated. The two diastereoisomers were separated by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>4</sub>OH = 90/9/1).

**2-Amino-2-[spiro(cyclopropane-2':2"-indan)-1'-yl]ethylamine (diastereomer 1, 55c).** A solution of **54c** (3.12 g, 6.7 mmol) in a mixture AcOH/H<sub>2</sub>O (80/20, 200 mL) was plunged for 45 min in an oil bath at 90 °C. The acetic acid was then evaporated and the residue was dissolved in HCl (1 N, 100 mL), washed with ether ( $3 \times 75$  mL), basified with NaOH (9 N, 20 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> ( $3 \times 75$  mL), dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>4</sub>OH = 90/9/1) to afford the product **55c** as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.25–7.10 (m, 4H), 3.20–2.80 (m, 4H), 2.90 (dd, 1H), 2.70 (dd, 1H), 2.30 (m, 1H), 1.70–1.30 (m, 2H), 1.00–0.70 (m, 2H), 0.50 (m, 1H).

**4(5)-[Spiro(cyclopropane-2':2"-indan)-1'-yl]-4,5-dihydroimidazole, Hemifumarate (diastereomer 1, 20a).** A solution of compound **55c** (1.5 g, 6.3 mmol) and formamidine acetate (654 mg, 6.3 mmol) in EtOH (100 mL) was stirred for 14 h at room temperature. EtOH was then evaporated under reduced pressure and the white solid was taken up in acetone (75 mL) and *i*-PrOH (10 mL). The solution was filtered and fumaric acid (694 mg, 6.3 mmol), dissolved by gentle warming in acetone (25 mL) and *i*-PrOH (10 mL), was added. The solid **20a** was collected by filtration and dried under vacuum as a white powder (66%), mp 212 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.20 (s, 1H), 7.25–7.10 (m, 4H), 6.65 (s, 1H), 4.10 (m, 1H), 3.95– 3.75 (m, 2H), 3.45–3.15 (m, 2H), 2.80 (m, 2H), 1.35 (m, 1H), 0.95 (m, 1H), 0.60 (m, 1H). Anal. ( $C_{14}H_{16}N_2 \cdot 0.5C_4H_4O_4$ ) C, H, N.

**4(5)-[Spiro(cyclopropane-2':2"-indan)-1'-yl]-4,5-dihy-droimidazole, Fumarate (diastereomer 2, 20b).** Starting from the diamine **55d** (diastereomer 2), the compound was obtained as described for **20a, 20b** (68%), mp 178 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.25 (s, 1H), 7.30–7.10 (m, 4H), 6.45 (s, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.50 (m, 1H), 3.15–2.65 (m, 4H), 1.20 (m, 1H), 0.90 (m, 1H), 0.70 (m, 1H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

Spiro[(1,3-diazacyclopent-1-ene)-5:2'-(trans-1',2',3',4',-4'a,9',9'a,10'-octahydroanthracene)], Fumarate (21a). 7-(2-Bromobenzyl)-1,4-dioxaspiro[4.5]decan-8-one (56). To a THF solution of lithium diisopropylamide (1 M, 150 mL) cooled to -78 °C under N<sub>2</sub> was added dropwise a solution of 1,4-cyclohexanedione monoethylene ketal (20 g, 128 mmol) in THF (360 mL) and the cooling bath was removed. Stirring was continued for 1 h to give a cream colored solution. This solution was then cooled to -78 °C and 2-bromobenzyl bromide (35.2 g, 141 mmol) was added dropwise. After stirring for 30 min at 78 °C, the reaction was then allowed to warm to 0 °C and stirred 3 h at 0 °C before being partitioned between Et<sub>2</sub>O and  $H_2O$ . The solution was extracted with  $Et_2O$  (3  $\times$  100 mL) and the organic layer was washed with aqueous NaCl, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude compound was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 80/20) to yield the compound **56** (20 g, 50%) as a white solid, mp 123 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.50 (m, 1H), 7.20 (m, 2H), 7.05 (m, 1H), 3.95 (m, 4H), 3.35 (dd, 1H), 3.05 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.10-1.85 (m, 3H), 1.80 (m. 1H).

