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Stereoselective Synthesis of Novel (±)-*trans*-Dihydronarciclasine Analogues: Preparation of a Pivotal Intermediate Containing Two Methoxy Substituents

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Abstract

An efficient stereoselective synthesis of a pivotal intermediate, a cyclic allyl alcohol derivative containing two methoxy groups [(±)-**22**], using for the preparation of (±)-*trans*-dihydronarciclasine analogues was elaborated starting from easily available and inexpensive methyl gallate. This new synthetic route consists of 17 reaction steps, and provides an opportunity to obtain the wanted alkaloid derivative containing an additional methoxy group at position 11, in the ring A of the phenanthridone scaffold.

Keywords

alkaloids, phenanthridone scaffold, stereoselective synthesis

1 Introduction

Although the phenanthridone alkaloids are a relatively little group of the *Amaryllidaceae* alkaloids, several highly potent anticancerous compounds belong to this group, from which the most active ones are narciclasine (**1**), *trans*-dihydronarciclasine (**2**), pancratistatin (**3**) and *trans*-dihydrolycoricidine (**4**) [1] (Fig. 1).

In the nature, these alkaloids can be found in the species of genus *Narcissus, Zephyranthes* and *Hymenocallis*, but their concentrations are very low in these herbs, thus their biological investigations proved to be difficult [2–6]. Therefore, their chemical syntheses became necessary to obtain them in appropriate amounts. After their first total syntheses [7–10], a relatively large number of modified new ones was evaluated in the next two decades [1]. In parallel with these syntheses of the natural alkaloids, their new analogues were also prepared providing an opportunity to elucidate their structure–activity relationships (SAR) [11].

After developing new enantioselective total syntheses of the *ent*-forms of *trans*-dihydrolycoricidine [12] and *trans*-dihydronarciclasine [13] by us, the preparation of novel analogues of these compounds were also elaborated [14–16]. Since the literature syntheses of the abovementioned analogues were performed by changing the substituents of ring B or C, while the ring A remained untouched, we focused on the modification of the ring A of the phenanthridone scaffold.

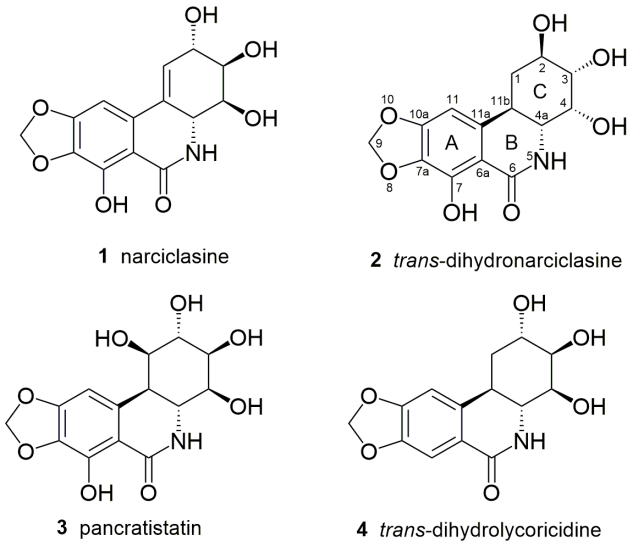

Fig. 1 Structures of the typical *Amaryllidaceae* alkaloids with high anticancerous activity (**1**–**4**)

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Herein, connecting to our previous works, we report an efficient stereoselective synthesis of a pivotal intermediate, a cyclic allyl alcohol derivative containing two methoxy groups in ring A, which can be used for the preparation of new (±)-*trans*-dihydronarciclasine analogues.

It seemed to be the best choice for the starting material of our new synthesis was apiolealdehyde (4,7-dimethoxybenzo[*d*][1,3]dioxole-5-carbaldehyde (**5**), which can easily be synthesised from apiole (5-allyl-4,7-dimethoxybenzo[*d*][1,3]dioxole), a naturally occurring compound, the main constituent of parsley oil [17]. Due to the high price of apiole, however, another starting compound was chosen for the synthesis of apiolealdehyde: the relatively inexpensive methyl gallate (**6**).

2 Experimental

2.1 Materials and methods

All reagents are commercially available from Merck. Melting points were measured on a Büchi 510 apparatus using a certified mercury thermometer (ASTM 2C). NMR spectra were recorded on a Bruker AV-300 or DRX-500 instrument operating at 300 or 500 MHz, in $CDCl_3$ and DMSO-d_6, respectively. IR spectra were recorded on a Bruker Tensor 37 FT-IR spectrophotometer. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column cromatography.

2.2 Preparation of methyl 2-ethoxy-7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate (7)

To a solution of **6** (9.2 g, 50.0 mmol) in toluene (400 cm^3) were added Amberlite® IR-120 (0.26 g), a strongly acidic cation exchange resin, and triethyl orthoformate (25 cm^3, 0.50 mmol), then the reaction mixture was stirred for 8 h under reflux. Next, the mixture was filtered, and the filtrate was evaporated *in vacuo* to afford **7** (11.93 g, 99%) as a white solid. M.p. 91–92 °C (Lit. m.p. compound **7** decomposes before melting [18]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42 (d, J = 1.9 Hz, 1H, 4-H_{Ar}), 7.20 (d, J = 1.9 Hz, 1H, 6-H_{Ar}), 6.97 (s, 1H, OCHO), 6.00 (br s, 1H, OH), 3.90 (s, 3H, $COOCH_3$), 3.70 (q, J = 4.8 Hz, 2H, OCH_2CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.9 ($COOCH_3$), 147.1 (3a-C_{Ar}), 138.7 (7-C_{Ar}), 137.1 (7a-C_{Ar}), 124.0 (5-C_{Ar}), 120.1 (OCHO), 114.0 (6-CH_{Ar}), 102.7 (4-CH_{Ar}), 59.7 (OCH_2CH_3), 52.4 ($COOCH_3$), 14.7 (OCH_2CH_3); IR (KBr) 3351, 1709, 1618, 1438, 1316, 1254, 1081, 1038, 765 cm^{-1}.

