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ORIGINAL PAPER

Synthesis of arylated norbornyl amino acid esters

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Abstract Palladium-catalyzed hydroarylation of optically active norbornenimide-protected amino acid esters was studied to stereoselectively synthesize a series of new *exo*-aryl(hetaryl)-substituted norbornyl amino acid methyl esters.

Keywords Amino acids · Aromaticity · C–C coupling · Homogeneous catalysis · Heterocycles

Introduction

Amino acids are among the simplest optically active compounds in nature. Polymers, peptides, and proteins constructed from them show a wide variety of functions such as electron transfer, information transfer, photoreactivity, and selective catalytic functions, which still can only partly be imitated by synthetic compounds [1–4]. The use of both natural (chiral pool) and unnatural α-amino acids and their derivatives as chiral reagents, auxiliaries, and ligands for asymmetric catalysis is widespread [5–7]. In medicinal chemistry, bicyclic amino acids have attracted general interest as complex, polyfunctional templates for new drug candidates from bioactive molecules. Conformationally restricted bicyclic amino acids deserve special interest due to their prominent role in drug design and development [8, 9]. Dyatkin and coworkers [10] have developed integrin antagonists by incorporating an azabicyclic amino acid group as a proline-mimetic scaffold. On the other hand, optically active aromatic α-amino acids are important molecular fragments in many molecules of biological importance such as cephalecins, nocardisins, and glycopeptides of the vancomycin family. Heteroaromatic α-amino acids are also an interesting and important class of amino acids, and in particular, naphthyl and biphenyl derivatives have received increased attention due to the large number of structural equivalents and synthetic applications of the heteroaromatic moiety [11]. Saaby and coworkers [12] have reported that synthesis of optically active aromatic and heteroaromatic α-amino acids was a challenge in organic chemistry, and a few research groups have succeeded in development of a catalytic asymmetric Strecker reaction or the Sharpless amino-hydroxylation reaction giving the corresponding hetaryl α-amino cyanides or alcohols.

Additionally, bi- and tricyclic imides represent an important class of substrates for biological and chemical applications [13, 14]. These molecules are reported to exhibit a wide variety of biological activities such as antitumor, anti-inflammatory, and antimicrobial effects [15]. There are few reports in literature on synthesis of *N*-substituted chiral maleimides which contain the norbornyl function in their skeleton. Biagini and coworkers [16] have synthesized some amino acid methyl esters containing a norbornene unit.

Therefore, we became interested in synthesis of new, protected chiral amino acid esters, which represent aryl-modified bicyclic imide systems at the same time, by reductive Heck reactions. Due to its broad synthetic potential as a stereoselective C–C coupling method, the Heck reaction has been the subject of several synthetic and

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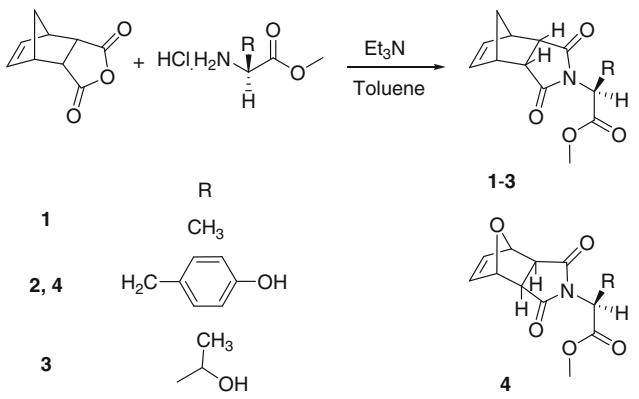
mechanistic studies over the last 30 years [17–20]. Originally developed to arylate acyclic alkenes, the reaction scope was later extended to cyclic compounds too. In previous work [21–24] it has been demonstrated by the Kaufmann group that palladium-catalyzed asymmetric Heck-type hydroarylations of bicyclic and tricyclic alkenes offer a valuable route to epibatidine analogs. Domino–Heck applications [25] are also feasible. We then extended the synthetic scope further by means of reductive Heck reactions of polyfunctionalized tricyclic molecules with a strained C=C bond and an acylamino imide or hydrazide group [26, 27].

