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ScienceDirect
Tetrahedron 64 (2008) 1786–1791
Tetrahedron
www.elsevier.com/locate/tet

Facile air-oxidation of *N*-homopiperonyl-5,6-dimethoxyhomophthalimide: simple and efficient access to nuevamine

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Received 31 August 2007; received in revised form 16 November 2007; accepted 29 November 2007
Available online 3 December 2007

Abstract

A facile six-step synthesis of naturally occurring (±)-nuevamine with 55% overall yield has been described, starting from methyl 2-(6-formyl-2,3-dimethoxyphenyl)acetate via the quantitative benzylic air-oxidation of the corresponding *N*-homopiperonyl-5,6-dimethoxyhomophthalimide to *N*-homopiperonyl-5,6-dimethoxyisoquinoline-1,3,4-trione as the key reaction, followed by base catalyzed regioselective alcoholysis of the trione with ring contraction, acid catalyzed dehydrative ring closure of the formed lactamol and decarboxylation pathway.

1. Introduction

The naturally occurring (±)-nuevamine (**1**)[1,2] from the *Berberis darwini* Hook species[1] is the first eminent member of the isoindolo[1,2-*a*]isoquinolinone family.[2] On the basis of synthesis,[2] the structure of nuevamine (**1**) has been reestablished with the alteration in the positions of two methoxy groups. Several general approaches for the synthesis of isoindoloisoquinoline skeleton are known in the literature.[3] Very recently, Couture and co-workers have reported two elegant approaches to **1** by using an aryne-mediated intramolecular cyclization and a Parham cyclization as the key reactions.[4] In the course of our studies on the total synthesis of gusanlung D,[5] we observed the facile air-oxidation of the benzylic methylene groups of the intermediate homophthalimides and taking advantage of the same, we now herein report a new simple and efficient access to the nuevamine (Schemes 1 and 2).

2. Results and discussion

In continuation of our studies on cyclic anhydrides chemistry,[6] starting from homophthalic anhydride (**3**) and homopiperonyl amine (**2**)[7] we prepared the homophthalimide **4**[8] in 92% yield (Scheme 1). We attempted a $NaBH_4$ reduction of homophthalimide **4** in methanol at room temperature with the aim of regioselectively reducing the more reactive unconjugated imide carbonyl group for the further enzymatic resolution and synthesis of gusanlung D. In the above reaction, we observed the formation of a new product in 70% yield but to our surprise, the ^1H NMR spectrum of the product revealed the absence of both the benzylic protons from the starting material **4**. Careful analysis of both the analytical and spectral data of the product indicated the formation of an isoindole **5** with a net oxidative ring contraction. Since we did not observe the formation of our originally desired reduced product, we presumed that a catalytic amount of $NaBH_4$ got converted into sodium methoxide in situ and thus, we proposed a facile air-oxidation of the benzylic carbon in the imide **4**, followed by very fast regioselective methanolysis (catalyzed by the methoxide) and an intramolecular ring closure pathway for the formation of α-hydroxy ester **5**. Our hypothesis was justified when we carried out the reaction of imide **4** in methanol using triethylamine as the base catalyst and obtained the same α-hydroxy ester **5** in 76% yield. Our literature search, then revealed that such type of serendipitous air oxidation of methylated homophthalimide, under the basic conditions, to the corresponding tertiary alcohol intermediate is known.[9,10] The lactamol **5** on treatment with catalytic amount of sulfuric

