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A convenient and highly stereoselective synthesis of 14-substituted 8,13-diazaoestrone analogues by domino ring closures

László Lázár,[a] Henri Kivelä,[b] Kalevi Pihlaja[b] and Ferenc Fülöp[a,*]

[a]*Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary*
[b]*Department of Chemistry, Structural Chemistry Group, University of Turku, FIN-20014 Turku, Finland*

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Abstract—By means of convenient domino ring closure reactions of 1-(2-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **2** and γ-oxo-acids, 14-substituted 8,13-diazaoestrone derivatives (**5** and **6**) were formed with ~100% diastereoselectivity.

The synthesis of steroid derivatives containing heteroatoms in various positions of the carbocyclic skeleton has gained wide attention in recent decades.[1] In consequence of their structural analogy, numerous azasteroid derivatives have proved to exert inhibitory activity on certain enzymes involved in the transformations of natural steroidal compounds, for example, antifungal azasteroids that block the ergosterol biosynthesis[2] or 5α-reductase-inhibitory azasteroids with antitestosterone activity.[3]

In the course of our previous studies on the preparation of 1,2,3,4-tetrahydroisoquinoline-condensed saturated 1,3- and 1,2,3-heterocycles,[4,5] tetrahydroisoquinoline 1,2- and 1,3-diamine derivatives were prepared from homoveratrylamine and N-protected α- or β-amino acids.[5] Diamine **2** could be obtained easily, either by simple transformation of 3-benzyloxycarbonylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-propanamide **1** or by catalytic hydrogenation of 3,4-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylacetonitrile **4**, obtained by cyanoacetic acid addition to 3,4-dihydroisoquinoline **3**.[6,7]

When compound **2** was reacted with levulinic acid or with 3-benzoylpropanoic acid in boiling toluene, 8,13-diazaoestrone analogue tetracycles **5a** and **5b** were formed in good yields.[8,9] NMR measurements indicated that tetracycles **5** were formed with practically full stereoselectivity (*de* ~ 100%), with the relative configurations depicted in Scheme 1; traces of the minor diastereomers could not be detected, even in the crude products. The ring closures of **2** with 2-formylbenzoic acid and 2-benzoylbenzoic acid resulted in 8,13-diazaoestrone benzologue pentacycles **6a** and **6b**, similarly with excellent diastereoselectivity.[8,9] In contrast with the earlier procedures for preparation of the 8,13-diazasteroid ring system, based on the ring closure of 1,2,3,4-tetrahydroisoquinoline-1-acetates with lactim ethers or reductive cyclization of 1-(2-succinylaminoethyl)-1,2,3,4-tetrahydroisoquinolines,[10] the present simple procedure is suitable for the preparation of 14-substituted derivatives.

The ^{1}H and ^{13}C NMR chemical shifts were assigned with the help of dqf-COSY, CH correlation, and CO-LOC measurements. The *syn*-diaxial relationship of the bridgehead H-9 and the 14-substituent was established for each compound by means of NOE difference experiments. The NOEs further revealed *trans* B/C ring fusion in **5a** and *cis* fusion in **5b**, **6a**, and **6b**, the latter probably driven by the steric demands from the phenyl substituent (**5b**) or the fused benzene ring (**6a**,**b**).

The ring closures of diamine **2** with γ-oxoacids can be categorised as domino type reactions,[11] since the formation of polycycles **5** and **6** proceeds by double cyclization. Domino ring closures were applied earlier for the preparation of various azasteroid derivatives.[12] The formation of **5** and **6** are the first examples of the syntheses of 8,13-diazasteroid systems via such reactions.

Keywords: Diamines; Isoquinolines; Azasteroids; Domino reactions; Stereoselective synthesis.
* Corresponding author. Tel.: +36-62-545564; fax: +36-62-545705; e-mail: fulop@pharma.szote.u-szeged.hu

