First Total Synthesis of (–)-Auranomide C and Its Derivatives

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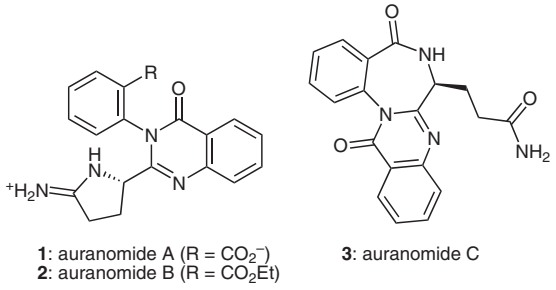
Received: 15.08.2013; Accepted after revision: 24.10.2013

Abstract: The first total synthesis of (–)-auranomide C has been achieved. The short synthetic strategy involves a reductive dehydrocyclization and the nucleophilic ring opening of a fused γ-lactam. The route allows for ease in synthesizing diverse derivatives in the side chain of the natural product.

Key words: auranomide, quinazolinobenzodiazepine, intramolecular cyclization, reductive dehydrocyclization, nucleophilic ring opening

Auranomide A (**1**), B (**2**), and C (**3**) are a new quinazolin-4-one derivatives (Figure 1) isolated recently from the marine-derived fungus *Penicillium aurantiogriseum* by Lixin Zhang et al. and their chemical structures were established by extensive NMR and MS studies.[1] Auranomides A–C exhibit moderate cytotoxic activity against human tumor cells. The structural similarities of auranomide C with several bioactive quinazolinobenzodiazepine alkaloids,[2–4] such as circumdatins, benzomalvins, asperlicins, and sclerotigenin, prompted us to undertake the total synthesis of auranomide C.

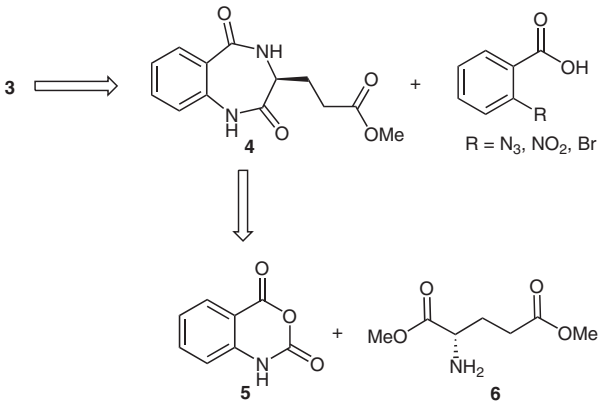


1: auranomide A (R = CO_2^-)
2: auranomide B (R = CO_2Et)
3: auranomide C

Figure 1 Structures of auranomide A, B, and C

Several methods have been reported for the synthesis of the quinazolinobenzodiazepine skeleton. The Snider, Thomas, and Eguchi groups separately reported the use of the intramolecular aza-Wittig tandem reaction for the total synthesis of sclerotigenin, circumdatin F, asperlicin C, and benzomalvin A.[5] Witt and Bergman reported the total synthesis of circumdatin F via formation of an iminobenzoxazine intermediate.[6] The synthesis of asperlicins C and E was reported by Bock et al following a regioselective annulation approach.[7] Liu and co-workers developed a one-pot domino procedure under microwave heating for the synthesis of racemic quinazolinobenzodiazepine.[8] Recently, acid-catalyzed dehydrocyclization[9] and copper-mediated N-arylation methodologies have been reported for the synthesis of the quinazolinobenzodiazepine skeleton.[10] Most recently, we reported the synthesis of enantiopure pyrroloquinazolino[1,4]benzodiazepine-2,5-diones employing a palladium-catalyzed amination–cyclization domino reaction and intended to use this methodology for the synthesis of auranomide C.[11]

Retrosynthetically, auranomide C (**3**) could be derived: (1) from compound **4** and 2-azidobenzoic acid under aza-Witting conditions, (2) by reductive dehydrocyclization of compound **4** with 2-nitrobenzoic acid, or (3) from palladium-catalyzed cyclization of **4** and 2-bromobenzoate (Scheme 1).



Scheme 1 Retrosynthetic analysis of (–)-auranomide C

Our synthesis began with the reductive amination of dimethyl glutamate **6** with benzaldehyde using sodium borohydride to afford the *N*-benzyl glutamate **7** (Scheme 2). To avoid spontaneous cyclization of *N*-benzyl glutamate **7** into pyroglutamate, the benzyl derivative was instantaneously coupled with 2-nitrobenzoyl chloride to afford **8** in 61% yield over two steps.[12]

It was gratifying to observe that the reduction followed by concomitant cyclization of **8** furnished 1,4-benzodiazepine-2,5-dione **9** in 82% yield with >99% ee. We intended to complete the synthesis of **11** via reductive dehydrocyclization;[9a] compound **9** was reacted with 2-nitrobenzoyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine in dichloromethane at 0 °C for 30 minutes. As the amide **10** was found to be unstable during

SYNTHESIS 2014, 46, 0189–0194
Advanced online publication: 14.11.2013
DOI: 10.1055/s-0033-1338558; Art ID: SS-2013-N0398-OP

work up, we reduced it with zinc in acetic acid at –20 °C without isolating the amide to obtain quinazolinobenzodiazepine **11** in 75% yield with complete racemization. Further efforts to preserve the enantiopurity of **11** proved to be difficult.

