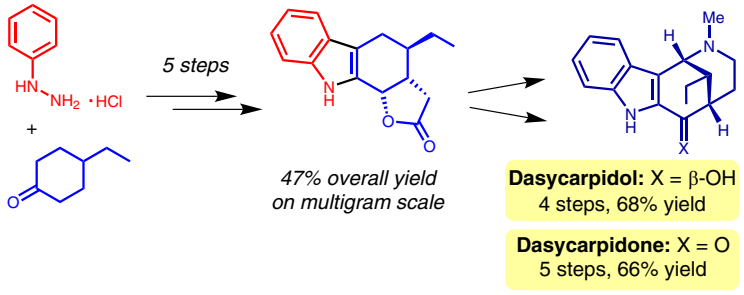
Synthesis S. Patir et al. Paper

Stereoselective Total Synthesis of (±)-Dasycarpidol and (±)-Dasycarpidone

Süleyman Patir[a]
Mustafa A. Tezeren[b]
Bekir Salih[c]
Erkan Ertürk*[b]

[a] Department of Chemistry Education, Faculty of Education, Hacettepe University, 06800 Beytepe, Ankara, Turkey
[b] Institute of Chemical Technology, TUBITAK Marmara Research Center, 41470 Gebze, Kocaeli, Turkey
[c] Department of Chemistry, Hacettepe University, 06800 Beytepe, Ankara, Turkey
erkan.erturk@tubitak.gov.tr



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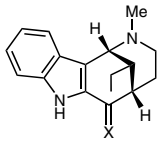
Abstract The protecting-group-free and scalable total syntheses of (±)-dasycarpidol and (±)-dasycarpidone, as well as the formal total synthesis of (±)-uleine, are presented starting from a common tetrahydrocarbazole-fused lactone that is conveniently prepared on multigram scale. The key azocino[4,3-*b*]indole skeleton is constructed via the DDQ-mediated dehydrogenative cyclization of a tetrahydrocarbazole derivative possessing an amide side chain. The syntheses of the target natural products are accomplished in high yields and in a few steps by employing readily available conventional reagents.

Key words dasycarpidone, dasycarpidol, uleine, azocino[4,3-*b*]indole, lactone

Natural products (NPs), the secondary metabolites of terrestrial and marine plants as well as fungi and bacteria, have been historically utilized in treating and preventing human diseases. Although the search for *de novo* 'truly new synthetic' entities as drug candidates was once widely respected, the key role of NPs and their analogues in drug development has been acclaimed again recently.[1–3] This is because natural-product-like drug candidates have provided screening collections with higher hit rate and lower side-effect probabilities.[4]

The indole alkaloids are encountered in a wide range of plants with a very large number of members and also continue to attract interest from both medicinal and synthetic standpoints.[5,6] Among them, uleine-type NPs exhibit remarkable biological activities such as anti-ulcer,[7a] anti-inflammatory,[7b] antimicrobial as well as acetylcholinesterase inhibitory activities, and further research toward their potential bioactivities is of current interest (Figure 1).[7] Accordingly, significant efforts have been devoted to synthesize uleine-type alkaloids efficiently.[8–12] As for dasycarpidol (**1**) and dasycarpidone (**2**), however, after their isolation from Brazilian *Aspidosperma* species in the 1960s,[13] the methods that have been hitherto developed for their syntheses need to be improved in terms of efficiency and stereoselectivity.[8–10] For instance, there has not been any report on the stereoselective synthesis of dasycarpidol.[8] It is worthy of mention that, besides uleine-type alkaloids (Figure 1), the 1,5-methanoazocino[4,3-*b*]indole scaffold is also found as a key structural element in other *Strychnos* alkaloids.[14]

