Synthesis Y. Nakayama et al. Special Topic

Total Synthesis of (–)-Stemoamide by Sequential Overman/Claisen Rearrangement

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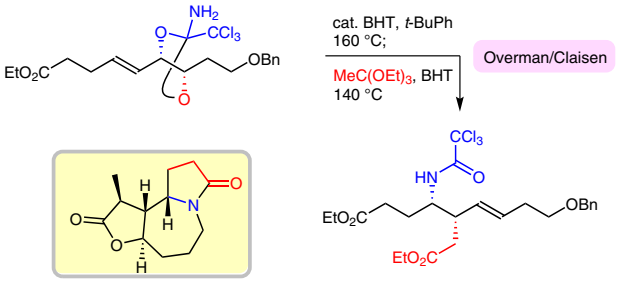

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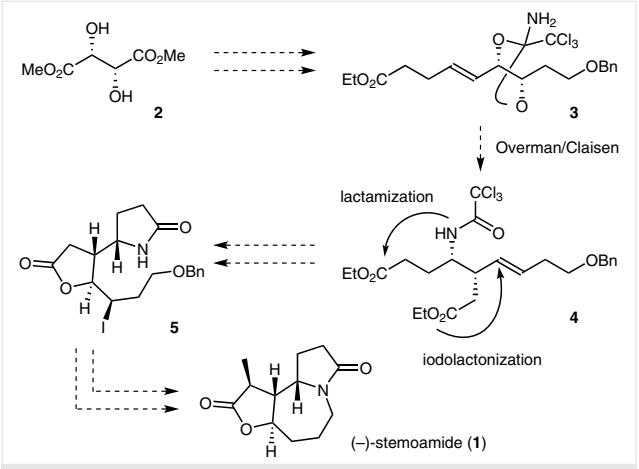
Abstract The enantioselective total synthesis of (–)-stemoamide using Overman/Claisen rearrangement of an allylic 1,2-diol is reported. The enantiopure allylic 1,2-diol was efficiently prepared from naturally occurring dimethyl tartrate. The chirality transfer reactions through two consecutive [3,3]-sigmatropic rearrangements proceeded with complete diastereoselectivity in a one-pot process.

Key words alkaloid, allylic compound, diol, sigmatropic rearrangement, total synthesis

Stemona alkaloids consist of polycyclic frameworks with the pyrrolo[1,2-*a*]azepine core as a common structure, and has been shown to possess a variety of biological activities such as insecticidal, anthelmintic, and antitussive effects.[1] For example, the roots of *Stemona tuberosa* have been used in Chinese and Japanese folk medicine as antitussive agents and insecticides. (–)-Stemoamide (**1**) was isolated from these extracts by the Xu group in 1992, and is now known as a representative alkaloid in this class (Scheme 1).[2] It contains a tricyclic structure including a γ-lactam and a γ-lactone moiety. This relatively simple structure renders it a synthetic target to demonstrate the utility of new methods. Williams and co-workers disclosed the first total synthesis of (–)-**1** in 1994.[3a] After their report, a number of racemic and enantioselective total syntheses have been reported by using their own strategies.[3,4] In this communication, we report the total synthesis of (–)-stemoamide (**1**), whose key step is the sequential Overman/Claisen rearrangement of an allylic 1,2-diol.

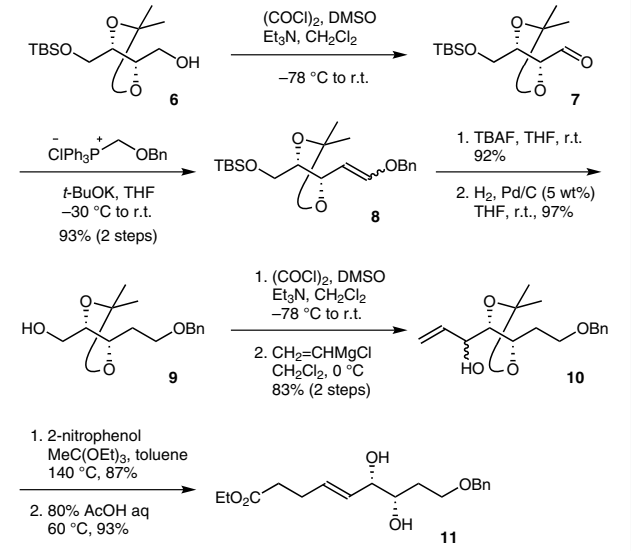
Our research group has reported synthetic strategy capitalizing on the sequential Overman/Claisen rearrangement[5,6] of acyclic allylic 1,2-diols, which derives from naturally occurring polyols such as tartaric acid and monosaccharides (Scheme 1).[7–10] In our synthetic plan for (–)-stemoamide (**1**), cyclic orthoamide **3** would be efficiently synthesized from dimethyl tartrate (**2**). Then, the sequential Overman/Claisen rearrangement of **3** would give access to acyclic intermediate **4**. This sequential reaction could install two consecutive stereocenters including the C–N bond. The subsequent cyclizations by iodolactonization and lactamization would differentiate two ethyl esters of **4**, and provide the bicyclic compound **5**, which would be converted into (–)-stemoamide (**1**).



Scheme 1 Synthetic plan for (–)-stemoamide (**1**)

Our total synthesis of (–)-stemoamide (**1**) began with one-carbon homologation using a Swern oxidation and a Wittig reaction of the known alcohol **6**,[11] which was prepared from dimethyl L-tartrate in three steps (Scheme 2). Cleavage of the TBS group in **8** with TBAF and hydrogenation of the enol ether provided the primary alcohol **9**. After Swern oxidation of **9**, exposure of the crude aldehyde to vinyl Grignard reagent provided allylic alcohol **10** in 83% yield

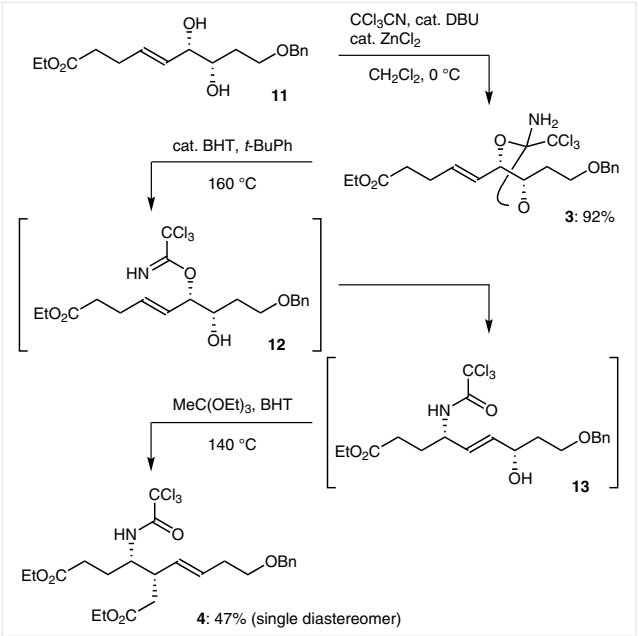
(2 steps). The resulting alcohol was subjected to the Johnson-type Claisen rearrangement at 140 °C in the presence of 2-nitrophenol,[12] providing the γ,δ-unsaturated ester in 87% yield. Allylic 1,2-diol **11** was then obtained by removal of the acetonide group in 80% aqueous AcOH.



