

A new route to optically pure highly functionalized tetrahydro-isoquinolines with a quaternary carbon stereocenter

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Abstract

A facile synthesis of highly substituted, optically pure tetrahydro-isoquinolines with a quaternary carbon stereocenter is described. Glycolic cleavage of 1,2-dihydroxy-hexahydro-pyrrolo-isoquinolines **1** affords a mixture of cyclic hemiacetals, which can be converted via intramolecular chemoselective Cannizzaro reaction into respective β -amino alcohols, whereas the IBX oxidation gives *N*-formyl aldehydes. We have demonstrated the utility of such synthons by the synthesis of (+)-6,7-dimethoxy-salsoline-1-carboxylic acid and its new 1-phenyl analogue. © 2008 Elsevier Ltd. All rights reserved.

Keywords: Stereoselective synthesis; Isoquinoline alkaloids; Cannizzaro reaction

1. Introduction

A number of isoquinoline alkaloids with a significant bioactivity possess a stereocenter located at the quaternary carbon atom, in the α -nitrogen position.¹ The Erythrina family,² e.g., erysotramidine or erythramine, contains a pyrrolo-isoquinoline skeleton, while the tetrahydro-isoquinoline motif is present in a variety of natural products, including cactus alkaloids³ (pevoruvic acid), mammalian alkaloids⁴ (salsoline carboxylic acid), Ecteinascidine family⁵ (ET743) and spirobenzo-quinoline alkaloids⁶ (parfumine, Fig. 1).

The stereoselective synthesis of isoquinoline alkaloids with a quaternary carbon stereocenter is not trivial, and generally utilizes a chiral starting material or auxiliaries. Despite the existence of modern catalytic methods for the asymmetric construction of molecules with quaternary carbon stereocenters⁷ the old-fashioned approach presented here should still be attractive, particularly when the chiral starting material is inexpensive, both enantiomers are easily available, and the synthesis is short and efficient.

In the course of our investigations on the synthesis of natural products, we have elaborated a simple stereocontrolled method for the preparation of C10b-substituted hexahydro-pyrrolo-isoquinolines **1** from L-tartaric acid.⁸ We realized that such compounds, containing the dihydroxy-pyrrolidinone moiety, can be easily modified to provide optically pure highly substituted tetrahydro-isoquinolines, suitable for the synthesis of natural and customized isoquinoline alkaloids.

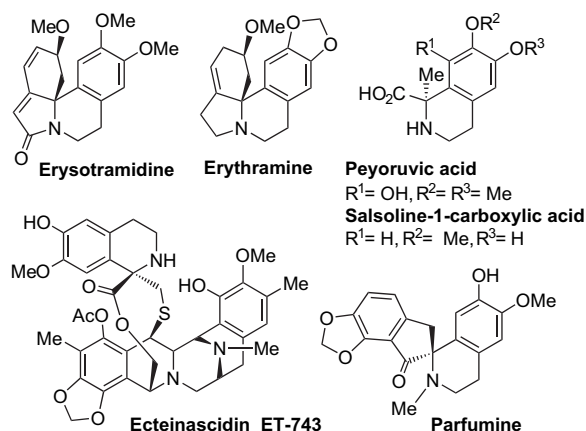


Figure 1.

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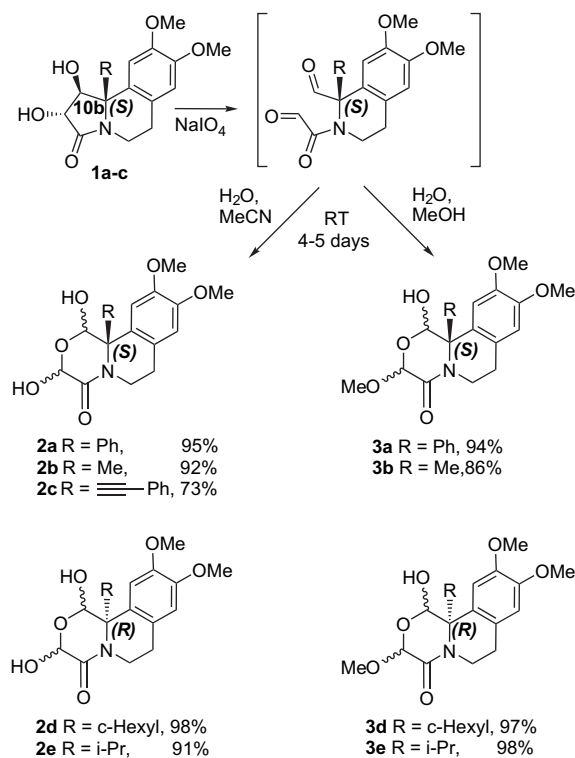
Herein, we describe new procedures for the conversion of 1,2-dihydroxy-hexahydro-pyrrolo-isoquinolines (**1**) into the following tetrahydro-isoquinoline derivatives: optically pure β -amino alcohols (**4**), *N*-formyl aldehydes (**5**) and β -amino acids (**7**).

2. Results and discussion

Imides derived from tartaric acid have been widely utilized in the asymmetric synthesis of natural products, employing various chemical transformations.⁹ However, the *trans*-diol within a pyrrolidinone ring has never been cleaved, as far as we know.

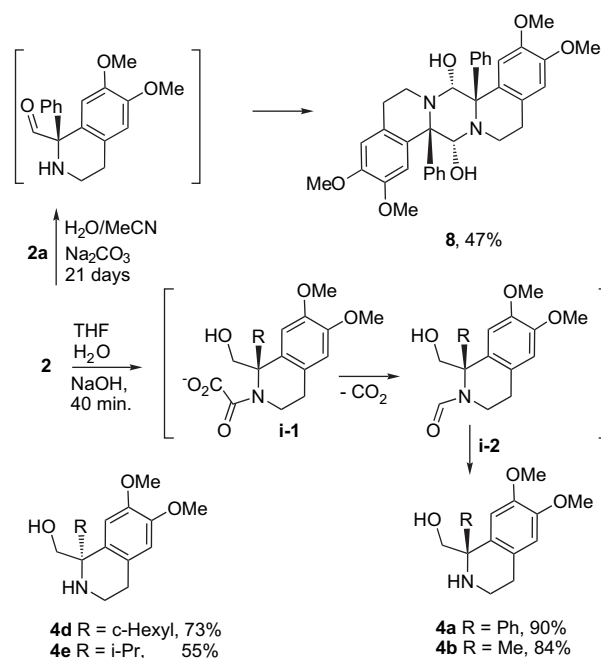
The C10b-(*S*)-1,2-dihydroxy-pyrrolo-isoquinolines **1a–c** were subjected to glycolic cleavage with sodium periodate in water–acetonitrile solution to furnish the diastereomeric mixture of cyclic hemiacetals **2a–c**, products of addition of water to the unstable dialdehyde (Scheme 1). Due to the steric hindrance, oxidation of the *trans*-diol with an adjacent tetra-substituted carbon atom was very slow (4–5 days) and required 4 equiv of sodium periodate for completion. Under the same conditions the glycolic cleavage of respective C10b-(*R*) epimers **1d–e**, gave hemiacetals **2d–e** in a high yield. The use of a water–methanol mixture resulted in the formation of the cyclic product of the addition of methanol to the aldehyde (i.e., compounds **3a–e**), in excellent yield.