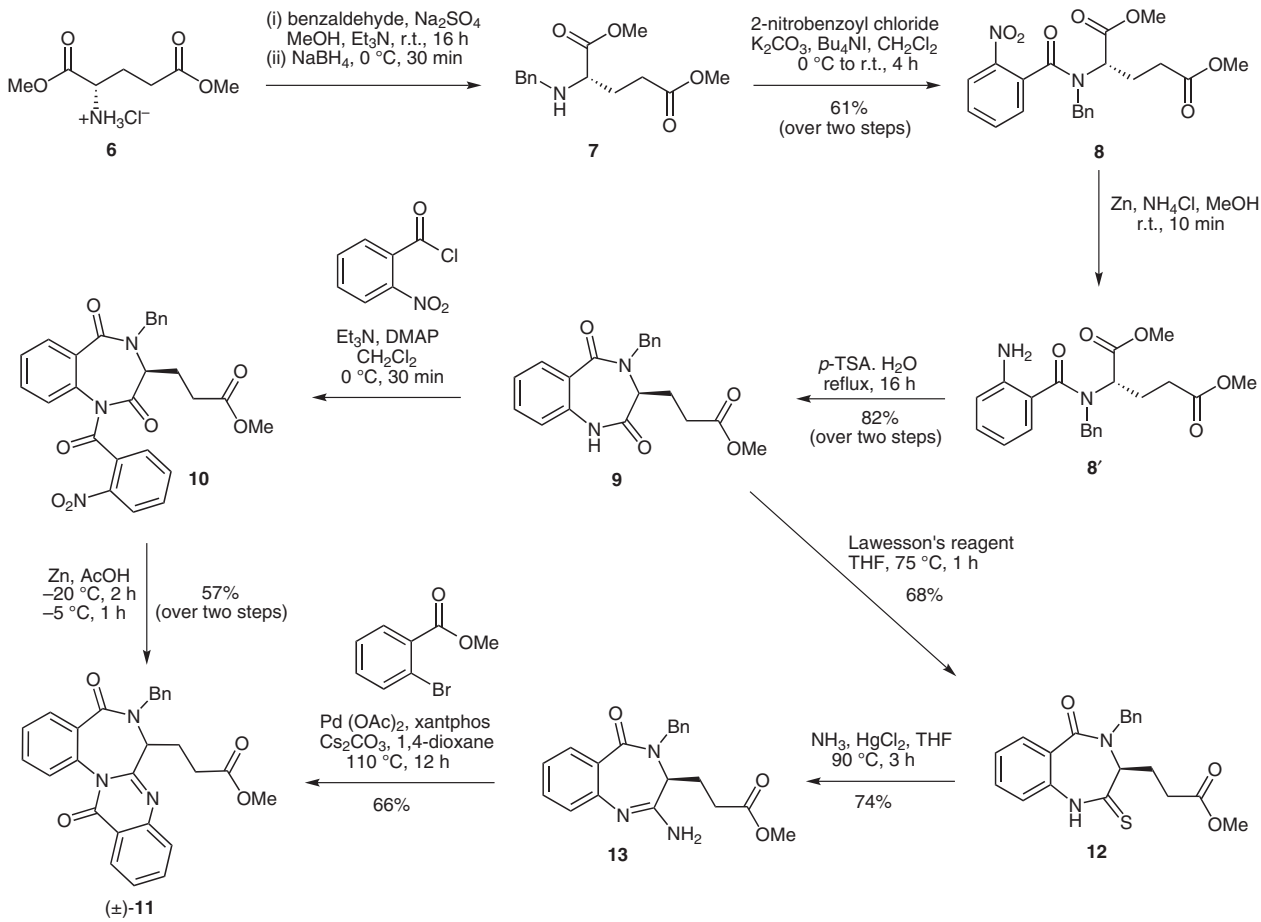
At this point, we turned to our earlier reported palladium-catalyzed approach[11] and converted the dilactam compound **9** into the mono thiolactam **12** by reacting with 0.6 equivalents of Lawesson's reagent in 68% yield. The thiolactam **12** was treated with ammonia gas in the presence of mercury(II) chloride to give the cyclic amidine **13** in good yields. Further, N-arylation and subsequent intramolecular cyclization of **13** with methyl 2-bromobenzoate under palladium-catalyzed conditions resulted again in the formation of racemic compound **11** in 66% yield.

