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Synthetic study of (+)-anthramycin using ring-closing enyne metathesis and cross-metathesis

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Abstract—Synthesis of (+)-anthramycin was examined. A pyrrolobenzodiazepine skeleton could be synthesized by reductive cyclization of pyrrolidine derivative, which was obtained by enyne metathesis. The conjugated enamide ester part of (+)-anthramycin derivative was constructed by cross-metathesis.

1. Introduction

(+)-Anthramycin, which has an antitumor activity, was isolated by Leimgruber[1a,b] in 1965, and the total synthesis of anthramycin was achieved by the same group[1c] and later by Stille.[1d] The remarkable structural feature of this skeleton is that it possesses a pyrrolobenzodiazepine skeleton and a dienamide group conjugated with nitrogen in a pyrrolidine ring. Since we have been interested in the structure of the dienamide group conjugated with nitrogen in a pyrrolidine ring, the total synthesis of (+)-anthramycin was planned because this structure would be constructed by ring-closing enyne metathesis[2,3] (RCM) and cross-metathesis[4] (CM) followed by isomerization of the resulting double bond (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. The conjugated amide part of (+)-anthramycin should be formed by cross-metathesis with an alkene part of the diene moiety in pyrrolobenzodiazepine derivative **1** followed by olefin isomerization. A pyrrolobenzodiazepine skeleton of **1** should be constructed by reductive cyclization of a nitro group and an ester group of pyrrolidine derivative **2**, which should be obtained by enyne metathesis[5] of **3**. The starting enyne **3** would be obtained from L-methionine.

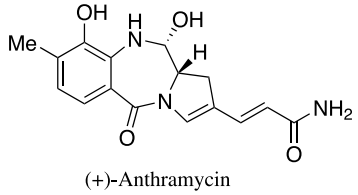
2. Construction of a pyrrolobenzodiazepine skeleton

Esterification of L-methionine followed by alkylation[6] with propargyl bromide and then protection of the secondary amine with the carbobenzyloxy group gave **4**. Conversion of sulfide **4** into sulfoxide **5** by treatment with $NaIO_4$ smoothly proceeded, and β-hydrogen elimination of the sulfoxymethyl group of **5** gave the desired enyne **3a** (Scheme 2).

To construct the pyrrolidine ring, enyne metathesis was carried out. When a CH_2Cl_2 solution of enyne **3a** and 5 mol% of first-generation of ruthenium carbene complex **6a** was stirred at room temperature under ethylene gas[5d] for 24 h, the desired pyrrolidine derivative **7** was obtained in 76% yield (Scheme 3).

Deprotection of the benzyloxy group of **7** with TMSCl in the presence of NaI[7] followed by condensation of *o*-nitrobenzoyl chloride **8a** gave **2a** in 76% yield. Construction of a pyrrolobenzodiazepine skeleton was carried out by treatment of **2a** with zinc-acetic acid[8] in CH_2Cl_2 and treatment of the resultant crude product with dil. HCl in THF to give **1a** in 86% yield via aniline derivative **9a**. Thus, a novel procedure for synthesis of a pyrrolobenzodiazepine skeleton could be developed (Scheme 4).

Subsequently, elongation of the carbon one-unit to the alkene part in **1a** was examined by cross-metathesis. When a CH_2Cl_2 solution of **1a**, (*Z*)-1,4-diacetoxy-but-2-ene **10** (10 equiv) and 15 mol% of second-generation ruthenium



(+)-Anthramycin

Figure 1.

Keywords: (+)-Anthramycin; Pyrrolobenzodiazepine skeleton; Deprotection.
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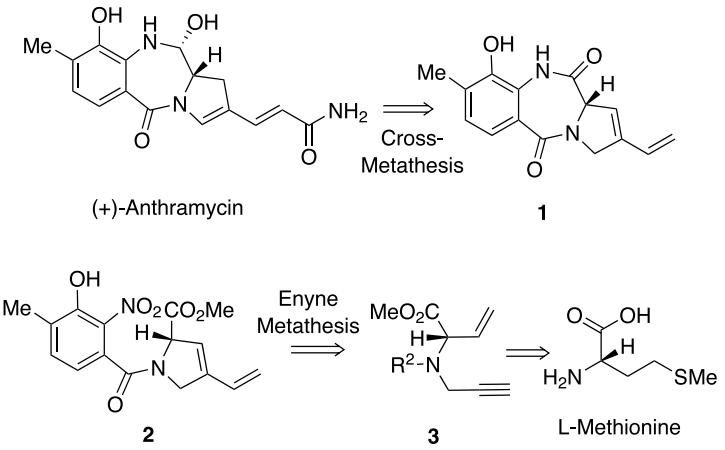
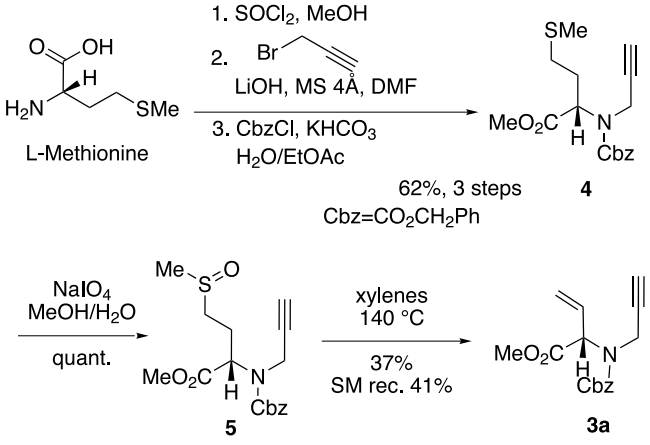
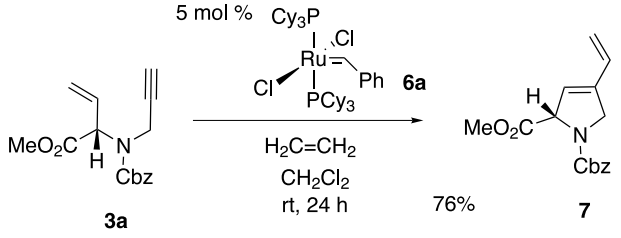


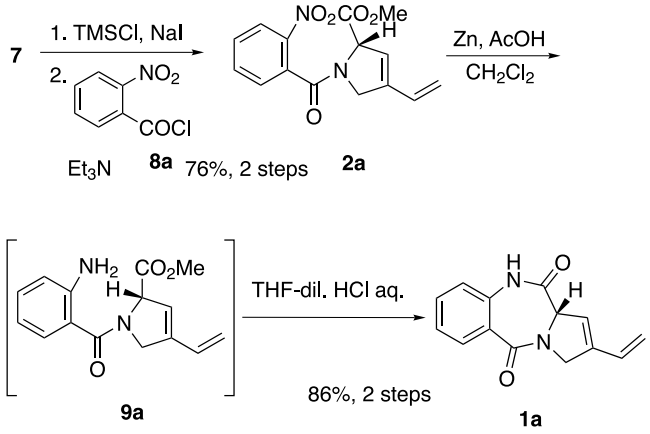
Scheme 1. Retrosynthetic analysis of anthramycin.



