Synthesis of (±)-Crispine A via a Nitrosoalkene Hetero-Diels–Alder Addition to Ethyl Vinyl Ether

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Dedicated to Professor N. Argyropoulos on the occasion of his retirement

Abstract: The synthesis of (±)-crispine A in 9 steps and 24% overall yield was achieved using a nitrosoalkene hetero-Diels–Alder addition to ethyl vinyl ether as the key step. The synthesis starts from commercial 3,4-dimethoxyphenylacetic acid and uses simple methods, easily accessible materials and inexpensive reagents. An isochroman derivative was unexpectedly formed in an attempted reduction of a dihydro-4*H*-1,2-oxazine intermediate.

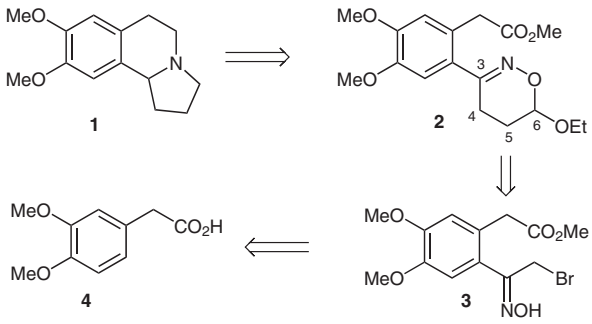
Key words: alkaloids, natural products, total synthesis, hetero-Diels–Alder reaction, hydrogenation

(*R*)-(+)-Crispine A (**1**, Scheme 1) was isolated in 2002 from *Carduus crispus* L.,[1] a popular invasive thistle occurring in Asia and Europe which has been used in Chinese folk medicine for the treatment of colds, stomach ache and rheumatism. This alkaloid has also been proved to inhibit the growth of some human cancer lines *in vitro* (SKOV3, KB and HeLa human cancer lines) and shows significant cytotoxic activity. As a result of this potent antitumor activity, various synthetic methods have been developed for the synthesis of crispine A, in both racemic[2] and enantiomerically pure form,[3] and a number of analogues have been prepared.[4]

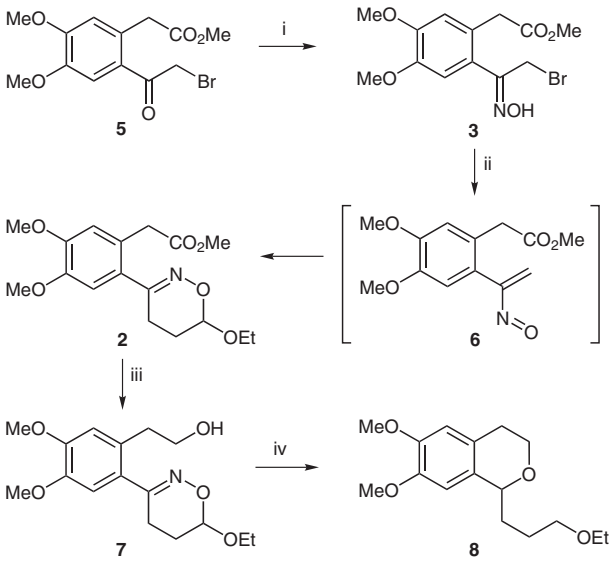
Our retrosynthetic plan towards (±)-crispine A involved a hetero-Diels–Alder addition reaction[5] of a nitrosoalkene, in situ generated from oxime **3** by 1,4-elimination of hydrogen bromide,[6] to ethyl vinyl ether to give adduct **2**. This compound has the requisite carbon skeleton and the target molecule could be prepared from it by standard reduction–condensation manipulations.[7] Compound **3** can be prepared from commercial 3,4-dimethoxyphenylacetic acid (**4**) by standard manipulations.[8]

Ketone **5** served as the immediate precursor for oxime **3** (Scheme 2). A solution of the oxime **3** in ethyl vinyl ether was treated with sodium carbonate to give adduct **2**, evidently via the intermediate unstable nitrosoalkene **6**, in 67% overall yield from **5**.

