HETEROCYCLES, Vol. 106, No. 11, 2023, pp. 1855 - 1865. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 4th September, 2023, Accepted, 29th September, 2023, Published online, 11th October, 2023
DOI: 10.3987/COM-23-14903

L-MALIC ACID AS CHIRAL AUXILIARY AND BUILDING BLOCK IN THE ASYMMETRIC SYNTHESIS OF (*S*)-(–)-CRISPINE A

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Abstract – The asymmetric synthesis of (*S*)-(–)-crispine A was performed using L-malic acid as chiral auxiliary and building block. Condensation of homoveratrylamine with L-malic acid led to imide which was further reduced and cyclized by *N*-acyliminium ion intermediate to pyrrolo[2,1-*a*]isoquinoline. Hydroxyl group at C-1 position was replaced by phenylthio one and removed by Raney nickel. Last step of the synthesis - reduction of lactam carbonyl group furnished (*S*)-(–)-crispine A with 99.99% ee. Additionally synthesis of racemic crispine A was performed staring from homoveratrylamine and succinic anhydride to furnish samples for enantiomeric excess determination by HPLC.

INTRODUCTION

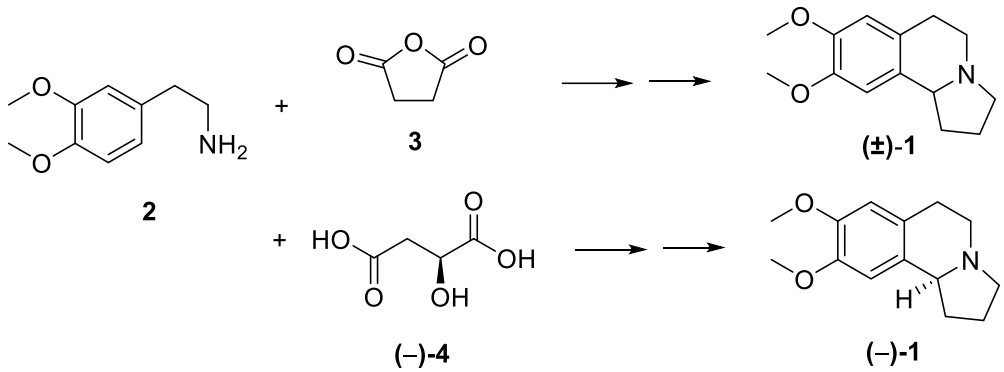
Crispine A (**1**), pyrrolo[2,1-*a*]isoquinoline alkaloid was isolated in 2002 by Zhao *et al*.[1] from *Carduus crispus* L. This plant has been used in China folk medicine for treatment of cold, stomachache and rheumatism. The screening test for the inhibitory effect on the growth of some human cancer lines *in vitro* showed that the extracts of *Carduus crispus* had significant cytotoxic activity.

Crispine A (**1**) was isolated in the form of white crystals and on the basis of spectral analysis Zhao *et al*. established its structure as (+)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline. The absolute configuration of dextrorotatory crispine A (**1**) was established as (*R*) in 2007 by Czarnocki *et al*.[2] Because of interesting biological activity of crispine A (**1**), a lot of scientific groups undertake efforts to evaluate methods of synthesis of this compound in racemic or optically active version. Why the pyrrolo[2,1-*a*]isoquinoline system is so important was pointed in 2007 by Snape and Turner *et al*.[3] in their publication in Chemical Communications. This paper was chosen as a "hot communicate". In 2011[4] and 2021[5] reviews were published describing syntheses and properties of pyrrolo[2,1-*a*]isoquinoline alkaloids. To construct pyrrolo[2,1-*a*]isoquinoline skeleton different strategies were applied. *N*-Acyliminium chemistry has emerged as one of the most efficient methodology. The pioneering work of Speckamp's

group[6,7] and Maryanoff's group[8] on the intramolecular acid-mediated cyclizaton of *N*-acyliminium ion intermediate on electron-rich aromatics rings as π-nucleophile partners has to be pointed out here.