Hydrolysis of the nitrogen substituent in the products of glycolic cleavage **2a–e** should lead to the optically pure amino aldehydes. In the presence of sodium carbonate in a water–acetonitrile solution at room temperature a very slow



Scheme 1. Glycolic cleavage of 1,2-dihydroxy-hexahydro-pyrrolo-isoquinolines **1a–e**.

hydrolysis of **2a** proceeded to give after 3 weeks the amino aldehyde as a crystalline dimer **8** (Scheme 2). The configuration at the hemiaminal carbon in dimer **8** was not established. Its NMR spectra indicated however the C_2 symmetry of the dimer **8**. An increase of the reaction temperature (up to 60–80 °C) resulted in a rapid substrate decomposition and the formation of tar-like products. The exposure of **2a** to a stronger base, sodium hydroxide, in water–tetrahydrofuran solution induced a very fast reaction yielding β -amino alcohol **4a** in a 90% yield. It appears that under the above conditions, the masked dialdehyde **2a** undergoes an intramolecular, highly chemo-selective Canizzaro reaction to give the intermediary ketocarboxylate **i-1**. The subsequent decarboxylation of **i-1**, followed by the hydrolysis of the *N*-formyl derivative **i-2** furnishes the final β -amino alcohol **4a**. Besides the well-documented examples of intramolecular Canizzaro reactions of α -ketoaldehydes,¹⁰ there are only a few reports concerning the accidental observation of this type of reaction.¹¹



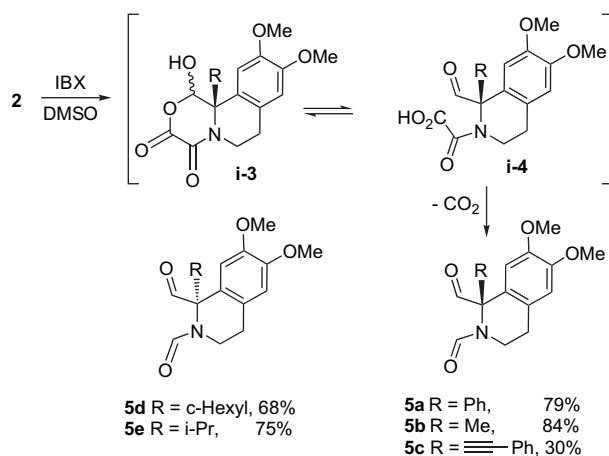
Scheme 2. Hydrolysis of nitrogen substituent in **2** leading to formation of β -amino alcohols via intramolecular Canizzaro reaction.

In order to study the scope of this methodology, several analogous optically pure 1-hydroxymethyl-tetrahydro-isoquinolines **4b–d** were obtained in a satisfactory yield.

Czarnocki et al.^{4c} described the preparation of the amino alcohol **4b** from (*L*)-tartaric acid, using an approach different to ours, and successfully utilized compound **4b** in the synthesis of (+)-6,7-dimethoxy-salsoline-1-carboxylic acid.

Aiming at the synthesis of 1-methyl-tetrahydro-isoquinoline-1-carboxylic acids of important bioactivity (Fig. 1) as well as their C1 substituted unnatural analogues, we focused our attention on masked dialdehydes **2**. We hoped that their oxidation followed by the hydrolysis of the nitrogen substituent would lead to amino acids suitable for further transformations.

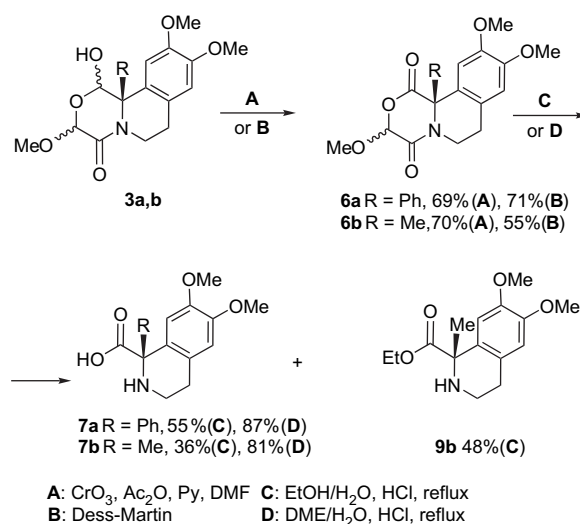
To verify our hypothesis, the model compound **2a** was subjected to the oxidation using common reagents such as PCC, potassium permanganate, sodium chlorite or Jones' reagent. In all cases, the formation of a complex mixture of products was observed. However, the oxidation of **2a** with 2-iodoxy benzoic acid (IBX)¹² gave a well-defined compound: *N*-formyl aldehyde **5a** in a 79% yield (Scheme 3). The plausible reaction pathway consists of IBX oxidation of the hemiacetal hydroxy group at α -position to the amide followed the decarboxylation of the resulting intermediate **i-3** via its open chain tautomer **i-4**. The isolation of *N*-formyl aldehyde strongly supports the proposed reaction mechanism for the preparation of β -amino alcohols **4a–e** (Scheme 2). Using this methodology we have prepared several additional aldehydes (**5b–e**) in good yield. Interestingly, the respective phenylethynyl derivative **5c** was obtained in 30% yield only. The analysis of the ¹H and ¹³C NMR spectroscopic data indicates that all *N*-formyl aldehydes **5a–e** exist as a $\sim$ 1:5–7 inseparable mixture of rotamers.



Scheme 3. Oxidation of **2** leading to *N*-formyl aldehydes.

The oxidation of model aldehyde **5a** with the above reagents in each case resulted in the formation of mixtures of products containing only a trace of an expected amino acid or its methyl ester, detected in the crude reaction mixtures by NMR and MS analysis.

