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Stereoselective syntheses of chiral (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones

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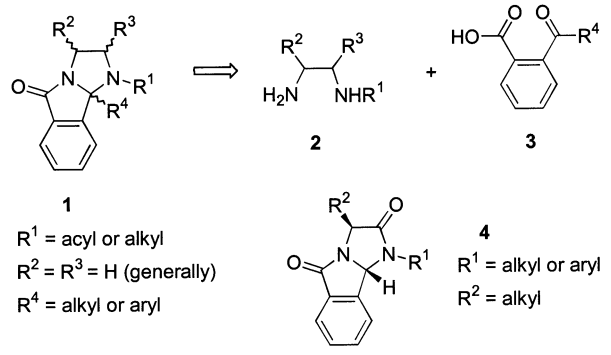
Abstract—Chiral (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones **11a**–**11f**, **14b**,**14c** and **17a**,**b** were prepared in 78–93% yields with high stereoselectivities (d.e. >99%) by the intermolecular condensations of 2-formylbenzoic acids **10** or **13** or 2-acetylbenzoic acid **15** with chiral diamines **9a**–**9f** and **9h**. Compounds **9a**–**9f** and **9h** were readily prepared in three steps from optically active *N*-Boc-α-amino acids **5a**–**5d**.

1. Introduction

1,2,3,9b-Tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones **1** possess antiinflammatory, analgesic, blood pressure lowering, spasmolytic, tranquilizing, and antitussive properties,[1] and are also useful sedative and hypotensive agents.[2] Compounds **1** ($R^1=COCH_2NH_2$, $R^2=R^3=H$, $R^4=Ar$) exhibit analgesic activity and are effective in treating rheumatism.[3] Furthermore, reductions of **1** with $LiAlH_4$ led to the benzodiazocines, which are appetite suppressants and central nervous system stimulants.[4]



Reported routes to 1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones **1** ($R^1=H$, $R^2=R^3=H$, $R^4=$alkyl or aryl) involve intermolecular condensations of 1,2-ethanediamines **2** with 2-alkanoyl-[5] or 2-aroyl-benzoic acids **3**.[1,5,6] 1-Acyl derivatives of **1** were prepared by the acylation of **1** ($R^1=H$) with anhydrides[1,6a] or acid chlorides.[1] In published examples of **1**, R^2 and R^3 groups are limited to hydrogen except for three examples (**1**: $R^1=H$, $R^2=R^3=CH_3$ or Ph; $R^1=H$, $R^2=CH_3$, $R^3=H$).[6a] A less common approach to **1** involves the reactions of 1,2-ethanediamines **2** with 2-bromobenzaldehyde under carbon monoxide via a palladium-catalyzed cascade intramolecular acylpalladation–cyclization sequence.[7] However, no stereoselective synthesis was reported, thus the final products **1** were hitherto obtained as racemic compounds or mixtures of diastereoisomers.

Following our recent stereoselective syntheses of (3*S*,9b*R*) - 1*H* - imidazo[2,1 - *a*]isoindole - 2,5(3*H*,9b*H*)-diones **4**,[8] we now report a simple and efficient synthesis of functionalized chiral (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones in good to excellent yields with high stereoselectivities starting from easily available *N*-Boc-α-amino acids **5**.

2. Results and discussion

2.1. Preparation of chiral diamines 9a–9f from *N*-Boc-α-amino acids 5a–5d (cf. Scheme 1)

The published method[9] readily provided *N*-Boc-α-amino amides **7a**–**7f** from the corresponding optically active *N*-Boc-α-amino acids **5a**–**5d** ($R^2=$Me, *i*-Pr, *i*-Bu, or $PhCH_2$) and primary amines **6** ($R^1=p$-$CH_3C_6H_4$, $PhCH_2$, or *c*-C_6H_{11}). We previously used excess HCl/

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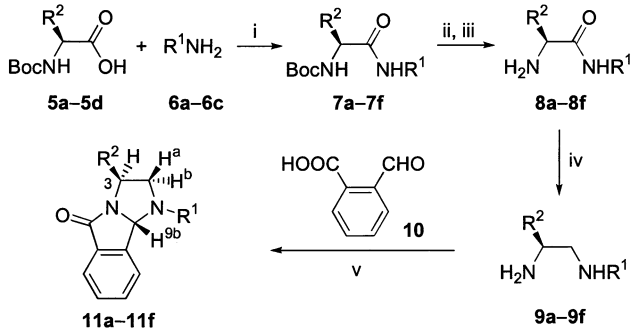


Scheme 1. For designation of R^1 and R^2 in series **a**–**f**, see Table 1. *Reagents and conditions*: (i) ClCOOBu-*i*, *N*-methylmorpholine; (ii) CF_3COOH; (iii) aq. NaOH; (iv) $LiAlH_4$/THF; (v) *p*-TsOH, PhH, Dean–Stark.

EtOAc (ca. 1 M) to remove the *N*-Boc protection group (usually needing 12–24 h until the disappearance of **7**),[8] but we now find that use of CF_3COOH (8 equiv.) in dry CH_2Cl_2 is a more efficient method to remove the Boc group (needing only 2–5 h) to give α-amino amides **8a**–**8f** (88–96%).

