# A Robust Route towards Functionalized Pyrrolizidines as Precursors for *Daphniphyllum* Alkaloids

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*Received: 05.11.2013; Accepted after revision: 03.01.2014*

**Abstract:** A diastereoselective Fráter–Seebach-type alkylation provides access to a highly functionalized pyrrolizidine, which could serve as a key building block for the total synthesis of *Daphniphyllum* alkaloids, such as oldhamine A.

**Key words:** *Daphniphyllum* alkaloids, pyrrolizidines, heterocycles, asymmetric synthesis, oldhamine A

*Daphniphyllum* alkaloids are attractive synthetic targets due to their architectural beauty and structural diversity. To date, more than a dozen different skeletal types have been identified, three of which are shown in Figure 1. (–)-Daphnezomine A (**1**) is the eponymous representative of the daphnezomine alkaloids and incorporates an aza-adamantane core in its polycyclic ring system. (–)-Daphlongeramine A (**2**), which is a paxdaphnine A-type alkaloid, features a furan moiety, which is connected to a highly fused core structure.[1] Another striking molecule is (+)-oldhamine A (**3**), a member of the daphnicyclidin-type alkaloids. The natural product was isolated in 2008 by Tan and coworkers from *Daphniphyllum oldhamii*, a dioecious evergreen tree native to the southeast of China. Its structure was elucidated by NMR spectroscopy as well as X-ray crystallography.[2] Oldhamine A features six fused rings, five stereogenic centers, one of which is quaternary, and a cyclopentadienide anion that forms an internal salt with an ammonium moiety present in a pyrrolizidine substructure in **3**. Herein we present an efficient and scalable synthesis of a highly functionalized pyrrolizidine that could serve as a synthetic precursor of **3**.

For economic reasons, we decided to aim for (–)-*ent*-oldhamine A (*ent*-**3**), the enantiomer of the natural product. Our retrosynthetic analysis of *ent*-**3** is shown in Scheme 1. Our plan was to install the quaternary stereocenter in *ent*-**3** with a stereoselective addition of a methyl cuprate to the fulvene system in precursor **4**, followed by intramolecular acylation of the resulting cyclopentadienide. Fulvene **4** can be further simplified retrosynthetically to pyrrolizidine **5**. Thus, we needed to develop a reliable strategy to access **5** and ultimately settled on L-pyroglutamic acid (**6**) or L-glutamic acid (**7**) as starting material.

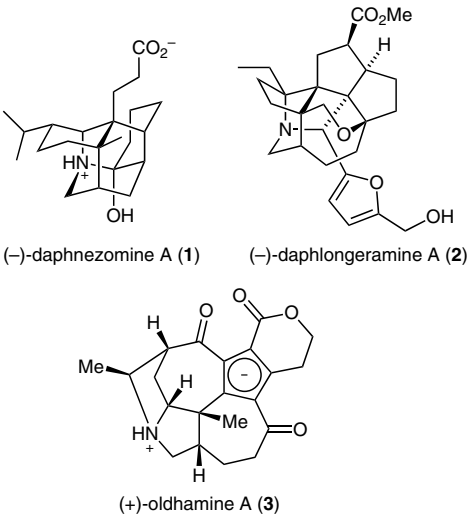
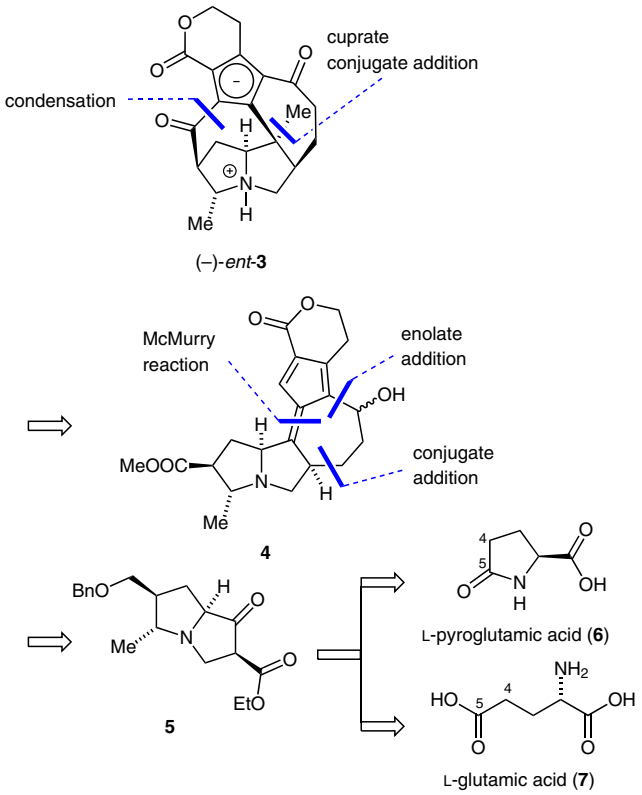