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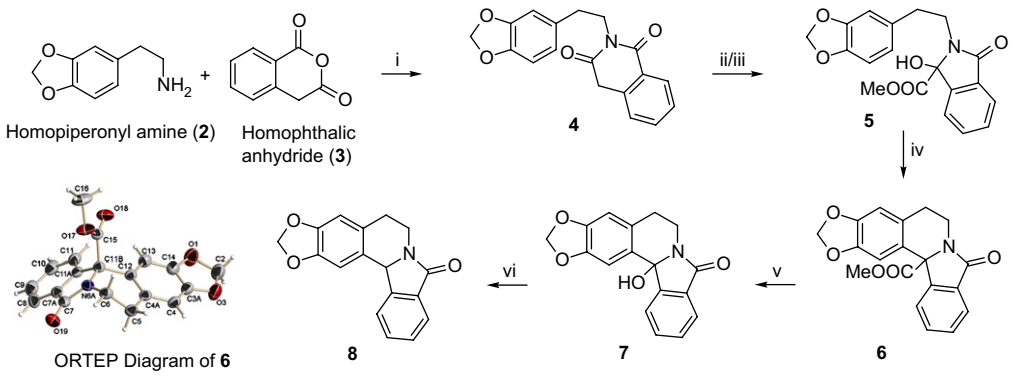
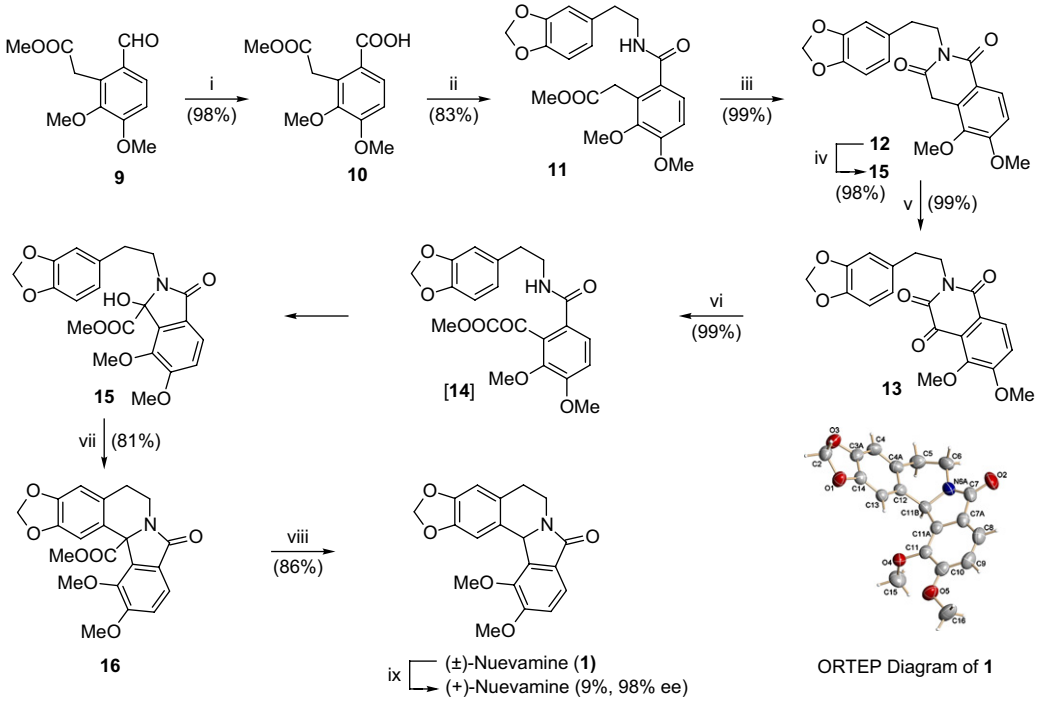
0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.11.104



Scheme 1. Synthesis of isoindoloisoquinoline. Reagents, conditions, and yields: (i) *o*-dichlorobenzene, reflux, 3 h (92%); (ii) $NaBH_4$, MeOH, rt, 20 h (70%); (iii) MeOH, NEt_3, rt, 12 h (76%); (iv) 6 M H_2SO_4+AcOH (1:2), rt, 2 h (84%); (v) NaCl, H_2O, DMSO, 175 °C, 30 min (79%); (vi) $NaBH_4$, TFA, rt, 5 h (85%).