Scheme 2 Synthesis of allylic 1,2-diol (**11**)

The stage was now set for the pivotal Overman/Claisen rearrangement of allylic 1,2-diol **11** (Scheme 3). Treatment of **11** with CCl_3CN (1.3 equiv) in the presence of catalytic amount of DBU and $ZnCl_2$ gave cyclic orthoamide **3** in 92% yield. Addition of $ZnCl_2$ was critical to prevent the generation of the undesired bis(imidate), which was formed by installation of two equivalents of CCl_3CN. A solution of cyclic orthoamide **3** and a catalytic amount of BHT (butylated hydroxytoluene, 4-methyl-2,6-di-*tert*-butylphenol)[8c,d,13] in *t*-BuPh was heated to 160 °C in a sealed tube, initiating the ring opening of the cyclic orthoamide. The Overman rearrangement of the generated imidate **12** provided allylic alcohol **13**, which was then subjected to the Johnson-type Claisen rearrangement in a one-pot sequence. The two free hydroxy groups of **11** was successfully differentiated through the sequential rearrangement without use of protecting groups. Furthermore, both chirality transfer reactions[14] took place in the highest level of the stereoselectivity, with **4** isolated in 47% yield as a single diastereomer.

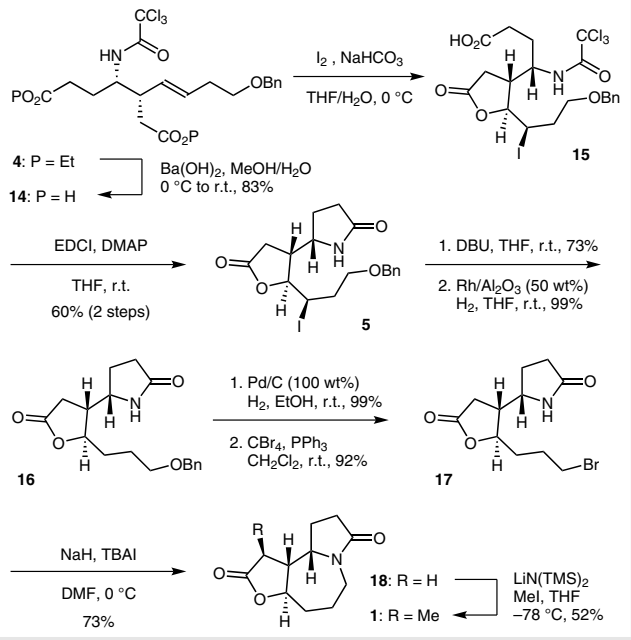
With acyclic compound **4** bearing two contiguous stereocenters in hand, we turned our attention to construct the tricyclic framework of (–)-stemoamide (**1**) (Scheme 4). The synthetic challenge in this stage was the differentiation of two ethyl esters embedded in **4**. Both ester groups were hydrolyzed with $Ba(OH)_2$ without affecting the trichloroacetamide. Gratifyingly, we found that iodolactonization of the resulting bis(acid) **14** successfully differentiate two carboxylic acids through the stereoselective synthesis of the γ-



Scheme 3 Sequential Overman/Claisen rearrangement in a one-pot sequence

lactone without generation of the seven-membered lactone. Furthermore, the cyclization of the trichloroacetamide was also not observed probably due to the suppression of the nucleophilicity by trichloromethyl group. The remaining carboxylic acid of **15** then underwent the γ-lactamization with EDCI [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride] and DMAP, accompanied by cleavage of the trichloroacetyl group to give **5** in 60% yield over two steps. Reduction of the alkyl iodide required the two-step procedure including elimination and hydrogenation with Rh/Al_2O_3. After conversion of benzyl ether **16** into bromide **17**, the seven-membered ring was then formed with NaH and TBAI in 73% yield.[3b] Finally, the total synthesis of (–)-stemoamide (**1**) was achieved by regio- and stereoselective methylation according to reported procedure.[3b,g] The spectral data of our synthetic sample was identical to those for natural products and previously reported synthetic samples on the basis of ^1H NMR, ^{13}C NMR, IR, HRMS, and optical rotation.

In summary, we have accomplished the total synthesis of (–)-stemoamide (**1**), featuring a sequential Overman/Claisen rearrangement of an enantiopure allylic 1,2-diol. The reaction differentiated two hydroxy groups without protection of the homoallylic alcohol, and proceeded in complete stereoselective fashion. The present synthesis demonstrated the utility of our method for enantioselective total syntheses of natural products.



Scheme 4 Total synthesis of (–)-stemoamide (**1**)

Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. Toluene, DMSO and *t*-BuPh were distilled from CaH_2. DMF was distilled from $CaSO_4$. MeOH was distilled from $CaSO_4$. All distilled solvents, CH_2Cl_2, and EtOH were dried over activated 3Å molecular sieves. THF (dehydrated, stabilizer free) was purchased from Kanto Chemical Co., Inc. Commercial reagents were used without further purification. TLC was performed on Merck 60 F254 precoated silica gel plates, which were visualized by exposure to UV (254 nm) or stained by submersion in ethanolic ninhydrin or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, Kanto Chemical Co., Inc.). Preparative TLC was performed on Merck 60 F254 0.5 mm precoated silica gel plates. ^{1}H NMR spectra were recorded at 500 MHz with JEOL ECA-500 spectrometers. ^{13}C NMR spectra were recorded at 125 MHz with Jeol ECA-500 spectrometers. Chemical shifts are reported in ppm with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26), C_6D_6 (7.16), CD_3OD (3.31); ^{13}C NMR: $CDCl_3$ (77.16), C_6D_6 (128.06), CD_3OD (49.00)]. Standard abbreviations were used to denote signal patterns. IR spectra were recorded using a Bruker Alpha FT-IR spectrometer. Mass spectra (ESI-TOF) were measured with a Waters, LCT Premier XE. Melting points were measured with a Mitamura-Riken microhot stage. Optical rotations were measured with a Jasco P-2100 polarimeter.

The structures of the intermediates **19**–**22** prepared during the synthetic sequence on the way to (–)-stemoamide (**1**) are provided along with their ^{1}H and ^{13}C NMR spectra in the Supporting Information.

({(4*S*,5*S*)-5-[2-(Benzyloxy)vinyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methoxy)(*tert*-butyl)dimethylsilane (8)

Oxalyl chloride (6.3 mL, 72 mmol) was added dropwise to a solution of DMSO (7.7 mL, 110 mmol) and CH_2Cl_2 (340 mL) at –78 °C. The solution was stirred for 30 min at –78 °C. A solution of alcohol **6**[11] (9.99 g, 36.1 mmol) in CH_2Cl_2 (18 mL) was then added dropwise via cannula at –78 °C. After stirring for 40 min at –78 °C, Et_3N (20 mL, 150 mmol) was added dropwise to the solution. The resulting mixture was stirred for 15 min at –78 °C, allowed to warm to r.t., quenched with sat. aq $NaHCO_3$ (90 mL) and H_2O (90 mL), and extracted with hexane (2 × 90 mL). The combined organic extracts were washed with H_2O (2 × 30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated to give the corresponding aldehyde **7**,[11] which was immediately used in the next reaction without further purification.

t-BuOK (16.2 g, 144 mmol) was added to a mixture of (benzyloxymethyl)triphenylphosphonium chloride (60.6 g, 144 mmol) and THF (340 mL) at –78 °C. The resulting mixture was allowed to warm to –30 °C. After stirring for 1.5 h at –30 °C, a solution of the crude aldehyde **7** in THF (18 mL) was added dropwise to the ylide via cannula at –30 °C. This mixture was stirred for 30 min at –30 °C, allowed to warm to r.t., quenched with sat. aq $NaHCO_3$ (90 mL) and H_2O (90 mL), and extracted with hexane (2 × 90 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 75:1 to 10:1) to give 12.8 g of a mixture of two enol ethers **8** (93% over 2 steps, *E*/*Z* = 1:1.2). For analytical samples, the two isomers were separated by HPLC (PEGASIL Silica 120-5, 250 × 20 mm, UV 254 nm, hexane/EtOAc, 9:1, 10 mL/min, *E*-isomer: t_R = 8.7 min, *Z*-isomer: t_R = 10.2 min).