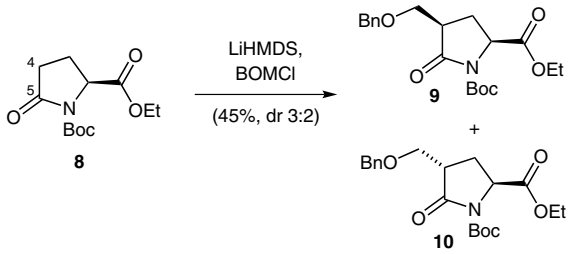

**Figure 1** A selection of norterpenoid alkaloids from the species *Daphniphyllum*




**Scheme 1** Retrosynthetic analysis of *ent*-**3**

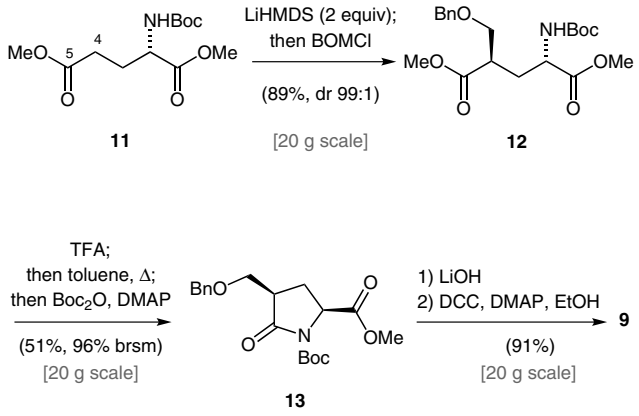
*SYNLETT* 2014, 25, 0741–0745
Advanced online publication: 13.02.2014
DOI: 10.1055/s-0033-1340677; Art ID: ST-2013-B1030-L

In the forward direction, we initially attempted to synthesize **5** from L-pyroglutamic acid (**6**). To this end, *N*-Boc pyrrolidinone **8**, which is readily available from **6**,[3] was treated with LiHMDS and benzyloxymethyl chloride (Scheme 2). However, the desired product was only obtained in a moderate yield of 27% and as a mixture with the undesired diastereomer and other side products, such as products of double alkylation.[4]