7-(2-Bromobenzyl)-8-methylene-1.4-dioxaspiro[4.5]decane (57). To a suspension of methyl(triphenyl)phosphonium iodide (25 g, 61.8 mmol) in toluene (50 mL) was added a toluene solution of freshly prepared sodium *t*-pentoxide (70 mL of 1 M solution) and the mixture was stirred at room temperature under  $N_2$  for 20 min. The ketone 56 (6.70 g, 20.6 mmol) in toluene (50 mL) was then added dropwise and the mixture was refluxed for 3 h. After cooling, the reaction was hydrolyzed with saturated aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O (3  $\times$  50 mL). The extract was washed with saturated aqueous NaCl, water and dried (MgSO<sub>4</sub>). Evaporation provided an oil which was purified by flash chromatography (SiO<sub>2</sub>, toluene/cyclohexane = 60/40) to give the pure alkene 57 (6 g, 90%) as a white powder, mp 68 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.55 (dd, 1H), 7.30-7.10 (m, 2H), 7.05 (m, 1H), 4.80 and 4.70 (2s, 2H), 4.00-3.80 (m, 4H), 3.20 (m, 1H), 2.85-2.60 (m, 2H), 2.50-2.25 (m, 2H), 1.85-1.60 (m, 3H), 1.60-1.40 (m, 1H)

**2-Dioxolanyl-***trans***-1,2,3,4,4a,9,9a,10-octahydroanthracene (58).** A solution of bromide **57** (5 g, 15.5 mmol), AIBN (510 mg, 0.02 mmol) and Bu<sub>3</sub>SnH (6.75 g, 23.2 mmol) in toluene (750 mL) under N<sub>2</sub> was refluxed for 5 h 30 min. The solvent was removed under reduced pressure and the residue was stirred rapidly for 3 h with a mixture of Et<sub>2</sub>O (120 mL) and saturated aqueous KF solution (120 mL). Filtration of the precipitate, extraction with Et<sub>2</sub>O (3 × 40 mL), drying (MgSO<sub>4</sub>) and concentration in vacuo gave an oily residue which was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/Et<sub>2</sub>O = 80/20) to yield the *trans*-octahydroanthracenic compound **58** (2 g, 50%), as a white solid, mp 71 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 7.10 (m, 4H), 3.95 (m, 4H), 2.85 (m, 2H), 2.00–1.30 (m, 8H), 2.50 (m, 2H).

*trans*-3,4,4a,9,9a,10-Hexahydro-1*H*-anthracen-2-one (59). A solution of the acetal **58** (6 g, 24.6 mmol) in acetone (100 mL) and water (25 mL) containing pyridinium tosylate (1.85 g, 7.4 mmol) was refluxed for 4 h. Excess solvent was then removed in vacuo, Et<sub>2</sub>O (500 mL) was added and the mixture was washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and saturated aqueous NaCl. The organic layer was dried (MgSO<sub>4</sub>) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 80/20) to give the ketone **59** (3.90 g, 80%) as a white solid, mp 99 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.10 (m, 4H), 2.95–2.65 (m,

2H), 3.05–2.55 (m, 2H), 2.60 (m, 2H), 2.60 and 2.20 (m, 2H), 1.70 (m, 2H), 2.25 and 1.56 (m, 2H).