acid in acetic acid at room temperature, underwent an expeditious intramolecular dehydrative ring closure to yield the isoindoloisoquinoline **6** with an angular carbomethoxy function in 84% yield. Finally, the structure of compound **6** was confirmed by using X-ray crystallographic analysis. The compound **6** on decarboxylation furnished the isoindoloisoquinoline **7** in 79% yield, with an angular hydroxyl function, as a result of the reaction of the formed intermediate carbanionic species with the dissolved oxygen. The compound **7** on $NaBH_4$–TFA reduction[3f] furnished via the corresponding iminium intermediate, the desired isoindoloisoquinoline **8** in 85% yield.

All the results summarized in Scheme 1, prompted us to launch a program toward the synthesis of nuevamine (Scheme 2). We started the synthesis of required 3,4-dimethoxyhomophthalic acid from the isovanillin and obtained the corresponding methyl 2-(6-formyl-2,3-dimethoxyphenyl)acetate (**9**) in six steps using the known procedure.[11] The aldehyde **9** on Jones oxidation gave the desired 3,4-dimethoxyhomophthalic acid mono-ester **10** in 98% yield. The *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI) induced intermolecular dehydrative coupling reaction of **10** with homopiperonyl amine gave the homophthalamic acid methyl ester **11** in 83% yield. The solution of ester **11** in methanol, on treatment with catalytic amount of triethylamine at room temperature immediately furnished the white precipitate of homophthalimide **12** in quantitative yield. Herein, the homophthalimide **12** was practically insoluble in methanol and we did not observe formation of any further air-oxidized product. However, the solution of imide **12** in DMSO+MeOH mixture (4:1), on treatment with catalytic amount of triethylamine under the oxygen atmosphere at room



Scheme 2. Synthesis of nuevamine. Reagents, conditions, and yields: (i) Jones reagent, acetone, rt, 5 h (98%); (ii) *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), HOBt, DMF, homopiperonyl amine, rt, 3 h (83%); (iii) MeOH, NEt_3, rt, 20 min (99%); (iv) DMSO+MeOH (4:1), NEt_3, oxygen atmosphere, rt, 24 h (98%); (v) DMSO, oxygen atmosphere, rt, 48 h (99%); (vi) MeOH, NEt_3, rt, 3 h (99%); (vii) TFA, rt, 2 h (81%); (viii) NaCl, DMSO, H_2O, 185 °C, 30 min (86%); (ix) $CHCl_3$+EtOAc (1:3), four recrystallizations of conglomerate, each 24 h (9%, 98% ee).

temperature for 24 h furnished the desired product **15** in 98% yield via the requisite facile air-oxidation pathway. At this stage, we decided to isolate and characterize the proposed intermediate trione **13**. In a control experiment, we stirred the solution of imide **12** in DMSO under the oxygen atmosphere for 48 h at the room temperature, specifically under the neutral conditions and noticed the facile air-oxidation of methylene group in **12** to the corresponding carbonyl group to form the trione **13** [both by the change in color of the reaction mixture (colorless to yellow) and thin layer chromatography (TLC)]. We could actually isolate the reactive trione **13** in 99% yield and its structure was established on the basis of analytical and spectral data. The isolated pure trione **13** was fairly stable at room temperature for 48 h plus time and then started undergoing the slow decomposition process. The freshly isolated trione on treatment with methanol–triethylamine at room temperature, again furnished the expected product **15** in quantitative yield via the unisolable intermediate keto-ester **14**. As expected, the lactamol **15** on acid catalyzed intramolecular dehydrative cyclization furnished the isoindoloisoquinoline **16** in 81% yield. Finally, the decarboxylation of the angular carbomethoxy function in **16** in the complete absence of oxygen, gave the desired natural product (±)-nuevamine (**1**) in 86% yield. Starting from aldehyde **9**, the nuevamine was obtained in six steps with 55% overall yield. The obtained analytical and spectral data for **1** were in complete agreement with the reported data[4] and the structure of nuevamine was further confirmed on the basis of X-ray crystallographic analysis. The single crystal X-ray data indicated that the crystalline nuevamine racemate is a rare conglomerate. As expected, the four successive recrystallizations of (±)-**1** from chloroform–ethyl acetate mixture (1:3) led to the spontaneous resolution to furnish the enantiomerically pure (+)-nuevamine in 9% recrystallization yield with 98% ee (by chiral HPLC).