RESULTS AND DISCUSSION

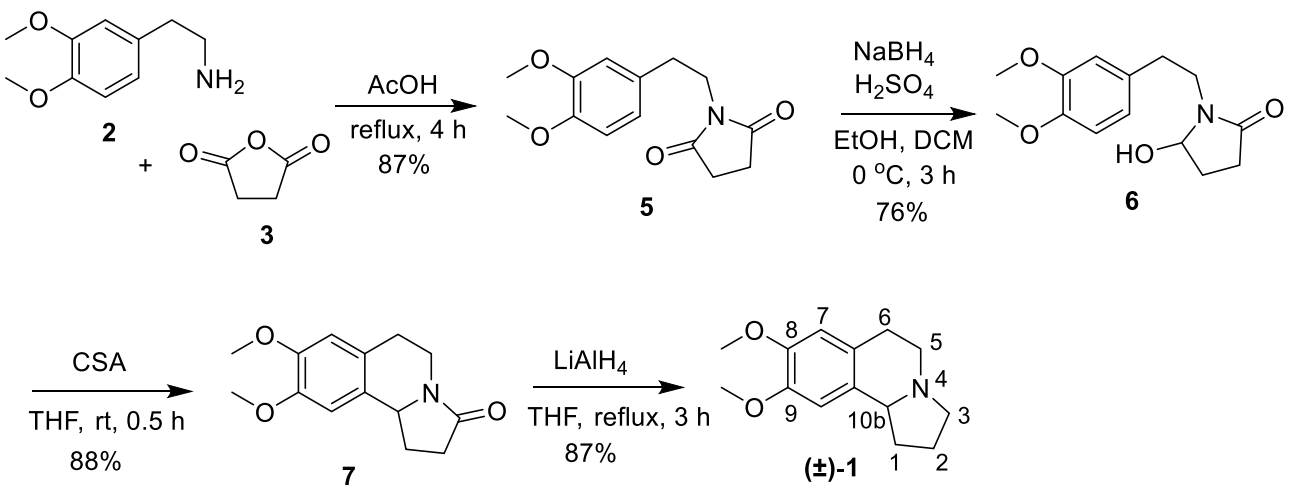
In continuation of our studies on stereoslective synthesis of isoquinoline alkaloids[9-11] we decided to make use of *N*-acyliminium ion cyclization in the new syntheses of crispine A (**1**). The first step of the syntheses was condensation of homoveratrylamine **2** with carbonyl compound (succinic anhydride **3** or L-(–)-malic acid **4**) followed by reduction and cyclization to pyrrolo[2,1-*a*]isoquinoline skeleton in racemic form (±)-**1** and optically active (*S*)-(–)-**1** (Scheme 1).



Scheme 1. Planed synthesis of racemic and optically active crispine A (**1**)

First we synthesized racemic crispine A (±)-**1** to obtain samples for evaluation of HPLC conditions for determination of the enantiomeric excess of optically active compounds of **1** and **7**. The first step of the synthesis was condensation of homoveratrylamine **2** with succinic anhydride **3** by a modified procedure of Opatz *et al*.[12] leading to *N*-[2-(3,4-dimethoxyphenyl)ethyl]succinimide **5** (Scheme 2). Reaction was carried out in refluxing acetic acid. Crude product was crystallized from methanol to give colorless crystals of **5** with mp 123-124 °C (lit.[13] mp 124-125 °C) and 87% yield. Next one of the carbonyl groups in imide **5** was regioselectively reduced using $NaBH_4$ with addition of 1N H_2SO_4. 1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-2-pyrrolidinone **6**[14,15] was obtained as colorless crystals with mp 97-101 °C (lit.[14] mp 107-110 °C) and 76% yield. Cyclization reaction of hydroxylactam **6** was carried out in the presence of acid. We have checked efficiency of different acids as a catalyst, for example trifluoroacetic acid (TFA), 10% HCl, $BF_3 \cdot Et_2O$ and optically active acids as L-(–)-malic acid, (2*S*,3*S*)-(+)-di-*O*-benzoyltartaric acid and (1*S*)-(+)-camphorsulphonic acid. The results of these experiments are summarized in Table 1. (1*S*)-(+)-Camphorsulphonic acid turned out to be most efficient because of short time of reaction (0.5 h) and high yield (88%). Using this optically active acid we

expected that it can be also an inductor of asymmetry. Unfortunately obtained lactam **7**[16-20] was racemic, mp 102-104 °C (lit.[16] mp 104 °C). Next we have evaluated HPLC analysis conditions (selection of chiral column and solvents mixture) for this compound. We have chosen Chiralcel OD-H analytical column and hexane and propan-2-ol mixture as eluent. On the HPLC chromatogram of (±)-**7** two peaks were present with t_R = 27.024 min (41.37%) and t_R = 28.730 min (58.63%)], respectively, (hexane/propan-2-ol = 3:1). The last step in the synthesis of racemic crispine A (±)-**1**[17-19,21] was reduction of carbonyl group in compound **7** using $LiAlH_4$ in refluxing anhydrous THF. After recrystallization of crude product we obtained pure crispine A (±)-**1** as light yellow crystals with mp 88-89 °C (lit.[21] mp 87-89 °C). The overall yield of the synthesis was 50%. On the HPLC chromatogram of (±)-**1** two peaks were present with t_R = 13.704 min (50.17%) and t_R = 17.971 (49.83%), respectively, (hexane/propan-2-ol = 3:1).