Scheme 2. Synthesis of substrates.



Scheme 3. Synthesis of a pyrrolidine derivative using enyne metathesis.



Scheme 4. Synthesis of a benzodiazepine derivative.

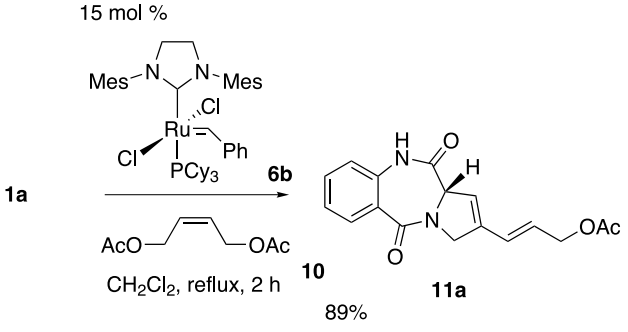
carbene complex **6b** was refluxed for 2 h, the desired cross-metathesis product **11a** was obtained in 89% yield (Scheme 5).

Thus, the carbon framework of anthramycin was constructed using RCM and CM as key steps.

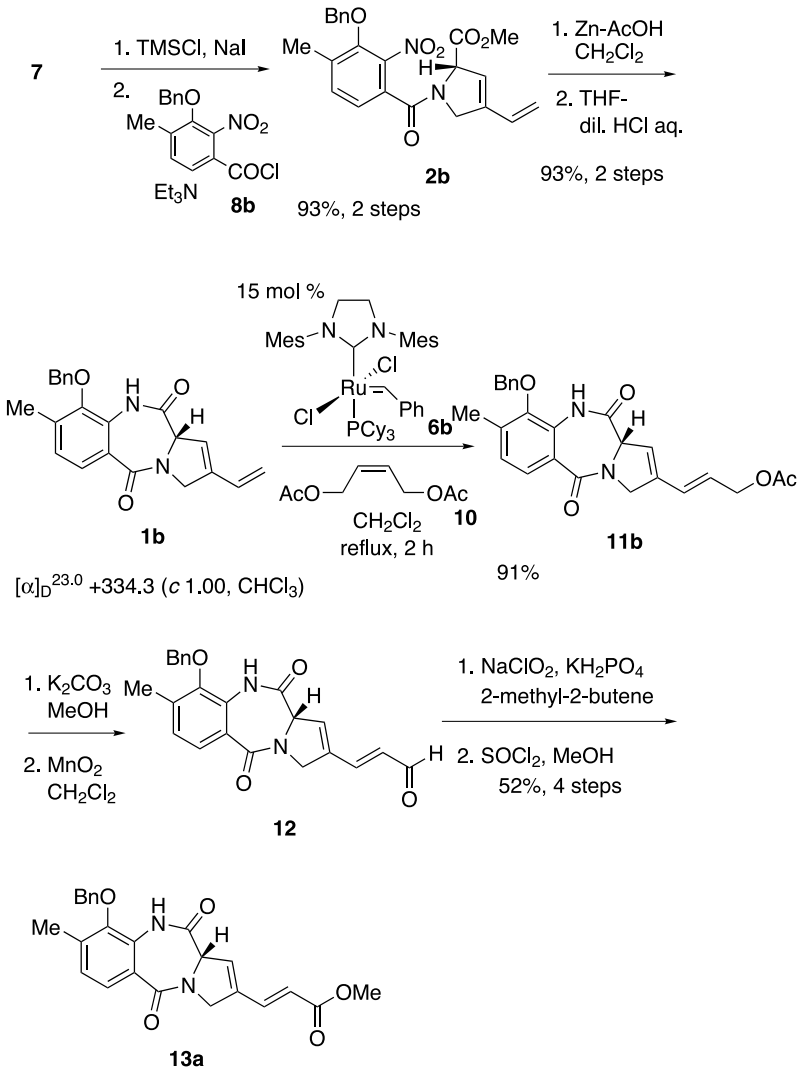
3. Synthetic study of anthramycin

Since a pyrrolobenzodiazepine skeleton was constructed from L-methionine, the total synthesis of anthramycin was examined. Deprotection of the benzyloxy group of **7** followed by condensation with 2-nitro-3-benzyloxy-4-methyl-benzoyl chloride **8b** afforded compound **2b**, which was treated in a similar manner to give **1b** in high yield. The $[\alpha]_D$ value +334.3 of this compound indicated that an optically active benzodiazepine derivative was produced in these processes. Cross metathesis of **1b** with **10** using **6b** smoothly proceeded to give **11b** in 91% yield. Then the ally alcohol part was converted into an ester group. Deprotection of the acetoxy group followed by treatment with MnO_2 gave aldehyde **12**, which was converted into ester **13a** in the usual manner (Scheme 6).

Further study of cross-metathesis was carried out to shorten the steps. When a CH_2Cl_2 solution of **1b**, 10 mol% of **6b** and methyl acrylate (10 equiv) was refluxed for 24 h, the desired compound **13a** was obtained in 41% yield. Furthermore, compound **1b** was treated with **6c** developed by Blechert[9] at room temperature to give **13a** in 63% yield (Scheme 7).

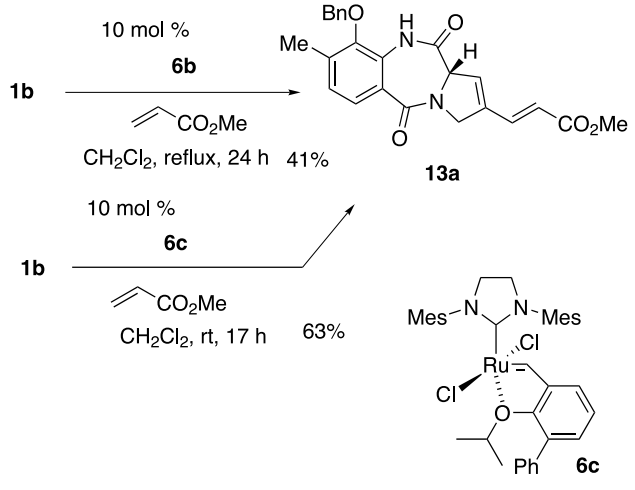


Scheme 5. Cross-metathesis.



Scheme 6. Synthesis of an anthramycine derivative.

