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A versatile approach for the asymmetric synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones

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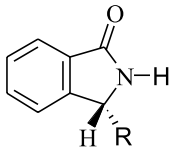
Dedicated to Professor Dr. Khi-Rui Tsai on the occasion of his 90th birthday

Abstract—Based on the use of (*R*)-*p*-benzyloxyphenylglycinol (**10**) as a new oxidatively cleavable chiral auxiliary, a flexible approach to (*R*)-3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones via a diastereoselective reductive-alkylation is developed. The oxidative cleavage of the chiral auxiliary by CAN under mild conditions ensured the access to (*R*)-3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones with *ee* at least 92%.

1. Introduction

3-Alkyl-2,3-dihydro-1*H*-isoindolin-1-ones (isoindolin-1-ones) **1** are the key structural feature of a number of synthetic and naturally occurring bioactive molecules. For example, PD-172938 (**2**) enantiomers show affinity for dopamine D_4 receptor,[1] pazinaclone (DN-2327)[2] (**3**) and pagoclone[3] (**4**) are anxiolytic drug candidates, while lennoxamine (**5**)[4] is an alkaloid isolated from barberries species (Fig. 1). Besides, (*S*)-3-methyl-isoindolin-1-one has been shown to be a valuable chiral auxiliary.[5] Consequently, the chemistry of 3-alkyl-isoindolin-1-ones has attracted much attention currently, and a number of valuable synthetic methods for such compounds have been developed.[6,7]



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However, in contrast to the great progress made in asymmetric synthesis within the last two decades, the methodology for the asymmetric synthesis of simple 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1** in high *ee* was rarely explored. Although a flexible approach to 3-aryl substituted 2,3-dihydro-*1H*-isoindolin-1-ones has been reported recently, to the best of our knowledge, (*R*)-3-methyl-isoindolin-1-one (**1a**), first reported by Oppolzer in 1990,[5a] and ten years later by Allin and co-workers,[7] remained the only 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-one (**1**) so far obtained by asymmetric synthesis with high *ee* value.

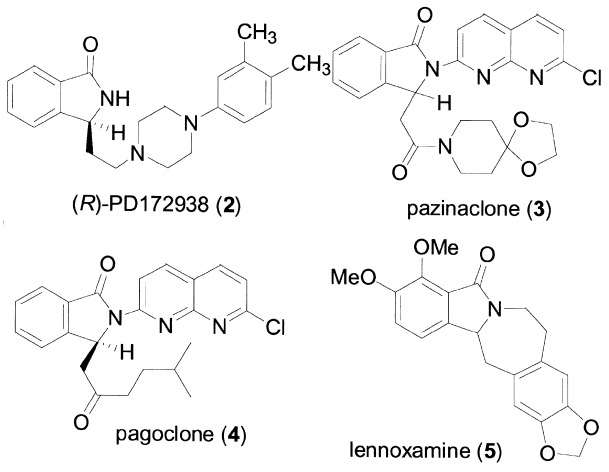

Figure 1.

It is worth mentioning that although four methods[7,9,10] have been reported for the asymmetric synthesis of *N*-substituted 3-alkyl-isoindolin-1-ones **6** starting from (*R*)-phenylglycinol, the removal of the *N*-chiral auxiliary to give **1** could not be achieved in a straightforward and racemization-free manner (vide infra).[6] Consequently, to develop versatile and flexible methods for the asymmetric synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1** is highly desirable. We herein report a flexible reductive-alkylation approach to 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1**

Keywords: Isoindolin-1-one; Chiral auxiliary; Benzyloxyphenylglycinol; Asymmetric synthesis.
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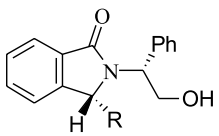
featuring the removal of the chiral auxiliary under racemization free conditions.[11]



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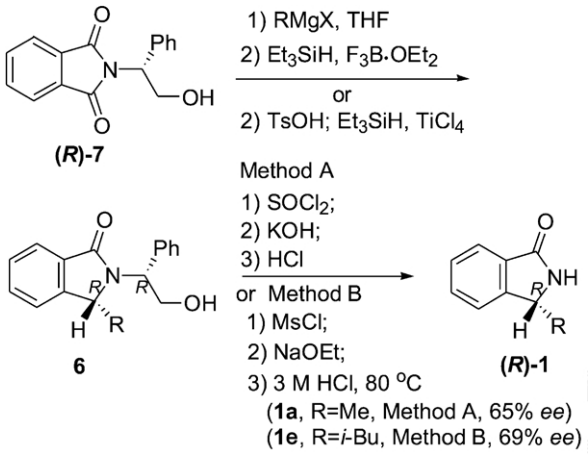
2. Results and discussion

In chiral auxiliary-based asymmetric synthetic methodology, the success of a chiral auxiliary depends, firstly, on its asymmetric induction, and secondly, on the feasibility of its smooth removal from the substrate after asymmetric induction. This is the case of (*R*)-phenylglycinol, a valuable chiral auxiliary gained widespread application in asymmetric syntheses.[12,13] The success of this chiral auxiliary is due partially to the easy cleavage of the benzylic auxiliary under hydrogenolysis conditions.[13] Further development for its cleavage under non-reductive conditions[14–16] has led to the extension of the scope of this chiral auxiliary.