At this moment, we planned for an alternate approach to circumvent the associated problem of racemization and also to accomplish the synthesis of enantiomerically pure auranomide C. Hence, we planned to rigidify the key intermediate compound by synthesizing the tricyclic compound **14** as tricyclic benzodiazepines are well documented to retain their chiral integrity during the annulation of benzodiazepinedione (Scheme 3).[5,9a,11]

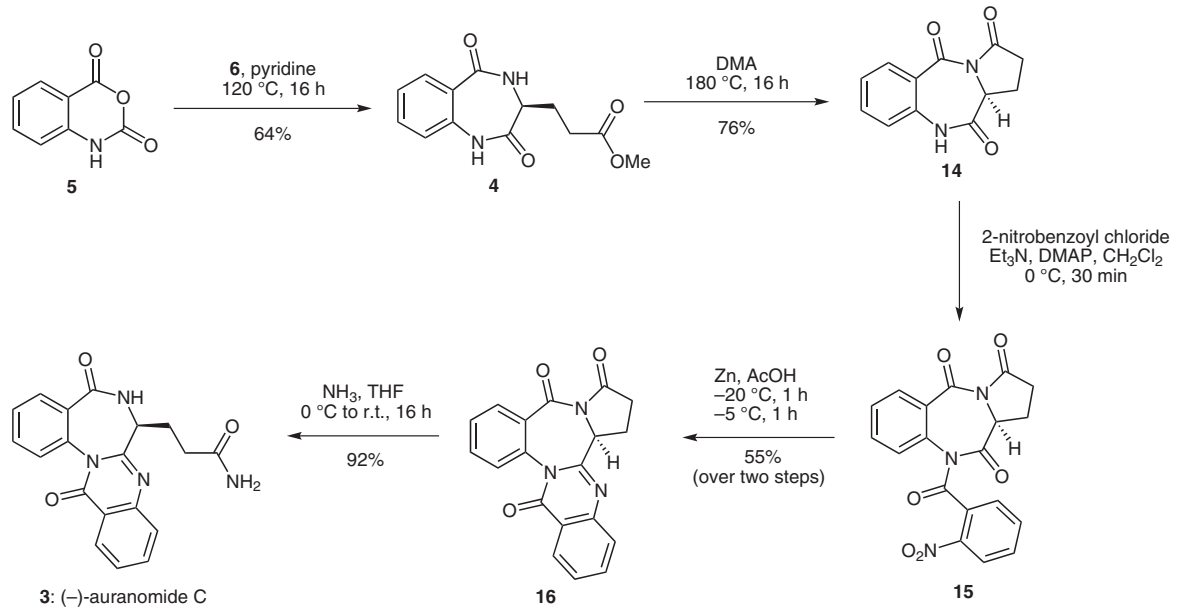
The dilactam compound **4** was synthesized by the dehydrocyclocondensation of isatoic anhydride **5** with glutamate **6** in good yield. The intramolecular cyclization of **4** to the tricyclic intermediate **14** was accomplished by heating in dimethylacetamide (DMA) at 180 °C.[13] It was gratifying to note that the amidation of compound **14** with 2-nitrobenzoyl chloride followed by reductive dehydrocyclization proceeded smoothly to furnish compound **16** in good yields and high enantiomeric excess (>98%). The final stage, nucleophilic ring opening of fused γ-lactam **16** with ammonia, afforded auranomide C (**3**) in high yield with 97.7% ee.[14] The spectral and analytical data for synthetic compound **3** were in complete agreement with the reported data for naturally occurring (–)-auranomide C.[4]

We conceived that the ring opening of compound **16** with various amines could give rise to diverse amide analogues of the natural product. Hence, we reacted compound **16** with primary amines **17a**,**b**, secondary amines **17c**–**e**, and an aromatic amine **17f** to obtain the corresponding amides **18**–**23**, respectively, in high yields (Table 1).

In conclusion, we have accomplished the first and efficient total synthesis of enantioenriched auranomide C and its amido derivatives via reductive dehydrocyclization and nucleophilic ring opening. The described short synthetic strategy is efficient and permits the synthesis of analogues of the natural product.

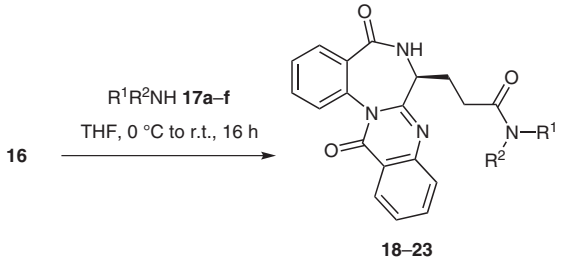


Scheme 2 Synthesis of the key intermediate of auranomide C



Scheme 3 Synthesis of (–)-auranomide C

Table 1 Synthesis of (–)-Auranomide C Derivatives



Entry	Amine	R^1	R^2	Product	Yield (%)
1	**17a**	H	Me	**18**	95
2	**17b**	H	Bn	**19**	90
3	**17c**	Me	Me	**20**	90
4	**17d**	$(CH_2)_4$		**21**	93
5	**17e**	$(CH_2)_5$		**22**	90
6	**17f**	H	Ph	**23**	95

