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Easy generation of an enantiopure general indolalkaloid building block by kinetic resolution

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Abstract

On treatment of racemic 1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline **7** with Boc-L-Ala and DCC the (1*S*)-enantiomer (1*S*)-**7** reacted much faster than (1*R*)-**7** and gave rise to 1-(2,2-dimethoxyethyl)-2-(*N*-*t*-Boc-L-alanyl)-1,2,3,4-tetrahydrocarboline. The untouched (1*R*)-enantiomer (1*R*)-**7** could be reisolated in enantiopure form.

1. Introduction

In an earlier paper we described the formation of a 2:1 mixture of the diastereomers methyl (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate **1** and methyl (1*S*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate **2** on treatment of L-tryptophan methyl ester with 1,1,3,3-tetramethoxypropane.[1] To elaborate this material into the alkaloid building blocks **3b** and **4b**, which had served very well in the diastereoselective preparation of ajmalicin and other indole and oxindole-alkaloids,[2–4] the Michael-addition with methylvinylketone was studied (Scheme 1).

The reaction rate of the (1*R*,3*S*)-diastereomer **1** in this Michael-addition proved to be higher than that of the (1*S*,3*S*)-diastereomer **2**, documented by the fact that after 5 days at room temperature the enantiopure ketone **5** was formed exclusively, albeit in low yield. Even if the reaction was driven to completion after 30 days, however, there was still a 2:1 mixture of epimers, with **5** prevailing.

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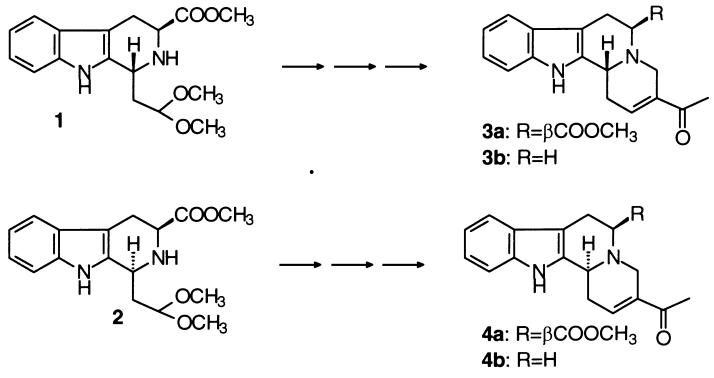
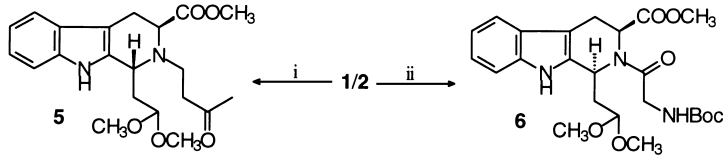


Scheme 1. Enantiopure 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizines were synthesized via Michael-addition, cyclization and dehydration

2. Results and discussion

Obviously, the Michael-addition of the nitrogen-atom and methyl vinyl ketone was under remarkable configurational control. In order to see if this has some generality the acylation process of methyl (1*R*,3*S* and 1*S*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate with Boc-Gly in the presence of DCC was studied. The selectivity of the acylation was clearly excellent and the diastereomer methyl (1*S*,3*S*)-1-(2,2-dimethoxyethyl)-2-(*N*-*t*-Boc-glycyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate **6** turned out to be the sole product of the reaction (Scheme 2).