Crombie and Hooper reduced 2-amino-*N*-phenylpropanamide with $LiAlH_4$ to 2-aminopropylaniline without reporting a detailed procedure.[10] Reduction of **8b** ($R^1 = p$-$CH_3C_6H_4$, $R^2 = i$-Bu) with 3 equiv. of $LiAlH_4$ in refluxing THF for 1 day gave a 1:1 mixture of **8b** and **9b**. When 6 equiv. of $LiAlH_4$ was used in refluxing THF for 2 days, chiral diamines **9a**–**9f** were obtained in more than 90% yields. Intermediates **7**, **8** and **9** were used as crude products without further purification for the subsequent steps.

2.2. Syntheses and stereoselectivities of (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones 11a–11f

Optically active (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones **11a**–**11f** were prepared as single enantiomers in 78–93% yields by the reactions of 2-formylbenzoic acid **10** with 1 equiv. of the chiral diamines **9a**–**9f** and catalytic *p*-toluenesulfonic acid (0.1 equiv.) in refluxing benzene for 12 h with a Dean–Stark apparatus to remove the water formed (Scheme 1). The isolated yields and the d.e. values (determined by the ^{1}H NMR spectra) of **11a**–**11f** are summarized in Table 1. Structures **11a**–**11f** are clearly supported by their ^{1}H, ^{13}C, NOESY NMR spectra and microanalyses. It is noteworthy that the same conditions for the reaction of **10** and N^1-phenyl-1,2-ethanediamine **9g** gave the desired **11g** in low yield (<10%); while completing the reaction under azeotropic reflux in toluene over 28 h improved the yield to 74%.

Table 1. Isolated yields of **11a**–**11f** with d.e. values

No.	R^1	R^2	Yield **11**[a] (d.e.[b] %)
a	*p*-$CH_3C_6H_4$-	CH_3	78 (>99)
b	*p*-$CH_3C_6H_4$-	*i*-Bu	90 (>99)
c	*p*-$CH_3C_6H_4$-	$PhCH_2$-	88 (>99)
d	*p*-$CH_3C_6H_4$-	*i*-Pr	93 (>99)
e	*c*-C_6H_{11}	*i*-Pr	78 (>99)
f	$PhCH_2$-	*i*-Pr	89 (>99)
g	Ph	H	74[c]

[a] Isolated yield based on the chiral diamine **9a**–**9f**.
[b] Determined by the ^{1}H NMR spectrum.
[c] Compound **11g** was obtained from N^1-phenyl-1,2-ethanediamine **9g** and **10** using azeotropic distillation in toluene for 28 h.

The absolute configuration of the new stereogenic center at the 9b-position in **11a**–**11f** was determined by NOESY experiments. ^{1}H NMR spectra show that H(9b) in **11a**–**11f** appears from 4.9 ppm to 6.1 ppm as a singlet; H(3) at 4.4–4.8 ppm as a multiplet. No distinct NOE effect was observed between H(9b) and H(3) in compounds **11a**–**11f**, when either H(9b) or H(3) was irradiated. This suggests that H(9b) and H(3) in **11a**–**11f** are located in a *trans*-orientation. Further irradiation of **11a** [at CH_3(3), 1.39 ppm (d)], **11b** [at *i*-$PrCH_2$-, 1.6 or 1.8 ppm (m)], **11c** [at $PhCH_2$-, 2.88 or 3.09 ppm (dd)] or **11d** [at C<u>H</u>$(CH_3)_2$, 1.8 ppm (m)] caused a strong positive NOE effect of H(9b), and vice versa. The similar positive NOE effect was observed between C<u>H</u>$(CH_3)_2$(3) and H(9b) for **11e**,**f**. This evidence directly demonstrates the *trans*-orientation of H(9b) and H(3). Therefore, enantiopure **11a**–**11f** were obtained as sole *trans*-isomers with the formation of three new bonds in a single step to form the tricyclic ring system.

The reaction mechanism is similar to that previously proposed.[8] The α-amino group in **9a**–**9f** attacks the aldehydic carbon atom (the most electrophilic center in **10**) to generate the transient intermediate α-carbinolamine **A**, which readily eliminates a molecule of water to afford the imine intermediate with more stable *E*(*trans*)-configuration. Conformation **B** of the imine intermediate is much more stable than conformation **C** due to the larger repulsion between R^2 group and -NHR^1 group in **C**. Therefore, the lone electron pair of the nitrogen in the predominant conformation **B** attacks the imine from below the ArC=N- coplane, followed by elimination of another water molecule, to form the *trans*-isomers **11a**–**11f** as the sole products. The *cis*-isomers **12a**–**12f** were not detected (cf. Fig. 1).

Interestingly, irradiation of **11a** [at CH_3(3)], **11b** (at *i*-$PrCH_2$), **11c** (at $PhCH_2$) or **11d**–**11f** [at C<u>H</u>$(CH_3)_2$] also caused a distinct positive NOE effect for one of the methylene hydrogens at the 2-position, thus this hydrogen is assigned as the *anti*-proton H^a (for one example **11a**, cf. Fig. 2). *anti*-H^a always appears at higher field than *syn*-H^b and its coupling constant with H(3) (ca. 3.2 Hz) is smaller than that of *syn*-H^b with H(3) (ca. 6.9 Hz).