What was remaining in order to construct the desired compound was a set of appropriate reduction–condensation reactions. Thus, the ester group of adduct **2** was reduced with lithium borohydride in tetrahydrofuran to give a 61% yield of alcohol **7**. Then, we tried to apply the reaction sequence we have developed for the stereoselective conversion of an oxazine ring into a pyrrolidine.[7] Surprisingly, however, when the reduction of the C=N bond with sodium cyanoborohydride ($NaBH_3CN$) in acetic acid was attempted, 1-(3-ethoxypropyl)-6,7-dimethoxyisochroman (**8**) was isolated in 43% yield.



Scheme 1 Retrosynthetic analysis of (±)-crispine A



Scheme 2 *Reagents and conditions*: (i) NH_2OH, MeOH, reflux, 24 h; (ii) ethyl vinyl ether, Na_2CO_3, r.t., 24 h, 67% from **5**; (iii) $LiBH_4$, THF, r.t., 8 h, 61%; (iv) $NaBH_3CN$, glacial AcOH, r.t., 2.5 h, 43%.

This is a quite interesting reaction and the mechanism depicted in Scheme 3 could account for the formation of **8**. Nitrogen protonation of the dihydro-4*H*-1,2-oxazine activates its C-3 center towards intramolecular 1,2-addition of the primary alcoholic group. The intermediately formed

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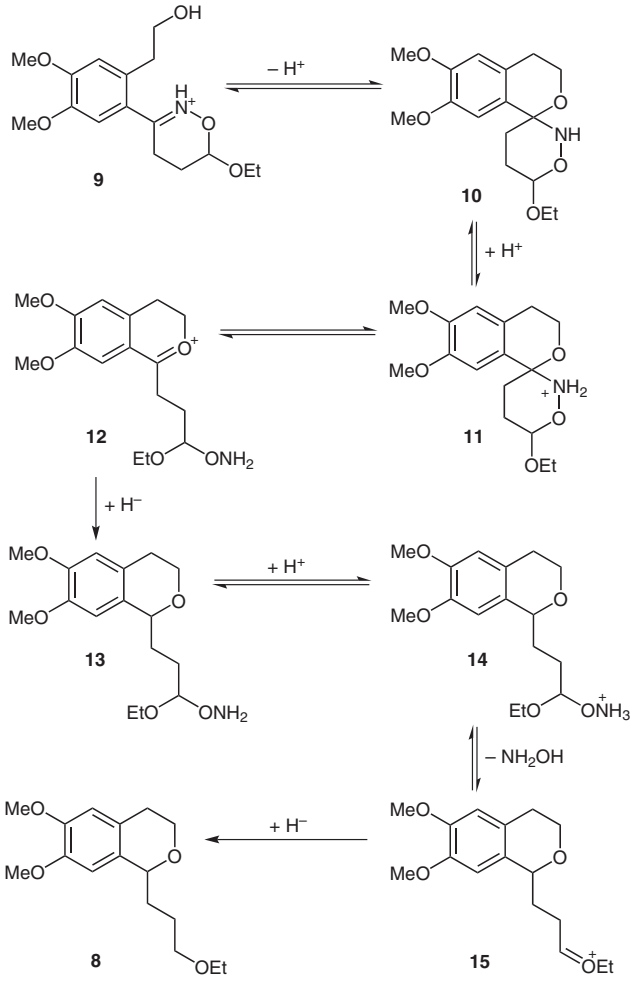
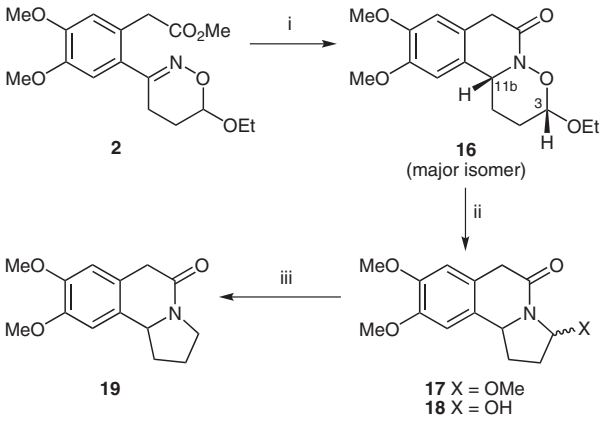
spiro-*N*,*O*-acetal **10** undergoes further reductive oxazine ring opening upon protonation in an O-assisted reaction to give isochroman **13**. The acetal group of this compound is finally reduced in the same way to give isochroman **8**. To the best of our knowledge, this is the first example of such a reaction of a dihydro-4*H*-1,2-oxazine system with an alcohol.[9] The scope and limitations of this reaction are under further examination.



