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Alternative and complementary approaches to the asymmetric synthesis of C3 substituted NH free or N-substituted isoindolin-1-ones

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Abstract—Complementary synthetic approaches to enantiomerically pure C3 alkylated or arylated NH free or N-substituted isoindolinones have been developed. The key step is elaboration of diversely substituted 2-alkyl- and arylbenzylamines, which can be submitted to a bis-metallation process followed by interception with a carbonylating agent. They can be also converted into *N*-alkylbromobenzylcarbamates or into bromobenzyldicarbamates and the assembly of the titled compounds can be readily ensured by reliance upon the Parham cyclization process.

1. Introduction

The 3-substituted isoindolinone ring system is generally regarded as a benzylic alcohol bioisostere liable to undergo metabolic oxidation, but has been shown to possess improved metabolic stability while retaining functionality.[1,2] Consequently this benzolactam system has recently emerged as a valuable pharmacophore exhibiting a wide range of therapeutic activities.[3] Typical examples are the anxiolytic drug candidate pagoclone[4] and PD-172938, which was shown to have affinity for the dopamine D_4 receptor[2] (Fig. 1). The isoindolinone skeleton is also an integral part of many naturally occurring substances such as lennoxamine and nuevamine (Fig. 1) and finally, (*R*)- and (*S*)-3-alkyl-1*H*-isoindolinones have been shown to be valuable chiral auxiliaries.[5] Consequently the chemistry of 3-alkyl and arylisoindolinones has attracted much attention and interest in these compounds continues unabated.[6] However, despite the great progress made in asymmetric synthesis within recent decades, few flexible methods are available for the asymmetric synthesis of simple 3-alkyl and arylisoindolin-1-ones **1** in high enantiomeric excess. Among these methods, the most straightforward ones are those where the alkyl groups at the C3 position are introduced directly onto a preconstructed isoindolinone equipped with a chiral auxiliary derived from the natural chiral pool or with a tailor made stereocontrolling agent.

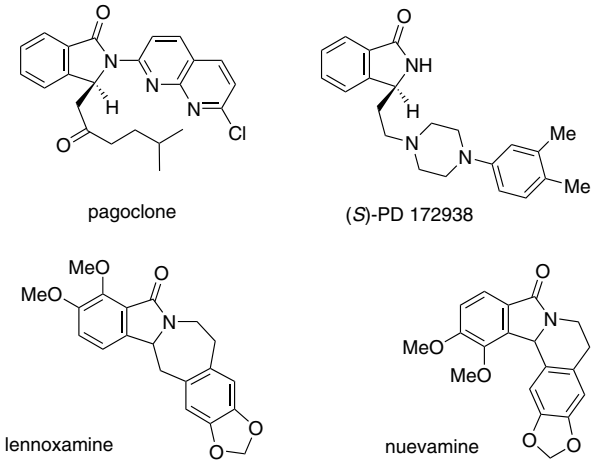

Figure 1.

This has been achieved by reaction of 3-metallated isoindolin-1-ones with electrophiles[7] (Scheme 1, path a) or by reaction of an *N*-acyliminium equivalent with nucleophiles[8] (Scheme 1, path b). A slight modification of the latter was also obtained by treatment of the *N*-acyliminium species deriving from a substituted model with a hydride

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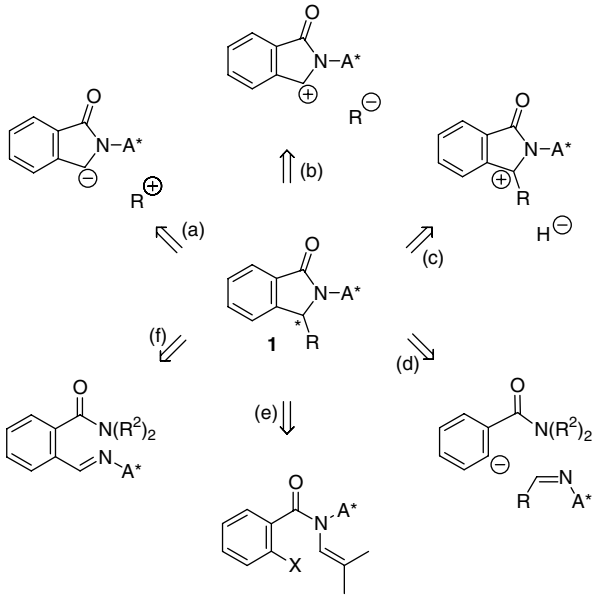
source[6,8d,9] (Scheme 1, path c). The fused compounds **1** were also assembled by a two component reaction involving an *ortho*-lithiated dialkylbenzamide with chiral hydrazones[10] (Scheme 1, path d), by Heck[11] or radical-induced[12] cyclization of aromatic (poly)enamides (Scheme 1, path e) and by a diastereoselective imine addition–cyclization sequence (Scheme 1, path f). An elegant method based upon the stereocontrolled synthesis of **1** via cyclization and rearomatization of α-aminocarbanionic species derived from *N*-benzylbenzamide derivatives and a chiral base has been also described.[13]

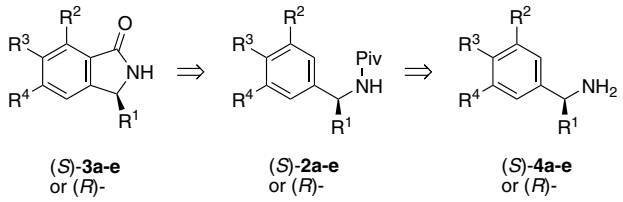


Scheme 1.

All of these methods including those involving resolution of racemic material,[14] usually proceeded in good yields but varying degrees of success have been claimed with regards to their enantioselectivities. This is undoubtedly due to the easy racemization of the C3 substituted isoindolin-1-one systems under basic, acidic, and reductive conditions.[10,14] These methods have been also fraught with difficulties associated with the removal of the chiral auxiliary A* from **1**, even though in this context, (*S*)-2-methoxymethyl-pyrrolidine,[8d] (*R*)-*para*-benzyloxyphenyl-glycinol,[9c] and (+)- or (−)-trans-2-(α-cumyl)cyclohexanol[7c] have been developed as more useful alternatives to the difficult to remove (*R*)-phenylglycinol.[8a,9a,b] These operations trigger off the formation of NH free isoindolinones released from the chiral appendage and consequently few studies have achieved success for the asymmetric synthesis of 2,3-disubstituted models. Furthermore, the developed methods suffer from several drawbacks and particularly from the restriction in the choice of substituents at the specific positions on the basic aromatic nucleus (namely, via paths a–d). Accordingly, the development of a flexible method for the enantioselective synthesis of NH free and N-substituted 3-alkyl- and arylisosindolin-1-ones still constitutes an area of current interest and alternative methods are currently the object of synthetic endeavor.

2. Results and discussion

In this context, we initially planned to develop the synthetic approach portrayed in retrosynthetic synthesis in Scheme 2. We anticipated that the interception of the dilithiated species derived from the chiral aromatic pivaloyl amides **2a**–**e** with a carbonylating agent would provide a general route to optically active C3 substituted isoindolin-1-ones **3a**–**e**. To the best of our knowledge, this technique has to date been confined to the synthesis of a model, that is (*S*)-(+)-3-methylisoindolinone from the commercially available (*R*)-(−)-α-methylbenzylamine and has been claimed to proceed with poor yield (24%).[5b]

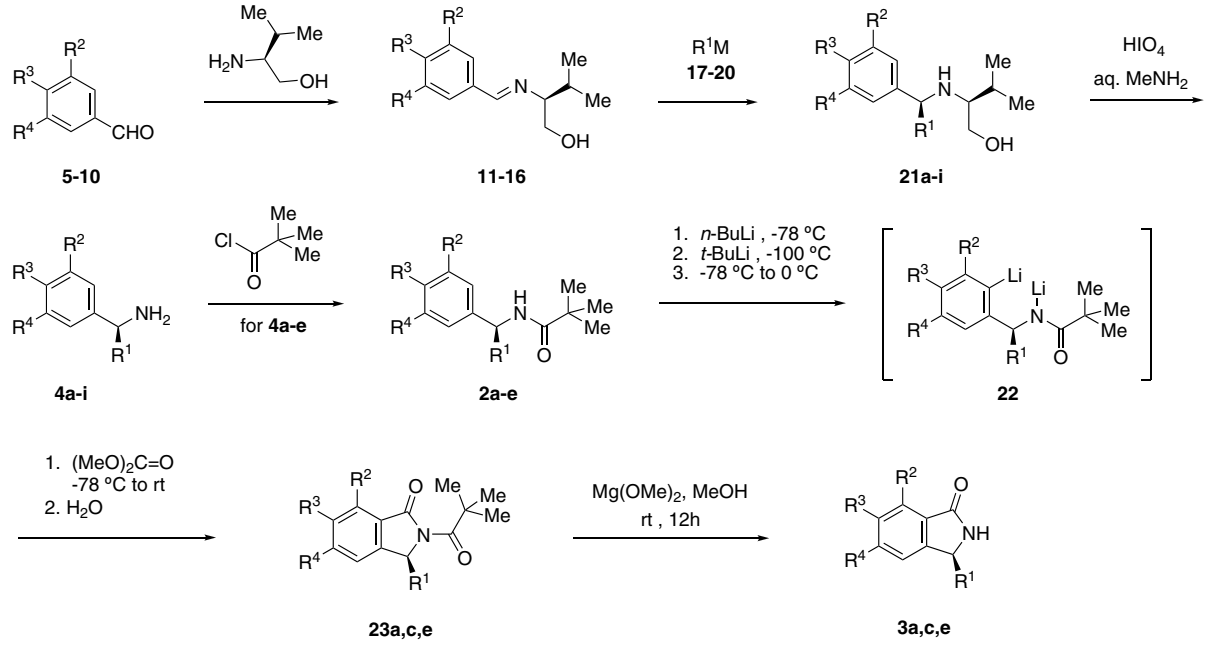


(*S*)-**3a-e** or (*R*)- (*S*)-**2a-e** or (*R*)- (*S*)-**4a-e** or (*R*)-

Scheme 2.