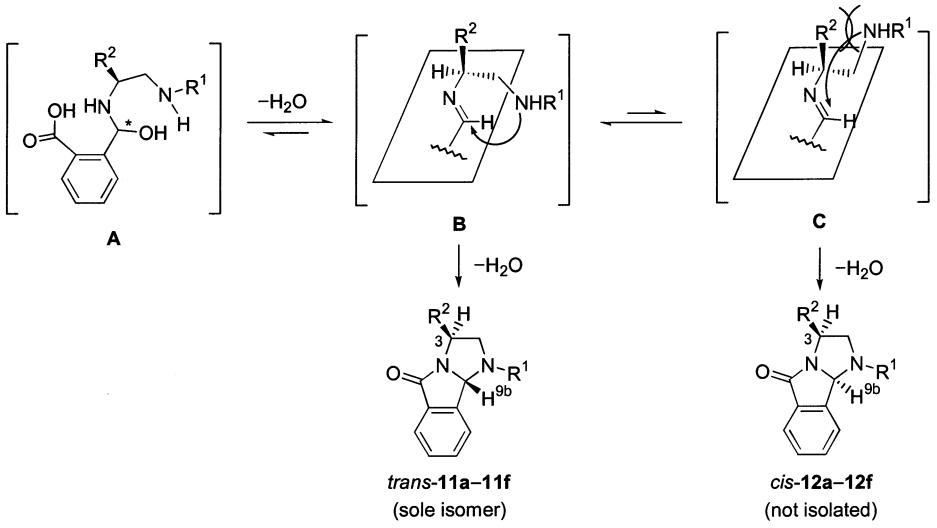


Figure 1.

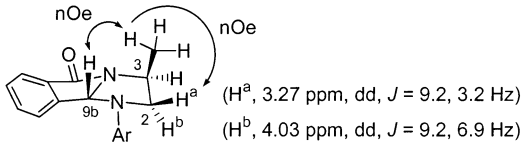


Figure 2. Nuclear Överhauser effect for **11a**.

2.3. Syntheses of 1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]-isoindol-5-ones 14a,b and 17a,b

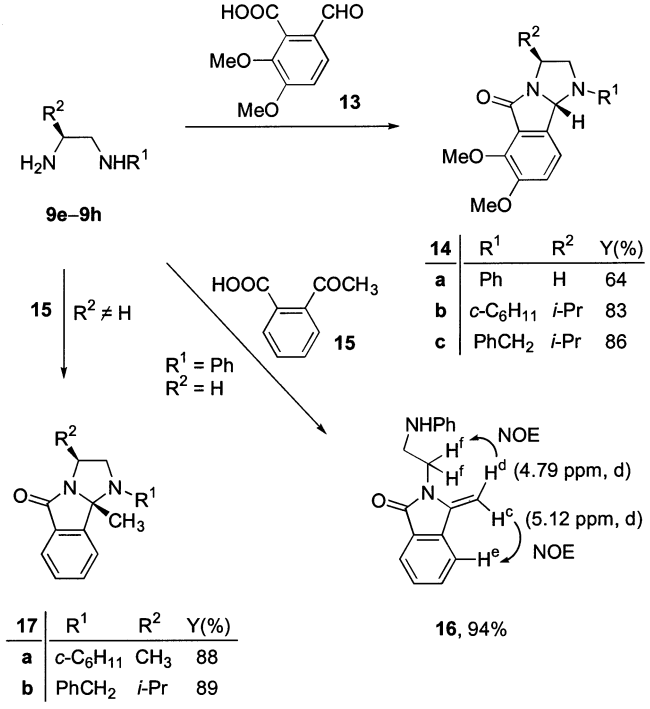
The reaction of 2-formyl-5,6-dimethoxybenzoic acid **13** with N^1-phenyl-1,2-ethanediamine **9g** gave 6,7-dimethoxy-1-phenyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one **14a** in 64% yield using azeotropic distillation in toluene for 28 h. Similarly, **14b** and **14c** were obtained from the reactions of **13** with **9e** and **9f** in 83 and 86% yields, respectively (Scheme 2).

Interestingly, condensation of N^1-phenyl-1,2-ethanediamine **9g** with 2-acetylbenzoic acid **15** produced 2-(2-anilinoethyl)-3-methylene-1-isoindolinone **16** rather than a tricyclic structure. The ^{1}H, ^{13}C NMR spectra of **16** show the disappearance of the methyl group and the existence of two hydrogens attached to a carbon–carbon double bond. The GC–MS result [GC–MS (EI): 264 (M^+)] together with combustion analysis data, further support the structure **16** (cf. Scheme 2). Furthermore, H^c is believed to appear at lower field (5.12 ppm, doublet); while H^d resonates at higher field (4.80 ppm, doublet), due to the positive NOE effect between H^c and H^e (7.68 ppm, doublet). The formation of **16** is probably because of competitive deprotonation at the methyl group and the deprotonation at -NHPh moiety in the transient *N*-acyliminium cation.

Nevertheless, reaction of 2-acetylbenzoic acid **15** with chiral diamines **9h** and **9f** ($R^2 \neq H$) furnished the desired enantiopure (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo-[2,1-*a*]isoindol-5-ones **17a**,**b** in 88 and 89% yields, respectively. The NOESY results also prove the *trans*-configurations for **17a**,**b** due to the positive NOE effect between CH_3(9b) with CH_3(3) in **17a** and C<u>H</u>$(CH_3)_2$(3) in **17b**, respectively.