Isomerization of the double bond in a pyrrolidine ring was carried out. When a toluene solution of **13a** was refluxed in the presence of a catalytic amount of $RuHCl(CO)(PPh_3)_3$ for 8 h, further isomerized pyrrole derivative **14** was obtained in 66% yield. On the other hand, when an EtOH solution of **13a** and $RhCl_3 \cdot 3H_2O$[10] was heated at 110 °C in a sealed tube, the desired isomerization product **15a** was obtained along with the corresponding ethyl ester **15b**. Thus, **13b** was prepared from **1b** and ethyl acrylate using **6c** and was treated with $RhCl_3 \cdot 3H_2O$ in EtOH at 110 °C to give **15b** in 50% yield (Scheme 8).

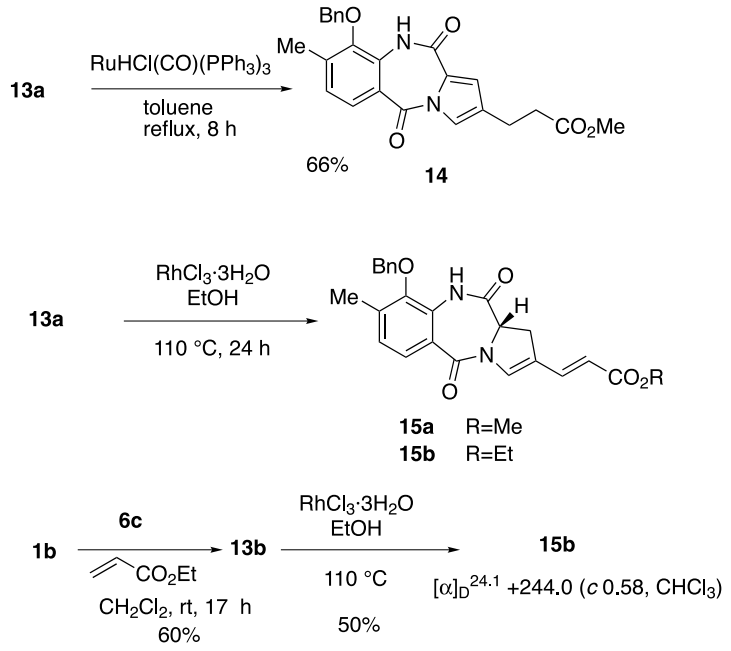


Scheme 7. Cross-metathesis.

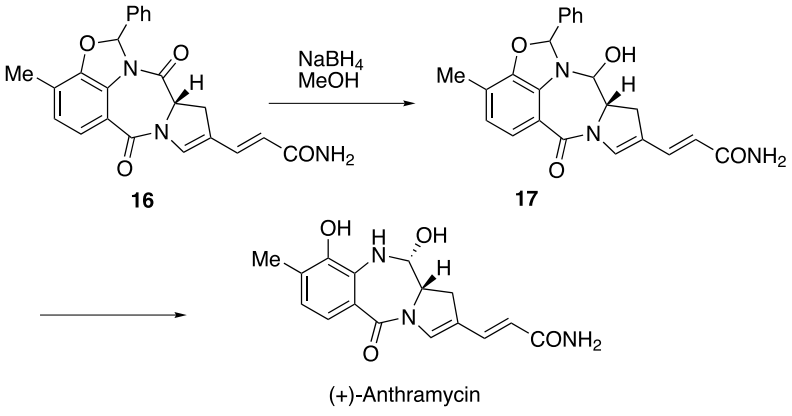
Stille has succeeded in the total synthesis of (+)-anthramycin.[2] In his total synthesis, the aminal part of **17** was constructed by treatment of **16** with $NaBH_4$ and deprotection of **17** gave (+)-anthramycin (Scheme 9).

Thus, debenzylation of **15b** was carried out by treatment with CF_3CO_2H and $BF_3 \cdot Et_2O$ followed by protection of the phenol and the amide nitrogen as a benzylidene acetal to give **19**, which was treated with $NaBH_4$ to give aminal **20** (Scheme 10).

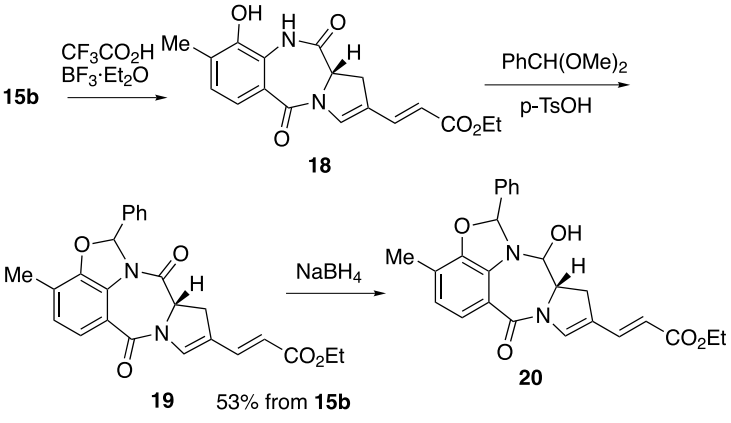
Thus, we succeeded in the synthesis of an anthramycin derivative **20** having the desired functional groups from commercially available L-methionine using ring-closing enyne metathesis and cross-metathesis as the key steps. Coversion of the ester group into an amide group for the total synthesis of (+)-anthramycin is further investigated.



Scheme 8. Isomerization of the double bond.



Scheme 9. Stille's synthesis of anthramycin.



Scheme 10. Conversion of **15b** into aminal **20**.

4. Experimental

4.1. General

All manipulations were carried out under an atmosphere of argon unless otherwise mentioned. Ethylene gas was purified by passage through the aqueous CuCl solution (2 g of CuCl in 180 mL of saturated NH_4Cl aqueous) and concentrated H_2SO_4 and then KOH tubes. Ruthenium complexes **6a** and **6b** were purchased from Strem Chemicals. Ruthenium complex **6c** was prepared according to the literature procedure.[9] All other solvents and reagents were purified when necessary using standard procedure.