In continuation of our research we switched to other substrates (compounds **3a** and **3b**) possessing only one free hydroxyl group. We were very pleased to see that the oxidation of hemiacetals **3a** and **3b** using Corey's procedure with chromium(VI) reagent¹³ gave **6a** and **6b** in 69% and 70% yield, respectively (Scheme 4). IBX was not an effective oxidant of **3a** and **3b**, however, the more reactive Dess–Martin periodinane¹⁴ furnished **6a** and **6b** in a good yield. Finally, having protected amino acids **6a** and **6b** in hand, we proceeded with their hydrolysis. The solution of **6a** in a mixture of ethanol–water–HCl_{aq} was refluxed for 7 h (procedure C) to give amino acid **7a** in 55% yield. The procedure C, applied to **6b** resulted in the formation of **7b**^{4c} and its corresponding ethyl ester **9b**, isolated in 36% and 48% yield, respectively. The hydrolysis of **6a** and **6b** performed in 1,2-dimethoxy-ethane–water–HCl_{aq} mixture (procedure D) was much faster and after 3 h of



Scheme 4. Synthesis of (+)-6,7-dimethoxy-salsoline-1-carboxylic acid **7b** and its 1-phenyl analogue **7a**.

heating at reflux gave **7a** and **7b** in 87% and 81% yield, respectively.

3. Concluding remarks

In summary, we have elaborated a new synthesis of highly substituted, optically pure tetrahydro-isoquinolines, new synthons for the preparation of isoquinoline alkaloids. Glycolic cleavage of 1,2-dihydroxy-hexahydro-pyrrolo-isoquinolines affords a mixture of cyclic hemiacetals, which can be converted via intramolecular chemoselective Cannizzaro reaction into the corresponding β -amino alcohols, whereas the IBX oxidation of the same mixtures gives *N*-formyl aldehydes. We have also demonstrated the utility of such synthons by the synthesis of (+)-6,7-dimethoxy-salsoline-1-carboxylic acid **7b** and its new 1-phenyl analogue **7a**.

We believe that the presented methodology can be applied in the diversity-oriented synthesis of new bioactive heterocycles.

4. Experimental

4.1. General

Optical rotations were measured at 23 °C with a JASCO Dip-360 digital polarimeter. IR spectra were obtained using an FT-IR-1600 Perkin–Elmer FTIR spectrophotometer and reported in reciprocal centimetres (cm^{−1}). ¹H NMR spectra were recorded in CDCl₃ (except where indicated otherwise) using a Bruker AM 500 spectrometer. Chemical shifts are quoted in δ parts per million relative to TMS for ¹H and CDCl₃ for ¹³C NMR. Coupling constants *J* are reported in hertz. Mass spectra were recorded using an AMD 640 or a Mariner mass spectrometer. Kugelrohr distillation was performed using Buchi glass oven B585. HPLC analyses were performed with a Shimadzu LC-8A chromatograph with

Hibar® 250-4 LiChrosob® Si 60 (5 µm). Thin-layer chromatography was carried out on precoated silica gel (Merck Kieselgel 60 F₂₅₄, 0.2 mm layer thickness). Visualization of the developed chromatogram was performed by UV absorbance and cerium molybdate water solution. Flash column chromatography was performed using Merck Kieselgel (230–400 mesh). All air and moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware using anhydrous solvents. Most reagents were obtained from commercial suppliers and were used without further purification, unless noted. THF was distilled from Na and benzophenone, dichloromethane and toluene were distilled from CaH₂.

4.2. General procedure for the preparation of 4a-substituted 2,4-dihydroxy-6,7-dimethoxy-4,4a,9,10-tetrahydro-3-oxa-10a-aza-phenanthren-1-ones (2a–e)

1,2-Dihydroxy-hexahydro-pyrrolo-isoquinolines **1a**, **b**, **d** were obtained from corresponding optically pure diacetates by alkaline hydrolysis and used in the next step without further purification.⁸ Compounds **1c** and **1e** were obtained from the corresponding optically pure 2-*tert*-butyldimethylsilyloxy derivatives⁸ by deprotection of the 2-hydroxy group. Typical deprotection procedure: 2-*tert*-butyldimethylsilyloxy-pyrrolo-isoquinoline (5 mmol) was dissolved in THF (5 mL), treated with HF–pyridine (70% HF–Py, 1 mL) and stirred at room temperature for 24 h. Reaction was quenched with careful addition of satd solution of Na₂CO₃ until pH 9, diluted with water (20 mL) and extracted with methylene chloride (3×30 mL). Collected extracts were dried (MgSO₄) and evaporated in vacuo. Obtained residue was filtrated through a pad of silica gel using ethyl acetate as an eluent to give 1,2-dihydroxy-pyrrolo-isoquinoline in >95% yield, which was used in the next step without further purification.

Into a solution of **1** (10 mmol) in acetonitrile (50 mL), sodium (meta)periodate (40 mmol) dissolved in water (100 mL) was added in one portion. Reaction was stirred intensively at room temperature for 4–5 days, until all substrate was consumed (TLC control). Then, the solution was concentrated in vacuo to ~50% of initial volume and extracted with ethyl acetate (3×100 mL). Collected extracts were dried (MgSO₄) and evaporated in vacuo to give **2** as a mixture of diastereomers.

4.2.1. Compound 2a

Yield: 3.533 g, 95%; yellowish solid; IR (CH₂Cl₂): 3545, 3313, 2939, 1641 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₂₀H₂₁NO₆Na: 394.1261. Found: 394.1280. Selected spectral data taken from the crude reaction mixture of four diastereomers in the ratio of ~1:1.5:3.5:5. ¹H NMR: 5.14, 5.37, 5.41, 5.59, 5.63, 5.76, 5.87 and 5.94 (8s, H-C2, H-C4), 6.59, 6.62, 6.56, 6.81, 6.98, 7.18, 7.64 (7s, missing one proton due to overlap, H-C5, H-C8). ¹³C NMR (selected data of two predominated isomers): 27.2, 27.3 (C9), 39.6, 40.4 (C10), 67.3, 67.9 (C4a), 87.6, 89.5, 91.1, 94.5 (C2, C4), 166.2, 167.8 (C1).