3. Conclusion

In summary, we have developed an efficient route to enantiopure (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo-[2,1-*a*]isoindol-5-ones **11a**–**11f**, **14b**, **14c** and **17a** and **17b** in good to excellent yields with high stereoselectivities through intermolecular condensations of 2-formylbenzoic acids **10** or **13** or 2-acetylbenzoic acid **15** with chiral diamines **9a**–**9f** and **9h**, which were readily prepared in three steps from *N*-Boc-α-amino acids **5a**–**5d**. Thus, three new bonds are simultaneously formed in one step to generate the novel tricyclic ring system.



14	R^1	R^2	Y(%)
a	Ph	H	64
b	c-C_6H_{11}	*i*-Pr	83
c	$PhCH_2$	*i*-Pr	86

17	R^1	R^2	Y(%)
a	c-C_6H_{11}	CH_3	88
b	$PhCH_2$	*i*-Pr	89

Scheme 2.

4. Experimental

THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) NMR spectra, and NOESY spectra were recorded on a Gemini 300 MHz NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as the internal reference). Optical rotation values were measured by a Perkin–Elmer 341 polarimeter using the sodium D line. Column chromatography was performed on silica gel (200–425 mesh). All of the reactions were carried out under N_2.

4.1. General procedures for the preparation of chiral diamines 9a–9f and 9h from *N*-Boc-α-amino acids 5a–5d

Synthesis of N-Boc-α-amino amides ***7a–7f***: *N*-Boc-α-amino amides **7a–7f** were prepared from *N*-Boc-α-amino acids **5a–d** and primary amines **6a–6c** in more than 89% yields according to our recent paper.[8]

Removal of N-Boc protecting group: The previous conditions used to remove *N*-Boc with HCl/EtOAc were modified as follows: *N*-Boc-α-amino amide **7a–7f** (3 mmol) was treated with CF_3COOH (2.7 g, 24 mmol) in dry CH_2Cl_2 (25 mL) at room temperature until TLC showed the disappearance of **7** (usually needs 2–5 h). Usual work-up gave the α-amino amides **8a–8f** in more than 88% yields.

Reduction of ***8a–8f*** *with* $LiAlH_4$: A mixture of the α-amino amide **8a–8f** (3 mmol) and $LiAlH_4$ (powder, 0.68 g, 18 mmol) in dry THF (30 mL) was heated under reflux for 2 days. The mixture was slowly quenched with water under ice-bath cooling. The precipitate formed was filtered off and washed with CH_2Cl_2. The combined filtrate was washed with 1 M NaOH, brine and dried over anhyd. K_2CO_3. Removal of solvents afforded chiral diamine **9a–9f**, which was directly used for the subsequent reaction. GC analyses show that the purity of **9a–9f** is more than 92%.

Compound **9h** was similarly prepared from *N*-Boc-α-amino acid **5a** ($R^2 = CH_3$) and cyclohexylamine.

4.1.1. (2*S*)-*N*^{1}-(4-Methylphenyl)-1,2-propanediamine 9a. Yellowish oil; yield 96%; ^{1}H NMR: δ 1.20 (d, $J=7.1$ Hz, 3H), 1.20–1.80 (br s, 2H), 2.31 (s, 3H), 2.90 (dd, $J=12.1$, 8.0 Hz, 1H), 3.14–3.22 (m, 2H), 3.80–4.25 (br s, 1H), 6.62 (d, $J=8.4$ Hz, 2H), 7.05 (d, $J=8.1$ Hz, 2H); ^{13}C NMR: δ 20.1, 21.8, 45.9, 52.3, 112.8, 126.1, 129.5, 146.0.

4.1.2. (2*S*)-*N*^{1}-(4-Methylphenyl)-4-methyl-1,2-pentanediamine 9b. Colorless oil; yield 93%; ^{1}H NMR: δ 0.91 (d, $J=6.5$ Hz, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 1.28 (t, $J=6.7$ Hz, 2H), 1.20–1.40 (br s, 2H), 1.70–1.81 (m, 1H), 2.24 (s, 3H), 2.79 (dd, $J=11.8$, 8.7 Hz, 1H), 3.00–3.08 (m, 1H), 3.13–3.20 (m, 1H), 3.80–4.10 (br s, 1H), 6.56 (d, $J=8.1$ Hz, 2H), 7.00 (d, $J=8.0$ Hz, 2H); ^{13}C NMR: δ 20.3, 22.1, 23.5, 24.7, 45.7, 48.4, 51.3, 113.1, 126.5, 129.7, 146.3.

4.1.3. (2*S*)-*N*^{1}-(4-Methylphenyl)-3-phenyl-1,2-propanediamine 9c. Yellowish oil; yield 94%; ^{1}H NMR: δ 1.02–1.40 (br s, 2H), 2.23 (s, 3H), 2.56 (dd, $J=13.3$, 8.4 Hz, 1H), 2.78–2.94 (m, 2H), 3.18–3.27 (m, 2H), 3.90–4.05 (br s, 1H), 6.53 (d, $J=8.2$ Hz, 2H), 6.97 (d, $J=8.0$ Hz, 2H), 7.18–7.32 (m, 5H); ^{13}C NMR: δ 20.3, 42.7, 50.3, 52.1, 113.0, 126.3, 126.5, 128.4, 129.1, 129.6, 138.7, 146.1.