2.3 Preparation of methyl 2-ethoxy-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (8)

To a solution of **7** (8.93 g, 37.2 mmol) in acetone (140 cm^3) were added anhydrous K_2CO_3 (5.14 g, 37.2 mmol) and methyl iodide (6.00 cm^3, 8.66 g, 61.0 mmol). The reaction mixture was stirred for 8 h under reflux. The insoluble solid was filtered and washed with acetone. The filtrate was evaporated *in vacuo* to give **8** (9.23 g, 98%) as a white solid. M.p. 47–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.36 (d, J = 2.2 Hz, 1H, 4-H_{Ar}), 7.27 (d, J = 2.2 Hz, 1H, 6-H_{Ar}), 6.97 (s, 1H, OCHO), 3.96 (s, 3H, OCH_3), 3.89 (s, 3H, $COOCH_3$), 3.77 (q, J = 4.8 Hz, 2H, OCH_2CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.4 ($COOCH_3$), 147.0 (3a-C_{Ar}), 138.0 (7-C_{Ar}), 137.5 (7a-C_{Ar}), 124.3 (5-C_{Ar}), 122.7 (OCHO), 109.7 (6-CH_{Ar}), 103.5 (4-CH_{Ar}), 59.7 (OCH_2CH_3), 56.6 (OCH_3), 52.2 ($COOCH_3$), 14.8 (OCH_2CH_3); IR (KBr) 2983, 1723, 1643, 1438, 1246, 1095, 924, 762 cm^{-1}.

2.4 Preparation of methyl 3,4-dihydroxy-5-methoxybenzoate (9)

To a solution of **8** (13.7 g, 53.9 mmol) in MeOH (70 cm^3) was added 2M aqueous HCl solution (95 cm^3) dropwise within 1 h. The reaction mixture was stirred at room temperature for additional 4 h, then the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (130 cm^3), and kept at 0–5 °C for 24 h. The precipitated white by-product (a gallic acid derivate) was removed by filtration, and the filtrate was evaporated *in vacuo* to afford the crude product which was recrystallized from MeOH to give **9** (9.60 g, 87%) as a pale yellow solid. M.p. 108–109 °C (Lit. m.p. 110–111 °C [19]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, J = 2.2 Hz, 1H, 2-H_{Ar}), 7.23 (d, J = 2.2 Hz, 1H, 6-H_{Ar}), 5.88 (br s, 1H, 4-OH), 5.49 (br s, 1H, 3-OH), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$,) δ (ppm) 167.6 ($COOCH_3$), 147.2 (5-C_{Ar}), 144.2 (3-C_{Ar}), 138.5 (4-C_{Ar}), 120.4 (1-C_{Ar}), 110.8 (2-CH_{Ar}), 104.9 (6-CH_{Ar}), 56.0 (OCH_3), 51.9 ($COOCH_3$); IR (KBr) 3382, 1708, 1593, 1506, 1436, 1243, 1161, 1058, 1000, 964, 726 cm^{-1}.

2.5 Preparation of methyl 2-bromo-3,4-dihydroxy-5-methoxybenzoate (10)

To a solution of **9** (3.05 g, 15.4 mmol) in $CHCl_3$ (77 cm^3) was added 1,3-dibromo-5,5-dimethylhydantoin (2.24 g, 7.83 mmol, DBDMH) in small portions within 2.5 h. After stirring the reaction mixture at room temperature for 22 h, a 10% aqueous $Na_2S_2O_4$ solution (50 cm^3) was added to it. After 30 min additional stirring, the phases were sperated

and the organic one was dried over Na_2SO_4. The solvent was removed *in vacuo* to yield **10** (3.90 g, 92%) as pale yellow crystals. M.p. 124–125 °C (Lit. m.p. 141 °C [20]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.19 (s, 1H, 6-H_{Ar}), 5.98 (bs, 1H, 4-OH), 5.84 (bs, 1H, 3-OH), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.9 (*C*$OOCH_3$), 145.7 (5-C_{Ar}), 141.4 (3-C_{Ar}), 136.7 (4-C_{Ar}), 121.8 (1-C_{Ar}), 107.1 (2-C_{Ar}), 103.3 (6-CH_{Ar}), 56.4 (OCH_3), 52.3 (COO*C*H_3); IR (KBr) 3461, 3341, 1717, 1601, 1429, 1292, 1210, 1101, 1018, 923, 776 cm^{-1}.

2.6 Preparation of methyl 4-bromo-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (11)

To a solution of **10** (5.82 g, 21.0 mmol) in DMF (162 cm^3) were added anhydrous KF (6.14 g, 0.11 mol) and CH_2Br_2 (5 cm^3, 12.4 g, 71.3 mmol). The reaction mixture was stirred at 85–90 °C under an Ar atmosphere for 12 h. After cooling it to room temperature, the solvent was removed *in vacuo*, and water (20 cm^3) was added to the residue. It was extracted with Et_2O (4 × 20 cm^3), then the combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was also removed *in vacuo* to afford **11** (4.53 g, 75%) as a yellow solid. M.p. 92–93 °C (Lit. m.p. 103–104 °C [21]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (s, 1H, 6-H_{Ar}), 6.14 (s, 2H, OCH_2O), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.4 (*CO*OCH_3), 148.0 (3a-C_{Ar}), 142.2 (7-C_{Ar}), 138.3 (7a-C_{Ar}), 124.2 (5-C_{Ar}), 112.4 (6-CH_{Ar}), 102.4 (4-C_{Ar}), 94.4 (OCH_2O), 56.8 (OCH_3), 52.3 (COO*C*H_3); IR (KBr) 1724, 1433, 1324, 1248, 1175, 1107, 1041, 935 cm^{-1}.