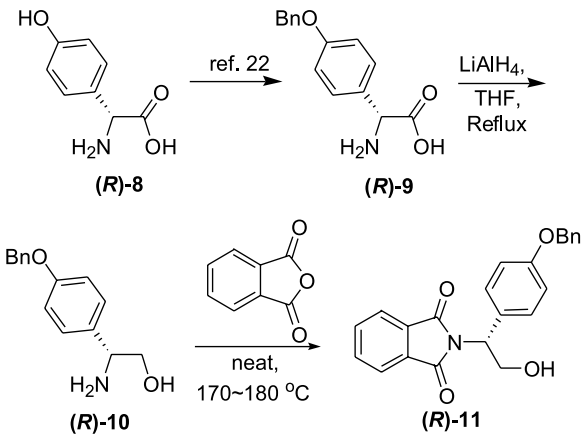
During the asymmetric synthesis of amides or lactams using phenylglycinol as a chiral auxiliary, apart from the widely used dissolving metal reduction method,[17] only two alternative procedures[18] have been used for the removal of benzylic auxiliary group from the nitrogen (e.g., Scheme 1, **6→1**). Recently, inspired from the pioneering work of Meyers,[19] we have developed a versatile and flexible reductive alkylation approach to optically active 3-alkylisoindolin-1-one derivatives (**7→6**, Scheme 1).[10] However, attempted removal of the chiral auxiliary (2-hydroxy-1-phenylethyl group) from the nitrogen of **6** (R=Me, *i*-Bu) by above-mentioned procedures[18] resulted in extensive racemization (Scheme 1). In the recent asymmetric synthesis of 3-aryl-isoindolin-1-ones, Enders and co-workers[8] also noted that attempted cleavage of N–N bond of the chiral auxiliary SAMP under reductive conditions led to either complex mixture or racemization.



Scheme 1.

The easy racemization of the 3-carbon-subsituted isoindolin-1-one systems under acidic, basic or reductive conditions (vide supra), account for the importance of developing a new chiral auxiliary, which is cleavable under mild racemization-free conditions. *N*-*p*-Alkyloxybenzyl group is cleavable under mild oxidative conditions,[20,21] and (*R*)-*N*-*p*-hydroxyphenylglycinol is a cheap and commercially available amino acid. Based on the considerations, we decided to test (*R*)-*N*-*p*-benzyloxylphenylglycinol as a new chiral auxiliary for the asymmetric synthesis of 3-alkylisoindolinones, in hoping that at the end of the synthesis, the *N*-*p*-alkyloxybenzyl group could be removed under racemization-free oxidative conditions.

To this end, cheap and easily available (*R*)-*p*-hydroxyphenylglycine **8** was converted to *O*-benzylether **9** by a known procedure.[22] The reduction of **9** with lithium aluminum hydride in refluxing tetrahydrofuran led to the crude (*R*)-*p*-benzyloxyphenylglycinol (**10**), which was subjected to react with phthalic anhydride without further purification, under solvent-free conditions[23] (170–180 °C, 14–15 h). In this way, (*R*)-**11** {white crystal, mp 132–133 °C (ether), $[\alpha]_D^{20}=+7.4$ (*c* 0.9, $CHCl_3$)} was obtained in 79% yield (Scheme 2).



Scheme 2.

With multi-gram quantities of (*R*)-**11** available, the reductive-alkylation was investigated. The reaction of (*R*)-**11** with 2.5 equiv. of methyl magnesium iodide at −15 to −10 °C led smoothly to the formation of α-hydroxylactam **12a** (Table 1, entry 1) in 98% yield as a 1.2:1 diastereomeric mixture (the stereochemistry was not determined). Although the two diastereomers of **12a** are separable by column chromatography on silica gel, they were unseparated and used in the next step as diastereomeric mixture, since the subsequent reductive dehydroxylation was expected to proceed via the *N*-acyliminium ion intermediate **A**.[24] Indeed, when the diastereomeric mixture of **12a** was subjected to a boron trifluoride etherate mediated triethylsilane reduction,[25,10] diastereoisomer **13a** formed predominately. The two diastereomers **13a**/**14a** were separated by flash chromatography on silica gel, from which the diastereomeric ratio of **13a**/**14a** was determined as 75:25 (Scheme 3).