**2-Amino-***trans***1,2,3,4,4a,9,9a,10-octahydroanthracene2-carbonitrile (60).** To a vigorously stirred solution, maintained under N<sub>2</sub> and containing the above ketone **59** (1.25 g, 6.2 mmol), MeOH (30 mL) and water (15 mL) were added KCN (410 mg, 6.3 mmol) and NH<sub>4</sub>Cl (340 mg, 6.3 mmol) successively. After stirring for 12 h at 20 °C, the solution was diluted in CH<sub>2</sub>Cl<sub>2</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The organic phase was washed with saturated aqueous NaCl, dried (Mg-SO<sub>4</sub>) and evaporated. The residue was then treated with 7 N methanolic NH<sub>3</sub> solution (25 mL) and stirred in a closed vessel for 12 h at 20 °C. Evaporation under reduced pressure provided the desired aminonitrile **60** (1.39 g, 100%) as a white solid, mp 128 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.10 (m, 4H), 2.90–2.85 (2t, 2H), 2.60–2.45 (m, 2H), 2.20–1.25 (m, 8H), 1.90 (m, 2H).

2-Aminomethyl-trans-1,2,3,4,4a,9,9a,10-octahydroanthracen-2-ylamine (61). A solution of the above aminonitrile 60 (1.39 g, 6.1 mmol) in anhydrous THF (35 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (350 mg, 9.2 mmol) in anhydrous THF (35 mL) at -20 °C under N<sub>2</sub>. The mixture was stirred for 1 h 30 min before hydrolysis by addition of H<sub>2</sub>O (2.3 mL), 35% aqueous NaOH (4.6 mL) and  $H_2O$  (4.9 mL). The resulting suspension was filtered and the filtrate evaporated to afford an oily residue which, after purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH = 90/10/1) gave a mixture of two diastereoisomers (85/15) 61a/61b (0.505 g, 36%) as a white solid. The two diastereoisomers were separated by HPLC (Kromasil 100.10 C18, 210 nm, CH<sub>3</sub>CN/  $H_2O/CF_3CO_2H = 170/830/5$ ). **61a:** mp 123 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.50–7.00 (m, 4H), 7.05 (m, 4H), 3.00 (s, 2H), 2.75 (m, 2H), 2.70-2.30 (m, 2H), 2.00-1.30 (m, 8H). 61b: mp 183 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.05 (m, 4H), 2.80 (m, 2H), 2.55 (s, 2H), 2.50 (m, 2H), 1.90-1.00 (m, 8H), 1.40 (m, 4H).

Spiro[(1,3-diazacyclopent-1-ene)-5:2'-(trans-1',2',3',4',-4'a,9',9'a,10'-octahydroanthracene)], Fumarate (21a). A mixture of the above diamine 61a (0.495 g, 2.2 mmol) and formamidine acetate (258 mg, 2.5 mmol) in EtOH (10 mL) was stirred at 20 °C under N2 for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et<sub>2</sub>O and basified with 35% aqueous NaOH; the mixture was extracted with  $CH_2Cl_2$  (3  $\times$  10 mL) and the organic layer washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated. The solid residue was dissolved in EtOH (10 mL) and treated with a solution of fumaric acid (0.225 g, 1.9 mmol) in EtOH (10 mL). After evaporation and recrystallization of the residue from EtOH, compound 21a was obtained as a white powder (0.50 g, 65%), mp 233-237 °C. <sup>1</sup>H NMR (TFA-*d*<sub>1</sub>): δ 7.75 (s, 1H), 6.75 (s, 1H), 6.70 (m, 4H), 3.10 (s, 2H), 2.55 (m, 2H), 2.20 and 2.10 (m, 2H), 1.80 (m, 3H), 1.60 (m, 1H), 1.30 (m, 1H), 1.20 (m, 2H), 0.96 (m, 1H). Anal.  $(C_{16}H_{20}N_2 \cdot C_4H_4O_4)$  C, H, N.

