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Article

A Chiron-based Approach for the Synthesis of Tricyclic Tyrosine Analogue†

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A chiron approach-based enantioselective synthesis of designed tricyclic tyrosine analogue *D*-**2** was developed. A SmI_2-mediated free radical cyclization, an intramolecular Friedel-Crafts reaction and an intramolecular Mannich reaction served as key steps. These key steps were optimized and repeated in good yields. All the stereochemistries in the synthesis were established and confirmed.

Keywords chiron approach, tyrosine analogue, enantioselective synthesis, signal transduction

Introduction

In light of important role played by signal transduction in normal cell growth and function, it is not surprising that aberrations in these signaling pathways can contribute to a variety of diseases, including several cancers.[1] For this reason, development of pTyr (phosphotyrosyl)-dependent signaling inhibitors has become a significant research objective.[2] In the process of binding to SH2 (Src homology 2) domains, entropy penalties must be paid for the selection of proper binding conformations. As a general principle, conformationally constrained analogues (such as analogues of phenyl alanine[3] and tyrosine[4]) have often been used to enhance binding affinity by reducing these entropy penalties. The X-ray and solution structures of liganded SH2 domains have provided a clear definition of relevant binding geometries,[5] which would be an essential starting point for design of such conformationally constrained pTyr analogues. In the case of SH2-domoain-directed pTyr mimetics, tricyclic analogue **2** has been designed (Figure 1) that contains within their skeletons tyrosyl residues, whose χ_1 and χ_2 torsion angles are very closely approximating to those observed in a pTyr reside ligated to the p56lck SH2 domain respectively. Importantly, when **2** is docked into the SH2 domain, the appended constrained framework is situated away from the protein, minimizing steric hindrance.

In 1997, Burke and colleagues[6] first reported the design principles of **2** and a synthetic route of racemic **1**. Based on this idea, a methyl group was added on the β-position of the amino acid to block the by-reactions during the synthesis. In principle, this methyl group is not necessary for such a constrained conformation. In order to investigate its potential roles in certain inhibitor design, the efficient and enantioselective synthesis of **2** was explored by us recently.[7] Herein, we report an enantioselective synthesis of the *D*-enantiomer of this tricyclic analogue **2**. Two aims we are going to achieve through the project of *D*-**2**: one is to develop a new synthetic route for both *L*-**2** and *D*-**2**, and the other is to evaluate the effects caused by both enantiomers of **2** in the future SH2 domain ligands studies. In this established chiron approach-initiated synthesis, an intramolecular Mannich reaction, an intramolecular Friedel-Crafts reaction and a SmI_2 mediated free radical reaction served as the key reactions. More importantly, the advantage of future diversity development on such an SH2 domain inhibitor scaffold, which is generally represented by **3**, would give the inhibitor design and development more flexibility.

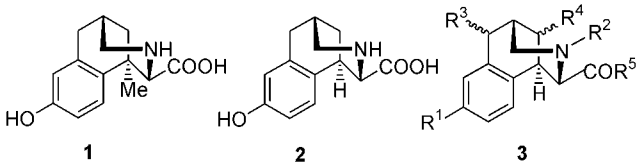

Figure 1 Structures of conformation-constrained tyrosine analogues.

Results and discussion

According to general principles of retro-synthesis, the tricyclic skeleton *D*-**2** was converted to a β-amino ketone synthon **A** after several operations of functional group addition (FGA). Upon this basic skeleton, a further Mannich reaction-based disconnection afforded the

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tetralone precursor **B**. With the knowledge of Friedel-Crafts reaction, the bond between carbonyl and phenyl ring was broken down to give a linear amino acid **C**. The three-carbon acid side chain in the resultant structure **C** could be introduced by a SmI_2-mediated free radical addition to ketone **E** in an indirect way through a lactone intermediate **D**. To construct ketone **E**, a quick way is to use a reaction of a 4-bromoanisole-derived organometallic reagent with an active *L*-serine derivative **G** (Figure 2). Using *L*-serine as a chiral starting material, the first stereogenic center was unambiguously introduced.