For this purpose, a variety of enantiopure benzylamine derivatives **4a**–**i** was prepared by the three step sequence depicted in Scheme 3 (Table 1). Initially the appropriate aromatic carboxaldehydes **5**–**10** were converted into the corresponding prochiral aldimines **11**–**16** by refluxing with enantiomerically pure (*S*)-valinol. The resulting benzylideneamines **11**–**16** were subsequently allowed to react with a variety of alkyllithiated or Grignard reagents **17**–**20** to provide very satisfactory yields of aromatic aminoalcohols **21a**–**i**, which were obtained with good diastereoselection[15] (Table 1). Chromatographic treatment afforded the major and single diastereomer detectable by NMR and subsequent treatment with periodic acid delivered the required chiral non-racemic amines **4a**–**i** as highly enantioenriched materials (⩾96% ee by chiral HPLC analysis). The absolute configurations as well as the enantiopurity of these benzylamines were further determined by comparing the specific rotation values with those of authentic samples (see Section 4). At this stage, the bismetallation/carbonylation process could be a priori envisaged but this possibility was not investigated. It has been demonstrated that only trace amounts of the annulated product could be detected upon treatment of an unsubstituted dimethoxybenzylamine or its monosilylated protected version under these conditions.[16] Modification of the protecting group was then envisaged and we opted for the pivaloyl group, which was easily connected to chiral amines **4a**–**e** to give access to the desired pivaloyl amides **2a**–**e** almost quantitatively (Table 2). For the assembly of the targeted isoindolinones, compounds **2a**–**e** were sequentially exposed to *n*-Buli and *t*-BuLi at low temperature and the transient dilithiated species **22** was captured with dimethyl carbonate in the sequence (Scheme 3).

This procedure delivered a modest yield of the C3 methylated product **23a** but rather satisfactory yields of the alkoxylated analogues **23c** and **23e**. This is probably due to



Scheme 3.

Table 1. Aldimines **11**–**16**, aminoalcohols **21a**–**i**, and benzylamines **4a**–**i** prepared via Scheme 3

Aldehyde	R^2	R^3	R^4	**11**–**16**	Yield (%)	R^1M	**21a**–**i**	De[a] (%)	Yield[b] (%)	**4a**–**i**	Yield[c] (%)
5	H	H	H	**11**	95	MeLi **17**	**21a**	80	65	**4a**	76
5	H	H	H	**11**	93	*i*-PrMgBr **18**	**21b**	86	61	**4b**	63
6	MeO	H	H	**12**	96	MeLi **17**	**21c**	85	67	**4c**	71
6	MeO	H	H	**12**	94	*n*-BuLi **19**	**21d**	77	59	**4d**	65
7	OCH_2O		H	**13**	95	MeLi **17**	**21e**	80	64	**4e**	69
8	H	MeO	MeO	**14**	96	MeLi **17**	**21f**	82	59	**4f**	65
9	MeO	MeO	MeO	**15**	95	PhLi **20**	**21g**	>96	78	**4g**	66
10	MeO	*i*-PrO	MeO	**16**	95	*n*-BuLi **19**	**21h**	87	65	**4h**	63
9	MeO	MeO	MeO	**15**	96	*i*-PrMgBr **18**	**21i**	86	62	**4i**	70

[a] Determined by ^1H NMR spectroscopy of the crude product.
[b] Yield of isolated (*S*,*S*)-diastereomer.
[c] ee $\geqslant$ 96% determined by chiral HPLC (Chiracel OD, UV detector, hexanes–*i*-PrOH, 50:50 as eluent).

Table 2. Pivaloyl amides **2a**–**e** and isoindolinones **23a**,**c**,**e** and **3a**,**c**,**e** prepared via Scheme 3

Amine **4a**–**e**	R^1	R^2	R^3	R^4	**2a**–**e**	Yield (%)	**23a**,**c**,**e**, **24b**,**d**	Yield (%)	**3a**–**e**	Yield[a] (%)
4a	Me	H	H	H	**2a**	92	**23a**	55	**3a**	92
4b	*i*-Pr	H	H	H	**2b**	88	**24b**	65	—	—
4c	Me	MeO	H	H	**2c**	93	**23c**	76	**3c**	90
4d	*n*-Bu	MeO	H	H	**2d**	87	**24d**	63	—	—
4e	Me	OCH_2O		H	**2e**	91	**23e**	72	**3e**	91

[a] ee $\geqslant$ 96% determined by chiral HPLC (Chiralpak AD, UV detector, hexanes–*i*-PrOH, 95:5 as eluent).

the fact that, even though methoxy and methylenedioxy groups rank modestly in the hierarchy of *ortho*-directing metallation groups,[17] their cooperative effect strongly facilitates the bis-metallation process giving rise to the annulated compounds. Unfortunately in the case of pivaloyl amides **2b** and **2d** only opened models **24b** and **24d** (Fig. 2) were obtained and all attempts to force the annulation process to occur under acidic or basic conditions and by screening the nature of the reagent, temperature profile, and time proved unsuccessful. Failure of cyclization or racemization was also observed instead.[7c]

Removal of the pivaloyl functionality from the annulated products **23a**,**c**,**e** was easily and efficiently accomplished under mild conditions by treatment with magnesium methoxide in methanol (Scheme 3, Table 2). This procedure spared the stereochemistry at the C3 position and the enantiopurity of our synthetic NH free compounds **3a**,**c**,**e** could be

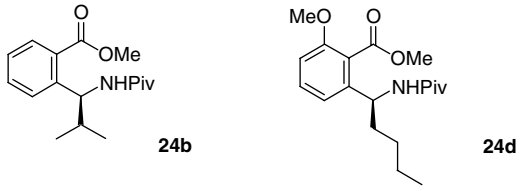
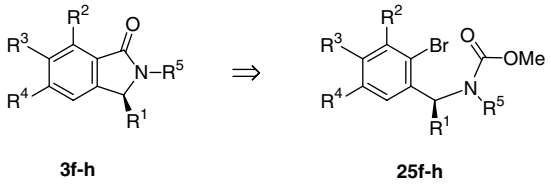


Figure 2.

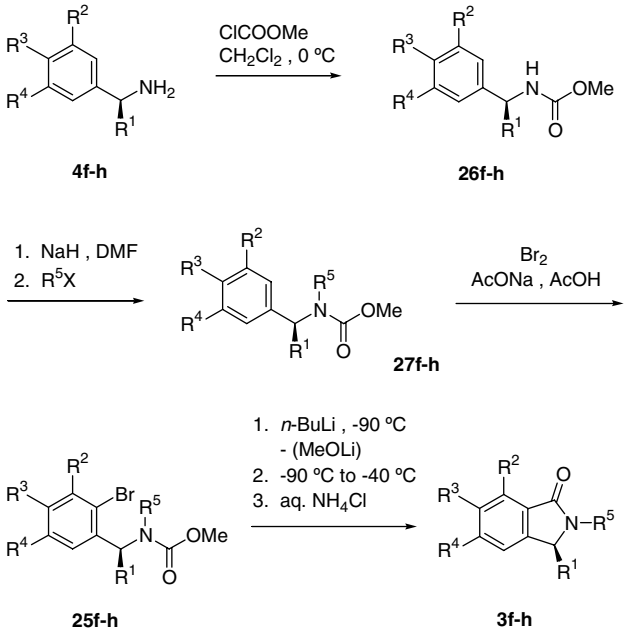
clearly established from the specific rotation and spectroscopic data of authentic samples assembled by a conceptually different synthetic route, for example (*S*)-**3a**: {$[\alpha]_D^{25} = -45.0$ (*c* 0.59, EtOH); (*R*)-**3a**: lit.[8d] $[\alpha]_D = +44.0$ (*c* 0.56, EtOH)}.

Owing to the rather limited scope of this synthetic approach, we decided to switch our plans and set out to achieve an alternative strategy for securing the formation of a variety of N-substituted 3-alkyl- and arylisoindolinones **3f–h**. The key step of the new synthetic approach, which is depicted in retrosynthetic Scheme 4, is based upon the construction of the C3 substituted isoindolinone template by the Parham type cyclization of chiral halogenoaryl carbamates **25f–h**.



Scheme 4.

The Parham process hinges upon aromatic lithiation and subsequent trapping with an internal electrophile.[18] The first facet of the synthesis was the elaboration of the parent carbamates **25f–h**. This was readily accomplished as shown in Scheme 5 by treatment with methyl chloroformate of the suitably substituted and enantiopure benzylamine derivatives **4f–h** which were easily obtained from the corresponding aromatic aminoalcohols **21f–h** (Scheme 3, Table 1). N-Alkylation of the resulting **26f–h** proceeded uneventfully to afford the benzylcarbamates **27f–h**. The methoxy and methylenedioxy groups on the basic benzene nucleus of **27f–h** were prone to force and facilitate the regioselective bromination of the opened carbamates and installation of the bromine atom could be readily secured under standard conditions thereby providing **25f–h** candidates for the planned anionic cyclization process. Exposure of the bromoarylcarbamates **25f–h** to *n*-BuLi at −90 °C ensured



Scheme 5.

the mandatory bromine/lithium interconversion and led to complete consumption of the starting material and to the isolation of the targeted isoindolinones **3f–h** in fairly good yields (Table 3). All of the products exhibited a plus specific rotation value, which corresponds to the (3*S*)-configuration.[7c] Interestingly this annulation technique tolerates the presence of bulky alkyl (e.g., **3h**) and aromatic (e.g., **3g**) substituents.

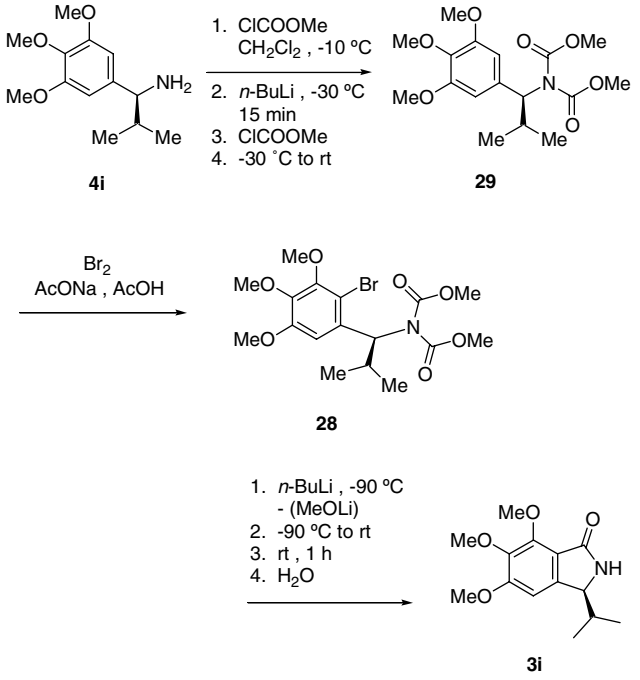
To extend the scope of this new synthetic approach, the development of a conceptually related synthetic route liable to give access to free NH models while circumventing the erratic nature of an ultimate N-deprotection step[8,9] was investigated.