(*E*)-8

Colorless oil; R_f = 0.67 (hexane/EtOAc, 3:1); $[\alpha]_D^{28}$ –14.4 (*c* 1.05, $CHCl_3$).

IR (film): 2930, 2858, 1655, 1252, 1171, 1021, 838 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.39–7.30 (m, 5 H), 6.65 (d, *J* = 12.6 Hz, 1 H), 4.89 (dd, *J* = 12.6, 8.9 Hz, 1 H), 4.80 (d, *J* = 11.5 Hz, 1 H), 4.75 (d, *J* = 11.5 Hz, 1 H), 4.30 (dd, *J* = 8.9, 8.9 Hz, 1 H), 3.80–3.67 (m, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.1 (CH), 136.5 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 108.5 (C), 101.6 (CH), 81.9 (CH), 76.7 (CH), 71.5 (CH_2), 62.2 (CH_2), 27.4 (CH_3), 27.0 (CH_3), 26.0 (CH_3), 18.5 (C), –5.2 (CH_3), –5.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}O_4SiNa$: 401.2124; found: 401.2114.

(*Z*)-8

Colorless oil; R_f = 0.64 (hexane/EtOAc, 3:1); $[\alpha]_D^{26}$ +1.5 (*c* 1.25, $CHCl_3$).

IR (film): 2930, 2858, 1668, 1370, 1253, 1217, 1075, 837 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.29 (m, 5 H), 6.24 (dd, *J* = 6.3, 0.9 Hz, 1 H), 4.91 (ddd, *J* = 8.9, 8.3, 0.9 Hz, 1 H), 4.85 (d, *J* = 12.6 Hz, 1 H), 4.79 (d, *J* = 12.6 Hz, 1 H), 4.49 (dd, *J* = 8.9, 6.3 Hz, 1 H), 3.80–3.66 (m, 3 H), 1.42 (s, 6 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.0 (CH), 137.1 (C), 128.7 (CH), 128.2 (CH), 127.6 (CH), 108.8 (C), 104.4 (CH), 82.5 (CH), 74.4 (CH_2), 71.4 (CH), 62.8 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 26.1 (CH_3), 18.6 (C), –5.2 (CH_3), –5.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}O_4SiNa$: 401.2124; found: 401.2114.

{(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (9)

Bu_4NF (1.0 M in THF, 44 mL, 44 mmol) was added to a solution of enol ether **8** (*E*/*Z* = 1:1.2, 12.8 g, 33.7 mmol) in THF (340 mL) at 0 °C. This solution was allowed to warm to r.t., maintained for 1 h at r.t., and quenched with sat. aq NH_4Cl (85 mL) and H_2O (85 mL). The mixture was extracted with EtOAc (2 × 85 mL). The combined organic extracts

were washed with brine (25 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to give 8.19 g of a mixture of two alcohols **19** (92%, *E*/*Z* = 1:1.2). For analytical samples, the two isomers were separated by HPLC (PEGASIL Silica 120-5, 250 × 20 mm, UV 254 nm, hexane/EtOAc 2:3, 10 mL/min, *Z*-isomer: t_R = 9.0 min, *E*-isomer: t_R = 10.5 min).

(*E*)-19

Colorless oil; R_f = 0.56 (hexane/EtOAc, 1:1); $[\alpha]_D^{24}$ –63.2 (*c* 0.99, EtOAc).

IR (film): 3455, 2986, 2873, 1655, 1380, 1169, 1051 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ = 7.14–7.03 (m, 5 H), 6.42 (d, *J* = 12.6 Hz, 1 H), 4.82 (dd, *J* = 12.6, 8.9 Hz, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.34 (d, *J* = 12.0 Hz, 1 H), 4.30 (dd, *J* = 8.9, 8.9 Hz, 1 H), 3.64–3.58 (m, 2 H), 3.43–3.36 (m, 1 H), 1.68 (s, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR (C_6D_6, 125 MHz): δ = 151.1 (CH), 137.1 (C), 128.7 (CH), 128.4 (CH), 127.7 (CH), 108.5 (C), 102.3 (CH), 82.2 (CH), 76.3 (CH), 71.4 (CH_2), 60.8 (CH_2), 27.6 (CH_3), 27.2 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_4Na$: 287.1259; found: 287.1265.

(*Z*)-19

Colorless oil; R_f = 0.62 (hexane/EtOAc, 1:1); $[\alpha]_D^{23}$ –39.5 (*c* 1.11, EtOAc).

IR (film): 3460, 2986, 2934, 2876, 1667, 1372, 1217, 1062 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ = 7.11–7.01 (m, 5 H), 5.79–5.76 (m, 1 H), 5.18 (dd, *J* = 8.3, 8.0 Hz, 1 H), 4.53 (dd, *J* = 8.3, 6.3 Hz, 1 H), 4.31–4.21 (m, 2 H), 3.81–3.74 (m, 2 H), 3.70–3.63 (m, 1 H), 2.30–1.90 (m, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR (C_6D_6, 125 MHz): δ = 148.1 (CH), 137.3 (C), 128.8 (CH), 128.4 (CH), 127.6 (CH), 108.9 (C), 105.4 (CH), 82.6 (CH), 74.1 (CH_2), 72.2 (CH), 62.0 (CH_2), 27.5 (CH_3), 27.2 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_4Na$: 287.1259; found: 287.1265.

Pd/C (10%, 410 mg, 5.0 wt%) was added to a solution of alcohols **19** (*E*/*Z* = 1:1.2, 8.19 g, 31.0 mmol) in THF (160 mL) at r.t. The mixture was stirred under H_2 (1 atm) at r.t. for 14 h, filtered through a pad of Celite, washed with EtOAc (160 mL), and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 7:1 to 1:1) to give 8.01 g of alcohol **9** (97%); colorless oil; R_f = 0.52 (hexane/EtOAc, 1:1); $[\alpha]_D^{21}$ –23.6 (*c* 1.08, $CHCl_3$).