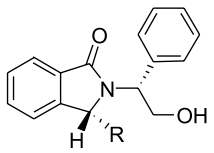
The stereochemistry of the major diastereomer **13a** was tentatively assigned as (3*R*,1′*R*) by the comparison of its ^{1}H NMR spectral data with that of an analogue, de-benzyloxy-**15**, whose structure was determined by a single-crystal X-ray crystallographic analysis.[10] This assignment was

Table 1. Preparation of **13** via the reductive alkylation of **11**

Entry	RMgX	Compounds **12** (yield, %)	Compounds **13/14** (yield, %)	Diastereomeric ratio[a] (**13/14**)
1	MeMgI	**12a** (98)	**13/14a** (98)	75:25
2	EtMgBr	**12b** (88)	**13/14b** (79)	88:12
3	*n*-PrMgBr	**12c** (93)	**13/14c** (96)	81:19
4	*n*-BuMgBr	**12d** (73)	**13/14d** (98)	81:19
5	*i*-BuMgBr	**12e** (89)	**13/14e** (94)	83:17
6	*n*-C_5H_{11}MgBr	**12f** (83)	**13/14f** (67)	73:27
7	*n*-C_7H_{15}MgBr	**12g** (83)	**13/14g** (79)	70:30

[a] Determined by chromatograph separation.

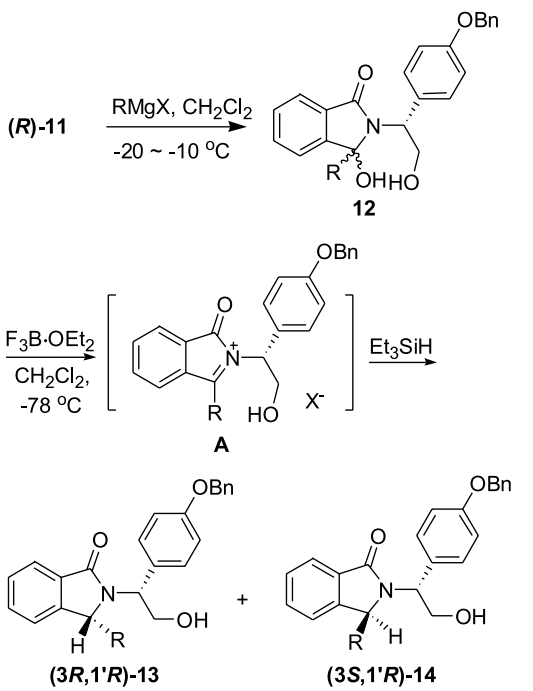
finally confirmed by its transformation into known (*R*)-3-methyl-isoindolin-1-one **1a** (vide infra).



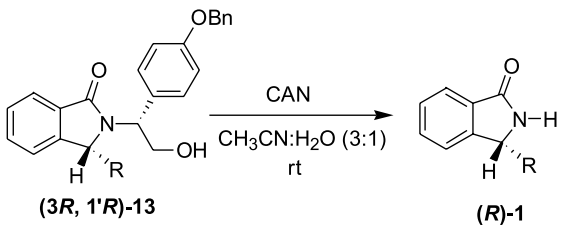
(3*R*,1'*R*)-15

Extension of the same reductive alkylation procedure to other Grignard reagents led to the corresponding products **13b–g** and **14b–g** in diastereoselectivity varied from 70:30 to 88:12 (Table 1, entries 2–7). Although the diastereoselectivity in this step is not high, the easy separation of the diastereomers by flash chromatography on silica gel allows the ready isolation of the diastereomer **13** in pure form.

Next, the key oxidative removal of the chiral auxiliary was investigated. The treatment of *N*-substituted 3-methylisoindolin-1-one (**13a**) with four molar equivalents of ceric ammonium nitrate (CAN)[21] in a mixed solvent system (MeCN–H_2O, 3:1, rt, 30 min.) led smoothly to the desired (*R*)-3-methylisoindolin-1-one (**1a**) as white crystals [mp 112–115 °C; lit.[5c] mp 102–103 °C for (*S*)-**1a**]. By comparing with a racemic sample, the enantiomeric excess of **1a** was determined to 97% based on HPLC analysis on a chiral column (eluent: 2.5% IPA in hexane, λ=270 nm). The specific rotation of the synthesized (*R*)-3-methyl-isoindolin-1-one **1a** {$[\alpha]_D^{20}$=+39.1 (*c* 1.0, MeOH)} is in agreement with that reported by Stevenson and co-workers {$[\alpha]_D^{20}$=−39.8 (*c* 0.6, EtOH) for (*S*)-**1a**},[5c] but different, both in the sense and in the magnitude, from that reported by Allin {$[\alpha]_D^{20}$=−89.7 (*c* 1.7, MeOH) for (*R*)-**1a**, *ca*. 96% *ee*} (Scheme 4).[7]



Scheme 3.



(3*R*, 1'*R*)-13 **(*R*)-1**

Scheme 4.

Following the same procedure as described for **13a**, the oxidative cleavages of **13b–13g** by CAN were performed. The results were listed in Table 2. Except in the case of **13b** (Table 2, entry 2), other 3-substituted isoindolin-1-ones were obtained in high chemical yield and with *ee* % value no less than 92%.