The choice of a bromobenzyldicarbamate originated from the following premises; (i) the carbamate group is endowed with a remarkable propensity to react with basic and nucleophilic reagents in particular with alkoxy moieties inter and intra molecularly;[19] (ii) such alkoxy moieties are expected to be released upon the Parham cyclization process applied to bromobenzylcarbamates (Scheme 6), and (iii) such alkoxide species are of insufficient kinetic basicity to alter the stereochemical outcome at the benzylic position of C3 substituted isoindolinones.[5b] We then embarked on the synthesis of the representative carbamate **28** chosen as a model for the study (Scheme 6). Initially the polyalkoxylated benzylamine **4i** obtained via **21i**, as described in

Table 3. Carbamates **26f–h**, **27f–h**, **25f–h** and acylcarbamates **28** and **29** as precursors of isoindolinones **3f–i**

R^1	R^2	R^3	R^4	Chiralamine	**26f–h**	Yield (%)	R^5	**27f–h, 29**	Yield (%)	**25f–h, 28**	Yield (%)	R^5	**3f–i**	Yield[a] (%)
Me	H	MeO	MeO	**4f**	**26f**	89	Me	**27f**	85	**25f**	73	Me	**3f**	76
Ph	MeO	MeO	MeO	**4g**	**26g**	72	Me	**27g**	83	**25g**	78	Me	**3g**	71
n-Bu	MeO	*i*PrO	MeO	**4h**	**26h**	75	Bn	**27h**	80	**25h**	76	Bn	**3h**	69
i-Pr	MeO	MeO	MeO	**4i**	—	—	COOMe	**29**	65 (2 steps)	**28**	75	H	**3i**	55

[a] ee ⩾ 96% determined by chiral HPLC (Chiralpak AD, UV detector, hexanes–*i*-PrOH).



Scheme 6.

Scheme 3, was differentially diacylated to provide dicarbamate **29** with fairly good yield (65%, two steps). Compound **29** was regioselectively brominated to furnish the rather congested bromobenzyldicarbamate **28**. This compound was subsequently exposed to *n*-BuLi at −90 °C and we were pleased to observe that gentle warming to rt and stirring for an additional 1 h delivered the virtually enantiopure free NH isoindolinone **3i** with a satisfactory yield (55%) and with a minus specific rotation value, which corresponded to the (3*S*)-configuration.[4,7c,8d]

3. Conclusion

In conclusion two alternative and complementary synthetic routes to obtain enantiomerically pure C3 alkylated or arylated NH free or N-substituted isoindolinones have been developed starting from chiral 2-alkyl- or arylbenzylam;ines, which in turn were obtained enantiomerically pure by using (*S*)-valinol as the source of chirality. The first method is based upon the interception of the dimetallated species derived from these benzylamines with a carbonylating agent. The second and conceptually new synthetic approach has been performed on reliance with the Parham cyclization process applied to halogenated N-substituted carbamates and dicarbamate easily assembled from the appropriate benzylamines. It is worth mentioning that the described protocol is interesting from a synthetic point of view when taking into account the large number of poly and diversely alkoxylated benzylamines available by the reported method. This approach should also lead to the synthesis of a wide range of enantiomers of isoindolinones owing to the availability of either antipode of the starting aminoalcohol.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on Bruker AM 300 spectrometer. They were referenced against internal tetramethylsilane; Coupling constants (*J*) are rounded to the nearest 0.1 Hz. Optical rotations were measured on a Perkin Elmer P 241 polarimeter. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use.

Carboxaldehyde **10** was prepared according to a reported procedure.[20]

4.2. Synthesis of aldimines 11–16

A solution of aromatic carboxaldehydes **5**–**10** (10 mmol) and (*S*)-valinol (1.03 g, 10 mmol) in toluene (70 mL) was refluxed in a Dean–Stark apparatus for 3 h. The solvent was distilled under vacuum to afford a residue, which was recrystallized from hexanes.

4.2.1. (*S*)-3-Methyl-{[1-phenylmethylidene]amino}butan-1-ol 11. Mp 69–70 °C (lit.:[21] 70–71°C); $[\alpha]_D^{25} = -34.5$ (*c* 1.88, $CHCl_3$) {lit.:[21] $[\alpha]_D^{25} = -83.3$, (*c* 0.3, $CHCl_3$)}.

4.2.2. (*S*)-2-{[1-(3-Methoxyphenylmethylidene)]amino}-3-methylbutan-1-ol 12. Mp 42–45 °C; $[\alpha]_D^{25} = -21.1$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 0.95 (d, $J = 6.9$ Hz, 6H, $2 \times CH_3$), 1.97 (sext, $J = 6.9$ Hz, 1H, CH), 3.00–3.03 (m, 1H, CH), 3.57 (br s, 1H, OH), 3.62–3.71 (m, 1H, CH_2), 3.74–3.81 (m, 1H, CH_2), 3.83 (s, 3H, OCH_3), 6.97–7.05 (m, 1H, H_{arom}), 7.31–7.37 (m, 2H, H_{arom}), 7.38–7.42 (m, 1H, H_{arom}), 8.25 (s, 1H, CH=N) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ 18.2 (CH_3), 19.5 (CH_3), 29.9 (CH), 54.7 (OCH_3), 63.7 (CH_2), 78.8 (CH), 112.4 (CH), 116.4 (CH), 121.0 (CH), 129.5 (CH), 138.3 (C) 147.5 (C), 160.6 (CH=N) ppm. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.43; H, 8.76; N, 6.23.

4.2.3. (*S*)-2-{[1-Benzo[1,3]dioxol-5-ylmethylidene]amino}-3-methylbutan-1-ol 13. Mp 58–59 °C; $[\alpha]_D^{25} = -51.8$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 0.91 (d, $J = 6.7$ Hz, 3H, CH_3), 0.92 (d, $J = 6.7$ Hz, 3H, CH_3), 1.92 (sext, $J = 6.7$ Hz, 1H, CH), 2.88 (br s, 1H, OH), 2.98 (m, 1H, CH), 3.56–365 (m, 1H, CH_2), 3.72–3.78 (m, 1H, CH_2), 6.06 (s, 2H, OCH_2O), 6.90 (d, $J = 7.9$ Hz, 1H, H_{arom}), 7.20 (d, $J = 7.9$ Hz, 1H, H_{arom}), 7.37 (s, 1H, H_{arom}), 8.18 (s, 1H, CH=N) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ 17.9 (CH_3), 19.4 (CH_3), 29.9 (CH), 63.8 (CH_2), 78.4 (CH), 101.5 (OCH_2O), 106.2 (CH), 107.8 (CH), 124.2

(CH), 131.7 (C), 148.2, (C), 149.6 (C), 159.6 (CH=N) ppm. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.25; N, 6.11.

4.2.4. (*S*)-2-{[1-(3,4-Dimethoxyphenylmethylidene)]amino}-3-methylbutan-1-ol 14. Mp 105–106 °C (lit.:[15c] 102–104 °C); $[\alpha]_D^{25} = -41.0$ (*c* 1.06, $CHCl_3$) {lit.:[15c] $[\alpha]_D^{25} = -42.0$, (*c* 0.2, MeOH)}.

4.2.5. 3-Methyl-2-{[1-(3,4,5-trimethoxyphenyl) meth-(*Z*)-yl-idene]amino}butan-1-ol 15. Oil; $[\alpha]_D^{25} = -13.0$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 0.91 (d, $J = 6.7$ Hz, 3H, CH_3), 0.92 (d, $J = 6.7$ Hz, 3H, CH_3), 1.94 (sext, $J = 6.7$ Hz, 1H, CH), 2.96–3.02 (m, 1H, CH), 3.15 (br s, 1H, OH), 3.64–3.85 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.87 (s, 6H, $2 \times OCH_3$), 7.10 (s, 2H, H_{arom}), 8.16 (s, 1H, CH=N) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ 18.3 (CH_3), 19.4 (CH_3), 29.9 (CH), 55.5 ($2 \times OCH_3$), 59.8 (O CH_3), 63.8 (CH_2), 78.8 (CH), 105.4 ($2 \times CH$), 132.1 (C), 140.1, (C), 153.5 ($2 \times C$), 160.6 (CH=N) ppm. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.82; H, 8.07; N, 4.73.

4.2.6. (*S*)-2-{[1-(4-Isopropoxy-3,5-dimethoxyphenyl)-methylidene]amino}-3-methylbutan-1-ol 16. Mp 101–102 °C; $[\alpha]_D^{25} = -80.1$ (*c* 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, $J = 6.9$ Hz, 3H, CH_3), 0.94 (d, $J = 6.6$ Hz, 3H, CH_3), 1.29 (d, $J = 6.1$ Hz, 3H, CH_3), 1.31 (d, $J = 6.1$ Hz, 3H, CH_3), 1.94 (sept, $J = 6.7$ Hz, 1H, CH), 2.92 (dt, $J = 3.1$, 8.2 Hz, 1H, CH), 3.79 (dd, $J = 3.1$, 11.3 Hz, 1H, CH_2), 3.84 (s, 6H, $2 \times OCH_3$), 3.90 (br s, 1H, OH), (sext, $J = 6.7$ Hz, 1H, CH), 3.92 (dd, $J = 3.2$, 11.3 Hz, 1H, CH_2), 4.41 (sext, $J = 6.1$ Hz, 1H, CH), 6.84 (s, 2H, H_{arom}), 7.95 (s, 1H, CH=N) ppm; ^{13}C NMR (75 MHz, $CHCl_3$): δ 19.4 (CH_3), 19.7 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 30.1 (CH), 56.1 ($2 \times OCH_3$), 64.5 (CH_2), 75.5 (CH), 79.3 (CH), 105.2 ($2 \times CH$), 130.8 (C), 138.2, (C), 153.8 ($2 \times C$), 162.0 (CH=N) ppm. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.87; H, 8.98; N, 4.77.

4.3. Synthesis of aminoalcohols 21a–i

A solution of the appropriate organolithium (MeLi, *n*-BuLi or PhLi) derivative (31 mmol) was added dropwise to a solution of imines **11**–**16** (10 mmol) in Et_2O (60 mL) at 0 °C. The solution was then stirred at rt for 20 h. For **21b** and **21i**, *i*-PrMgBr (2 M solution in THF, 31 mmol, 15.5 mL) was added dropwise to a solution of imines **11**, **15** (10 mmol) in THF (60 mL) at 0 °C and the solution was then stirred at 50 °C for 20 h. The reaction mixture was carefully quenched with water, and the ethereal layer washed with water (30 mL) and brine (20 mL). Evaporation of the solvents in vacuo left an oily residue, which was purified by flash column chromatography using a mixture of Et_2O–Et_3N–hexanes (50:10:40) as eluent to furnish a pale yellow oil.

4.3.1. (*S*)-3-Methyl-2-((*S*)-1-phenylethylamino)butan-1-ol 21a. $[\alpha]_D^{25} = -12.6$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, $J = 6.8$ Hz, 3H, CH_3), 0.92 (d, $J = 6.8$ Hz, 3H, CH_3), 1.38 (d, $J = 6.6$ Hz, 3H, CH_3), 1.76 (sext, $J = 6.8$ Hz, 1H, CH), 2.33 (m, 1H, CH), 3.36 (dd, $J = 5.6$, 10.6 Hz, 1H, CH_2), 3.64 (dd, $J = 4.2$, 10.6 Hz, 1H, CH_2), 3.88 (q, $J = 6.6$ Hz, 1H, ArCH), 7.26–7.35 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 19.5 (CH_3), 24.2 (CH_3), 29.4 (CH), 60.1 (CH_2), 55.4 (CH), 61.1 (CH), 126.5 ($2 \times CH$), 127.1, 128.5 ($2 \times CH$), 145.8 (C) ppm. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.45; H, 10.22; N, 6.69.