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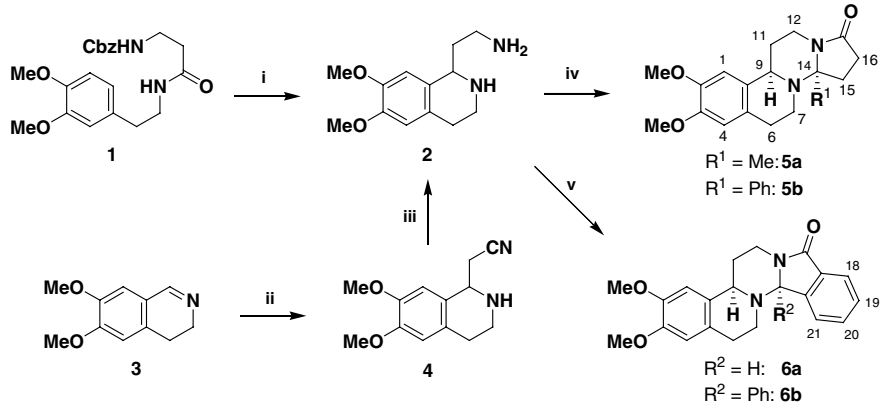
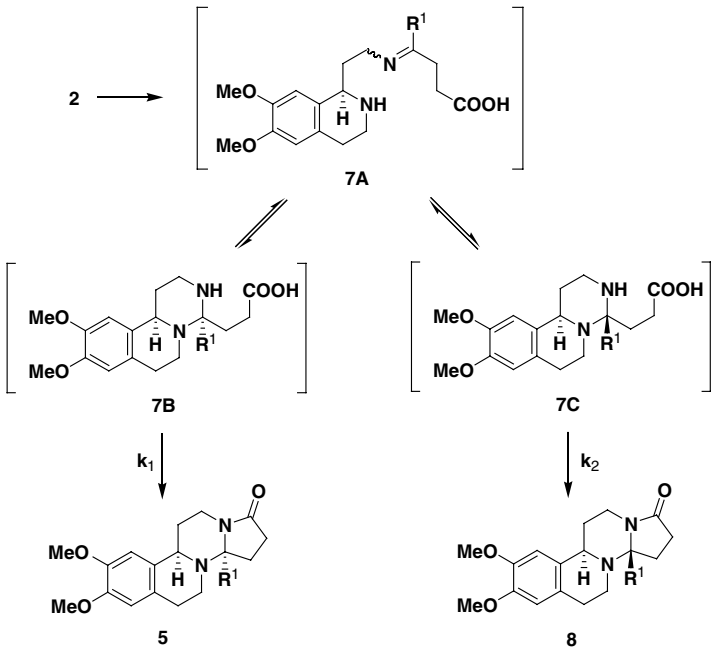


Scheme 1. Reagents and conditions: (i) see Ref. 5b; (ii) see Ref. 6; (iii) H_2, Raney-Ni, NH_3, MeOH, 50 °C, 50 atm, 6 h, 71%; (iv) $R^1CO(CH_2)_2COOH$, toluene, Δ, 1–2 h, 70–74%; (v) $R^2COC_6H_4COOH$, toluene, Δ, 1–4 h, 61–65%.



Scheme 2.

The cyclic intermediates (e.g., **7**) in the formation of **5** and **6** possess a ring-chain tautomeric character (Scheme 2), the second ring closure of which shifts the tautomeric equilibrium. The high diastereoselectivity (**5** ≫ **8**) of the overall process can be explained as a result of the kinetic control ($k_1 \gg k_2$) governing the second cyclization step.[13] Similar domino reactions of N-unsubstituted aminoalcohols or diamines and the corresponding γ- or δ-oxoacids often proceed with considerable stereoselectivity and are widely used for the preparation of nitrogen-bridged bicyclic lactams.[14]

The above results demonstrate that the domino ring closures of tetrahydroisoquinoline diamines with γ-oxo acids comprise a convenient route for synthesis of the 8,13-diazasteroid ring system. Further investigations on the scope and limitations of this reaction, including the effects of the substituents and the ring size, are in progress.