4.1.4. (2*S*)-*N*^{1}-(4-Methylphenyl)-3-methyl-1,2-butanediamine 9d. Yellowish oil; yield 91%; ^{1}H NMR: δ 0.94 (d, $J=6.4$ Hz, 3H), 0.96 (d, $J=6.5$ Hz, 3H), 1.17 (br s, 2H), 1.60–1.70 (m, 1H), 2.23 (s, 3H), 2.69–2.84 (m, 2H), 3.20 (dd, $J=11.4$, 2.7 Hz, 1H), 3.99 (br s, 1H), 6.56 (d, $J=8.4$ Hz, 2H), 6.98 (d, $J=8.1$ Hz, 2H); ^{13}C NMR: δ 17.8, 19.3, 20.3, 32.5, 48.5, 56.1, 113.1, 126.4, 129.7, 146.4.

4.1.5. (2*S*)-*N*^{1}-Cyclohexyl-3-methyl-1,2-butanediamine 9e. Yellowish oil; yield 90%; ^{1}H NMR: δ 0.90 (d, $J=6.3$ Hz, 3H), 0.92 (d, $J=6.6$ Hz, 3H), 1.05–1.40 (m, 6H), 1.56–1.92 (m, 5H), 2.23 (br s, 3H), 2.32–2.48 (m, 2H), 2.56–2.62 (m, 1H), 2.77 (dd, $J=11.4$, 3.3 Hz, 1H); ^{13}C NMR: δ 17.7, 19.3, 24.8, 25.0, 26.0, 32.5, 33.2, 33.4, 50.7, 56.5, 57.0.

4.1.6. (2*S*)-*N*^{1}-Benzyl-3-methyl-1,2-butanediamine 9f. Colorless oil; yield 94%; ^{1}H NMR: δ 0.89 (d, $J=6.9$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 1.43 (s, 3H), 1.53–1.63 (m, 1H), 2.39 (dd, $J=11.4$, 9.3 Hz, 1H), 2.58–2.69 (m, 1H), 2.72 (dd, $J=11.4$, 3.3 Hz, 1H), 3.79 (d, $J=7.5$ Hz, 2H), 7.23–7.33 (m, 5H); ^{13}C NMR: δ 17.8, 19.4, 32.3, 53.6, 54.1, 56.5, 126.8, 128.0, 128.3, 140.6.

4.1.7. (2*S*)-*N*^{1}-Cyclohexyl-1,2-propanediamine 9h. Yellowish oil; yield 90%; ^{1}H NMR: δ 1.10 (d, $J=6.3$ Hz, 3H), 1.16–1.32 (m, 5H), 1.60–1.64 (m, 2H), 1.72–1.78 (m, 2H), 1.91–1.99 (m, 2H), 2.39–2.52 (m, 2H), 2.71 (dd, $J=11.8$, 4.1 Hz, 1H), 3.01–3.10 (m, 3H); ^{13}C NMR: δ 21.7, 24.9, 25.0, 25.9, 32.8, 33.1, 46.6, 54.3, 56.9.

4.2. General procedure for the preparation of 1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones 11a–11g

A mixture of a crude diamine **9a–9f** (1.0 mmol), 2-formylbenzoic acid (10, 0.15 g, 1.0 mmol) and *p*-$CH_3C_6H_4SO_3H\cdot H_2O$ (0.02 g, 0.1 mmol) was heated under reflux in benzene (25 mL) for 12 h using a Dean–Stark apparatus. After cooling, most of the solvent was evaporated in vacuo and the residue was diluted with EtOAc. The organic phase was washed with 1 M NaOH, brine and dried over anhyd. Na_2SO_4. After removal of solvents in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (8:1 to 4:1) as an eluent to give the final product **11a–11f**.

Compound **11g** was obtained from **10** and N^1-phenyl-1,2-ethanediamine **9g** with 0.1 equiv. of *p*-TsOH using azeotropic distillation in toluene for 28 h.

4.2.1. (3*S*,9b*S*)-1-(4-Methylphenyl)-3-methyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11a. White needles; yield 78%; mp 108–109°C; $[\alpha]_D^{25}=-482$ (*c* 1.68, $CHCl_3$); ^{1}H NMR: δ 1.39 (d, $J=6.6$ Hz, 3H), 2.32 (s, 3H), 3.27 (dd, $J=9.2$, 3.2 Hz, 1H, H^a), 4.03 (dd, $J=9.2$, 6.9 Hz, 1H, H^b), 4.52–4.61 (m, 1H), 6.06 (s, 1H, NCHN), 6.91 (d, $J=8.4$ Hz, 2H), 7.16 (d, $J=8.2$ Hz, 2H), 7.49 (dd, $J=5.5$, 3.0 Hz, 2H), 7.70 (dd, $J=5.6$, 3.2 Hz, 1H), 7.82 (dd, $J=5.5$, 3.0 Hz, 1H); ^{13}C NMR: δ 20.4, 20.8, 49.7, 61.0, 74.8, 115.4, 124.2, 124.3, 129.0, 129.6, 129.9, 132.4, 133.2, 144.6, 145.1, 172.4. Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.61; H, 6.57; N, 10.11%.