Table 2. Synthesis of (*R*)-**1** by oxidative *N*-deprotection of **13**

Entry	Compounds (*R*)-**1** (yield, %)	*ee* (%) of (*R*)-**1**
1	**1a** (84)	97
2	**1b** (63)	92
3	**1c** (86)	97
4	**1d** (90)	92
5	**1e** (88)	93
6	**1f** (88)	94
7	**1g** (82)	97

In summary, a versatile and flexible approach to (*R*)-3-alkyl-isoindolin-1-ones **1**, in high enantiomeric purity (*ee*≥92%), is developed via a diastereoselective reductive-alkylation procedure.[26] The use of (*R*)-*p*-benzyloxyphenylglycinol (**10**) as a new oxidatively cleavable chiral auxiliary is the key to reach high enantiomeric purity of the 3-alkyl-isoindolin-1-ones **1**. This method is versatile in scope, because various C-3 alkyl substituents can be introduced easily by Grignard reaction. The application of present method to the asymmetric synthesis of 3-alkyl-isoindolin-1-one-based bioactive compounds is in progress.

3. Experimental

3.1. General

All melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity+500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass Spectrum (ESI direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (200–300 mesh). Solvent THF was distilled over sodium, with dichloromethane being distilled over P_2O_5.

3.1.1. (*R*)-*N*-[2-Hydroxy-1-(4-benzyloxyphenyl)ethyl]-phthalimide (11). A mixture of phthalic anhydride (0.288 g, 1.943 mmol) and (*R*)-2-hydroxy-1-(4-benzyloxyphenyl)- ethylamine (0.45 g, 1.85 mmol), which obtained by $LiAlH_4$ reduction of known (*R*)-(4-benzyloxyphenyl)-glycinol,[21] was stirred at 170–180 °C for 15 h. The mixture was then cooled to rt, before CH_2Cl_2 was added. The resulting solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel to give **11** (544 mg, yield 79%) as a pale yellow solid. R_f: 0.29 (AcOEt–P.E.=1:2). White crystal. Mp 132~133 °C (ether). $[\alpha]_D^{20}$=+7.4 (*c* 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3461, 3062, 3033, 2926, 1771, 1707, 1610, 1584, 1512, 1463, 1389, 1363, 1331, 1242, 1179, 1111, 1069, 1013 cm^{-1}. ^{1}H NMR (500 MHz) δ: 2.45 (dd, *J*=4.6, 8.2 Hz, 1H, OH), 4.21 (ddd, *J*=4.6, 5.0, 11.4 Hz, 1H, C*H*$_2$OH), 4.61 (ddd, *J*=8.2, 8.6, 11.4 Hz, 1H, C*H*$_2$OH), 5.03 (s, 2H, OCH_2Ph), 5.42 (dd, *J*=5.0, 8.6 Hz, 1H, C*H*CH$_2$OH), 6.88–7.90 (m, 13H, Ar) ppm. MS (ESI, *m*/*z*): 375 [(M+2H)$^+$, 34], 374 (M+H$^+$, 69), 356 [(M+H–H$_2$O)$^+$, 29], 227 (100), 209 (51). HRESIMS calcd for [$C_{23}H_{19}NO_4$+H]$^+$: 374.1392. Found: 374.1391. Anal. Calcd for $C_{23}H_{19}NO$: C, 73.97; H, 5.13; N, 3.75. Found: C, 74.25; H, 5.32; N, 3.55.

3.2. General procedure for the reductive alkylation of (*R*)-phthalimide derivative (11)

To a cooled (−15 to −10 °C) solution of **11** (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a Grignard reagent (3.0 mmol) in diethyl ether under nitrogen atmosphere. After stirred at the same temperature for 4 h, the reaction was quenched with saturated aqueous solution of ammonium chloride (6 mL) and extracted with dichloromethane (3×30 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuum. Filtration with a short pad of column eluting with ethyl acetate-petroleum ether (1:1) yielded a mixture of two diastereomers **12**. The diastereomeric ratio could be obtained either from flash chromatographic separation or from ^{1}H NMR spectra of the crude mixture.

To a cooled (−78 °C) solution of diastereomer mixture **12** (1.0 mmol) in dry dichloromethane (10 mL) was added dropwise triethylsilane (10 mmol) and boron trifluoride etherate (3.0 mmol) under nitrogen atmosphere. After stirring at −78 °C for 6 h, the mixture allowed to react at rt and stirred overnight. The reaction was quenched by saturated aqueous sodium bicarbonate and extracted with dichloromethane (3×20 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuum. The crude was purified by flash column chromatography on silica gel with ethyl acetate–petroleum ether (1:2) as eluent to give **13**.