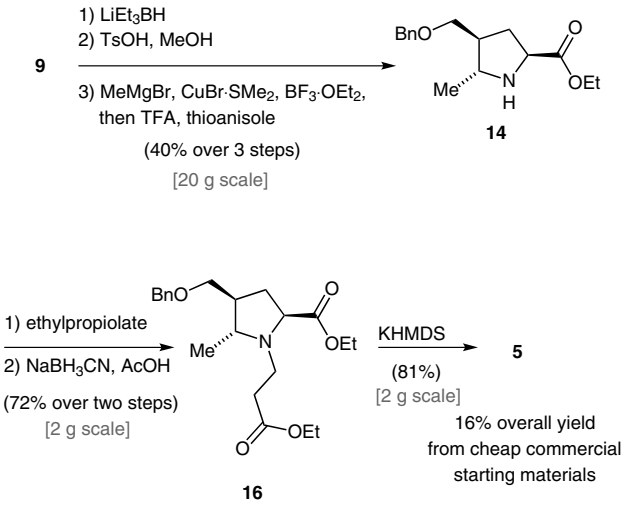

**Scheme 2** Synthesis of benzyl ether **9** starting from L-pyroglutamic acid derivative **8**[4]

Since such a poor yield and diastereoselectivity at the beginning of a synthetic route was unacceptable, we next investigated the alkylation of an acyclic precursor,[5] following a precedent provided by Hanessian (Scheme 3).[6] Treatment of glutamate **11** with two equivalents of LiHMDS and subsequent addition of BOMCl resulted in a clean and high-yielding transformation into benzyl ether **12**. No formation of the diastereomer was observed in this Fráter–Seebach-type alkylation. In order to convert diester **12** into the corresponding lactam, it was successively treated with TFA for N-deprotection, heated for two days in toluene and finally protected again as the *N*-Boc lactam. Compound **13** was then converted into ethyl ester **9** by saponification of the methyl ester with LiOH followed by esterification of the resulting material with ethanol in the presence of DCC and DMAP. This transesterification was necessary since the Fráter–Seebach alkylation did only proceed in good selectivity with the methyl ester present in **11**, but subsequent reactions failed if the methyl ester was retained.




**Scheme 3** Synthesis of benzyl ether **9**, starting from L-glutamic acid derivative **11**

Next, lactam **9** was reduced using Super-Hydride® and the resulting hemiaminal was converted into the methylated *N*,*O*-acetal using toluenesulfonic acid in methanol (Scheme 4).[4] A subsequent cuprate addition to the iminium ion generated in situ by treatment with boron trifluoride diethyl etherate followed by exposure of the resulting product to TFA in the presence of thioanisole furnished amine **14** in good overall yield. A small sample of **14** was hydrolyzed to give the corresponding amino acid **15** as a crystalline material, which could be characterized by X-ray crystallography, confirming the relative stereochemistry (Figure 2).




**Scheme 4** Synthesis of the pyrrolizidine portion **5** present in *ent*-**3**

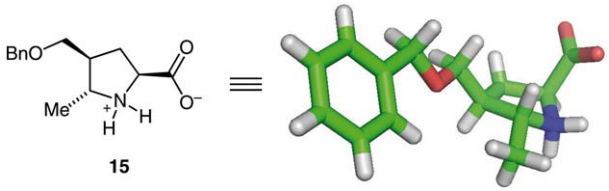



**Figure 2** Chemical structure and crystal structure of amino acid **15**

Attempts to further functionalize **14** via a conjugate addition to various acrylates were unsuccessful, presumably due to the high sterical hindrance of the secondary amine. However, when ethyl propiolate was used, the reaction took place instantaneously, forming a vinylogous carbamate in an almost quantitative yield. Without further purification, this compound was reduced with sodium cyanoborohydride in the presence of acetic acid to give the tertiary amine **16** in good overall yield. Finally, KHMDS was found to be the best base to initiate a Claisen–Dieckmann condensation, which afforded the desired pyrrolizidine **5** as a single diastereomer. The configuration of the newly generated stereogenic center was established by NOE experiments (see Supporting Information).

In summary, we have developed a scalable route for a key building block in the synthesis of pyrrolizidine-containing

*Daphniphyllum* alkaloids. Our route yields multigram quantities of **5**, proceeds over 13 steps, and requires only six chromatographic purifications. The usefulness of Fráter–Seebach alkylations for the synthesis of 2,4-*anti*-substituted glutamate derivatives has been confirmed. Our building block could not only prove useful for a total synthesis of oldhamine A but also for other *Daphniphyllum* alkaloids, such as the enantiomer of (–)-daphnipaxinin.

(*S*)-1-*tert*-Butyl ethyl 5-oxopyrrolidine-1,2-dicarboxylate (**8**) and (*S*)-dimethyl 2-(*tert*-butoxycarbonylamino)pentanedioate (**11**) were prepared according to literature procedures.[5,3]