Results and discussion

In this work, we first prepared optically active (*S*)-*N*-*endo*-norbornenyl amino acid methyl esters **1–3** and (*S*)-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl)-3-(4-hydroxyphenyl)propionic acid methyl ester (**4**) as new starting compounds (except **1**) in good yields using North's procedure (Scheme 1). The new structures were assigned by their ^{1}H nuclear magnetic resonance (NMR) data. In addition to ^{13}C NMR, distortionless enhancement by polarization transfer (DEPT), and Fourier-transform infrared (FT-IR) spectral data and elemental analyses, which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

Treatment of **1** with 1-chloro-4-iodobenzene and 1-iodo-4-methoxybenzene under reductive Heck conditions gave the pure products **5** and **6** after chromatographic separation on silica gel as single diastereomers in isolated yields of 78–80% (Scheme 2).

The same reductive Heck arylation conditions were successfully applied to the reaction of **2** with 1-iodo-4-methoxybenzene and 1-iodonaphthalene to give the new



Scheme 1

exo-arylated heterocycles **7** and **8** in good yields after chromatographic separation.

We also synthesized **9** and **10** from **3** with 2-iodothiophene and 1-chloro-2-iodobenzene and prepared **11** and **12** from **4** with iodobenzene and 2-iodothiophene as new 8-*exo*-compounds under the same Heck arylation conditions (Scheme 3).

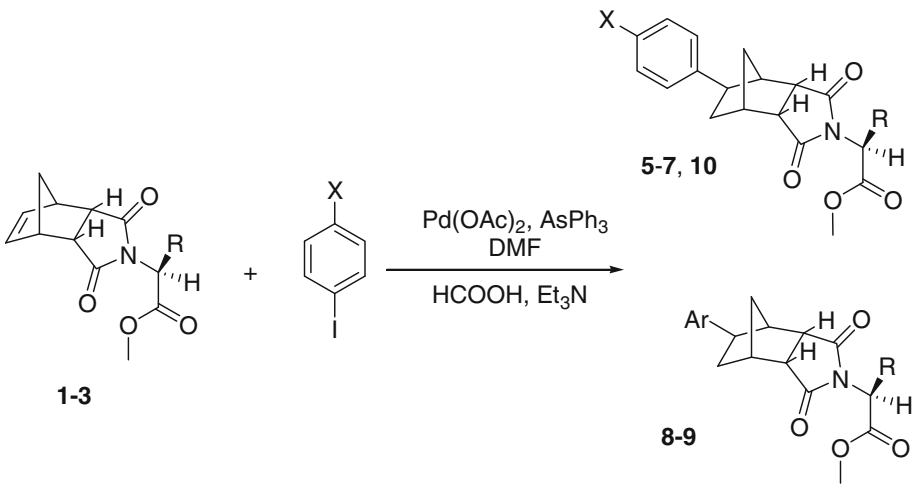
We expected to obtain two diastereomers after reductive Heck reactions due to the unsymmetric structures of **1–4**, but we observed only one set of signals. This was probably due to a rather long distance between the two chiral centers. The stereochemistry was inferred from their NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C-8 substituent was confirmed by the fact that H_8 showed no significant interaction with H_1. The geminal protons at C-9 were identified by vicinal coupling to H_1. Additionally, H–H correlation spectroscopy (COSY) spectra showed cross peaks between H_2 and H_6 and between H_8 and H_9. We observed diastereotopic methoxy protons as two singlets in the ^{1}H NMR spectra of **5**, **6**, and **10–12**. In addition to ^{13}C NMR, DEPT, and FT-IR spectral data and elemental analyses, which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

In conclusion, in presence of triphenylarsine as ligand, palladium-catalyzed hydroarylation of readily accessible optically active norbornyl amino acid methyl esters **1–4** was shown to be a stereoselective, versatile, and high-yield approach to synthesis of aryl and heteroaryl derivatives of tricyclic amino acid methyl esters **5–12**, which proved useful for construction of novel heterocycles of potential pharmacological interest.