Synthesis started form alcohol **4**, which was obtained very easily from *L*-serine using Norman's method,[8] in four steps and 73% total yield. After Swern oxidation of alcohol **4**, the freshly prepared Garner's aldehyde was treated with *p*-methoxyphenylmagnesium bromide[9] to afford the secondary alcohol **5** as a mixture (the ratio is 8∶1 by ^{1}H NMR) in 81% overall yield (Scheme 1). The diastereomeric mixture was then converted into a single ketone **6** (99.6% *ee* by HPLC) using PDC oxidation in DCM. Cleavage of acid-sensitive protective groups on **6** followed by amino group and hydroxyl group protections by ethyl chloroformate and acetic anhydride successively afforded acetrate **8** (96.0% *ee* by HPLC). A SmI_2-mediated free radical reaction[10] of ketone **8** with methyl acylate generated a *tert*-alcohol intermediate, which immediately cyclized *in situ* to give lactone **9**. It is noteworthy that HMPA was necessary to such a cyclization.[11] In the case without HMPA, the starting material did not disappear even after 24 h at room temperature. Optimization of this cyclization found that SmI_2-*t*-BuOH-methyl acrylate/ketone **8** (molar ratio＝6∶1.5∶2 ∶1) at 0 ℃ gave the best result. The stereochemistry of lactone unit in **9** was not determined and the mixture was used forward directly. Solvent effect was observed in the following hydrogenolysis step. When EtOAc or MeOH was selected as the solvent for reductive ring-open, no product or little product was found under normal or even higher H_2 pressures. While the reaction was performed in acetic acid with a catalytic amount of $HClO_4$,[12] lactone **9** was hydrogenolyzed (10% Pd-C) easily to afford acid **10** in a satisfactory yield (91%, mixture of two isomers).

Friedel-Crafts reaction of acid **10** was proved to be very problematic. After *in situ* production of corresponding acid chloride by treatment of acid **10** with oxayl chloride in the presence of a catalytic amount of DMF, subsequent Friedel-Crafts reaction all gave no product in the presence of a variety of Lewis acids, including $AlCl_3$, $SnCl_4$, $FeCl_3$, $ZnCl_2$, $BF_3 \cdot Et_2O$ *etc*. Finally, the solvent system was found to play a key role for this reaction sequence. After optimization, a mixed solvent system (CH_2Cl_2/CS_2＝1/6) was proved to be the best. Friedel-Crafts reaction of **10** promoted by $AlCl_3$ in above solvent system afforded ketones **11a** and **11b** in 80% yield with a molar ratio of 2∶1 (**11a**/**11b**).

After refluxing **11a** with conc. HCl for 10 h, an amino alcohol intermediate was formed. However, no product was detected when the above amino alcohol was refluxed with paraformaldehyde in EtOH[13] (Scheme 2). Finally, Mannich reaction occurred when refluxing the amino alcohol with aqueous HCHO in EtOH. Protecting the amino group in Mannich product with methyl chloroformate gave alcohol **12** finally.

Swern oxidation of alcohol **12** followed by treatment with $NaClO_2$ and CH_2N_2 afforded the corresponded ester **13** in 76% yield over three steps (89.4% *ee* by HPLC). Partial racemization of compound **9** was explained by the contribution of oxygen anion which was