4.3.2. (*S*)-3-Methyl-2-((*S*)-2-methyl-1-phenylpropyl-amino)-butan-1-ol 21b. $[\alpha]_D^{25} = -28.8$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, $J = 6.7$ Hz, 3H, CH_3), 0.80–0.86 (m, 6H, $2 \times CH_3$), 1.06 (d, $J = 6.7$ Hz, 3H, CH_3), 1.68 (sext, $J = 6.7$ Hz, 1H, CH), 1.87 (sext, $J = 6.7$ Hz, 1H, CH), 2.13 (m, 1H, CH), 3.31 (d, $J = 7.6$ Hz, 1H, ArCH), 3.44 (dd, $J = 3.1$, 10.8 Hz, 1H, CH_2), 3.62 (dd, $J = 4.0$, 10.8 Hz, 1H, CH_2), 7.19 (d, $J = 6.7$ Hz, 2H, H_{arom}), 7.24–7.35 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3), 19.4 (CH_3), 19.8 (CH_3), 20.2 (CH_3), 29.3 (CH), 34.5 (CH), 59.1 (CH_2), 61.0 (CH), 66.5 (CH), 126.8 (CH), 127.1 ($2 \times CH$), 128.1 ($2 \times CH$), 143.1 (C) ppm. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.71; H, 10.69; N, 5.78.

4.3.3. (*S*)-2-[(*S*)-1-(3-Methoxyphenyl)ethylamino]-3-methyl-butan-1-ol 21c. $[\alpha]_D^{25} = -22.1$ (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, $J = 6.8$ Hz, 3H, CH_3), 0.92 (d, $J = 6.8$ Hz, 3H, CH_3), 1.36 (d, $J = 6.5$ Hz, 3H, CH_3), 1.75 (sext, $J = 6.8$ Hz, 1H, CH), 2.32 (q, $J = 5.1$ Hz, 1H, CH), 3.36 (dd, $J = 5.1$, 10.5 Hz, 1H, CH_2), 3.63 (dd, $J = 4.1$, 10.5 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.85 (q, $J = 6.8$ Hz, 1H, ArCH), 6.80 (d, $J = 8.1$ Hz, 1H, H_{arom}), 6.85–6.90 (m, 2H, H_{arom}), 7.26 (t, $J = 8.2$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 19.6 (CH_3), 24.3 (CH_3), 29.4 (CH), 55.2 (CH), 55.4 (OCH_3), 60.0 (CH_2), 61.1 (CH), 112.2 (CH), 112.25 (CH), 118.8 (CH), 129.5 (CH), 147.6 (C), 159.7 (C) ppm. Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.62; H, 10.02; N, 5.74.

4.3.4. (*S*)-2-[(*S*)-1-(3-Methoxyphenyl)pentylamino]-3-methylbutan-1-ol 21d. $[\alpha]_D^{25} = -17.1$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84–0.91 (m, 9H, $3 \times CH_3$), 1.05–1.37 (m, 4H, $2 \times CH_2$), 1.50–1.83 (m, 3H, CH + CH_2), 2.45 (m, 1H, CH), 3.38 (dd, $J = 4.1$, 10.6 Hz, 1H, CH_2), 3.56–3.64 (m, 2H, CH + CH_2), 3.82 (s, 3H, OCH_3), 6.79–6.84 (m, 3H, H_{arom}), 7.25 (t, $J = 8.0$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.9 (CH_3), 19.6 (CH_3), 55.1 (OCH_3), 22.7 (CH_2), 28.8 (CH_2), 29.4 (CH), 38.0 (CH_2), 59.7 (CH_2), 60.5 (CH), 60.9 (CH), 112.0 (CH), 112.8 (CH), 119.4 (CH), 129.4 (CH), 146.4 (C), 159.7(C) ppm. Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.98; H, 10.41; N, 5.22.

4.3.5. (*S*)-2-((*S*)-1-Benzo[1,3]dioxol-5-ylethylamino)-3-methylbutan-1-ol 21e. $[\alpha]_D^{25} = -51.8$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, $J = 6.8$ Hz, 3H, CH_3), 0.89 (d, $J = 6.8$ Hz, 3H, CH_3), 1.30 (d, $J = 6.5$ Hz, 3H, CH_3), 1.73 (sext, $J = 6.8$ Hz, 1H, CH), 2.29 (m, 1H, CH), 3.17

(br s, 1H, OH), 3.35 (dd, $J = 5.2$, 10.6 Hz, 1H, CH_2), 6.36 (dd, $J = 4.2$, 10.6 Hz, 1H, CH_2), 3.78 (q, $J = 6.5$ Hz, 1H, ArCH), 5.92 (s, 2H, OCH_2O), 6.71–6.74 (m, 2H, H_{arom}), 6.81 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 19.5 (CH_3), 24.3 (CH_3), 29.3 (CH), 55.2 (CH), 60.0 (CH_2), 61.0 (CH), 100.9 (OCH_2O), 106.6 (CH), 108.0 (CH), 119.7 (CH), 139.9 (C), 146.4 (C), 147.8 (C) ppm. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.11; H, 8.24; N, 5.61.

4.3.6. (*S*)-2-[(*S*)-1-(3,4-Dimethoxyphenyl)ethylamino]-3-methylbutan-1-ol 21f. $[\alpha]_D^{25} = -24.9$ (c 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (d, $J = 6.8$ Hz, 3H, CH_3), 0.85 (d, $J = 6.8$ Hz, 3H, CH_3), 1.29 (d, $J = 6.5$ Hz, 3H, CH_3), 1.67 (sext, $J = 6.8$ Hz, 1H, CH), 2.21 (q, $J = 5.2$ Hz, 1H, CH), 3.32 (dd, $J = 5.0$, 10.6 Hz, 1H, CH_2), 3.57 (dd, $J = 4.2$, 10.6 Hz, 1H, CH_2), 3.77 (q, $J = 6.5$ Hz, 1H, ArCH), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.75 (s, 2H, H_{arom}), 6.82 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8 (CH_3), 19.4 (CH_3), 24.5 (CH_3), 29.3 (CH), 55.1 (OCH_3), 55.7 (OCH_3), 55.8 (CH), 60.0 (CH_2), 61.1 (CH), 109.3 (CH), 110.9 (CH), 118.7 (CH), 138.5 (C), 147.9 (C), 149.0 (C) ppm. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.51; H, 9.45; N, 5.17.

4.3.7. (*S*)-3-Methyl-2-{[phenyl-(3,4,5-trimethoxyphenyl)-methyl]amino}butan-1-ol 21g. $[\alpha]_D^{25} = +25.3$ (c 1.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, $J = 6.1$ Hz, 3H, CH_3), 0.97 (d, $J = 6.1$ Hz, 3H, CH_3), 1.95 (sext, $J = 6.1$ Hz, 1H, CH), 2.42–2.46 (m, 1H, CH), 3.46 (dd, $J = 6.0$, 10.8 Hz, 1H, CH_2), 3.63 (dd, $J = 4.1$, 10.8 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.85 (s, 6H, $2 \times OCH_3$), 4.94 (s, 1H, CH), 6.66 (s, 2H, H_{arom}), 7.19–7.44 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4 (CH_3), 19.5 (CH_3), 28.7 (CH), 56.1 ($2 \times OCH_3$), 60.4 (CH_2), 60.8 (OCH_3), 61.1 (CH), 64.4 (CH), 104.4 ($2 \times CH$), 127.2 (CH), 127.3 ($2 \times CH$), 128.6 ($2 \times CH$), 139.8 ($2 \times C$), 143.9 (C), 153.2 ($2 \times C$) ppm. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.91; H, 8.36; N, 3.77.

4.3.8. (*S*)-2-[1-(4-Isopropoxy-3,5-dimethoxyphenyl)-pentylamino]-3-methylbutan-1-ol 21h. $[\alpha]_D^{25} = -12.5$ (c 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.81–0.89 (m, 9H, $3 \times CH_3$), 1.07–1.38 (m, 7H, $3 \times CH_2 + CH$), 1.28 (d, $J = 6.1$ Hz, 3H, CH_3), 1.30 (d, $J = 6.1$ Hz, 3H, CH_3), 2.24 (dd, $J = 4.2$, 6.7, 1H, CH), 3.34 (d, $J = 4.2$, 10.7 Hz, 1H, CH_2), 3.51 (dd, $J = 6.9$, 7.0 Hz, 1H, CH), 3.61 (dd, $J = 4.2$, 10.7 Hz, 1H, CH_2), 3.82 (s, 6H, $2 \times OCH_3$), 4.34 (sept, $J = 6.1$ Hz, 1H, CH), 6.43 (s, 2H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.0 (CH_3), 19.6 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 22.7 (CH_2), 28.8 (CH_2), 29.4 (CH), 38.0 (CH_2), 56.0 ($2 \times OCH_3$), 59.8 (CH_2), 61.0 (CH), 61.1 (CH), 75.1 (CH), 103.8 ($2 \times CH$), 134.9 (C), 140.1 (C), 153.7 ($2 \times C$) ppm. Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.71; H, 9.91; N, 4.03.

4.3.9. (*S*)-3-Methyl-2-[2-methyl-1-(3,4,5-trimethoxyphenyl)-propylamino]butan-1-ol 21i. $[\alpha]_D^{25} = -33.9$ (c 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.7$ Hz, 3H, CH_3), 0.84 (d, $J = 6.7$ Hz, 3H, CH_3), 0.88 (d, $J = 6.7$ Hz, 3H, CH_3), 1.04 (d, $J = 6.7$ Hz, 3H, CH_3), 1.69 (sext, $J = 6.7$ Hz, 1H, CH), 1.81 (sext, $J = 6.7$ Hz, 1H, CH), 2.14 (ddd, $J = 3.0$, 3.4, 3.9 Hz, 1H, CH), 3.22 (d, $J = 7.6$ Hz, 1H, CH), 3.45 (dd, $J = 3.0$, 10.8 Hz, 1H, CH_2), 3.61 (dd, $J = 3.9$, 10.8 Hz, 1H, CH_2), 3.84 (s, 9H, $3 \times OCH_3$), 6.40 (s, 2H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 19.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 29.3 (CH), 34.7 (CH), 56.1 ($2 \times OCH_3$), 59.2 (CH_2), 60.8 (OCH_3), 60.9 (CH), 66.7 (CH), 104.4 ($2 \times CH$), 139.1 ($2 \times C$), 152.9 ($2 \times C$) ppm. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.24; H, 9.44; N, 4.21.