3. Conclusions

In summary, we have demonstrated a noteworthy total synthesis of nuevamine by taking the advantage of facile air-oxidation propensity of the active methylene group in homophthalimide to the corresponding carbonyl group. We feel that the observed air-oxidation process is general in nature and would be useful to design the congeners of nuevamine and several other types of natural and unnatural carbocycles and heterocycles.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on Brucker AC 200 spectrometer (200 MHz). ^{13}C NMR spectra were recorded on Brucker ACF 200, ACF 400, and DRX 500 NMR spectrometers (50, 100, and 125 MHz, respectively). FTIR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. Column chromatographic separations were done on silica gel (60–120 mesh). Commercially available $NaBH_4$, Jones reagent, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), piperonal, homophthalic anhydride, acetic anhydride, and nitromethane were used.

4.2. 2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-4H-isoquinoline-1,3-dione (*4*)

A stirred solution of homopiperonyl amine (1.00 g, 6.06 mmol) and homophthalic anhydride (980 mg, 6.06 mmol) was heated at reflux in *o*-dichlorobenzene (20 mL) for 3 h. After cooling the reaction mixture, it was loaded on silica gel column and initially the column was eluted with petroleum ether for the removal of *o*-dichlorobenzene and then it was eluted with petroleum ether–ethyl acetate mixture (6:4) to obtain pure compound **4** as a crystalline yellow solid (1.72 g, 92% yield). Mp 158 °C (lit.[8] 156–157 °C); IR ($CHCl_3$) ν_{max} 1709, 1662, 1607, 1352, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.75–2.90 (m, 2H), 4.02 (s, 2H), 4.05–4.25 (m, 2H), 5.92 (s, 2H), 6.73 (s, 2H), 6.81 (s, 1H), 7.28 (d, J=8 Hz, 1H), 7.45 (t, J=8 Hz, 1H), 7.60 (dt, J=8 and 2 Hz, 1H), 8.22 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.7, 36.3, 41.6, 100.7, 108.1, 109.3, 121.7, 125.2, 127.0, 127.6, 129.0, 132.2, 133.5, 134.0, 146.0, 147.5, 164.6, 169.7. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.02; H, 4.81; N, 4.59.

4.3. 2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-1-hydroxy-3-oxo-2,3-dihydro-1H-isoindole-1-carboxylic acid methyl ester (*5*)

Method A: to a solution of imide **4** (400 mg, 1.29 mmol) in MeOH (15 mL) was added $NaBH_4$ (123 mg, 3.22 mmol) and the reaction mixture was stirred for 20 h at room temperature. After addition of water (20 mL) to the reaction mixture, it was extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether–ethyl acetate mixture (85:15) as an eluent furnished **5** as a crystalline solid (321 mg, 70% yield). *Method B*: to a solution of imide **4** (400 mg, 1.29 mmol) in MeOH (15 mL) was added NEt_3 (0.50 mL) and the reaction mixture was stirred for 12 h at room temperature. Reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether–ethyl acetate mixture (85:15) as an eluent furnished **5** as a crystalline solid (349 mg, 76% yield). Mp 162–164 °C; IR ($CHCl_3$) ν_{max} 3431, 1749, 1707, 1502, 1491, 1439, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.75–3.05 (m, 2H), 3.20–3.45 (m, 1H), 3.65–3.85 (m, 1H), 3.72 (s, 3H), 4.69 (br s, 1H), 5.92 (s, 2H), 6.65–6.80 (m, 3H), 7.40–7.50 (m, 1H), 7.50–7.65 (m, 2H), 7.75–7.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.6, 41.9, 54.1, 88.3, 100.8, 108.3, 109.3, 121.7 (2 carbons), 123.6, 130.4, 131.5, 132.5, 132.6, 143.2, 146.1, 147.6, 167.9, 171.5. Anal. Calcd