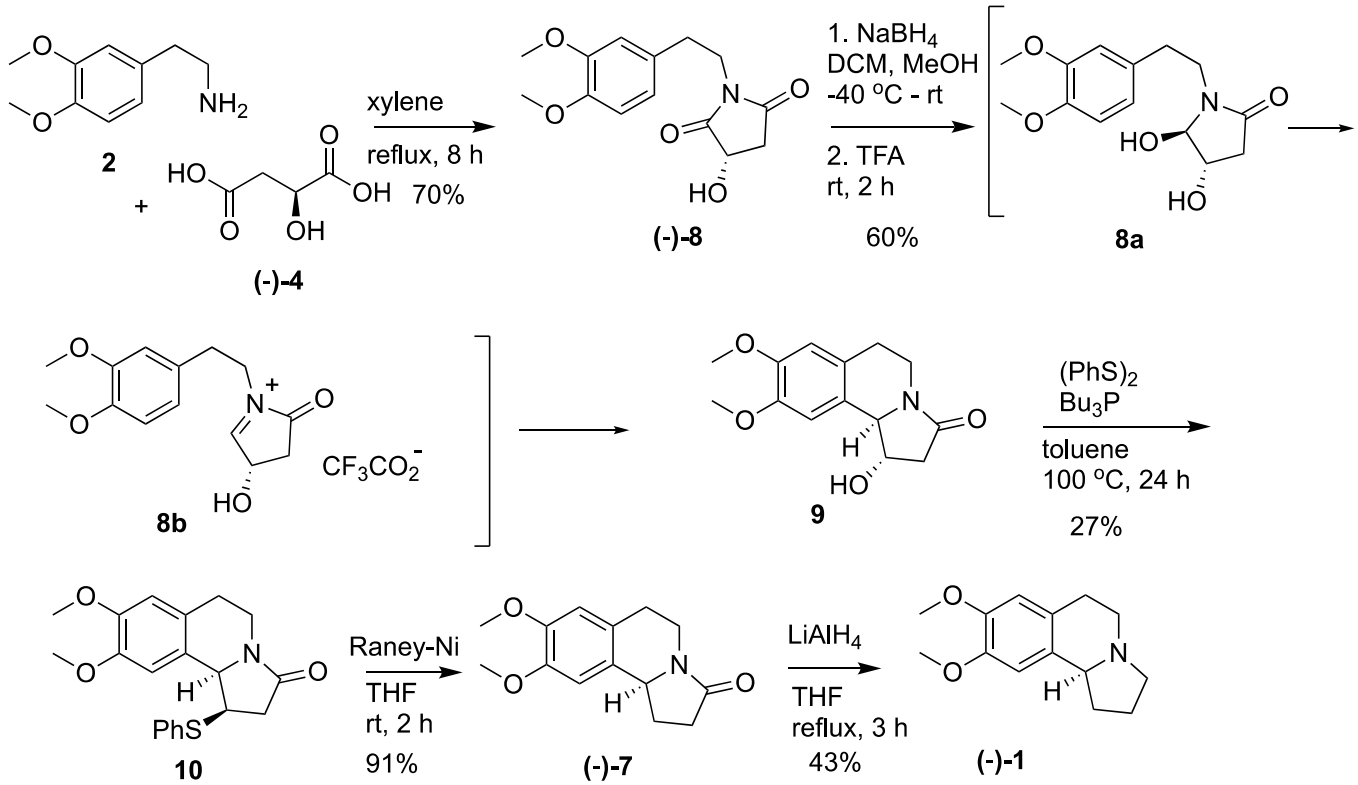
Scheme 2. Synthesis of racemic crispine A (±)-**1**

Table 1. Cyclization reaction of hydroxylactam **6** to lactam **7**

Entry	Reagent	Solvent	Time (h)	Yield (%)
1	$BF_3 \cdot Et_2O$	DCM	28	23
2	TFA	THF	7	12
3	(2*S*,3*S*)-(+)-di-*O*-benzoyltartaric acid	THF	6	41
4	L-(–)-malic acid	THF	3	52
5	10% HCl	THF	0.5	39
6	(1*S*)-(+)-camphorsulphonic acid	THF	0.5	88

For the asymmetric synthesis of crispine A **1** we have chosen L-(–)-malic acid **4** as chiral auxiliary and building block. L-(–)-Malic acid has been used by Lee and Park *et al.*[22] in the synthesis of levorotatory (10b*S*)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (not shown).