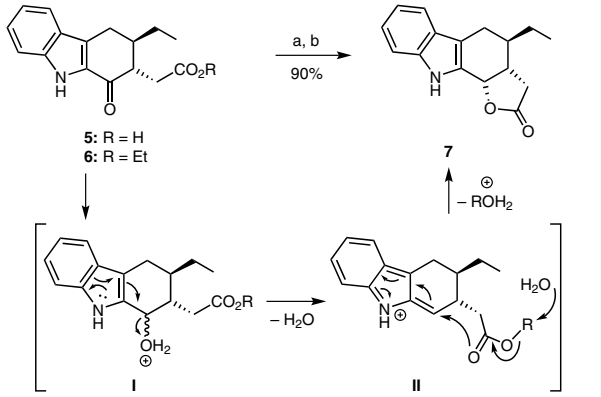


1: X = α-OH, β-H (dasycarpidol)
2: X = O (dasycarpidone)
3: X = CH_2 (uleine)
4: X = α-CH_2OH, β-H (13-hydroxyuleine)

Figure 1 Structures of uleine-type indole alkaloids

Recently, we observed that the *trans*-disubstituted tetrahydrocarbazol-1-one derivatives **5** and **6** could be converted into the lactone **7** in high yield after their reduction with $NaBH_4$ and subsequent exposure of the reaction mixture to aqueous HCl (Scheme 1).[15] As depicted in Scheme 1, a Brønsted acid catalyzed ring-closing mechanism might be proposed for the formation of the lactone **7** since its formation is irrespective of whether the starting material bears a carboxylic acid (**5**) or a carboxylic ester (**6**) functionality.[16] Due to the *cis* configuration of the lactone ring, we reasoned that the lactone **7** might be a useful precursor for the divergent and stereocontrolled synthesis of uleine-type alkaloids. On the other hand, it is noteworthy that the lactone **7** can be prepared in 47% overall yield and in just five steps starting from phenylhydrazine hydrochloride and 4-ethyl-

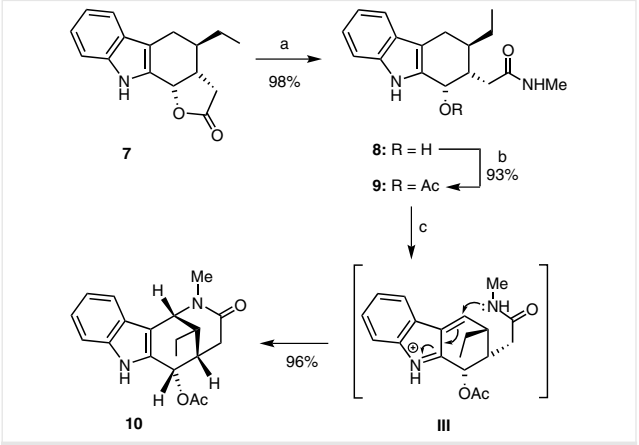
cyclohexanone.[15] Herein, we report our recent endeavors dealing with the stereocontrolled total synthesis of racemic dasycarpidol [(±)-**1**], dasycarpidone [(±)-**2**] as well as the formal synthesis of racemic uleine [(±)-**3**] starting from **7**.



Scheme 1 Formation of the tetrahydrocarbazole-fused lactone **7** via Brønsted acid catalysis. *Reagents and conditions*: (a) $NaBH_4$, THF–MeOH, 55 °C, 2 h (for **5**); –78 °C, 2 h (for **6**); (b) HCl (20%), 0 °C.

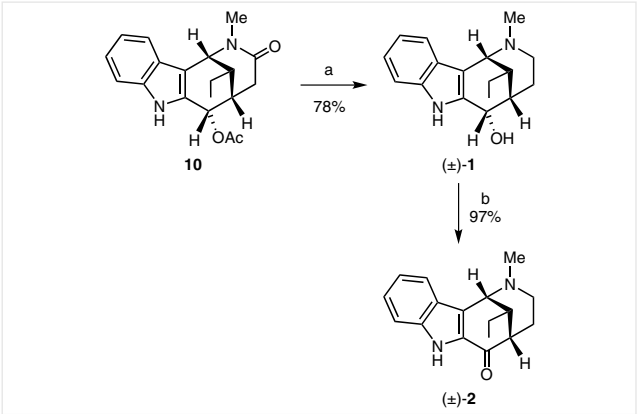
First, trimethylaluminum-mediated aminolysis of the lactone **7** with methylamine was carried out (Scheme 2).[17] This attempt led to the formation of the amide **8** in 98% yield. The hydroxy group of the amide **8** had to be protected before subjecting it to the DDQ-mediated ring-closing reaction, because oxidation of the hydroxy group of **8** into the oxo functionality took place instead of the formation of corresponding azocino[4,3-*b*]indole when it was treated with DDQ. Therefore, the labile hydroxy group of the amide **8** was readily protected as an acetate ester in 93% yield by treatment with acetic anhydride in the presence of triethylamine. The obtained secondary amide **9** bearing an ester functionality was then subjected to the DDQ-mediated dehydrogenative cyclization that was recently developed in our laboratory.[11f,14b] Thus, the preparation of the key azocino[4,3-*b*]indole derivative **10** was completed in high yield and in a facile manner. Remarkably, there was no *cis*–*trans* epimerization during the entire process.