All solvents were purified by standard procedures prior to use and all commercial chemicals were used as received. TLC analysis: Merck precoated plates (silica gel 60 F254); melting point: Meltemp apparatus (uncorrected); ^{1}H and ^{13}C NMR: Varian Unity instrument at r.t. at 300 and 400 MHz with reference to internal solvent; mass spectra: Micro mass QuattroMicro™ API-autospectrometer using APCI technique; HRMS TOF-ES: Waters-Alliance 2695 Separation Module/Q-TOF Micromass; IR: Perkin Elmer FT-IR spectrophotometer; Optical rotations: Jasco P-1030 polarimeter. Enantiomeric excess was determined by HPLC analysis using Chiralpak IC column (250 × 4.6 mm, 5 micron), mobile phase: hexane–EtOH (1:1) with 0.1% Et_2NH at 1.0mL/min. Petroleum ether (PE) used refers to the fraction boiling in the 60–80 °C range. All isolated compounds had purity greater than 98% (area percent) as judged by HPLC analysis area method.

Dimethyl (*S*)-2-(*N*-Benzyl-2-nitrobenzamido)pentanedioate (8)
To a mixture of L-glutamic acid dimethyl ester hydrochloride (**6**, 5 g, 23.69 mmol) and benzaldehyde (2.76 g, 26.06 mmol) in MeOH (50 mL) was added Et_3N (4.0 mL, 28.43 mmol) and anhydrous Na_2SO_4 (2 g) at 0 °C; the mixture was stirred at r.t. for 16 h. The mixture was filtered and the filtrate was concentrated to half its volume, treated with $NaBH_4$ (1.08 g, 28.43 mmol) at 0 °C and then stirred at this temperature for 30 min. The mixture was concentrated; the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated to obtain crude **7** (3.5 g). The crude **7** was dissolved in CH_2Cl_2 (50 mL), K_2CO_3 (5.2 g, 37.73 mmol) and Bu_4NI (2.78 g, 7.54 mmol) were added, the mixture was cooled to 0 °C and treated with 2-nitrobenzoyl chloride (2.4 mL, 18.11 mmol), and it was stirred at r.t. for 4 h. The mixture was quenched with H_2O (70 mL) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel, 100–200 mesh, PE–EtOAc, 7:3) to afford **8** (6.0 g, 61%) as a white solid; mp 88–89 °C; $[\alpha]_D^{25}$ –74.0 (*c* 0.1, DMSO); R_f = 0.50 (PE–EtOAc, 1:1).

IR (KBr): 3441, 2951, 1747, 1648, 1524 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 7.5 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 7.89–7.67 (m, 2 H), 7.52–7.45 (m, 2 H), 7.37–7.24 (m, 3 H), 4.42 (s, 2 H), 4.15 (m, 1 H), 3.65 (s, 3 H), 3.57 (s, 3 H), 2.50–2.32 (m, 2 H), 2.20–1.98 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.9, 170.1, 167.6, 144.6, 138.0, 135.5, 135.0, 131.8, 130.6, 130.5, 128.3, 128.1, 127.6, 125.1, 124.8, 57.5, 53.0, 51.9, 51.3, 30.0, 23.6.

MS (APCI): *m*/*z* = 415 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_7$: 415.1505; found: 415.1507.

Methyl (*S*)-3-(4-Benzyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-3-yl)propanoate (9)
A solution of **8** (5 g, 12.07 mmol) and NH_4Cl (3.23 g, 60.38 mmol) in MeOH (50 mL) was treated with zinc powder (7.85 g, 120.77 mmol) at r.t. After 10 min, the mixture was filtered through a Celite pad and washed with MeOH. The combined filtrates were concentrated to ca. 25 mL; *p*-TSA·H_2O (1.14 g, 6.03 mmol) was added and

the mixture refluxed for 16 h, cooled to r.t., and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100–200 mesh, $CHCl_3$–MeOH, 9.8:0.2) to give **9** (3.5 g, 82%) as a white solid; mp 102–103 °C; $[\alpha]_D^{25}$ –20.0 (*c* 0.1, DMSO); R_f = 0.5 ($CHCl_3$–MeOH, 9.5:0.5).

IR (KBr): 3436, 1747, 1646 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.54 (d, *J* = 18.4 Hz, 1 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.55–7.49 (m, 1 H), 7.35–7.22 (m, 6 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 5.09 (d, *J* = 14.8 Hz, 0.5 H), 4.82 (d, *J* = 15.6 Hz, 0.5 H), 4.59 (d, *J* = 15.6 Hz, 0.5 H), 4.48 (d, *J* = 14.8 Hz, 0.5 H), 4.20–4.12 (m, 1 H), 3.50 (s, 3 H), 2.27–2.19 (m, 2.5 H), 2.0–1.90 (m, 0.5 H), 1.65–1.57 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (major rotamer) = 171.1, 168.1, 165.3, 138.0, 137.1, 136.6, 135.5, 132.4, 130.8, 128.4, 127.7, 126.6, 125.8, 124.0, 120.6, 63.6, 54.4, 51.4, 29.9, 23.9.