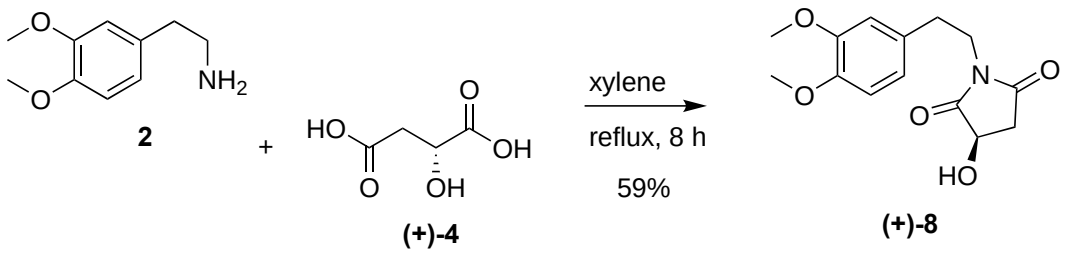
We started our synthesis with condensation of homoveratrylamine **2** with L-(–)-malic acid **4** carried out using Dean-Stark apparatus in refluxing xylene (Scheme 3). Crude product was recrystallized from ethyl acetate to give pure (3*S*)-1-(3,4-dimethoxyphenethyl)-3-hydroxypyrrolidine-2,5-dione **8** with mp 123-126 °C (lit.[23] mp 125 °C) with 70% yield and $[\alpha]_D$ –51.4 (*c* 1.0, MeOH) (lit.[23] $[\alpha]_D$ –67.2 (*c* 3.20, $CHCl_3$)). The spectra of imide **8** were in agreement with literature data.[23]



Scheme 3. Synthesis of optically active crispine A **1**

On the HPLC chromatogram of (–)-**8** it was one peak present with t_R = 30.263 min [hexane/propan-2-ol = 3:1] but it was not obvious whether it came from only one enantiomer. Our optical rotation and literature one were measured in different solvents. To be sure that we have only one enantiomer of imide **8** we have undertaken synthesis of opposite enantiomer of imide (+)-**8** using D-(+)-malic acid **4** and homoveratrylamine **2** (Scheme 4). We obtained new dextrorotatory product **8** with $[\alpha]_D$ +53.1 (*c* 1.0, MeOH). On the HPLC chromatogram of compound (+)-**8** one peak with t_R = 31.500 min was present. We have prepared a 'racemic sample' of imide **8** from equal amounts of (+)- and (–)-enantiomers and run it in HPLC. On the chromatogram of 'our racemic sample' two peaks were present with t_R = 29.416 min

[55.64% (*S*)] and t_R = 31.416 min [44.36% (*R*)], respectively. This experiment confirmed enantiomeric purity of our stereoisomers and accuracy of the evaluated method for enantiomeric excess determination.



Scheme 4. Synthesis of (3*R*)-1-(3,4-dimethoxyphenethyl)-3-hydroxypyrrolidine-2,5-dione **8**