Next, the azocino[4,3-*b*]indole derivative **10** was evaluated as a precursor for the synthesis of dasycarpidol [(±)-**1**] and dasycarpidone [(±)-**2**] (Scheme 3). Of the various hydridic reducing agents utilized for the reduction of **10**, Red-Al® [sodium bis(2-methoxyethoxy)aluminum dihydride] turned out to be the most effective. Indeed, treatment of **10** with Red-Al® in tetrahydrofuran directly delivered dasycarpidol in 78% yield. Thus, the first total synthesis of dasycarpidol [(±)-**1**] was accomplished in 68% overall yield from the lactone **7** with full control of the stereochemistry.[18] It was then expected that dasycarpidol [(±)-**1**] could be converted into dasycarpidone [(±)-**2**]. Whereas Swern, Corey–Kim as well as Albright–Goldman oxidation protocols did not give rise to the formation of dasycarpidone [(±)-**2**] from



Scheme 2 Synthesis of the azocino[4,3-*b*]indole derivative **10**. *Reagents and conditions*: (a) $AlMe_3$ (2.0 M in hexanes), $MeNH_2$, CH_2Cl_2, r.t., overnight; (b) Ac_2O, Et_3N, CH_2Cl_2, r.t., overnight; (c) DDQ, THF, r.t., 8 h.

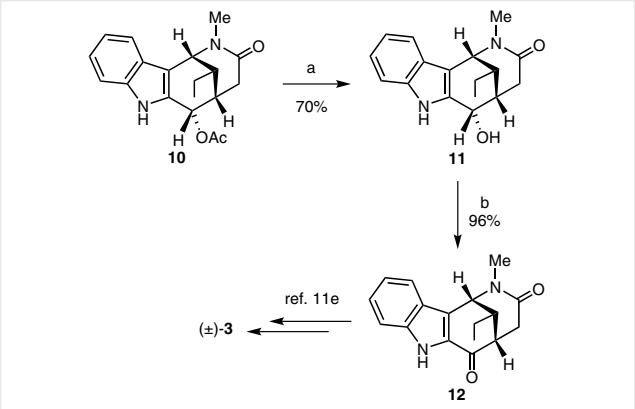
dasycarpidol [(±)-**1**], treatment of dasycarpidol with manganese(IV) oxide in acetone furnished dasycarpidone in almost quantitative yield (97%). The overall yield of dasycarpidone was determined to be 66% starting from **7**.



Scheme 3 Synthesis of racemic dasycarpidol [(±)-**1**] and dasycarpidone [(±)-**2**]. *Reagents and conditions*: (a) Red-Al®, THF, 0 °C to r.t., overnight; (b) MnO_2, acetone, r.t., 1 h.

Our attention then turned to exploiting azocino[4,3-*b*]indole derivative **10** as a starting material for the synthesis of uleine [(±)-**3**]. Attempts to hydrolyze the ester group of **10** using aqueous NaOH gave the desired product **11** in very low yield along with a number of unidentified side products. Fortunately, treatment of **10** with an excess of DIBAL-H (diisobutylaluminum hydride) in THF at –78 °C resulted in reduction of the ester group into the hydroxy group while the lactam group remained intact (Scheme 4). Upon treatment with manganese(IV) oxide in acetone at room temperature, the resulting indole derivative **11** could be converted into **12** in 96% yield. Recently, we used compound **12** for a convenient synthesis of uleine [(±)-**3**].[11e] As a

result, besides dasycarpidol and dasycarpidone, the azocino[4,3-*b*]indole derivative **10** was shown to be a useful intermediate for the synthesis of uleine.