4.1.1. (*S*)-4-Methylsulfanyl-2-prop-2-ynylamino-butyric acid methyl ester (A). To a solution of activated MS 4 Å (13 g) in DMF (50 mL) was added $LiOH \cdot H_2O$ (2.26 g, 53.8 mmol), and the suspension was stirred at 0 °C for 20 min. To this mixture was added L-methionine methyl ester hydrochloride (5 g, 25 mmol), and the suspension was stirred at 0 °C for 45 min. To this mixture was added propargyl bromide (2.3 mL, 25 mmol), and the mixture was stirred at room temperature for 28 h. After the solution was filtered through celite, the filtrate was washed with brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) to yield title compound **A** (3.1 g, 62%) as a colorless oil. IR (neat) ν 3287, 2950, 2917, 2840, 1732, 1435, 1204, 1168, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85–2.03 (m, 2H), 2.10 (s, 3H), 2.23 (dd, J=2.4, 2.4 Hz, 1H), 2.36 (br, 1H), 2.60 (m, 2H), 3.42 (dd, J=2.4, 17.2 Hz, 1H), 3.48 (dd, J=2.4, 17.2 Hz, 1H), 3.59 (dd, J=7.6, 5.6 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (CH_3), 30.2 (CH_2), 32.4 (CH_2), 36.8 (CH_2), 51.8 (CH_3), 58.7 (CH), 71.6 (CH), 81.1 (C), 174.6 (C); LRMS *m/z* 201 (M^+), 186, 162, 154, 142, 127, 114, 94; HRMS Calcd for $C_9H_{15}NO_2S$ (M^+) 201.0823, found 201.0803. Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.72; H, 7.47; N, 6.99. $[\alpha]_D^{23.9} = -14.2$ (*c* 1.00, $CHCl_3$).

4.1.2. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-4-methylsulfanyl-butyric acid methyl ester (4). To a solution of **A** (2.86 g, 14.2 mmol) and $KHCO_3$ (7.1 g, 71 mmol) in EtOAc/H_2O (1/1, 140 mL) was added CbzCl (3.0 mL, 21 mmol), and the solution was stirred at 0 °C for 14 h. The organic layer was washed with 10% HCl aq., brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 4:1) to yield **4** (4.76 g, quant.) as colorless oil. IR (neat) ν 3285, 2952, 2917, 2120, 1740, 1704, 1455, 1410, 1318, 1257, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 2.06 (s, 1.5H), 2.11 (s, 1.5H), 2.17–2.34 (m, 2H), 2.26 (br, 1H), 2.55–2.71 (m, 2H), 3.60 (s, 1.5H), 3.72 (s, 1.5H), 4.00–4.25 (m, 2H), 4.65 (m, 0.5H), 4.82 (m, 0.5H), 5.11–5.24 (m, 2H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two rotamers 15.3 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 30.8 (CH_2), 35.5 (CH_2), 36.5 (CH_2), 52.2 (CH_3), 52.3 (CH_3), 57.9 (CH), 58.2 (CH), 67.7 (CH_2), 67.8 (CH_2), 72.0 (CH), 72.3 (CH), 79.1 (C), 79.4 (C), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 135.8 (C), 136.0 (C), 155.4 (C), 155.5 (C), 171.2 (C), 171.3 (C); LRMS *m/z* 335 (M^+), 304, 276, 261, 244, 200, 170, 91; HRMS Calcd for $C_{17}H_{21}NO_4S$ (M^+) 335.1191, found 335.1185. Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.79; H, 6.39; N, 4.23. $[\alpha]_D^{23.4} = -50.9$ (*c* 1.00, $CHCl_3$).

4.1.3. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-4-methanesulfinyl-butyric acid methyl ester (5). To a solution of **4** (4.38 g, 13.0 mmol) in MeOH/H_2O (1/1, 64 mL) was added $NaIO_4$ (2.9 mL, 13.6 mmol) slowly, and the solution was stirred at 0 °C for 4 h. After the solution was filtered through celite, the filtrate was washed with brine, dried over $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography on silica gel (MeOH/ethyl acetate 1:10) to yield **5** (4.56 g, quant.) as colorless oil. IR (neat) ν 3282, 2953, 1740, 1700, 1456, 1413, 1257, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two diastereomers (ratio 3:2) 2.29 (t, J=2.4 Hz, 1H), 2.37 (br, 1H), 2.47–2.61 (m, 4H), 2.76–2.83 (m, 2H), 3.60 (s, 1.2H), 3.73 (s, 1.8H), 4.06–4.25 (m, 2H), 4.53 (m, 0.4H), 4.74 (m, 0.6H), 5.09–5.20 (m, 2H), 7.34–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two diastereomers 22.2 (CH_2), 22.6 (CH_2), 22.9 (CH_2), 23.6 (CH_2), 35.4 (CH_2), 35.6 (CH_2), 36.4 (CH_2), 36.7 (CH_2), 38.1 (CH_3), 38.6 (CH_3), 50.3 (CH_2), 50.5 (CH_2), 50.9 (CH_2), 52.3 (CH_3), 58.1 (CH), 58.4 (CH), 67.7 (CH_2), 72.5 (CH), 72.8 (CH), 78.8 (C), 79.0 (C), 127.4 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.2 (CH), 135.4 (C), 135.6 (C), 155.4 (C), 155.3 (C), 170.1 (C); LRMS *m/z* 351 (M^+), 320, 288, 261, 228, 152, 91; HRMS Calcd for $C_{17}H_{21}NO_5S$ (M^+) 351.1140, found 351.1128. Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.88; H, 6.03; N, 4.06.

4.1.4. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-but-3-enoic acid methyl ester (3a). A solution of **5** (13 g) in xylene (50 mL) was refluxed at 140 °C for 60 h. To this solution was added ethyl acetate and the solution was washed with 3% H_2O_2 aq., brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) to yield **3a** (3.1 g, 37%) as colorless oil, and **5** (5 g, 41%) was recovered. IR (neat) ν 3288, 2953, 2122, 1746, 1710, 1560, 1449, 1409, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 2.24 (br, 1H), 3.60 (br, 2H), 3.75 (br, 3H), 4.20 (br, 1H), 5.20 (br, 2H), 5.38 (m, 2H), 6.14 (ddd, J=6.2, 10.3, 17.0 Hz, 1H), 7.34–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 35.3 (CH_2), 36.3 (CH_2), 52.2 (CH_3), 61.2 (CH), 67.7 (CH_2), 71.7 (CH), 72.2 (CH), 79.0 (C), 79.5, (C), 119.6 (CH_2), 120.0 (CH_2), 127.5 (CH), 127.9 (CH×2), 128.2 (CH×2), 130.5 (CH), 130.8 (CH), 135.7 (C), 135.9 (C), 154.8 (C), 155.2 (C), 170.1 (C); LRMS *m/z* 287 (M^+), 272, 255, 228, 196, 184, 152, 91; HRMS Calcd for $C_{14}H_{14}NO_2$ ($M^+ - CO_2Me$) 228.1024, found 228.1034. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.81; H, 6.08; N, 4.90. $[\alpha]_D^{24.8} = -13.6$ (*c* 0.25, $CHCl_3$).