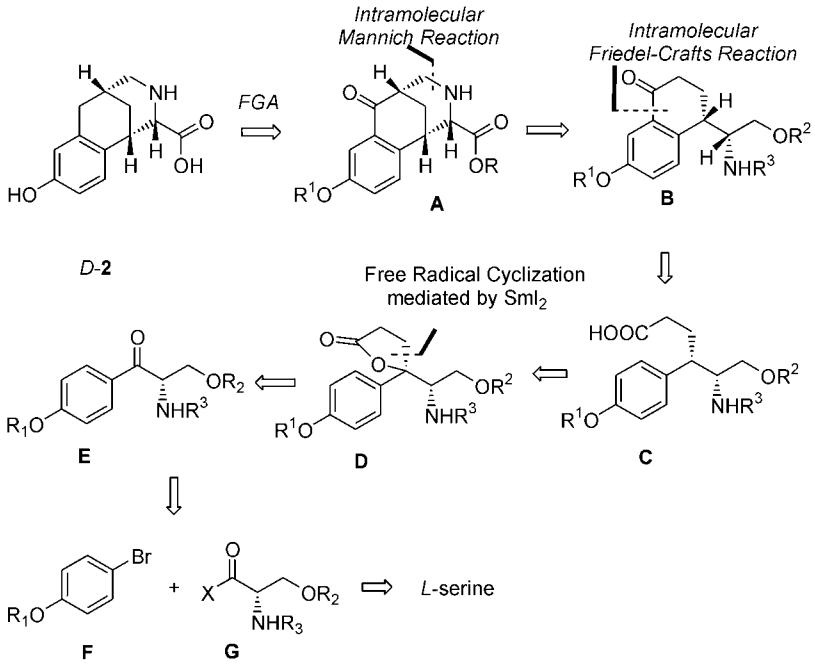
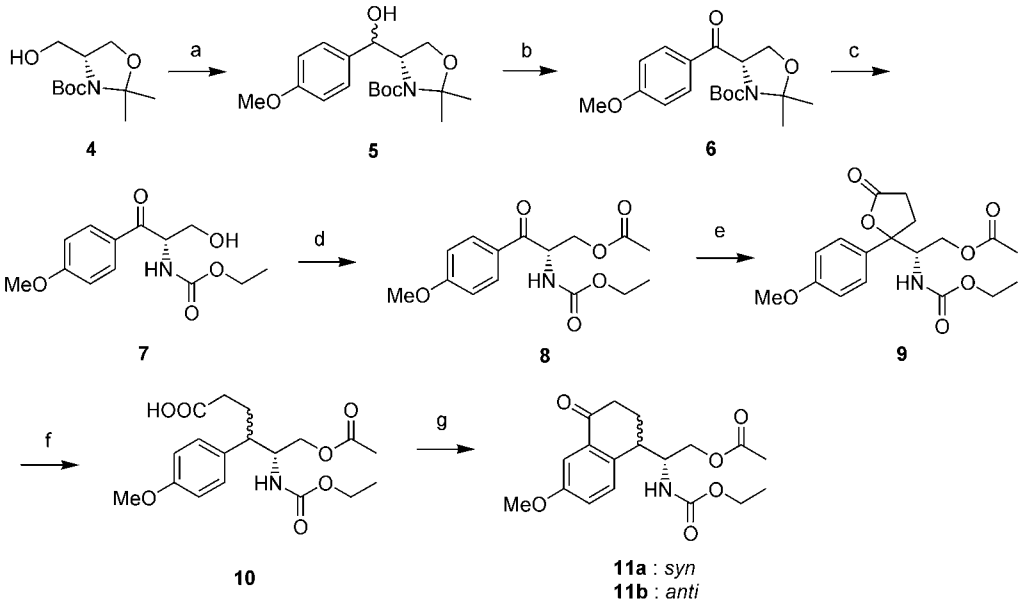


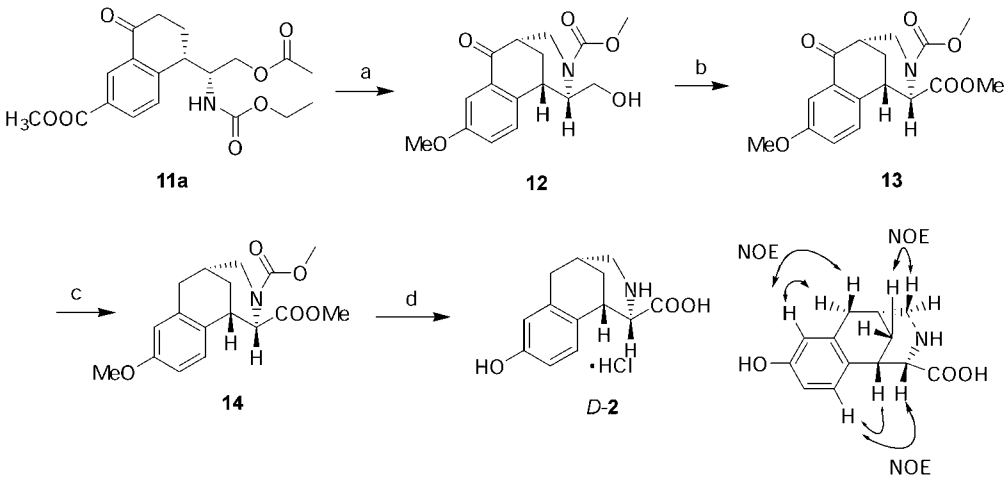
Figure 2 Retro-synthetic analysis for tyrosine analogue *D*-**2**.

Scheme 1



Reagents and conditions: a) 1. $(COCl)_2$, DMSO, Et_3N; 2. *p*-methoxyphenylmagnesium bromide. 81% over two steps. b) PDC, CH_2Cl_2, 80%. c) 1. 3 mol/L HCl in EtOAc; 2. ClCOOEt, $KHCO_3$, dioxane and H_2O, 100% over two steps. d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 80%. e) methyl acrylate, ^{t}BuOH, SmI_2, HMPA/THF, 56%. f) 10% Pd/C, $HClO_4$ (70%), CH_3COOH, 91%. g) 1. $(COCl)_2$, DMF (cat.), CS_2-CH_2Cl_2; 2. $AlCl_3$, CH_2Cl_2, 83% over two steps (**11a** : **11b**＝1.8—2.0∶1).