4.2.2. Compound 2b

Yield: 2.84 g, 92%; white solid; IR (KBr): 3487, 3248, 2933, 1642 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₁₅H₁₉NO₆Na: 332.1104. Found: 332.1110. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio of ~1:1.4:2.4, fourth is hardly detected by NMR techniques. ¹H NMR (DMSO-*d*₆): 1.52, 1.56 and 1.68 (3s, *Me*-C4a), 3.68, 3.69, 3.72, 3.73 and 3.745 (5s, missing one proton due to overlap, *Me*OAr), 5.75, 6.68, 6.70, 6.68, 6.85 and 7.33 (6s, *H*-C5, *H*-C8). ¹³C NMR (DMSO-*d*₆): 60.7, 61.3, 61.6 (C4a), 86.9, 87.8, 89.1, 90.4, 93.9, 94.6 (C2, C4), 126.8, 127.0, 127.3, 129.6, 123.0, 130.1 (C4b, C8a), 146.7, 147.1, 147.1, 147.6, 147.5, 147.6 (C6, C7), 164.3, 164.9, 165.5 (C1).

4.2.3. Compound 2c

Yield: 2.890 g, 73%; white solid; IR (CH₂Cl₂): 3332, 2939, 2227, 1669 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₂₂H₂₁NO₆Na: 418.1261. Found: 418.1247. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio of ~1:3.1(B):5.5(A), fourth is hardly detected by NMR techniques. *Diastereomer A*: ¹H NMR (selected data): 3.87, 3.88 (2s, 6H, *Me*OAr), 5.55, 5.67 (2s, 2H, *H*-C2, *H*-C4), 6.63, 6.94 (2s, 2H, *H*-C5, *H*-C8). ¹³C NMR (selected data): 28.0, 37.2, 55.9, 56.1, 60.9, 87.8, 95.2, 109.0, 111.5, 148.4, 148.8, 166.5. *Diastereomer B*: ¹H NMR (selected data): 3.86, 3.89 (2s, 6H, *Me*OAr), 5.34, 5.62 (2s, 2H, *H*-C2, *H*-C4), 6.59, 7.53 (2s, 2H, *H*-C5, *H*-C8). ¹³C NMR (selected data): 28.4, 37.9, 55.9, 56.2, 61.7, 85.4, 87.4, 91.66, 111.1, 111.2, 147.7, 148.9, 165.2.

4.2.4. Compound 2d

Yield: 3.70 g, 98%; white solid, IR (CH₂Cl₂): 3318, 2936, 1732, 1653 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₂₀H₂₇NO₆Na: 400.1730. Found: 400.1725. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio of ~1:1.3:3.6, fourth is hardly detected by NMR techniques. *Major diastereomer*: ¹H NMR: 3.85, 3.86 (2s, 6H, *Me*OAr), 5.29, 5.69 (2s, 2H, *H*-C2, *H*-C4), 6.59, 6.63 (2s, 2H, *H*-C5, *H*-C8). ¹³C NMR: 26.2, 26.8, 27.4, 27.8, 28.3, 30.2, 39.0, 48.8, 55.8, 56.4, 67.6, 87.7, 94.0, 109.2, 111.6, 127.2, 127.8, 147.6, 147.9, 167.9.

4.2.5. Compound 2e

Yield: 3.072 g, 91%; yellowish solid; IR (KBr): 3385, 2964, 1732, 1640 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₁₇H₂₃NO₆Na: 360.1417. Found: 360.1412. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio of ~1:1.7:5, fourth is hardly detected by NMR techniques. *Major diastereomer*: ¹H NMR: 0.96, 1.09 (2d, 6H, *J*=7.0 Hz, *i*-Pr), 5.28, 5.65 (2s, 2H, *H*-C2, *H*-C4), 6.61, 6.65 (2s, 2H, *H*-C5, *H*-C8). ¹³C NMR: 18.3, 21.0, 27.9, 38.2, 38.7, 55.8, 56.3, 67.5, 87.7, 94.5, 108.8, 111.6, 127.0, 127.9, 147.8, 148.0, 167.9.

4.3. General procedure for the preparation of 4a-substituted 4-hydroxy-2,6,7-trimethoxy-4,4a,9,10-tetrahydro-3-oxa-10a-aza-phenanthren-1-ones (**3a–e**)

The same reaction condition as described for preparation **2a–e**, except solvent: methanol was used instead of acetonitrile.

4.3.1. Compound **3a**

Yield: 3.621 g, 94%; yellowish solid; IR (CH₂Cl₂): 3533, 3316, 2962, 1663 cm⁻¹. MS (EI, HR) *m/z*: (M⁺) calcd for C₂₁H₂₃NO₆: 385.1525. Found: 385.1535. Selected spectral data taken from the crude reaction mixture of four diastereomers in the ratio of ~1:1.2:2.6:2.9. ¹H NMR: 3.56, 3.59, 3.60, 3.69 (4s, MeO-C2), 5.00, 5.11, 5.13, 5.20, 5.59, 5.73, 5.83, 5.87 (8s, H-C2, H-C4). ¹³C NMR (major isomer) 27.2 (C9), 39.4 (C10), 55.9, 56.2 (MeO-Ar), 67.4 (C4a), 90.7, 96.8 (C4, C2), 110.8 (C5, C8), 147.3, 148.8 (C6, C7), 163.4 (C1).

4.3.2. Compound **3b**

Yield: 2.78 g, 86%; white solid; IR (CH₂Cl₂): 3578, 3318, 2939, 1662 cm⁻¹. MS (EI, HR) *m/z*: (M⁺) calcd for C₁₆H₂₁NO₆: 323.1369. Found: 323.1364. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio of ~1:1.8:1.9, fourth is hardly detected by NMR techniques. ¹H NMR: 3.52, 3.56, 3.59 (3s, MeO-C2), 4.93, 4.96, 5.13, 5.20, 5.41, 5.42 (6s, H-C2, HC4), 6.55, 6.56, 6.57, 6.61, 7.33 (5s, missing one proton due to overlap, H-C5, H-C8). ¹³C NMR: 20.4, 26.5, 26.6, 28.4, 28.6, 29.3, 35.5, 37.7, 36.1 (Me-C4a, C9, C10), 61.0, 62.0, 62.1 (C4a), 91.6, 94.6, 94.8, 95.9, 96.1, 96.4 (C2, C4), 162.9, 163.0, 162.4 (C1).

4.3.3. Compound **3d**

Yield: 3.80 g, 97%; white solid; IR (CH₂Cl₂): 3685, 3578, 2935, 1658 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₂₁H₂₉NO₆Na: 414.1887. Found: 414.1889. Selected spectral data taken from the crude reaction mixture of four diastereomers in the ratio ~1:1.7:5.5(B):6.1(A). Diastereomers A+B. ¹H NMR: 3.477, 3.60 (2s, MeO-C2), 5.11, 5.18, 5.59, 5.63 (4s, H-C2, H-C4), 6.65, 6.62, 6.66, 7.30 (4s, H-C5, H-C8). ¹³C NMR: 66.2, 67.0 (C4a), 93.2, 94.6, 94.8, 95.9 (C2, C4), 164.4, 164.8 (C1).