IR (film): 3451, 2987, 2933, 2869, 1371, 1215, 1093 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.27 (m, 5 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.02 (dt, *J* = 8.3, 6.0 Hz, 1 H), 3.82 (ddd, *J* = 8.3, 4.3, 3.7 Hz, 1 H), 3.78 (ddd, *J* = 11.7, 5.2, 3.7 Hz, 1 H), 3.65 (dt, *J* = 9.5, 6.0 Hz, 1 H), 3.66–3.60 (m, 1 H), 3.60 (dt, *J* = 9.5, 6.6 Hz, 1 H), 2.05 (dd, *J* = 7.5, 5.2 Hz, 1 H), 1.92 (ddd, *J* = 6.6, 6.0, 6.0 Hz, 2 H), 1.41 (s, 3 H), 1.40 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.3 (C), 128.6 (CH), 127.85 (CH), 127.82 (CH), 108.7 (C), 81.5 (CH), 74.9 (CH), 73.3 (CH_2), 67.2 (CH_2), 62.1 (CH_2), 33.4 (CH_2), 27.4 (CH_3), 27.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}O_4$: 267.1596; found: 267.1602.

1-{(4*S*,5*S*)-5-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}prop-2-en-1-ol (10)

Oxalyl chloride (4.1 mL, 47 mmol) was added dropwise to a solution of DMSO (5.0 mL, 71 mmol) and CH_2Cl_2 (150 mL) at –78 °C. The resulting solution was stirred for 40 min at –78 °C. A solution of alcohol **9** (4.21 g, 15.8 mmol) in CH_2Cl_2 (8.0 mL) was then added dropwise via cannula at –78 °C. After stirring for 1 h at –78 °C, Et_3N (13 mL, 95 mmol) was added dropwise to the solution. The resulting mixture was stirred for 10 min at –78 °C, allowed to warm to r.t., quenched with sat. aq $NaHCO_3$ (40 mL) and H_2O (40 mL), and extracted with hexane (2 × 50 mL). The combined organic extracts were washed with H_2O (2 × 12 mL) and brine (12 mL), dried (Na_2SO_4), and concentrated to give the corresponding aldehyde, which was immediately used in the next reaction without further purification.

Vinylmagnesium bromide (1.0 M in THF, 32 mL, 32 mmol) was added to a solution of the crude aldehyde in CH_2Cl_2 (160 mL) at 0 °C. This solution was stirred for 1.5 h at 0 °C, quenched with sat. aq NH_4Cl (40 mL) and H_2O (40 mL), and extracted with hexane (2 × 40 mL). The combined organic extracts were washed with brine (12 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1 to 6:1) to give 3.82 g of a mixture of allylic alcohols **10** (83% over 2 steps, dr = 1:1). For analytical samples, the two isomers were separated by HPLC (PEGASIL Silica 120-5, 250 × 20 mm, UV 254 nm, hexane/EtOAc, 3:2, 10 mL/min, less polar diastereomer: t_R = 9.1 min, polar diastereomer: t_R = 9.7 min).

10 (Less Polar Diastereomer)

Colorless oil; R_f = 0.76 (hexane/EtOAc, 1:1); $[\alpha]_D^{21}$ –38.5 (*c* 1.10, $CHCl_3$).

IR (film): 3455, 2986, 2867, 1371, 1215, 1091 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.26 (m, 5 H), 5.90 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1 H), 5.36 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1 H), 5.24 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1 H), 4.51 (s, 2 H), 4.30–4.26 (m, 1 H), 4.10 (ddd, *J* = 8.0, 8.0, 3.4 Hz, 1 H), 3.76 (dd, *J* = 8.0, 4.9 Hz, 1 H), 3.66 (ddd, *J* = 9.5, 6.9, 5.7 Hz, 1 H), 3.61 (ddd, *J* = 9.5, 7.5, 6.3 Hz, 1 H), 2.40 (br s, 1 H), 2.00 (dddd, *J* = 14.0, 7.5, 6.9, 3.4 Hz, 1 H), 1.87 (dddd, *J* = 14.0, 8.0, 6.3, 5.7 Hz, 1 H), 1.40 (s, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.3 (C), 136.2 (CH), 128.5 (CH), 127.83 (CH), 127.77 (CH), 116.9 (CH_2), 108.8 (C), 83.0 (CH), 74.9 (CH), 73.2 (CH_2), 72.4 (CH), 67.4 (CH_2), 34.3 (CH_2), 27.4 (CH_3), 27.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}O_4$: 293.1753; found: 293.1755.

10 (Polar Diastereomer)

Colorless oil; R_f = 0.71 (hexane/EtOAc, 1:1); $[\alpha]_D^{22}$ –16.3 (*c* 1.01, $CHCl_3$).

IR (film): 3448, 2986, 2870, 1371, 1215, 1089 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.26 (m, 5 H), 5.86 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1 H), 5.35 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1 H), 5.23 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1 H), 4.51 (s, 2 H), 4.14–4.10 (m, 1 H), 4.09 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1 H), 3.73 (dd, *J* = 8.0, 4.3 Hz, 1 H), 3.65 (ddd, *J* = 9.5, 6.6, 5.4 Hz, 1 H), 3.59 (ddd, *J* = 9.5, 7.7, 6.0 Hz, 1 H), 2.34 (d, *J* = 6.6 Hz, 1 H), 1.96 (dddd, *J* = 14.0, 7.7, 6.6, 4.0 Hz, 1 H), 1.87 (dddd, *J* = 14.0, 8.0, 6.0, 5.4 Hz, 1 H), 1.410 (s, 3 H), 1.405 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.4 (C), 137.2 (CH), 128.5 (CH), 127.79 (CH), 127.76 (CH), 117.0 (CH_2), 109.1 (C), 83.5 (CH), 75.1 (CH), 73.2 (CH_2), 72.3 (CH), 67.2 (CH_2), 33.8 (CH_2), 27.6 (CH_3), 27.2 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}O_4$: 293.1753; found: 293.1742.

Ethyl (6*S*,7*S*,*E*)-9-(Benzyloxy)-6,7-dihydroxynon-4-enoate (11)

A sealed tube was charged with allylic alcohols **10** (dr = 1:1, 3.82 g, 13.1 mmol), $MeC(OEt)_3$ (48 mL, 260 mmol), 2-nitrophenol (5.45 g, 39.2 mmol), and toluene (130 mL). The solution was heated to 140 °C and stirred for 6 h at 140 °C. The resulting solution was cooled to r.t., and concentrated. The residue was purified by silica gel column chro-

matography (hexane/EtOAc, 20:1 to 9:1) to give 4.09 g of ethyl ester **20** (87%); yellow oil; R_f = 0.57 (hexane/EtOAc, 3:1); $[\alpha]_D^{22}$ +20.5 (*c* 0.98, $CHCl_3$).

IR (film): 2985, 2935, 2864, 1735, 1370, 1241, 1168, 1095, 1041 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.26 (m, 5 H), 5.84–5.75 (m, 1 H), 5.46 (dd, *J* = 15.5, 8.0 Hz, 1 H), 4.50 (s, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.00 (dd, *J* = 8.0, 8.0 Hz, 1 H), 3.78 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1 H), 3.62 (ddd, *J* = 9.2, 6.9, 5.7 Hz, 1 H), 3.57 (ddd, *J* = 9.2, 6.9, 6.9 Hz, 1 H), 2.41–2.34 (m, 4 H), 1.87 (dddd, *J* = 14.3, 6.9, 6.9, 4.0 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.394 (s, 3 H), 1.390 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.9 (C), 138.5 (C), 134.3 (CH), 128.5 (CH), 128.0 (CH), 127.74 (CH), 127.68 (CH), 108.5 (C), 82.4 (CH), 77.8 (CH), 73.1 (CH_2), 67.1 (CH_2), 60.5 (CH_2), 33.7 (CH_2), 32.1 (CH_2), 27.7 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 14.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{30}O_5Na$: 385.1991; found: 385.1992.