**(2*S*,4*R*)-1-*tert*-Butyl 2-Ethyl 4-(Benzyloxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate (9) from 8[4]**

To a solution of HMDS (56.3 mL, 256 mmol, 1.30 equiv) in THF (88.0 mL) was added a solution of *n*-BuLi (2.50 M in hexanes, 95.6 mL, 241 mmol, 1.20 equiv) dropwise at 0 °C. After complete addition, the mixture was allowed to warm to r.t. and stirred for another 30 min at this temperature. The resulting LiHMDS solution was cooled to –78 °C and to this solution was added dropwise a solution of **8** (51.7 g, 201 mmol, 1.00 equiv) in THF (200 mL) over the course of 20 min. Then, HMPA (45.4 mL, 261 mmol, 1.30 equiv) was added over the course of 5 min, and the mixture was stirred for 1 h at –78 °C. The resulting mixture was cannulated to a cooled solution of benzyloxymethyl chloride (55.7 mL, 402 mmol, 2.00 equiv) in THF (100 mL) at –78 °C over the course of 25 min and stirred for 1 h at this temperature. The reaction was quenched with a 1:1 mixture of $H_2O$ and a sat. aq $NH_4Cl$ solution (35.0 mL) and after warming to r.t., the bulk of the solvent was removed in vacuo. The residue was diluted with $Et_2O$ (1000 mL) and successively washed with a sat. aq $NaHCO_3$ solution (800 mL) and brine (800 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica, EtOAc–hexanes = 1:10 → 1:2) to give **9** as a colorless oil (20.8 g, 27%) and **10** as a colorless oil (13.6 g, 18%).

**Compound 9**

$R_f$ = 0.34 (EtOAc–hexanes, 1:2). $^1$H NMR (300 MHz, $CHCl_3$): δ = 7.40–7.26 (m, 5 H), 4.65–4.42 (m, 3 H), 4.23–4.10 (m, 2 H), 3.76 (dd, *J* = 9.4, 4.2 Hz, 1 H), 3.66 (dd, *J* = 9.4, 7.3 Hz, 1 H), 2.99–2.79 (m, 1 H), 2.67–2.43 (m, 1 H), 2.16–1.96 (m, 1 H), 1.49 (s, 9 H), 1.24 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (75 MHz, $CHCl_3$): δ = 173.0, 171.3, 149.3, 137.8, 128.6, 128.4 (2 C), 127.7 (2 C), 83.6, 73.3, 69.1, 61.5, 57.6, 43.6, 27.9 (3 C), 25.0, 14.1. IR: 2981, 1791, 1748, 1719, 1369, 1318, 1153 cm$^{-1}$. $[\alpha]_D^{18}$ –47.6 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{20}H_{27}NNaO_6$: 400.1736 $[M + Na]^+$; found: 400.1731.

**Compound 10**

$R_f$ = 0.38 (EtOAc–hexanes, 1:2). $^1$H NMR (300 MHz, $CHCl_3$): δ = 7.36–7.25 (m, 5 H), 4.58–4.44 (m, 3 H), 4.25–4.15 (m, 2 H), 3.71 (ddd, *J* = 13.1, 9.5, 4.6 Hz, 2 H), 2.87 (dddd, *J* = 10.5, 9.1, 5.5, 3.7 Hz, 1 H), 2.35 (ddd, *J* = 13.3, 10.5, 9.9 Hz, 1 H), 2.20–2.12 (m, 1 H), 1.48 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (150 MHz, $CHCl_3$): δ = 173.0, 171.4, 149.3, 137.8, 128.4, 127.7 (2 C), 127.6 (2 C), 83.5, 73.4, 68.4, 61.6, 57.4, 42.8, 27.9 (3 C), 25.6, 14.2. IR: 2980, 1791, 1748, 1719, 1369, 1154 cm$^{-1}$. $[\alpha]_D^{18}$ –34.9 (*c* 1.0, MeOH). ESI-HRMS: m/z calcd for $C_{20}H_{27}NNaO_6$: 400.1736 $[M + Na]^+$; found: 400.1729.