4.3.4. Compound **3e**

Yield: 3.438 g, 98%; yellowish solid; IR (KBr): 3420, 2963, 1643 cm⁻¹. MS (ES, HR) *m/z*: (M+Na⁺) calcd for C₁₈H₂₅NO₆Na: 374.1574. Found: 374.1591. Selected spectral data taken from the crude reaction mixture of four diastereomers. Three diastereomers are in the ratio ~1:1.3:1.7, fourth is hardly detected by NMR techniques. ¹H NMR: 3.48, 3.58, 3.84 (3s, 9H, MeO-C2), 4.92, 4.92, 5.10, 5.16, 5.52, 5.61 (6s, 6H, H-C2, H-C4), 6.57, 6.63, 6.63, 6.67, 7.31 (s, 6H, H-C5, H-C8, missing one proton due to overlap). ¹³C NMR: 18.3, 18.8, 19.0, 20.9, 21.0, 22.1, 27.9, 28.1, 29.1, 31.8, 37.7, 37.9, 38.2, 38.5, 38.6, 55.7, 55.7, 56.0, 56.2, 56.3,

56.4, 57.1, 57.6, 66.1, 66.9, 67.0, 92.9, 94.6, 94.9, 95.0, 95.1, 95.8, 108.7, 108.9, 111.1, 111.5, 111.6, 111.7, 126.5, 127.2, 127.8, 127.9, 128.0, 128.3, 147.1, 147.2, 147.8, 147.9, 148.0, 148.1, 164.5, 164.6, 164.8 (missing one carbon due to overlap).

4.4. General procedure for the preparation of amino alcohols **4a, b, d** and **e**

Into a solution of **2** (4 mmol) in tetrahydrofuran (20 mL), sodium hydroxide (24 mmol, 0.96 g) dissolved in water (20 mL) was added in one portion. Reaction was stirred intensively at room temperature for ~0.5 h. Then, the solution was diluted with water (50 mL) and extracted with methylene chloride (3×50 mL). Collected extracts were dried (MgSO₄) and evaporated in vacuo. Crude **4** was crystallized or purified on silica gel using mixture of CH₂Cl₂–MeOH–NH₃ (aq)=95–94:4–5:0.5–0.1 as an eluent.

4.4.1. (1S) (6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-methanol (**4a**)

Yield: 1.08 g, 90%; foam; [α]_D²³ –28.5 (c 5.0, CH₂Cl₂); IR (film, CH₂Cl₂): 3319, 2934, 1609 cm⁻¹. MS (ES, HR) *m/z*: (M+H⁺) calcd for C₁₈H₂₂NO₃: 300.1594. Found: 300.1613. ¹H NMR: 2.00 (br s, 2H, exchangeable with D₂O), 2.72 (m, 1H), 2.82 (m, 1H), 2.99 (m, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 3.95 (d, 1H, J=11.0 Hz), 4.13 (d, 1H, J=11.0 Hz), 6.44 (s, 1H), 6.64 (s, 1H), 7.28 (m, 5H). ¹³C NMR: 29.6, 38.9, 55.8, 56.0, 63.2, 67.5, 110.5, 111.9, 127.2, 127.8, 128.3, 128.9, 130.0, 145.7, 147.4, 147.9.

4.4.2. (1S) (6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-methanol (**4b**)

Yield: 0.797 g, 84%; colourless crystals; mp 147–149 °C (acetone); Lit.^{4c} yellowish oil; [α]_D²³ –18.9 (c 3.0, CHCl₃); Lit.^{4c} [α]_D²³ –9.2 (c 3.09, CHCl₃); IR (CH₂Cl₂): 3340, 2960, 1610 cm⁻¹. MS (ES, HR) *m/z*: (M+H⁺) calcd for C₁₃H₂₀NO₃: 238.1437. Found: 238.1428. Anal. Calcd for C₁₃H₁₉NO₃: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.85; H, 8.05; N, 5.99. ¹H NMR: 1.42 (s, 3H), 2.58 (br s, 2H, exchangeable with D₂O), 2.71 (m, 2H), 3.03 (m, 1H), 3.10 (m, 1H), 3.48 (d, 1H, J=10.7 Hz), 3.69 (d, 1H, J=10.7 Hz), 3.84 and 3.85 (two s, 6H), 6.57 and 6.61 (two s, 2H). ¹³C NMR: 26.1, 29.8, 38.7, 55.8, 56.1, 56.6, 68.1, 108.8, 111.9, 127.6, 131.6, 141.6, 147.7.

4.4.3. (1R) (1-Cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl)-methanol (**4d**)

Yield: 0.892 g, 73%; foam; [α]_D²³ +30.8 (c 0.48, CH₂Cl₂); IR (CH₂Cl₂): 3364, 2933, 1610 cm⁻¹. MS (ES, HR) *m/z*: (M+H⁺) calcd for C₁₈H₂₈NO₃: 306.2063. Found: 306.2058. ¹H NMR: 1.00–1.30 (m, 5H), 1.45 (m, 1H), 1.60–1.80 (m, 4H), 1.92 (m, 1H), 2.58 (m, 1H), 2.68 (m, 1H), 2.90 (m, 1H), 3.17 (m, 1H), 3.58 (d, 1H, J=10.5 Hz), 3.74 (d, 1H, J=10.5 Hz), 3.85 and 3.86 (two s, 6H), 6.56 (s, 1H), 6.61 (s, 1H). ¹³C NMR: 26.5, 26.9, 27.0, 27.5, 28.2, 30.3, 39.9, 47.6, 55.7, 56.2, 61.4, 66.6, 108.6, 111.7, 128.9, 130.9, 147.2, 147.6.