**Spiro**[(1,3-diazacyclopent-1-ene)-5:2'-(*trans*-1',2',3',4',-4'a,9',9'a,10'-octahydroanthracene)], Fumarate (21b). The derivate 21b was prepared according to the procedure described for 21a and obtained as a white solid, mp 215 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.35 (s, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 3.55 (s, 2H), 2.85-2.70 (m, 2H), 2.50-2.35 (m, 2H), 2.00-1.35 (m, 8H). Anal. (C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

Spiro{(1,3-diazacyclopent-1-ene)-5:3'-[spiro(cyclobutane-1':2''-indan)]}, Fumarate (22). Indan-2,2-dicarboxylic Acid, Dimethyl Ester (63). A solution of 1,2-di(bromomethyl)benzene (62; 30 g, 115 mmol), dimethyl malonate (15.20 g, 115 mmol) and K<sub>2</sub>CO<sub>3</sub> (31.50 g, 230 mmol) in ethylmethyl-acetone (600 mL) under N<sub>2</sub> was refluxed for 14 h. After cooling, the reaction was filtered and the filtrate evaporated. The oily residue was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc = 80/20) to give the diester 63 (16 g, 60%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.15 (m, 4H), 3.75 (s, 6H), 3.65 (s, 4H).

**2,2-Bis(bromomethyl)indan (64).** A solution of the diester **63** (8 g, 34.2 mmol) in anhydrous THF (25 mL) and Et<sub>2</sub>O (50 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (3.25 g, 85.5 mmol) in anhydrous THF (10 mL) and Et<sub>2</sub>O (20 mL) at

20 °C under N<sub>2</sub>. The mixture was stirred for 1 h 30 min before being hydrolyzed by addition of H<sub>2</sub>O (21 mL), 35% aqueous NaOH (43 mL) and H<sub>2</sub>O (45 mL). The resulting suspension was filtered and the filtrate evaporated to give the diol (5.79 g, 85%) as a white solid, used without further purification, mp 109 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.15 (m, 4H), 3.75 (d, 4H), 2.85 (s, 4H), 2.35 (s, 2H). To a solution of diol (5.53 g, 27.4 mmol) in pyridine (20 mL) under N2 at 0 °C was added p-toluenesulfonyl chloride (13 g, 68.5 mmol). After stirring for 4 h at 20 °C, the mixture was filtered and the precipitate washed with 1 N HCl and Et<sub>2</sub>O to give the ditosylate (14 g, 100%) as a white solid, mp 135 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.75 (d, 4H), 7.40 (d, 4H), 7.10 (m, 4H), 3.95 (s, 4H), 2.75 (s, 4H), 2.50 (s, 6H). A mixture of the ditosylate (14 g, 27.3 mmol) and LiBr (9.30 g, 109 mmol) in DMF (22 mL) under N<sub>2</sub> was refluxed for 5 h and added to approximately 40 mL of crushed ice. The reaction was extracted with Et<sub>2</sub>O (3  $\times$  20 mL) and the organic layer was washed with water and saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the pure compound 64 (7.20 g, 86%) as a white solid, mp 48.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.15 (s, 4H), 3.70 (s, 4H), 3.05 (s, 4H).

Spiro[(1-amino-1-cyanocyclobutane)-3:2'-indan] (65). To a refluxing solution of NaH (2.30 g, 56 mmol), in anhydrous THF (22 mL) was added dropwise a mixture of N-(diphenylmethylene)aminoacetonitrile (2.46 g, 11.2 mmol) and compound 64 (3.4 g, 11.2 mmol) in anhydrous THF (22 mL). The solution was refluxed for 24 h before being cooled and hydrolyzed by addition of water. The mixture was extracted with EtOAc (3  $\times$  60 mL) and the organic layer was washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was then treated with 1 N HCl (30 mL) and Et<sub>2</sub>O (30 mL) and vigorously stirred for 12 h at 20 °C. The two layers were separated and the acidic phase was washed with Et<sub>2</sub>O, basified with 35% aqueous NaOH and extracted with  $CH_2Cl_2$  (3 × 40 mL). The organic layer was washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated to give the desired aminonitrile 65 as a brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.15 (m, 4H), 3.20 (s, 2H), 3.10 (s, 2H), 2.45 (m, 4H), 1.85 (m, 2H).