3.2.1. (3*R*,1′*R*)-3-Methyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13a). Diastereomeric ratio: 75:25, combined yield 98%. (3*R*,1′*R*)-**13a** (major diastereomer): R_f: 0.27 (AcOEt–P.E.=1:2). Colorless oil. $[\alpha]_D^{20}$=+54.4 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3366, 2924, 2847, 1664, 1611, 1583, 1510, 1468, 1454, 1468, 1409, 1354, 1300, 1240, 1178, 1079, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.8 Hz, 3H, CH_3), 4.08 (ddd, *J*=3.4, 7.2, 12.4 Hz, 1H, C*H*$_2$OH), 4.35 (q, *J*=6.8 Hz, 1H, NCHMe), 4.44 (ddd, *J*=7.2, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.72 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH$_2$OH), 4.85 (dd, *J*=7.2, 7.9 Hz, 1H, OH), 5.03 (s, 2H, OCH_2Ph), 6.88–7.88 (m, 13H, Ar) ppm. MS (ESI, *m*/*z*): 396 (M+Na$^+$, 6), 375 [(M+2H)$^+$, 25], 374 (M+H$^+$, 100). HRESIMS calcd for [$C_{24}H_{23}NO_3$+H]$^+$: 374.1756. Found: 374.1754.

3.2.2. (3*R*,1′*R*)-3-Ethyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13b). Diastereomeric ratio: 88:12, combined yield 79%. (3*R*,1′*R*)-**13b** (major diastereomer): R_f: 0.51 (AcOEt–P.E.=1:1). White solid. Mp 111–113 °C. $[\alpha]_D^{20}$=+51.0 (*c* 0.7, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3366, 3083, 3058, 3027, 2967, 2934, 2878, 1664, 1616, 1491, 1469, 1454, 1421, 1361, 1332, 1301, 1066 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (: 0.56 (t, *J*=7.5 Hz, 3H, CH_3), 1.92–2.12 (m, 2H, CH_2Me), 4.10 (ddd, *J*=3.4, 7.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.40 (dd, *J*=5.1, 7.1 Hz, 1H, OH), 4.45 (ddd, *J*=5.1, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.57 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH$_2$OH), 4.98 (t, *J*=7.2 Hz, 1H, NCH), 5.02 (s, 2H, OCH_2Ph), 6.84–6.88 (m, 2H, Ar), 7.22–7.60 (m, 10H, Ar), 7.80–7.88 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 389 [(M+2H)$^+$, 26], 388 (M+H$^+$, 100). HRESIMS calcd for [$C_{25}H_{25}NO_3$+H]$^+$: 388.1913. Found: 388.1909.

3.2.3. (3*R*,1′*R*)-3-*n*-Propyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13c). Diastereomeric ratio: 81:19, combined yield 96%. (3*R*,1′*R*)-**13c** (major diastereomer): R_f: 0.32 (AcOEt–PE=1:2). Colorless oil. $[\alpha]_D^{20}$=+42.4 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3378, 3039, 2954, 2871, 1667, 1611, 1510, 1462, 1411, 1237, 1176, 1023 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (: 0.80 (t, *J*=6.8 Hz, 3H, CH_3), 1.08–1.20 (m, 1H, $(CH_2)_2$Me), 1.82–2.00 (m, 3H, $(CH_2)_2$Me), 4.08 (ddd, *J*=3.5, 6.0, 12.3 Hz, 1H, C*H*$_2$OH), 4.38 (dd, *J*=6.0, 7.8 Hz, 1H, OH), 4.45 (ddd, *J*=7.8, 8.1, 12.3 Hz, 1H, C*H*$_2$OH), 4.62 (dd, *J*=3.5, 8.1 Hz, 1H, C*H*CH$_2$OH), 4.96 (t, *J*=7.2 Hz, 1H, NCH), 5.02 (s, 2H, OCH_2Ph), 6.88–6.95 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.25–7.60 (m, 8H, Ar), 7.80–7.83 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 403 [(M+2H)$^+$, 27], 402

(M+H, 100). HRESIMS calcd for $[C_{26}H_{27}NO_3+H]^+$: 402.2069. Found: 402.2058.

3.2.4. (3*R*,1′*R*)-3-*n*-Butyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13d). Diastereomeric ratio: 81:19, combined yield 98%. (3*R*,1′*R*)-**13d** (major diastereomer): R_f: 0.63 (AcOEt–PE=1:1). White solid. Mp 88–90 °C. $[\alpha]_D^{20}$=+38.0 (*c* 1.1, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3345, 2921, 2852, 1659, 1577, 1540, 1511, 1462, 1421, 1376, 1303, 1241, 1175, 1098, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.80 (t, *J*=7.3 Hz, 3H, CH_3), 1.04–1.28 (m, 4H, $(CH_2)_3Me$), 1.84–2.00 (m, 2H, $(CH_2)_3Me$), 4.10 (ddd, *J*=3.4, 5.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.39 (dd, *J*=3.0, 5.1 Hz, 1H, OH), 4.44 (ddd, *J*=3.0, 8.0, 12.4 Hz, 1H, C*H*$_2$OH), 4.60 (dd, *J*=3.4, 8.0 Hz, 1H, C*H*CH_2OH), 4.98 (t, *J*=7.4 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.96 (m, 2H, Ar), 7.16–7.60 (m, 10H, Ar), 7.82–7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 438 (M+Na^+, 5), 417 [(M+2H)$^+$, 31], 416 (M+H^+, 100). HRESIMS calcd for $[C_{27}H_{29}NO_3+H]^+$: 416.2226. Found: 416.2224.