2.7 Preparation of 4-bromo-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylic acid (12)

To a solution of **11** (5.68 g, 19.6 mmol) in *i*-PrOH (43 cm^3) was added KOH (1.24 g, 22.1 mmol) in water (1 cm^3), and it was heated to reflux and stirred for 6 h. It was cooled below 10 °C and acidified with concentrated HCl (3 cm^3) to pH = 2. The precipitated crude product was filtered and dried, then it was recrystallized from *i*-PrOH to give **12** (4.23 g, 79%) as a white solid. M.p. 236–237 °C (Lit. m.p. 242–243 °C [22]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 12.60 (s, 1H, COOH), 7.44 (s, 1H, 6-H_{Ar}), 6.17 (s, 2H, OCH_2O), 3.96 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.2 (COOH), 147.5 (3a-C_{Ar}), 144.8 (7-C_{Ar}), 138.2 (7a-C_{Ar}), 126.8 (5-C_{Ar}), 106.8 (6-CH_{Ar}), 102.8 (4-C_{Ar}), 102.0 (OCH_2O), 56.5 (OCH_3); IR (KBr) 2940, 2840, 1868, 1623, 1432, 1346, 1167, 1110, 1042, 932 cm^{-1}.

2.8 Preparation of apiolic acid (4,7-dimethoxybenzo[*d*][1,3]dioxole-5-carboxylic acid) (13)

To a solution of freshly prepared NaOMe (13.5 g, 0.25 mol) in MeOH (93 cm^3) were added compound **12** (4.59 g, 16.7 mmol) and Cu (0.30 g, 4.7 mmol). The reaction mixture was heated to reflux and stirred for 30 h. The precipitated material was filtered and washed thoroughly with hot water (150 cm^3). The filtrate was acidified with concentrated H_2SO_4 to pH = 2, then kept at 0–5 °C for 24 h. The yellowish, precipitated crude product was also filtered and dried, then it was recrystallized from EtOH to afford **13** (3.64 g, 82%) as a white solid. M.p. 185–189 °C (Lit. m.p. 173–174 °C [22]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 12.40 (s, 1H, COOH), 7.41 (s, 1H, 6-H_{Ar}), 6.13 (s, 2H, OCH_2O), 3.50 (s, 6H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.6 (COOH), 141.9 (3a-C_{Ar}), 141.0 (7-C_{Ar}), 140.1 (4-C_{Ar}), 140.0 (7a-C_{Ar}), 118.3 (5-C_{Ar}), 106.7 (6-CH_{Ar}), 102.1 (OCH_2O), 62.0 (4-OCH_3), 56.5 (7-OCH_3); IR (KBr) 2844, 1865, 1633, 1429, 1326, 1168, 1070, 857 cm^{-1}.

2.9 Preparation of 4,7-dimethoxybenzo[*d*][1,3]dioxole (14)

A solution of **13** (1.20 g, 5.31 mmol) in *N*,*N*-dimethylaniline (4 cm^3, DMA) was heated to reflux and stirred until the gas evolving (CO_2) ceased (5 h). Then, the reaction mixture was cooled to room temperature and a 10% aqueous NaOH solution (10 cm^3) was added. After its extracting with CH_2Cl_2 (10 cm^3) and evaporating the organic solvent, the crude product was distilled *in vacuo* to afford **14** (0.44 g, 46%) as a light brown oil, which was spontaneously solidified. B.p. 122–124 °C/0.3 Torr; m.p. 75–76 °C (Lit. m.p. 76.5–77.5 °C [23]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.85 (s, 2H, 5- and 6-H_{Ar}), 5.96 (s, 2H, OCH_2O), 3.81 (s, 6H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.1 (4- and 7-OCH_3), 130.6 (3a- and 7a-C_{Ar}), 110.3 (5- and 6-CH_{Ar}), 100.0 (OCH_2O), 57.1 (2 × OCH_3); IR (KBr) 3073, 2838, 1732, 1514, 1466, 1309, 1108, 1083, 953 cm^{-1}.

2.10 Preparation of apiolealdehyde (4,7-dimethoxybenzo[*d*][1,3]dioxole-5-carbaldehyde) (5)

To a mixture of $POCl_3$ (0.40 cm^3, 0.66 g, 4.28 mmol) and *N*-methylformanilide (0.40 cm^3, 0.44 g, 3.24 mmol, NMFA) was added compound **14** (0.45 g, 2.50 mmol). The reaction mixture was stirred at room temperature for 3 h, and it was left for standing overnight. Then, water (10 cm^3) was added to it, and it was extracted with Et_2O (3 × 10 cm^3). The combined organic phase was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After evaporating the

solvent, the crude product was purified by column chromatography (hexane–EtOAc, 2:1) to give **5** (0.29 g, 59%) as a white solid. M.p. 99–101 °C (Lit. m.p. 99–101 °C [24]); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.24 (s, 1H, CHO), 7.08 (s, 1H, 6-H_{Ar}), 6.10 (s, 2H, OCH_2O), 4.06 (s, 3H, 4-OCH_3), 3.89 (s, 3H, 7-OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 183.1 (CHO), 155.5 (3a-C_{Ar}), 147.7 (4-C_{Ar}), 147.4 (7-C_{Ar}), 147.2 (7a-C_{Ar}), 128.8 (5-C_{Ar}), 101.3 (6-CH_{Ar}), 98.0 (OCH_2O), 56.0 (4-OCH_3), 51.8 (7-OCH_3); IR (KBr) 2907, 2859, 1659, 1632, 1593, 1238, 1146, 1071, 639 cm^{-1}.