Experimental

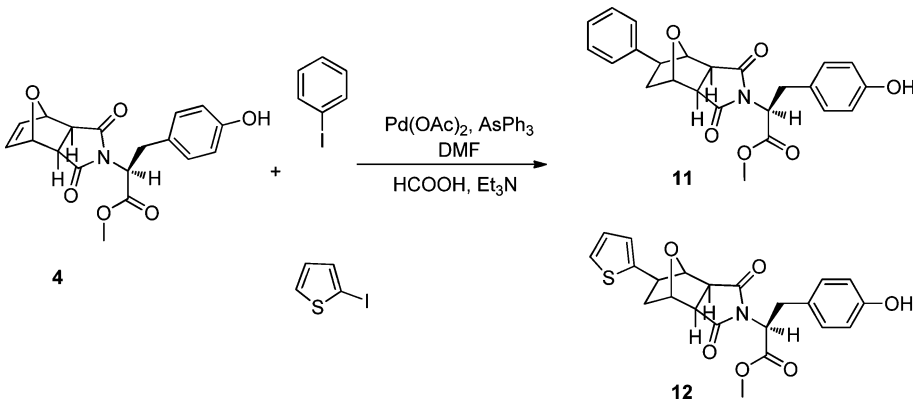
All reactions were carried out under nitrogen atmosphere unless otherwise indicated. Reactions were monitored by thin-layer chromatography. Visualization of the developed chromatograms was performed either with ultraviolet (UV) light or $KMnO_4$ stain. Products were purified by silica gel chromatography with solvent gradient of ethyl acetate:*n*-hexane to afford the title compounds. IR spectra were obtained with a Perkin Elmer FT-IR instrument, and absorption frequencies are reported in cm^{-1}. Melting points were determined with a Gallenkamp digital thermometer. NMR spectra were determined with a Bruker AC-400 and a Varian-INOVA-500 spectrometer. NMR 2D experiments were measured with a Bruker AC-400 spectrometer. Tetramethylsilane was used as internal standard and $CDCl_3$ as the solvent. Signal multiplicities in the NMR spectra are reported as follows: s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet. Mass

Scheme 2



Compound	R	X	Ar
5	CH_3	Cl	
6	CH_3	OMe	
7	H_2C—OH	OMe	
8	H_2C—OH		
9	CH_3 OH		
10	CH_3 OH	Cl	

Scheme 3



spectra were measured with an Agilent 6890N GC-System-5973 IMSD. Optical rotation values were determined with a polarimeter model AA-55 series from Optical Activity Ltd.

*General procedure for synthesis of **1–4***

To a solution of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (*exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-

dicarboxylic anhydride for **4**) (44 mmol) and triethylamine (80 mmol) in 150 cm^3 toluene was added amino acid methyl ester hydrochloride (40 mmol). The resulting mixture was heated at reflux for 15 h, then the cooled reaction mixture was washed with 2 M hydrochloric acid (3 × 50 cm^3), and the aqueous phase back-extracted with 30 cm^3 ethyl acetate. The combined organic phase was washed with saturated ammonium carbonate (2 × 50 cm^3) and 30 cm^3 H_2O. The organic layer was dried ($MgSO_4$), and the solvent removed. The residue was submitted to column chromatography using mixtures of ethyl acetate: *n*-hexane or crystallization from a suitable solvent.

Methyl [2α(S),3aα,4α,7α,7aα]-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)propanoate (**1**, $C_{13}H_{15}NO_4$)

The general procedure described above was used with *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and (*S*)-alanine methyl ester to afford **1** (68%) as a colorless solid identical to the product described in Ref. [16].

Methyl [2α(S),3aα,4α,7α,7aα]-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-3-(4-hydroxyphenyl)propanoate (**2**, $C_{19}H_{19}NO_5$)

The general procedure described above was used with *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and (*S*)-tyrosine methyl ester to afford **2** (73%) as a colorless solid. M.p.: 141–142 °C (recrystallization from ethyl acetate:*n*-hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 8.6 Hz, H_{10a}), 1.54 (d, J = 8.6 Hz, H_{10s}), 3.05 (dd, J = 4.7, 7.8 Hz, 1H, CH_2), 3.11–3.20 (m, 4H, H_1, H_2, H_6, H_7), 3.32 (dd, J = 4.7, 11.7 Hz, 1H, CH_2), 3.67 (s, 3H, OCH_3), 4.85 (dd, J = 5.5, 11.7 Hz, 1H, N–CH), 5.50 (brs, H_8), 5.75 (brs, H_9), 6.22 (brs, OH), 6.65 (d, J = 8.6 Hz, 2H, Ar), 6.92 (d, J = 8.6 Hz, 2H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.16 (CH_2), 44.91 (C_7), 45.11 (C_1), 45.94 (C_6), 46.06 (C_2), 52.41 (C_{10}), 52.90 (OCH_3), 53.25 (N–CH), 115.44 (ArC), 128.14 (C), 130.37 (ArC), 134.32 (C_8), 134.54 (C_9), 155.26 (C–OH), 169.12 (C=O), 177.46 (C=O), 177.76 (C=O) ppm; FT-IR (ATR): $\bar{\nu}$ = 3,418 (OH), 3,058, 2,992, 2,952, 2,872, 1,764 (C=O), 1,742 (C=O), 1,687 (C=O), 1,614, 1,596, 1,516, 1,437, 1,387, 1,248, 1,226, 1,165 cm^{-1}; GC–MS (EI, 70 eV): m/z = 341 (M^+), 326, 310, 293, 179, 162, 107, 91, 59; $[\alpha]_D^{20}$ = +76.6° cm^2 g^{-1} (c = 0.018 g cm^{-3}, chloroform).