Acknowledgements

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7. A mixture of aminonitrile **4** (13.93 g, 0.06 mol), MeOH (150 mL), 25% NH_3 in MeOH (150 mL), and Raney-Ni (5 g) was hydrogenated in an autoclave at 50 °C and 50 atm for 6 h. The catalyst was then filtered off and the solvent was evaporated to give an oil, which was dissolved in MeOH (20 mL) and converted to a crystalline dihydrochloride of **2** with 20% ethanolic HCl (30 mL) and Et_2O (150 mL). The crystals were filtered off and recrystallized from a mixture of 95% MeOH–Et_2O. Pure diamine base **2** was obtained from the above dihydrochloride by alkaline treatment (10% NaOH), extraction (CH_2Cl_2), and evaporation under reduced pressure.
   2. 2HCl: Yield: 13.20 g (71%), mp 282–284 °C (lit.[15] mp 277 °C). IR (KBr) ν_{max}: 3440, 2940, 1518, 1226, 1115 cm^{-1}. ^1H NMR (D_2O, 399.78 MHz) δ: 2.42–2.60 (m, 2H, $CHCH_2$), 3.04–3.39 (m, 4H, $ArCH_2$, NCH_2), 3.49–3.60 (m, 1H, NCH_2), 3.62–3.73 (m, 1H, NCH_2), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.72–4.80 (m, overlapped with the signal of H_2O, 1H, 1-C*H*), 6.94 (s, 1H, C_6H_2), 6.99 (s, 1H, C_6H_2).
8. A mixture of the diamine **2** (0.71 g, 3 mmol) and the corresponding γ-oxo acid (3 mmol) was refluxed in toluene (40 mL), until no more starting materials could be detected by TLC (1–4 h). The solvent was then evaporated and the oily or crystalline residue (the NMR spectrum of which showed a *de* of ~100% in each case) was purified by means of column chromatography (on silica gel, using EtOAc (**5b**, **6a**,**b**) or a 4:1 mixture of EtOAc and MeOH (**5a**) as eluent) and recrystallization (*i*-Pr_2O–EtOAc=2:1).
   5a: Yield: 0.70 g (74%), mp 128–130 °C. IR (KBr) ν_{max}: 1676, 1522, 1422, 1209 cm^{-1}. ^1H NMR ($CDCl_3$, 399.78 MHz) δ: 1.36 (s, 3H, CH_3), 1.55 (tdd, 1H, J = 5.3, 11.5, 13.0 Hz (×2), H-11x), 2.04–2.17 (m, 2H, H-15x, H-15y), 2.22 (m, 1H, H-11y), 2.39–2.53 (m, 3H, H-7x, H-16x, H-16y), 2.63 (m, 1H, H-6x), 2.93–3.07 (m, 3H, H-6y, H-7y, H-12x), 3.85 (s, 6H, 2×OCH_3), 3.93 (br d, 1H, J = 11.5 Hz, H-9), 4.19 (ddd, 1H, J = 1.7, 5.3, 13.5 Hz, H-12y), 6.57 (s, 1H, H-4), 6.65 (s, 1H, H-1). ^{13}C NMR ($CDCl_3$, 100.54 MHz) δ: 14.0 (CH_3), 29.7 (C-16), 29.9 (C-6), 31.4 (C-11), 33.8 (C-15), 35.6 (C-12), 43.8 (C-7), 55.0 (C-9), 55.9 (OCH_3), 56.0 (OCH_3), 77.4 (C-14), 108.5 (C-1), 111.4 (C-4), 126.9 (C-5), 129.4 (C-10), 147.4 (C-2), 147.5 (C-3), 171.8 (C-17). HRMS (EI): calcd for $C_{18}H_{24}N_2O_3$ 316.1787, found: 316.1780.
