Short, asymmetric synthesis of epi-morphine ACNO analogues

Nicolas Heureux,[a] Johan Wouters,[b] Bernadette Norberg[b] and István E. Markó*[a]

[a] Unité de Chimie Organique et Médicinale, Université catholique de Louvain, Place Pasteur 1, 1348 Louvain-la-Neuve, Belgium. Fax: 0032 10472788; Tel: 0032 10472782; E-mail: marko@chim.ucl.ac.be [b] Laboratoire de Chimie Biologique Structurale, Facultés Universitaires Notre-Dame de la Paix, Rue Grafé 2, 5000 Namur, Belgium. Fax: 0032 81724530; Tel: 0032 81724550; E-mail: johan.wouters@fundp.ac.be

Experimental section

2-benzyl-3,4,9,9a,10,11,12,12a-octahydropyrido[3,4-d]carbazol-1(2H)-one 6

To ethyleneglycol (150 ml), Na (6.11 g, 250 mmol) was added in small portions and the mixture was heated to 50°C until deprotonation occurs. To the yellow solution thus obtained, **5** (1.50 g, 4.30 mmol) then monohydrated hydrazine (18.3 ml, 380 mmol) were added and the solution heated to 185°C for 3h. After cooling, 40 ml of water were added then the mixture was extracted with dichloromethane (3 x 100 ml). The combined extracts were washed by saturated aqueous NaCl (100 ml), dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography (silicagel, dichloromethane-methanol 100 : 1) to give **5** (994 mg, 70%) as a white solid.

IR (film, cm^{-1}) 3312, 3028 and 1624; **^{1}H NMR** (250 MHz, $CDCl_3$, Me_4Si) 7.20-7.27 (5H, m, 5 x CH_{Ph}), 6.94 (1H, dd, *J* 7.6 and 7.6, CHCHC*H*CH), 6.76 (1H, d, *J* 7.6, C*H*CHCHCH), 6.54-6.60 (2H, m, CHC*H*CHC*H*), 4.58 (2H, s, 2 x NCH_2Ph), 3.58 (1H, br s, N*H*), 3.39 (1H, dd, *J* 4.4 and 6.4, NHC*H*(C)CH_2), 3.28-3.33 (2H, m, 2 x $CH_2CH_2NCH_2Ph$), 2.62 (1H, dd, *J* 4.4 and 7.9, NCOC*H*(C)CH_2), 1.28-2.08 (8H, m, 2 x $CH_2CH_2NCH_2Ph$ and 6 x $CH_2CH_2CH_2$); **^{13}C NMR** (62.5 MHz, $CDCl_3$) 171.9 (CO), 149.3 (NH*C*(C)CH), 137.4 (NHC(*C*)CH), 134.8 (*C*CHCHCHCHCH), 128.8 (C*C*HCHCHCHCH), 128.5 (CCH*C*HCH*C*HCH), 128.1 (CCHCH*C*HCHCH), 127.7 (CHCH*C*HCH), 122.8 (CH*C*HCHCH), 119.2 (*C*HCHCHCH), 110.6 (CHCHCH*C*H), 62.6 (NHCH(C)CH_2), 50.7 (NCH_2Ph), 45.8 (NHCH(*C*)CH_2), 44.9 ($CH_2CH_2NCH_2Ph$), 43.9 (NCO*C*H(C)CH_2), 29.3 ($CH_2CH_2NCH_2Ph$), 28.2 ($CH_2CH_2CH_2$), 25.3 ($CH_2CH_2CH_2$), 19.7 ($CH_2CH_2CH_2$); **HRMS** (*m/z*, TOF ES+) 333.1956 ($M+H^+$ requires 333.1967); **MS** (*m/z*, APCI+) 333 (100, $M+H^+$).