Methyl [2α(2S,3R),3aα,4α,7α,7aα]-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-3-hydroxybutanoate (**3**, $C_{14}H_{17}NO_5$)

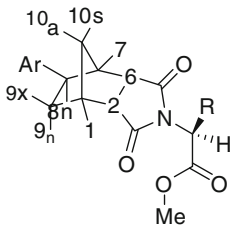
The general procedure described above was used with *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and (*S*)-threonine methyl ester to afford **3** (50%) as a colorless oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (d, J = 4.8 Hz, 3H, CH_3), 1.53 (d, J = 8.8 Hz, H_{10a}), 1.72 (d, J = 8.8 Hz, H_{10s}), 3.33–3.66 (m, 4H, H_1, H_2, H_6, H_7), 3.68 (s, 3H, OCH_3), 3.97 (d, J = 9.3 Hz, 1H, N–CH), 4.38 (brs, OH), 4.60 (d, J = 4.8 Hz, CH), 6.10 (s, 2H, H_8, H_9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.45 (CH_3), 45.31 (CH_2), 45.37 (C_2), 46.22 (C_6), 46.62 (C_1), 52.72 (C_7), 52.95 (OCH_3), 59.59 (N–CH), 66.55 (C–OH), 135.11 (C_8, C_9), 167.90 (C=O), 177.91 (C=O), 178.93 (C=O) ppm; FT-IR (ATR): $\bar{\nu}$ = 3,417 (OH), 3,063, 2,984, 2,952, 2,870, 1,743 (C=O), 1,691 (C=O), 1,455, 1,435, 1,384, 1,277, 1,181 cm^{-1}; GC–MS (EI, 70 eV): m/z = 282 (M^++2), 264, 235, 220, 154, 137, 66; $[\alpha]_D^{20}$ = +15.3° cm^2 g^{-1} (c = 0.018 g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4β,7β,7aα]-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(4-hydroxyphenyl)propanoate (**4**, $C_{18}H_{17}NO_6$)

The general procedure described above was used with *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and (*S*)-tyrosine methyl ester to afford **4** (37%) as a colorless oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (d, J = 6.2 Hz, H_2), 2.69 (d, J = 6.2 Hz, H_6), 3.18 (dd, J = 5.5, 14.1 Hz, 1H, CH_2), 3.34 (dd, J = 5.5, 14.1 Hz, 1H, CH_2), 3.68 (s, 3H, OCH_3), 4.81 (dd, J = 4.7, 10.9 Hz, 1H, N–CH), 5.02 (s, H_1), 5.15 (s, H_7), 5.44 (brs, OH), 6.38 (s, 2H, H_8, H_9), 6.60 (d, J = 8.6 Hz, 2H, Ar), 6.93 (d, J = 8.6 Hz, 2H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.52 (CH_2), 46.21 (C_6), 46.29 (C_2), 51.77 (OCH_3), 53.16 (N–CH), 79.74 (C_1), 79.77 (C_7), 114.36 (ArC), 126.76 (ArC), 129.16 (ArC), 135.48 (C_8), 135.73 (C_9), 154.22 (C), 161.61 (C), 167.72 (C=O), 174.34 (C=O) ppm; FT-IR (ATR): $\bar{\nu}$ = 3,405 (OH), 3,012, 2,956, 1,775 (C=O), 1,738 (C=O), 1,694 (C=O), 1,614, 1,596, 1,516, 1,438, 1,391, 1,245, 1,202, 1,166, 875 cm^{-1}; GC–MS (EI, 70 eV): m/z = 311 (M^++1-OMe), 294, 218, 177, 147, 132, 94; $[\alpha]_D^{20}$ = −34.4° cm^2 g^{-1} (c = 0.018 g cm^{-3}, chloroform).