Scheme 3 Plausible reaction mechanism for the reductive conversion of dihydro-4*H*-1,2-oxazine **7** into isochroman **8**

Facing such problems in our initial plan, we decided to manipulate firstly the oxazine ring. Thus, the C=N bond of adduct **2** was reduced with $NaBH_3CN$ in acetic acid; spontaneous cyclization afforded an 85% yield of compound **16** (Scheme 4). Several attempted reductions of **16**, such as with lithium aluminum hydride or borane, failed since they gave a very complex mixture of products, probably because this is a quite active amide. Finally, we achieved the N–O bond cleavage with Raney nickel and hydrogen in methanol or ethyl acetate–water, in the presence of boric acid, to give methyl ether **17** in good yield or alcohol **18** in poor yield, respectively. Both of these compounds were further reduced with $NaBH_3CN$ in acetic acid to furnish lactam **19**, which upon lithium aluminum hydride reduction gives the desired (±)-crispine A, according to the literature.[2c]



Scheme 4 *Reagents and conditions*: (i) $NaBH_3CN$, glacial AcOH, r.t., 2.5 h, 85% (dr 16:1); (ii) **17**: Raney Ni, H_2, H_3BO_3, MeOH, reflux, 5 d, 80%; **18**: Raney Ni, H_2, H_3BO_3, EtOAc, H_2O, reflux, 4 d, 23%; (iii) $NaBH_3CN$, glacial AcOH, r.t., 12 h, 80% from **17** and 70% from **18**.

It is interesting to note that the $NaBH_3CN$ reduction of compound **2** proceeds with very good diastereoselectivity (dr 16:1). As indicated by the ^1H NMR spectrum, the dihydro-4*H*-1,2-oxazine ring of compound **2** adopts a pseudo-chair conformation with an axial ethoxy group (for H-6, $\delta = 5.16$, t, $J = 2.5$ Hz). Due to resonance, the aryl group prefers, most probably, a coplanar arrangement with the C=N double bond, which allows an *anti* hydride addition relative to the ethoxy group. This was confirmed by the ^1H NMR signals of H-11b ($\delta = 4.78$, m)[10] and H-3 ($\delta = 5.04$, d, $J = 3.0$ Hz) in **16**, the latter being equatorial, whereas for the minor epimer (*epi*-**16**) the same signals appear at $\delta = 4.71$ (d, $J = 11.4$ Hz) and 4.84 (dd, $J = 9.6$ and 2.1 Hz), respectively, indicating thus that both protons are axial. This high diastereoselectivity, together with the fact that the two diastereomers can be easily separated chromatographically, allows the possibility of the asymmetric synthesis of crispine A using a chiral enol ether.[11]

In conclusion, we report here a new approach to (±)-crispine A, an alkaloid isolated from *Carduus crispus* which inhibits the growth of some human cancer lines *in vitro* and shows significant cytotoxic activity. Our method starts from easily accessible materials and uses simple methods and inexpensive reagents to give the target crispine A in 24% overall yield from 3,4-dimethoxyphenylacetic acid. The fact that there is a highly diastereoselective $NaBH_3CN$ reduction of the dihydro-4*H*-1,2-oxazine ring allows the potential asymmetric synthesis of crispine A, which is under consideration. In addition, an interesting reduction of a dihydro-4*H*-1,2-oxazine by $NaBH_3CN$ in acetic acid to an isochroman derivative was observed when a free alcoholic hydroxy group was present in the molecule.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Bruker Avance III 300-MHz spectrometer. Chemical shifts are given in parts per million and *J* in hertz using solvent or tetramethylsilane as an internal reference. IR spectra were recorded on a Perkin Elmer FTIR instrument. High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol as the matrix or on an IonSpec FTMS instrument (matrix-assisted laser desorption/ionization, MALDI) with 2,5-dihydroxybenzoic acid as the matrix. All commercially available, reagent grade quality materials were used without further purification. All solvents were purified by standard procedures before use. Dry solvents were obtained by literature methods and stored over molecular sieves. All reactions were conducted under a nitrogen atmosphere. All reactions were monitored on commercially available, precoated Kieselgel 60 F254 TLC plates (layer thickness: 0.25 mm). Compounds were visualized by the use of a UV lamp or/and *p*-anisaldehyde ethanolic solution and warming. Column chromatography was performed in the usual way using Merck 60 (40–60 μm) silica gel.