A solution of ethyl ester **20** (4.09 g, 11.3 mmol) and AcOH/H_2O (4:1, 28 mL) was heated to 60 °C, and maintained at 60 °C for 5.5 h. The resulting solution was cooled to r.t., and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1 to 1:2) to give 3.40 g of allylic 1,2-diol **11** (93%); yellow oil; R_f = 0.30 (hexane/EtOAc, 1:1); $[\alpha]_D^{24}$ +1.7 (*c* 1.44, $CHCl_3$).

IR (film): 3435, 2921, 2865, 1732, 1097 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.27 (m, 5 H), 5.79–5.72 (m, 1 H), 5.51 (dd, *J* = 15.5, 6.9 Hz, 1 H), 4.52 (s, 2 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.90 (dd, *J* = 6.9, 6.3, 1.2 Hz, 1 H), 3.70 (ddd, *J* = 9.2, 6.0, 4.9 Hz, 1 H), 3.68–3.63 (m, 2 H), 2.42–2.34 (m, 4 H), 1.80 (dddd, *J* = 14.6, 6.0, 4.6, 3.7 Hz, 1 H), 1.79–1.72 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.1 (C), 137.9 (C), 132.3 (CH), 130.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 75.7 (CH), 73.8 (CH), 73.5 (CH_2), 68.5 (CH_2), 60.5 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 27.7 (CH_2), 14.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}O_5Na$: 345.1678; found: 345.1678.

Ethyl (*E*)-5-{(4*S*,5*S*)-2-Amino-5-[2-(benzyloxy)ethyl]-2-(trichloromethyl)-1,3-dioxolan-4-yl}pent-4-enoate (3)

DBU (470 µL, 3.2 mmol) was added dropwise to a mixture of allylic 1,2-diol **11** (3.40 g, 10.5 mmol), CCl_3CN (1.4 mL, 14 mmol), $ZnCl_2$ (144 mg, 1.05 mmol), and CH_2Cl_2 (110 mL) at 0 °C. The mixture was maintained at 0 °C for 19 h, allowed to warm to r.t., and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 7:1 to 4:1) to give 4.52 g of a diastereomeric mixture of the two orthoamides **3** (92%, dr = 1:1). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250 × 20 mm, UV 254 nm, hexane/EtOAc, 2:1, 10 mL/min, less polar diastereomer: t_R = 13.5 min, polar diastereomer: t_R = 21.1 min).

3 (Less Polar Diastereomer)

Colorless oil; R_f = 0.72 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$ –6.9 (*c* 1.33, $CHCl_3$).

IR (film): 3418, 3341, 2922, 2867, 1733, 1207, 1095, 824 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36–7.26 (m, 5 H), 5.87–5.80 (m, 1 H), 5.52 (dd, *J* = 15.5, 8.3 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.45 (dd, *J* = 8.9, 8.3 Hz, 1 H), 4.28 (ddd, *J* = 8.9, 7.7, 4.3 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.66 (ddd, *J* = 9.5, 6.0, 6.0 Hz, 1 H), 3.61 (ddd, *J* = 9.5, 7.5, 6.0 Hz, 1 H), 2.57 (br s, 2 H), 2.42–2.35 (m, 4 H), 2.02–1.90 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.8 (C), 138.3 (C), 136.1 (CH), 128.5 (CH), 127.80 (CH), 127.76 (CH), 126.8 (CH), 114.5 (C), 103.8 (C), 86.3 (CH), 80.0 (CH), 73.2 (CH_2), 66.5 (CH_2), 60.6 (CH_2), 33.5 (CH_2), 30.9 (CH_2), 27.6 (CH_2), 14.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}Cl_3NO_5Na$: 488.0774; found: 488.0779.

3 (Polar Diastereomer)

Colorless oil; R_f = 0.65 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$ –14.6 (*c* 0.85, $CHCl_3$).

IR (film): 3415, 3336, 2922, 2869, 1733, 1206, 1095, 824 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.26 (m, 5 H), 5.94–5.86 (m, 1 H), 5.56 (dd, *J* = 15.5, 8.3 Hz, 1 H), 4.54 (dd, *J* = 8.9, 8.3 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.26 (ddd, *J* = 8.9, 6.9, 5.2 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.64 (dt, *J* = 9.2, 6.0 Hz, 1 H), 3.60 (dt, *J* = 9.2, 6.6 Hz, 1 H), 2.51 (br s, 2 H), 2.42–2.35 (m, 4 H), 1.98–1.88 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.8 (C), 138.4 (C), 136.3 (CH), 128.6 (CH), 127.76 (CH), 127.72 (CH), 125.4 (CH), 114.6 (C), 103.9 (C), 84.2 (CH), 82.2 (CH), 73.2 (CH_2), 66.4 (CH_2), 60.6 (CH_2), 33.5 (CH_2), 32.4 (CH_2), 27.7 (CH_2), 14.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}Cl_3NO_5Na$: 488.0774; found: 488.0765.

Diethyl (3*S*,4*S*)-3-[(*E*)-4-(Benzyloxy)but-1-en-1-yl]-4-(2,2,2-trichloroacetamido)heptanedioate (4)

A sealed tube was charged with orthoamide **3** (604 mg, 1.29 mmol), BHT (14.3 mg, 64.7 µmol), and *t*-BuPh (43 mL). The solution was heated to 160 °C for 15 d. After cooling to r.t., $MeC(OEt)_3$ (1.2 mL, 6.5 mmol) and BHT (428 mg, 1.94 mmol) were added to the solution of the generated allylic amino alcohol. The solution was then heated to 140 °C for 75 min. After cooling to r.t., the solution was directly purified by silica gel column chromatography (hexane/EtOAc, 9:1) to give 328 mg of trichloroacetamide **4** (47%); colorless oil; R_f = 0.83 (hexane/EtOAc, 1:1); $[\alpha]_D^{25}$ –15.3 (*c* 1.09, $CHCl_3$).

IR (film): 3334, 2981, 2929, 2856, 1732, 1714, 1518, 1176, 821 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.24 (m, 5 H), 6.98 (d, *J* = 9.5 Hz, 1 H), 5.63 (dd, *J* = 15.2, 6.9 Hz, 1 H), 5.36 (ddt, *J* = 15.2, 9.5, 1.2 Hz, 1 H), 4.48 (s, 2 H), 4.15–4.06 (m, 4 H), 3.94–3.86 (m, 1 H), 3.48 (t, *J* = 6.6 Hz, 2 H), 2.78–2.70 (m, 1 H), 2.47 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.39 (dd, *J* = 15.8, 7.7 Hz, 1 H), 2.39–2.25 (m, 4 H), 2.01 (dddd, *J* = 14.6, 7.5, 7.5, 3.2 Hz, 1 H), 1.68 (dddd, *J* = 14.6, 10.9, 7.5, 6.6 Hz, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.4 (C), 172.3 (C), 162.1 (C), 138.4 (C), 131.8 (CH), 129.8 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 92.9 (C), 73.0 (CH_2), 69.6 (CH_2), 60.9 (CH_2), 60.9 (CH_2), 54.2 (CH), 44.0 (CH), 37.2 (CH_2), 33.1 (CH_2), 30.7 (CH_2), 26.5 (CH_2), 14.31 (CH_3), 14.29 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{33}Cl_3NO_6$: 536.1373; found: 536.1373.