**(2*R*,4*S*)-Dimethyl 2-(Benzyloxymethyl)-4-(*tert*-butoxycarbonylamino)pentanedioate (12)**

To a solution of HMDS (36.4 mL, 171 mmol, 2.31 equiv) in THF (30.4 mL) was added a solution of *n*-BuLi (2.50 M in hexanes, 62.2 mL, 156 mmol, 2.10 equiv) dropwise at 0 °C. After complete addition, the mixture was allowed to warm to r.t. and stirred for another 30 min at this temperature. The resulting LiHMDS solution was cooled to –78 °C and to this solution was added dropwise a solution of **11** (20.4 g, 74.1 mmol, 1.00 equiv) in THF (200 mL) over the course of 20 min. After being stirred for 30 min at this temperature, a solution of BOMCl (20.5 mL, 148 mmol, 2.00 equiv) in THF (200 mL) was added dropwise over the course of 20 min to be stirred for additional 3 h at –78 °C. The reaction mixture was quenched with an aq 1.00 M HCl solution (100 mL), and the bulk of solvent was removed in vacuo. The residue was redissolved in $Et_2O$ (500 mL) and washed with a sat. aq $NaHCO_3$ solution (500 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica, EtOAc–hexanes = 1:10 → 1:2) to give **12** as a colorless oil (26.1 g, 89%). $R_f$ = 0.38 (EtOAc–hexanes = 1:3). $^1$H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 7.39–7.23 (m, 5 H), 5.13 (br s, 0.5 H) 4.70 (s, 2 H), 4.55–4.50 (m, 1 H), 4.35 (br s, 0.5 H), 3.76–3.63 (m, 6.5 H), 2.88–2.75 (m, 0.5 H), 2.52–2.29 (m, 1 H), 2.24–1.92 (m, 3 H), 1.46 (s, 4.5 H), 1.45 (s, 4.5 H). $^{13}$C NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ = 174.1, 173.2, 172.7, 172.6, 155.4, 155.4, 141.0, 137.9, 128.5 (2 C), 128.2 (2 C), 127.9, 127.8, 127.7 (2 C), 127.6 (2 C), 127.5, 127.0, 80.1, 80.0, 73.1, 70.1, 65.3, 52.4, 52.3, 52.1, 52.0, 51.8, 42.6, 31.1, 30.1, 28.3, 28.2 (3 C), 27.8 (3 C). IR: 3370, 2978, 1731, 1712, 1512, 1366, 1160 cm$^{-1}$. $[\alpha]_D^{19}$ –39.6 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{20}H_{29}NNaO_7$: 418.1842 $[M + Na]^+$; found: 418.1835.

**(2*R*,4*R*)-1-*tert*-Butyl 2-Methyl 4-(Benzyloxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate (13)**

A mixture of **12** (17.9 g, 45.4 mmol, 1.00 equiv), $CH_2Cl_2$ (50.0 mL) and TFA (46.0 mL) was stirred for 1 h at r.t. After removal of the solvent in vacuo, the residue was diluted with a sat. aq $Na_2CO_3$ solution (30.0 mL) and a sat. aq $NaHCO_3$ solution (270 mL) and subsequently extracted with $Et_2O$ (5 × 350 mL). The combined extracts were washed with brine (500 mL), dried over $MgSO_4$, and concentrated. The resulting residue was dissolved in toluene (150 mL) and heated to reflux for 48 h. The mixture was allowed to cool to r.t. and concentrated to give a brown oil. To a solution of this residual oil in $CH_2Cl_2$ (60.0 mL) was added DMAP (6.65 g, 54.4 mmol, 1.20 equiv), $Boc_2O$ (10.9 g, 49.9 mmol, 1.10 equiv), and $Et_3N$ (6.94 mL, 49.9 mmol, 1.10 equiv) to be stirred for 16 h at r.t. The reaction mixture was diluted with $Et_2O$ (350 mL), washed with an aq 1.00 M HCl solution (350 mL), a sat. aq $NaHCO_3$ solution (350 mL) and brine (250 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc–hexanes = 1:5 → 1:2) to give **13** as a colorless oil (8.46 g, 51%) along with recovered starting material (**12**, 7.71 g, 45%). $R_f$ = 0.25 (EtOAc–hexanes = 1:3). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.09 (m, 5 H), 4.52 (td, *J* = 9.1, 6.2 Hz, 1 H), 4.45 (d, *J* = 3.4 Hz, 2 H), 3.79–3.56 (m, 5 H), 2.90–2.77 (m, 1 H), 2.49 (dt, *J* = 13.6, 9.5 Hz, 1 H), 2.05 (dt, *J* = 13.4, 6.7 Hz, 1 H), 1.46 (s, 9 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 173.0 171.7, 149.2, 137.8, 128.4 (2 C), 127.7 (2 C), 127.6, 83.6, 73.3, 69.0, 57.5, 52.3, 43.6, 27.8 (3 C), 25.0. IR: 1727, 1181 cm$^{-1}$. $[\alpha]_D^{18}$ –42.2 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{19}H_{25}NNaO_6$: 386.1580 $[M + Na]^+$; found: 386.1575.