for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.13; H, 5.00; N, 4.06.

4.4. Methyl 7-oxo-5,6-dihydro-7H-1,3-dioxa-6a-aza-indeno[5,6-c]fluorene-11b-carboxylate (**6**)

To a solution of **5** (600 mg, 1.69 mmol) in acetic acid (6 mL) was added sulfuric acid (6 M, 3 mL) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (25 mL×3). The combined organic layer was successively washed with water, 5% aqueous $NaHCO_3$ solution, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether–ethyl acetate mixture (8:2) as an eluent furnished **6** as a crystalline solid (478 mg, 84% yield). Mp 185–187 °C; IR ($CHCl_3$) ν_{max} 1736, 1697, 1614, 1504, 1487, 1391, 1246, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.65–3.10 (m, 2H), 3.60–3.80 (m, 1H), 3.74 (s, 3H), 4.35–4.55 (m, 1H), 5.93 (d, J=12 Hz, 1H), 5.94 (d, J=12 Hz, 1H), 6.61 (s, 1H), 7.44 (s, 1H), 7.53 (dt, J=8 and 1 Hz, 1H), 7.65 (dt, J=8 and 1 Hz, 1H), 7.86 (d, J=8 Hz, 1H), 8.04 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.7, 36.9, 53.4, 69.3, 101.2, 107.3, 108.8, 123.9, 124.2, 126.3, 128.5, 129.4, 131.7, 132.0, 143.4, 146.4, 147.6, 167.5, 170.1. Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.75; H, 4.63; N, 4.08.

4.5. 11b-Hydroxy-5,11b-dihydro-6H-1,3-dioxa-6a-aza-indeno[5,6-c]fluoren-7-one (**7**)

To a stirred solution of compound **6** (400 mg, 1.18 mmol) in a mixture of DMSO (20 mL) and water (1 mL) was added NaCl (76 mg, 1.30 mmol) and the reaction mixture was heated for 30 min at 175 °C. The reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether–ethyl acetate mixture (1:1) as an eluent gave compound **7** as a crystalline solid (276 mg, 79% yield). Mp 175–176 °C; IR (Nujol) ν_{max} 3250, 1678, 1462, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.60–2.74 (m, 1H), 2.76–2.96 (m, 1H), 3.35 (ddd, J=13, 11, and 4 Hz, 1H), 4.08 (ddd, J=13, 5, and 2 Hz, 1H), 5.92 (dd, J=10 and 2 Hz, 2H), 6.55 (s, 1H), 7.38 (s, 1H), 7.46 (t, J=8 Hz, 1H), 7.63 (t, J=8 Hz, 1H), 7.65 (d, J=6 Hz, 1H), 7.97 (dd, J=8 and 2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 29.2, 34.6, 85.9, 101.3, 108.0, 108.5, 122.7, 124.2, 128.5, 129.5, 130.5, 130.7, 132.7, 146.3, 147.2, 148.9, 166.3. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.43; N, 4.74. Found: C, 69.02; H, 4.52; N, 4.55.