Scheme 2



Reagents and conditions: a) 1. conc. HCl, refluxed for 10 h; 2. HCHO (aq.), EtOH, refluxed for 5 h; 3. 6 mol/L HCl, refluxed for 2 h; 4. ClCOOMe, $KHCO_3$, dioxane-H_2O, 45% over four steps. b) 1. Dess-Martin periodinane, CH_2Cl_2; 2. $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, ^{t}BuOH-H_2O; 3. CH_2N_2, Et_2O, 75% over three steps. c) 1. 1,3-propanedithiol, BF_3•OEt_2; 2. Raney nickel, EtOH, 53% over two steps. d) 6 mol/L HCl, refluxed for 4 d, 100%.

generated by SmI_2. Removal of the carbonyl in **13** was achieved by a two-step protocol including sulfur ketal formation and reduction with Raney nickel in EtOH to give ester **14**. *D*-Tyrosine analogue *D*-**2** was finally obtained by refluxing **14** in 6 mol/L HCl for 4 d. Stereochemistries of compound *D*-**2** were finally confirmed again by NOE studies (see Scheme 2).

Summary

In conclusion, a chiron approach-based enantioselective synthesis of designed tricyclic tyrosine analogue *D*-**2** was developed. Free radical cyclization mediated by SmI_2, intramolecular Friedel-Crafts reaction and intramolecular Mannich reaction served as key steps. All the stereochemistries in the synthesis were established and confirmed. The key reactions were optimized and

repeated in good yields. The present synthesis and methodology would be a good starting point to obtain these conformation-constrained tyrosine analogues, which are potentially allowed to develop new SH2 domain inhibitors. The chemical diversity studies upon **2** and **3** and further development of new SH2 domain inhibitors on basis of this scaffold are in progress.

Experimental

General methods

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded at 300 MHz and are reported in parts per million (δ) downfield relative to TMS as internal standard, and ^{13}C NMR spectra were recorded at 75 MHz and assigned in parts per million (δ). Flash column chromatography was performed on silica gel (10—40 μm) using a mixture of petroleum ether and ethyl acetate as the eluent.

(*S*)-4-(4-Methoxybenzoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (6)

To a solution of oxalyl chloride (13.4 mL, 0.157 mmol) in dry CH_2Cl_2 (250 mL) was added slowly DMSO (22.4 mL, 0.315 mmol) in dry CH_2Cl_2 at −78 ℃ under N_2. After 20 min, alchohol **4** (21.2 g, 91.7 mmol) in dry CH_2Cl_2 (100 mL) was added. After the reaction was stirred for additional 2 h, Et_3N (100 mL) was added at −78 ℃ and the mixture was warmed to room temperature. H_2O (400 mL) was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was used directly without further purification.

To a solution of the above freshly prepared aldehyde in dry THF (400 mL) at −78 ℃, was added *p*-methoxyphenylmagnesium bromide (300 mL, 1 mol/L, 0.30 mmol) over 30 min. After 2 h at −78 ℃, the mixture was warmed to r.t., and sat. NH_4Cl was added to quench the reaction. The mixture was extracted with Et_2O. The combined Et_2O layers were washed with H_2O and brine, and dried over Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by flash column chromatography to give **5** as a yellow oil (25.0 g, 81%, the ratio of isomers is 8∶1).

To a sloution of **5** in dry CH_2Cl_2 (225 mL) were added crashed molecular sieves (10 g) and PDC (42.3 g, 0.112 mmol). After being stirred at r.t. overnight, the mixture was filtered through a celite. The solid was washed with CH_2Cl_2 for several times. The combined CH_2Cl_2 layers were concentrated and the residue was purified by flash column chromatography to give **6** as a white solid (20.0 g, 80%). m.p. 130—132 ℃ (recrystallized from petroleum ether & ethyl acetate) $[\alpha]_D^{20}$ −43.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.96—7.87 (m, 2H), 7.00—6.90 (m, 2H), 5.45 (dd, *J*= 7.4, 3.0 Hz, 0.4H), 5.34 (dd, *J*=7.6, 3.8 Hz, 0.6H), 4.35—4.26 (m, 1H), 3.97—3.87 (m, 4H), 1.80—1.20 (m, 15H); IR (KBr) *v*: 1702, 1687, 1599, 1170, 1097, 848 cm^{-1}; EIMS *m/z*: 320 $(M-CH_3)^+$. Anal. calcd for $C_{18}H_{25}NO_5$: C 64.46, H 7.51, N 4.18; found C 64.42, H 7.51, N 3.98. 99.6% *ee* by HPLC (a chiracel OD column, UV detector 254 nm, eluent *i*-PrOH/hexane (8∶2, *V/V*), flow rate 0.7 mL/min.).