*General procedure for synthesis of hydroarylation products of **1–4***

A solution of 5.6 mg $Pd(OAc)_2$ (0.025 mmol) and 33.7 mg $AsPh_3$ (0.11 mmol) in 3 cm^3 dry DMF was stirred in a Schlenk flask under nitrogen at 65 °C for 15 min in order to form the catalyst complex. Then, 306 mg aryl iodide (1.5 mmol), **1** (or **2**–**4**) (1.00 mmol), 354 mg triethylamine (3.5 mmol), and 138 mg formic acid (3.0 mmol) were added. The mixture was heated to 65 °C for 24–48 h. After cooling to rt, 50 cm^3 brine was added, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated, and the residue purified by chromatography.



Methyl [2α(2S),3aα,4α,5a,7α,7aα]-2-[5-(4-chlorophenyl)-octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]-propanoate (**5**, $C_{19}H_{20}ClNO_4$)

The general procedure described above was used with **1** and 1-chloro-4-iodobenzene to afford **5** (78%) as a colorless oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.51$ (d, $J = 7.3$ Hz, 4H, CH_3, H_{10a}), 1.72–1.85 (m, 3H, H_{10s}, H_{9x}, H_{9n}), 2.77–2.84 (m, 2H, H_1, H_7), 3.06–3.18 (m, 3H, H_2, H_6, H_{8n}), 3.65, 3.67 (2s, 3OCH_3), 4.76 (dq, $J = 0.9$, 7.3 Hz, 1H, N–CH), 7.05 (dd, $J = 5.9$, 8.8 Hz, 2H, Ar), 7.17 (d, $J = 8.8$ Hz, 2H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.48$ (CH_3), 31.61 (C_9), 39.81 (C_{10}), 40.20 (C_8), 44.91 (C_2), 46.74 (C_6), 46.92 (C_1), 47.29 (C_7), 47.95 (OCH_3), 51.63 (N–CH), 127.38 (ArC), 127.54 (ArC), 130.88 (C), 142.32 (C), 168.60 (C=O), 175.80 (C=O), 176.06 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}043$, 2,955, 2,885, 1,770 (C=O), 1,744 (C=O), 1,698 (C=O), 1,492, 1,455, 1,381, 1,227, 1,118, 820 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 361$ (M^+), 346, 332, 163, 125, 59; $[\alpha]_D^{20} = -13.1°$ cm^2 g^{-1} ($c = 0.018$ g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4α,5a,7α,7aα]-2-[octahydro-5-(4-methoxyphenyl)-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]propanoate (**6**, $C_{20}H_{23}NO_5$)

The general procedure described above was used with **1** and 1-iodo-4-methoxybenzene to afford **6** (80%) as a colorless oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$–1.55 (m, H_{10a}), 1.57 (d, $J = 7.8$ Hz, 3H, CH_3), 1.83–1.99 (m, 3H, H_{10s}, H_{9x},H_{9n}), 2.81–2.90 (m, 2H, H_1, H_7), 3.12–3.23 (m, 3H, H_2, H_6, H_{8n}), 3.71, 3.73 (2s, 3OCH_3), 3.77 (s, 3H, OCH_3), 4.83 (dq, $J = 1.9$, 7.8 Hz, 1H, N–CH), 6.83 (dd, $J = 2.3$, 8.6 Hz, 2H, Ar), 7.09 (dd, $J = 2.3$, 8.6 Hz, 2H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.75$ (CH_3), 32.77 (CH_2), 39.89 (C_9), 41.20 (C_8), 47.85 (C_2), 48.25 (C_6), 48.57 (C_1), 48.85 (C_7), 49.18 (OCH_3), 52.89 (OCH_3), 55.51 (N–CH), 114.03 (ArC), 128.22 (ArC), 137.04 (C), 158.12 (C), 169.90 (C=O), 177.47 (C=O), 177.51 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}014$, 2,954, 2,916, 2,838, 1,770 (C=O), 1,746 (C=O), 1,698 (C=O), 1,609, 1,581, 1,511, 1,455, 1,382, 1,243, 1,198, 1,178, 825 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 357$ (M^+), 326, 298, 268, 253, 172, 134, 59; $[\alpha]_D^{20} = -17.7°$ cm^2 g^{-1} ($c = 0.010$ g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4α,5a,7α,7aα]-2-[octahydro-5-(4-methoxyphenyl)-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]-3-(4-hydroxyphenyl)propanoate (**7**, $C_{26}H_{27}NO_6$)