(3*S*,4*S*)-3-[(*E*)-4-(Benzyloxy)but-1-en-1-yl]-4-(2,2,2-trichloroacetamido)heptanedioic Acid (14)

$Ba(OH)_2{\cdot}8H_2O$ (3.28 g, 10.4 mmol) was added to a solution of trichloroacetamide **4** (558 mg, 1.04 mmol) in MeOH/H_2O (2:1, 52 mL) at 0 °C. The solution was allowed to warm to r.t., maintained for 1.5 h at r.t., quenched with 4 M aq HCl (5.2 mL), and extracted with $CHCl_3$ (6 × 10 mL). The combined organic extracts were washed with brine (7 mL), dried (Na_2SO_4), and concentrated. The residue was purified by

silica gel column chromatography (hexane/EtOAc, 3:2 to 2:3) to give 417 mg of bis(acid) **14** (83%), colorless crystals; mp 102.0–103.5 °C; R_f = 0.19 (EtOAc); $[\alpha]_D^{26}$ –16.0 (*c* 1.62, $CHCl_3$).

IR (film): 3298, 2931, 1707, 1521, 821 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.25 (m, 5 H), 6.93 (d, *J* = 9.5 Hz, 1 H), 5.66 (dd, *J* = 15.5, 6.9 Hz, 1 H), 5.35 (dd, *J* = 15.5, 9.5 Hz, 1 H), 4.49 (s, 2 H), 4.05–3.96 (m, 1 H), 3.51 (dt, *J* = 9.5, 6.3 Hz, 1 H), 3.49 (dt, *J* = 9.5, 6.6 Hz, 1 H), 2.80–2.72 (m, 1 H), 2.54 (dd, *J* = 16.0, 6.6 Hz, 1 H), 2.44 (dd, *J* = 16.0, 7.2 Hz, 1 H), 2.42–2.30 (m, 4 H), 2.01 (dddd, *J* = 14.6, 7.5, 7.2, 2.9 Hz, 1 H), 1.61 (ddt, *J* = 14.6, 11.2, 6.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 178.9 (C), 177.8 (C), 162.2 (C), 138.2 (C), 132.4 (CH), 129.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 92.8 (C), 73.0 (CH_2), 69.4 (CH_2), 53.6 (CH), 43.6 (CH), 36.9 (CH_2), 33.1 (CH_2), 30.3 (CH_2), 26.0 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}Cl_3NO_6Na$: 502.0567; found: 502.0558.

(*S*)-5-{(2*S*,3*R*)-2-[(*R*)-3-(Benzyloxy)-1-iodopropyl]-5-oxotetrahydrofuran-3-yl}pyrrolidin-2-one (5)

I_2 (1.25 g, 4.91 mmol) was added to a mixture of bis(acid) **14** (787 mg, 1.64 mmol), $NaHCO_3$ (619 mg, 7.37 mmol), and THF/H_2O (1:1, 55 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C, quenched with 20% aq $Na_2S_2O_3$ (5.5 mL) and 1 M aq HCl (5.5 mL), and extracted with $CHCl_3$ (6 × 15 mL). The combined organic extracts were washed with brine (8 mL), dried (Na_2SO_4), and concentrated. The residue was filtered through a pad of silica gel, washed with hexane/EtOAc (1:1, 400 mL), and concentrated to give iodolactone **15**, which was immediately used in the next reaction without further purification.

EDCI·HCl (859 mg, 4.48 mmol) was added to a solution of iodolactone **15**, DMAP (547 mg, 4.48 mmol), and THF (150 mL) at r.t. The solution was maintained for 16.5 h at r.t. and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give 436 mg of γ-lactam **5** (60% over 2 steps); colorless crystals; mp 124.0–125.0 °C; R_f = 0.22 (EtOAc); $[\alpha]_D^{25}$ +5.1 (*c* 0.91, $CHCl_3$).

IR (film): 3223, 2925, 2865, 1781, 1694, 1176, 1098, 748 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.72–7.40 (m, 1 H), 7.37–7.27 (m, 5 H), 4.50 (s, 2 H), 4.42 (ddd, *J* = 10.3, 6.3, 4.0 Hz, 1 H), 4.27 (dd, *J* = 6.0, 2.9 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.69 (ddd, *J* = 9.5, 5.2, 4.0 Hz, 1 H), 3.60 (ddd, *J* = 9.5, 9.2, 4.0 Hz, 1 H), 2.82 (dd, *J* = 18.6, 10.0 Hz, 1 H), 2.69–2.62 (m, 1 H), 2.38 (dd, *J* = 18.6, 3.4 Hz, 1 H), 2.40–2.25 (m, 2 H), 2.24–2.13 (m, 2 H), 1.84 (dddd, *J* = 14.6, 10.3, 4.0, 4.0 Hz, 1 H), 1.78–1.68 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 179.4 (C), 175.0 (C), 137.9 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 83.8 (CH), 73.5 (CH_2), 69.1 (CH_2), 56.4 (CH), 43.7 (CH), 35.6 (CH), 35.3 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 24.3 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}INO_4$: 444.0672; found: 444.0674.

(*S*)-5-{(2*R*,3*R*)-2-[3-(Benzyloxy)propyl]-5-oxotetrahydrofuran-3-yl}pyrrolidin-2-one (16)

DBU (32 µL, 210 µmol) was added dropwise to a solution of γ-lactam **5** (62.7 mg, 141 µmol) and THF (4.8 mL) at 0 °C. This solution was allowed to warm to r.t., and maintained for 12.5 h at r.t., and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give 32.7 mg of alkene **21** (73%); colorless oil; R_f = 0.56 (EtOAc/MeOH, 9:1); $[\alpha]_D^{25}$ +41.8 (*c* 1.43, $CHCl_3$).

IR (film): 3225, 2921, 2857, 1778, 1694, 1204, 1173, 1113, 974 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (br s, 1 H), 7.37–7.27 (m, 5 H), 5.98 (dt, *J* = 15.5, 4.9 Hz, 1 H), 5.77 (ddtd, *J* = 15.5, 7.2, 1.4, 1.4 Hz, 1 H), 4.70 (dd, *J* = 7.2, 7.2 Hz, 1 H), 4.53 (s, 2 H), 4.06 (dd, *J* = 4.9, 1.4 Hz, 2 H), 3.80–3.74 (m, 1 H), 2.64 (dd, *J* = 17.5, 8.6 Hz, 1 H), 2.47 (dd, *J* = 17.5, 8.6 Hz, 1 H), 2.42–2.35 (m, 1 H), 2.34 (dd, *J* = 8.6, 7.5 Hz, 2 H), 2.25 (dtd, *J* = 12.6, 7.5, 7.5 Hz, 1 H), 1.77–1.68 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 179.3 (C), 175.1 (C), 138.0 (C), 132.4 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 81.9 (CH), 72.8 (CH_2), 69.3 (CH_2), 54.6 (CH), 47.0 (CH), 30.3 (CH_2), 30.2 (CH_2), 25.5 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{22}NO_4$: 316.1549; found: 316.1548.