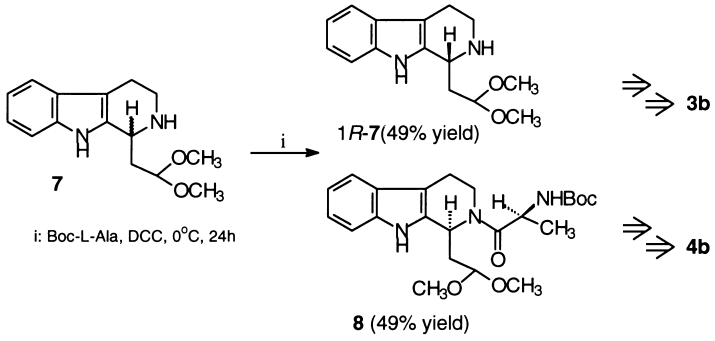
Scheme 2. Reactions and conditions: (i) methyl vinyl ketone, room temperature, 5 days, 33% yield; (ii) Boc-Gly, DCC, 0°C, 24 h, 48% yield. The reaction rate of the (1*R*,3*S*)-diastereomer in Michael-addition was higher than that of the (1*S*,3*S*)-diastereomer; in contrast, the reaction rate of the (1*S*,3*S*)-diastereomer in acylations was higher than that of the (1*R*,3*S*)-diastereomer

Since the C_1-configuration seemed to determine the steric outcome of the acylation process it was of course interesting to acylate racemic (1*RS*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline **7**, which was easily generated from 1,1,3,3-tetramethoxypropane and tryptamine, with the configurationally well-defined Boc-L-Ala hoping for a kinetic resolution.

The enantiomerically pure 1-(2,2-dimethoxyethyl)-2-(*N*-*t*-Boc-L-alanyl)-1,2,3,4-tetrahydrocarboline **8** was obtained in 49% yield and from the non-reacted portion (1*R*)-**7** was reisolated in 49% yield (Scheme 3). Since the NMR signals of this material, in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium as shift reagent, did not show any line splitting the enantiomeric purity should be higher than 95% ee.

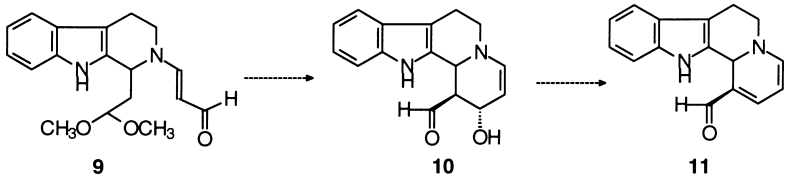
While (1*R*)-**7** can be taken to **4a** directly in high yield by a well established procedure,[1] **8** needs a preceding chemical or enzymatic amide hydrolysis, which is under active investigation and optimization in our laboratory.

Finally, three compounds which are generated when **7** is formed in an excess of 1,1,3,3-tetramethoxypropane deserve a closer inspection. They were shown to be the vinylogue amide **9**, the hydroxyaldehyde **10** and the corresponding elimination product **11** by extensive NMR studies including NOE measurements (Scheme 4). Since the en–amide double bond is configurationally highly



Scheme 3. In the acylation of racemic **7** with Boc-L-Ala only enantiomer (1*S*)-**7** was converted into enantiomerically pure amide **8**; the non-reacted enantiomer (1*R*)-**7** was reisolated

flexible under acidic conditions the aldol cyclization to form **10** and the subsequent diene formation by elimination can easily be rationalized.



Scheme 4. In the presence of an excess of 1,1,3,3-tetramethoxypropane, **7** was converted into 1-(2,2-dimethoxyethyl)-2-propenanyl-1,2,3,4-tetrahydrocarboline **9**, 2-hydroxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-1-aldehyde **10** and 6,7,12,12b-tetrahydroindolo[2,3-*a*]quinolizine-1-aldehyde **11**

The results reported here underline the remarkable directing effect of substituents in the 1-position of the tetrahydrocarbolines in acylation reactions at the neighboring NH group which can lead to a clear cut kinetic resolution.

3. Experimental

All reactions were carried out under nitrogen (1 bar). ^{1}H NMR spectra were recorded at 500 MHz on an ARX-500 instrument in deuteriochloroform with tetramethylsilane as internal standard. IR spectra were recorded with a Perkin–Elmer 983 instrument and mass spectra with a ZAB-MS (70 ev) spectrometer. Chromatography was performed with Qingdao silica gel H. Optical rotations were determined on Schmidt and Haensch Polartronic D instruments at 20°C.