2.11 Preparation of 4',7'-dimethoxy-5'-(2-nitrovinyl)-benzo[*d*][1,3]dioxole (15)

To a solution of **5** (0.85 g, 4.04 mmol) in acetic acid (6 mL) containing NH_4OAc (0.74 g, 9.60 mmol) was added nitromethane (1.5 mL, 1.71 g, 28.0 mmol). The reaction mixture was heated to reflux and stirred for 2.5 h. Then it was cooled down to room temperature and ice-cold water (20 mL) was added. The mixture was kept at 0–5 °C for 30 min. The precipitated orange crystals were filtered and dried to afford **15** (0.84 g) in 82% yield. M.p. 157–159 °C (Lit. m.p. 166–167 °C [25]); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.04 (d, J = 13.5 Hz, 1H, CH=*CH*NO_2), 7.76 (d, J = 13.5 Hz, 1H, *CH*=$CHNO_2$), 6.64 (s, 1H, 6'-H_{Ar}), 6.08 (s, 2H, OCH_2O), 4.06 (s, 3H, 4'-OCH_3), 3.90 (s, 3H, 7'-OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.4 (3'a-C_{Ar}), 139.9 (7'-C_{Ar}), 139.8 (4'-C_{Ar}), 137.6 (*CH*=$CHNO_2$), 136.0 (7'a-C_{Ar}), 134.5 (CH=*CH*NO_2), 118.5 (5'-C_{Ar}), 106.8 (6'-CH_{Ar}), 102.1 (OCH_2O), 61.5 (4'-OCH_3), 56.5 (7'-OCH_3); IR (KBr) 3093, 1618, 1593, 1487, 1457, 1431, 1310, 1236, 1070, 967 cm^{-1}.

2.12 Preparation of (±)-4-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-5-nitropentan-2-one [(±)-16]

To a solution of **15** (0.84 g, 3.32 mmol) and L-proline (0.095 g, 0.83 mmol) in DMSO (30 mL) was added acetone (11.5 ml, 156 mmol, 9.09 g), and the reaction mixture was stirred at room temperature for 44 h. Then saturated NH_4Cl solution (36 mL) was added, and after a 5 min stirring water (14 mL) was also poured into the reaction mixture. It was then extracted with $CHCl_3$ (3 × 22 mL), and the combined organic phase was washed with water and brine, then dried over Na_2SO_4. After evaporating the solvent, the crude product was recrystallized from MeOH to give (±)-**16** (1.00 g, 97%) as a light brown solid. M.p. 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.29 (s, 1H, 6'-H_{Ar}), 5.97 (s, 2H, OCH_2O), 4.68 (d, 2H, J = 7.2 Hz, CH_2NO_2), 4.09 (p, J = 7.2 Hz, 1H, 4-CH), 3.98 (s, 3H, 7'-OCH_3), 3.85 (s, 3H, 4'-OCH_3), 2.92 (d, J = 6.6 Hz, 2H, CH_2CO), 2.14 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 206.6 (CO), 142.4 (3'a-C_{Ar}), 140.0 (7'-C_{Ar}), 139.6 (4'-C_{Ar}), 138.3 (7'a-C_{Ar}), 127.7 (5'-C_{Ar}), 106.5 (6-CH_{Ar}), 101.6 (OCH_2O), 76.7 (CH_2NO_2), 60.8 (4'-OCH_3), 56.5 (7'-OCH_3), 43.4 (*CH*$_2$CO), 34.7 (4-CH), 30.3 (CO*CH*$_3$); IR (KBr) 3435, 2912, 1711, 1509, 1368, 1142, 1070, 1003, 966, 858 cm^{-1}.

2.13 Preparation of (±)-3-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-5-hydroxy-4-nitrocyclohexan-1-one [(±)-17]

To a solution of freshly prepared NaOMe (0.80 g, 14.8 mmol) in abs. Et_2O (10 cm^3) were added freshly distilled ethyl formate (2.0 cm^3, 1.83 g, 24.8 mmol) and subsequently compound (±)-**16** (1.00 g, 3.21 mmol). The reaction mixture was stirred at room temperature for 20 h, then water (7 cm^3) was slowly added to it under cooling, and the phases were seperated. The organic one was extracted with water (3 × 5 cm^3), then the combined aqueous phase was acidified with acetic acid to pH = 4. The precipitated pale yellow solid was filtered, washed with water and dried to afford (±)-**17** (0.60 g) in 55% yield. M.p. 143–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 6.74 (s, 1H, 6'-H_{Ar}), 6.00 (s, 2H, OCH_2O), 4.70 (d, J = 7.8 Hz, 1H, $CHNO_2$), 4.38 (s, 1H, OH), 4.30 (m, 1H, *CH*OH), 4.11 (m, 1H, 3-CH), 3.86 (s, 3H, 7'-OCH_3), 3.78 (s, 3H, 4'-OCH_3), 2.56 (m, 2H, 2-CH_2), 2.44 (m, 2H, 6-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 207.6 (CO), 142.1 (3'a-C_{Ar}), 139.9 (7'-C_{Ar}), 138.9 (4'-C_{Ar}), 138.2 (7'a-C_{Ar}), 126.6 (5'-C_{Ar}), 106.2 (6'-CH_{Ar}), 101.6 (OCH_2O), 87.0 (CH_2NO_2), 69.7 (CHOH), 60.5 (4'-OCH_3), 56.4 (7'-OCH_3), 44.7 (6-CH_2), 44.6 (2-CH_2), 39.7 (3-CH); IR (KBr) 3354, 2360, 1716, 1551, 1507, 1456, 1353, 1138, 1070, 1051, 982 cm^{-1}.

2.14 Preparation of (±)-9-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-8-nitro-1,4-dioxaspiro[4.5]decan-7-ol [(±)-18]

To a solution of anhydrous oxalic acid (2.24 g, 24.9 mmol) in freshly distilled MeCN (37 cm^3) were added ethylene glycol (6.4 cm^3, 7.12 g, 115 mmol) and compound (±)-**17** (0.90 g, 2.65 mmol). The reaction mixture was stirred at room temperature for 110 h, then it was poured into a cooled saturated $NaHCO_3$ solution (113 cm^3), and pH was kept above 8. The precipitated light brown solid was collected by filtration, washed with saturated $NaHCO_3$ solution (15 cm^3) and water (2 × 15 cm^3), then dried to give (±)-**18** (0.78 g) in 77% yield. M.p. 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.30 (s, 1H, 6'-H_{Ar}), 6.02 (s, 2H, OCH_2O), 5.10–5.06 (m, 1H, $CHNO_2$), 4.88 (s, 1H, OH), 4.80–4.76 (m, 1H, *CH*OH), 4.20–4.16 (m, 1H, 9-CH), 4.04 (s, 3H, 7'-OCH_3),