The general procedure described above was used with **2** and 1-iodo-4-methoxybenzene to afford **7** (68%) as a colorless oil (column chromatography from ethyl acetate: *n*-hexane 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (d, $J = 10.9$ Hz, H_{10a}), 1.48–1.77 (m, 3H, H_{10s}, H_{9x}, H_{9n}), 2.46–2.50 (m, H_{8n}), 2.71–2.76 (m, 2H, CH_2), 2.91–3.10 (m, 2H, H_1, H_7), 3.35–3.49 (m, 2H, H_2, H_6), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.07 (dd, $J = 5.8$, 9.7 Hz, 1N–CH), 5.75 (brs, OH), 6.64 (dd, $J = 2.3$, 8.6 Hz, 2H, Ar), 6.78–6.82 (dd, $J = 2.3$, 8.6 Hz, 2H, Ar), 6.96–7.03 (m, 4H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.06$ (C_{10}), 39.87 (CH_2), 40.71 (C_9), 41.15 (C_7), 45.91 (C_1), 46.08 (C_8), 48.35 (C_6), 48.88 (C_2), 53.08 (OCH_3), 53.46 (OCH_3), 55.49 (N–CH), 113.91 (ArC), 115.65 (ArC), 115.70 (ArC), 128.07 (ArC), 128.12 (ArC), 128.22 (ArC), 128.24 (ArC), 130.25 (ArC), 136.94 (C), 137.06 (C), 155.19 (C), 157.91 (C), 169.19 (C=O), 177.97 (C=O), 178.11 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}416$ (OH), 3,022, 2,968, 2,838, 1,743 (C=O), 1,690 (C=O), 1,614, 1,595, 1,513, 1,441, 1,384, 1,245, 1,206, 1,174, 1,160, 820, 804 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 449$ (M^+), 403, 327, 310, 270, 239, 218, 204, 107, 59; $[\alpha]_D^{20} = -60.4°$ cm^2 g^{-1} ($c = 0.014$ g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4α,5a,7α,7aα]-2-[octahydro-5-(1-naphthyl)-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]-3-(4-hydroxyphenyl)propanoate (**8**, $C_{29}H_{27}NO_5$)

The general procedure described above was used with **2** and 1-iodonaphthalene to afford **8** (66%) as a light yellow solid. M.p.: 172–174 °C (column chromatography from ethyl acetate:*n*-hexane 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.39$ (d, $J = 9.8$ Hz, H_{10a}), 1.64–1.72 (m, 2H, H_{9x}, H_{9n}), 1.77 (d, $J = 9.8$ Hz, H_{10s}), 2.77 (brs, H_7), 2.92 (dd, $J = 4.9$, 7.8 Hz, H_{8n}), 3.00 (brs, H_1), 3.29–3.37 (m, 2H, CH_2), 3.40 (d, $J = 5.8$ Hz, H_2), 3.43 (d, $J = 5.8$ Hz, H_6), 3.75 (s, 3H, OCH_3), 5.06 (dd, $J = 5.8$, 9.7 Hz, 1N–CH), 5.36 (brs, OH), 6.48 (d, $J = 7.8$ Hz, 2H, Ar), 6.95 (dd, $J = 8.8$, 10.7 Hz, 2H, Ar), 7.16 (d, $J = 7.8$ Hz, 1H, Ar), 7.31 (dd, $J = 7.8$, 12.7 Hz, 1H, Ar), 7.41 (dd, $J = 7.8$, 12.7 Hz, 1H, Ar), 7.47–7.50 (m, 1H, Ar), 7.63 (d, $J = 7.8$ Hz, 1H, Ar), 7.76 (d, $J = 7.8$ Hz, 1H, Ar), 8.03 (dd, $J = 8.8$, 13.9 Hz, 1H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 37.38$ (CH_2), 38.64 (C_{10}), 39.02 (CH_2), 44.39 (C_7), 47.35 (C_1), 47.51 (C_8), 47.53 (C_6), 47.72 (C_2), 51.83 (OCH_3), 52.44 (N–CH), 114.39 (ArC), 114.53 (ArC), 121.03 (ArC), 121.14 (ArC), 123.12 (ArC), 123.89 (ArC), 124.63 (ArC), 125.17 (ArC), 126.01 (ArC), 127.65 (ArC), 129.10 (ArC), 131.04 (C), 133.03 (C), 138.74 (C), 153.74 (C), 167.98 (C), 176.43 (C=O), 176.72 (C=O), 176.87 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}268$ (OH), 3,017, 2,979,

2,946, 2,891, 1,737, 1,703, 1,683, 1,615, 1,595, 1,517, 1,440, 1,388, 1,239, 1,199, 1,162, 798, 773 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 469$ (M^+), 438, 347, 330, 290, 275, 254, 240, 107, 59; $[\alpha]_D^{20} = +57.8°$ cm^2 g^{-1} ($c = 0.014$ g cm^{-3}, chloroform).