Scheme 4 Preparation of the precursor (±)-**12** for uleine [(±)-**3**]. *Reagents and conditions*: (a) DIBAL-H (1.0 M in hexanes), THF, –78 °C, 0.5 h; (b) MnO_2, acetone, r.t., 1 h.

In summary, we have developed divergent and efficient routes for the stereoselective syntheses of dasycarpidol [(±)-**1**], dasycarpidone [(±)-**2**], and uleine [(±)-**3**]. Our synthetic strategy exhibits certain useful features: (1) Due to the fact that the starting material, the lactone **7**, is readily available on multigram scale, our synthetic strategy provides a scalable approach.[19] (2) No protection–deprotection steps are needed which makes our syntheses protecting-group-free.[20] (3) Target molecules are accessible in a few steps starting from **7**, e.g., four steps for dasycarpidol and five steps for dasycarpidone are required.[21,22] (4) All synthetic steps have high yields while utilizing conventional reagents. In our opinion, all these features are in good accordance with the majority of criteria established for an 'ideal synthesis'.[21–23] Bearing in mind the above-mentioned advantageous points of our synthetic strategy, its further applications for the syntheses of other indole alkaloids as well as the development of enantioselective versions are in progress in our laboratory. Finally, we believe that congeners of the lactone **7** will become versatile starting materials for the synthesis of diverse alkaloids bearing carbazole units.[5]

All reactions were carried out under an inert atmosphere of dry nitrogen (N_2) using oven-dried glassware. All synthetic compounds are in their racemic form. Tetrahydrofuran (THF) was freshly distilled under N_2 from sodium/benzophenone immediately prior to use. Acetone was dried over magnesium sulfate ($MgSO_4$) and distilled under N_2. Methanol (MeOH) was dried over magnesium (Mg) under N_2 prior to use. Triethylamine (Et_3N) was distilled under N_2 from calcium hydride (CaH_2). 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ), diisobutylaluminum hydride (DIBAL-H), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al® 40% in toluene), methylamine ($MeNH_2$, 2.0 M in THF), trimethylaluminum ($AlMe_3$, 2.0 M in hexanes), acetic anhydride (Ac_2O), and manganese(IV) oxide (MnO_2) were purchased from commercial suppliers and used as received. Thin-layer chromatography (TLC) was conducted on aluminum sheets that were pre-coated with silica gel (SIL G/UV_{254} from MN GmbH & Co.); the spots were visualized under UV light (λ = 254 nm) and/or by staining with phosphomolybdic acid. Chromatographic separations were performed using silica gel (MN-silica gel 60, 230–400 mesh). All melting points were determined in open glass capillary tubes by means of a BÜCHI Melting Point B-540 apparatus and values are uncorrected. Infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer (ν_{max} in cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a 500 MHz NMR spectrometer at 25 °C. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.26, DMSO-d_6: δ 2.50) and carbon resonance of the solvent ($CDCl_3$: δ 77.00, DMSO-d_6: δ 39.52). NMR peak multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained in MeOH on a Bruker micrOTOF-Q.