4.4. Synthesis of chiral benzylamines 4a–i

A mixture of aq methylamine (40%, 2 mL) and periodic acid (7.8 mmo1, 1.78 g, as a solution in H_2O, 16 mL) was added to a stirred solution of aminoalcohols **21a–i** (3 mmol) in MeOH (18 mL) at rt. After stirring for 3 h, the mixture was extracted with Et_2O (3×10 mL). The ether extracts were combined and mixed with aq HCl (4 M, 6 mL). The mixture was concentrated to remove ether, stirred for 30 min to ensure complete hydrolysis of the imine, and further concentrated to remove MeOH. The remaining aqueous solution was extracted with Et_2O (2×10 mL) and the ethereal extracts were discarded. After neutralization with NaOH (6 M) at 0 °C, the aqueous layer was extracted with Et_2O (3×10 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The oily residue was purified by flash column chromatography on silica gel with a mixture Et_2O–hexanes–MeOH–Et_3N (30:60:5:5) as eluent to furnish a colorless oil.

4.4.1. (*S*)-1-Phenylethylamine 4a. $[\alpha]_D^{25} = -34.6$ (c 0.9, $CHCl_3$) {lit.:[22] $[\alpha]_D^{25} = -35.1$ (c 1.0, $CHCl_3$)}.

4.4.2. (*S*)-2-Methyl-1-phenylpropylamine 4b. $[\alpha]_D^{25} = -12.3$ (c 1.06, $CHCl_3$) {lit.:[23] −10.8 (c 1.0, $CHCl_3$)}.

4.4.3. (*S*)-1-(3-Methoxyphenyl)ethylamine 4c. $[\alpha]_D^{25} = -26.8$ (c 1.15, $CHCl_3$) {lit.:[22] −26.0 (c 0.8, $CHCl_3$)}.

4.4.4. (*S*)-1-(3-Methoxyphenyl)pentylamine 4d. $[\alpha]_D^{25} = -7.3$ (c 1.01, $CHCl_3$) ppm; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H, CH_3), 1.09–1.40 (m, 4H, $2 \times CH_2$), 1.56 (br s, 2H, NH_2), 1.66 (q, $J = 7.0$ Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.82 (t, $J = 7.0$ Hz, 1H, ArCH), 6.78 (d, $J = 8.0$ Hz, 1H, H_{arom}), 6.88–6.91 (m, 2H, H_{arom}), 7.24 (t, $J = 8.0$ Hz, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.7 (CH_2), 28.8 (CH_2), 39.3 (CH_2), 55.1 (CH_3), 56.3 (CH), 111.9 (CH), 112.1 (CH), 118.7 (CH), 129.4 (CH), 148.6 (C), 159.7 (C) ppm. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.37; H, 10.05; N, 7.32.

4.4.5. (*S*)-1-Benzo[1,3]dioxol-5-ylethylamine 4e. $[\alpha]_D^{25} = -24.8$ (c 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, $J = 6.6$ Hz, 3H, CH_3), 1.46 (br s, 2H, NH_2), 4.01 (q, $J = 6.6$ Hz, 1H, CH), 5.88 (s, 2H, OCH_2O), 6.69–6.78 (m, 2H, H_{arom}), 6.84 (s, 1H, H_{arom}) ppm; ^{13}C NMR

(75 MHz, $CDCl_3$): δ 25.8 (CH_3), 51.1 (CH), 100.8 (OCH_2O), 106.2 (CH), 108.0 (CH), 118.6 (CH), 142.0 (C), 146.2 (C), 147.6 (C) ppm. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.28; H, 6.69; N, 8.54.

4.4.6. (*S*)-1-(3,4-Dimethoxyphenyl)ethylamine 4f. $[\alpha]_D^{25} = -24.2$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (d, $J = 6.6$ Hz, 3H, CH_3), 1.68 (br s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.10 (q, $J = 6.6$ Hz, 1H, CH), 6.80–6.93 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8 (CH_3), 51.0 (CH), 55.8 (OCH_3), 55.9 (OCH_3), 109.0 (CH), 111.0 (CH), 117.6 (CH), 140.4 (C), 147.8 (C), 148.9 (C) ppm. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.03; H, 8.51; N, 7.69.

4.4.7. (*S*)-1-Phenyl-1-(3,4,5-trimethoxyphenyl)methylamine 4g. $[\alpha]_D^{25} = +24.4$ (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (br s, 2H, NH_2), 3.83 (s, 3H, OCH_3), 3.84 (s, 6H, $2 \times OCH_3$), 5.17 (s, 1H, CH), 6.65 (s, 2H, H_{arom}), 7.33–7.40 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1 ($2 \times OCH_3$), 59.9 (CH), 60.8 (OCH_3), 103.8 ($2 \times CH$), 126.8 ($2 \times CH$), 127.1 (CH), 128.5 ($2 \times CH$), 136.8 (C), 141.3 (C), 145.5 (C), 153.2 ($2 \times C$) ppm. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.45; H, 7.14; N, 4.87.

4.4.8. (*S*)-1-(4-Isopropoxy-3,5-dimethoxyphenyl)pentylamine 4h. $[\alpha]_D^{25} = -1.2$ (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $J = 6.9$ Hz, 3H, CH_3), 1.29 (d, $J = 6.1$ Hz, 6H, $2 \times CH_3$), 1.25–1.38 (m, 4H, $2 \times CH_2$), 1.52–1.65 (m, 4H, $CH_2 + NH_2$), 3.76–3.87 (m, 7H, $2 \times OCH_3 + CH$), 4.32 (sept, $J = 6.1$, 1H, CH), 6.53 (s, 2H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1 ($2 \times OCH_3$), 59.9 (CH), 60.8 (OCH_3), 103.8 ($2 \times CH$), 126.8 ($2 \times CH$), 127.1 (CH), 128.5 ($2 \times CH$), 136.8 (C), 141.3 (C), 145.5 (C), 153.2 ($2 \times C$) ppm. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.11; H, 9.59; N, 5.12.

4.4.9. (*S*)-2-Methyl-1-(3,4,5-trimethoxyphenyl)-propylamine 4i. $[\alpha]_D^{25} = +3.5$ (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (d, $J = 6.6$ Hz, 3H, CH_3), 0.89 (d, $J = 6.6$ Hz, 3H, CH_3), 1.44 (br s, 2H, NH_2), 1.71 (sext, $J = 6.6$ Hz, 1H, CH), 3.43 (d, $J = 7.3$ Hz, 1H, CH), 3.72 (s, 3H, OCH_3), 3.75 (s, 6H, $2 \times OCH_3$), 6.45 (s, 2H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (CH_3), 19.7 (CH_3), 35.3 (CH), 55.7 ($2 \times OCH_3$), 60.4 (OCH_3), 62.5 (CH), 103.6 ($2 \times CH$), 136.4 (C), 141.1 (C), 152.6 ($2 \times C$) ppm. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.48; H, 8.63; N, 5.87.

4.5. Synthesis of pivaloyl amides 23a–e

Trimethylacetylchloride (2.66 mg, 2.2 mmol) was added dropwise to a stirred solution of benzylamines **4a–e** (2 mmol) and Et_3N (610 mg, 6 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was then stirred at rt for 15 min,. washed with water (3×20 mL), and dried ($MgSO_4$). Evaporation of the solvent left a white solid, which was recrystallized from hexanes–toluene.

4.5.1. 2,2-Dimethyl-*N*-((*S*)-1-phenylethyl)propionamide 2a. Mp 117–118 °C (lit.:[5b] 115–117 °C); $[\alpha]_D^{25} = -106.6$ (*c* 1.09, $CHCl_3$) {lit.[24] $[\alpha]_D^{25} = -107.3$ (*c* 0.8, EtOH)}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H, $3 \times CH_3$), 1.49 (d, $J = 7.1$ Hz, 3H, CH_3), 5.12 (quint, $J = 7.1$ Hz, 1H, CH), 5.85 (br s, 1H, NH), 7.24–7.36 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ CH_3 21.7 (CH_3), 27.6 ($3 \times CH_3$), 38.6 (C), 48.4 (CH), 126.0 (CH), 127.2 (CH), 128.6 (CH), 143.5 (C), 177.4 (CO) ppm.

4.5.2. 2,2-Dimethyl-*N*-((*S*)-2-methyl-1-phenylpropyl)-propionamide 2b. Mp 124–125 °C; $[\alpha]_D^{25} = -87.5$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, $J = 6.7$ Hz, 3H, CH_3), 0.95 (d, $J = 6.7$ Hz, 3H, CH_3), 1.22 (s, 9H, $3 \times CH_3$), 2.06 (sext, $J = 6.7$ Hz, 1H, CH), 4.77 (t, $J = 8.0$ Hz, 1H, Ar-CH), 5.98 (br s, 1H, NH), 7.19–7.36 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (CH_3), 19.7 (CH_3), 27.6 ($3 \times CH_3$), 33.5 (CH), 38.8 (C), 58.6 (CH), 126.7 ($2 \times CH$), 127.0 (CH), 128.4 ($2 \times CH$), 141.8 (C), 177.5 (CO) ppm. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.05; H, 10.01; N, 6.21.

4.5.3. *N*-[(*S*)-1-(3-Methoxyphenyl)ethyl]-2,2-dimethylpropionamide 2c. Mp 69–70 °C; $[\alpha]_D^{25} = -76.8$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 9H, $3 \times CH_3$), 1.47 (d, $J = 6.9$ Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.08 (pent, $J = 6.9$ Hz, 1H, CH), 5.85 (br d, $J = 6.9$ Hz, 1H, NH), 6.81 (d, $J = 6.8$ Hz, 1H, H_{arom}), 6.84 (s, 1H, H_{arom}), 6.89 (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.23–7.30 (m, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (CH_3), 27.6 ($3 \times CH_3$), 38.6 (C), 48.5 (CH), 55.2 (CH_3), 112.0 (CH), 112.3 (CH), 118.3 (CH), 129.7 (CH), 145.2 (C), 159.8 (C), 177.5 (CO) ppm. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.19; H, 9.08; N, 6.12.

4.5.4. *N*-[(*S*)-1-(3-Methoxyphenyl)pentyl]-2,2-dimethylpropionamide 2d. Mp 115–116 °C; $[\alpha]_D^{25} = -71.2$ (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.8$ Hz, 3H, CH_3), 1.21 (s, 9H, $3 \times CH_3$), 1.26–1.36 (m, 4H, $2 \times CH_2$), 1.77 (q, $J = 7.5$ Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.90 (q, $J = 7.5$ Hz, 1H, Ar-CH), 5.84 (br s, 1H, NH), 1.77–1.82 (m, 2H, H_{arom}), 6.87 (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.25 (t, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 27.6 ($3 \times CH_3$), 28.4 (CH_2), 36.1 (CH_2), 38.6 (CH), 53.1 (CH), 55.2 (CH_3), 112.2 (CH), 112.4 (CH), 118.6 (CH), 129.6 (CH), 144.5 (C), 159.7 (C), 177.5 (CO) ppm. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.45; H, 10.05; N, 5.12.