Next step of the synthesis was regioselective reduction of carbonyl group in hydroxyimide (–)-**8**. We decided to try to perform this reaction without protection of hydroxyl group in imide **8** (short and simply method). The method evaluated for reduction of racemic imide **5** did not lead to expected dihyroxylactam **8a**. Also other methods described by Speckamp[24] or Park[22] did not lead to expected product. So we decided to combine reduction step with cyclization without isolation of reduced intermediate **8a**. Hydroxyimide (–)-**8** was dissolved in dichloromethane with addition of methanol under an argon atmosphere and reduced with $NaBH_4$ at low temperature (starting from –40 °C to –10 °C). Then water was added to reaction mixture and next solvents were evaporated to give white precipitate. Trifluoroacetic acid was added and mixture was stirred at room temperature for 2 h. After work-up pure product hydroxylactam **9** was isolated with 62% yield and mp 202-203 °C, $[\alpha]_D$ –167.2 (*c* 1.0, MeOH), t_R = 19.099 min (HPLC, hexane/propan-2-ol = 3:1). To our knowledge this enantiomer is not described in literature. The structure was confirmed by spectral analysis. From analysis of ^{1}H NMR spectra and HPLC chromatogram we concluded that the reduction combined with cyclization produced only a single diastereomer resulting from a diastereospecific attack of the large benzene ring on the least hindered side opposite to the C-4 hydroxyl group of the acyliminium ion **8b**. Signals of protons at C-1 (δ = 4.21−4.42, m) and C-10b (δ = 4.57, d, *J* = 6.59 Hz) turned out to be diagnostic and compared with literature data they led to conclusion that protons at C-1 and C-10b have to be in *trans* position.[22,25] It indicated that absolute configuration of the new created stereogenic center at C-10b in compound (−)-**9** should be (*R*), which will be confirmed by results of further synthesis. To our knowledge such cyclization reaction were usually performed with protection of hydroxyl group at C-3 by ether or ester group in 2,5-pyrrolidinedione ring and we have evaluated reaction conditions without protection of hydroxyl group. In the next step hydroxyl group has to be removed from pyrrolidinone ring in compound (–)-**9**. It has been done without interruption of a new stereogenic center at C-10b. First we have tried to replaced hydroxyl group with halogen using the following reaction conditions: $SOCl_2$ in DMF, Br_2 and PPh_3 in pyridine, KI in H_3PO_4

and I_2 and PPh_3 in refluxing toluene. All this attempts failed. So we decide to replace it by phenylthio group which could be further removed using Raney-nickel. For introduction of phenylthio group we used method elaborated by Hata group,[26] and further developed by Kotsuki[27] and Skarżewski[28] groups. Using this method primary or secondary alcohols can be transformed into sulfides by using a combination of organic disulfides and tertiary phosphines such as Bu_3P-PhSSPh reagent system. In case of chiral compounds conversion of the absolute configuration took place.[28] Treatment of the compound (–)-**9** with diphenyl disulfide and tributylphospine in toluene under argon atmosphere in a sealed tube at 100 °C for 24 h led to substitution of C-1 hydroxyl group by phenylthio one. The product **10** was isolated as white crystals with mp 185-186 °C and $[\alpha]_D$ –227.6 (*c* 0.31, MeOH), $[\alpha]_D$ –221.8 (*c* 0.34, $CHCl_3$) and 27% yield. Structure of this new compound was confirmed by spectral analysis. Phenylthio group was removed from compound (–)-**10** using Raney nickel in THF solution at room temperature. After work-up lactam (–)-**7** was obtained as colorless oil with 91% yield and $[\alpha]_D$ –160.3 (*c* 1.0, MeOH) (lit.[30] $[\alpha]_D$ +171.0 (*c* 0.32, CH_2Cl_2)) for opposite enantiomer. The last step of the synthesis was $LiAlH_4$ reduction of lactam (–)-**7** to crispine A **1**. The reaction was carried out in refluxing THF for 3 h. After work-up pure crispine A **1** was isolated with 43% yield and 99.99% ee (HPLC), $[\alpha]_D$ –97.5 (*c* 0.245, MeOH), lit.[29] $[\alpha]_D$ –95.4 (*c* 1, MeOH). The absolute configuration of crispine A was confirmed as (*S*) by the comparison of the sign of the specific rotation measured. Thus configuration of C-10b in compound (–)-**7** is (*S*), and in compounds (–)-**10** and (–)-**9** has to be (*R*) what we have suggested earlier.

EXPERIMENTAL

Melting points were determined on a Koffler block and are uncorrected. IR spectra: Bruker FT-IR IFS 113V. NMR spectra: Bruker Avance 600 MHz, Varian Gemini 300, with TMS as the internal standard. Mass spectra: AM D402. Optical rotations: Perkin-Elmer polarimeter 242B at 20 °C. Analytical HPLC: Waters HPLC system with Chiralcel OD-H column (250 x 4.6 mm), flow rate 0.5 mL/min. Merck DC-Alufolien Kieselgel 60_{254} were used for TLC and Kieselgel 60 (70-230 mesh ASTM) for column chromatography. All compounds were purchased from Sigma-Aldrich Co. and used as received. THF was freshly distilled from $LiAlH_4$.

N-[2-(3,4-Dimethoxyphenyl)ethyl]succinimide 5.