(*S*)-[1-Hydroxymethyl-2-(4-methoxyphenyl)-2-oxo-ethyl]-carbamic acid ethyl ester (7)

To a mixture of MeOH (2.0 mL, 49.3 mmol) and EtOAc (10 mL) at 0 ℃ was added CH_3COCl (3.4 mL, 47.6 mmol). After being stirred for 15 min at 0 ℃, **6** (1.0 g, 3.0 mmol) was added in one port. After stirring for 45 min at r.t., the solvent was removed *in vacuo*. The white solid was re-dissolved in H_2O (15 mL) and dioxane (15 mL), $KHCO_3$ (750 mg, 7.5 mmol) was added. The mixture was cooled to 0 ℃ and ClCOOEt (0.45 mL, 4.7 mmol) was added. The reaction was then warmed to rt and stirred for additional 20 min. Dioxane was removed *in vacuo* and the resultant aqueous phase was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **7** as a white solid (800 mg, 100%). m.p. 58.5—59.5 ℃ (recrystallized from petroleum ether & ethyl acetate). $[\alpha]_D^{20}$ +1.5 (*c* 1.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.00—7.90 (m, 2H), 6.98—6.88 (m, 2H), 6.12—6.02 (m, 1H), 5.35—5.25 (m, 1H), 4.10 (q, *J*=7.1 Hz, 2H), 3.95 (m, 1H), 3.85 (s, 3H), 3.77 (m, 1H), 3.40 (m, 1H), 1.20 (t, *J* =7.1 Hz, 3H); IR (KBr) *v*: 3402, 1666, 1181, 1077, 854 cm^{-1}; EIMS *m/z*: 250 $(M-OH)^+$. Anal. calcd for $C_{13}H_{17}NO_5$: C 58.42, H 6.41, N 5.24; found C 58.32, H 6.62, N 5.19.

Acetic acid (2*S*)-ethoxycarbonylamino-3-(4-methoxyphenyl)-3-oxo-propyl ester (8)

To a solution of **7** (3.50 g, 13.1 mmol) in dry CH_2Cl_2 (40 mL) at 0 ℃ was added DMAP (0.25 g, 2.0 mmol), Et_3N (3.8 mL, 27.0 mmol), and Ac_2O (1.4 mL, 14.8 mmol) in dry CH_2Cl_2 (15 mL). After stirring for 2 h at r.t., water was added to the mixture. The mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **8** as a white solid (3.23 g, 80%). m.p. 77.9—78.9 ℃ (recrystallized from petroleum ether & ethyl acetate). $[\alpha]_D^{20}$ +45.1 (*c* 1.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.06—7.96 (m, 2H), 7.00—6.92 (m, 2H), 5.85—5.80 (m, 1H), 5.59—5.52 (m, 1H), 4.50 (dd, *J*=11.1, 4.2 Hz, 1H), 4.20—4.10 (m, 3H), 3.90 (s, 3H), 2.00 (s, 3H), 1.22 (t, *J* =6.9 Hz, 3H); EIMS *m/z*: 292 $(M-OH)^+$; IR (KBr) *v*: 3319, 1736, 1252, 1071, 854 cm^{-1}. Anal. calcd for $C_{15}H_{19}NO_6$: C 58.25, H 6.19, N 4.53; found C 58.27, H

6.26, N 4.37. 96.0% *ee* by HPLC (a chiracel AD column, UV detector 254 nm, eluent *i*-PrOH/hexane (8∶2, *V/V*), flow rate 0.7 mL/min.).