Methyl [2α(2S,3R),3aα,4α,5a,7α,7aα]-2-[octahydro-1,3-dioxo-5-(2-thienyl)-4,7-methano-2H-isoindol-2-yl]-3-hydroxybutanoate (**9**, $C_{18}H_{21}NO_5S$)

The general procedure described above was used with **3** and 2-iodothiophene to afford **9** (74%) as a colorless oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 5.5$ Hz, 3H, CH_3), 1.65 (d, $J = 10.9$ Hz, H_{10a}), 1.82–1.88 (m, H_{10s}), 1.96–2.03 (m, 2H, H_{9x}, H_{9n}), 2.92 (brs, 2H, H_1, H_7), 3.22–3.40 (m, 3H, H_2, H_6, H_{8n}), 3.78 (s, 3H, OCH_3), 3.94 (dd, $J = 9.4$, 13.3 Hz, 1H, CH), 4.53–4.62 (m, OH), 4.80 (dd, $J = 3.1$, 4.7 Hz, 1H, CH), 6.78–6.80 (m, 1H, Ar), 6.91 (ddd, $J = 1.6$, 5.5, 8.6 Hz, 1H, Ar), 7.13 (dd, $J = 1.6$, 5.5 Hz, 1H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.56$ (CH_3), 35.35 (CH_2), 38.19 (C_8), 39.87 (C_9), 40.45 (C_7), 47.52 (C_1), 48.63 (C_6), 49.08 (C_2), 53.11 (OCH_3), 59.65 (CH–OH), 66.41 (N–CH), 123.68 (ArC), 127.01 (ArC), 149.81 (ArC), 168.02 (C), 178.18 (C=O), 179.02 (C=O), 179.21 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}438$ (OH), 3,068, 2,970, 2,881, 1,744 (C=O), 1,693 (C=O), 1,455, 1,435, 1,381, 1,277, 1,177, 740, 697 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 363$ (M^+), 346, 319, 304, 281, 215, 165, 148, 66; $[\alpha]_D^{20} = +7.70°$ cm^2 g^{-1} ($c = 0.018$ g cm^{-3}, chloroform).

Methyl [2α(2S,3R),3aα,4α,5a,7α,7aα]-2-[5-(4-chlorophenyl)-octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]-3-hydroxybutanoate (**10**, $C_{20}H_{22}ClNO_5$)

The general procedure described above was used with **3** and 1-chloro-2-iodobenzene to afford **10** (67%) as a yellow oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.18$ (dd, $J = 3.9$, 6.8 Hz, 3H, CH_3), 1.60 (d, $J = 8.8$ Hz, H_{10a}), 1.66–1.75 (m, H_{10s}), 1.83–1.90 (m, H_{9x}), 1.98–2.03 (m, H_{9n}), 2.16 (ddd, $J = 1.9$, 8.8, 10.7 Hz, H_{8n}), 2.87 (brs, H_7), 2.93 (d, $J = 5.8$ Hz, H_1), 3.16–3.33 (m, 3H_2, H_6, 1CH), 3.71, 3.72 (2s, 3OCH_3), 4.52 (brs, OH), 4.77 (t, $J = 4.8$ Hz, 1H, N–CH), 7.06–7.09 (m, 1H, Ar), 7.13–7.18 (m, 2H, Ar), 7.29 (d, $J = 6.8$ Hz, 1H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.45$ (CH_3), 31.59 (CH_2), 38.82 (C_8), 38.90 (C_9), 39.17 (C_7), 43.19 (C_1), 47.58 (C_6), 407.87 (C_2), 51.89 (OCH_3), 58.47 (CH–OH), 65.28 (N–CH), 125.52 (ArC), 126.46 (ArC), 129.08 (ArC), 133.68 (ArC), 140.91 (C), 166.89 (C), 176.84 (C=O), 176.93 (C=O), 177.60 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}426$, 3,063, 2,971, 2,881, 1,743, 1,695, 1,436, 1,378, 1,276, 1,190, 751 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 391$ (M^+), 376, 361, 331, 314, 275, 231, 215, 165, 66; $[\alpha]_D^{20} = -8.80°$ cm^2 g^{-1} ($c = 0.013$ g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4β,5β,7β,7aα]-2-(octahydro-1,3-dioxo-5-phenyl-4,7-epoxy-2H-isoindol-2-yl)-3-(4-hydroxyphenyl)propanoate (**11**, $C_{24}H_{23}NO_6$)