4.2.2. (3*S*,9b*S*)-1-(4-Methylphenyl)-3-isobutyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11b. Colorless prisms; yield 90%; mp 61–62°C; $[\alpha]_D^{25}=-449$ (*c* 1.78, $CHCl_3$); ^{1}H NMR: δ 0.96 (d, $J=6.6$ Hz, 3H), 1.07 (d, $J=6.5$ Hz, 3H), 1.33–1.39 (m, 1H), 1.56–1.63 (m, 1H), 1.80–1.85 (m, 1H), 2.31 (s, 3H), 3.27 (dd, $J=9.0$, 2.7 Hz, 1H, H^a), 4.00 (dd, $J=9.3$, 6.9 Hz, 1H, H^b), 4.47–4.55 (m, 1H), 6.03 (s, 1H, NCHN), 6.88 (d, $J=8.2$ Hz, 2H), 7.15 (d, $J=8.0$ Hz, 2H), 7.46 (dd, $J=5.4$, 3.0 Hz, 2H), 7.71 (dd, $J=5.4$, 3.0 Hz, 1H), 7.81 (dd, $J=5.4$, 3.3 Hz, 1H); ^{13}C NMR: δ 20.4, 21.9, 23.1, 25.3, 43.7, 52.4, 59.7, 74.5, 114.9, 124.1, 124.1, 128.5, 129.5, 129.8, 132.3, 133.2, 144.7, 145.3, 172.4. Anal. calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.67; H, 7.83; N, 8.73%.

4.2.3. (3*S*,9b*S*)-1-(4-Methylphenyl)-3-benzyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11c. White microcrystals; yield 88%; mp 128–129°C; $[\alpha]_D^{25}=-376$ (*c* 1.57, $CHCl_3$); ^{1}H NMR: δ 2.31 (s, 3H), 2.88 (dd, $J=13.9$, 8.2 Hz, 1H), 3.09 (dd, $J=13.9$, 6.2 Hz, 1H), 3.42 (dd, $J=9.6$, 3.2 Hz, 1H, H^a), 3.87 (dd, $J=9.6$, 6.7 Hz, 1H, H^b), 4.70–4.79 (m, 1H), 5.93 (s, 1H, NCHN), 6.83 (d, $J=8.5$ Hz, 2H), 7.13 (d, $J=8.0$ Hz, 2H), 7.21–7.30 (m, 5H), 7.47 (dd, $J=5.6$, 3.1 Hz, 2H), 7.67 (dd, $J=5.4$, 3.2 Hz, 1H), 7.81 (dd, $J=5.4$, 3.1 Hz, 1H); ^{13}C NMR: δ 20.4, 40.3, 54.9, 58.0, 75.2, 115.1, 124.1, 124.3, 126.7, 128.5, 128.8, 129.3, 129.5, 129.8, 132.4, 133.1, 137.2, 144.4, 145.4, 172.6. Anal. calcd for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.18; H, 6.32; N, 7.95%.

4.2.4. (3*S*,9b*S*)-1-(4-Methylphenyl)-3-isopropyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11d. Colorless flakes; yield 93%; mp 55–56°C; $[\alpha]_D^{25}=-373$ (*c* 1.66, $CHCl_3$); ^{1}H NMR: δ 1.01 (d, $J=6.4$ Hz, 3H), 1.03 (d, $J=6.4$ Hz, 3H), 1.76–1.87 (m, 1H), 2.31 (s, 3H), 3.39 (dd, $J=9.3$, 3.6 Hz, 1H, H^a), 4.02 (dd, $J=9.0$, 7.2 Hz, 1H, H^b), 4.14 (td, $J=7.5$, 3.6 Hz, 1H), 5.97 (s, 1H, NCHN), 6.91 (d, $J=8.4$ Hz, 2H), 7.15 (d, $J=8.1$ Hz, 2H), 7.45–7.48 (m, 2H), 7.68 (dd, $J=5.6$, 3.3 Hz, 1H), 7.81 (dd, $J=5.6$, 3.3 Hz, 1H); ^{13}C NMR: δ 18.9, 19.1, 20.4, 32.5, 58.0, 59.8, 75.8, 115.5, 124.0, 124.2, 129.0, 129.4, 129.8, 132.2, 133.2, 144.6, 145.4, 172.7. Anal. calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.01; H, 7.54; N, 9.06%.

4.2.5. (3*S*,9b*S*)-1-Cyclohexyl-3-isopropyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11e. Colorless oil; yield 78%; $[\alpha]_D^{25}=-32.5$ (*c* 1.66, $CHCl_3$); ^{1}H NMR: δ 0.99 (d, $J=6.6$ Hz, 3H), 1.08 (d, $J=6.6$ Hz, 3H), 1.12–1.41 (m, 5H), 1.70–2.00 (m, 5H), 2.00–2.11 (m, 1H), 2.89–2.99 (m, 2H), 3.48 (t, $J=7.8$ Hz, 1H), 3.78 (dt, $J=15.3$, 15.0 Hz, 1H), 5.17 (s, 1H, NCHN), 7.44–7.54 (m, 3H), 7.80 (d, $J=6.9$ Hz, 1H); ^{13}C NMR: δ 18.6, 19.6, 24.6, 25.6, 26.2, 26.2, 32.5, 33.5, 52.9, 56.3, 59.8, 76.4, 123.4, 124.5, 129.2, 131.6, 134.2, 144.1, 173.0. Anal. calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.30; H, 8.83; N, 9.36%.