Acetic acid (2*S*)-ethoxycarbonylamino-2-[2-(4-methoxyphenyl)-5-oxo-tetrahydrofuran-2-yl]ethyl ester (9)

To a solution of SmI_2 in THF (200 mL, 0.1 mol/L, 20.0 mmol) at 0 ℃ was added HMPA (10 mL). After stirring for 15 min, *t*-BuOH (0.46 mL, 4.84 mmol), methylacrylate (0.60 mL, 6.69 mmol) and **8** (2.0 g, 6.28 mmol) in dry THF (10 mL) was added successively to the mixture. The mixture was turned to brown yellow and then diluted HCl (aq., 0.5 mol/L, 30 mL) was added. The mixture was extracted with Et_2O and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **9** as a yellow oil (1.29 g, 56%). $[\alpha]_D^{20}$ +32.1 (*c* 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.20 (m, 2H), 6.96—6.90 (m, 2H), 5.20 (d, *J*=9.9 Hz, 1H), 4.40—4.30 (m, 1H), 4.20—4.00 (m, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 3.70 (m, 1H), 2.80 (m, 1H), 2.60—2.20 (m, 3H), 2.00 (s, 3H), 1.20 (t, *J*=7.1 Hz, 3H); IR (film) *v*: 3323, 1782, 1743, 1180, 1074, 836 cm^{-1}; EIMS *m/z*: 365 (M^+); ESIMS *m/z* (%): 366 (MH^+, 15), 388 [$(M+Na)^+$, 82]; HR-ESIMS calcd for ($C_{18}H_{23}NO_7$ + Na) 388.1372; found 388.1367.

(5*S*,6*RS*)-6-Acetoxy-5-ethoxycarbonylamino-4-(4-methoxyphenyl)-hexanoic acid (10)

To a solution of **9** (830 mg, 2.27 mmol) in acetic acid (25 mL) were added Pd/C (10%, 400 mg) and $HClO_4$ (70%, 0.5 mL). The mixture was stirred for 24 h at r.t. under H_2 (1.0×10^5 Pa). The solid was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography to give **10** as a colorless oil (760 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.10—7.00 (m, 2H), 6.89—6.78 (m, 2H), 4.90 (m, 1H), 4.50 (m, 1H), 4.20—3.85 (m, 4H), 3.80 (s, 3H), 2.90 (m, 1H), 2.70 (m, 1H), 2.30—2.00 (m, 6H), 1.30—1.10 (m, 3H); IR (film) *v*: 3333, 2929, 1716, 1248, 1070, 834 cm^{-1}; EIMS *m/z*: 350 $(M—OH)^+$. Anal. calcd for $C_{18}H_{25}NO_7$: C 58.85, H 6.86, N 3.81; found C 58.40, H 7.19, N 3.37.

Acetic acid (2*S*)-ethoxycarbonylamino-2-(6-methoxy-4-oxo-1,2,3,4-tetrahydronaphth-1-yl)ethyl ester (11)

To a solution of **10** (362 mg, 0.99 mmol) in CS_2 (10 mL) and CH_2Cl_2 (2.0 mL) at r.t. was added slowly $(COCl)_2$ (175 μL, 2.1 mmol) and DMF (10 μL, 0.13 mmol). After being stirred at rt for 45 min, the mixture was concentrated *in vacuo*. To the solution of above residue in dry CH_2Cl_2 (10 mL), was added $AlCl_3$ (450 mg, 3.38 mmol). After the mixture was stirred overnight, HCl (aq., 0.5 mol/L) was added. The mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give **11a** and **11b** (288 mg in total, 83%, **11a**∶**11b**=1.8∶1). Data for **11a**: m.p. 86.0—87.0 ℃ (recrystallized from petroleum ether & ethyl acetate). $[\alpha]_D^{20}$ −61.2 (*c* 1.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.52 (d, *J*=2.8 Hz, 1H), 7.14 (d, *J*=8.5 Hz, 1H), 7.05 (dd, *J*=8.5, 2.8 Hz, 1H), 4.93 (m, 1H), 4.30—4.00 (m, 5H), 3.80 (s, 3H), 3.09—2.99 (m, 2H), 2.60 (m, 1H), 2.25—2.15 (m, 2H), 2.10 (s, 3H), 1.30—1.20 (m, 3H); IR (film) *v*: 3343, 1741, 1683, 1241, 1060, 836 cm^{-1}; EIMS *m/z*: 304 $(M-OEt)^+$; ESIMS *m/z* (%): [372.1, $(M+Na)^+$], [367.2, $(M+NH_4)^+$], [350.2, $(M+H)^+$]; HR-ESIMS cacld for ($C_{18}H_{23}NO_6$+Na) 372.1423, found 372.1417. Data for **11b**: m.p. 107—108 ℃ (recrystallized from petroleum ether & ethyl acetate). $[\alpha]_D^{20}$ +88.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.53 (d, *J*=2.8 Hz, 1H), 7.17 (d, *J*=8.5 Hz, 1H), 7.02 (dd, *J*=8.5, 2.8 Hz, 1H), 4.62 (m, 1H), 4.32 (m, 1H), 4.20—3.90 (m, 4H), 3.80 (s, 3H), 3.10 (m, 1H), 2.75 (m, 1H), 2.53 (m, 1H), 2.30 (m, 1H), 2.20—2.00 (m, 4H), 1.30—1.20 (m, 3H); IR (film) *v*: 3350, 2926, 1735, 1688, 1237, 1092, 870 cm^{-1}; EIMS *m/z*: 304 $(M-OEt)^+$. Anal. calcd for $C_{18}H_{23}NO_6$: C 61.88, H 6.64, N 4.00; found C 61.84, H 6.50, N 3.62.