4.5.5. *N*-(*S*)-(1-Benzo[1,3]dioxol-5-ylethyl)-2,2-dimethylpropionamide 2e. Mp 97–98 °C; $[\alpha]_D^{25} = -86.2$ (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H, $3 \times CH_3$), 1.44 (d, $J = 6.8$ Hz, 3H, CH_3), 4.93–5.07 (m, 1H, CH), 5.77 (br s, 1H, NH), 5.94 (s, 2H, OCH_2O), 5.71–6.83 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (CH_3), 27.5 ($3 \times CH_3$), 38.6 (C), 48.3 (CH), 101.0 (O CH_2O), 106.7 (CH), 108.3 (CH), 119.2 (CH), 137.6 (C), 146.6 (C), 147.8 (C), 177.4 (CO) ppm. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.21; H, 7.65; N, 5.79.

4.6. Synthesis of isoindolinones 23a,c,e

A solution of pivaloyl amides **2a**–**e** (1 mmol) in Et_2O (10 mL) was cooled at −78 °C under Ar. *n*-BuLi (1.6 M solution in hexanes, 1 mmol, 0.62 mL) was quickly added and after stirring for 30 min the mixture was cooled to −100 °C and *t*-BuLi (1.7 M solution in pentane, 1.2 mmol, 0.70 mL) was then added dropwise. The mixture was stirred at −78 °C for 4 h and then at 0 °C for 30 min. The solution was re-cooled to −78 °C and dimethylcarbonate (135 mg, 1.5 mmol) was added dropwise. The solution was allowed to warm to rt and quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined extracts were dried ($MgSO_4$)and evaporated in vacuo to leave an oily residue, which was purified by flash column chromatography on silica gel using AcOEt–hexanes (30:70) as eluent.

4.6.1. (*S*)-2-(2,2-Dimethylpropionyl)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 23a. Mp 58–59 °C; $[\alpha]_D^{25} = +28.9$ (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H, 3 × CH_3), 1.51 (d, $J = 6.3$ Hz, 3H, CH_3), 5.32 (q, $J = 6.3$ Hz, 1H, CH), 7.44 (d, $J = 7.4$ Hz, 1H, H_{arom}), 7.49 (t, $J = 7.4$ Hz, 1H, H_{arom}), 7.65 (t, $J = 7.4$ Hz, 1H, H_{arom}), 7.86 (d, $J = 7.4$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9 (CH_3), 26.2 (3 × CH_3), 41.9 (C), 57.1 (CH), 122.3 (CH), 125.0 (CH), 128.5 (CH), 133.8 (CH), 130.4 (C), 147.6 (C), 166.1 (CO), 180.2 (CO) ppm. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.56; H, 7.49; N, 5.97.

4.6.2. (*S*)-2-(2,2-Dimethylpropionyl)-7-methoxy-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 23c. Mp 65–66 °C; $[\alpha]_D^{25} = -3.9$ (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 9H, 3 × CH_3), 1.47 (d, $J = 6.5$ Hz, 3H, CH_3), 3.98 (s, 3H, OCH_3), 5.24 (q, $J = 6.5$ Hz, 1H, CH), 6.88 (d, $J = 8.1$ Hz, 1H, H_{arom}), 6.96 (d, $J = 7.3$ Hz, 1H, H_{arom}), 7.53–7.59 (m, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 26.2 (3 × CH_3), 41.9 (C), 56.1 (CH_3), 55.9 (CH), 110.0 (CH), 114.1 (CH), 135.5 (CH), 144.7 (C), 150.4 (C), 158.6 (C), 164.8 (CO), 180.2 (CO) ppm. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.10; H, 7.35; N, 5.06.

4.6.3. (*S*)-7-(2,2-Dimethylpropionyl)-6-methyl-6,7-dihydro-8*H*-1,3-dioxolo[4,5-*e*]isoindol-8-one 23e. Oil; $[\alpha]_D^{25} = +2.0$ (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, 3 × CH_3), 1.49 (d, $J = 6.3$ Hz, 3H, CH_3), 5.29 (q, $J = 6.3$ Hz, 1H, CH), 6.17 (s, 2H, OCH_2O), 6.84 (d, $J = 7.7$ Hz, 1H, H_{arom}), 7.06 (d, $J = 7.7$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (CH_3), 26.1 (3 × CH_3), 42.0 (C), 57.5 (CH), 103.2 (OCH_2O), 113.5 (CH), 114.1 (CH), 140.5 (C), 144.6 (C), 148.5 (C), 163.7(C), 180.1 (2 × CO) ppm. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.44; H, 6.31; N, 4.96.

4.6.4. 2-[(*S*)-1-(2,2-Dimethylpropionylamino)-2-methylpropyl]benzoic acid methyl ester 24b. Mp 59–60 °C; $[\alpha]_D^{25} = -80.5$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.67 (d, $J = 6.7$ Hz, 3H, CH_3), 0.99 (d, $J = 6.7$ Hz, 3H, CH_3), 1.17 (s, 9H, 3 × CH_3), 2.00–2.17 (m, 1H, CH), 3.91 (s, 3H, OCH_3), 4.94 (t, $J = 9.8$ Hz, 1H, Ar-CH), 7.29 (t, $J = 7.6$ Hz, 1H, H_{arom}), 7.34–7.46 (m, 2H, H_{arom}), 7.40 (br s, 1H, NH), 7.88 (d, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (CH_3), 19.7 (CH_3), 27.6 (3 × CH_3), 32.0 (CH), 52.5 (C), 60.0 (CH_3), 127.1 (CH), 131.6 (2 × CH), 132.4 (2 × CH), 128.6 (C), 143.1 (C), 169.4 (CO), 177.7 (CO) ppm. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.82; H, 8.59; N, 5.01.

4.7. Synthesis of isoindolinones 3a,c,e

$Mg(OMe)_2$ (1 M solution in MeOH, 1.5 mL, 1.5 mmol) was added to a stirred solution of *N*-pivaloyl isoindolinones **23a**,**c**,**e** (0.5 mmol) in MeOH (6 mL). Stirring was maintained overnight at rt. After evaporation of the solvent the residue was dissolved in AcOEt (20 mL) and washed with satd aq NH_4Cl solution (10 mL). The aqueous layer was then re-extracted with AcOEt (10 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent the solid residues **3a** and **3e** were recrystallized from Et_2O–acetonitrile to give a white solid. Product **3c** was purified by column chromatography on silica gel using AcOEt as eluent.

4.7.1. (*S*)-3-Methyl-2,3-dihydro-1*H*-isoindol-1-one 3a. Mp 118–119 °C (lit.:[9d] 112–115 °C); $[\alpha]_D^{25} = -45.0$ (*c* 0.59, EtOH) {lit.:[8d] (*R*)-isomer, $[\alpha]_D^{25} = +44.0$ (*c*0.56, MeOH)}.

4.7.2. (*S*)-7-Methoxy-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 3c. Oil; $[\alpha]_D^{25} = -2.2$ (*c* 0.5, DMSO); ^1H NMR (300 MHz, DMSO-d_6): δ 1.49 (d, $J = 6.7$ Hz, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.63 (q, $J = 6.7$ Hz, 1H, CH), 6.89 (d, $J = 7.9$ Hz, 1H, H_{arom}), 6.98 (d, $J = 7.9$ Hz, 1H, H_{arom}), 7.50 (t, $J = 7.9$ Hz, 1H, H_{arom}), 7.53 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5 (CH_3), 52.1 (CH), 55.9 (CH_3), 109.9 (CH), 114.3 (CH), 118.1 (C), 133.7 (CH), 152.1 (C), 157.5 (C), 170.3 (CO) ppm. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.05; H, 6.13; N, 7.86.

4.7.3. (*S*)-6-Methyl-6,7-dihydro-8*H*-1,3-dioxolo[4,5-*e*]isoindol-8-one 3e. Mp 189–190 °C; $[\alpha]_D^{25} = -12.4$ (*c* 1.03, DMSO); ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (d, $J = 6.6$ Hz, 3H, CH_3), 4.53 (q, $J = 6.6$ Hz, 1H, CH), 6.12 (d, $J = 0.9$ Hz, 1H, OCH_2O), 6.13 (d, $J = 0.9$ Hz, 1H, OCH_2O), 6.95 (d, $J = 7.9$ Hz, 1H, CH_{arom}), 7.09 (d, $J = 7.9$ Hz, 1H, CH_{arom}), 8.53 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3 (CH_3), 52.2 (CH), 102.7 (OCH_2O), 111.6 (CH), 115.5 (CH), 114.8 (C), 143.1 (C), 143.3 (C), 148.1 (C), 166.8 (CO) ppm. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 63.02; H, 4.78; N, 7.02.

4.8. Synthesis of carbamates 26f–h

Methyl chloroformate (208 mg, 2.2 mmol) was added dropwise to a solution of benzylamines **4f**–**h** (2 mmol) and Et_3N (610 mg, 6 mmol) in CH_2Cl_2 (20 mL). The solution was stirred at rt for 15 min. The mixture was washed with water (3 × 20 mL) and dried over $MgSO_4$. Evapora-

tion of the solvent left a white solid, which was recrystallized from hexanes–toluene.

4.8.1. [(*S*)-1-(3,4-Dimethoxyphenyl)ethyl]carbamic acid methyl ester 26f. Mp 92–94 °C; $[\alpha]_D^{25} = -65.2$ (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, $J = 6.8$ Hz, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.71–4.84 (m, 1H, CH), 5.04 (br s, 1H, NH), 6.77–6.91 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (CH_3), 50.4 (CH), 52.0 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 109.6 (CH), 111.1 (CH), 117.7 (CH), 136.2 (C), 148.2 (C), 149.0 (C), 156.2 (CO) ppm. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.43; H, 6.93; N, 5.98.

4.8.2. (*S*)-[Phenyl-(3,4,5-trimethoxyphenyl)methyl]carbamic acid methyl ester 26g. Mp 128–129 °C; $[\alpha]_D^{25} = -3.4$ (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, OCH_3), 3.81 (s, 6H, $2 \times OCH_3$), 3.84 (s, 3H, OCH_3), 5.37 (br d, $J = 7.5$ Hz, 1H, NH), 5.92 (br d, $J = 7.5$ Hz, 1H, CH), 6.46 (s, 2H, CH_{arom}), 7.25–7.29 (m, 2H, H_{arom}), 7.30–7.38 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4 (OCH_3), 56.1 ($2 \times OCH_3$), 59.0 (CH), 60.8 (OCH_3), 104.4 ($2 \times CH$), 127.7 ($2 \times CH$), 127.6 (CH), 128.6 ($2 \times CH$), 137.2 (C), 137.4 (C), 141.5 (C), 153.3 ($2 \times C$), 156.3 (CO) ppm. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.01; H, 6.33; N, 3.98.