*3.1. (1*RS*)-1-(2,2-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline 7*

(a) The stirring solution of 31.2 mg (0.2 mmol) of tryptamine in 5 ml of chloroform and 3 ml of methanol was acidified with 80 mg of concentrated hydrochloric acid to pH 2 at room temperature. To this solution 32.8 mg (0.2 mmol) of 1,1,3,3-tetramethoxypropane was added. The reaction mixture was stirred at room temperature for 45 h, by which time TLC analysis ($CHCl_3$:CH_3OH, 16:1) indicated complete disappearance of tryptamine, and neutralized with sodium carbonate. After filtration and evaporation the residue was purified by chromatography with $CHCl_3$:CH_3OH (30:1) and furnished 39.0 mg (75%) of **7**, as a colorless powder. Mp 148–150°C; IR (KBr): ν/cm^{-1}=3176 and 3119 (NH), 3090 (C=C-H), 2930, 2850 and 2736 (CH, CH_2 and CH_3), 1605 (NH), 1321 and 1280 (C-O-C), 1124, 1075 and 738

(1,2-disubstituted phenyl); ^{1}H NMR (DMSO-d_6): δ=1.859 [ddd, *J*=7.5 Hz, *J*=3.4 Hz, *J*=1.6 Hz, 1H, $(MeO)_2CHCH_2$], 1.898 (s, 1H, NH), 2.339 [ddd, *J*=7.5 Hz, *J*=3.4 Hz, *J*=1.6 Hz, 1H, $(MeO)_2CHCH_2$], 2.689 (m, *J*=12.0 Hz, 2H, CH_2CH_2NHCH), 3.024 (m, *J*=12.1 Hz, 2H, CH_2CH_2NHCH), 3.306 (s, 3H, OCH_3), 3.332 (s, 3H, OCH_3), 4.363 (dd, *J*=7.5 Hz, *J*=1.6 Hz, 1H, CH_2CH_2NHCH), 4.741 [dd, *J*=7.5 Hz, *J*=3.4 Hz, 1H, $(MeO)_2CH$], 6.964 (t, *J*=7.2 Hz, 1H, aromatic H), 7.055 (t, *J*=6.9 Hz, 1H, aromatic H), 7.306 (d, *J*=7.8 Hz, 1H, aromatic H), 7.393 (d, *J*=7.2 Hz, 1H, aromatic H), 9.472 (s, 1H, pyrrole NH); MS (100°C), *m/e* (%): 260 (33.0) [M^+], 228 (13.0) [M^+-MeOH], 213 (32.0) [$M^+-MeOH-CH_3$], 199 (21) [$M^+-(MeO)_2+H$], 171 (100) [$M^+-(MeO)_2-CHCH_2$]. $C_{15}H_{20}N_2O_2$ calcd: C, 69.21; H, 7.74; N, 10.76; found: C, 69.30; H, 7.80; N, 10.80; mol. mass: 260.34.

(b) Using procedure (a) with excess (49.2 mg, 0.30 mmol) of 1,1,3,3-tetramethoxypropane, besides 42 mg (76%) of **7**, 5 mg of 1-(2,2-dimethoxyethyl)-2-propenanyl-1,2,3,4-tetrahydrocarboline **9**, 3 mg of 2-hydroxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]-quimolizine-1-aldehyde **10** and 4 mg of 6,7,12,12b-tetrahydroindolo[2,3-*a*]quinolizine-1-aldehyde **11** were isolated.