2-benzyl-3,4,9,9a,10,11,12,12a-octahydropyrido[3,4-d]carbazol-1(2H)-one 6'

Step a

To a solution of **5** (0.45 g, 1.30 mmol) in glacial acetic acid (20 ml), 1,2-ethanedithiol (0.20 ml, 2.35 mmol) and $BF_3.OEt_2$ (0.33 ml, 2.60 mmol) were added and the reaction mixture was stirred at 65°C for 1h30. After cooling, 100 ml of water were added then the mixture was carefully neutralised with aqueous $NaHCO_3$. The aqueous mixture was then extracted with dichloromethane (3 x 100 ml), the combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The yellow solid obtained (0.50 g) was used without further purification in the next step.

Step b

To the crude dithio derivative (0.50 g), prepared in step a, a suspension of washed (5 x 20 ml of methanol) Raney-nickel (10g) in methanol (200 ml) was added the reaction mixture was stirred at reflux for 1h30. After cooling, the mixture was then quickly filtered over celite®, the filtrate dried over $MgSO_4$ and evaporated under reduced pressure. The residue was then purified by column chromatography (silicagel, dichloromethane-methanol 50 : 1) to give **6'** (0.28 g, 64%) as a white solid.

IR (film, cm^{-1}) 3315, 3028 and 1634; **^{1}H NMR** (500 MHz, $CDCl_3$, Me_4Si) 7.26-7.36 (5H, m, 5 x CH_{Ph}), 7.00 (1H, dd, *J* 7.5 and 7.5, CHCHC*H*CH), 6.64-6.67 (2H, m, C*H*CHCHCH and CHCHCHC*H*), 6.52 (1H, dd, *J* 7.5 and 7.5, CHC*H*CHCH), 4.85 (1H, d_{AB}, *J* 14.0, NCH_2Ph), 4.39 (1H, d_{AB}, *J* 14.0, NCH_2Ph),

3.62 (1H, br s, N*H*), 3.27 (1H, dd, *J* 6.0 and 9.5, NHC*H*(C)CH_2), 3.15 (1H, dd, *J* 7.0 and 12.5, NCOC*H*(C)CH_2), 3.02 (1H, ddd, *J* 5.5, 12.5 and 12.5, CH_2CH_2NCH_2Ph), 2.46-2.49 (1H, m, CH_2CH_2NCH_2Ph), 2.32-2.34 (1H, m, CH_2CH_2NCH_2Ph), 2.08-2.12 (1H, m, $CH_2CH_2CH_2$), 1.80 (1H, ddd, *J* 6.5, 12.5 and 12.5, CH_2CH_2NCH_2Ph), 1.66-1.77 (2H, m, C$H_2CH_2CH_2$), 1.11-1.30 (3H, m, 2 x $CH_2CH_2CH_2$ and C$H_2CH_2CH_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) 170.7 (CO), 150.2 (NH*C*(C)CH), 136.9 (NHC(*C*)CH), 129.0 (*C*CHCHCHCHCH), 128.7 (C*C*HCHCHCHCH), 128.4 (CCH*C*HCH*C*HCH), 127.8 (CCHCH*C*HCHCH), 127.3 (CHCH*C*HCH), 124.1 (CH*C*HCHCH), 118.6 (*C*HCHCHCH), 111.2 (CHCHCH*C*H), 65.8 (NH*C*H(C)CH_2), 50.2 (NCH_2Ph), 47.9 (NHCH(*C*)CH_2), 45.9 (CH_2CH_2NCH_2Ph), 43.9 (NCO*C*H(C)CH_2), 33.0 (*C*H_2CH_2NCH_2Ph), 30.2 ($CH_2CH_2CH_2$), 22.8 (*C*$H_2CH_2CH_2$), 21.9 ($CH_2CH_2CH_2$); **MS** (*m/z*, APCI+) 333 (100, M+H$^+$).

2-benzyl-3,4,10,11,12,12a-hexahydropyrido[3,4-d]carbazol-1(2H)-one 7

To a solution of $BnNMe_3Cl$ (1.02 g, 5.47 mmol) and **6** (1.82 g, 5.46 mmol) in dry dichloromethane (150 ml) at -40°C, $KMnO_4$ (880 mg, 5.57 mmol) was added and the solution kept at this temperature for 2h30. The brown mixture was then quickly filtered over celite® and the filtrate washed with saturated aqueous $NaHCO_3$ (2 x 50 ml) and water (50 ml). The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography (silicagel, dichloromethane-ethyl acetate-triethylamine 66 : 33 : 1) to give **7** (1.28 g, 71%) as an orange solid.