The general procedure described above was used with **4** and iodobenzene to afford **11** (65%) as a yellow crystals. M.p.: 168–171 °C (column chromatography from ethyl acetate:*n*-hexane 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.78$–1.86 (m, H_{9x}), 2.04–2.10 (m, H_{9n}), 2.76–2.88 (m, 3H, H_2, H_6, H_{8n}), 3.16 (ddd, $J = 2.3$, 10.9, 11.0 Hz, 1H, CH_2), 3.33 (dd, $J = 4.7$, 14.0 Hz, 1H, CH_2), 3.68, 3.69 (2s, 3OCH_3), 4.59 (s, H_1), 4.68 (s, H_7), 4.77–4.81 (m, 1H, N–CH), 4.89 (d, $J = 5.5$ Hz, OH), 6.60–6.63 (m, 2H, Ar), 6.91–6.93 (d, $J = 6.8$ Hz, 2H, Ar), 7.11–7.22 (m, 5H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 33.33$ (CH_2), 40.50 (CH_2), 47.69 (CH), 49.78 (C_6), 50.15 (C_2), 53.08 (CH_3), 54.56 (N–CH), 79.15 (C_1), 84.75 (C_7), 115.60 (ArC), 127.04 (ArC), 127.35 (ArC), 127.37 (ArC), 128.87 (ArC), 130.50 (ArC), 130.53 (ArC) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}437$ (OH), 3,015, 2,954, 2,921, 1,775 (C=O), 1,740 (C=O), 1,696 (C=O), 1,614, 1,596, 1,515, 1,494, 1,392, 1,246, 1,203, 1,166, 836, 701, 672 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 406$ (M^+), 391, 362, 345, 327, 313, 283, 172, 146, 129, 112, 57; $[\alpha]_D^{20} = +88.94°$ cm^2 g^{-1} ($c = 0.013$ g cm^{-3}, chloroform).

Methyl [2α(2S),3aα,4β,5β,7β,7aα]-2-[octahydro-1,3-dioxo-5-(2-thienyl)-4,7-epoxy-2H-isoindol-2-yl]-3-(4-hydroxyphenyl)propanoate (**12**, $C_{22}H_{21}NO_6S$)

The general procedure described above was used with **4** and 2-iodothiophene to afford **12** (63%) as a yellow oil (column chromatography from ethyl acetate:*n*-hexane 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.87$–1.94 (m, H_{9n}), 2.08 (dd, $J = 8.8$, 12.7 Hz, H_{9x}), 2.74–2.86 (m, 2H_2, H_6), 3.14–3.24 (m, 2H, H_{8n}, CH_2), 3.32 (dd, $J = 4.9$, 9.7 Hz, 1H, CH_2), 3.67, 3.68 (2s, 3OCH_3), 4.67 (brs, H_7), 4.76–4.80 (m, 1H, N–CH), 4.90 (d, $J = 5.8$ Hz, H_1), 5.32 (brs, OH), 6.60–6.63 (m, 2H, Ar), 6.76 (s, 1H, Ar), 6.82–6.84 (m, 1H, Ar), 6.91–6.93 (m, 2H, Ar), 7.07 (d, $J = 4.9$ Hz, 1H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 39.60$ (CH_2), 41.76 (CH_2), 38.82 (C_8), 38.90 (C_9), 42.00 (CH), 48.26 (C_6), 48.34 (C_2), 51.83 (OCH_3), 53.31 (N–CH), 77.78 (C_1), 83.72 (C_7), 114.37 (ArC), 122.86 (ArC), 123.05 (ArC), 125.71 (ArC), 127.35 (ArC), 127.38 (ArC), 129.31 (ArC), 146.03 (C), 153.59 (C), 167.56 (C), 174.60 (C=O), 174.91 (C=O), 174.96 (C=O) ppm; FT-IR (ATR): $\bar{\nu} = 3{,}398$ (OH), 3,063, 2,987, 2,953, 1,776 (C=O), 1,738 (C=O), 1,696 (C=O), 1,614, 1,596, 1,516, 1,438, 1,392, 1,247, 1,204, 1,166, 830, 701, 657 cm^{-1}; GC–MS (EI, 70 eV): $m/z = 429$ (M^++2), 329, 313, 296, 219, 206, 178, 165, 149, 122, 107; $[\alpha]_D^{20} = -40.70°$ cm^2 g^{-1} ($c = 0.018$ g cm^{-3}, chloroform).

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