Methyl 2-{2-[2-Bromo-1-(hydroxyimino)ethyl]-4,5-dimethoxyphenyl}acetate (3)

To a well-stirred soln of ketone **5**[8b] (1.267 g, 3.83 mmol) in MeOH (30 mL) was added NH_2OH (0.8 g, 11.5 mmol) and the resultant mixture was refluxed for 24 h. After the mixture was cooled to r.t., the MeOH was removed and the crude product was purified by flash chromatography (EtOAc–hexane, 1:3) to give **3** as an amorphous solid; yield: 0.929 g (70.5%).

FTIR (film): 3423, 2953, 2848, 1735, 1607, 1521 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.67 (s, 3 H), 3.86 (s, 2 H), 3.88 (s, 6 H), 4.40 (s, 2 H), 6.76 (s, 1 H), 6.91 (s, 1 H), 9.47 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 38.3, 45.3, 51.9, 55.6, 55.7, 109.9, 113.1, 123.9, 124.8, 147.3, 147.9, 153.8, 172.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}BrNO_5$: 346.0285; found: 346.0278.

Methyl 2-[2-(6-Ethoxy-5,6-dihydro-4*H*-1,2-oxazin-3-yl)-4,5-dimethoxyphenyl]acetate (2)

To a soln of oxime **3** (0.929 g, 2.68 mmol) in freshly distilled ethyl vinyl ether (30 mL), Na_2CO_3 (1.420 g, 13.4 mmol) was added and the reaction mixture was stirred at r.t. for 24 h. The mixture was filtered through a Celite® pad and the excess ethyl vinyl ether was evaporated. The crude product was purified by flash chromatography (EtOAc–hexane, 1:3 to 1:2) to give **2** as a pale yellow oil; yield: 0.859 g (95%).

FTIR (film): 2942, 1738, 1607, 1523 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 2.06 (m, 2 H), 2.33 (ddd, *J* = 18.3, 5.1, 3.6 Hz, 1 H), 2.60 (ddd, *J* = 18.3, 10.8, 9.0 Hz, 1 H), 3.66 (dq, *J* = 9.6, 7.2 Hz, 1 H), 3.67 (s, 3 H), 3.73 (d, *J* = 16.2 Hz, 1 H), 3.79 (d, *J* = 16.2 Hz, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.94 (dq, *J* = 9.6, 7.2 Hz, 1 H), 5.16 (t, *J* = 2.5 Hz, 1 H), 6.76 (s, 1 H), 6.79 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.0, 20.7, 23.3, 38.3, 52.0, 56.0, 56.1, 63.5, 94.4, 110.8, 113.8, 124.7, 129.6, 148.0, 149.1, 159.0, 172.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_6$: 338.1598; found: 338.1582.

2-(2-(6-Ethoxy-5,6-dihydro-4*H*-1,2-oxazin-3-yl)-4,5-dimethoxyphenyl)ethanol (7)

Compound **2** (0.323 g, 0.96 mmol) was dissolved in anhyd THF (3 mL) and $LiBH_4$ (0.041 g, 1.91 mmol) was added at 0 °C. The mixture was warmed to r.t. and then stirred for 8 h. The reaction was quenched by the addition of H_2O, the organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc–hexane, 2:1 to 1:1) to give **7** as a colorless oil; yield: 0.182 g (61%).

FTIR (film): 3387 (br), 2937, 1607, 1517 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.70 (br s, 1 H), 2.10 (m, 2 H), 2.40 (dt, *J* = 18.3, 4.5 Hz, 1 H), 2.58 (dt, *J* = 18.3, 9.9 Hz, 1 H), 2.90 (m, 2 H), 3.66 (dq, *J* = 9.9, 7.2 Hz, 1 H), 3.85 (m, 2 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 3.94 (dq, *J* = 9.9, 7.2 Hz, 1 H), 5.18 (t, *J* = 2.5 Hz, 1 H), 6.72 (s, 1 H), 6.79 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 21.0, 23.5, 35.5, 55.9, 56.1, 63.7, 63.9, 94.4, 110.5, 112.9, 129.0, 130.4, 147.5, 149.7, 159.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}NO_5$: 310.1649; found: 310.1650.