N-Methyl-(3β-ethyl-1-hydroxy-1,2,3,4-tetrahydrocarbazol-2-yl)-acetamide [(±)-8]

Anhydrous CH_2Cl_2 (30 mL) was placed in a 100 mL oven-dried round-bottomed Schlenk flask equipped with a magnetic stir bar under N_2. $MeNH_2$ (2 mL, 2.0 M solution in THF) was added into the reaction flask at –10 °C under N_2 using a syringe, which was followed by the addition of $AlMe_3$ (2 mL, 2.0 M solution in hexanes) using a syringe. After stirring at –10 °C for 30 min under N_2, the mixture was allowed to warm to r.t. Next, a solution of 4-ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-*a*]carbazol-2(10b*H*)one [(±)-**7**] (0.37 g, 1.45 mmol) in anhydrous THF (10 mL) was added dropwise using a syringe and the reaction mixture was stirred at r.t. overnight under N_2. After quenching with 10% Na_2CO_3 (50 mL), the organic layer was separated by using a separating funnel and dried over Na_2SO_4. After removing all the volatile components by rotary evaporation in vacuo, the residue was crystallized from Et_2O affording the amide (±)-**8** (0.41 g, 1.42 mmol, 98%) as a white solid.

Mp 207 °C; R_f = 0.3 (silica gel; EtOAc).

FTIR (KBr): 3410 (s), 3231 (s), 2959 (s), 1652 (m), 935 (s) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 1.23–1.31 (m, 1 H), 1.49–1.54 (m, 1 H), 1.88 (br s, 1 H), 2.15 (dd, *J* = 14.1, 6.8 Hz, 1 H), 2.25–2.32 (m, 2 H), 2.37 (dd, *J* = 14.1, 7.3 Hz, 1 H), 2.59 (d, *J* = 4.4 Hz, 3 H), 2.83 (dd, *J* = 15.7, 5.0 Hz, 1 H), 4.71 (t, *J* = 4.9 Hz, 1 H), 5.05 (d, *J* = 6.4 Hz, 1 H), 6.93 (t, *J* = 7.4 Hz, 1 H), 7.02 (t, *J* = 7.4 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 4.2 Hz, 1 H), 10.67 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.4 (CH_3), 24.1 (CH_2), 24.8 (CH_2), 25.6 [C(O)HNCH_3], 34.4 (CH_2), 35.4 (CH), 41.2 (CH), 62.9 (CH), 107.9 (C), 111.1 (CH), 117.97 (CH), 118.02 (CH), 120.7 (CH), 126.8 (C), 135.7 (C), 136.3 (C), 172.9 (HN–C=O).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}N_2O_2Na$: 309.1574; found: 309.1567.

N-Methyl-(1-acetoxy-3β-ethyl-1,2,3,4-tetrahydrocarbazol-2-yl)-acetamide [(±)-9]

To an ice-cold solution of the amide (±)-**8** (1.63 g, 5.69 mmol) in anhydrous CH_2Cl_2 (30 mL) under N_2 were added Et_3N (5 mL) and Ac_2O (3.5 mL) successively. After being stirred at r.t. overnight, the reaction mixture was quenched with 10% Na_2CO_3 (30 mL) and extracted with

CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crystallization of the crude product from MTBE–cyclohexane (1:1) yielded 1.73 g (5.27 mmol, 93%) of the title compound [(±)-**9**] as a white solid.

Mp 145–157 °C; R_f = 0.5 (silica gel; EtOAc).

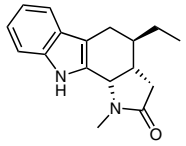
FTIR (KBr): 3357 (s), 3245 (s), 2960 (s), 1709 (s), 1635 (s), 739 (s) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.97 (t, J = 7.4 Hz, 3 H), 1.26–1.35 (m, 1 H), 1.52–1.60 (m, 1 H), 1.90 (m, 1 H), 2.05 (s, 3 H), 2.19–2.28 (m, 2 H), 2.37 (dd, J = 16.1, 7.3 Hz, 1 H), 2.53 (m, 1 H), 2.57 (d, J = 4.5 Hz, 3 H), 2.88 (dd, J = 16.1, 5.0 Hz, 1 H), 5.94 (d, J = 4.1 Hz, 1 H), 6.97 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.78 (br d, J = 4.4 Hz, 1 H), 10.56 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.1 (CH_3), 20.9 [OC(O)CH_3], 24.0 (CH_2), 24.6 (CH_2), 25.5 [C(O)HNCH_3], 34.7 (CH_2), 36.5 (CH), 38.3 (CH), 66.1 (CH), 110.4 (C), 111.6 (CH), 118.2 (CH), 118.4 (CH), 121.6 (CH), 126.2 (C), 130.6 (C), 136.6 (C), 170.4 (O–C=O), 171.6 (HN–C=O).