4.8.3. (*S*)-1-(4-Isopropoxy-3,5-dimethoxyphenyl)pentyl]carbamic acid methyl ester 26h. Oil; $[\alpha]_D^{25} = -22.3$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.2$ Hz, 3H, CH_3), 1.31 (d, $J = 6.3$ Hz, 6H, $2 \times CH_3$), 1.34–1.53 (m, 4H, $2 \times CH_2$), 1.77–1.98 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.83 (s, 6H, $2 \times OCH_3$), 4.48 (sept, $J = 6.3$ Hz, 1H, CH), 4.73–4.88 (m, 1H, CH), 5.16 (br s, 1H, NH), 6.48 (s, 2H, CH_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 21.8 ($2 \times CH_3$), 23.0 (CH_2), 28.9 (CH_2), 32.0 (CH_2), 52.0 (OCH_3), 56.2 ($2 \times OCH_3$), 58.8 (CH), 74.8 (CH), 105.2 ($2 \times CH$), 134.6 (C), 136.2 (C), 152.9 ($2 \times C$), 158.1 (CO) ppm. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.80; H, 8.44; N, 3.95.

4.9. Synthesis of N-substituted carbamates 27f–h

Carbamates **26f–h** (3.5 mmol) were added portionwise to a stirred suspension of sodium hydride (10.5 mmol, 250 mg) in dry DMF (50 mL). The mixture was further stirred at 50 °C for 2 h, then cooled to 0 °C. Alkylating agent (MeI or BnBr, 7 mmol) was added and the mixture allowed to warm to rt. After quenching with an aq NH_4Cl (10 mL) and evaporation of the DMF under vacuum the oily residue was dissolved in Et_2O (50 mL). The solution was washed with aq NH_4Cl (20 mL), water (20 mL), brine (20 mL), and then dried over $MgSO_4$. After concentration, the oily residue was purified by column chromatography on silica gel using AcOEt–hexanes (30:70) as eluent to give a colorless oil.

4.9.1. [(*S*)-1-(3,4-Dimethoxyphenyl)ethyl]methylcarbamic acid methyl ester 27f. $[\alpha]_D^{25} = -115.6$ (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, $J = 7.0$ Hz, 3H, CH_3), 2.56 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 3.84 (s, 6H, $2 \times OCH_3$), 5.49 (br s, 1H, ArCH), 6.71–6.88 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 (CH_3), 28.0 (NCH_3), 52.6 (OCH_3), 55.7 (CH), 55.8 (OCH_3), 55.9 (OCH_3), 110.6 ($2 \times CH$), 118.9 (CH), 133.3 (C), 148.2 (C), 148.9 (C), 157.1 (CO) ppm. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.45; H, 7.77; N, 5.42.

4.9.2. (*S*)-Methyl[phenyl-(3,4,5-trimethoxyphenyl)methyl]-carbamic acid methyl ester 27g. $[\alpha]_D^{25} = -11.2$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.74 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 3.78 (s, 6H, $2 \times OCH_3$), 3.85 (s, 3H, OCH_3), 6.39 (s, 2H, H_{arom}), 6.59 (br s, 1H, ArCH), 7.19–7.22 (m, 2H, H_{arom}), 7.28–7.38 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1 (NCH_3), 53.0 (OCH_3), 56.1 ($2 \times OCH_3$), 60.8 (OCH_3), 63.0 (CH), 105.8 ($2 \times CH$), 127.5 (CH), 128.4 ($2 \times CH$), 128.5 ($2 \times CH$), 135.0 (C), 137.3 (C), 139.1 (C), 148.2 (C), 153.2 (C), 157.4 (CO) ppm. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.93; H, 6.95; N, 4.01.

4.9.3. (*S*)-*N*-Benzyl[1-(4-isopropoxy-3,5-dimethoxyphenyl)-pentyl]carbamic acid methyl ester 27h. $[\alpha]_D^{25} = -52.2$ (*c* 1.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, $J = 6.9$ Hz, 3H, CH_3), 1.17–1.38 (m, 10H, $2 \times CH_3 + 2 \times CH_2$), 1.76–1.88 (m, 2H, CH_2), 3.74 (s, 9H, $3 \times OCH_3$), 4.16–4.45 (m, 3H, $CH_2Ph + CH$), 5.29 (br s, 1H, ArCH), 6.48 (s, 2H, H_{arom}), 6.90–7.08 (m, 2H, H_{arom}), 7.11–7.18 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.4 ($2 \times CH_3$), 22.5 (CH_2), 28.7 (CH_2), 31.1 (CH_2), 46.9 (CH_2), 52.7 (OCH_3), 56.1 ($2 \times OCH_3$), 59.5 (CH), 75.2 (CH), 105.7 ($2 \times CH$), 126.7 ($2 \times CH$), 127.2 (CH), 128.0 ($2 \times CH$), 135.2 (C), 135.5 (C), 139.1 (C), 153.6 ($2 \times C$), 157.7 (CO) ppm. Anal. Calcd for $C_{25}H_{35}NO_5$: C, 69.90; H, 8.21; N, 3.26. Found: C, 69.69; H, 8.03; N, 3.02.

4.10. Synthesis of brominated N-substituted carbamates 25f–h

Bromine (440 mg, 2.75 mmol) was added dropwise under stirring to a solution of **27f–h** (630 mg, 2.5 mmol) and potassium acetate (374 mg, 2.75 mmol) in acetic acid (15 mL). Stirring was maintained for 16 h at rt, the solution was concentrated under vacuum and the residue dissolved in CH_2Cl_2 (30 mL). The solution was washed successively with saturated aq Na_2CO_3 solution (10 mL), aq sodium thiosulfate solution (10%, 10 mL), and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The crude oily residue was purified by column chromatography using AcOEt–hexanes (30:70) as eluent to deliver a yellow solid.

4.10.1. [(*S*)-1-(2-Bromo-3,4-dimethoxyphenyl)ethylcarbamic acid methyl ester 25f. Mp 52–53 °C; $[\alpha]_D^{25} = -63.5$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, $J = 6.8$ Hz, 3H, CH_3), 2.58 (s, 3H, N–CH_3), 3.72 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.42 (q, $J = 6.8$ Hz, 1H, CH), 6.85 (s, 1H, H_{arom}), 7.04 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8 (CH_3), 29.2 (CH_3), 52.7 (OCH_3), 53.7 (CH), 56.1 (OCH_3), 56.15

(OCH_3), 111.3 (CH), 115.2 (C), 116.0 (CH), 131.6 (C), 148.1 (C), 148.7 (C), 156.6 (CO) ppm. Anal. Calcd for $C_{13}H_{18}BrNO_4$: C, 47.00; H, 5.46; N, 4.22. Found: C, 47.26; H, 5.23; N, 4.51.

4.10.2. (*S*)-[(2-Bromo-3,4,5-trimethoxyphenyl)phenylmethyl]-methylcarbamic acid methyl ester 25g. Oil; $[\alpha]_D^{25} = -0.3$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.73 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.34 (s, 1H, H_{arom}), 6.69 (s, 1H, CH), 7.12–7.15 (m, 2H, H_{arom}), 7.28–7.36 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.0 (NCH_3), 53.1 (OCH_3), 56.1 (OCH_3), 61.0 (OCH_3), 61.1 (OCH_3), 63.3 (CH), 109.6 (CH), 111.7 (C), 127.5 (CH), 127.9 (2 × CH), 128.6 (2 × CH), 134.9 (C), 139.0 (C), 144.4 (C), 151.2 (C), 152.4 (C), 157.2 (CO) ppm. Anal. Calcd for $C_{19}H_{22}BrNO_5$: C, 53.79; H, 5.23; N, 3.30. Found: C, 53.97; H, 5.04; N, 3.44.

4.10.3. (*S*)-*N*-Benzyl-[1-(2-bromo-4-isopropoxy-3,5-dimethoxyphenyl)pentyl]carbamic acid methyl ester 25h. Oil; $[\alpha]_D^{25} = -20.7$ (*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.8$ Hz, 3H, CH_3), 1.12–1.43 (m, 10H, 2 × CH_3 + 2 × CH_2), 1.72–2.08 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.22 (d, $J = 16.1$ Hz, 1H, $PhCH_2$), 4.31–4.46 (m, 2H, $PhCH_2$ + CH), 5.42 (t, $J = 7.7$ Hz, 1H, ArCH), 6.72 (s, 1H, H_{arom}), 6.97–7.05 (m, 2H, H, H_{arom}), 7.06–7.22 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.4 (CH_3), 22.5 (CH_3), 22.6 (CH_2), 28.5 (CH_2), 32.0 (CH_2), 47.7 (CH_2), 52.8 (OCH_3), 56.1 (OCH_3), 59.1 (CH), 60.5 (OCH_3), 76.2 (CH), 108.3 (CH), 113.1 (C), 126.7 (2 × CH), 127.1 (CH), 127.9 (2 × CH), 133.8 (C), 138.7 (2 × C), 140.7 (C), 151.4 (C), 153.0 (CO) ppm. Anal. Calcd for $C_{25}H_{34}BrNO_5$: C, 59.06; H, 6.74; N, 2.75. Found: C, 59.22; H, 6.65; N, 2.98.

4.11. Synthesis of isoindolinones 3f–h

A solution of *n*-BuLi (0.71 mL, 1.6 M in hexane, 1.14 mmol) was added dropwise by syringe at −90 °C under N_2 to a solution of carbamates **25f–h** (347 mg, 1.04 mmol) in dry THF (30 mL). The reaction mixture was stirred at −90 °C for 20 min then allowed to warm to −40 °C over a period of 30 min. After the addition of saturated aq NH_4Cl (5 mL) at −40 °C, the mixture was diluted with water (20 mL), extracted with Et_2O (3 × 25 ml) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent in vacuo left an oily residue, which was purified by flash column chromatography on silica gel using AcOEt as eluent to furnish isoindolinone **3f–h** as a yellow oil.

4.11.1. (*S*)-6,7-Dimethoxy-2,3-dimethyl-2,3-dihydro-1*H*-isoindol-1-one 3f. Mp 175–176 °C; $[\alpha]_D^{25} = -14.3$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (d, $J = 6.7$ Hz, 3H, CH_3), 3.08 (s, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.32 (q, $J = 6.7$ Hz, 1H, CH), 6.85 (s, 1H, H_{arom}), 7.27 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2 (CH_3), 27.1 (NCH_3), 56.2 (2 × OCH_3), 57.3 (CH), 104.1 (CH), 105.1 (CH), 124.2 (C), 140.3 (C), 149.6 (C), 152.4 (C), 168.3 (CO) ppm. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.24; H, 7.02; N, 6.03.