4.6. 5,11b-Dihydro-6H-1,3-dioxa-6a-aza-indeno[5,6-c]-fluoren-7-one (**8**)

To a stirred solution of the compound **7** (200 mg, 0.67 mmol) in TFA (7 mL) was added $NaBH_4$ (26 mg, 0.70 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with 5% aqueous solution of $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether–ethyl acetate mixture (1:1) as an eluent furnished pure compound **8** as a crystalline solid (160 mg, 85% yield). Mp 179–180 °C; IR ($CHCl_3$) ν_{max} 1686, 1618 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70–2.85 (m, 1H), 2.90–3.09 (m, 1H), 3.45 (ddd, J=12, 9, and 4 Hz, 1H), 4.38 (dt, J=12 and 6 Hz, 1H), 5.56 (s, 1H), 5.93 (d, J=16 Hz, 2H), 6.65 (s, 1H), 7.08 (s, 1H), 7.50 (t, J=8 Hz, 1H), 7.61 (t, J=8 Hz, 1H), 7.81 (d, J=8 Hz, 1H), 7.88 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.3, 38.1, 59.0, 101.0, 105.4, 109.0, 123.2, 123.8, 127.1, 128.1, 128.4, 131.4, 132.6, 144.1, 146.4, 146.7, 167.8. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 73.22; H, 4.83; N, 5.16.

4.7. 3,4-Dimethoxy-2-(2-methoxy-2-oxoethyl)benzoic acid (**10**)

To a stirred solution of compound **9** (700 mg, 2.94 mmol) in acetone (20 mL) was added Jones reagent (6 mL) in dropwise fashion at room temperature and the reaction mixture was stirred for 4 h. The excess of reagent was quenched by addition of *i*-PrOH. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (25 mL×3). The organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure compound **10** as a crystalline solid (732 mg, 98% yield). Mp 128–130 °C; IR ($CHCl_3$) ν_{max} 1734, 1686, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.70 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 4.18 (s, 2H), 6.91 (d, J=8 Hz, 1H), 7.96 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5, 51.8, 55.8, 60.8, 110.2, 121.0, 129.0, 131.7, 147.8, 156.8, 172.0, 172.3. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.54. Found: C, 56.64; H, 5.55.

4.8. Methyl 2-(6-(2-(benzo[d][1,3]dioxol-5-yl)ethyl carbamoyl)-2,3-dimethoxyphenyl)acetate (**11**)

To a stirred solution of compound **10** (650 mg, 2.55 mmol) in DMF (15 mL) at 0 °C were slowly added HOBt (413 mg, 3.06 mmol) and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI, 535 mg, 2.80 mmol). The reaction mixture was stirred under inert atmosphere for 20 min. Homopiperonyl amine (420 mg, 2.55 mmol) in DMF (7 mL) was added to the above reaction mixture in a dropwise fashion over 10 min and it was further stirred for 4 h at room temperature. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (25 mL×3). The organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent gave **11** as a white crystalline solid (851 mg, 83% yield). Mp 120–121 °C; IR ($CHCl_3$) ν_{max} 1734, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$,

200 MHz) δ 2.81 (t, J=8 Hz, 2H), 3.62 (q, J=6 Hz, 2H), 3.70 (s, 3H), 3.78 (s, 3H), 3.83 (s, 2H), 3.87 (s, 3H), 5.93 (s, 2H), 6.43 (t, J=6 Hz, 1H), 6.62–6.78 (m, 3H), 6.83 (d, J=8 Hz, 1H), 7.17 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.4, 35.2, 41.1, 52.1, 55.7, 60.5, 100.8, 108.3, 109.0, 110.9, 121.6, 123.6, 127.0, 130.0, 132.6, 146.1, 147.6, 147.8, 153.9, 168.9, 173.7. Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.77; N, 3.49. Found: C, 63.02; H, 5.80; N, 3.61.