4.1.5. (*S*)-4-Vinyl-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (7). To a solution of **3a** (1.1 g, 3.8 μmol) in CH_2Cl_2 (77 mL, 0.05 M) was added **6a** (158 mg, 191 μmol, 5 mol%), and the solution was stirred under an atmosphere of ethylene for 24 h. To this solution was added an excess of ethyl vinyl ether. After the solvent was removed, the residue was purified by flash

column chromatography on silica gel (hexane/ethyl acetate 4:1) to yield **7** (840 mg, 76%) as a colorless crystal. Mp 58–60 °C; IR (film) ν 3065, 2952, 2868, 1754, 1713, 1645, 1596, 1416, 1355, 1205, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 3.59 (s, 1.5H), 3.75 (s, 1.5H), 4.34–4.45 (m, 2H), 5.06–5.29 (m, 5H), 5.64 (s, 0.5H), 5.69 (s, 0.5H), 6.42 (dd, J=17.6, 10.8 Hz, 0.5H), 6.43 (dd, J=17.6, 11.2 Hz, 0.5H), 7.29–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two rotamers 52.1 (CH_2), 52.3 (CH_3), 52.4 (CH_3), 52.6 (CH_2), 66.5 (CH), 66.8 (CH), 67.1 (CH_2), 67.2 (CH_2), 117.9 (CH_2), 118.3 (CH_2), 121.6 (CH), 121.8 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.5 (CH), 129.6 (CH), 136.3 (C), 136.3 (C), 140.5 (C), 140.6 (C), 153.7 (C), 154.2 (C), 170.0 (C), 170.3 (C); LRMS m/z 287 (M^+), 256, 243, 228, 196, 184, 152, 91; HRMS Calcd for $C_{16}H_{17}NO_4$ (M^+) 287.1158, found 287.1144. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.83; H, 5.95; N, 4.89. $[\alpha]_D^{20.8}=-241.1$ (c 1.00, $CHCl_3$).

4.1.6. (*S*)-1-(2-Nitro-benzoyl)-4-vinyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid methyl ester (2a). To a solution of **7** (92 mg, 0.32 μmol) in CH_3CN (3 mL) was added NaI (330 mg, 2.2 mmol) and TMSCl (0.26 mL, 2 mmol) at 0 °C and the solution was stirred at room temperature for 10 h. To this solution was added MeOH (1 mL) at 0 °C. After the solvent was removed, the residue was dissolved in CH_2Cl_2 (1 mL). To this solution was added Et_3N (1 mL) and *o*-nitrobenzoyl chloride (107 mg, 0.6 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The whole solution was stirred at 0 °C for 8 h. To this solution were added MeOH and saturated $Na_2S_2O_3$ aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ether 2:1) to yield **2a** (73.5 mg, 76%, 2 steps) as pale yellow oil. IR (neat) ν 1742, 1659, 1595, 1531, 1485, 1424, 1348, 1265, 1207, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (two rotamers, major/minor 3/1) major rotamer 3.81 (s, 3H), 4.09 (d, J=16.0 Hz, 1H), 4.23–4.27 (m, 1H), 4.93 (d, J=17.6 Hz, 1H), 5.18 (d, J=10.8 Hz, 1H), 5.49 (br, 1H), 5.81 (br, 1H), 6.41 (dd, J=17.6, 10.8 Hz, 1H), 7.56–7.71 (m, 2H), 7.77 (m, 1H), 8.22 (d, J=8.0 Hz, 1H), minor rotamer 3.54 (s, 3H), 4.53–4.58 (m, 1H), 4.79 (m, 1H), 4.86 (d, J=15.2 Hz, 1H), 5.31 (d, J=17.6 Hz, 1H), 5.35 (d, J=10.8 Hz, 1H), 5.61 (br, 1H), 6.47 (dd, J=17.6, 10.8 Hz, 1H), 7.45 (d, J=7.6 Hz, 1H), 7.56–7.71 (m, 2H), 8.19 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ major rotamer 52.7 (CH_3), 53.6 (CH_2), 66.1 (CH), 118.0 (CH_2), 121.9 (CH), 124.6 (CH), 128.4 (CH), 129.4 (CH), 130.2 (CH), 132.5 (C), 134.6 (CH), 139.7 (C), 144.8 (C), 165.9 (C), 169.4 (C), minor rotamer 52.5 (CH_3), 53.6 (CH_2), 67.7 (CH), 119.1 (CH_2), 120.8 (CH), 124.7 (CH), 129.1 (CH), 129.3 (CH), 130.3 (CH), 131.8 (C), 134.1 (CH), 140.4 (C), 144.7 (C), 166.4 (C), 169.7 (C); LRMS m/z 303 ($M^+ + 1$), 270, 243, 150, 93; HRMS Calcd for $C_{13}H_{11}N_2O_3$ ($M^+ - CO_2Me$) 243.0769, found 243.0765. $[\alpha]_D^{21.2}=-200.6$ (c 0.59, $CHCl_3$).

4.1.7. (*S*)-2-Vinyl-3,11a-dihydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (1a). To a solution of **2a** (46 mg, 0.15 μmol) and Zn dust (400 mg) in CH_2Cl_2 (2 mL) was slowly added AcOH (0.1 mL) at 0 °C. The solution was stirred at room temperature for 30 min and then the solution was filtered through celite. The filtrate was washed with saturated $NaHCO_3$ aq., brine, and dried over Na_2SO_4. After the solvent was removed, the crude aniline **9a** was dissolved in THF (5 mL) and 0.2% HCl aq. (5 mL). The whole solution was stirred at room temperature for 12 h. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **1a** (31 mg, 86%, 2 steps) as a colorless crystal. Mp 210 °C (dec.); IR (nujol) ν 3223, 2855, 1693, 1655, 1614, 1484, 1457, 1376, 1252, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, J=2.4, 15.2 Hz, 1H), 4.72 (d, J=15.2 Hz, 1H), 4.94 (br, 1H), 5.29 (d, J=17.6 Hz, 1H), 5.35 (d, J=10.8 Hz, 1H), 5.93 (br, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 7.31 (dd, J=8.4, 8.0 Hz, 1H), 7.51 (ddd, J=1.6, 8.0, 8.0 Hz, 1H), 7.77 (br, 1H), 8.05 (dd, J=8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0 (CH_2), 63.9 (CH), 118.5 (CH_2), 120.8 (CH), 121.1 (CH), 125.2 (CH), 126.1 (C), 129.7 (CH), 131.3 (CH), 132.6 (CH), 135.0 (C), 139.8 (C), 164.9 (C), 171.0 (C); LRMS m/z 240 (M^+), 211, 120; HRMS Calcd for $C_{14}H_{12}N_2O_2$ (M^+) 240,0899, found 240,0894. $[\alpha]_D^{23.9}=+499.1$ (c 1.00, $CHCl_3$).