4.4.4. (1R) (1-Isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl)-methanol (**4e**)

Yield: 0.584 g, 55%; foam; $[\alpha]_{\text{D}}^{23} +25.6$ (c 1.68, CH_2Cl_2); IR (CH_2Cl_2): 3362, 2961, 1609 cm^{-1} . MS (ES, HR) m/z : ($\text{M}+\text{H}^+$) calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_3$: 266.1750. Found: 266.1754. ^1H NMR: 0.81 (d, 3H, $J=6.9$ Hz), 0.99 (d, 3H, $J=6.9$ Hz), 2.15 (h, 1H, $J=6.9$ Hz), 2.61 (m, 1H), 2.69 (m, 1H), 2.74 (br s, exchangeable with D_2O), 2.94 (m, 1H), 3.19 (m, 1H), 3.61 (d, 1H, $J=10.6$ Hz), 3.74 (d, 1H, $J=10.6$ Hz), 3.84 and 3.85 (two s, 6H), 6.57 and 6.62 (two s, 2H). ^{13}C NMR: 17.1, 18.4, 30.2, 36.6, 39.9, 55.7, 56.1, 61.3, 67.1, 108.6, 111.7, 128.8, 130.9, 147.3, 147.6.

4.5. 2,3,9,10-Tetramethoxy-7a,14a-diphenyl-5,6,7,7a,12,13,14,14a-octahydro-6a,13a-diaza-dibenzo[a,h]anthracene-7,14-diol (**8**)

Into a solution of **2a** (0.7 mmol, 0.260 g) in acetonitrile (8 mL) sodium carbonate (3.2 mmol, 8 mL of 0.4 M $\text{Na}_2\text{CO}_3\text{--H}_2\text{O}$) was added in one portion. The reaction mixture was initially stirred for 1 h at room temperature then stirring was switched off, and left for 2 weeks at this temperature. Precipitated crystals were filtrated, washed with acetonitrile– $\text{H}_2\text{O}=1:1$ mixture and dried. Yield 0.099 g, 47%; colourless crystals; mp 263–266 °C (ethyl acetate); $[\alpha]_{\text{D}}^{23} +193.9$ (c 1.2, CH_2Cl_2); IR (CH_2Cl_2): 2938, 1610 cm^{-1} . MS (ES, HR) m/z : ($\text{M}+\text{OH}^+$) calcd for $\text{C}_{36}\text{H}_{37}\text{N}_2\text{O}_5$: 577.2697. Found: 577.2719. ^1H NMR: 2.46 (m, 2H), 2.88 (m, 2H), 3.36 (m, 4H), 3.78 (s, 6H), 3.79 (s, 6H), 5.39 (s, 2H), 6.51 (s, 2H), 6.93 (s, 2H), 7.03 (m, 10H). ^{13}C NMR: 27.5, 49.0, 55.8, 56.2, 74.0, 104.2, 110.0, 111.5, 125.1, 126.7, 127.9, 130.1, 131.1, 144.7, 147.3, 147.4.

4.6. General procedure for the preparation of N-formyl aldehydes (**5a–e**)

Into a solution of **2** (9 mmol) in DMSO (30 mL), 2-iodoxy benzoic acid (18 mmol, 5.04 g) was added in one portion. Reaction was heated to 45 °C and stirred for 2–3 h until all substrate was consumed (TLC control). Then, the solution was poured into water (200 mL) and extracted with ethyl acetate (3×100 mL). Collected extracts were washed with water (2×100 mL), dried (MgSO_4) and evaporated in vacuo. Crude **5** was purified on silica gel.

4.6.1. (1S) 6,7-Dimethoxy-1-phenyl-3,4-dihydro-1H-isoquinoline-1,2-dicarbaldehyde (**5a**)

Yield: 2.196 g, 75%; colourless crystals; mp 148–150 °C (diethyl ether); $[\alpha]_{\text{D}}^{23} +100.4$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2939, 2855, 1727, 1666 cm^{-1} . MS (EI, HR) m/z : (M^+) calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$: 325.1314. Found: 325.1308. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.13; H, 5.81; N, 4.08. Selected data taken from ~1:5.5 mixture of rotamers. *Major rotamer*. ^1H NMR: 2.88 (m, 1H), 3.15 (m, 1H), 3.38 (m, 1H), 3.66 (s, 3H), 3.75 (m, 1H, overlap with protons of minor rotamer), 3.91 (s, 3H), 6.38 (s, 1H), 6.71 (s, 1H), 8.09 (s, 1H), 9.45 (s, 1H). ^{13}C NMR: 29.6, 40.5, 55.9, 56.0, 71.9,

111.3, 112.4, 148.2, 149.4, 161.6, 190.8. *Minor rotamer*. ^1H NMR: 2.82 (m, 1H), 2.95 (m, 1H), 3.65 (s, 3H), 3.75 (m, 2H, overlap with proton major rotamer), 3.90 (s, 3H), 6.35 (s, 1H), 6.73 (s, 1H), 8.01 (s, 1H), 9.88 (s, 1H). ^{13}C NMR: 28.2, 36.8, 55.9, 56.1, 73.8, 111.7, 112.1, 148.2, 149.3, 163.2, 194.4.

4.6.2. (1S) 6,7-Dimethoxy-1-methyl-3,4-dihydro-1H-isoquinoline-1,2-dicarbaldehyde (**5b**)

Yield: 1.99 g, 84%; colourless crystals; mp 180–181 °C (ethyl acetate); $[\alpha]_{\text{D}}^{23} -96.2$ (c 0.9, CH_2Cl_2); IR (CH_2Cl_2): 2940, 2838, 1729, 1666 cm^{-1} . MS (EI, HR) m/z : (M^+) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: 263.1157. Found: 263.1153. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.87; H, 6.52; N, 5.25. ^1H Selected spectral data taken from ~1:17 mixture of rotamers. *Major rotamer*. NMR: 1.77 (s, 3H), 2.87 (m, 1H), 3.08 (m, 1H), 3.45 (m, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 3.92 (m, 1H), 6.61 (s, 1H), 8.23 (s, 1H), 9.16 (s, 1H). ^{13}C NMR: 19.9, 29.8, 41.1, 55.9, 56.0, 66.4, 110.1, 111.6, 122.6, 127.2, 148.5, 148.9, 161.9, 193.7. *Minor rotamer*. NMR: 1.81 (s, 3H), 2.92 (m, 1H), 3.24 (m, 1H), 4.54 (m, 1H), 6.51 (s, 1H), 6.70 (s, 1H), 8.18 (s, 1H), 9.31 (s, 1H).