The compound was prepared by a modified procedure of Opatz *et al*.[12] To the solution of homoveratrylamine **2** (1.812 g, 10 mmol) in acetic acid (30 mL) succinic anhydride **3** (1.800 g, 18 mmol) was added and mixture was refluxed for 4 h. Next the reaction mixture was cooled and acetic acid was evaporated under reduced pressure. The crude product **5** was crystallized from MeOH to give colorless crystals (2.280 g, 87% yield); mp 123-124 °C (lit.[13] mp 124-125 °C).

The spectral characteristics of our sample corresponded to the literature data.[12,13]

1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-2-pyrrolidinone 6.

The solution of imide **5** (2.0 g, 7.6 mmol) in EtOH (20 mL) and DCM (0.5 mL) was cooled to 0 °C. Then $NaBH_4$ (2.8 g, 76 mmol) and 1N ethanolic H_2SO_4 (7.6 mL) were added portionwise. Progress of reaction was monitored by tlc. On the end to the reaction mixture saturated aqueous $NaHCO_3$ solution (27 mL) was added. Phases were separated and the aqueous one was extracted with DCM (3 x 25 mL). Combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure led to the oily residue which was digested in Et_2O to give colorless precipitate of **6** (1.53 g, 76% yield); mp 97-101 °C (lit.[14] mp 107-110 °C); MS *m/z* 265 (M^+, 6), 165 (12), 164 (100), 151 (32), 107 (6), 68 (11); HRMS: calcd for $C_{14}H_{19}NO_4$ 265.13141, found 265.13215.

The other spectral characteristics of our sample corresponded to the literature data.[14,15]

8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one 7.

To the solution of hydroxylactam **6** (265 mg, 1 mmol) in THF (10 mL) the solution of (1*S*)-(+)-camphorsulphonic acid (700 mg, 3 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 30 min at room temperature. Next, Et_2O (5 mL) was added and stirring was continued for 15 min. Reaction mixture was neutralized with 5% aqueous NaOH, phases were separated and aqueous one was extracted with DCM (3 x 15 mL). Combined organic extracts were dried over anhydrous $MgSO_4$ and solvents were evaporated under reduced pressure to give colorless oil. It was digested with Et_2O to yield colorless precipitate of **7** (217 mg, 88% yield); mp 102-104 °C (lit.[16] mp 104 °C); HPLC (hexane/propan-2-ol = 3:1) t_R = 27.024 min (41.37%), t_R = 28.730 min (58.63%).

The spectral characteristics of our sample corresponded to the literature data for (±)-**7**.[16-20]

8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline, crispine A (±)-1.

To the suspension of $LiAlH_4$ (120 mg, 3.16 mmol) in anhydrous THF (10 mL) solution of lactam **7** (250 mg, 1.01 mmol) in THF (5 mL) was added dropwise at reflux. Reaction mixture was refluxed for 3 h and cooled to room temperature. Next 20% NaOH (2 mL) and H_2O (2 mL) were added dropwise and stirring was continued for 30 min. Resulting precipitate was filtered off and mother liquor was extracted with DCM (3 x 20 mL). Combined organic extracts were dried over anhydrous $MgSO_4$ and solvents were evaporated under reduced pressure to give an oil. It was recrystallised from a mixture of EtOH-*i*-Pr_2O (5:1, v/v) to yield light yellow crystals of crispine A (±)-**1** (205 mg, 87% yield); mp 88-89 °C (lit.[21] mp 87-89 °C). HPLC (hexane/propan-2-ol = 3:1) t_R = 13.704 min (50.17%), t_R = 17.971 (49.83%).

The spectral characteristics of our sample corresponded to the literature data.[17-19,21]

(3*S*)-(–)-1-(3,4-Dimethoxyphenethyl)-3-hydroxypyrrolidine-2,5-dione 8.

L-(–)-Malic acid **4** (2.5 g, 18.7 mmol) in xylene (150 mL) was heated in round bottom flask with Dean-Stark apparatus. To the clear solution 2-(3,4-dimethoxyphenyl)ethylamine **2** (5.7 g, 20.5 mmol) was added dropwise with intensive stirring. The reaction mixture was refluxed for 8 h. Then mixture was

cooled to room temperature and solvent was evaporated. The resulted precipitate was recrystallized from EtOAc to give pure imide **8** (3.6 g, 70% yield); mp 123-124 °C (lit.[23] mp 125 °C); $[\alpha]_D$ –51.4 (*c* 1.0, MeOH), lit.[23] $[\alpha]_D$ –67.2 (*c* 3.20, $CHCl_3$); HPLC (hexane/propan-2-ol = 3:1) t_R = 30.263 min.