*4.9. 2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-5,6-dimethoxyisoquinoline-1,3(2H,4H)-dione (**12**)*

To a stirred solution of compound **11** (750 mg, 2.03 mmol) in MeOH (20 mL) at room temperature was added catalytic amount of NEt_3 (1 drop) and the reaction mixture was stirred for 30 min. The obtained white precipitate was filtered out and washed with MeOH (5 mL) and dried in vacuo to provide pure compound **12** as a snow-white crystalline solid (683 mg, 99% yield). Mp 216–217 °C; IR (Nujol) ν_{max} 1705, 1666, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.76–2.81 (m, 2H), 3.88 (s, 3H), 3.96 (s, 5H), 4.07–4.19 (m, 2H), 5.93 (s, 2H), 6.74 (s, 2H), 6.82 (s, 1H), 7.02 (d, J=8 Hz, 1H), 7.99 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.0, 33.9, 41.5, 55.9, 60.3, 100.8, 108.2, 109.4, 111.5, 118.4, 121.8, 125.9, 128.2, 132.5, 144.6, 146.1, 147.6, 156.6, 164.3, 169.9. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.90; H, 5.01; N, 3.53.

*4.10. 2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-5,6-dimethoxyisoquinoline-1,3,4(2H)-trione (**13**)*

The solution of compound **12** (100 mg, 0.27 mmol) in DMSO (5 mL) was stirred under the oxygen atmosphere for 24 h at room temperature. To the formed yellow colored reaction mixture was added ethyl acetate (20 mL) and the total organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure compound **13** as a yellow solid (102 mg, 99% yield). Mp 155–157 °C; IR ($CHCl_3$) ν_{max} 1724, 1707, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.81–2.93 (m, 2H), 3.97 (s, 3H), 4.01 (s, 3H), 4.12–4.23 (m, 2H), 5.93 (s, 2H), 6.73 (s, 2H), 6.80 (s, 1H), 7.35 (d, J=10 Hz, 1H), 8.15 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.1, 41.8, 56.7, 60.8, 101.0, 108.5, 109.2, 118.1, 121.7, 122.5, 124.8, 126.4, 132.6, 145.9, 147.5, 149.3, 157.5, 157.9, 162.2, 173.0. Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.57; H, 4.61; N, 3.58.

*4.11. Methyl 2-(2-(benzo[d][1,3]dioxyl-5-yl)ethyl)-1-hydroxy-6,7-dimethoxy-3-oxoisoindoline-1-carboxylate (**15**)*

Method A: to the stirred solution of compound **13** (50 mg, 0.13 mmol) in MeOH (5 mL) was added catalytic amount of NEt_3 (1 drop) at room temperature and the reaction mixture was further stirred for 3 h. Concentration of the reaction mixture in vacuo directly furnished compound **15** as a faint brown solid (53 mg, 99% yield). *Method B*: to the solution of compound **12** (500 mg, 1.35 mmol) in mixture of DMSO (20 mL) and MeOH (5 mL) was added NEt_3 (0.5 mL) and the reaction mixture was stirred under the oxygen atmosphere at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **15** as a faint brown solid (548 mg, 98% yield). Mp 145–146 °C; IR ($CHCl_3$) ν_{max} 3483, 1742, 1701, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.68–2.97 (m, 2H), 3.30–3.48 (m, 1H), 3.51–3.70 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.81 (s, 1H), 5.92 (s, 2H), 6.65–6.78 (m, 3H), 7.04 (d, J=8 Hz, 1H), 7.53 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.6, 41.3, 53.9, 56.1, 61.0, 86.3, 100.8, 108.2, 109.2, 114.1, 119.6, 121.6, 124.4, 132.5, 136.1, 143.6, 146.0, 147.5, 156.1, 167.5, 171.5. Anal. Calcd for $C_{21}H_{21}NO_8$: C, 60.71; H, 5.09; N, 3.37. Found: C, 60.52; H, 5.00; N, 3.44.