4.1.8. (11a*S*, *E*)-Acetic acid 3-(5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-allyl ester (11a). To a solution of **1a** (4.3 mg, 18 μmol) and **10** (29 μL, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was added **6b** (2.4 mg, 3 μmol, 15 mol%), and the solution was degassed through freeze–pump–thaw cycle. The whole solution was refluxed 50 °C for 2 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **11a** (5 mg, 89%) as a colorless crystal. Mp 185 °C (dec.); IR (film) ν 3240, 1745, 1688, 1640, 1264, 734, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 4.49 (dd, J=3.2, 16.0 Hz, 1H), 4.68 (d, J=6.0 Hz, 2H), 4.72 (m, 1H), 4.94 (br, 1H), 5.80 (dt, J=15.6, 6.0 Hz, 1H), 5.97 (br, 1H), 6.52 (d, J=15.6 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.51 (ddd, J=1.6, 8.0, 8.0 Hz, 1H), 8.04 (dd, J=1.6, 8.0 Hz, 1H), 8.47 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_3), 53.1 (CH_2), 63.9 (CH_2), 64.1 (CH), 121.1 (CH), 121.6 (CH), 125.3 (CH), 125.9 (C), 126.1 (CH), 127.9 (CH), 131.3 (CH), 132.7 (CH), 135.0 (C), 138.5 (C), 164.8 (C), 170.5 (C), 170.8 (C); LRMS m/z 312 (M^+), 281, 252, 224, 191, 133, 120; HRMS Calcd for $C_{17}H_{16}N_2O_4$ (M^+) 312.1110, found 312.1106. $[\alpha]_D^{20.7}=+402.0$ (c 0.93, $CHCl_3$).

4.1.9. (2*S*)-1-(3-Benzyloxy-4-methyl-2-nitro-benzoyl)-4-vinyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid methyl ester (2b). To a solution of **7** (70 mg, 0.24 μmol) in CH_3CN (2 mL) was added NaI (298 mg, 2 mmol) and TMSCl (0.26 mL, 2 mmol) at 0 °C and the solution was stirred at room temperature for 5 h. To this solution was added MeOH (1 mL) at 0 °C. After the solvent was removed, the residue was dissolved in CH_2Cl_2 (1 mL). To this solution was added Et_3N (1 mL) and *o*-nitrobenzoyl chloride **8b** (83 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The whole solution was stirred at 0 °C for 12 h. To this solution was added MeOH (1 mL) and saturated $Na_2S_2O_3$ aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated.

The residue was purified by column chromatography on silica gel (hexane/ether 1:1) to yield **2b** (93 mg, 93%) as pale yellow oil. IR (neat) ν 1748, 1658, 1641, 1563, 1538, 1493, 1429, 1364, 1265, 1209, 1181, 1056, 1030, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (two rotamers, major/minor 3/1) major rotamer 2.42 (s, 3H), 3.78 (s, 3H), 4.27 (d, J= 13.6 Hz, 1H), 4.39–4.44 (m, 1H), 4.99 (d, J=10.4 Hz, 1H), 5.02 (d, J=17.6 Hz, 1H), 5.12 (d, J=10.4 Hz, 1H), 5.23 (d, J=10.8 Hz, 1H), 5.42 (br, 1H), 5.79 (s, 1H), 6.43 (dd, J= 17.6, 10.8 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.34–7.45 (m, 6H), minor rotamer δ 2.37 (s, 3H), 3.64 (s, 3H), 4.46–4.51 (m, 1H), 4.74 (d, J=15.6 Hz, 1H), 4.94–5.11 (blind, 3H), 5.28 (d, J=17.6 Hz, 1H), 5.34 (d, J=10.8 Hz, 1H), 5.66 (s, 1H), 6.56 (blind, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.34–7.45 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 16.4 (CH_3), 52.5 (CH_3), 53.9 (CH_2), 66.1 (CH), 76.5 (CH_2), 117.9 (CH_2), 121.6 (CH), 121.7 (CH), 122.2 (CH), 128.1 (CH×2), 128.4 (CH×2), 129.3 (CH), 129.5 (C), 133.9 (CH), 135.6 (C), 135.9 (C), 139.7 (C), 143.1 (C), 149.2 (C), 164.8 (C), 169.1 (C), minor rotamer δ 16.4 (CH_3), 52.3 (CH_2), 52.5 (CH_3), 67.9 (CH), 76.5 (CH_2), 118.9 (CH_2), 121.0 (CH), 121.0 (CH), 122.4 (CH), 128.2 (CH×2), 128.4 (CH×2), 129.1 (C), 129.2 (CH), 133.7 (CH), 135.5 (C), 135.9 (C), 140.2 (C), 142.8 (C), 149.1 (C), 165.2 (C), 169.8 (C); LRMS m/z 422 (M^+), 363, 270, 91; HRMS Calcd for $C_{23}H_{22}N_2O_6$ (M^+) 422.1477, found 422.1489. $[\alpha]_D^{22.1}=-230.4$ (c 0.90, $CHCl_3$).

4.1.10. (11a*S*)-9-Benzyloxy-8-methyl-2-vinyl-3,11a-dihydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (1b). To a solution of **2b** (570 mg, 1.35 μmol) and Zn dust (6.0 g) in CH_2Cl_2 (15 mL) was slowly added AcOH (1.2 mL) at 5 °C and the solution was stirred at room temperature for 20 min and was filtered through celite. The filtrate was washed with brine, and dried over Na_2SO_4. After the solvent was removed, the crude aniline was dissolved in THF (10 mL) and 0.2% HCl aq. (30 mL). The whole solution was stirred at room temperature for 24 h. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1) to yield **1b** (451 mg, 93%, 2 steps) as a colorless crystal. IR (nujol) ν 2924, 2854, 1703, 1654, 1622, 1606, 1566, 1497, 1461, 1428, 1376, 1262, 1211, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.43 (dd, J=4.0, 16.0 Hz, 1H), 4.50 (br, 1H), 4.65 (d, J=16.0 Hz, 1H), 4.88 (d, J=10.8 Hz, 1H), 4.96 (d, J=10.8 Hz, 1H), 5.24 (d, J=17.6 Hz, 1H), 5.31 (d, J= 10.8 Hz, 1H), 5.81 (s, 1H), 6.55 (dd, J=17.6, 10.8 Hz, 1H), 7.12 (d, J=8.0 Hz, 1H), 7.31–7.37 (m, 5H), 7.70 (d, J= 8.0 Hz, 1H), 7.83 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (CH_3), 52.8 (CH_2), 63.6 (CH), 75.2 (CH_2), 118.2 (CH_2), 120.7 (CH), 124.7 (C), 126.2 (CH), 127.2 (CH), 128.5 (CH), 128.6 (CH), 128.9 (C), 129.6 (C), 129.7 (CH), 135.3 (C), 135.4 (C), 139.6 (C), 145.6 (C), 164.4 (C), 169.7 (C); LRMS m/z 360 (M^+), 269, 241, 91; HRMS Calcd for $C_{22}H_{20}N_2O_3$ (M^+) 360.1474, found 360.1472. Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.19; H, 5.69; N, 7.86. $[\alpha]_D^{23.0}=+334.3$ (c 1.00, $CHCl_3$).