(1*S*,9*S*,12*R*)-12-Hydroxymethyl-5-methoxy-8-oxo-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-11-carboxylic acid methyl ester (12)

A mixture of **11a** (180 mg, 0.52 mmol) in conc. HCl (10 mL) was refluxed for 10 h until it was concentrated *in vacuo*. To a solution of the above residue (white solid) in EtOH (5.0 mL) was added HCHO (36% aq., 0.20 mL). The mixture was heated to reflux for 5 h until concentrated *in vacuo*. The residue was then dissolved in HCl (aq., 6 mol/L, 10 mL) and heated to reflux for 2 h. The mixture was concentrated again and the residue was dissolved in dioxane (5.0 mL) and H_2O (5.0 mL). To this solution was added $KHCO_3$ (78 mg, 0.78 mmol) and ClCOOMe (48 μL, 0.62 mmol). After being stirred for 2 h, the mixture was diluted with water and extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **12** as a colorless oil (72 mg, 45% from **11a**). $[\alpha]_D^{20}$ −46.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.45 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 4.45—4.05 (m, 2H), 4.00—3.80 (m, 5H), 3.50—3.20 (m, 5H), 2.75—2.65 (m, 2H), 2.35—2.24 (m, 2H); IR (film) *v*: 3448, 2955, 1685, 1448, 1284, 1024, 757, 526 cm^{-1}; EIMS *m/z* (%): 305 (M^+, 3.89); ESIMS *m/z* (%): 306.1 (MH^+, 42), 328.1 [$(M+Na)^+$, 100]; HR-EIMS calcd for ($C_{16}H_{19}NO_5$ − OCH_3) 274.1079; found 274.1086.

(1*S*,9*S*,12*R*)-12-Methoxycarbonyl-5-methoxy-8-oxo-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-11-carboxylic acid methyl ester (13)

To a solution of **12** (72 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) at r.t. was added Dess-Martine periodinane (200 mg, 0.47 mmol). After stirring for 2 h, sat.

$Na_2S_2O_3$ and sat. $NaHCO_3$ were added. After additional 10 min, the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. To a solution of the residue in ^tBuOH (5.0 mL) and H_2O (1.0 mL), was added KH_2PO_4 (96 mg, 0.71 mmol), 2-methyl-2-butene (0.30 mL, 2.82 mmol) and $NaClO_2$ (128 mg, 1.41 mmol). After stirring for 30 min, sat. Na_2SO_3 was added to quench the reaction. The mixture was acidified with HCl (aq., 1 mol/L) to pH=5 and then extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in Et_2O again, and CH_2N_2 was added slowly. After stirring for 10 min, acetic acid was added to remove the excess CH_2N_2. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography to give **13** as a colorless oil (60 mg, 75% from **12**). $[\alpha]_D^{20}$ −75.2 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.50 (m, 1H), 7.30 (m, 1H), 7.10 (m, 1H), 4.80 (s, 0.6H), 4.65 (s, 0.40H), 4.40—4.20 (m, 1H), 3.86—3.75 (m, 6H), 3.70—3.40 (m, 5H), 2.70 (m, 1H), 2.40 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.1/198.5 (conformer), 170.7, 159.1, 157.0/156.4, 137.0, 133.8/133.5, 129.3/ 128.9, 122.3, 109.0, 60.2/59.9, 59.2, 55.4, 52.9/52.5, 45.2/44.7, 41.3, 35.3, 28.1; IR (film) *v*: 2955, 1743, 1709, 1686, 1447, 1229, 1022, 792, 525 cm^{-1}; EIMS *m/z* (%): 334 (MH^+, 0.58), 333 (M^+, 3.38), 275 (18.11), 274 (100), 43 (43.76); HR-EIMS calcd for $C_{17}H_{19}NO_6$ 333.1212, found 333.1241. 89.4% *ee* by HPLC (a chiracel AS column, UV detector 254 nm, eluent *i*-PrOH/hexane (3∶7), flow rate 0.7 mL/min.).