All attempts to detect a reasonable molecular ion peak failed by using the ESI technique. HRMS analyses gave a strong peak around 269, which is excellently consistent with the exact mass of the lactam (±)-**13** depicted in Figure 2.

HRMS (ESI$^+$): m/z [M + H]$^+$ calcd for $C_{17}H_{21}N_2O$: 269.1648; found: 269.1644.



(±)-**13**

Figure 2 Structure of lactam (±)-**13**

6-Acetoxy-12β-ethyl-2-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(±)-10]

The acetoxy-amide (±)-**9** (5.00 g, 15.22 mmol) was placed in a 250 mL oven-dried round-bottomed Schlenk flask equipped with a magnetic stir bar. The reaction flask was evacuated for 15 min and back-filled with dry N_2. The acetoxy-amide (±)-**9** was then dissolved by adding anhydrous THF (100 mL) into the reaction flask. DDQ (4.54 g, 20.00 mmol) was added in one portion and the resulting reaction mixture was stirred at r.t. for 8 h under N_2. After quenching the reaction mixture with 10% Na_2CO_3 (100 mL), the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4. After all the volatile components had been removed by rotary evaporation in vacuo, the residue was purified by silica gel chromatography eluting with EtOAc–Et_3N (10:1) to give 4.76 g (14.58 mmol, 96%) of the title compound [(±)-**10**] as a white solid.

Mp 142–145 °C; R_f = 0.5 (silica gel; EtOAc–Et_3N, 10:1).

FTIR (KBr): 3247 (m) 2930 (m), 1743 (s), 1628 (s), 744 (s) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.97 (t, J = 7.4 Hz, 3 H), 1.30–1.38 (m, 2 H), 1.40 (s, 1 H), 2.18 (s, 3 H), 2.45–2.48 (m, 2 H), 2.75 (m, 1 H), 2.93 (s, 3 H), 4.52 (d, J = 1.4 Hz, 1 H), 6.12 (d, J = 6.0 Hz, 1 H), 7.04 (dt, J = 7.5, 1.0 Hz, 1 H), 7.11 (dt, J = 7.5, 1.0 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 1 H), 7.68 (d, J = 7.9 Hz, 1 H), 11.17 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.9 (CH_3CH_2), 21.0 [OC(O)CH_3], 22.3 (CH_3CH_2), 31.6 [CH_2–C(O)N], 33.6 (CH_3N), 34.0 (CH), 43.9 (CH), 52.9 (CH), 66.9 (CH), 111.6 (CH), 112.9 (C), 118.5 (CH), 119.3 (CH), 121.8 (CH), 125.8 (C), 129.5 (C), 136.4 (C), 169.3 (O–C=O), 170.2 (N–C=O).

HRMS (ESI$^+$): m/z [M + H]$^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1703; found: 327.1699.

rac-Dasycarpidol [(±)-1]

An oven-dried 25 mL Schlenk tube, capped with a glass stopper and equipped with a magnetic stir bar, was evacuated under heating with a blow-drier for 15 min. After the tube had cooled to r.t., dry N_2 was back-filled and the glass stopper was replaced with a rubber septum under a positive pressure of N_2. The lactam (±)-**10** (653 mg, 2.0 mmol, 1.00 equiv) was placed in the tube and dissolved by the addition of absolute THF (8 mL) as the solvent. After the reaction mixture had been cooled to 0 °C in an ice bath, sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al®) (3.25 mL of 60% in toluene, 10.0 mmol, 5.00 equiv) was added into the solution using a syringe. After stirring at r.t. overnight, the reaction was quenched by the addition of sat. $NaHCO_3$ solution (8 mL). After THF had been removed by rotary evaporation under reduced pressure, the aq residue was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. After all the volatile components had been removed by rotary evaporation in vacuo, the residue was purified by silica gel column chromatography eluting with EtOAc–MeOH–Et_3N (10:1:0.5) to give racemic dasycarpidol [(±)-**1**] (421 mg, 1.56 mmol, 78%) as an amorphous white solid.