Compound **9**: IR (KBr): ν/cm^{-1}=3450 (NH), 3027 and 3010 (C=C-H), 2960 and 2830 (CH, CH_2 and CH_3), 2815 and 2725 (CHO), 1730 (C=O), 1630 (olefinic C=C), 1600, 1500, 1450 and 1400 (aromatic C=C), 1380 (CH_3), 1345 (C-O-C), 1115, 1080 and 1050 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=2.23 [m, 1H, $(MeO)_2CHCH_2$], 2.28 [m, 1H, $(MeO)_2CHCH_2$], 2.89 (m, 1H, CH_2CH_2N), 2.98 (m, 1H, CH_2CH_2N), 3.46 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.73 (m, 1H, CH_2CH_2N), 3.82 (m, 1H, CH_2CH_2N), 4.64 [s, broad, 1H, $(MeO)_2CHCH_2CH$], 5.00 [s, broad, 1H, $(MeO)_2CHCH_2CH$], 5.49 (t, broad, 1H, NCH=*CH*CHO), 7.20 (d, broad, *J*=9.0 Hz, 1H, N*CH*=CHCHO), 7.18 (t, *J*=7.3 Hz, 1H, aromatic H), 7.23 (t, *J*=7.7 Hz, 1H, aromatic H), 7.39 (d, *J*=8.0 Hz, 1H, aromatic H), 7.52 (d, *J*=7.8 Hz, 1H, aromatic H), 8.97 (s, 1H, pyrrole H), 9.18 (d, *J*=8.0 Hz, 1H, C*H*O); FAB-MS, *m/e*: 315 (20) [M+H]$^+$. $C_{18}H_{22}N_2O_3$ calcd: C, 68.77; H, 7.05; N, 8.91; found: C, 68.90; H, 7.14; N, 8.71; mol. mass: 314.16.

Compound **10**: IR (KBr): ν/cm^{-1}=3500–3400 (NH and OH), 3025 and 3010 (C=C-H), 2965 and 2820 (CH, CH_2 and CH_3), 2820 and 2730 (CHO), 1740 (C=O), 1635 (olefinic C=C), 1605, 1515, 1450 and 1415 (aromatic C=C), 1385 (CH_3), 1350 (C-O-C), 1120, 1095 and 1050 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=1.78 (s, 1H, OH), 1.85 (m, 1H, NCH*CH*CHO), 3.07 (t, *J*=6.5 Hz, 2H, CH_2CH_2N), 3.55 (m, *J*=6.5 Hz, 2H, CH_2CH_2N), 4.94 [t, *J*=5.0 Hz, 1H, NCHCH(CHO)*CH*(OH)], 5.41 [m, 1H, N*CH*CH(CHO)CH(OH)], 7.08 [t, *J*=5.1 Hz, 1H, NCH=CHCH(OH)], 8.32 [d, *J*=12.2 Hz, 1H, N*CH*=CHCH(OH)], 7.17 (t, *J*=5.0 Hz, 1H, aromatic H), 7.25 (t, *J*=10.0 Hz, 1H, aromatic H), 7.42 (d, *J*=10.0 Hz, 1H, aromatic H), 7.60 (d, *J*=10.0 Hz, 1H, aromatic H), 9.10 (m, *J*=5.0 Hz, 1H, C*H*O), 10.10 (s, 1H, pyrrole NH); FAB-MS, *m/e*: 269 (31) [M+H]$^+$. $C_{16}H_{16}N_2O_2$ calcd: C, 71.62; H, 6.01; N, 10.44; found: C, 71.80; H, 6.15; N, 10.20; mol. mass: 268.12.

Compound **11**: IR (KBr): ν/cm^{-1}=3449 (NH), 3030 and 3011 (C=C-H), 2960 and 2819 (CH, CH_2 and CH_3), 2820 and 2720 (CHO), 1729 (C=O), 1629 (olefinic C=C), 1600, 1510, 1460 and 1400 (aromatic C=C), 1120, 1085 and 1050 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=3.07 (t, *J*=6.5 Hz, 2H, CH_2CH_2NCH), 3.55 (m, *J*=6.5 Hz, 2H, CH_2CH_2NCH), 5.13 (s, 1H, CH_2CH_2NCH), 6.70 (m, *J*=5.0 Hz, 1H, NCH=CH*CH*=CCHO), 7.08 (t, *J*=0.5 Hz, 1H, NCH=*CH*CH=CCHO), 7.17 (t, *J*=5.0 Hz, 1H, aromatic H), 7.25 (t, *J*=10.0 Hz, 1H, aromatic H), 7.42 (d, *J*=10.0 Hz, 1H, aromatic H), 7.60 (d, *J*=10.0 Hz, 1H, aromatic H), 8.32 (d, *J*=12.2 Hz, 1H, N*CH*CHCH=CCHO), 9.10 (t, *J*=5.0 Hz, 1H, *CHO*), 10.10 (s, 1H, pyrrole H); FAB-MS, *m/e*: 251 (25) [M+H]$^+$. $C_{16}H_{14}N_2O$ calcd: C, 76.78; H, 5.64; N, 11.19; found: C, 76.85; H, 5.49; N, 11.00; mol. mass: 250.11.