4.11.2. (*S*)-5,6,7-Trimethoxy-2-methyl-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3g. Oil; $[\alpha]_D^{25} = +5.7$ (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 5.19 (s, 1H, CH), 6.39 (s, 1H, H_{arom}), 7.15–7.18 (m, 2H, H_{arom}), 7.37–7.39 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.4 (NCH_3), 56.2 (OCH_3), 61.4 (OCH_3), 62.7 (OCH_3), 66.1 (CH), 101.4 (CH), 116.3 (C), 127.5 (2 × CH), 128.7 (CH), 129.2 (2 × CH), 137.3 (C), 141.8 (C), 143.4 (C), 151.1 (C), 157.2 (C), 167.1 (CO) ppm. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.79; H, 5.98; N, 4.70.

4.11.3. (*S*)-2-Benzyl-3-butyl-6-isopropoxy-5,7-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one 3h. Oil; $[\alpha]_D^{25} = -40.2$ (*c* 1.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.66–0.85 (m, 1H, CH_2), 0.78 (t, $J = 7.2$ Hz, 3H, CH_3), 0.86–1.06 (m, 1H, CH_2), 1.16 (quint, $J = 7.3$ Hz, 2H, CH_2), 1.30 (d, $J = 6.0$ Hz, 3H, CH_3), 1.32 (d, $J = 6.1$ Hz, 3H, CH_3), 1.73–1.98 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.08 (d, $J = 15.0$ Hz, 1H, $ArCH_2$), 4.11 (s, 3H, OCH_3), 4.30 (t, $J = 4.0$ Hz, 1H, CH), 4.42 (sept, $J = 6.1$ Hz, 1H, CH), 5.28 (d, $J = 15.0$ Hz, 1H, $ArCH_2$), 6.57 (s, 1H, H_{arom}), 7.26–7.31 (m, 5H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.5 (2 × CH_3), 22.6 (CH_2), 24.0 (CH_2), 30.1 (CH_2), 43.7 (CH_2), 56.2 (OCH_3), 58.0 (CH), 62.1 (OCH_3), 76.1 (CH), 100.4 (CH), 117.2 (C), 127.4 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 137.6 (C), 139.7 (C), 142.6 (C), 152.0 (C), 157.7 (C), 167.1 (CO) ppm. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.51. Found: C, 72.83; H, 7.98; N, 3.77.

4.12. (*S*)-*N*,*N*-Di(methoxycarbonyl)-2-methyl-1-(3,4,5-trimethoxyphenyl)propylamine 29

A solution of benzylamine **4i** (2 mmol, 750 mg) and Et_3N (6 mmol, 610 mg) in CH_2Cl_2 (20 mL) was added dropwise over 30 min to a well stirred solution of methyl chloroformate (2 mmol, 190 mg) in CH_2Cl_2 (20 mL) maintained at −10 °C. The mixture was stirred at 0 °C for 30 min, washed with satd aq $NaHCO_3$ (2 × 10 mL), and brine (10 mL) then dried over $MgSO_4$. After evaporation of the solvent the crude product was dissolved in THF (10 mL) and cooled to −30 °C. *n*-BuLi (1.6 M solution in hexanes, 2.1 mmol, 1.35 mL) was added and the mixture was stirred for further 30 min at −30 °C. A solution of methyl chloroformate (2 mmol, 190 mg) in THF (5 mL) was then added and the mixture was stirred for 30 min at 0 °C. The mixture was diluted with water (20 mL), extracted with Et_2O (3 × 25 ml) after which the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent in vacuo left an oily residue which was purified by flash column chromatography using AcOEt–hexanes (50:50) as eluent to furnish dicarbamate **29** as a colorless oil (475 mg, 67%); $[\alpha]_D^{25} = -48.1$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, $J = 6.4$ Hz, 3H, CH_3), 1.00 (d, $J = 6.4$ Hz, 3H, CH_3), 2.82 (sext, $J = 6.4$ Hz, 1H, CH), 3.77 (s, 6H, 2 × OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 4.85 (d, $J = 11.2$ Hz, 1H, CH), 6.69 (s, 2H, H_{arom}) ppm; ^{13}C

NMR (75 MHz, $CDCl_3$): δ 19.7 (CH_3), 21.2 (CH_3), 29.0 (CH), 58.8 ($2\times OCH_3$), 56.1 ($2\times OCH_3$), 60.8 (OCH_3), 67.9 (CH), 106.3 ($2\times CH$), 134.4 (C), 137.4 (C), 152.7 ($2\times C$), 155.1 ($2\times C$) ppm. Anal. Calcd for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.30; H, 7.12; N, 3.68.

4.13. (*S*)-*N*,*N*-Di(methoxycarbonyl)-2-methyl-1-(2-bromo-3,4,5-trimethoxyphenyl)propylamine 28

Bromination of **29** was carried out as described for **25f–h** to furnish **28** as a colorless oil in 75% yield. $[\alpha]_D^{25} = +6.5$ (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, $J = 6.7$ Hz, 3H, CH_3), 1.07 (d, $J = 6.6$ Hz, 3H, CH_3), 2.82 (sext, $J = 6.6$, 6.7 Hz, 1H, CH), 3.78 (s, 6H, $2\times OCH_3$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.27 (d, $J = 11.1$ Hz, 1H, CH), 7.26 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6 (CH_3), 20.3 (CH_3), 29.8 (CH), 53.8 ($2\times OCH_3$), 56.1 (OCH_3), 60.9 (OCH_3), 61.0 (OCH_3), 66.3 (CH), 109.7 (CH), 113.0 (C), 133.8 (C), 143.6 (C), 150.3 (C), 152.1 (C), 154.8 ($2\times C$) ppm. Anal. Calcd for $C_{17}H_{24}BrNO_7$: C, 47.02; H, 5.57; N, 3.23. Found: C, 47.29; H, 5.29; N, 3.01.

4.14. (*S*)-3-Isopropyl-5,6,7-trimethoxy-2,3-dihydro-1*H*-isoindol-1-one 3i

A solution of *n*-BuLi (0.69 mL, 1.6 M in hexane, 1.1 mmol) was added dropwise by syringe at −90 °C under N_2 to a solution of dicarbamate **28** (434 mg, 1 mmol) in dry THF (30 mL). The reaction mixture was stirred at −90 °C for 10 min then allowed to warm to rt and stirred at rt for 1 h. After the addition of H_2O (20 mL), the mixture was extracted with Et_2O (3×25 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent in vacuo left a solid residue which was purified by flash column chromatography on silica gel using AcOEt as eluent to furnish isoindolinone **3i** (146 mg, 55%). Mp 167–168 °C; $[\alpha]_D^{25} = -48.1$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (d, $J = 6.8$ Hz, 3H, CH_3), 1.10 (d, $J = 6.8$ Hz, 3H, CH_3), 2.19 (dq, $J = 3.3$, 6.8 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 4.42 (d, $J = 3.3$ Hz, 1H, CH), 6.64 (s, 1H, H_{arom}), 7.10 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3 (CH_3), 19.8 (CH_3), 31.9 (CH), 56.3 (OCH_3), 61.4 (OCH_3), 61.8 (CH), 62.5 (OCH_3), 100.8 (CH), 141.5 (C), 144.5 (C), 147.3 (C), 151.6 (C), 157.6 (C), 170.2 (CO) ppm. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 4.28. Found: C, 63.48; H, 7.03; N, 4.41.

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References

1. Luzzio, F. A.; Mayorov, A. V.; Ng, S. S. W.; Kruger, E. A.; Figg, W. D. *J. Med. Chem.* **2003**, *46*, 3793–3799.
2. Belliotti, T. R.; Brink, W. A.; Kersten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Chem. Med. Lett.* **1998**, *8*, 1499–1502.
3. For the antihypertensive activity, see: (a) Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361–365; For the antipsychotic activity, see: (b) Linden, M.; Hadler, D.; Hofmann, S. *Hum. Psychopharmacol.* **1997**, *12*, 445–452; (c) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166; (d) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 149–157; For the antiinflammatory activity, see: (e) Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyao Gongye* **1985**, *16*, 543–544; *Chem. Abstr.* **1986**, *105*, 6378; (f) For the anaesthesic activity, see: Laboratori Baldacci, S.P.A. Japanese Patent 5,946,268, 1984; *Chem. Abstr*. **1984**, *101*, 54922; (g) For the antiulcer activity, see: Lippmann, W. U.S. Patent 4,267,189, 1981; *Chem. Abstr*. **1981**, *95*, 61988; For the antiviral activity, see: (h) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215–1217; (i) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623–2625; (j) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517; For the antileukemic activity, see: (k) Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521–524.
4. Stuk, T. L.; Assink, B. K.; Bates, R. C., Jr.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851–855.
5. (a) Mc Alonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 67–79; (b) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015–5018.
6. Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2005**, *61*, 1335–1344, and references cited therein.
7. (a) Perard-Viret, J.; Prangé, T.; Tomas, A.; Royer, J. *Tetrahedron* **2002**, *58*, 5103–5108; (b) Deniau, E.; Enders, D. *Tetrahedron* **2001**, *57*, 2581–2588; (c) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95–98.
8. (a) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 141–142; (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627–3630; (c) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905–4908; (d) Deniau, E.; Enders, D.; Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2253–2258.
9. (a) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 143–146; (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1715–1721; (c) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *Tetrahedron* **2004**, *60*, 1247–1253; (d) Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651–1657.
10. Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528–1535.
11. Grigg, R.; Dorrity, M. J. R.; Malone, J. F.; Mongkolausssavaratana, T.; Norbert, W. D. J. A.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 3075–3076.
12. Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775–778.
13. Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059–3062.
14. (a) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368–373; (b) Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265–8266; (c) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835–1843.

15. (a) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 31–40; (b) Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull.* **1983**, *31*, 2183–2191; (c) Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716–6721.
16. Lete, E.; Collado, I.; Sotomayor, N.; Vicente, T.; Villa, M.-J. *J. Heterocycl. Chem.* **1995**, *32*, 1751–1756.
17. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312.
18. Reviews: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305; (b) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, 2nd ed.; Pergamon: New York, 1990; (c) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Exeter, 1995; Vol. 11, pp 66–92; (d) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*; Atanassi, O., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2001; pp 393–418; (e) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Elsevier Science Ltd: Oxford, 2002.
19. (a) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724; (b) Rico, R.; Bermejo, F. *Tetrahedron Lett.* **1996**, *37*, 5809–5812; (c) Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S. *J. Org. Chem.* **2002**, *67*, 4702–4706.
20. Trachsel, D. *Helv. Chim. Acta* **2002**, *85*, 3019–3026.
21. Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2139–2146.
22. Atobe, M.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2004**, *69*, 5595–5607.
23. Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, *8*, 139–142.
24. Dunina, V. V.; Plugina, R. I.; Potapov, V. M.; Rukhadze, E. G. *Zhur. Org. Khim.* **1977**, *13*, 1616–1620.