IR (film, cm^{-1}) 3058 and 1636; **^{1}H NMR** (250 MHz, $CDCl_3$, Me_4Si) 7.51 (1H, d, *J* 7.9, CHCHCHC*H*), 7.20-7.33 (6H, m, 5 x CH_{Ph} and CHCHC*H*CH), 6.93 (1H, dd, *J* 7.9 and 7.9, CHC*H*CHCH), 6.82 (1H, d, *J* 7.9, C*H*CHCHCH), 4.72 (1H, d_{AB}, *J* 13.9, NCH_2Ph), 4.62 (1H, d_{AB}, *J* 13.9, NCH_2Ph), 3.52 (1H, ddd, *J* 5.2, 12.3 and 12.3, CH_2CH_2NCH_2Ph), 3.30-3.36 (1H, m, CH_2CH_2NCH_2Ph), 2.79-2.84 (1H, dd, *J* 6.3 and 12.7, NCOC*H*(C)CH_2), 2.39-2.58 (2H, m, 2 x CH_2CH_2CH_2), 2.16-2.24 (3H, m, 2 x CH_2CH_2NCH_2Ph and C$H_2CH_2CH_2$), 1.74-1.96 (1H, m, C$H_2CH_2CH_2$), 1.35-1.53 (1H, m, CH_2CH_2CH_2), 1.08-1.20 (1H, m, CH_2CH_2CH_2); **^{13}C NMR** (62.5 MHz, $CDCl_3$) 186.0 (C=N), 170.4 (CO), 154.5 (NH*C*(C)CH), 142.2 (NHC(*C*)CH), 136.9 (*C*CHCHCHCHCH), 128.9 (C*C*HCHCHCHC*H* and CHCH*C*HCH), 128.6 (CCH*C*HCH*C*HCH), 128.0 (CCHCH*C*HCHCH), 125.2 (CH*C*HCHCH), 122.9 (*C*HCHCHCH), 120.9 (CHCHCH*C*H), 55.2 (NHCH(*C*)CH_2), 50.4 (NCH_2Ph), 48.9 (CH_2CH_2NCH_2Ph), 44.0 (NCO*C*H(C)CH_2), 29.4 (*C*H_2CH_2NCH_2Ph), 27.6 ($CH_2CH_2CH_2$ and *C*$H_2CH_2CH_2$), 24.2 ($CH_2CH_2CH_2$); **HRMS** (*m/z*, TOF ES+) 353.1632 (M+Na$^+$ requires 353.1630); **MS** (*m/z*, APCI+) 331 (100, M+H$^+$).

2-benzyl-3,4,10,11,12,12a-hexahydro-9a-hydroxy-2H-benzofuro[3,2-e]isoquinolin-1(9aH)-one 8

To a suspension of **7** (30 mg, 0.10 mmol) in aqueous HCl (4% v/v, 3 ml) at 0°C, an aqueous solution of $NaNO_2$ (1M, 150 µl, 0.15 mmol) was added dropwise and the mixture stirred at room temperature for 20h. The green suspension was then extracted with dichloromethane (3 x 10 ml), the combined extracts were dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography (silicagel, dichloromethane-ethyl acetate-triethylamine 66 : 33 : 1) to give **7** (29 mg, 91%) as an orange solid.