3.2.5. (3*R*,1′*R*)-3-*iso*-Butyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13e). Diastereomeric ratio: 83:17, combined yield, 94%. (3*R*,1′*R*)-**13e** (major diastereomer): R_f: 0.60 (AcOEt–PE=1:1). Colorless oil. $[\alpha]_D^{20}$=+34.2 (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 3367, 3033, 2955, 2925, 2868, 1666, 1611, 1583, 1510, 1468, 1454, 1413, 1334, 1239, 1177, 1114, 1061, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.70 (d, *J*=6.4 Hz, 3H, CH_3), 0.92 (d, *J*=6.4 Hz, 3H, CH_3), 1.66–1.88 (m, 3H, CH_2CHMe_2), 4.10 (ddd, *J*=3.4, 7.0, 12.4 Hz, 1H, C*H*$_2$OH), 4.33 (dd, *J*=3.2, 7.0 Hz, 1H, OH), 4.43 (ddd, *J*=3.2, 7.8, 12.4 Hz, 1H, C*H*$_2$OH), 4.66 (dd, *J*=3.4, 7.8 Hz, 1H, C*H*CH_2OH), 5.02 (s, 2H, OCH_2Ph), 5.04 (t, *J*=7.9 Hz, 1H, NCH), 6.85–6.90 (m, 2H, Ar), 7.15–7.21 (m, 2H, Ar), 7.28–7.58 (m, 8H, Ar), 7.82–7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 438 (M+Na^+, 36), 417 [(M+2H)$^+$, 24], 416 (M+H^+, 100). HRESIMS calcd for $[C_{27}H_{29}NO_3+H]^+$: 416.2226. Found: 416.2220.

3.2.6. (3*R*,1′*R*)-3-*n*-Pentyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13f). Diastereomeric ratio: 73:27, combined yield 67%. (3*R*,1′*R*)-**13f** (major diastereomer): R_f: 0.63 (AcOEt–P.E.=1:1). White crystal. Mp 104–108 °C. $[\alpha]_D^{20}$=+32.1 (*c* 1.0, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3369, 3034, 2928, 2862, 1665, 1611, 1510, 1465, 1409, 1303, 1240, 1177, 1114, 1021 cm^{-1}. ^1H- NMR (500 MHz, $CDCl_3$) δ: 0.80 (t, *J*=6.9 Hz, 3H, CH_3), 0.68–0.74 (m, 1H, $(CH_2)_4Me$), 1.08–1.22 (m, 5H, $(CH_2)_4Me$), 1.86–2.00 (m, 2H, $(CH_2)_4Me$), 4.10 (ddd, *J*=3.4, 6.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.39 (dd, *J*=3.1, 6.1 Hz, 1H, OH), 4.44 (ddd, *J*=3.1, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.60 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH_2OH), 4.95 (t, *J*=7.4 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.92 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.38–7.60 (m, 8H, Ar), 7.88 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 431 [(M+2H)$^+$, 40], 430 (M+H^+, 100). HRESIMS calcd for $[C_{28}H_{31}NO_3+H]^+$: 430.2382. Found: 430.2381.

3.2.7. (3*R*,1′*R*)-3-*n*-Heptyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13g). Diastereomeric ratio: 70:30, combined yield 79% (3*R*,1′*R*)-**13g** (major diastereomer): R_f: 0.59 (AcOEt–PE=1:2). White crystal. Mp 104∼105 °C (ether). $[\alpha]_D^{20}$=+31.7 (*c* 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3371, 3037, 2929, 2858, 1668, 1612, 1511, 1462, 1409, 1238, 1177, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.85 (t, *J*=7.2 Hz, 3H, CH_3), 1.06–1.20 (m, 7H, $(CH_2)_6Me$), 1.20–1.30 (m, 2H, $(CH_2)_6Me$), 1.66–1.78 (m, 1H, $(CH_2)_6Me$), 1.86–1.98 (m, 2H, $(CH_2)_6Me$), 4.12 (ddd, *J*=3.7, 6.8, 11.7 Hz, 1H, C*H*$_2$OH), 4.40 (dd, *J*=6.8, 7.8 Hz, 1H, OH), 4.46 (ddd, *J*=7.8, 7.8, 11.7 Hz, 1H, C*H*$_2$OH), 4.62 (dd, *J*=3.7, 7.8 Hz, 1H, C*H*CH_2OH), 4.98 (t, *J*=7.0 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.95 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.25–7.45 (m, 6H, Ar), 7.55–7.60 (m, 2H, Ar), 7.84 (d, 1H, Ar) ppm. MS (ESI, *m*/*z*): 480 (M+Na^+, 7), 459 [(M+2H)$^+$, 29], 458 (M+H^+, 100). HRESIMS calcd for $[C_{30}H_{35}NO_3+H]^+$: 458.2695. Found: 458.2695.