3.2. Methyl (1S,3S)-1-(2,2-dimethoxyethyl)-2-(N-t-Boc-glycyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate **6**

A solution of 35.0 mg (0.20 mmol) of Boc-Gly, 27.0 mg (0.20 mmol) of HOBt, 46.0 mg (0.22 mmol) of DCC and 5 ml of anhydrous THF was stirred at 0°C for 24 h. The DCU precipitated was removed by filtration. To the filtrate 63.6 mg (0.2 mmol) of methyl (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (**2** and **1**), which was prepared according to the literature,[3] and 22.5 mg (0.22 mmol) of *N*-methylmorpholine were added. The reaction mixture was stirred at room temperature for 1 h. On evaporation the residue was purified and separated by chromatography ($CHCl_3$:CH_3OH, 30:1) to afford 45.9 mg (48%) of (1*S*,3*S*)-**6**, and 30.8 mg (48%) of **1**.

Compound **1**: IR (KBr): ν/cm^{-1}=3441 and 3401 (NH), 3010 (C=C-H), 2960 and 2838 (CH, CH_2 and CH_3), 1742 (C=O), 1600, 1500 and 1456 (aromatic C=C), 1325 and 1273 (C-O-C), 1125 and 1072 (1,2-disubstituted phenyl). ^{1}H NMR: δ/ppm=2.20 [t, *J*=4.1 Hz, 1H, $(MeO)_2CHCH_2CH$], 2.31 [t, *J*=7.2 Hz, 1H, $(MeO)_2CHCH_2CH$], 2.40 (s, 1H, NH), 2.94 (m, *J*=2.1 Hz, 1H, CH_2CHCO_2Me), 3.13 (m, *J*=2.0 Hz, 1H, CH_2CHCO_2Me), 3.35, [s, 3H, $CH(OCH_3)_2$], 3.47 [s, 3H, $CH(OCH_3)_2$], 3.74 (s, 3H, CO_2CH_3), 3.97 (dd, *J*=7.0 Hz, *J*=3.1 Hz, 1H, $CHNHCHCO_2Me$), 4.35 (t, *J*=7.0 Hz, 1H, $CHNHCHCO_2Me$), 4.65 [t, *J*=7.0 Hz, 1H, $(MeO)_2CHCH_2CH$] 7.15 (m, *J*=7.0 Hz, 2H, aromatic H), 7.34 (d, *J*=8.0 Hz, 1H, aromatic H), 7.49 (d, *J*=8.0 Hz, 1H, aromatic H), 8.54 (s, 1H, pyrrole NH); FAB-MS, *m/e* (%): 319 (36.0) $[M+H]^+$; [α]=−46.8 (*c* 0.05 in $CHCl_3$).