IR (film, cm^{-1}) 3223 and 1612; **^{1}H NMR** (500 MHz, $CDCl_3$, Me_4Si) 7.31-7.37 (5H, m, 5 x CH_{Ph}), 7.14 (1H, dd, *J* 8.0 and 8.0, CHCHC*H*CH), 6.74-6.82 (3H, m, C*H*C*H*CHC*H*), 4.77 (1H, d_{AB}, *J* 14.0, NCH_2Ph), 4.54 (1H, d_{AB}, *J* 14.0, NCH_2Ph), 3.57-3.62 (1H, m, CH_2CH_2NCH_2Ph), 3.43-3.48 (1H, m, CH_2CH_2NCH_2Ph), 2.15-2.28 (4H, m, NCOC*H*(C)CH_2, CH_2CH_2NCH_2Ph and 2 x CH_2CH_2CH_2), 1.89-1.93 (1H, m, CH_2CH_2NCH_2Ph), 1.61-1.81 (4H, m, C$H_2CH_2CH_2$ and CH_2CH_2CH_2); **^{13}C NMR** (125 MHz, $CDCl_3$) 170.6 (CO), 156.2 (NH*C*(C)CH), 136.9 (NHC(*C*)CH), 134.1 (*C*CHCHCHCHCH), 128.7 (C*C*HCHCHCHC*H* and CCH*C*HCH*C*HCH), 128.6 (CCHCH*C*HCHCH), 127.7 (CH*C*HCHCH), 123.7 (*C*HCHCHCH), 121.7 (CHCH*C*HCH), 110.9 (CHCHCH*C*H), 109.2 (OCOH), 50.5 (NCH_2Ph), 49.8 (CH_2CH_2NCH_2Ph), 49.2 (NHCH(*C*)CH_2), 44.0 (NCO*C*H(C)CH_2), 31.9 ($CH_2CH_2CH_2$), 24.6 (*C*H_2CH_2NCH_2Ph), 22.4 (*C*$H_2CH_2CH_2$), 20.4 ($CH_2CH_2CH_2$); **HRMS** (*m/z*, TOF ES+) 372.1567 (M+Na$^+$ requires 372.1576); **MS** (*m/z*, APCI-) 348 (100, M-H$^-$).

2-benzyl-3,4,10,11,12,12a-hexahydro-2H- benzofuro[3,2-e]isoquinolin-1(9aH)-one 9

To a suspension of **8** (100 mg, 0.29 mmol) in dry dichloromethane, triethylsilane (1.56 ml, 9.77 mmol) and trifluoroacetic acid (1.60 ml, 20.8 mmol) were added and the solution was stirred at room temperature for 30min. After concentration under reduced pressure, the residue was dissolved in

dichloromethane (30 ml), washed with water (3 x 30 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (silicagel, dichloromethane-methanol 125 : 1) to give **9** (95 mg, 99%) as a yellow viscous oil.

IR (film, cm^{-1}) 1632; **^{1}H NMR** (250 MHz, $CDCl_3$, Me_4Si) 7.25-7.40 (5H, m, 5 x CH_{Ph}), 7.13 (1H, dd, *J* 7.1 and 7.1, CHCHC*H*CH), 6.75-6.89 (3H, m, C*H*C*H*CHC*H*), 4.72 (1H, d_{AB}, *J* 14.7, NCH_2Ph), 4.63 (1H, d_{AB}, *J* 14.7, NCH_2Ph), 4.37 (1H, dd, *J* 4.8 and 4.8, OC*H*(C)CH_2), 3.31-3.55 (2H, m, $CH_2CH_2NCH_2Ph$), 2.58 (1H, dd, *J* 5.2 and 7.9, NCOC*H*(C)CH_2), 1.56-2.13 (8H, m, $CH_2CH_2NCH_2Ph$ and $CH_2CH_2CH_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) 171.2 (CO), 158.5 (NH*C*(C)CH), 137.1 (NHC(*C*)CH), 134.5 (*C*CHCHCHCHCH), 128.8 (C*C*HCHCHCH*C*H and CCH*C*HCH*C*HCH), 128.6 (CCHCH*C*HCHCH), 127.8 (CH*C*HCHCH), 123.2 (*C*HCHCHCH), 121.1 (CHCH*C*HCH), 110.6 (CHCHCH*C*H), 85.8 (O*C*H(C)CH_2), 50.7 (NCH_2Ph), 46.1 ($CH_2CH_2NCH_2Ph$), 45.8 (NHCH(*C*)CH_2), 43.5 (NCO*C*H(C)CH_2), 28.8 ($CH_2CH_2CH_2$), 26.2 ($CH_2CH_2NCH_2Ph$), 24.6 ($CH_2CH_2CH_2$), 18.6 ($CH_2CH_2CH_2$); **HRMS** (*m/z*, TOF ES+) 334.1815 ($M+H^+$ requires 334.1807); **MS** (*m/z*, APCI+) 334 (100, $M+H^+$).