**(2*S*,4*R*)-1-*tert*-Butyl 2-Ethyl 4-(Benzyloxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate (9) from 13**

To a solution of **13** (1.50 g, 4.13 mmol, 1.00 equiv) in EtOH (25.0 mL) was added a 1.50 M aq LiOH solution (5.50 mL, 8.26 mmol, 2.00 equiv). The mixture was stirred for 4 h at r.t. and was then concentrated in vacuo. The residue was diluted with an aq 1.00 M HCl solution (250 mL) and extracted with $CH_2Cl_2$ (3 × 250 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was redissolved in $CH_2Cl_2$ (25.0 mL), and to the solution was added DCC (937 mg, 4.54 mmol, 1.10 equiv), DMAP (555 mg, 4.54 mmol, 1.10 equiv), and EtOH (2.00 mL, 33.9 mmol, 8.20 equiv) to be stirred for 16 h at r.t. Then, the mixture was filtered, and the filter cake was washed with $Et_2O$ (3 × 50.0 mL). The combined filtrates were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by

column chromatography (silica, EtOAc–hexanes = 1:5 → 1:1) gave **9** as a colorless oil (1.41 g, 91%). The analytical data of the sample were identical with the material prepared from **8**.

**(2*S*,4*S*,5*R*)-Ethyl 4-(Benzyloxymethyl)-5-methylpyrrolidine-2-carboxylate (14)**

To a solution of **9** (18.3 g, 48.4 mmol, 1.00 equiv) in THF (250 mL) was added dropwise a solution of $LiEt_3BH$ (1.00 M in THF, 58.0 mL, 58.0 mmol, 1.00 equiv) at –78 °C over the course of 10 min. After being stirred for 30 min, the reaction was quenched with a sat. aq $NaHCO_3$ solution (20.0 mL) and allowed to warm to 0 °C. To the mixture was added $H_2O_2$ (25.0 mL) in one portion and stirred at 0 °C for 30 min. The solvent was removed in vacuo, and the residue was redissolved in a 2:1 mixture of EtOAc and $H_2O$ (810 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to a colorless oil. To a solution of this residual oil (ca. 18.0 g) in MeOH (255 mL) was added PTSA·$H_2O$ (1.84 g, 9.67 mmol, 0.200 equiv) to be stirred for 18 h at r.t. The reaction was quenched with a sat. aq $NaHCO_3$ solution (22.0 mL), the solvent was removed in vacuo, and the residue was redissolved in a mixture of $Et_2O$ (540 mL) and $H_2O$ (270 mL). The organic layer was separated, washed with brine (180 mL), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil.