Compound (1*S*,3*S*)-**6**: IR (KBr): ν/cm^{-1}=3450 and 3400 (NH), 3005 (C=C-H), 2960 and 2830 (CH, CH_2, and CH_3), 1745 and 1706 (ester C=O), 1670 (amide C=O), 1600, 1545 and 1430 (aromatic C=C), 1395, 1380 and 1370 (CH_3), 1325 and 1270 (C-O-C), 1120 and 1070 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=1.50 [s, 9H, $-C(CH_3)_3$], 2.18 (m, 1H, $CHCH_2CH(OCH_3)_2$], 2.43 [m, 1H, $CHCH_2CH(OCH_3)_2$], 3.08 (dd, *J*=4.7 Hz, *J*=1.5 Hz, 1H, $CH_2CHCOOCH_3$), 3.60 (m, 1H, $CH_2CHCOOCH_3$), 3.66 [s, 6H, $CH_2CH(OCH_3)_2$], 3.46 (s, 3H, $COOCH_3$), 4.06 (dd, *J*=12.8 Hz, *J*=0.4 Hz, 1H, $NCOCH_2NH$), 4.21 (dd, *J*=12.2 Hz, *J*=0.4 Hz, 1H, $NCOCH_2NH$), 4.82 (d, *J*=5.5 Hz, 1H, $CH_2CHCOOCH_3$), 4.93 [dd, J=9.6 Hz, *J*=3.2 Hz, 1H, $CHCH_2C(OCH_3)_2$], 5.38 [d, *J*=7.6 Hz, 1H, $CH_2CH(OCH_3)_2$], 5.70 (m, 1H, $NCOCH_2NHCO$), 7.14 (t, *J*=7.1 Hz, 1H, aromatic H), 7. 24 (t, *J*=7.3 Hz, 1H, aromatic H), 7.40 (d, *J*=8.0 Hz, 1H, aromatic H), 7.57 (d, *J*=8.0 Hz, 1H, aromatic H), 9.18 (s, 1H, pyrrole NH); FAB-MS, *m/e* (%): 476 (40.1) $[M+H]^+$; [α]=−13.0 (*c* 0.02 in $CHCl_3$). $C_{24}H_{33}N_3O_7$ calcd: C, 60.62; H, 6.99; N, 8.84; found: C, 60.80; H, 6.90; N, 8.76; mol. mass: 475.54.

3.3. Methyl (1R,3S)-1-(2,2-dimethoxyethyl)-2-(N-t-Boc-glycyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate **6**

Using the procedure preparing (1*S*, 3*S*)-**6** (reaction time 60 h) from 16.0 mg (0.05 mmol) of **1** 23.0 mg (96%) of (1*R*,3*S*)-**6** were obtained.

Compound (1*R*,3*S*)-**6**: IR (KBr): ν/cm^{-1}=3445 and 3395 (NH), 3010 (C=C-H), 2965 and 2841 (CH, CH_2 and CH_3), 1740 and 1700 (ester C=O), 1675 (amide C=O), 1605, 1550 and 1450 (aromatic C=C), 1395, 1380 and 1369 (CH_3), 1321 and 1268 (C-O-C), 1119 and 1072 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=1.50 [s, 9H, $-C(CH_3)_3$], 2.30 [m, 1H, $CHCH_2CH(OCH_3)_2$], 2.62 [m, 1H, $CHCH_2CH(OCH_3)_2$], 3.14 [m, 1H, $CH_2CHCOOCH_3$], 3.34 (m, 1H, $CH_2CHCOOCH_3$), 3.52 [s, 6H, $CH_2CH(OCH_3)_2$], 3.57 (s, 3H, $COOCH_3$), 3.80 (d, *J*=15.1 Hz, 2H, $NCOCH_2NH$), 4.70 (m, 1H, $CH_2CHCOOCH_3$), 4.82 [m, 1H, $CHCH_2CH$-$(OCH_3)_2$], 5.50 (m, 1H, $NCOCH_2NHCO$), 5.54 [m, 1H, $CHCH_2CH(OCH_3)_2$], 7.15 (t, *J*=7.2 Hz, 1H, aromatic H), 7.20 (t, *J*=6.5 Hz, 1H, aromatic H), 7.40 (d, *J*=7.7 Hz, aromatic H), 7.52 (d, *J*=7.5 Hz, 1H, aromatic H), 8.55 (s, 1H, pyrrole NH); FAB-MS, *m/e* (%):

476 (30.2) $[M+H]^+$; [α]=+80 (*c* 0.02 in $CHCl_3$). $C_{24}H_{33}N_3O_7$ calcd: C, 60.62; H, 6.99; N, 8.84; found: C, 60.70; H, 6.89; N, 8.69; mol. mass: 475.54.