2-benzyl-2,3,4,9a,10,11,12,12a-octahydro-1H- benzofuro[3,2-e]isoquinoline 10

To a suspension of $LiAlH_4$ (41 mg, 1.08 mmol) in dry diethylether (40 ml), a solution of **9** (90 mg, 0.27 mmol) in dry diethylether (25 ml) was added and the mixture heated to reflux for 3h. After it was cooled, 30 ml of aqueous saturated Na_2SO_4 were carefully added and the mixture was extracted with dichloromethane (3 x 30 ml). The combined extracts were dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography (silicagel, dichloromethane-methanol 50 : 1) to give **10** (84 mg, 98%) as a colorless viscous oil.

IR (film, cm^{-1}) 2926, 2856 and 2804; **^{1}H NMR** (500 MHz, $CDCl_3$, Me_4Si) 7.47 (1H, d, *J* 7.0, CCHCHC*H*CHCH), 7.29-7.36 (4H, m, CC*H*C*H*CHC*H*C*H*), 7.24 (1H, d, *J* 7.0, C*H*CHCHCH), 7.11 (1H, dd, *J* 7.2 and 7.2, CHCHC*H*CH), 6.81-6.86 (2H, m, CHC*H*CHC*H*), 4.20 (1H, br s, OC*H*(C)CH_2), 3.59 (1H, d_{AB}, *J* 13.5, NCH_2Ph), 3.49 (1H, d_{AB}, *J* 13.5, NCH_2Ph), 2.76 (1H, br s, $CH_2CH_2NCH_2Ph$), 2.68 (1H, ddd, *J* 3.5, 11.5 and 11.5, $CH_2CH_2NCH_2Ph$), 2.50 (1H, dd, *J* 3.5 and 12.0, $CHCH_2NCH_2Ph$), 2.38 (1H, dd, *J* 3.5 and 12.0, $CHCH_2NCH_2Ph$), 1.99-2.05 (2H, m, $CH_2CH_2NCH_2Ph$), 1.73-1.84 (2H, m, $CH_2CH_2CH_2$), 1.53-1.69 (4H, m, C*H*CH_2NCH_2Ph, 2 x $CH_2CH_2CH_2$ and 1 x $CH_2CH_2CH_2$), 1.39-1.41 (1H, m, $CH_2CH_2CH_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) 158.7 (NH*C*(C)CH), 138.9 (NHC(*C*)CH), 128.7 (*C*CHCHCHCHCH), 128.1 (C*C*HCHCHCH*C*H and CCH*C*HCH*C*HCH), 127.7 (CCHCH*C*HCHCH), 126.8 (CH*C*HCHCH), 124.5 (*C*HCHCHCH), 120.0 (CHCH*C*HCH), 110.2 (CHCHCH*C*H), 87.1 (O*C*H(C)CH_2), 63.3 (NCH_2Ph), 54.9 (CHCH_2NCH_2Ph), 51.5 ($CH_2CH_2NCH_2Ph$), 44.4 (OCH(*C*)CH_2), 39.0 (*C*HCH_2NCH_2Ph), 30.4 ($CH_2CH_2CH_2$), 26.3 ($CH_2CH_2NCH_2Ph$), 26.2 ($CH_2CH_2CH_2$), 20.3 ($CH_2CH_2CH_2$); **HRMS** (*m/z*, TOF ES+) 320.2011 ($M+H^+$ requires 320.2014); **MS** (*m/z*, APCI+) 320 (100, $M+H^+$).

methyl (2'*R*, 3*R*, 5'*R*)-1'-benzyl-6'-oxo-5'-(2-oxopropyl)spiro[indole-3,4'-piperidine]-2'-carboxylate 14