4.6.3. (1S) 6,7-Dimethoxy-1-phenylethynyl-3,4-dihydro-1H-isoquinoline-1,2-dicarbaldehyde (**5c**)

Yield: 0.943 g, 30%; white solid; $[\alpha]_{\text{D}}^{23} -24.9$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3054, 2940, 2837, 2233, 1739, 1673 cm^{-1} . MS (ES, HR) m/z : ($\text{M}+\text{Na}^+$) calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4\text{Na}$: 372.1206. Found: 372.1203. Selected data taken from ~1:1.6 mixture of rotamers. *Major rotamer*. ^1H NMR: 2.86 (m, 1H, overlap with protons minor rotamer), 3.10 (m, 1H), 3.59 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 3.99 (m, 1H, overlap with protons of minor rotamer), 6.65 (s, 1H), 6.99 (s, 1H), 8.29 (s, 1H), 9.09 (s, 1H). ^{13}C NMR: 29.5, 41.4, 56.0, 56.2, 64.3, 85.3, 86.1, 111.0, 111.5, 120.4, 122.1, 148.8, 149.6, 162.0, 188.4. *Minor rotamer*. ^1H NMR: 2.71 (m, 1H), 2.86 (m, 1H, overlap with protons of major rotamer), 3.69 (m, 1H), 3.90 (s, 1H), 3.91 (s, 1H), 3.99 (m, 1H, overlap with protons of major rotamer), 6.70 (s, 1H), 7.19 (s, 1H), 8.84 (s, 1H), 9.35 (s, 1H). ^{13}C NMR: 27.6, 37.0, 56.0, 56.3, 66.3, 82.1, 93.5, 110.8, 111.8, 120.2, 120.7, 148.5, 149.8, 162.9, 188.6.

4.6.4. (1R) 1-Cyclohexyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-1,2-dicarbaldehyde (**5d**)

Yield: 2.028 g, 68%; colourless crystals; mp 182–183 °C (acetone); $[\alpha]_{\text{D}}^{23} +93.5$ (c 1.1, CH_2Cl_2); IR (CH_2Cl_2): 2934, 2855, 1724, 1669 cm^{-1} . MS (EI, HR) m/z : (M^+) calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4$: 331.1783. Found: 331.1789. Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.79; H, 7.67; N, 4.29. Selected data taken from ~1:3.2 mixture of rotamers. *Major rotamer*. ^1H NMR: 3.53 (m, 1H), 3.82 (s, 3H), 3.86 (s, 1H), 3.93 (m, 1H, overlap with proton minor rotamer), 6.59 (s, 1H), 6.60 (s, 1H), 8.28 (s, 1H), 9.11 (s, 1H). ^{13}C NMR: 26.56 (overlap with carbon), 27.5, 29.4, 29.8, 30.3, 43.4, 45.7, 55.8, 56.1, 72.8, 110.2, 111.6, 120.8, 128.4, 148.6, 148.8, 162.5, 191.2. *Minor rotamer*. ^1H NMR:

3.83 (s, 3H), 3.87 (s, 3H), 3.93 (m, 1H, overlap with proton of major rotamer), 4.90 (m, 1H), 6.56 (s, 1H), 6.65 (s, 1H), 8.00 (s, 1H), 9.10 (s, 1H). ^{13}C NMR: 26.2, 26.3, 27.3, 28.6, 28.63, 29.0, 36.7, 44.7, 55.9, 56.2, 74.3, 109.9, 111.9, 119.0, 130.2, 148.7, 149.2, 162.5, 192.6.

4.6.5. (1R) 1-Isopropyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-1,2-dicarbaldehyde (**5e**)

Yield: 1.967 g, 75%; colourless crystals; mp 144–147 °C (*tert*-butyl methyl ether); $[\alpha]_{\text{D}}^{23} +115.0$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2968, 2837, 1721, 1669 cm^{-1} . MS (EI, HR) m/z : (M^+) calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: 291.1470. Found: 291.1464. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.82; H, 7.25; N, 4.83. Selected spectral data taken from ~1:2.4 mixture of rotamers. *Major rotamer*. ^1H NMR: 0.80 (d, 3H, $J=7.2$ Hz), 1.13 (d, 3H, $J=6.6$ Hz), 2.82 (m, 1H), 2.97 and 3.08 (two m, 2H), 3.53 (m, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 3.94 (m, 1H), 6.59 and 6.61 (two s, 2H), 8.30 (s, 1H), 9.13 (s, 1H). ^{13}C NMR: 19.1, 19.2, 30.3, 35.1, 43.4, 55.9, 56.0, 72.83, 110.3, 111.6, 121.3, 128.2, 148.6, 148.9, 162.5, 191.4. *Minor rotamer*. ^1H NMR: 1.02 (d, 1H, $J=6.6$ Hz), 4.92 (m, 1H), 8.02 (s, 1H), 9.11 (s, 1H). ^{13}C NMR: 17.7, 18.3, 29.0, 34.2, 36.7, 55.9, 56.1, 74.3, 109.9, 111.9, 130.0, 161.9, 192.7.

4.7. General procedures for the preparation of compounds **6a** and **6b**

Procedure A. Chromium(VI) oxide (7.5 mmol, 0.75 g) was dissolved in dichloromethane–DMF (4:1 v/v, 20 mL), treated with pyridine (25 mmol, 2 mL) and stirred at room temperature for 15 min. Compound **3** (2.5 mmol) in dichloromethane–DMF (4:1 v/v, 10 mL) was added followed by acetic anhydride (18 mmol, 1.7 mL). The mixture was stirred at room temperature for 40 min, quenched with ethanol (1 mL), poured into satd solution NaHCO_3 (40 mL) and extracted with ethyl acetate (1×100 mL, 2×40 mL). Collected extracts were washed with water (3×100 mL), dried (MgSO_4) and evaporated in vacuo. Crude **6** was purified on silica gel.

Procedure B. Into a pre-cooled, to 0 °C, solution of **3** (0.3 mmol) in dichloromethane (2 mL), Dess–Martin periodinane (0.6 mmol, 0.254 g) was added in dichloromethane (2 mL). Reaction was warmed up to room temperature and stirred for 3–5 h until all substrate was consumed (TLC control). Then, the solution was poured into satd solution of sodium bicarbonate (10 mL) and extracted with dichloromethane (3×10 mL). Collected extracts were washed with water (2×10 mL), dried and evaporated in vacuo. Crude **6** was purified on silica gel.