**Spiro**[(1-aminocyclobutane)-3:2'-indan]-1-methylamine (66). A solution of the above aminonitrile 65 (1.49 g, 7.1 mmol) in 2 N methanolic NH<sub>3</sub> solution (140 mL) was hydrogenated over 50% aqueous Raney Nil at room temperature for 5 h. The reaction was filtered to remove the catalyst and concentrated to give an oil which was purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH = 90/10/1), providing the corresponding diamine **66** (1.04 g, 70%) as a pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.15 (m, 5H), 3.10 and 3.00 (2s, 4H), 2.80 (s, 2H), 2.15 and 1.95 (m, 4H).

Spiro{(1,3-diazacyclopent-1-ene)-5:3'-[spiro(cyclobutane-1':2"-indan)]}, Fumarate (22). A mixture of the above diamine 66 (1.03 g, 4.8 mmol) and formamidine acetate (0.576 g, 5.5 mmol) in EtOH (20 mL) was stirred at 20 °C under N2 for 12 h. The solvent was evaporated and the residue taken up in 1 N HCl. The acidic phase was washed with Et<sub>2</sub>O and basified with 35% aqueous NaOH; the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic layer washed with saturated aqueous NaCl, dried (MgSO<sub>4</sub>) and evaporated. The solid residue was dissolved in EtOH (20 mL) and treated with a solution of fumaric acid (557 mg, 4.8 mmol) in EtOH (20 mL). After evaporation and recrystallization of the residue from EtOH, the derivate 22 was obtained as a white powder (1.26 g, 80%), mp 189 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.05 (s, 1H), 7.20-7.00 (m, 4H), 6.45 (s, 2H), 3.95 (s, 2H), 3.00 (s, 4H), 2.35 (m, 4H). Anal. (C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

**4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4(5)-methyl-4,5-dihydroimidazole, Fumarate (23). 1-(3,4-Dihydronaphthalen-2-yl)propan-2-one (67).** A vigorously stirred suspension of 2-tetralone (13.15 g, 90 mmol), (2-oxopropyl)phosphonic acid diethyl ester (20.16 g, 104 mmol) and K<sub>2</sub>CO<sub>3</sub> (24.9 g, 180 mmol) in H<sub>2</sub>O (30 mL) was heated under reflux for 3 h. After cooling (0 °C), the mixture was diluted with water (30 mL) and extracted with ether (4 × 100 mL). The combined extracts were dried and concentrated. The resulting oily residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt: 95/5) to afford **67** as a colorless oil (9 g, 54%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20–6.95 (m, 4H), 6.35 (s, 1H), 3.30 (s, 1H), 2.55 (t, 2H), 2.30 (t, 2H), 2.20 (s, 3H).

**4(5)-[(3,4-Dihydronaphthalen-2-yl)methyl]-4(5)-methyl-4,5-dihydroimidazole, Fumarate (23).** Starting from the ketone **67**, the compound was obtained as described for **4a**, as a white powder (75%), mp 146–148 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.10 (s, 1H), 7.20–6.95 (m, 4H), 6.40 (s, 2H), 6.35 (s, 1H), 3.55 (AB system, 2H), 2.70 (m, 2H), 2.50 (m, 2H), 2.20 (s, 3H), 2.30 (m, 2H), 1.35 (s, 3H). Anal. (C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

4(5)-[(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (24a,b). Ethyl (2-Methyl-1,2,3,4-tetrahydronaphthalen-1-on-2-yl)acetate (68). To a solution of 2-methyl-1-tetralone (1 g, 6.25 mmol) in anhydrous THF (50 mL), KO-t-Bu (0.77 g, 6.9 mmol) was added portionwise at -60 °C under a N<sub>2</sub> atmosphere. The reaction mixture was brought to 0 °C, stirred 1 h at that temperature and cooled again to -60 °C, when a solution of ethyl iodoacetate (1.47 g, 6.9 mmol) in anhydrous THF (2 mL) was added dropwise. The solution was maintained at -60 °C under stirring and brought to room temperature overnight. The reaction mixture was quenched by dropwise addition of water (50 mL), extracted with ether ( $2 \times 100$  mL), the pooled organic phases were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford 68 as a brown oil which was purified through column chromatography (SiO<sub>2</sub>, cyclohexane/AcOEt =90/10) and used without further purification.  $^1\!H$  NMR (CDCl\_3):  $\delta$  8.05 (m, 1H), 7.45 (m, 1H), 7.30 (m, 1H), 7.25 (m, 1H), 4.15 (q, 2H), 3.20-2.85 (d + m, 2H), 2.55-2.35 (m, 1H), 1.95 (m, 1H), 1.25 (s, 3H), 1.20 (t, 3H).