Step a

To a solution of (*E*)-4-oxo-2-pentenoic acid (1.04 g, 9.11 mmol) and Et_3N (2.20 ml, 15.8 mmol) in dry dichloromethane (170 ml) at 0°C, **13** (2.00 g, 6.49 mmol) and BOPCl (2.42 g, 9.51 mmol) were added and the reaction mixture was stirred at 0°C for 3h then at room temperature for 3h. The solution was quenched by the addition of water (100 ml) and the organic layer was separated and washed with aqueous saturated NH_4Cl (200 ml) and saturated aqueous $NaHCO_3$ (200 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The brown viscous oil obtained (3.08 g) was used without further purification in the next step.

Step b

To a solution of the crude amide (3.08 g), prepared in step a and dissolved in dry dichloromethane (200 ml), was added silica gel (40 g) and the reaction mixture was stirred at room temperature for 20h. The SiO_2 was then filtered and washed with a mixture of dichloromethane and methanol (9 : 1, 3 x 150 ml). The combined organic layers were evaporated under reduced pressure and the residue was purified by column-chromatography (silica gel, dichloromethane-ethyl acetate 2 : 1) to give **14** as a pale brown solid (1.67 g, 64% overall from **13**).

[a]$_D^{20}$ -79.3 (*c* 0.0128 g/ml in DCM) **IR** (film, cm^{-1}) 3053, 1744, 1713, 1651 and 1450; **^{1}H NMR** (500 MHz, $CDCl_3$, Me_4Si) 7.90 (1H, s, N=CH), 7.59 (1H, d, *J* 7.5, NCC*H*CHCHCH), 7.39-7.44 (5H, m, 5 x CH_{Ph}), 7.33 (1H, dd, *J* 7.5 and 7.5, NCCHC*H*CHCH), 6.95 (1H, dd, *J* 7.5 and 7.5, NCCHCHC*H*CH), 6.48 (1H, d, *J* 7.5, NCCHCHCHC*H*), 5.52 (1H, d_{AB}, *J* 14.5, NCH_2Ph), 4.29 (1H, dd, *J* 6.5 and 8.5, C*H*CO_2CH_3), 3.97 (1H, d_{AB}, *J* 14.5, NCH_2Ph), 3.80-3.82 (4H, m, NCOC*H*(C)CH_2 and CO_2CH_3), 2.72 (1H, dd, *J* 8.5 and 13.5, CH_2CHCO_2CH_3), 2.63 (1H, dd, *J* 7.5 and 17.5, CH_2COCH_3), 2.04 (3H, s, $COCH_3$), 1.82 (1H, dd, *J* 6.5 and 13.5, CH_2CHCO_2CH_3), 1.25 (1H, dd, *J* 4.0 and 17.5, CH_2COCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) 206.2 (CH_2*C*OCH_3), 176.9 (N=C), 171.5 (*C*O_2CH_3), 169.6 (NCO), 155.4 (N*C*CHCHCHCH), 137.6 (NCCHCHCHC*H*C), 135.3 (*C*CHCHCHCHCH), 129.7 (C*C*HCHCHCHC*H*CH), 128.9 (CCH*C*HCH*C*HCHCH), 128.8 (CCHCH*C*HCHCH), 128.2 (NCCH*C*HCHCH), 126.7 (NCCHC*H*C*H*CH), 122.5 (NCCHCHCH*C*H), 121.8 (NC*C*HCHCHCH), 58.4 (NCOCH(*C*)CH_2), 56.9 (CO_2*C*H_3), 52.9 (N*C*H_2Ph), 49.6 (*C*HCO_2CH_3), 39.7 (NCO*C*H(C)CH_2), 39.2 (*C*H_2COCH_3), 30.8 (CH_2CO*C*H_3), 30.2 (*C*H_2CHCO_2CH_3); **HRMS** (*m/z*, TOF ES+) 405.1806 (M+H$^+$ requires 405.1814); **MS** (*m/z*, APCI+) 405 (100, M+H$^+$), 347 (62, M-CO_2CH_3+2H$^+$).