The spectra of imide **8** are in agreement with literature data.[23]

(3*R*)-(+)-1-(3,4-Dimethoxyphenethyl)-3-hydroxypyrrolidine-2,5-dione 8.

Compound (+)-**8** was obtained using the same procedure as for (3*S*)-enantiomer **8** from D-malic acid **4** (0.5 g, 3.7 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine **2** (0.72 g, 4 mmol) in xylene (30 mL). Pure imide **8** (0.611 g, 59% yield) was obtained with mp 123-126 °C (EtOAc); $[\alpha]_D$ +53.1 (*c* 1.0, MeOH); IR (KBr) 3409, 2937, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (dd, *J* = 4,67 Hz, *J* = 18,11 Hz, 1H), 2,85 (t, *J* = 7,68 Hz, 2H), 3.05 (dd, *J* = 8,32 Hz, *J* = 18,11 Hz, 1H), 3.27 (broad s, 1H, disappears on treatment with D_2O), 3.69−3.78 (m, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.56 (dd, *J* = 8.37 Hz, *J* = 4.80 Hz, 1H), 6.65−6.84 (m, 3H); MS *m/z* 279 (M^+, 6), 261 (18), 164 (85), 151 (100), 149 (15), 91 (18); HR MS: calcd for $C_{14}H_{17}NO_5$ 279.11069, found 279.10820; HPLC (hexane/propan-2-ol = 3:1) t_R = 31.501 min.; 'racemic sample' t_R = 29.416 min [55.64% (*S*)] and t_R = 31.416 min [44.36% (*R*)]

The spectra of imide (+)-**8** are in agreement with our data and literature data published for (–)-**8**.[23]

(1*S*,10b*R*)-(–)-1-Hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one 9.

Hydroxyimide (–)-**8** (1 g, 3.58 mmol) was dissolved in anhydrous DCM (4.6 mL) and next anhydrous MeOH (2.3 mL) was added under an argon atmosphere. The mixture was cooled to temperature –40 °C (cryostat). $NaBH_4$ (145 mg, 3.8 mmol) was added portionwise at this temperature. The temperature of cryostat was allowed to reach –10 °C and stirring was continued for next 2 h at this temperature. Next H_2O (6.9 mL) was added to the reaction mixture and stirring was continued to reach room temperature in cryostat (approximately 1 h). Solvents were evaporated yielding white precipitate. CF_3CO_2H (6 mL) was added to the precipitate and mixture was stirred for 2 h at room temperature. Then the reaction mixture was neutralized with 20% aqueous NaOH and extracted with $CHCl_3$. Combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. The obtained residue was crystallized from a mixture of MeOH-*i*Pr_2O (5:2, v/v) yielding white crystals of **9** (0.592 g, 62% yield); mp 202-203 °C; $[\alpha]_D$ –167.2 (*c* 1.0, MeOH); IR (KBr) 3292, 2924, 1668 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.57−2.68 (m, 2H), 2.74−2.84 (m, 2H), 2.87−3.02 (m, 1H), 3.10 (broad s, 1H, disappears on treatment with D_2O), 3.86 (s, 3H), 3.88 (s, 3H), 4.26−4.37 (m, 2H), 4.57 (d, *J* = 6.59 Hz, 1H), 6.61 (s, 1H), 7.03 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.0, 36.8, 41.2, 55.9, 56.0, 63.4, 73.4, 107.9, 111.4, 125.2, 126.9, 148.1 (2x), 170.7; MS *m/z* 263 (M^+, 77), 262, (22), 234 (72), 232 (35), 191 (100), 190 (45), 176 (73); HR MS: calcd for $C_{14}H_{17}NO_4$ 263.11575, found 263.11727; HPLC (hexane/propan-2-ol = 3:1) t_R = 19.099 min.