MS (APCI): *m*/*z* = 353 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_4$: 353.1501; found: 353.1503.

Methyl (*S*)-3-(4-Benzyl-5-oxo-2-thioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-3-yl)propanoate (12)

To a suspension of **9** (3.0 g, 8.52 mmol) in THF (30 mL) was added Lawesson's reagent (2.41 g, 5.96 mmol) and the mixture was heated at 75 °C for 1 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100–200 mesh, PE–EtOAc, 7.5:3.5) to give **12** (1.3 g, 68%) as a yellow solid; mp 126–127 °C; $[\alpha]_D^{25}$ –92.0 (*c* 0.1, DMSO); R_f = 0.6 (PE–EtOAc, 1:1).

IR (KBr): 3436, 2946, 1727, 1640 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.50 (br s, 1 H), 7.89–7.85 (m, 1 H), 7.64–7.54 (m, 1 H), 7.42–7.23 (m, 7 H), 4.86–4.64 (m, 2 H), 4.44–4.33 (m, 1 H), 3.48 (s, 3 H), 2.44–1.98 (m, 3 H), 1.72–1.52 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (major rotamer) = 200.2, 171.8, 164.7, 136.9, 136.1, 132.5, 131.2, 128.3 (2 C), 127.4, 127.0 (2 C), 126.7, 125.5, 120.5, 70.5, 53.9, 51.3, 29.9, 23.7.

MS (APCI): *m*/*z* = 369 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3S$: 369.1273; found: 369.1256.

Methyl (*S*)-3-(2-Amino-4-benzyl-5-oxo-4,5-dihydro-3*H*-1,4-benzodiazepin-3-yl)propanoate (13)

A suspension of **12** (2.0 g, 5.43 mmol) and $HgCl_2$ (1.7 g, 6.52 mmol) in dry THF (50 mL) was heated to 90 °C and NH_3 gas was bubbled into the mixture for a period of 2 h at 90 °C. The bubbling of ammonia gas ceased and the mixture was stirred for an additional 1 h at this temperature. The mixture was filtered through Celite which was washed (MeOH–THF, 1:1), and the combined filtrates were concentrated. The residue was washed repetitively with acetone followed by Et_2O to give **13** (1.4 g, 74%) as an off-white solid; mp 166–167 °C; $[\alpha]_D^{25}$ –494.0 (*c* 0.1, DMSO); R_f = 0.3 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3368, 1741, 1593, 1470 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.72 (d, *J* = 8.0 Hz, 1 H), 7.37–7.26 (m, 5 H), 6.99–6.92 (m, 3 H), 4.84 (d, *J* = 15.2 Hz, 1 H), 4.57 (d, *J* = 15.2 Hz, 1 H), 4.14 (t, *J* = 7.6 Hz, 1 H), 3.46 (s, 3 H), 2.05–1.90 (m, 2 H), 1.52–1.36 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.8, 166.6, 159.6, 147.2, 137.5, 131.6, 130.4, 128.3, 128.2, 127.9 (2 C), 127.2, 126.8, 125.2, 121.1, 59.2, 53.6, 51.3, 29.9, 23.9.

MS (APCI): *m*/*z* = 352 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{22}N_3O_3$: 352.1661; found: 352.1677.

Methyl 3-(6-Benzyl-5,13-dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalen-7-yl)propanoate [(±)-11]

Method A: To a solution of **9** (0.5 g, 1.42 mmol), Et_3N (0.4 mL, 2.84 mmol), and DMAP (0.07 g, 0.56 mmol) in CH_2Cl_2 (10 mL) was added 2-nitrobenzoyl chloride (0.22 mL, 1.70 mmol) at 0 °C and the mixture was stirred at this temperature for 30 min. The mixture was cooled to –20 °C, and AcOH (5 mL) and zinc powder (0.92 g, 14.20 mmol) were added. After 2 h, the temperature was slowly warmed to –5 °C and the mixture was stirred for additional 1 h. The mixture was filtered through Celite; the filtrate was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 100–200 mesh, PE–EtOAc, 7:3) to give (±)-**11** (0.37 g, 57%).

Method B: A solution of compound **13** (0.2 g, 0.57 mmol) and methyl 2-bromobenzoate (0.122 g, 0.57 mmol) in 1,4-dioxane (5 mL) was degassed and backfilled with argon, followed by the addition of $Pd(OAc)_2$ (6 mg, 5 mol%), xantphos (22 mg, 10 mol%), and Cs_2CO_3 (371 mg, 1.13 mmol). The mixture was heated at 110 °C for 12 h, cooled to r.t., and concentrated. The residue was dissolved in $CHCl_3$, washed with 10% citric acid solution and then brine, dried (Na_2SO_4), and concentrated. The crude compound was purified by column chromatography to afford (±)-**11** (0.17 g, 66%) as a gummy solid; R_f = 0.4 (PE– EtOAc, 1:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 6.8 Hz, 1 H), 8.01 (d, *J* = 7.2 Hz, 1 H), 7.72 (t, *J* = 6.8 Hz, 1 H), 7.62–7.48 (m, 5 H), 7.23–7.21 (m, 2 H), 7.06 (t, *J* = 7.2 Hz, 2 H), 6.99–6.94 (m, 1 H), 4.94 (d, *J* = 16.0, 1 H), 4.70–4.65 (m, 2 H), 3.55 (s, 3 H), 2.78–2.74 (m, 1 H), 2.44–2.22 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 168.1, 161.2, 152.0, 145.7, 137.5, 134.4, 133.1, 131.3, 131.0, 128.9, 128.3 (2 C), 127.7, 127.6, 127.5, 127.5, 127.3, 127.2 (2 C), 127.0, 121.3, 57.4, 51.6, 45.6, 30.5, 22.8.