(1*S*,9*R*,12*R*)-5-Methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-11,12-dicarboxylic acid dimethyl ester (14)

To a solution of **13** (52 mg, 0.16 mmol) in dry CH_2Cl_2 (10 mL), were added propane-1,3-dithiol (52 μL, 0.52 mmol) and BF_3•Et_2O (30 μL, 0.24 mmol). After stirring for 48 h at r.t., sat. $NaHCO_3$ was added and the reaction mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give a colorless oil (67 mg). To a solution of the above oil in EtOH (10 mL) was added Raney nickel (*ca.* 0.5 g). After stirring for 20 min at rt, Raney nickel was filtered off through a pad of celite, the filtrate was conentrated *in vacuo* and the residue was re-dissolved in EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **14** as a colorless solid (27 mg, 53% from **13**). m.p. 140.0—141.0 ℃ (recrystallized from petroleum ether & ethyl acetate). $[\alpha]_D^{20}$ −5.2 (*c* 1.40, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.10 (m, 1H), 6.70 (m, 1H), 6.60 (m, 1H), 4.70 (d, *J*=2.4 Hz, 0.5H), 4.50 (d, *J*=2.4 Hz, 0.5H), 4.10 (d, *J*=13.2 Hz, 0.5H), 3.90 (d, *J* = 13.2 Hz, 0.5H), 3.80—3.70 (m, 6H), 3.60—3.30 (m, 5H), 3.10 (m, 1H), 2.80 (m, 1H), 2.20 (m, 1H), 1.85—1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3, 158.3, 157.3/156.9 (conformer), 137.9/137.5, 130.0, 129.1/128.9, 113.0/112.7, 112.2/111.7, 61.5/61.1, 55.0, 52.7/52.3, 48.7/48.5, 35.0, 34.8, 34.2, 26.3, 25.9; IR (KBr) *v*: 2997, 1738, 1207, 854, 618 cm^{-1}; EIMS *m/z* (%): 320 (MH^+, 3), 319 (M^+, 15), 261 (20), 260 (100); HR-EIMS calcd for ($C_{17}H_{21}NO_5$ − COOMe) 260.1287, found 260.1286.

(1*S*,9*R*,12*R*)-5-Hydroxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-12-carboxylic acid hydrochloride (*D*-2)

A mixture of compound **14** (44 mg, 0.14 mmol) in HCl (6 mol/L, 10 mL) was refluxed for 4 d. The mixture was concentrated *in vacuo* to give *D*-**2** as a white solid (38 mg, 100%). m.p. 280—283 ℃ $[\alpha]_D^{20}$ −28.7 (*c* 0.35, H_2O). ^1H NMR (300 MHz, D_2O) δ: 7.20 (d, *J*= 8.3 Hz, 1H), 6.80 (d, *J*=8.3 Hz, 1H), 6.75 (s, 1H), 4.15 (s, 1H), 3.70 (dd, *J*=13.0, 3.0 Hz, 1H), 3.60 (s, 1H), 3.30 (d, *J*=13.0 Hz, 1H), 3.20 (dd, *J*=18.4, 6.8 Hz, 1H), 2.90 (d, *J*=18.4 Hz, 1H), 2.50 (s, 1H), 2.00 (d, *J*= 13.6 Hz, 1H), 1.85 (d, *J*=13.6 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 173, 157, 140, 132, 129, 118, 117, 63, 50, 35, 35, 27, 26; IR (KBr) *v*: 3220, 2413, 1704, 1449, 1230, 1167, 807, 657, 545 cm^{-1}; EIMS *m/z* (%): 234 (MH^+, 1.91), 233 (M^+, 16.03), 189 (16.03), 188 (100), 145 (45.69), 88 (85.05); ESIMS *m/z* (%): 235 [(M+ 2H)$^+$, 15], 234 (MH^+, 100); HR-ESI calcd for ($C_{13}H_{15}NO_3$+H) 234.1130, found 234.1125.

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