1-(3-Ethoxypropyl)-6,7-dimethoxyisochroman (8)

To a cold, stirred soln of alcohol **7** (0.068 g, 0.22 mmol) in glacial AcOH (1.3 mL) was added $NaBH_3CN$ (0.044 g, 0.7 mmol) at 0 °C and the mixture was stirred at r.t. for 2.5 h. Then, it was diluted with CH_2Cl_2 (2 mL) and neutralized with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with EtOAc (3 × 3 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash chromatography (EtOAc–hexane, 2:1) to give **8** as a colorless oil; yield: 0.027 g (43%).

FTIR (film): 2932, 2855, 1611, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 6.9 Hz, 3 H), 1.75 (m, 3 H), 2.10 (m, 1 H), 2.60 (dt, *J* = 15.9, 3.6 Hz, 1 H), 2.90 (ddd, *J* = 15.9, 9.0, 5.1 Hz, 1 H), 3.47 (m, 4 H), 3.75 (m, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.11 (m, 1 H), 4.71 (d, *J* = 7.8 Hz, 1 H), 6.57 (s, 1 H), 6.59 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.3, 25.4, 28.6, 32.5, 55.8, 56.0, 63.1, 66.0, 70.5, 75.2, 107.5, 111.4, 126.0, 130.1, 147.4 (2 × C).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}O_4$: 281.1747; found: 281.1748.

(3*R,11b*S**)-3-Ethoxy-9,10-dimethoxy-2,3,7,11b-tetrahydro[1,2]oxazino[3,2-*a*]isoquinolin-6(1*H*)-one (16)**

To a cold, stirred soln of adduct **2** (0.477 g, 1.4 mmol) in glacial AcOH (8.4 mL) was added $NaBH_3CN$ (0.282, 4.5 mmol) at 0 °C. The mixture was stirred at r.t. for 2.5 h, then diluted with CH_2Cl_2 (8 mL) and neutralized with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash chromatography (EtOAc–hexane, 1:1) to give firstly the minor isomer (*epi*-**16**, 0.021 g), followed by **16** (0.348 g), as colorless oils; combined yield: 85%.

Major Isomer 16

FTIR (film): 2935, 1669, 1613, 1521 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 1.95 (m, 3 H), 2.10 (m, 1 H), 3.63 (dq, *J* = 9.3, 7.1 Hz, 1 H), 3.65 (dd, *J* = 18.3, 2.2 Hz, 1 H), 3.74 (dd, *J* = 18.3, 2.2 Hz, 1 H), 3.84 (s, 6 H), 4.21 (dq, *J* = 9.3, 7.1 Hz, 1 H), 4.78 (m, 1 H), 5.04 (d, *J* = 3.0 Hz, 1 H), 6.52 (s, 1 H), 6.56 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.7, 27.9, 29.4, 35.5, 55.9, 56.0, 60.6, 65.3, 99.9, 107.6, 109.9, 121.3, 125.2, 148.3, 148.9, 162.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}NO_5$: 308.1492; found: 308.1487.

(3*R,11b*R**)-3-Ethoxy-9,10-dimethoxy-2,3,7,11b-tetrahydro[1,2]oxazino[3,2-*a*]isoquinolin-6(1*H*)-one (*epi*-16)**

FTIR (film): 2933, 1668, 1613, 1521 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.68 (m, 1 H), 1.96 (m, 1 H), 2.08 (m, 1 H), 2.25 (m, 1 H), 3.64 (s, 2 H), 3.86 (s, 6 H), 3.90 (dq, *J* = 9.9, 7.1 Hz, 1 H), 4.21 (dq, *J* = 9.9, 7.1 Hz, 1 H), 4.71 (d, *J* = 11.4 Hz, 1 H), 4.84 (dd, *J* = 9.6, 2.1 Hz, 1 H), 6.55 (s, 1 H), 6.60 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 15.2, 30.7, 33.6, 35.8, 55.9, 56.0, 60.4, 66.3, 103.2, 108.1, 110.0, 121.0, 124.9, 148.3, 148.9, 163.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}NO_5$: 308.1492; found: 308.1486.