MS (APCI): *m*/*z* = 454 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_4$: 454.1767; found: 454.1790.

Methyl (*S*)-3-(2,5-Dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-3-yl)propanoate (4)

A mixture of isatoic anhydride **5** (3.38 g, 20.85 mmol) and L-glutamic acid dimethyl ester hydrochloride (**6**, 5 g, 20.85 mmol) in pyridine (50 mL) was heated at 120 °C for 16 h. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100–200 mesh, $CHCl_3$–MeOH, 9.5:0.5) to afford **4** (3.5 g, 64%) as an off-white solid; mp 182–183 °C; $[\alpha]_D^{25}$ +332 (*c* 0.1, DMSO); R_f = 0.4 ($CHCl_3$–MeOH, 9.5:0.5).

IR (KBr): 3173, 2929, 1728, 1678, 1660 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.41 (br s, 1 H), 8.48 (d, *J* = 5.4 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.22 (1 H, t, *J* = 7.5 Hz, 1 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 3.74–3.67 (m, 1 H), 3.56 (s, 3 H), 2.47–2.40 (m, 2 H), 2.08–2.00 (m, 1 H), 1.88–1.81 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.8, 171.3, 167.7, 136.6, 132.2, 130.4, 126.2, 123.9, 120.9, 51.3, 50.8, 29.6, 23.1.

MS (APCI): *m*/*z* = 263 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_4$: 263.1032; found: 263.1037.

(*S*)-1*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepine-3,5,11(2*H*,10*H*,11a*H*)-trione (14)

A solution of **4** (1 g, 3.82 mmol) in DMA (5 mL) was heated to reflux for 16 h. The solution was cooled to r.t. and concentrated under reduced pressure. The residue was suspended with H_2O (1 mL) and stirred for 15 min. The precipitated solid was collected by filtration,

washed with H_2O and dried to give pure **14** (0.67 g, 76%) as an off-white solid; mp 138–139 °C; $[\alpha]_D^{25}$ +498 (*c* 0.1, DMSO); R_f = 0.50 ($CHCl_3$–MeOH, 9.5:0.5).

IR (KBr): 3510, 2903, 1771, 1681 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.71 (br s, 1 H), 7.85–7.55 (m, 2 H), 7.35–7.20 (m, 2 H), 4.70–4.60 (m, 1 H), 2.95–2.90 (m, 1 H), 2.72–7.80 (m, 1 H), 2.25–2.20 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.3, 169.6, 164.0, 136.6, 133.6, 131.3, 125.8, 124.3, 121.6, 56.0, 30.9, 17.8.

MS (APCI): *m*/*z* = 231 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}N_2O_3$: 231.0770; found: 231.0758.

(2*S*)-6,14,22-Triazapentacyclo[12.8.0.0^{2,6}.0^{8,13}.0^{16,21}]docosa-1(22),8,10,12,16(21),17,19-heptaene-5,7,15-trione (16)

To a solution of **14** (1.5 g, 6.52 mmol), Et_3N (1.83 mL, 13.04 mmol), and DMAP (0.31 g, 2.60 mmol) in CH_2Cl_2 (15 mL) was added 2-nitrobenzoyl chloride (1.03 mL, 7.82 mmol) at 0 °C and the mixture was stirred at this temperature for 30 min. The mixture was cooled to –20 °C, and AcOH (15 mL) and zinc powder (4.24 g, 65.21 mmol) were added. After 1 h, the temperature was slowly warmed to –5 °C and the mixture was stirred for 1 h. The mixture was filtered through Celite; the filtrate was poured into cold sat. aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude compound was washed with Et_2O to give **16** (1.2 g, 55%) as an off-white solid; mp 261–262 °C; $[\alpha]_D^{25}$ –34.0 (*c* 0.1, $CHCl_3$); R_f = 0.70 ($CHCl_3$–MeOH, 9.5:0.5).

IR (KBr): 3432, 2923, 1646, 1615 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.18 (d, *J* = 8.1 Hz, 1 H), 7.93–7.83 (m, 2 H), 7.77–7.71 (m, 2 H), 7.66–7.58 (m, 3 H), 5.08 (d, *J* = 8.1 Hz, 1 H), 2.96–2.73 (m, 2 H), 2.56–2.48 (m, 1 H), 2.34–2.23 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.1, 163.5, 161.1, 152.6, 145.6, 134.9, 132.7, 131.8, 131.2, 130.2, 129.2, 128.8, 127.6, 127.5, 126.7, 121.5, 58.4, 31.6, 18.9.