Mp 98–114 °C (dec.); R_f = 0.3 (silica gel; EtOAc–MeOH–Et_3N, 10:1:0.5).

FTIR (KBr): 3400 (s), 3246 (s), 2931 (s), 1725 (m), 1454 (s), 740 (s) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.85 (t, J = 7.4 Hz, 3 H), 1.08–1.16 (m, 2 H), 1.48–1.55 (m, 1 H), 1.81 (dt, J = 12.3, 3.3 Hz, 1 H), 2.05 (m, 3 H), 2.07 (s, 3 H), 2.19 (dd, J = 11.4, 4.7 Hz, 1 H), 3.85 (d, J = 1.8 Hz, 1 H), 4.84 (d, J = 5.7 Hz, 1 H), 5.34 (br s, 1 H), 6.91 (dt, J = 15.0, 1.1 Hz, 1 H), 6.98 (dt, J = 15.0, 1.1 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 11.07 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.0 (CH_3), 23.1 (CH_2), 25.5 (CH_2), 35.5 (CH), 44.2 (CH_3), 46.1 (CH_2), 46.9 (CH), 55.5 (CH), 63.3 (CH), 103.3 (C), 111.0 (CH), 118.3 (CH), 118.6 (CH), 120.1 (CH), 128.4 (C), 136.2 (C), 138.3 (C).

HRMS (ESI$^+$): m/z [M + H]$^+$ calcd for $C_{17}H_{23}N_2O$: 271.1810; found: 271.1821.

rac-Dasycarpidone [(±)-2]

An oven-dried 25 mL Schlenk tube, capped with a glass stopper and equipped with a magnetic stir bar, was evacuated under heating with a blow-drier for 15 min. After the tube had cooled to r.t., dry N_2 was back-filled and the glass stopper was replaced with a rubber septum under a positive pressure of N_2. Dasycarpidol [(±)-**1**] (50 mg, 0.185 mmol) was placed in the tube and dissolved by the addition of anhydrous acetone (6 mL) as the solvent. MnO_2 (1.0 g, 11.5 mmol, 62.50 equiv) was added in one portion and the resulting reaction mixture was stirred at r.t. for 1 h under N_2. The mixture was filtered through a pad of Celite® and rinsed with MeOH. The filtrate was concentrated by rotary evaporation under reduced pressure and then dried under high vacuum (10^{-3} mbar for 12 h) to afford racemic dasycarpidone [(±)-**2**] as a pale oil in almost quantitative yield (48 mg, 0.179 mmol, 97%).

R_f = 0.5 (silica gel; CH_2Cl_2–MeOH, 9:1).

FTIR (KBr): 3258 (s), 2931 (s), 1651 (s), 1468 (s), 746 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.26–1.34 (m, 3 H), 1.94–1.99 (m, 1 H), 2.08–2.17 (m, 1 H), 2.34 (s, 3 H), 2.36 (tt, *J* = 7.5, 2.4 Hz, 1 H), 2.61–2.65 (m, 1 H), 2.73 (m, 1 H), 4.35 (d, *J* = 2.3 Hz, 1 H), 7.19 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.38 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 10.39 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.8 (CH_3), 24.9 (CH_2), 30.1 (CH_2), 44.0 (CH_3), 46.0 (CH_2), 46.4 (CH), 49.6 (CH), 56.3 (CH), 112.9 (CH), 119.7 (C), 120.9 (CH), 121.8 (CH), 126.7 (CH), 127.6 (C), 132.9 (C), 138.4 (C), 193.5 (C=O).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O$: 269.1648; found: 269.1639.