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

Compound **9** (131 mg, 0.5 mmol) and $(PhS)_2$ (330 mg, 1.5 mmol) in toluene (3 mL) were placed in glass vial under argon atmosphere. Tributylphospine (405 mg, 2 mmol) was added and vial was closed and heated at 100 °C with stirring for 24 h. Navy blue color of the solution indicated the end of the reaction. Reaction mixture was placed in round bottom flask and solvent was evaporated in vacuum. Obtained navy blue precipitate was crystallized from MeOH and washed with Et_2O yielding compound (–)-**10** (47.7 mg, 27% yield) as a white crystals; mp 185-186 °C; $[\alpha]_D$ –227.6 (*c* 0.31, MeOH); $[\alpha]_D$ –221.8 (*c* 0.34, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.57 (d, *J* = 16.74 Hz, 1H), 2.66 (d, *J* = 12.9 Hz, 1H), 2.84−3.03 (m, 3H), 3.76 (s, 3H), 3.89 (s, 3H), 4.34 (t, *J* = 5.49 Hz , 1H), 4.37−4.46 (m, 1H), 5.14 (d, *J* = 4.94 Hz, 1H), 6.50 (s, 1H), 6.64 (s, 1H), 7.19−7.23 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.43, 37.11, 39.90, 48.19, 55.82, 55.84, 60.33, 109.38, 111.22, 123.60, 127.31, 127.57, 128.88 (2x), 132,48 (2x), 133.76, 147.76, 148.28, 171.48; MS *m/z* 355 (M^+, 3), 246 (29), 245 (100), 216 (18), 176 (20); HR MS: calcd for $C_{20}H_{21}NO_3S$ 355.12433, found 355,12320; HPLC (hexane/propan-2-ol = 3:1) t_R = 36.859 min.

(10b*S*)-(–)-8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(*2H)*-one 7.

To the solution of compound **10** (266 mg, 0.79 mmol) in THF (20 mL) Raney nickel (4.0 g) was added. Reaction mixture was stirred for 2 h at room temperature. Next catalyst was filtered off on a pad of Celite and washed with Et_2O. Filtrate was evaporated to yield lactam **7** as colorless oil (169 mg, 91% yield); $[\alpha]_D$ –160.3 (*c* 1.0, MeOH), lit.[30] $[\alpha]_D$ +171.0 (*c* 0.32, CH_2Cl_2) for opposite enantiomer; IR (film) 2938, 2859, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80−1.89 (m, 1H), 2.48−2,55 (m, 2H), 2.58−2.66 (m, 2H), 2.83−2.94 (m, 1H), 2.97−3.06 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.28−4.35 (m, 1H), 4.73 (t, *J* = 7.7 Hz, 1H), 6.57 (s, 1H), 6.62 (s, 1H); MS *m/z* 247 (M^+, 48), 246 (100), 232 (18), 231 (8), 230 (20), 216 (30), 204 (10), 190 (19), 176 (12); HR MS: calcd for $C_{14}H_{17}NO_3$ 247.12085, found 247.12169; HPLC (hexane/propan-2-ol = 3:1) t_R = 27.739 min.

(10b*S*)-(–)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline, crispine A 1.

To the solution of lactam (–)-**7** (85 mg, 0.35 mmol) in anhydrous THF (20 mL) $LiAlH_4$ (85 mg, 4.20 mmol) was added portionwise. Reaction mixture was refluxed for 3 h and cooled to room temperature. Next H_2O (1.4 mL) and 10% aqueous NaOH (0.8 mL) were added dropwise. Resulting precipitate was filtered off and mother liquor was extracted with DCM (3 x 20 mL). Combined organic extracts were dried over anhydrous $MgSO_4$ and solvents were evaporated under reduced pressure to give an oil. It was chromatographed on silica gel (CH_2Cl_2, CH_2Cl_2/MeOH 50:1) yielding optically active crispine A **1** (35 mg, 43% yield); $[\alpha]_D$ –97.5 (*c* 0.245, MeOH), lit.[29] $[\alpha]_D$ –95.4 (*c* 1, MeOH); MS *m/z* 233 (M^+, 30), 232 (100), 216 (18), 205 (32,5), 190 (40); ^{1}H NMR ($CDCl_3$) δ 1.66−1.79 (m, 1H), 1.82−1.99 (m, 2H), 2.28−2.37 (m, 1H), 2.53−2.77 (m, 3H), 2.97−3.10 (m, 2H), 3,14−3.21 (m, 1H), 3.41−3.47 (m, 1H), 3.84

(s, 3H), 3.85 (s, 3H), 6.57 (s, 1H), 6.61 (s, 1H); HPLC (hexane/propan-2-ol = 3:1) t_R = 13.237 min (99.99% ee).

SUPPLEMENTARY MATERIAL

Spectra and HPLC chromatograms of compounds **1**, **7** - **10** relevant to this paper are available online.

DECLARATION OF COMPETING INTEREST

The author declares no competing financial interest.

ACKNOWLEDGEMENTS

Master's students Marek Przybylski, Marta Stelmaszczyk and Krystian Kołodziej are gratefully acknowledged for preliminary experiments.

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