4.1.11. (11a*S*,*E*)-Acetic acid 3-(9-benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-allyl ester (11b). To a solution of **1b** (115 mg, 0.32 μmol) and **10** (0.5 μL, 0.3 mmol) in CH_2Cl_2 (6.4 mL) was added **6b** (13.5 mg, 16 μmol, 5 mol%), and the solution was degassed through freeze–pump–thaw cycle. The whole solution was refluxed for 12 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **11b** (126 mg, 91%) as a colorless crystal. Mp 138–140 °C; IR ($CHCl_3$) ν 3242, 1737, 1692, 1637, 1568, 1500, 1462, 1425, 1361, 1229, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.43 (s, 3H), 4.41 (dd, J=3.2, 15.6 Hz, 1H), 4.51 (br, 1H), 4.63 (d, J= 15.6 Hz, 1H), 4.66 (d, J=5.6 Hz, 2H), 4.88 (d, J=11.2 Hz, 1H), 4.96 (d, J=11.2 Hz, 1H), 5.77 (dt, J=16.0, 5.6 Hz, 1H), 5.85 (s, 1H), 6.49 (d, J=16.0 Hz, 1H), 7.12 (d, J= 8.0 Hz, 1H), 7.31–7.37 (m, 5H), 7.70 (d, J=8.0 Hz, 1H), 7.81 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3), 20.9 (CH_3), 53.0 (CH_2), 63.6 (CH), 64.0 (CH_2) 75.3 (CH_2), 121.6 (CH), 124.3 (C), 126.1 (CH), 126.3 (CH), 127.3 (CH), 127.8 (CH), 128.7 (CH×2), 128.7 (CH), 128.9 (CH×2), 129.6 (C), 135.3 (C), 138.3 (C), 145.6 (C), 164.4 (C), 169.5 (C) 170.4 (C); LRMS m/z 432 (M^+), 372, 341, 281, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1675. $[\alpha]_D^{19.8}=+331.7$ (c 1.00, $CHCl_3$).

4.1.12. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid methyl ester (13a). A solution of **11b** (22 mg, 51 μmol) in MeOH (2 mL) was added K_2CO_3 (12 mg, 87 μmol) at 0 °C and the solution was stirred at 0 °C for 9 h. To this solution was added saturated NH_4Cl aq. and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield crude alcohol (21 mg) as a colorless crystal. To the solution of crude alcohol (21 mg) in CH_2Cl_2 (2 mL) was added MnO_2 (70 mg) and the whole suspension was stirred at room temperature for 3 days. The solution was filtered through celite and the filtrate was concentrated to give crude aldehyde **12** (20.5 mg), which was dissolved in *t*-BuOH/H_2O (1 mL, 3.5/1). To this solution was added KH_2CO_3 (73 mg, 0.5 mmol), 2-methyl-2-butene (0.2 mL, 2 mmol), and $NaClO_2$ (23 mg, 0.25 mmol) and the solution was stirred at room temperature for 3 h. To this solution was added saturated $Na_2S_2O_3$ aq. and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield carboxylic acid (25 mg) as a colorless solid. A solution of crude carboxylic acid (25 mg) in MeOH (2 mL) was added $SOCl_2$ (10 drops) at 0 °C and the solution was stirred at room temperature for 18 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **13a** (11 mg, 52%, 4 steps) as a colorless crystal. Mp 189–191 °C; IR (nujol) ν 3215, 3065, 2854, 1722, 1699, 1645, 1623, 1565, 1499, 1462, 1376, 1315, 1261, 1225, 1174, 1072, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.79 (s, 3H), 4.45 (dd, J=3.6, 16.0 Hz, 1H), 4.55 (m, 1H), 4.66 (d, J=16.0 Hz, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.98 (d, J=11.2 Hz, 1H), 5.89 (d, J=15.6 Hz, 1H), 6.21 (br, 1H), 7.14 (d, J=8.0 Hz, 1H), 7.31–7.38 (m, 5H), 7.47 (d, J=15.6 Hz, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.76 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3), 51.9 (CH_3), 52.7 (CH_2), 63.9 (CH), 75.4 (CH_2) 121.9 (CH), 124.1 (C), 126.4 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH×2),

128.8 (CH), 129.0 (CH×2), 129.6 (C), 135.3 (C), 135.7 (C), 136.2 (CH), 137.6 (C), 145.7 (C), 164.5 (C), 166.5 (C) 169.1 (C); LRMS *m/z* 418 (M^+), 327, 91; HRMS Calcd for $C_{24}H_{22}N_2O_5$ (M^+) 418.1528, found 418.1529. $[\alpha]_D^{20.5} = +313.4$ (*c* 1.00, $CHCl_3$).

4.1.13. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid methyl ester (13a). To a solution of **1b** (19 mg, 50 μmol) and methyl acrylate (0.05 μL, 0.5 mmol) in degassed CH_2Cl_2 (1 mL) was added **6c** (5.0 mg, 7 μmol, 13 mol%), and the solution refluxed for 17 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1–1:1) to yield **13a** (13.8 mg, 63%) as a colorless crystal.

4.1.14. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (13b). To a solution of **1b** (105 mg, 0.29 μmol) and ethyl acrylate (0.3 μL, 2.9 mmol) in degassed CH_2Cl_2 (2.8 mL) was added a solution of **6c** (21 mg, 30 μmol, 10 mol%) in degassed CH_2Cl_2 (3 mL), and the solution was stirred at room temperature for 17 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **13b** (75.3 mg, 60%) as an amorphous solid. IR ($CHCl_3$) *ν* 1702, 1630, 1570, 1500, 1463, 1423, 1370, 1313, 1230, 1210, 1207, 1183, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=7.1 Hz, 3H), 2.44 (s, 3H), 4.24 (q, *J*=7.3 Hz, 2H), 4.44 (dd, *J*=3.6, 15.7 Hz, 1H), 4.56 (m, 1H), 4.66 (d, *J*=15.7 Hz, 1 H), 4.89 (d, *J*=11.2 Hz, 1H), 4.97 (d, *J*=11.2 Hz, 1H), 5.89 (d, *J*=16.0 Hz, 1H), 6.20 (s, 1H), 7.13 (d, *J*=8.2 Hz, 1H), 7.31–7.33 (m, 2H), 7.36–7.38 (m, 3H), 7.45 (d, *J*=16.0 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.78 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 14.1 (CH_3), 16.6 (CH_3), 52.7 (CH_2), 60.7 (CH_2), 63.8 (CH), 75.4 (CH_2) 122.4 (CH), 124.2 (C), 126.4 (CH), 127.5 (CH), 128.5 (CH), 128.7 (CH×2), 128.8 (CH), 129.0 (CH×2), 129.7 (C), 135.4 (CH), 135.7 (C), 135.9 (CH), 137.7 (C), 145.8 (C), 164.5 (C), 166.1 (C) 169.2 (C); LRMS *m/z* 432 (M^+), 360, 341, 269, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1683. $[\alpha]_D^{23.5} = +312.1$ (*c* 1.00, $CHCl_3$).