3.3. General procedure for the oxidative deprotection of *N*-substituted 3-alkyl-isoindolin-1-ones (13)

To a solution of diastereomeric mixture **13** (1.0 mmol) in a mixed MeCN–H_2O solvent system (3:1, 4 mL) was added ceric ammonium nitrate (2.192 g, 4.0 mmol) at rt. After stirred at the same temperature for 30 min, H_2O (10 mL) was added. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, then dried over anhydrous Na_2SO_4. The crude was purified by flash column chromatography on silica gel with ethyl acetate-petroleum ether (2:1) as eluent to give **1**.

3.3.1. (*R*)-Methyl-2,3-dihydro-1*H*-isoindolin-1-one (1a). Yield 84%. White crystal. Mp 112–115 °C (CH_2Cl_2) [lit.[5c] mp 102–103 °C for (*S*)-**1a**; lit.[6e] mp 118–119 °C for racemic **1a**]. $[\alpha]_D^{20}$=+39.1 (*c* 1.0, MeOH) {lit.[5c] $[\alpha]_D^{20}$=−39.8 (*c* 1.0, MeOH) for (*S*)-enantiomer; lit.[7] $[\alpha]_D^{20}$=−89.7 (*c* 1.7, MeOH) for (*R*)-enantiomer}. IR (KBr, Pellet) ν_{max}: 3193, 3079, 3021, 2923, 1688, 1655, 1540, 1454, 1416, 1260, 1206, 1138, 1084, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.51 (d, *J*=6.8 Hz, 3H, CH_3), 4.54 (q, *J*=6.8 Hz, 1H, CHMe), 6.90 (s, 1H, NH), 7.40–7.60 (m, 3H, Ar), 7.84 (d, *J*=7.50 Hz, 1H, Ar) ppm. MS (ESI, *m*/*z*): 170 (M+Na^+, 77), 148 (M+H^+, 100). HRESIMS calcd for $[C_9H_9NO+H]^+$: 148.0762. Found: 148.0755.

3.3.2. (*R*)-Ethyl-2,3-dihydro-1*H*-isoindolin-1-one (1b). Yield 63%. White crystal. Mp 128–131 °C (CH_2Cl_2) [lit.[27] mp 105 °C for racemic **1b**]. $[\alpha]_D^{20}$=+52.0 (*c* 0.6, MeOH). IR (KBr, Pellet) ν_{max}: 3209, 2961, 2925, 2855, 1690, 1654, 1462, 1421, 1312, 1209, 1143 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (t, *J*=7.4 Hz, 3H, CH_3), 1.66–1.76 (m, 1H, CH_2Me), 1.98–2.06 (m, 1H, CH_2Me), 4.60 (dd, *J*=4.9, 7.6 Hz, 1H, NCH), 7.10 (br s, 1H, NH), 7.42–7.61 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 184 (M+Na^+, 7), 163 [(M+2H)$^+$, 11], 162 (M+H^+, 100). HRESIMS calcd for $[C_{10}H_{11}NO+H]^+$: 162.0919. Found: 162.0918.

3.3.3. (*R*)-*n*-Propyl-2,3-dihydro-1*H*-isoindolin-1-one (1c). Yield 86%. White crystal. Mp 108–109 °C (CH_2Cl_2) [lit.[28] mp 135–136 °C (H_2O) for racemic **1c**]. $[\alpha]_D^{20}$=+57.2 (*c* 0.7, MeOH). R_f: 0.48 (AcOEt–PE=1:1). IR (KBr, Pellet) ν_{max}: 3211, 2958, 2927, 2869, 1680, 1465, 1423, 1306,

745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, J=7.3 Hz, 3H, CH_3), 1.36–1.44 (m, 2H, $(CH_2)_2Me$), 1.48–1.56 (m, 1H, $(CH_2)_2Me$), 1.59–1.68 (m, 1H, $(CH_2)_2Me$), 4.64 (dd, J=4.4, 7.7 Hz, 1H, NCH), 7.40–7.60 (m, 3H, Ar), 7.60 (br s, 1H, NH), 7.83 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 373 [$(2M^+Na)^+$, 17], 351 [$(2M^+H)^+$, 7], 198 ($M+Na^+$, 51), 177 [$(M+2H)^+$, 14], 176 ($M+H^+$, 100). HRESIMS calcd for $[C_{11}H_{13}NO+H]^+$: 176.1075. Found: 176.1068.