Rh/Al_2O_3 (5%, 103 mg, 50 wt%) was added to a solution of alkene **21** (206 mg, 653 µmol) and THF (22 mL) at r.t. The mixture was stirred under H_2 atmosphere (1 atm) at r.t. for 1 d, filtered through a pad of Celite, washed with EtOAc (20 mL), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 1:0 to 9:1) to give 204 mg of benzyl ether **16** (99%); colorless oil; R_f = 0.56 (EtOAc/MeOH, 9:1); $[\alpha]_D^{23}$ +20.1 (*c* 1.17, $CHCl_3$).

IR (film): 3236, 2928, 2859, 1771, 1694, 1206, 1175, 1101 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.26 (m, 6 H), 4.49 (s, 2 H), 4.29 (ddd, *J* = 7.7, 5.4, 3.7 Hz, 1 H), 3.76–3.71 (m, 1 H), 3.54 (ddd, *J* = 10.3, 9.2, 4.9 Hz, 1 H), 3.49 (ddd, *J* = 9.2, 6.3, 4.6 Hz, 1 H), 2.66 (dd, *J* = 17.8, 9.2 Hz, 1 H), 2.42 (dd, *J* = 17.8, 6.9 Hz, 1 H), 2.33 (dd, *J* = 9.2, 6.9 Hz, 2 H), 2.34–2.27 (m, 1 H), 2.23 (ddt, *J* = 12.9, 7.7, 6.9 Hz, 1 H), 1.88–1.65 (m, 5 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 179.1 (C), 175.5 (C), 138.4 (C), 128.5 (CH), 127.84 (CH), 127.80 (CH), 81.9 (CH), 73.1 (CH_2), 69.5 (CH_2), 55.4 (CH), 45.7 (CH), 32.2 (CH_2), 30.6 (CH_2), 30.2 (CH_2), 25.7 (CH_2), 25.3 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{24}NO_4$: 318.1705; found: 318.1706.

(*S*)-5-[(2*R*,3*R*)-2-(3-Bromopropyl)-5-oxotetrahydrofuran-3-yl]pyrrolidin-2-one (17)

Pd/C (10%, 112 mg, 100 wt%) was added to a solution of benzyl ether **16** (112 mg, 353 µmol) and EtOH (12 mL) at r.t. The mixture was stirred under H_2 atmosphere (1 atm) at r.t. for 18.5 h, filtered through a pad of Celite, washed with EtOH (15 mL), and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$ to EtOH) to give 79.7 mg of alcohol **22** (99%); colorless crystals; mp 107.0–108.0 °C; R_f = 0.14 (EtOAc/MeOH, 4:1); $[\alpha]_D^{26}$ +53.6 (*c* 1.16, MeOH).

IR (film): 3307, 2932, 2877, 1767, 1683, 1205 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 4.39 (ddd, *J* = 8.3, 5.7, 3.7 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.62 (dt, *J* = 10.9, 6.0 Hz, 1 H), 3.60 (dt, *J* = 10.9, 6.0 Hz, 1 H), 2.73 (dd, *J* = 17.2, 8.6 Hz, 1 H), 2.47 (dd, *J* = 17.2, 7.2 Hz, 1 H), 2.43 (dddd, *J* = 12.9, 8.6, 7.2, 5.7 Hz, 1 H), 2.37–2.27 (m, 3 H), 1.88–1.59 (m, 5 H).

^{13}C NMR (CD_3OD, 125 MHz): δ = 181.3 (C), 178.3 (C), 83.9 (CH), 62.3 (CH_2), 56.7 (CH), 46.7 (CH), 32.6 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 26.0 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}NO_4Na$: 250.1055; found: 250.1059.

PPh_3 (112 mg, 426 µmol) was added to a solution of alcohol **22** (64.5 mg, 284 µmol), CBr_4 (282 mg, 851 µmol), and CH_2Cl_2 (9.5 mL) at 0 °C. The solution was allowed to warm to r.t., maintained for 10 h at r.t., and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 19:1) to give 75.6 mg of bromide **17** (92%); colorless oil; R_f = 0.41 (EtOAc/MeOH, 9:1); $[\alpha]_D^{26}$ +24.5 (*c* 1.19, $CHCl_3$).

IR (film): 3225, 2928, 1771, 1694, 1259, 1201, 1181 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 6.69 (br s, 1 H), 4.28 (ddd, *J* = 9.2, 6.0, 3.4 Hz, 1 H), 3.84–3.79 (m, 1 H), 3.50 (ddd, *J* = 10.0, 7.5, 5.2 Hz, 1 H), 3.46 (ddd, *J* = 10.0, 6.9, 5.4 Hz, 1 H), 2.70 (dd, *J* = 17.8, 9.2 Hz, 1 H), 2.44 (dd, *J* = 17.8, 7.5 Hz, 1 H), 2.41–2.29 (m, 4 H), 2.16–2.07 (m, 1 H), 2.04–1.91 (m, 2 H), 1.81–1.73 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 179.3 (C), 175.3 (C), 81.1 (CH), 55.3 (CH), 45.9 (CH), 33.7 (CH_2), 33.3 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 25.3 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}BrNO_3Na$: 312.0211; found: 312.0215.

(3a*R*,10a*S*,10b*R*)-Octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(1*H*)-dione (18)[3b]

NaH (63% in oil, 14 mg, 360 µmol) was added to a solution of bromide **17** (35.1 mg, 121 µmol), TBAI (4.5 mg, 12.1 µmol) and DMF (12 mL) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C, quenched with 1 M aq HCl (1.5 mL), and stirred for 14 h. The reaction mixture was extracted with EtOAc (6 × 2 mL). The combined organic extracts were washed with brine (2 × 2 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 1:0 to 19:1) to give 18.5 mg of azepane **18** (73%); colorless oil; R_f = 0.42 (EtOAc/MeOH, 4:1); $[\alpha]_D^{24}$ –143.2 (*c* 1.07, $CHCl_3$).

IR (film): 2935, 1775, 1676, 1420, 1185, 1015 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 4.29 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1 H), 4.15 (ddd, *J* = 13.8, 2.3, 2.3 Hz, 1 H), 3.99 (ddd, *J* = 10.6, 6.9, 6.3 Hz, 1 H), 2.85 (dddd, *J* = 12.6, 10.3, 8.9, 6.9 Hz, 1 H), 2.71–2.64 (m, 1 H), 2.65 (dd, *J* = 17.5, 8.9 Hz, 1 H), 2.61 (dd, *J* = 17.5, 12.6 Hz, 1 H), 2.45–2.36 (m, 3 H), 2.07 (dddd, *J* = 12.3, 6.3, 5.7, 3.4 Hz, 1 H), 1.91–1.82 (m, 1 H), 1.71 (dddd, *J* = 12.3, 10.6, 10.6, 10.6 Hz, 1 H), 1.62–1.51 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 174.8 (C), 174.2 (C), 79.9 (CH), 56.2 (CH), 45.0 (CH), 40.3 (CH_2), 34.8 (CH_2), 31.1 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 22.8 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}NO_3$: 210.1130; found: 210.1131.