4.2.6. (3*S*,9b*S*)-1-Benzyl-3-isopropyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 11f. White needles; yield 89%; mp 102–103°C; $[\alpha]_D^{25}=+1.3$ (*c* 1.58, $CHCl_3$); ^{1}H NMR: δ 0.94 (d, $J=6.9$ Hz, 3H), 1.07 (d, $J=6.9$ Hz, 3H), 1.78–1.89 (m, 1H), 2.59 (t, $J=9.2$ Hz, 1H, H^a), 3.44–3.50 (m, 2H), 3.77 (dt, $J=7.8$, 7.8 Hz, 1H), 4.15 (d, $J=12.6$ Hz, 1H), 4.93 (s, 1H, NCHN), 7.26–7.31 (m, 5H), 7.39 (dd, $J=5.1$, 3.0 Hz, 1H), 7.49–7.52 (m, 2H), 7.82 (dd, $J=6.6$, 3.3 Hz, 1H); ^{13}C NMR: δ 18.5, 19.8, 33.6, 56.5, 59.7, 60.5, 81.4, 123.3, 124.4, 127.4, 128.4, 128.7, 129.5, 131.8, 134.2, 137.5, 143.5, 173.0. Anal. calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.20; H, 7.41; N, 9.07%.

4.2.7. 1-Phenyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]-isoindol-5-one 11g. Colorless flakes; yield 74%; mp 140–141°C; ^{1}H NMR: δ 3.48 (dt, $J=11.1$, 8.4 Hz, 1H), 3.64 (td, $J=8.4$, 2.4 Hz, 1H), 3.84 (dt, $J=8.3$, 8.3 Hz, 1H), 4.34 (ddd, $J=11.1$, 7.2, 2.4 Hz, 1H), 6.12 (s, 1H, NCHN), 6.90 (t, $J=7.5$ Hz, 1H), 6.97 (d, $J=8.1$ Hz, 2H), 7.35 (t, $J=8.1$ Hz, 2H), 7.49–7.52 (m, 2H), 7.77 (dd, $J=5.1$, 3.3 Hz, 1H), 7.84 (dd, $J=5.1$, 3.3 Hz, 1H); ^{13}C NMR: δ 42.1, 52.9, 75.3, 114.4, 118.9, 124.2, 124.3, 129.4, 129.6, 132.6, 132.9, 145.4, 146.5, 172.7. Anal. calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.82; N, 11.21%.

4.3. General procedure for the reaction of 2-formyl-5,6-dimethoxybenzoic acid 13 and diamines 9e–9g

Using 2-formyl-5,6-dimethoxybenzoic acid **13** instead of 2-formylbenzoic acid **10** to react with **9g**, **9e** or **9f**, the same procedure as used for the preparation of **11g** led to **14a**. The same procedure as used for the preparation of **11a**–**11f** led to **14b** and **14c**, respectively.

4.3.1. 1-Phenyl-6,7-dimethoxy-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 14a. Colorless flakes; yield 64%; mp 142–143°C; ^{1}H NMR: δ 3.39 (dt, $J=9.3$, 9.3 Hz, 1H), 3.58 (t, $J=8.4$ Hz, 1H), 3.82 (dt, $J=8.7$, 8.7 Hz, 1H), 3.85 (s, 3H), 4.08 (s, 3H), 4.26–4.36 (m, 1H), 5.99 (s, 1H, NCHN), 6.86 (t, $J=7.2$ Hz, 1H), 6.92 (d, $J=8.1$ Hz, 2H), 7.00 (d, $J=8.4$ Hz, 1H), 7.33 (t, $J=7.2$ Hz, 2H), 7.39 (d, $J=8.4$ Hz, 1H); ^{13}C NMR: δ 42.1, 52.5, 56.5, 62.3, 74.2, 114.4, 116.6, 118.7, 119.1, 124.6, 129.3, 138.5, 146.5, 147.3, 153.4, 170.9. Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.75; H, 6.07; N, 8.97%.

4.3.2. (3*S*,9b*S*)-1-Cyclohexyl-3-isopropyl-6,7-dimethoxy-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 14b. Colorless oil; yield 83%; $[\alpha]_D^{25}=-47.5$ (*c* 1.66, $CHCl_3$); ^{1}H NMR: δ 0.97 (d, $J=6.9$ Hz, 3H), 1.07 (d, $J=6.6$ Hz, 3H), 1.26–1.42 (m, 4H), 1.68–1.81 (m, 5H), 1.91–1.95 (m, 1H), 2.04–2.08 (m, 1H), 2.83–2.96 (m, 2H), 3.45 (t, $J=8.3$ Hz, 1H), 3.75 (dt, $J=7.7$, 7.7 Hz, 1H), 3.89 (s, 3H), 4.07 (s, 3H), 5.05 (s, 1H, NCHN), 7.06, 7.09 (AB, $J=8.1$ Hz, 2H); ^{13}C NMR: δ 18.8, 19.8, 24.4, 25.7, 26.2, 26.3, 32.7, 33.6, 52.8, 56.1, 56.6, 60.1, 62.4, 75.3, 116.1, 118.5, 126.1, 137.3, 147.6, 153.6, 171.5. Anal. calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.18; H, 8.56; N, 7.79%.