4.02 (s, 3H, 4'-OCH_3), 3.96–3.91 (m, 4H, OCH_2CH_2O), 2.30–1.80 (m, 4H, 6-CH_2 and 10-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.3 (3'a-C_{Ar}), 140.7 (4'-C_{Ar}), 140.1 (7'-C_{Ar}), 138.3 (7'a-C_{Ar}), 128.8 (5'-C_{Ar}), 107.2 (6'-CH_{Ar}), 106.9 (5-C), 101.6 (OCH_2O), 88.1 (CH_2NO_2), 69.9 (CHOH), 64.2 (OCH_2CH_2O), 60.3 (4'-OCH_3), 56.3 (7'-OCH_3), 40.1 (6-CH_2), 38.7 (10-CH_2), 38.0 (9-CH); IR (KBr) 3462, 2942, 1551, 1435, 1190, 1064, 952 cm^{-1}.

2.15 Preparation of (±)-8-amino-9-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-1,4-dioxaspiro[4.5]decan-7-ol [(±)-19]

Over a 10% Pd/C catalyst (Selcat Q, 0.12 g) compound (±)-**18** (0.40 g, 1.04 mmol) was hydrogenated in MeOH (50 cm^3) in a 250 cm^3 stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 12 bar and 80 °C for 7 h. After the hydrogen uptake was finished, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to afford (±)-**19** (0.35 g, 95%) as a pale yellow solid. M.p. 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.31 (s, 1H, 6-H_{Ar}), 5.98 (s, 2H, OCH_2O), 4.58 (s, 1H, OH), 4.22–4.18 (m, 1H, 9-CH), 4.02 (s, 3H, 7'-OCH_3), 3.98 (s, 3H, 4'-OCH_3), 3.95–3.92 (m, 4H, OCH_2CH_2O), 3.80–3.76 (m, 1H, *CH*OH), 2.39 (br s, 2H, NH_2), 2.30–1.80 (m, 4H, 6-CH_2 and 10-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.7 (3'a-C_{Ar}), 140.3 (7'-C_{Ar}), 139.7 (4'-C_{Ar}), 138.4 (7'a-C_{Ar}), 128.9 (5'-C_{Ar}), 106.7 (5-C), 106.4 (6'-CH_{Ar}), 101.6 (OCH_2O), 70.3 (CHOH), 64.2 (OCH_2CH_2O), 60.5 (4'-OCH_3), 59.9 ($CHNH_2$), 56.3 (7'-OCH_3), 40.0 (6-CH_2), 38.9 (9-CH), 37.5 (10-CH_2); IR (KBr) 3445, 2936, 1506, 1455, 1431, 1137, 1062, 984 cm^{-1}.

2.16 Preparation of (±)-7-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-9-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl) carbamic acid methyl ester [(±)-20]

Half of the required methyl chloroformate (0.07 cm^3, 85.4 mg, 0.90 mmol), 3% aqueous NaOH solution (2 cm^3), and subsequently the other half of methyl chloroformate (0.07 cm^3, 85.4 mg, 0.90 mmol) were added to a solution of (±)-**19** (0.30 g, 0.85 mmol) in THF (7.4 cm^3). The reaction mixture was stirred rigorously at room temperature for 51 h, then it was poured into water (25 cm^3) and extracted with EtOAc (4 × 20 cm^3). The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to give (±)-**20** (0.30 g, 86%) as a light brown solid. M.p. 153–157 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48 (s, 1H, *NH*$COOCH_3$), 6.40 (s, 1H, 6'-H_{Ar}), 5.98 (s, 2H, OCH_2O), 4.33 (s, 1H, OH), 4.25 (td, J = 11.3 and 4.3 Hz, 1H, *CH*$NHCOOCH_3$), 4.09–4.05 (m, 1H, *CH*OH), 3.98 (s, 3H, 4'-OCH_3), 3.96 (s, 3H, 7'-OCH_3), 3.90–3.82 (m, 4H, OCH_2CH_2O), 3.51–3.47 (m, 1H, 7-CH), 2.20–2.00 (m, 4H, 6-CH_2 and 10-CH_2), 1.91 (s, 3H, NHCO*OCH$_3$*); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.9 (NH*CO*OCH_3) 142.7 (3'a-C_{Ar}), 140.1 (7'-C_{Ar}), 139.8 (4'-C_{Ar}), 138.4 (7'a-C_{Ar}), 130.5 (5'-C_{Ar}), 107.9 (5-C), 106.6 (6'-CH_{Ar}), 101.6 (OCH_2O), 70.2 (CHOH), 64.3 (OCH_2CH_2O), 60.5 (4'-OCH_3), 56.3 (7'-OCH_3), 56.2 (*CH*$NHCOOCH_3$), 38.8 (6-CH_2), 38.7 (9-CH), 36.7 (10-CH_2), 23.0 (NHCO*OCH$_3$*); IR (KBr) 3477, 3355, 2927, 1723, 1638, 1541, 1516, 1450, 1319, 1129, 1073, 914 cm^{-1}.