*4.12. 10,11-Dimethoxy-7-oxo-5,6-dihydro-7H-1,3-dioxa-6a-aza-indeno[5,6-c]fluorene-11b-carboxylic acid methyl ester (**16**)*

The solution of compound **15** (400 mg, 0.96 mmol) in TFA (10 mL) was stirred at room temperature for 2 h. To the reaction mixture was added ethyl acetate (30 mL) and organic layer was washed with 5% aqueous solution of $NaHCO_3$, water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (3:7) as an eluent gave compound **16** as a crystalline solid (309 mg, 81% yield). Mp 233–235 °C; IR ($CHCl_3$) ν_{max} 1742, 1686, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.71 (dt, J=16 and 6 Hz, 1H), 3.01 (ddd, J=16, 8, and 6 Hz, 1H), 3.40 (ddd, J=14, 9, and 6 Hz, 1H), 3.73 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.30 (ddd, J=12, 7, and 4 Hz, 1H), 5.90 (dd, J=9 and 2 Hz, 2H), 6.58 (s, 1H), 7.08 (d, J=8 Hz, 1H), 7.58 (d, J=10 Hz, 1H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.5, 37.0, 53.3, 56.2, 60.2, 70.0, 101.0, 108.4, 109.4, 113.8, 119.8, 125.2, 127.6, 128.3, 137.3, 143.9, 146.3, 147.3, 156.1, 167.7, 170.6. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.81; N, 3.54. Found: C, 63.32; H, 4.71; N, 3.59.

*4.13. 10,11-Dimethoxy-5,11b-dihydro-6H-1,3-dioxa-6a-aza-indeno[5,6-c]fluoren-7-one [Nuevamine (±)-**1**]*

To the stirred solution of compound **16** (200 mg, 0.50 mmol) in the mixture of DMSO (7 mL) and H_2O (1 mL) was added NaCl (32 mg, 0.55 mmol). The reaction mixture was deoxygenated by bubbling excess of nitrogen gas for 3 h and it was heated for 30 min at 185 °C. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine, and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether–ethyl acetate mixture (3:7) as an eluent furnished the desired compound **1** as a crystalline

solid (146 mg, 86% yield). Mp 214–215 °C (ethyl acetate) (lit.[1] 212 °C); IR ($CHCl_3$) ν_{max} 1680, 1651, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.78–3.12 (m, 2H), 3.57 (dt, J=12 and 6 Hz, 1H), 3.98 (s, 3H), 4.00 (s, 3H), 3.95–4.15 (m, 1H), 5.63 (s, 1H), 5.90 (dd, J=12 and 2 Hz, 2H), 6.67 (s, 1H), 7.07 (d, J=8 Hz, 1H), 7.32 (s, 1H), 7.59 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.8, 38.7, 56.2, 58.3, 60.5, 100.9, 107.4, 108.4, 113.2, 119.7, 126.6, 128.4, 128.8, 136.1, 144.3, 146.4, 146.7, 155.4, 167.5. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.24; H, 5.04; N, 4.12. Found: C, 67.09; H, 5.11; N, 4.15.

4.14. (+)-Nuevamine

The conglomerate (±)-nuevamine (120 mg) on four successive recrystallizations from the chloroform–ethyl acetate mixture (1:3, 1 mL/20 mg) with 24 h as the each recrystallization time furnished the enantiomerically pure (+)-nuevamine (11 mg, 9% recrystallizations yield, 98% ee by chiral HPLC). Mp 215 °C; $[\alpha]_D^{20}$ +185 (c 1.0, $CHCl_3$). *HPLC details*: column: chiralcel OD (250×4.6 mm), mobile phase: isopropyl alcohol–hexane (20:80), wavelength: 254 nm, flow rate: 1 mL/min, retention time: 17.6 min (+)-isomer, 23.4 min (−)-isomer.

4.15. Supporting information

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 659028 and 659029. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

P.B.W. thanks CSIR, New Delhi and S.E. thanks UGC, New Delhi, for the awards of research fellowships. We thank Mrs. S.S. Kunte from NCL, Pune for the chiral HPLC data.

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