MS (APCI): *m*/*z* = 332 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{14}N_3O_3$: 332.1035; found: 332.1028.

Nucleophilic Ring Opening; General Procedure

A solution of **16** (0.1 g, 0.30 mmol) in THF (3 mL) was cooled to 0 °C and saturated THF–NH_3 (0.2 mL) was added for the synthesis of **3** or a solution of amine **17a**–**f** (2 equiv) in THF (0.5 mL) for **18**–**23**. The mixture was allowed to stir at r.t. for 16 h and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100–200 mesh, 2–5% MeOH–$CHCl_3$) to obtain the corresponding amide **3**, **18**–**23**.

(*S*)-3-(5,13-Dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalen-7-yl)propanamide (3, Auranomide C)

Off-white solid; yield: 97 mg (92%); mp 263–264 °C; $[\alpha]_D^{25}$ –68.0 (*c* 0.1, MeOH) [Lit.[4] $[\alpha]_D^{20}$ –63.0 (*c* 0.1, MeOH]; R_f = 0.3 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3335, 3198, 2936, 1688, 1646, 1622 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.82 (d, *J* = 5.7 Hz, 1 H), 8.31 (s, 1 H), 8.19 (d, *J* = 7.8 Hz, 1 H), 7.90 (t, *J* = 7.2 Hz, 1 H), 7.77 (t, *J* = 7.2 Hz, 1 H), 7.65–7.58 (m, 4 H), 7.25 (br s, 1 H), 6.74 (br s, 1 H), 4.22–4.10 (m, 1 H), 2.35–2.14 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.1, 167.3, 161.4, 156.2, 146.3, 135.6, 133.4, 131.7, 131.1, 129.3 (2 C), 129.1, 128.0, 127.9, 127.3, 121.4, 53.6, 31.3, 24.6.

MS (APCI): *m*/*z* = 349 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_4O_3$: 349.1301; found: 349.1300.

(*S*)-3-(5,13-Dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalen-7-yl)-*N*-methylpropanamide (18)

Off-white solid; yield: 103 mg (95%); mp 198–199 °C; $[\alpha]_D^{25}$ –36.0 (*c* 0.1, MeOH); R_f = 0.40 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3432, 2923, 1646, 1615 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.81 (d, *J* = 6.0 Hz, 1 H), 8.19 (d, *J* = 8.1 Hz, 1 H), 8.01 (d, *J* = 5.4 Hz, 1 H), 7.90 (t, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 6.6 Hz, 2 H), 7.70–7.54 (m, 3 H), 6.64 (d, *J* = 6.6 Hz, 1 H), 4.10–4.05 (m, 1 H), 2.98 (s, 3 H), 2.20–2.05 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 168.8, 161.5, 154.2, 146.8, 145.8, 134.6, 133.3, 131.4, 130.2, 129.4, 128.9, 127.4, 127.1, 121.1, 106.4, 53.6, 39.2, 32.2, 26.2.

MS (APCI): *m*/*z* = 363 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_3$: 363.1457; found: 363.1470.

(*S*)-*N*-Benzyl-3-(5,13-dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-b]naphthalen-7-yl)propanamide (19)

Off-white solid; yield: 119 mg (90%); mp 153–154 °C; $[\alpha]_D^{25}$ –64.0 (*c* 0.1, MeOH); R_f = 0.6 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3431, 2923, 1658, 1617 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.82 (d, *J* = 6.3 Hz, 1 H), 8.30 (t, *J* = 6.3 Hz, 1 H), 8.19 (d, *J* = 6.9 Hz, 1 H), 7.91 (t, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 6.0 Hz, 2 H), 7.71– 7.58 (m, 3 H), 7.34–7.21 (m, 4 H), 7.16–7.13 (m, 2 H), 4.21–4.16 (m, 3 H), 2.48–2.35 (m, 3 H), 2.27–2.15 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 169.0, 161.4, 154.0, 145.7, 138.2, 134.5, 133.2, 131.3, 130.1, 129.4, 128.9, 128.6, 128.3 (3 C), 127.6, 127.4 (2 C), 127.3, 127.0, 120.9, 53.5, 43.4, 32.4, 25.7.

MS (APCI): *m*/*z* = 439 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{23}N_4O_3$: 439.1770; found: 439.1768.

(*S*)-3-(5,13-Dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalen-7-yl)-*N*,*N*-dimethylpropanamide (20)

Off-white solid; yield: 102 mg (90%); mp 178–179 °C; $[\alpha]_D^{25}$ –110.0 (*c* 0.1, MeOH); R_f = 0.60 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3436, 2923, 1616 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.80 (d, *J* = 6.3 Hz, 1 H), 8.19 (d, *J* = 7.5 Hz, 1 H), 7.90 (t, *J* = 8.1 Hz, 1 H), 7.77 (t, *J* = 8.7 Hz, 2 H), 7.67– 7.57 (m, 4 H), 4.24–4.22 (m, 1 H), 2.93 (s, 3 H), 2.78 (s, 3 H), 2.39–2.32 (m, 3 H), 2.20–2.14 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 167.7, 161.5, 154.5, 146.1, 134.7, 133.3, 131.1, 130.6, 129.9, 128.8, 128.3, 127.7, 127.5, 127.3, 121.5, 53.9, 37.1, 35.6, 29.3, 24.3.