(3*R*, 4a*R*, 9a*R*, 12a *R*)-methyl 2-benzyl-1,11-dioxo-1,2,3,4,9,9a,10,11,12,12a-decahydropyrido[3,4-d]carbazole-3-carboxylate 15

To a solution of **14** (82 mg, 0.21 mmol) in dry tetrahydrofuran (4 ml), $LiOH.H_2O$ (8.5 mg, 0.21 mmol) was added and the reaction mixture was stirred at room temperature for 100h. The solution was quenched by the addition of saturated aqueous NH_4Cl (10 ml) and the mixture was extracted with dichloromethane (3 x 15 ml). The combined organic extracts were dried over $MgSO_4$, evaporated under reduced pressure and the residue purified by column-chromatography (silica gel, dichloromethane-methanol 30 : 1) to give **15** as a pale yellow solid (65 mg, 79%).

[a]$_D^{20}$ +27.6 (*c* 0.0106 g/ml in DCM) **IR** (film, cm^{-1}) 3358, 1740, 1717 and 1643; **^{1}H NMR** (500 MHz, $CDCl_3$, Me_4Si) 7.34-7.41 (5H, m, 5 x CH_{Ph}), 6.95 (1H, dd, *J* 7.5 and 7.5, CHCHC*H*CH), 6.50 (1H, d, *J* 8.0, C*H*CHCHCH), 6.26 (1H, dd, *J* 7.5 and 7.5, CHC*H*CHCH), 6.14 (1H, d, *J* 7.5, CHCHCHC*H*), 5.39 (1H, d_{AB}, *J* 14.0, NCH_2Ph), 4.16 (1H, dd, *J* 7.0 and 10.5, C*H*CO_2CH_3), 3.96 (1H, d_{AB}, *J* 14.0, NCH_2Ph), 3.93 (1H, dd, *J* 3.0 and 6.0, NHC*H*(C)CH_2), 3.80 (1H, br s, NH), 3.72 (3H, s, CO_2CH_3), 3.17 (1H, dd, *J* 4.5 and 12.5, NCOC*H*(C)CH_2), 2.90 (1H, dd, *J* 5.0 and 18.5, CH_2COCH_2CHNH), 2.68 (1H, dd, *J* 6.0 and 15.0, CH_2COCH_2CHNH), 2.50 (1H, dd, *J* 6.5 and 13.0, CH_2CHCO_2CH_3), 2.23-2.30 (2H, m, CH_2COCH_2CHNH and CH_2COCH_2CHNH), 2.13 (1H, dd, *J* 10.5 and 13.5, CH_2CHCO_2CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) 207.9 (CH_2*C*OCH_3), 172.2 (*C*O_2CH_3), 169.4 (NCO), 149.6 (N*C*CHCHCHCH), 134.9 (NCCHCHCHCH*C*), 130.0 (*C*CHCHCHCHCH), 129.3 (C*C*HCHCHCHC*H*CH), 128.6 (CCH*C*HCH*C*HCHCH), 128.1 (CCHCH*C*HCHCH), 126.1 (NCCH*C*HCHCH), 124.3 (NCCHCH*C*HCH), 119.1 (NCCHCHCHC*H*CH), 110.2 (NC*C*HCHCHCH), 75.0 (*C*HCO_2CH_3), 64.8 (NHCH(C)CH_2), 56.9 (CO_2*C*H_3), 52.7 (NCH_2Ph), 49.1 (NHCH(*C*)CH_2), 45.9 (CH_2COCH_2CHNH), 43.1 (NCOCH(C)CH_2), 38.3 (*C*H_2COCH_2CHNH), 38.0 (*C*H_2CHCO_2CH_3); **HRMS** (*m/z*, TOF ES+) 405.1801 (M+H$^+$ requires 405.1814); **MS** (*m/z*, APCI+) 405 (100, M+H$^+$).