(–)-Stemoamide (1)

n-BuLi (1.4 M in hexane, 190 µL, 270 µmol) was added to a solution of $(TMS)_2NH$ (65 µL, 270 µmol) and THF (1.0 mL) at –78 °C. The solution was maintained for 15 min at –78 °C. A solution of azepane **18** (16.0 mg, 76.5 µmol) in THF (500 µL) was then added dropwise to the solution of $LiN(TMS)_2$ via cannula at –78 °C. The resulting solution was allowed to warm to –40 °C, stirred for 1 h at –40 °C, cooled to –78 °C, and stirred for 1 h. MeI (5.9 µL, 120 µmol) was then added dropwise to the solution at –78 °C. After stirring for 15 min at –78 °C, the solution was allowed to warm to r.t., and maintained for 13.5 h at r.t. The solution was quenched with sat. aq NH_4Cl (1.0 mL) and 20% aq $Na_2S_2O_3$ (1.0 mL), and extracted with EtOAc (4 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 1:0 to 9:1) to give 8.9 mg of (–)-stemoamide (**1**) (52%); colorless crystals; mp 184.0–185.0 °C (Lit.[3k] mp 184–185 °C); R_f = 0.52 (EtOAc/MeOH, 4:1); $[\alpha]_D^{21}$ –180.7 (*c* 0.89, MeOH) {Lit.[3a] $[\alpha]_D^{26}$ –181 (*c* 0.89, MeOH)}.

IR (film): 2938, 1765, 1685, 1422, 1192, 1009 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 4.20 (ddd, *J* = 10.3, 10.3, 3.2 Hz, 1 H), 4.19–4.13 (m, 1 H), 3.99 (ddd, *J* = 10.9, 6.4, 6.4 Hz, 1 H), 2.69–2.62 (m, 1 H), 2.60 (dq, *J* = 12.3, 6.9 Hz, 1 H), 2.45–2.36 (m, 4 H), 2.08–2.02 (m, 1 H), 1.91–1.81 (m, 1 H), 1.71 (dddd, *J* = 11.7, 10.9, 10.9, 10.9 Hz, 1 H), 1.59–1.47 (m, 2 H), 1.31 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.5 (C), 174.2 (C), 77.8 (CH), 56.0 (CH), 52.8 (CH), 40.4 (CH_2), 37.5 (CH), 34.9 (CH_2), 30.8 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}NO_3$: 224.1287; found: 224.1291.

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Supporting Information

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References

(1) For reviews, see: (a) Pilli, R. A.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117. (b) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421. (c) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908.

(2) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

(3) For total syntheses of stemoamide, see: (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (b) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063. (c) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (d) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (e) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (f) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (g) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211. (h) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287. (i) Torssell, S.; Wanngren, E.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 4246. (j) Bates, R. W.; Sridhar, S. *Synlett* **2009**, 1979. (k) Honda, T.; Matsukawa, T.; Takahashi, K. *Org. Biomol. Chem.* **2011**, *9*, 673. (l) Wang, Y.; Zhu, L.; Zhang, Y.; Hong, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 2787. (m) Mi, X.; Wang, Y.; Zhu, L.; Wang, R.; Hong, R. *Synthesis* **2012**, *44*, 3432. (n) Li, Z.; Zhang, L.; Qiu, F. G. *Asian J. Org. Chem.* **2014**, *3*, 52.

(4) For formal total syntheses of stemoamide, see: (a) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295. (b) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 349. (c) Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528. (d) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2006**, 2664. (e) Chavan, S. P.; Harale, K. R.; Puranik, V. G.; Gawade, R. L. *Tetrahedron Lett.* **2012**, *53*, 2647. (f) Muñoz-Bascón, J.; Hernández-Cervantes, C.; Padial, N. M.; Álvarez-Corral, M.; Rosales, A.; Rodríguez-García, I.; Oltra, J. E. *Chem. Eur. J.* **2014**, *20*, 801. (g) Brito, G. A.; Sarotti, A. M.; Wipf, P.; Pilli, R. A. *Tetrahedron Lett.* **2015**, *56*, 6664.

(5) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. For reviews on the Overman rearrangement, see: (b) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Vol. 66; Overman, L. E., Ed.; Wiley: New York, **2005**, 1–107.

(6) For selected recent reviews on the Claisen rearrangement, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597. (c) Majumdar, K. C.; Nandi, R. K. *Tetrahedron* **2013**, *69*, 6921. (d) Fernandes, R. A.; Chowdhury, A. K.; Kattanguru, P. *Eur. J. Org. Chem.* **2014**, 2833.

(7) For selected recent reviews on cascade, tandem, and domino reactions including a sigmatropic rearrangement, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (c) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (d) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092. (e) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133.

(8) For the Overman rearrangement of allylic 1,2-diols, see: (a) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1376. (b) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687. (c) Hama, N.; Aoki, T.; Miwa, S.; Yamazaki, M.; Sato, T.; Chida, N. *Org. Lett.* **2011**, *13*, 616. (d) Nakayama, Y.; Sekiya, R.; Oishi, H.; Hama, N.; Yamazaki, M.; Sato, T.; Chida, N. *Chem. Eur. J.* **2013**, *19*, 12052. (e) Tsuzaki, S.; Usui, S.; Oishi, H.; Yasushima, D.; Fukuyasu, T.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 1704. For pioneering works on the orthoamide-type Overman rearrangement of allylic 1,2-diols, see: (f) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037. (g) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

(9) We reported the cascade-type Claisen rearrangement of allylic 1,2-diols in the total synthesis of (–)-morphine, see: (a) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358. (b) Ichiki, M.; Tanimoto, H.; Miwa, S.; Saito, R.; Sato, T.; Chida, N. *Chem. Eur. J.* **2013**, *19*, 264. We also documented the development of the orthoamide-type Claisen rearrangement and the application to the total synthesis of (–)-kainic acid, see: (c) Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756. (d) Kitamoto, K.; Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya, N.; Sato, T.; Chida, N. *Eur. J. Org. Chem.* **2012**, 4217.

(10) For selected examples of sequential reactions including sigmatropic rearrangements, see: (a) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281. (b) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (c) Raucher, S.; Burks, J. E. Jr.; Hwang, K.-J.; Svedberg, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 1853. (d) Mikami, K.; Taya, S.; Nakai, T.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 5447. (e) Mulzer, V. J.; Bock, H.; Eck, W.; Buschmann, J.; Luger, P. *Angew. Chem., Int. Ed. Eng.* **1991**, *30*, 414. (f) Posner, G. H.; Carry, J.-C.; Crouch, R. D.; Johnson, N. *J. Org. Chem.* **1991**, *56*, 6987. (g) Villemin, D.; Hachemi, M. *Synth. Commun.* **1996**, *26*, 1329. (h) Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 3289. (i) Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863. (j) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371. (k) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067. (l) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569. (m) Pelc, M. J.; Zakarian, A. *Org. Lett.* **2005**, *7*, 1629. (n) Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, *9*, 3837. (o) Ilardi, E. A.; Isaacman, M. J.; Qin, Y.-C.; Shelly, S. A.; Zakarian, A. *Tetrahedron* **2009**, *65*, 3261.

(11) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

(12) (a) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977. (b) Tanimoto, H.; Kato, T.; Chida, N. *Tetrahedron Lett.* **2007**, *48*, 6267. (c) Kato, T.; Tanimoto, H.; Yamada, H.; Chida, N. *Heterocycles* **2010**, *82*, 563. (d) Ammenn, J.; Altmann, K.-H.; Belluš, D. *Helv. Chim. Acta* **1997**, *80*, 1589.

(13) Ammenn, J.; Altmann, K.-H.; Belluš, D. *Helv. Chim. Acta* **1997**, *80*, 1589.

(14) For selected reviews on chirality transfer through sigmatropic rearrangement, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (b) Nubbemeyer, U. *Synthesis* **2003**, 961.