3,8,9-Trimethoxy-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one (17)

Compound **16** (0.150 g, 0.49 mmol) was dissolved in MeOH (5 mL) and H_3BO_3 (0.603 g, 9.8 mmol) was added, together with a catalytic amount of Raney Ni and $MgSO_4$, under a H_2 atmosphere. The mixture was heated at 70 °C for 5 d in a sealed tube and then it was filtered through a short Celite® pad and neutralized with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (EtOAc–hexane, 1:1, to EtOAc) to give an oily product, as a mixture of diastereomers (~2:1, by ^{1}H NMR spectroscopy); combined yield: 0.109 g (80%). The diastereomers were separated by careful chromatography of a small amount of the mixture (silica gel, EtOAc–hexane, 3:1, to EtOAc).

Major Isomer

^{1}H NMR ($CDCl_3$): δ = 1.95 (m, 2 H), 2.10 (m, 1 H), 2.62 (m, 1 H), 3.48 (s, 3 H), 3.50 (d, *J* = 18.3 Hz, 1 H), 3.67 (dd, *J* = 18.3, 3.0 Hz, 1 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 4.82 (dt, *J* = 7.2, 3.0 Hz, 1 H), 5.65 (dd, *J* = 6.0, 2.4 Hz, 1 H), 6.65 (s, 1 H), 6.68 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 30.1, 30.2, 37.5, 55.9, 56.1, 56.4, 58.0, 87.0, 107.9, 110.3, 123.4, 127.1, 148.1, 148.6, 168.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4Na$: 300.1206; found: 300.1197.

Minor Isomer

^{1}H NMR ($CDCl_3$): δ = 1.95–2.5 (m, 4 H), 3.38 (s, 3 H), 3.51 (s, 2 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.53 (dd, *J* = 10.2, 5.5 Hz, 1 H), 5.36 (d, *J* = 4.7 Hz, 1 H), 6.71 (s, 1 H), 6.72 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 27.1, 31.6, 39.6, 55.9, 56.2, 57.1, 59.6, 86.4, 107.3, 110.7, 125.9, 129.3, 147.9, 148.6, 170.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4Na$: 300.1206; found: 300.1201.

3-Hydroxy-8,9-dimethoxy-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one (18)

Compound **16** (0.120 g, 0.39 mmol) was dissolved in EtOAc–H_2O (4:1, 5 mL) and H_3BO_3 (0.483 g, 7.8 mmol) was added, together with a catalytic amount of Raney Ni and $MgSO_4$, under a H_2 atmosphere. The mixture was heated at 60 °C for 4 d in a sealed tube and then it was filtered through a short Celite® pad. More EtOAc was added and the mixture was neutralized with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (EtOAc–hexane, 1:1, to EtOAc) to give the product, as an inseparable mixture of diastereomers; yield: 0.024 g (23%).

^{1}H NMR ($CDCl_3$): δ = 1.80–2.70 (m, 4 H), 3.45 (d, *J* = 18.0 Hz, 1 H), 3.61 (dt, *J* = 18.0, 3.3 Hz, 1 H), 3.86 and 3.87 (2 × s, 6 H), 4.62 and 4.85 (2 × m, 2 H), 5.76 (m, 1 H), 6.65, 6.68 and 6.70 (3 × s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 28.9/29.7, 31.5/31.6, 37.7/38.6, 56.1, 56.2/56.3, 58.1/60.1, 80.6/81.7, 107.8, 110.5/110.7, 123.9/124.6, 127.7/128.5, 148.2, 148.8, 169.4/169.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_4$: 264.1235; found: 264.1228.

8,9-Dimethoxy-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one (19)

To a cold, stirred soln of the diastereomeric mixture of methyl ether **17** (0.070 g, 0.25 mmol) in glacial AcOH (1.5 mL) was added $NaBH_3CN$ (0.021 g, 0.33 mmol) at 0 °C. The mixture was stirred at r.t. for 12 h, then diluted with CH_2Cl_2 (2 mL) and neutralized with sat. aq Na_2CO_3 soln. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash chromatography (EtOAc) to give **19** as a solid; yield: 0.049 g (80%); mp 162–164 °C (Lit.[2c] 163–165 °C); ^{1}H and ^{13}C NMR data identical to those reported in the literature.[2c]

Under the same reaction conditions, compound **19** was obtained in 70% yield from alcohol **18**.

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