2.17 Preparation of (±)-6-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-4-oxocyclohex-2-en-1-yl)carbamic acid methyl ester [(±)-21]

A solution of (±)-**20** (0.30 g, 0.73 mmol) and *p*-TsOH (0.25 g, 1.31 mmol) in acetone (17 cm^3) was heated to reflux and stirred for 2.5 h. After cooling to room temperature, it was poured into saturated $NaHCO_3$ solution (34 cm^3) and extracted with $CHCl_3$ (4 × 20 cm^3). The combined organic phase was washed with water and brine, dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford (±)-**21** (0.26 g, 97%) as a light brown solid. M.p. 127–130 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.43 (s, 1H, *NH*$COOCH_3$), 7.32 (s, 1H, 6'-H_{Ar}), 7.00 (d, J = 9.8 Hz, 1H, CH=*CH*CO), 6.98 (d, J = 9.8 Hz, 1H, *CH*=CHCO), 6.96 (s, 2H, OCH_2O), 4.72–4.66 (m, 1H, *CH*$NHCOOCH_3$), 3.99 (s, 3H, 7'-OCH_3), 3.96 (s, 3H, 4'-OCH_3), 3.52–3.46 (m, 1H, 6-CH), 2.44–2.40 (m, 2H, 5-CH_2), 1.93 (s, 3H, HNCO*OCH$_3$*); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 197.4 (4-CO), 172.6 (NH*CO*OCH_3) 142.0 (3'a-C_{Ar}), 140.0 (7'-C_{Ar}), 139.3 (*CH*=CHCO), 138.3 (4'-C_{Ar}), 138.2 (7'a-C_{Ar}), 130.5 (5'-C_{Ar}), 129.7 (CH=*CH*CO), 106.4 (6'-CH_{Ar}), 101.6 (OCH_2O), 60.6 (4'-OCH_3), 56.4 (7'-OCH_3), 49.9 (*CH*$NHCOOCH_3$), 41.3 (5-CH_2), 39.6 (6-CH), 22.8 (NHCO*OCH$_3$*); IR (KBr) 3420, 2935, 1717, 1683, 1556, 1507, 1433, 1138, 1062, 953 cm^{-1}.

2.18 Preparation of (±)-6-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5-yl)-4-hydroxycyclohex-2-en-1-yl)carbamic acid methyl ester [(±)-22]

A solution of (±)-**21** (0.26 g, 0.71 mmol) and $CaCl_2$ (0.38 g, 3.42 mmol) in abs. MeOH (8 cm^3) was stirred at room temperature for 30 min. Then, $NaBH_4$ (0.14 g, 3.78 mmol) was added in one portion and the reaction mixture was further stirred at room temperature for 19 h. Thereafter, it

was poured into water (37 cm^3) and extracted with EtOAc (4 × 25 cm^3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude product was purified by preparative TLC ($CHCl_3$–acetone, 8:1) to give (±)-**22** (80 mg, 31%) as a brown solid. M.p. 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.42 (s, 1H, *NH*$COOCH_3$), 6.40 (s, 1H, 6'-H_{Ar}), 6.07–6.02 (m, 2H, CH=CH), 5.98 (s, 2H, OCH_2O), 4.99–4.95 (m, 1H, *CH*$NHCOOCH_3$), 4.45 (m, 1H, *CH*OH), 4.10 (s, 1H, OH), 3.96 (s, 3H, 7'-OCH_3), 3.94 (s, 3H, 4'-OCH_3), 3.14–3.10 (m, 1H, 6-CH), 2.30–2.10 (m, 2H, 5-CH_2), 1.93 (s, 3H, NHCO*OCH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.2 (NH*CO*OCH_3) 142.0 (3'a-C_{Ar}), 140.0 (7'-C_{Ar}), 138.5 (4'-C_{Ar}), 138.2 (7'a-C_{Ar}), 134.5 (CH=*CH*CO), 130.6 (5'-C_{Ar}), 127.2 (*CH*=CHCO), 105.1 (6'-CH_{Ar}), 101.6 (OCH_2O), 65.6 (CHOH), 60.6 (4'-OCH_3), 56.4 (7'-OCH_3), 50.0 (*CH*$NHCOOCH_3$), 37.4 (6-CH), 33.9 (5-CH_2), 22.8 (NHCO*OCH*$_3$); IR (KBr) 3344, 2952, 1685, 1538, 1506, 1455, 1433, 1140, 1060, 991, 803 cm^{-1}.

3 Results and discussion

3.1 Synthesis of apiolealdehyde (5)

At first, to achieve the selective monomethylation of a hydroxy group of compound **6**, it is necessary to block its two adjacent hydroxy ones. Although many reagents could be used for this purpose, such as phosgene [26], oxalyl chloride [27], diphenyldichloromethane [28, 29] or methylene iodide [30], their applications were not successful due to the low yield, the difficult removing the protective group or the very expensive reagent. However, using triethyl orthoformate [31], in the presence of a cation exchange resin (Amberlite® IR-120), in toluene resulted in methyl 2-ethoxy-7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate (**7**) in quantitative yield (Fig. 2). The forming ethanol was removed by azeotropic destillation (Dean–Stark apparatus) to make complete this equilibrium reaction.

Next, compound **7** can readily be methylated with methyl iodide, in the presence of K_2CO_3, in acetone to afford methyl 2-ethoxy-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (**8**)