3.3.4. (*R*)-*n*-Butyl-2,3-dihydro-1*H*-isoindolin-1-one (1d). Yield 90%. White crystal. Mp 69–71 °C (CH_2Cl_2) [Lit.[6e] mp 88–89 °C for racemic **1d**]. $[\alpha]_D^{20}$=+53.0 (*c* 0.8, MeOH). IR (KBr, Pellet) ν_{max}: 3270, 3078, 2955, 2922, 2852, 1695, 1576, 1540, 1465, 1376, 1203, 1137, 1098 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, J=7.1 Hz, 3H, CH_3), 1.22–1.50 (m, 4H, $(CH_2)_3Me$), 1.60–1.70 (m, 1H, $(CH_2)_3Me$), 1.9–2.0 (m, 1H, $(CH_2)_3Me$), 4.61 (dd, 1H, J=4.5, 7.6 Hz, NCH), 6.90 (br s, 1H, NH), 7.20–7.30 (m, 2H, Ar), 7.55 (m, 1H, Ar), 7.85 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 379 [$(2M+H)^+$, 8], 212 ($M+Na^+$, 4), 191 [$(M+2H)^+$, 12], 190 ($M+H^+$, 100). HRESIMS calcd for $[C_{12}H_{15}NO+H]^+$: 190.1232. Found: 190.1229. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.49; H, 7.99; N, 7.68.

3.3.5. (*R*)-*iso*-Butyl-2,3-dihydro-1*H*-isoindolin-1-one (1e). Yield 88%. White crystal. Mp 133–135 °C (CH_2Cl_2) [lit.[29] mp 153 °C (EtOH) for racemic **1e**]. $[\alpha]_D^{20}$=+64.1 (*c* 1.0, MeOH). IR (KBr, Pellet) ν_{max}: 3192, 3075, 2954, 2924, 2863, 1686, 1608, 1467, 1363, 1269, 1203, 1142, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.00 (d, J=6.6 Hz, 3H, CH_3), 1.06 (d, J=6.6 Hz, 3H, CH_3), 1.46–1.53 (m, 1H, CH_2CHMe_2), 1.72–1.78 (m, 1H, CH_2CHMe_2), 1.79–1.88 (m, 1H, CH_2CHMe_2), 4.64 (dd, J=4.0, 9.7 Hz, 1H, NCH), 6.60 (br s, 1H, NH), 7.42–7.58 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 212 ($M+Na^+$, 4), 191 [$(M+2H)^+$, 13] 190 ($M+H^+$, 100). HRESIMS calcd for $[C_{12}H_{15}NO+H]^+$: 190.1232. Found: 190.1229. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.14; H, 8.14; N, 7.32.

3.3.6. (*R*)-*n*-Pentyl-2,3-dihydro-1*H*-isoindolin-1-one (1f). Yield 88%. White crystal. Mp 56–58 °C (CH_2Cl_2). $[\alpha]_D^{20}$=+49.9 (*c* 0.7, MeOH). IR (KBr, Pellet) ν_{max}: 3218, 3073, 2925, 2855, 1696, 1541, 1465, 1360, 1301, 1260, 1198, 1142, 1086, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, J=6.9 Hz, 3H, CH_3), 1.24–1.38 (m, 5H, $(CH_2)_4Me$), 1.41–1.52 (m, 1H, $(CH_2)_4Me$), 1.58–1.70 (m, 1H, $(CH_2)_4Me$), 1.90–1.98 (m, 1H, $(CH_2)_4Me$), 4.61 (dd, J=4.5, 7.6 Hz, 1H, NCH), 7.20 (br s, 1H, NH), 7.41–7.58 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 407 [$(2M+H)^+$, 4], 205 [$(M+2H)^+$, 16], 204 ($M+H^+$, 100). HRESIMS calcd for $[C_{13}H_{17}NO+H]^+$: 204.1388. Found: 204.1386.

3.3.7. (*R*)-*n*-Heptyl-2,3-dihydro-1*H*-isoindolin-1-one (1g). Yield 82%. Colorless oil. $[\alpha]_D^{20}$=+50.8 (*c* 0.4, MeOH). IR (film) ν_{max}: 3216, 3077, 2927, 2857, 1697, 1611, 1465, 1361, 1307, 1141 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.86 (t, J=7.0 Hz, 3H, CH_3), 1.22–1.34 (m, 9H, $(CH_2)_6Me$), 1.42–1.48 (m, 1H, $(CH_2)_6Me$), 1.60–1.68 (m, 1H, $(CH_2)_6Me$), 1.92–1.94 (m, 1H, $(CH_2)_6Me$), 4.62 (dd, J=4.6, 7.5 Hz, 1H, NCH), 7.40–7.60 (m, 3H, Ar), 7.70 (br s, 1H, NH), 7.82 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 485 [$(2M+Na)^+$, 3], 232 ($M+H^+$, 100). HRESIMS calcd for $[C_{15}H_{21}NO+H]^+$: 232.1701. Found: 232.1691.

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