To a suspension of CuBr·$SMe_2$ complex (46.3 g, 225 mmol, 4.65 equiv) in $Et_2O$ (400 mL) was added dropwise a solution of MeMgBr (3.00 M in $Et_2O$, 75.0 mL, 225 mmol, 4.65 equiv) over the course of 15 min at –40 °C and stirred for 1 h at this temperature. Then, the resulting yellow suspension was cooled to –78 °C and $BF_3$·$OEt_2$ (27.8 mL, 225 mmol, 4.65 equiv) was added dropwise over the course of 15 min. After being stirred for 30 min at –78 °C, a solution of the residual colorless oil from the previous reaction (ca. 19.0 g) in $Et_2O$ (60.0 mL) was added over the course of 10 min. The flask was rinsed with additional $Et_2O$ (15.0 mL), and the reaction mixture was stirred for 15 min at –78 °C. Then, the mixture was allowed to warm to r.t. and stirred for 1 h at this temperature. The reaction was quenched by a dropwise addition of a 1:1 mixture of a sat. aq $NH_4Cl$ solution and a 28% aq $NH_3$ solution (260 mL). The resulting mixture was stirred for 30 min at r.t. and was then diluted with $Et_2O$ (250 mL). The organic layer was separated, washed with $H_2O$ (300 mL) and brine (250 mL), dried over $MgSO_4$, and concentrated in vacuo to give a residue that was redissolved in a mixture of $CH_2Cl_2$ (50.0 mL) and TFA (50.0 mL). To the mixture was added thioanisole (5.69 mL, 48.4 mmol, 1.00 equiv) to be stirred for 2 h at r.t. The reaction mixture was quenched by dropwise addition of a sat. aq $Na_2CO_3$ solution (100 mL) and was then poured into a sat. aq $NaHCO_3$ solution (800 mL). The mixture was extracted with $CH_2Cl_2$ (5 × 250 mL), the combined extracts were concentrated and after purification with column chromatography (silica gel, $CHCl_3$–MeOH–$Et_3N$, 100:1:1), **14** was obtained as a colorless oil (5.43 g, 40%). $R_f$ = 0.28 ($CHCl_3$–MeOH, 100:5). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.51–4.47 (m, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.89–3.81 (m, 1 H), 3.46 (dd, *J* = 9.2, 5.9 Hz, 1 H), 3.36 (dd, *J* = 9.2, 6.8 Hz, 1 H), 3.15–3.03 (m, 1 H), 2.46–2.40 (m, 1 H), 2.20 (br s, 1 H), 1.98–1.94 (m, 1 H), 1.76–1.69 (m, 1 H), 1.25 (t, *J* = 6.8 Hz, 3 H), 1.17 (d, *J* = 6.2 Hz, 3 H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 175.5, 138.4, 128.3 (2 C), 127.5, 127.4 (2 C), 73.1, 72.1, 60.9, 58.4, 56.7, 46.6, 34.1. 20.8, 14.2. IR: 2960, 2859, 1728, 1367, 1204 cm$^{-1}$. $[\alpha]_D^{19}$ –12.1 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{16}H_{23}NO_3$: 277.1678 $[M]^+$; found: 277.1685.

**(2*S*,4*S*,5*R*)-Ethyl 4-(Benzyloxymethyl)-1-(3-ethoxy-3-oxopropyl)-5-methylpyrrolidine-2-carboxylate (16)**

To a solution of **14** (2.20 g, 7.93 mmol, 1.00 equiv) in $CH_2Cl_2$ (8.50 mL) was added ethyl propiolate (0.890 mL, 8.73 mmol, 1.10 equiv) over the course of 1 min. After being stirred for 1 h at r.t., all volatile substances were removed in vacuo. An analytical sample of the crude material was purified by column chromatography (silica gel, EtOAc–hexanes, 1:10 → 1:5) to afford (2*S*,4*S*,5*R*)-ethyl 4-(benzyloxymethyl)-1-[(*E*)-3-ethoxy-3-oxoprop-1-enyl]-5-methylpyrrolidine-2-carboxylate as a colorless oil. $R_f$ = 0.21 (EtOAc–hexanes, 1:5). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 13.4 Hz, 1 H), 7.37–7.27 (m, 5 H), 4.54–4.39 (m, 3 H), 4.20–4.05 (m, 5 H), 3.69–3.56 (m, 1 H), 3.50 (dd, *J* = 9.5, 6.7 Hz, 1 H), 3.40 (dd, *J* = 9.5, 6.6 Hz, 1 H), 2.60–2.43 (m, 1 H), 2.13–2.02 (m, 1 H), 1.95–1.78 (m, 1 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.26–1.19 (m, 6 H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 172.1, 169.2, 145.7, 138.0, 128.4 (2 C), 127.7, 127.5 (2 C), 87.3, 77.2, 73.2, 70.8, 61.4, 60.1, 59.0, 45.7, 31.5, 18.8, 14.6, 14.1. IR: 1728, 1680 cm$^{-1}$. $[\alpha]_D^{19}$ –66.4 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{21}H_{30}NO_5$: 376.2124 $[M]^+$; found: 376.2118.