4.1.15. 3-(9-Benzyloxy-8-methyl-5,11-dioxo-10,11-dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-propionic acid methyl ester (14). To a solution of **13a** (3 mg, 18 μmol) in toluene (1 mL) was added $RuHCl(CO)(PPh_3)_3$ (1 mg), and the solution was stirred at 120 °C for 8 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **14** (2 mg, 66%) as a colorless crystal. ^1H NMR (270 MHz, $CDCl_3$) *δ* 2.40 (s, 3H), 2.65 (t, *J*=7.6 Hz, 2H), 2.89 (t, *J*=7.6 Hz, 2H), 3.70 (s, 3H), 4.91 (s, 2H), 7.08 (d, *J*=8.6 Hz, 1H), 7.40–7.50 (m, 6H), 7.92 (m, 1H), 8.16 (d, *J*=8.6 Hz, 1H), 8.75 (brs, 1H); LRMS *m/z* 418 (M^+), 387, 344, 327, 299, 243, 176, 148, 120.

4.1.16. (11a*S*,*E*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (15b). A solution of **13b** (4.3 mg, 18 μmol), $RhCl_3 \cdot 3H_2O$ (2.4 mg, 3 μmol, 15 mol%) and degassed EtOH (0.5 mL) was added in a sealed tube and was stirred at 110 °C for 24 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **15b** (5 mg, 50%) as a colorless crystal. IR (film) *ν* 3247, 2980, 2931, 1698, 1621, 1569, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.31 (t, *J*=7.3 Hz, 3H), 2.46 (s, 3H), 2.85 (dd, *J*=11.7, 16.1 Hz, 1H), 3.65 (dd, *J*=3.3, 16.1 Hz, 1H), 4.14 (dd, *J*=3.3, 11.7 Hz, 1H), 4.23 (q, *J*=7.3 Hz, 2H), 4.88 (d, *J*=11.3 Hz, 1H), 4.98 (d, *J*=11.3 Hz, 1H), 5.81 (d, *J*=15.6 Hz, 1H), 7.15 (d, *J*=8.1 Hz, 1H), 7.27 (s, 1H), 7.28–7.31 (m, 2H), 7.36–7.37 (m, 3H), 7.47 (d, *J*=15.6 Hz, 1H), 7.68 (d, *J*=8.1 Hz, 1H), 7.74 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 14.3 (CH_3), 16.7 (CH_3), 29.2 (CH_2), 56.7 (CH), 60.4 (CH_2), 75.5 (CH_2) 118.7 (CH), 122.9 (C), 123.9 (C), 126.8 (CH), 127.8 (CH), 128.8 (CH×2), 128.9 (CH), 129.2 (CH×2), 129.6 (C), 132.0 (CH), 135.3 (C), 136.5 (C), 137.1 (CH), 146.0 (C), 162.1 (C), 166.8 (C) 167.5 (C); LRMS *m/z* 432 (M^+), 387, 341, 295, 176, 120, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1689. $[\alpha]_D^{24.1} = +244.0$ (*c* 0.58, $CHCl_3$).

4.1.17. (11a*S*)-3-(9-Hydroxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (18). A mixture of crude **15b** (17 mg), TFA (1 mL), and $BF_3 \cdot Et_2O$ (0.05 mL) was stirred at room temperature for 10 min. To this solution were added MeOH and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield crude **18** (17 mg) as a colorless crystal. ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=6.8 Hz, 3H), 2.36 (s, 3H), 2.97 (dd, *J*=11.2, 15.6 Hz, 1H), 3.76 (dd, *J*=15.6, 3.6 Hz, 1H), 4.23 (q, *J*=6.8 Hz, 2H), 4.63 (dd, *J*=11.2, 3.6 Hz, 1H), 5.83 (d, *J*=16.0 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 1H), 7.34 (s, 1H), 7.37 (br, 1H), 7.50 (d, *J*=16.0 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 8.36 (br s, 1H); LRMS *m/z* 342 (M^+), 313, 297, 268, 176, 149, 120, 92.

4.1.18. Benzylidene acetal (19). A mixture of crude **18** (17 mg), benzaldehyde dimethylacetal (0.5 mL), and *p*-TsOH (1.7 mg) was warmed to 100 °C for 40 h. To this solution was added brine and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1) to yield **19** (9 mg, 53%) as a colorless crystal. IR ($CHCl_3$) *ν* 1698, 1650, 1593, 1499, 1457, 1398, 1259, 1223, 1177, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=6.8 Hz, 3H), 2.40 (s, 3H), 2.91 (dd, *J*=11.2, 15.2 Hz, 1H), 3.76 (dd, *J*=15.2, 4.0 Hz, 1H), 4.23 (q, *J*=6.8 Hz, 2H), 4.41 (dd, *J*=11.2, 4.0 Hz, 1H), 5.84 (d, *J*=16.0 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 1H), 7.34–7.56 (m, 8H), 7.72 (d, *J*=8.0 Hz, 1H); LRMS *m/z* 430 (M^+), 401, 385, 373, 356, 266, 236, 209, 121, 91; HRMS Calcd for $C_{25}H_{22}N_2O_5$ (M^+) 430.1528, found 430.1543.

4.1.19. Aminal (20). To a solution of **19** (2 mg) in MeOH (1 mL) was added $NaBH_4$ (4.4 mg) at 0 °C and the solution was stirred at 0 °C for 4 h. To this solution was added H_2O, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to

yield **20** (1.7 mg, 84%) as a colorless crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J=7.1 Hz, 3H), 2.08 (d, J=8.4 Hz, 1H), 2.19 (s, 3H), 2.92 (dd, J=15.6, 4.9 Hz, 1H), 3.13 (dd, J=11.4, 3.7 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 4.29 (dd, J=11.2, 4.8 Hz, 1H), 4.84 (d, J=8.6 Hz, 1H), 5.63 (d, J=15.6 Hz, 1H), 6.55 (s, 1H), 6.66 (d, J=8.5 Hz, 1H), 7.35 (d, J=8.5 Hz, 1H), 7.43–7.53 (m, 7H); LRMS *m/z* 432 (M^+), 414, 385, 356, 266, 238, 209; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1680.

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