(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetaldehyde (69). A suspension of 68 (15.3 g, 62 mmol), NaBH<sub>3</sub>CN (29.5 g, 470 mmol) and ZnI2 (29.7 g, 93 mmol) in (CH2Cl)2 (375 mL) was heated to reflux overnight under a N2 atmosphere. Insoluble materials were dissolved by addition of a mixture of NH<sub>4</sub>Cl (10%, 1 L) and HCl (0.5 N, 100 mL), the aqueous phase was extracted with AcOEt (3  $\times$  250 mL), the pooled organic phases were washed with Na<sub>2</sub>CO<sub>3</sub> (10%), dried (Mg-SO<sub>4</sub>) and concentrated to afford a mixture of ethyl (2-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetate and the corresponding alcohol (1/1) which was dissolved in anhydrous THF (100 mL) and added dropwise to a suspension of LiAlH<sub>4</sub> (1.5 g, 41 mmol) in THF (400 mL) kept at -10 °C. At the end of the addition, the temperature was raised to room temperature and the mixture stirred for 1 h. The reaction mixture was then quenched by the successive cautious additions of water (1.5 mL), NaOH (1 N, 1.5 mL) and water (3 mL). Ether (250 mL) was added and the suspension was stirred for 1.5 h, filtered and the filtrate concentrated to give 2-(2-methyl-1,2,3,4tetrahydronaphthalen-2-yl)ethanol (9.2 g, 75%). To a solution of this alcohol (8.6 g, 45 mmol) in THF (175 mL), IBX (13.95 g, 49 mmol) was added portionwise. The suspension was heated under reflux for 2 h, cooled and filtered. The solid was washed with THF (100 mL), the filtrates concentrated, the residue dissolved in ether (350 mL), the organic solution washed with Na<sub>2</sub>CO<sub>3</sub> (10%, 100 mL) and brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated to afford 69 as colorless oil (8.41 g, 99%) used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 7.20-7.00 (m, 4H), 4.15 (q, 2H), 2.85 (m, 2H), 2.65 (AB system, 2H), 2.30 (AB system, 2H), 1.85-1.55 (m, 2H), 1.25 (t, 3H), 1.10 (s, 3H).

**4(5)-[(2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4,5-dihydroimidazole, Fumarate (24a,b).** Starting from the aldehyde **69**, the compounds were obtained as described for **20a**. Diastereomer 1, **24a** (83%), mp 154 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.10 (s, 1H), 7.05 (m, 4H), 6.40 (s, 2H), 4.25 (m, 1H), 3.95 (m, 1H), 3.30 (m, 1H), 2.75 (m, 2H), 2.50 (AB system, 2H), 1.75–1.50 (m, 4H), 0.95 (s, 3H). Anal. (C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N. Diastereomer 2, **24b** (88%), mp 152 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.15 (s, 1H), 7.05 (m, 4H), 6.45 (s, 2H), 4.25 (m, 1H), 4.00 (m, 1H), 3.35 (m, 1H), 2.75 (m, 2H), 2.55 (AB system, 2H), 1.75–1.45 (m, 4H), 0.95 (s, 3H). Anal. (C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) H, N; C: calcd, 66.36; found, 65.72. **Acknowledgment.** The authors thank the expert technical assistance of Michele Hipeaux, Pascale Cadoret, and Pascal Vrillaud and also Stephane Mabic for assistance in preparation of the manuscript.

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JM001040G