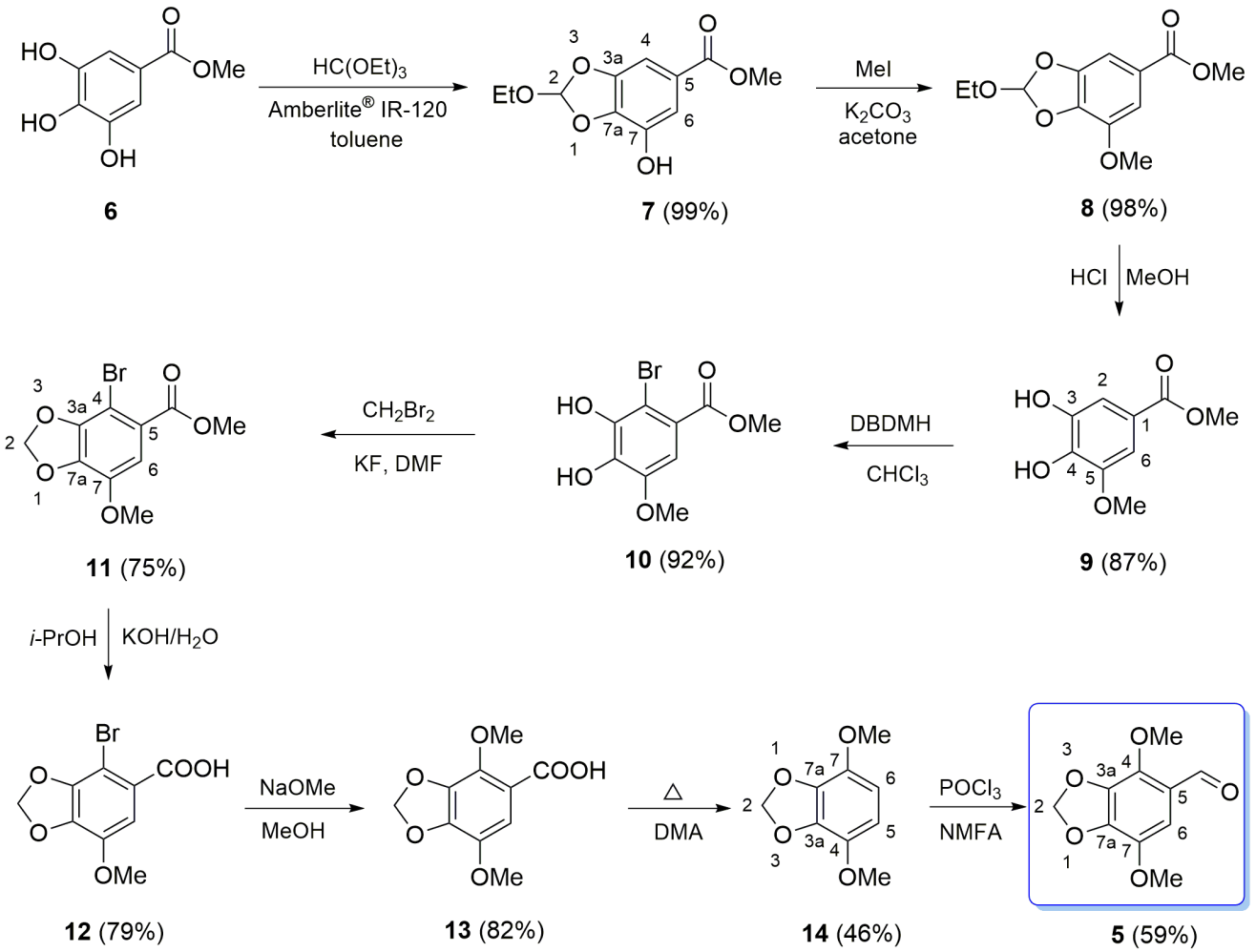

Fig. 2 A new synthesis of apiolealdehyde (**5**) starting from the readily available methyl gallate (**6**)

in excellent yield (98%). To remove the ethoxymethylene protecting group, compound **8** was easily hydrolised with methanolic hydrochloric acid to obtain methyl 3,4-dihydroxy-5-methoxybenzoate (**9**) in very good yield (87%) after recrystallization. A special brominating agent, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) [32], was used to achieve selectively the corresponding 2-bromo derivative (methyl 2-bromo-3,4-dihydroxy-5-methoxybenzoate, **10**) in very good yield (92%). Then, the benzodioxole ring was formed with dibromomethane in DMF, in the presence of KF to afford methyl 4-bromo-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (**11**) in good yield (75%).

After hydrolysing the methyl ester group of compound **11** using KOH in isopropyl alcohol and under reflux, the afforded bromo myristicin acid (4-bromo-7-methoxybenzo[*d*][1,3]dioxole-5-carboxylic acid, **12**) in 79% yield was reacted with NaOMe in methanolic solution by using Dallacker's method [22] to obtain apiolic acid (4,7-dimethoxybenzo[*d*][1,3]dioxole-5-carboxylic acid, **13**) in very good yield (82%). Then compound **13** was decarboxylated in *N,N*-dimethylaniline (DMA), under reflux applying Sato's modified method [33] to afford 4,7-dimethoxybenzo[*d*][1,3]dioxole (**14**) in moderate yield (46%) after vacuum distillation. Finally, the formylation of compound **14** was accomplished by using the Wilsmeyer–Haack reaction [$POCl_3$, *N*-methylformanilide (NMFA)] to obtain compound **5** in good yield (59%) after column chromatography.

3.2 Stereoselective synthesis of a cyclic allyl alcohol derivative containing two methoxy groups [(±)-22]

From this step, we have adapted our previously developed methods for the stereoselective total syntheses of some phenanthridone alkaloids and their analogues [12–15]. At first, as shown in Fig. 3, apiolealdehyde (**5**) was reacted with nitromethane in acetic acid, in the presence of NH_4OAc to give 4,7-dimethoxy-5-(2-nitrovinyl)benzo[*d*][1,3]dioxole (**15**) in good yield (82%).

The first asymmetric centre of the title molecule was formed by Michael addition of acetone to compound **15** in DMSO, in the presence of L-proline to afford racemic (±)-4-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-5-nitropentan-2-one [(±)-**16**] in excellent yield (97%). Although the pure enantiomer of this organocatalyst was applied, no enantioselectivity was observed in this reaction. In the next step, the ring C was formed by the Claisen–Henry reaction using ethyl formate and dry NaOMe in anhydrous diethyl ether to afford (±)-3-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-5-hydroxy-4-nitrocyclohexan-1-one [(±)-**17**] in a moderate yield (55%). Complete stereoselectivity was achieved in this cyclisation step which can be explained by the H-bond formation between the C-5 hydroxy and C-4 nitro groups, as observed by us previously [12–15].