4.7.1. (2S, 4aS) and (2R, 4aS), 2,6,7-tri-methoxy-4a-phenyl-9,10-dihydro-4aH-3-oxa-10a-aza-phenanthrene-1,4-diones (**6a**)

Yield: 0.661 g, 69% (procedure A), 0.082 g, 71% (procedure B); foam; IR (CH_2Cl_2): 3062, 2940, 1761, 1683, 1610 cm^{-1} . MS (EI, HR) m/z : (M^+) calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_6$: 383.1369. Found: 383.1360. Selected spectral data taken from the 1:1.4

mixture of two diastereomers. *Major epimer*. ^1H NMR: 2.60 (m, 1H, overlap with proton of minor diastereomer), 3.03 (m, 2H, overlap with proton of minor diastereomer), 3.54 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.62 (m, 1H), 5.33 (s, 1H), 6.66 (s, 1H), 7.13 (s, 1H). *Minor epimer*. ^1H NMR: 2.60 (m, 1H, overlap with proton of major diastereomer), 2.91 (m, 1H), 3.03 (m, 1H, overlap with two protons major diastereomer), 3.73 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.44 (m, 1H), 5.45 (s, 1H), 6.67 (s, 1H). ^{13}C NMR (mixture of diastereomers): 27.2, 27.3, 37.7, 38.8 (C9, C10), 55.8, 55.9, 56.03, 56.1 (*MeOAr*), 57.5, 58.0 (*MeO*), 68.3, 69.5 (C4a), 97.9, 99.4 (C2), 111.0, 111.1, 111.8, 111.9 (C5, C8), 147.2, 147.4, 149.1, 149.4 (C6, C7), 159.8, 162.4 (C1), 166.8, 167.8 (C4).

4.7.2. (2S, 4aS) and (2R, 4aS), 2,6,7-tri-methoxy-4a-methyl-9,10-dihydro-4aH-3-oxa-10a-aza-phenanthrene-1,4-diones (**6b**)

Yield: 0.562 g, 70% (procedure A), 0.053 g, 55% (procedure B); white solid; IR (CH_2Cl_2): 3007, 2940, 1762, 1682, 1611 cm^{-1} . MS (ES, HR) m/z : ($\text{M}+\text{Na}^+$) calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_6\text{Na}$: 344.1104. Found: 344.1088. Selected spectral data taken from the 1:1.1 mixture of two diastereomers. *Major epimer*. ^1H NMR: 2.03 (s, 3H), 2.95 (m, 2H), 3.06 (m, 1H), 3.70 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 4.82 (m, 1H, overlapped with minor epimer), 5.37 (s, 1H), 6.54 (s, 1H), 7.44 (s, 1H). *Minor epimer*. ^1H NMR: 1.97 (s, 3H), 2.65 (m, 2H), 3.20 (m, 1H), 3.54 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 4.82 (m, 1H, overlapped with major epimer), 6.57 (s, 1H), 7.29 (s, 1H). ^{13}C NMR (mixture of diastereomers): 27.4, 28.6 (*Me-C4a*), 30.2, 30.7, 36.5, 37.0 (C9, C10), 55.8, 55.9, 56.1, 56.2 (*MeOAr*), 57.2, 58.0 (*MeO-C4a*), 61.8, 61.9 (C4c), 97.3, 99.0 (C2), 109.5, 110.9, 111.6, 112.0 (C5, C8), 125.6, 126.3, 126.8, 127.1 (C4b, C8a), 147.5, 147.6, 148.8, 148.8 (C6, C7), 160.7, 161.7 (C1), 167.9, 169.8 (C4).

4.8. General procedures for the preparation of compounds **7a**, **7b** and **9b**

Procedure C. A stirred solution of compound **6** (0.45 mmol) in water (6 mL), ethanol (6 mL) and hydrochloric acid (35–38%, 0.75 mL) was heated at reflux. When TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The crude reaction mixture was subjected to flash chromatography.

Procedure D. A stirred solution of compound **6** (0.25 mmol) in 1,2-dimethoxyethane (5 mL) and hydrochloric acid (35–38%, 1 mL) was heated at reflux. When TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The crude mixture was subjected to flash chromatography.

4.8.1. (1S) 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid (**7a**)

Yield: 0.078 g, 55% (procedure C, reflux 7 h, eluent: methylene chloride–methanol–ammonia solution (25%)=95:5:0.5 v/v/v);

Yield: 0.068 g, 87% (procedure D, reflux 3 h); colourless crystals; mp 218–221 °C; $[\alpha]_D^{23} +0.63$ (c 0.5, MeOH); IR (KBr): 3436, 3055, 2961, 2378, 1635, 1609 cm^{-1} . MS (ES, HR) m/z : (M+Na⁺) calcd for C₁₈H₁₉NO₄Na: 336.1206. Found: 336.1223. ¹H NMR (CD₃OD): 2.92–3.18 (m, 3H), 3.44 (m, 1H), 3.63 (s, 3H), 3.85 (s, 3H), 6.79 (s, 1H), 7.27 (m, 3H), 7.39 (m, 3H). ¹³C NMR (CD₃OD): 26.1, 40.0, 56.4, 56.5, 72.0, 112.1, 114.3, 125.4, 126.4, 129.8, 130.1, 130.4, 141.5, 149.1, 150.6, 173.0.

4.8.2. (1S) 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid (**7b**)

Yield: 0.041 g, 36% (procedure C, reflux 72 h, eluent: methylene chloride–methanol–ammonia solution (25%)=78:20:2 v/v/v). Yield: 0.051 g, 81% (procedure D, reflux 3 h); hydrochloride of **7b** was obtained accordingly to Lit.^{4c} $[\alpha]_D^{23} +43.4$ (c 1.12, MeOH); Lit.^{4c} $[\alpha]_D^{23} +44.6$ (c 1.12, MeOH). ¹³C NMR (D₂O): 24.2, 24.3, 39.3, 55.7, 55.9, 110.3, 111.6, 123.5, 124.6, 147.4, 148.6, 172.7.

4.8.3. (1S) 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid ethyl ester (**9b**)

Yield: 0.60 g, 48% (procedure C, reflux 72 h, eluent: methylene chloride–methanol–ammonia solution (25%)=78:20:2 v/v/v). Oil, $[\alpha]_D^{23} +17.7$ (c 1.1, CH₂Cl₂); IR (film): 2935, 1723 cm^{-1} . MS (ES, HR) m/z : (M+H⁺) calcd for C₁₅H₂₂NO₄: 280.1543. Found: 280.1553. ¹H NMR: 1.26 (t, 3H, $J=7.1$ Hz), 1.65 (s, 3H), 2.20 (br s, 1H), 2.64 (m, 1H), 2.83 (m, 1H), 3.11 (m, 2H), 3.85 and 3.86 (two s, 6H), 4.18 (m, 2H), 6.55 (s, 1H), 6.95 (s, 1H). ¹³C NMR: 14.1, 28.5, 29.4, 40.4, 55.6, 56.0, 61.1, 61.4, 110.8, 111.4, 127.6, 128.9, 147.1, 148.1, 175.6.

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