12β-Ethyl-6-hydroxy-2-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(±)-11]

An oven-dried 25 mL Schlenk tube, capped with a glass stopper and equipped with a magnetic stir bar, was evacuated under heating with a blow-drier for 15 min. After the tube had cooled to r.t., dry N_2 was back-filled and the glass stopper was replaced with a rubber septum under a positive pressure of N_2. The lactam (±)-**10** (653 mg, 2.0 mmol, 1.00 equiv) was placed in the tube and dissolved by the addition of absolute THF (8 mL) as the solvent. After the reaction mixture had been cooled to –78 °C in a dry-ice/*i*-PrOH bath, DIBAL-H (8 mL of a 1.0 M solution in hexanes, 8.0 mmol, 4.00 equiv) was added into the reaction mixture using a syringe. After stirring the reaction mixture at –78 °C for 30 min under N_2, the reaction was quenched by the addition of sat. $NaHCO_3$ solution (8 mL). After the THF had been removed by rotary evaporation under reduced pressure, the aq residue was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. The volatile components were removed by rotary evaporation in vacuo and the residue was purified by silica gel column chromatography eluting with EtOAc–MeOH (10:0.5) to yield 400 mg (1.41 mmol, 70%) of the title compound [(±)-**11**] as a white solid.

Mp 176–200 °C (dec.); R_f = 0.5 (silica gel; EtOAc–MeOH, 10:0.5).

FTIR (KBr): 3450 (s), 3292 (s), 2926 (s), 1602 (s), 740 (s) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.96 (t, *J* = 7.4 Hz, 3 H), 1.23–1.36 (m, 3 H), 2.34–2.40 (m, 2 H), 2.71 (d, *J* = 18.7 Hz, 1 H), 2.94 (s, 3 H), 4.43 (s, 1 H), 4.97 (t, *J* = 5.7 Hz, 1 H), 5.49 (d, *J* = 5.8 Hz, 1 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 11.05 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.1 (CH_3), 22.2 (CH_2), 31.0 (CH_2), 34.1 (CH_3), 36.5 (CH), 44.1 (CH), 53.4 (CH), 63.4 (CH), 110.7 (C), 111.4 (CH), 118.2 (CH), 118.9 (CH), 121.0 (CH), 126.2 (C), 134.7 (C), 136.3 (C), 170.1 (N–C=O).

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_2$: 285.1598; found: 285.1593.

12β-Ethyl-2-methyl-3,6-dioxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(±)-12][11e]

The azocino[4,3-*b*]indole derivative (±)-**11** (200 mg, 0.70 mmol) was placed in a 50 mL oven-dried round-bottomed Schlenk flask, which was capped with a glass stopper and equipped with a magnetic stir bar. The reaction flask was evacuated for 15 min, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under a positive pressure of dry N_2. The indole (±)-**11** was dissolved by adding anhydrous acetone (10 mL). MnO_2 (600 mg, 6.90 mmol, ca. 10.00 equiv) was added in one portion and the resulting mixture was stirred at r.t. for 1 h under N_2. The mixture was filtered through a pad of Celite® and rinsed with MeOH. After the filtrate had been concentrated by rotary evaporation under reduced pressure and dried under high vacuum (10^{-3} mbar for 12 h), the title compound (±)-**12** was obtained as a white solid in almost quantitative yield (190 mg, 0.673 mmol, 96%).

Mp 285–290 °C (dec.); R_f = 0.5 (silica gel; EtOAc).

FTIR (KBr): 3215 (m), 2927 (m), 1666 (s), 1629 (s), 746 (s) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.22–1.35 (m, 2 H), 2.24 (d, *J* = 17.5 Hz, 1 H), 2.58 (m, 1 H), 2.94 (s, 3 H), 2.98 (m, 2 H), 4.88 (d, *J* = 1.7 Hz, 1 H), 7.17 (dt, *J* = 7.5, 0.8 Hz, 1 H), 7.35 (dt, *J* = 7.7, 1.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 12.02 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.6 (CH_3), 23.8 (CH_2), 33.6 (CH_3), 36.0 (CH_2), 45.3 (CH), 46.6 (CH), 53.2 (CH), 113.1 (CH), 120.8 (CH), 121.2 (CH), 125.0 (C), 126.5 (C), 126.6 (CH), 128.5 (C), 138.2 (C), 167.5 (N–C=O), 191.1 (C=O).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{18}N_2O_2Na$: 305.1260; found: 305.1262.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562528.

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