4.3.3. (3*S*,9b*S*)-1-Benzyl-3-isopropyl-6,7-dimethoxy-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 14c. Colorless needles; yield 86%; mp 79–80°C; $[\alpha]_D^{25}=+4.3$ (*c* 1.66, $CHCl_3$); ^{1}H NMR: δ 0.92 (d, $J=6.6$ Hz, 3H), 1.06 (d, $J=6.6$ Hz, 3H), 1.72–1.83 (m, 1H), 2.52 (t, $J=9.3$ Hz, 1H), 3.41–3.45 (m, 1H), 3.43, 4.12 (AB, $J=12.9$ Hz, 2H), 3.74 (dt, $J=7.8$, 7.8 Hz, 1H), 3.89 (s, 3H), 4.10 (s, 3H), 4.79 (s, 1H, NCHN), 7.03, 7.07 (AB, $J=8.1$ Hz, 2H), 7.22–7.32 (m, 5H); ^{13}C NMR: δ 18.6, 19.9, 33.6, 56.3, 56.6, 59.9, 60.3, 62.4, 80.4, 116.1, 118.3, 125.9, 127.4, 128.4, 128.7, 136.6, 137.5, 147.4, 153.4, 171.4. Anal. calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.38; H, 7.08; N, 7.61%.

4.4. General procedure for the reaction of 2-acetylbenzoic acid 15 with diamines

Using 2-acetylbenzoic acid **15** instead of 2-formylbenzoic acid **10** to react with **9g**, **9h** or **9f**, the same procedure as used for the preparation of **11a–f** led to **16**, **17a** and **17b**, respectively.

4.4.1. 2-(2-Anilinoethyl)-3-methylene-1-isoindolinone 16. Yellowish oil; yield 94%; ^{1}H NMR: δ 3.37 (t, $J=5.8$ Hz, 2H), 3.96 (t, $J=6.0$ Hz, 2H), 4.06 (br s, 1H, NH), 4.79 (d, $J=2.4$ Hz, 1H, H^d), 5.12 (d, $J=2.7$ Hz, 1H, H^c), 6.54 (d, $J=7.8$ Hz, 2H), 6.60 (t, $J=7.3$ Hz, 1H), 7.08 (t, $J=7.8$ Hz, 2H), 7.41 (t, $J=7.4$ Hz, 1H), 7.49 (t, $J=6.9$ Hz, 1H), 7.58 (d, $J=7.5$ Hz, 1H), 7.74 (d, $J=7.2$ Hz, 1H); ^{13}C NMR: δ 38.9, 42.6, 88.8, 112.5, 117.4, 119.9, 123.1, 128.9, 129.3, 129.5, 132.0, 136.3, 141.8, 147.6, 167.9; GC–MS (EI): 264 (M^+), 159, 119, 106 (base), 77, 51. Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.08; H, 5.85; N, 10.68%.

4.4.2. (3*S*,9b*S*)-1-Cyclohexyl-3,9b-dimethyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 17a. Colorless oil; yield 88%; $[\alpha]_D^{25}=+2.6$ (*c* 1.50, $CHCl_3$); ^{1}H NMR: δ 0.92–1.70 (m, 4H), 1.80–1.31 (m, 2H), 1.42 (d, $J=6.3$ Hz, 3H), 1.53–1.56 (m, 2H), 1.61 (s, 3H), 1.72–1.82 (m, 1H), 1.83–1.92 (m, 1H), 2.66–2.78 (m, 1H), 3.08 (dd, $J=10.5$, 7.7 Hz, 1H), 3.61 (dd, $J=10.5$, 7.8 Hz, 1H), 3.88–4.04 (m, 1H), 7.42–7.58 (m, 3H), 7.76 (d, $J=7.2$ Hz, 1H); ^{13}C NMR: δ 21.7, 23.3, 25.7, 25.8, 26.3, 31.8, 32.4, 50.0, 55.2, 56.2, 86.1, 122.4, 124.3, 128.9, 132.0, 133.2, 148.0, 172.4. Anal. calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.92; H, 8.73; N, 9.59%.

4.4.3. (3*S*,9b*S*)-1-Benzyl-3-isopropyl-9b-methyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one 17b. White needles; yield 89%; mp 157–158°C; $[\alpha]_D^{25}=+25.3$ (*c* 1.51, $CHCl_3$); ^{1}H NMR: δ 0.90 (d, $J=6.6$ Hz, 3H), 1.13 (d, $J=6.9$ Hz, 3H), 1.66 (s, 3H), 1.74–1.81 (m, 1H), 2.83 (dd, $J=9.9$, 8.1 Hz, 1H), 3.41 (d, $J=9.9$ Hz, 1H), 3.44, 3.87 (AB, $J=12.9$ Hz, 2H), 3.64 (dt, $J=7.8$, 7.8 Hz, 1H), 7.16–7.26 (m, 5H), 7.36–7.39 (m, 1H), 7.48–7.50 (m, 2H), 7.80 (dd, $J=6.1$, 3.4 Hz, 1H); ^{13}C NMR: δ 18.4, 19.0, 20.9, 35.0, 54.0, 58.9, 60.2, 85.4, 121.7, 124.4, 127.2, 128.3, 128.4, 129.2, 132.1, 132.6, 138.4, 148.1, 173.5. Anal. calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.52; H, 7.66; N, 8.75%.

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