(4a*R*, 9a*R*, 12a*R*)-2-benzyl-3,4,9a,10,12,12a-hexahydropyrido[3,4-d] carbazole-1,11(2H,9H)-dione 5

Step a

To a solution of **15** (90 mg, 0.22 mmol) in dry, degased dichloromethane (3 ml) at 0°C, $Me_2AlSeMe$ (2M in tol., 1.08 ml, 2.16 mmol) was added dropwise and the solution was stirred at room temperature for 22h. The solution was carefully quenched by the addition of saturated aqueous Na_2SO_4 (20 ml). The mixture was extracted with dichloromethane (3 x 20 ml), the combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The yellow gummy solid thus obtained (76 mg) was used without further purification into the next step.

Step b

To a solution of crude acylselenide (76 mg) in dry benzene (15 ml), Bu_3SnH (218 µl, 0.81 mmol) and AIBN (5 mg, 0.03 mmol) were added and the reaction mixture was heated to reflux for 1h, afterwards more Bu_3SnH (50 µl, 0.19 mmol) and AIBN (1 mg, 0.006 mmol) were added. After another 50 min. at reflux, the reaction mixture was cooled and saturated aqueous NaF (15 ml) was added. The

biphasic mixture was stirred at room temperature for 15 min. then extracted with dichloromethane (3 x 20 ml), the combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column-chromatography (silica gel, dichloromethane-methanol 50 : 1) to give **5** as a yellow solid (52 mg, 67% overall from **15**).

[a]$_D^{20}$ +36.8 (*c* 0.0063 g/ml in DCM) **IR** (film, cm^{-1}) 3054, 1718, 1639 and 1420; **^{1}H NMR** (300 MHz, $CDCl_3$, Me_4Si) 7.32-7.38 (5H, m, 5 x CH_{Ph}), 6.99-7.04 (1H, m, NHCCHC*H*CHCH), 6.49-6.58 (3H, m, NHCC*H*CHC*H*C*H*), 4.82 (1H, d_{AB}, *J* 13.8, NC*H*$_2$Ph), 4.56 (1H, d_{AB}, *J* 13.8, NC*H*$_2$Ph), 3.97 (1H, dd, *J* 2.4 and 7.2, NHCC*H*), 3.80 (1H, br s, NH), 3.27-3.41 (2H, m, CH_2C*H*$_2$NCH$_2$Ph), 3.18 (1H, dd, *J* 5.4 and 12.6, NCOC*H*(C)CH$_2$), 2.98 (1H, dd, *J* 5.4 and 18.6, NCOCH(C)C*H*$_2$), 2.72 (1H, dd, *J* 6.8 and 14.9, CH_2COC*H*$_2$CHNH), 2.34 (1H, dd, *J* 12.9 and 18.6, NCOCH(C)C*H*$_2$), 1.99-2.20 (3H, m, 2 x C*H*$_2$CH$_2$NCH$_2$Ph and 1 x CH_2COC*H*$_2$CHNH); **^{13}C NMR** (75 MHz, $CDCl_3$) 208.3 (CH_2*C*OCH_2), 169.9 (NCO), 149.3 (NH*C*CHCHCHCH), 136.8 (NHCCHCHCHCH*C*), 133.3 (*C*CHCHCHCHCH), 129.1 (C*C*HCHCHCHC*H*), 129.0 (CCH*C*HCH*C*HCH), 128.7 (CCHCH*C*HCHCH), 128.0 (NHCCH*C*HCHCH), 123.1 (NHCCHCH*C*HCH), 119.5 (NHCCHCHCH*C*H), 109.6 (NHC*C*HCHCHCH), 61.9 (NHC*C*H), 51.1 (N*C*H$_2$Ph), 46.9 (NCOCH(*C*)CH$_2$), 46.4 (CH_2CO*C*H$_2$CHNH), 44.3 (CH_2*C*H$_2$NCH$_2$Ph), 43.1 (NCO*C*H(C)CH$_2$), 38.5 (*C*H$_2$COCH$_2$CHNH), 34.3 (*C*H$_2$CH$_2$NCH$_2$Ph); **HRMS** (*m/z*, TOF ES+) 347.1766 (M+H$^+$ requires 347.1760); **MS** (*m/z*, APCI+) 347 (100, M+H$^+$).