MS (APCI): *m*/*z* = 377 $[M + H]^+$.

HRMS (TOF ES$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}N_4O_3$: 377.1614; found: 377.1634.

(*S*)-7-[3-Oxo-3-(pyrrolidin-1-yl)propyl]-6,7-dihydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalene-5,13-dione (21)

Off-white solid; yield: 113 mg (93%); mp 146–147 °C; $[\alpha]_D^{25}$ –82.0 (*c* 0.1, MeOH); R_f = 0.40 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3436, 2923, 1670, 1616 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.81 (d, *J* = 5.7 Hz, 1 H), 8.19 (d, *J* = 7.8 Hz, 1 H), 7.90 (t, *J* = 7.5 Hz, 1 H), 7.77 (t, *J* = 7.5 Hz, 2 H), 7.67– 7.56 (m, 4 H), 4.24–4.22 (m, 1 H), 3.36 (t, *J* = 6.6 Hz, 2 H), 3.22 (t, *J* = 6.9 Hz, 2 H), 2.51–2.33 (m, 3 H), 2.27–2.16 (m, 1 H), 1.90–1.71 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 167.7, 161.6, 154.5, 146.1, 134.7, 133.3, 131.1, 130.6, 129.9, 128.8, 128.3, 127.6, 127.5, 127.3, 121.5, 53.9, 46.6, 45.8, 30.5, 26.0, 24.4, 24.3.

MS (APCI): m/z = 403 $[M + H]^+$.

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{23}H_{23}N_4O_3$: 403.1770; found: 403.1750.

(*S*)-7-[3-Oxo-3-(piperidin-1-yl)propyl]-6,7-dihydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalene-5,13-dione (22)
Off-white solid; yield: 113 mg (90%); mp 155–156 °C; $[\alpha]_D^{25}$ –38.0 (*c* 0.1, MeOH); R_f = 0.50 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3451, 2926, 1616 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.80 (d, J = 6.0 Hz, 1 H), 8.19 (d, J = 8.1 Hz, 1 H), 7.90 (t, J = 8.4 Hz, 1 H), 7.76 (t, J = 8.4 Hz, 2 H), 7.67–7.56 (m, 4 H), 4.22–4.19 (m, 1 H), 3.41–3.39 (m, 4 H), 2.50–2.32 (m, 3 H), 2.20–2.14 (m, 1 H), 1.56–1.30 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 167.7, 161.5, 154.4, 146.1, 134.7, 133.3, 131.1, 130.6, 129.8, 128.8, 128.3, 127.6, 127.5, 127.3, 121.4, 54.0, 46.5, 42.9, 29.2, 26.4, 25.4, 24.6, 24.4.

MS (APCI): m/z = 417 $[M + H]^+$.

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{24}H_{25}N_4O_3$: 417.1927; found: 417.1914.

(*S*)-3-(5,13-Dioxo-5,6,7,13-tetrahydro-6,8,13a-triazabenzo[3,4]cyclohepta[1,2-*b*]naphthalen-7-yl)-*N*-phenylpropanamide (23)
Off-white solid; yield: 121 mg (95%); mp 171–172 °C; $[\alpha]_D^{25}$ –88.0 (*c* 0.1, MeOH); R_f = 0.40 ($CHCl_3$–MeOH, 9:1).

IR (KBr): 3434, 2923, 1672, 1617 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.84 (s, 1 H), 8.85 (d, J = 6.0 Hz, 1 H), 8.19 (d, J = 8.1 Hz, 1 H), 7.91 (t, J = 7.8 Hz, 1 H), 7.78–7.75 (m, 2 H), 7.67–7.55 (m, 4 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.25 (t, J = 7.5 Hz, 2 H), 7.00 (t, J = 7.2 Hz, 1 H), 4.25–4.23 (m, 1 H), 2.59–2.43 (m, 3 H), 2.30–2.25 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 169.3, 161.5, 154.0, 145.8, 137.9, 134.7, 133.4, 131.6, 130.0, 129.7, 129.0, 128.8 (2 C), 128.4, 127.5 (2 C), 127.1, 124.1, 121.1, 119.9 (2 C), 53.6, 33.6, 25.8.

MS (APCI): m/z = 425 $[M + H]^+$.

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{25}H_{21}N_4O_3$: 425.1614; found: 425.1627.

Acknowledgement

The authors are grateful to the GVK Biosciences management for financial support and encouragement.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(14) The enantiomeric purity was determined by comparing chiral HPLC area method with a racemic compound **3** which was synthesized similarly from the dimethyl DL-glutamate.