*3.4. (1*S*)-1-(2,2-Dimethoxyethyl)-2-(*N-t-*Boc*-L-*alanyl)-1,2,3,4-tetrahydrocarboline* **8**

A solution of 37.8 mg (0.20 mmol) of Boc-L-Ala, 27.0 mg (0.20 mmol) of HOBt, 46.0 mg (0.22 mmol) of DCC and 5 ml of anhydrous THF was stirred at 0°C for 24 h. The DCU precipitated was removed by filtration. To the filtrate 52.0 mg (0.2 mmol) of **7** and 22.5 mg (0.22 mmol) of *N*-methylmorpholine were added. The reaction mixture was stirred at room temperature for 2 h. On evaporation the residue was purified and separated by chromatography ($CHCl_3$:CH_3OH, 30:1) to afford 42.0 mg (49%) of (1*S*)-**8** and 25.5 mg (49%) of (1*R*)-**7**.

Compound (1*S*)-**8**: IR (KBr): ν/cm^{-1}=3446 and 3410 (NH), 3009 (C=C-H), 2961 and 2842 (CH, CH_2 and CH_3), 1711 (ester C=O), 1647 (amide C=O), 1610, 1550 and 1440 (aromatic C=C), 1395, 1380 and 1374 (CH_3), 1315 and 1269 (C-O-C), 1124 and 1070 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=1.38 [d, *J*=6.9 Hz, 3H, CO(*CH*$_3$)NHCO], 1.50 [s, 9H, C(*CH*$_3$)$_3$], 2.18 [dm, *J*=7.5 Hz, *J*=5.6 Hz, 2H, CH*CH*$_2$CH(OCH$_3$)$_2$], 2.93 (m, *J*=3.4 Hz, 1H, *CH*$_2$CH$_2$NCO), 3.15 (m, *J*=3.4 Hz, 1H, *CH*$_2$CH$_2$NCO), 3.42 (s, 3H, O*CH*$_3$), 3.50 (s, 3H, O*CH*$_3$), 3.52 (m, *J*=13.8 Hz, 1H, CH$_2$*CH*$_2$NCO), 4.20 (m, *J*=13.8 Hz, 1H, CH$_2$*CH*$_2$CO), 4.76 [m, 1H, *CH*CH$_2$CH(OCH$_3$)$_2$], 4.78 [m, 1H, COC*H*(CH$_3$)NHCO], 5.60 [d, *J*=8.2 Hz, 1H, COCH(CH$_3$)*NH*CO], 5.66 [dd, *J*=7.5 Hz, *J*=5.6 Hz, 1H, CHCH$_2$*CH*(OCH$_3$)$_2$], 7.12 (t, *J*=7.8 Hz, 1H, aromatic H), 7.21 (t, *J*=6.1 Hz, 1H, aromatic H), 7.37 (d, *J*=8.1 Hz, 1H, aromatic H), 7.50 (d, *J*=7.8 Hz, 1H, aromatic H), 8.65 (s, 1H, pyrrole *NH*); FAB-MS, *m/e* (%): 432 (30) $[M+H]^+$; [α]=−51.7 (*c* 1.2 in $CHCl_3$:CH_3OH, 1:1). $C_{23}H_{33}N_3O_5$ calcd: C, 61.73; H, 7.43; N, 9.39; found: C, 61.84; H, 7.30; N, 9.48; mol. mass: 431.53 (MS).