   5b: Yield: 0.79 g (70%), mp 200–203 °C. IR (KBr) ν_{max}: 1702, 1518, 1231, 1130 cm^{-1}. ^1H NMR ($CDCl_3$, 399.78 MHz) δ: 1.37 (m, 1H, H-11x), 1.94–2.09 (m, 2H, H-11y, H-15x), 2.46–2.63 (m, 3H, H-15y, H-16x, H-16y), 2.77 (m, 1H, H-6x), 2.99–3.23 (m, 4H, H-6y, H-7x, H-7y, H-12x), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.09 (dd, 1H, J = 3.2, 12.3 Hz, H-9), 4.26 (ddd, 1H, J = 1.3, 5.6, 13.3 Hz, H-12y), 6.32 (s, 1H, H-1), 6.62 (s, 1H, H-4), 7.30 (m, 1H, *p*-C_6H_5), 7.39 (m, 2H, *m*-C_6H_5), 7.51 (m, 2H, *o*-C_6H_5). ^{13}C NMR ($CDCl_3$, 100.54 MHz) δ: 26.2 (C-11), 29.5 (C-6), 30.1 (C-16), 33.2 (C-15), 36.8 (C-12), 37.2 (C-7), 54.0 (C-9), 55.9 (OCH_3), 55.9 (OCH_3) 84.0 (C-14), 109.5 (C-1), 111.2 (C-4), 125.8 (C-5), 126.0 (s, 2C, *o*-C_6H_5), 127.4 (*p*-C_6H_5), 129.2 (s, 2C, *m*-C_6H_5), 130.3 (C-10), 144.3 (*i*-C_6H_5), 147.3 (C-2), 147.7 (C-3), 174.5 (C-17). HRMS (EI): calcd for $C_{23}H_{26}N_2O_3$ 378.1943, found: 378.1932.
   6a: Yield: 0.64 g (61%), mp 209–211 °C (lit.[16] mp 153 °C). IR (KBr) ν_{max}: 1689, 1520, 1271, 1141 cm^{-1}. ^1H NMR ($CDCl_3$, 399.78 MHz) δ: 1.79 (m, 1H, H-11x), 2.11 (m, 1H, H-11y), 2.41 (ddd, 1H, J = 1.9, 6.5, 11.6 Hz, H-7x), 2.55 (m, 1H, H-6x), 2.74 (td, 1H, J = 4.2, 11.6 Hz (×2), H-7y), 2.89 (m, 1H, H-6y), 3.41 (td, 1H, J = 4.2, 13.0 Hz (×2), H-12x), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.33 (dd, 1H, J = 3.0, 12.0 Hz, H-9), 4.50 (ddd, 1H, J = 1.3, 5.7, 13.0 Hz, H-12y), 5.56 (s, 1H, H-14), 6.58 (s, 1H, H-4), 6.60 (s, 1H, H-1), 7.49–7.61 (m, 3H, H-19, H-20, H-21), 7.87 (m, 1H, H-18). ^{13}C NMR ($CDCl_3$, 100.54 MHz) δ: 26.3 (C-11), 28.6 (C-6), 36.4 (C-7), 38.5 (C-12), 55.9 (OCH_3), 56.0 (OCH_3), 58.8 (C-9), 76.3 (C-14), 109.6 (C-1), 111.5 (C-4), 123.3 (C-21), 123.9 (C-18), 125.7 (C-5), 129.3 (C-19), 129.5 (C-10), 131.6 (C-20), 133.7 (C-15), 140.8 (C-16), 147.4 (C-2), 148.0 (C-3), 165.5 (C-17). HRMS (EI): calcd for $C_{21}H_{22}N_2O_3$ 350.1630, found: 350.1630.
   6b: Yield: 0.83 g (65%), mp 233–235 °C. IR (KBr) ν_{max}: 1701, 1519, 1399, 1227, 1135 cm^{-1}. ^1H NMR ($CDCl_3$, 399.78 MHz) δ: 1.54 (m, 1H, H-11x), 2.14 (m, 1H, H-11y), 2.51–2.59 (m, 2H, H-6x, H-7x), 2.78 (td, 1H, J = 3.8 Hz, 11.9 Hz (×2), H-7y), 3.04 (m, 1H, H-6y), 3.32 (td, 1H, J = 4.2, 13.2 Hz (×2), H-12x), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.30 (dd, 1H, J = 3.1, 12.3 Hz, H-9), 4.55 (dd, 1H, J = 5.7, 13.2 Hz, H-12y), 6.42 (s, 1H, H-1), 6.60 (s, 1H, H-4), 7.23 (m, 1H, H-21), 7.29 (m, 1H, *p*-C_6H_5), 7.36 (br t, 2H, J = 7.4 Hz (×2), *m*-C_6H_5), 7.38–7.46 (m, 2H, H-19, H-20), 7.60 (br s, 2H, *o*-C_6H_5), 7.87 (m, 1H, H-18). ^{13}C NMR ($CDCl_3$, 100.54 MHz) δ: 26.2 (C-11), 29.2 (C-6), 36.0 (C-12), 37.9 (C-7), 53.8 (C-9), 55.88 (OCH_3), 55.92 (OCH_3) 84.2 (C-14), 109.8 (C-1), 111.3 (C-4), 123.2 (C-21), 124.1 (C-18), 125.9 (C-5), 126.4 (brs, 2C, *o*-C_6H_5), 128.0 (*p*-C_6H_5), 128.7 (C-19), 129.4 (s, 2C, *m*-C_6H_5), 130.0 (C-10), 130.9 (C-16), 131.9 (C-20), 139.6 (*i*-C_6H_5), 147.3 (C-2), 147.4 (C-15), 147.8 (C-3), 166.8 (C-17). HRMS (EI): calcd for $C_{27}H_{26}N_2O_3$ 426.1943, found: 426.1932.
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