Prior to the conversion of the nitro group into the amino one by catalytic hydrogenation, the carbonyl group of (±)-**17** was protected with ethylene glycol, in the presence of $(COOH)_2$, in anhydrous MeCN to afford (±)-9-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-8-nitro-1,4-dioxaspiro[4.5]decan-7-ol [(±)-**18**] in good yield (77%). Compound (±)-**18** was reduced to the corresponding amino derivative, such as (±)-8-amino-9-(4',7'-dimethoxybenzo[*d*][1,3]dio-xol-5'-yl)-1,4-dioxaspiro[4.5]decan-7-ol [(±)-**19**] in excel-lent yield (95%) over a 10% Pd/C catalyst (Selcat Q [34]), in methanol, at 80 °C and 12 bar. Subsequently, the *N*-acylation of compound (±)-**19** by an activated ester [35] was carried out with methyl chloroformate in a biphasic solvent mixture (water and THF) to obtain (±)-7-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-9-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)carbamic acid methyl ester [(±)-**20**] in very good yield (86%). The ketal protective group of (±)-**20** was removed in acetone containing a catalytic amount of *p*-TsOH under reflux, but water elimination also took place to afford (±)-6-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5'-yl)-4-oxocyclohex-2-en-1-yl)carbamic acid methyl ester [(±)-**21**] in excellent yield (97%). Then, the oxo group of was stereoselectively reduced with $NaBH_4$, in the presence of $CaCl_2$ in abs. methanol (Utimoto's method [36]) to obtain (±)-6-(4',7'-dimethoxybenzo[*d*][1,3]dioxol-5-yl)-4-hydroxycyclohex-2-en-1-yl)carbamic acid methyl ester [(±)-**22**] in moderate yield (31%) after preparative TLC. The stereoselectivity was presumably due to an axial attack of the small hydride ion derived from $NaBH_4$ enhanced by the coordination with Ca^{2+}, resulting in an equatorial position of the newly formed hydroxy group.

This cyclic allyl alcohol derivative containing two methoxy groups [(±)-**22**] is a pivotal intermediate of our total synthesis to obtain a novel (±)-*trans*-dihydronarciclasine analogue [(±)-**23**] containing an additional methoxy group at position 11, in the ring A of the phenanthridone scaffold.

4 Conclusion

In summary, a pivotal intermediate [(±)-**22**] using for the synthesis of a new (±)-*trans*-dihydronarciclasine alkaloid analogue [(±)-**23**] was efficiently prepared from methyl gallate (**6**), an inexpensive and readily available starting material, in 17 steps with 0.9% overall yield applying a newly developed synthetic route.

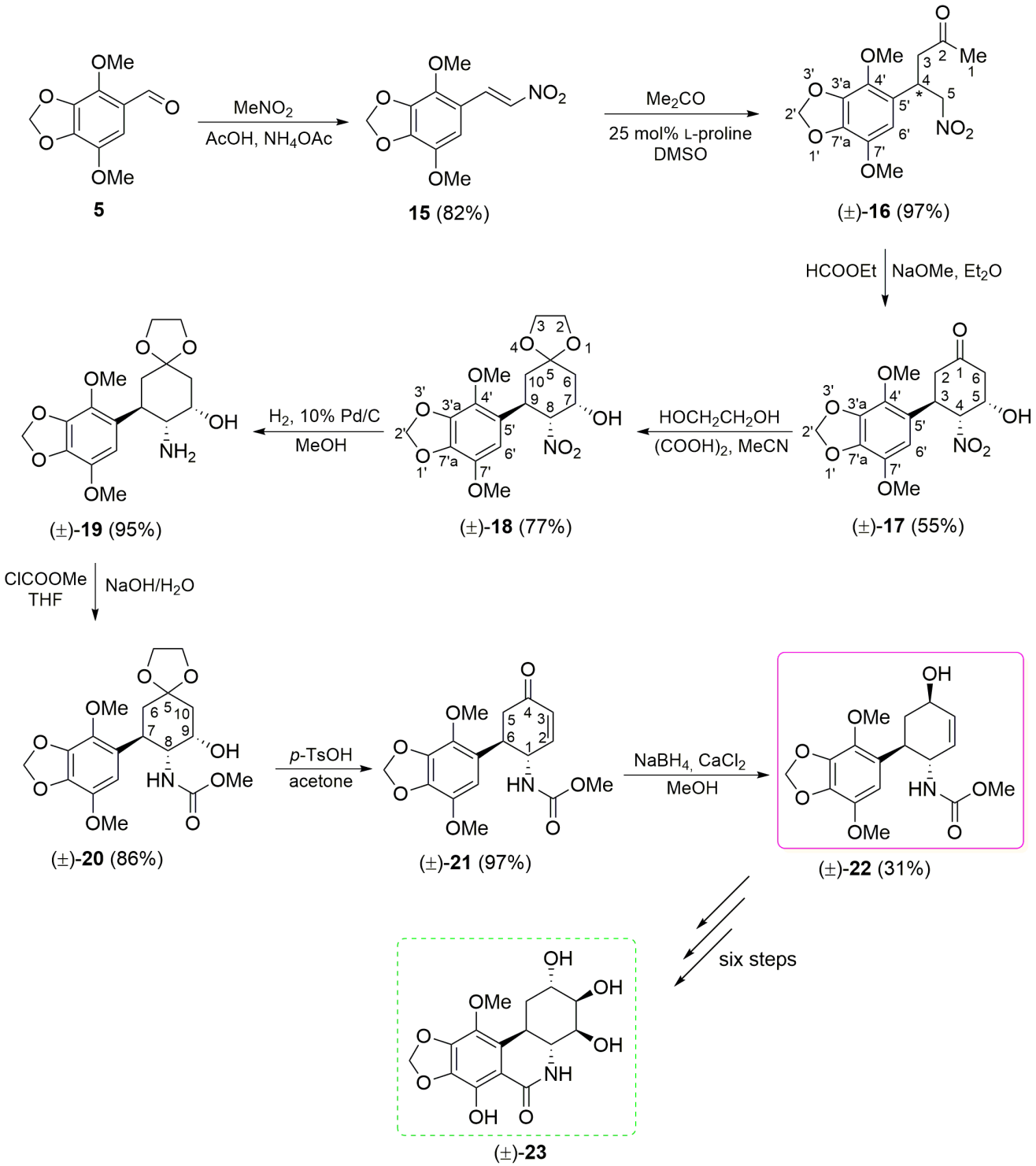

Fig. 3 Stereoselective synthetic route of a novel (±)-*trans*-dihydronarciclasine analogue [(±)-**23**] containing an additional methoxy group in the ring A of the phenanthridone scaffold

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