Compound (1*R*)-**7**: mp 144–145°C; IR (KBr): ν/cm^{-1}=3176 and 1605 (NH), 3084 (C=CH), 2941 and 2742 (CH, CH_2 and CH_3), 1318 and 1280 (C-O-C), 1122, 1073 and 736 (disubstituted phenyl CH); ^{1}H NMR: δ/ppm=1.25 (s, 1H, NH), 2.19 [ddd, *J*=14.0 Hz, *J*=8.5 Hz, *J*=4.6 Hz, 1H, (MeO)$_2$CH*CH*$_2$], 2.84 [ddd, *J*=14.0 Hz, *J*=4.6 Hz, *J*=3.0 Hz, 1H, (MeO)$_2$CH*CH*$_2$], 3.05 (m, *J*=11.9 Hz, 2H, *CH*$_2$CH$_2$NH), 3.45 (m, *J*=11.0 Hz, 2H, CH$_2$*CH*$_2$NH), 3.50 (s, 3H, OCH$_3$), 3.55 (s, 3H, OCH$_3$), 4.60 [dd, *J*=8.5 Hz, *J*=3.0 Hz, 1H, *CH*CH$_2$CH(OCH$_3$)$_2$], 4.69 [t, *J*=4.6 Hz, 1H, (MeO)$_2$*CH*], 7.13 (t, *J*=6.9 Hz, 1H, aromatic H), 7.17 (t, *J*=7.1 Hz, 1H, aromatic H), 7.21 (d, *J*=7.1 Hz, aromatic H), 7.37 (d, *J*=8.1 Hz, 1H, aromatic H), 9.10 (s, 1H, pyrrole NH); MS (120°C), *m/e* (%): 260 (32.5) $[M^+]$, 227 (100) $[M^+-MeOH-H]$, 213 (30.5) $[M^+-MeOH-CH_3]$, 199 (21.7) $[M^+-2OCH_3+H]$, 171 (100) $[M^+-(MeO)_2CHCH_2]$; [α]=+20.8 (*c* 0.93 in MeOH). $C_{15}H_{20}N_2O_2$ calcd: C, 69.21; H, 7.74; N, 10.76; found: C, 69.32; H, 7.85; N, 10.69; mol. mass: 260.34 (MS).

*3.5. (1*R*)-1-(2,2-Dimethoxyethyl)-2-(*N-t-*Boc*-L-*alanyl)-1,2,3,4-tetrahydrocarboline* **8**

Using the procedure for preparing (1*S*)-**8** (reaction time 70 h) from 13.0 mg (0.05 mmol) of (1*R*)-**7** 21.0 mg (97%) of (1*R*)-**8** were obtained. IR (KBr): ν/cm^{-1}=3450 and 3401 (NH), 3015 (C=C-H), 2960 and 2838 (CH, CH_2 and CH_3), 1700 (ester C=O), 1670 (amide C=O), 1607, 1551 and 1445 (aromatic C=C), 1396, 1381 and 1376 (CH_3), 1320 and 1270 (C-O-C), 1120 and 1075 (1,2-disubstituted phenyl); ^{1}H NMR: δ/ppm=1.43 [d, *J*=6.9 Hz, 3H, NCOCH(*CH*$_3$)NHCO], 1.50 [s, 9H, C(*CH*$_3$)$_3$], 2.20 [m, *J*=14.0 Hz, 2H, CH*CH*$_2$CH(OCH$_3$)$_2$], 2.91 (m, 1H, *CH*$_2$CH$_2$NCO), 2.93 (m, 1H, *CH*$_2$CH$_2$NCO), 3.46 (s, 3H, *OCH*$_3$), 3.50 (s, 3H, *OCH*$_3$), 3.52 (m, *J*=13.5 Hz, 1H, CH$_2$*CH*$_2$NCO), 4.14 (dm, *J*=13.5 Hz, *J*=4.6 Hz, 1H, CH$_2$*CH*$_2$NCO), 4.76 [m, 1H, NCO*CH*(CH$_3$)NHCO], 4.78 [m, 1H, *CH*CH$_2$CH(OCH$_3$)$_2$], 5.57 [d, *J*=7.9 Hz, 1H, NCOCH(CH$_3$)*NH*CO], 5.78 [t, *J*=6.9 Hz, 1H, CHCH$_2$*CH*(OCH$_3$)$_2$], 7.19 (t, *J*=7.5 Hz,

1H, aromatic H), 7.24 (t, *J*=6.5 Hz, 1H, aromatic H), 7.35 (d, *J*=7.2 Hz, 1H, aromatic H), 7.50 (d, *J*=7.6 Hz, 1H, aromatic H), 8.60 (s, 1H, pyrrole NH); FAB-MS, *m/e* (%): 432 (35) $[M+H]^+$; $[\alpha]$=+32.6 (*c* 1.9 in $CHCl_3$:CH_3OH, 1:1). $C_{23}H_{33}N_3O_5$ calcd: C, 61.73; H, 7.43; N, 9.39; found: C, 61.59; H, 7.49; N, 9.51; mol. mass: 431.24 (MS).

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