The crude material obtained as described above was redissolved in glacial acid (5.00 mL, 87.3 mmol, 11.0 equiv). To this solution was added $NaBH_3CN$ (1.00 g, 15.9 mmol, 2.00 equiv), and the resulting mixture was stirred for 30 min at r.t. The reaction was quenched by dropwise addition of a 10% aq HCl solution (15.0 mL). After being stirred for 15 min, a sat. aq $Na_2CO_3$ solution (30.0 mL) was added dropwise, and the resulting mixture was poured into a sat. aq $NaHCO_3$ solution (270 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 150 mL), the combined extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to a colorless crude product, which was purified by column chromatography (EtOAc–hexanes, 1:11 → 1:9) to give **16** as a colorless oil (2.16 g, 72%). $R_f$ = 0.28 (EtOAc–hexanes, 1:5). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.19 (m, 5 H), 4.53–4.45 (m, 2 H), 4.13–4.04 (m, 4 H), 3.83–3.69 (m, 1 H), 3.50 (dd, *J* = 9.0, 6.7 Hz, 1 H), 3.40 (dd, *J* = 8.9, 7.7 Hz, 1 H), 3.08–2.91 (m, 2 H), 2.78–2.67 (m, 1 H), 2.54–2.42 (m, 2 H), 2.36–2.24 (m, 1 H), 2.08–1.97 (m, 1 H), 1.67–1.57 (m, 1 H), 1.24–1.19 (m, 6 H), 1.08 (d, *J* = 5.9 Hz, 3 H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 174.3, 172.3, 138.5, 128.3 (2 C), 127.5 (2 C), 127.4, 73.3, 73.1, 62.2, 60.3, 60.1, 59.9, 45.3, 43.4, 34.2, 31.1, 18.1, 14.3, 14.2. IR: 2977, 2854, 1729, 1369, 1179 cm$^{-1}$. $[\alpha]_D^{19}$ –63.8 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{21}H_{32}NO_5$: 378.2280 $[M + H]^+$; found: 378.2273.

**(2*S*,5*R*,6*S*,7a*S*)-Ethyl 6-(Benzyloxymethyl)-5-methyl-1-oxohexahydro-1*H*-pyrrolizine-2-carboxylate (5)**

To a mixture of **16** (1.67 g, 4.40 mmol, 1.00 equiv) and toluene (18.0 mL) was added a solution of KHMDS (0.500 M in toluene, 2.00 mL, 8.80 mmol, 2.00 equiv) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and was then allowed to warm to r.t. to be stirred for 0.5 h at this temperature. The reaction was quenched with a sat. aq $NH_4Cl$ solution (20.0 mL), diluted with a sat. aq $NH_4Cl$ solution (500 mL), and extracted with $CH_2Cl_2$ (5 × 150 mL). The aqueous phase was diluted with a sat. aq $Na_2CO_3$ solution (100 mL) and extracted with $CH_2Cl_2$ (3 × 150 mL). A second time, the aqueous phase was diluted with a sat. aq $Na_2CO_3$ solution (100 mL) and extracted with $CH_2Cl_2$ (2 × 150 mL). The combined extracts were concentrated and purified by reversed phase column chromatography ($H_2O$–MeOH, 5:1 → 2:1) to give **5** as a colorless solid (1.13 g, 81%). $R_f$ = 0.33 ($CHCl_3$–MeOH, 100:10). $^1$H NMR (400 MHz, acetone-$d_6$): δ = 7.35–7.24 (m, 5 H), 4.51–4.47 (m, 2 H), 4.16–4.09 (m, 2 H), 3.67–3.29 (m, 5 H), 2.71–2.47 (m, 1 H), 2.33–2.20 (m, 1 H), 2.10–2.07 (m, 1 H), 2.04–1.94 (m, 1 H), 1.72–1.58 (m, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 5.9 Hz, 3 H). $^{13}$C NMR (100 MHz, acetone-$d_6$): δ = 214.9, 168.4, 138.9, 128.2 (2 C), 127.3 (2 C), 127.3, 72.6, 71.5, 71.1, 61.2, 60.7, 48.7, 47.1, 30.1, 29.2, 18.2, 13.6. IR: 2978, 1677, 1580, 1452, 1260, 1171, 1071 cm$^{-1}$. $[\alpha]_D^{19}$ –36.2 (*c* 1.0, MeOH). ESI-HRMS: *m/z* calcd for $C_{19}H_{25}NO_4$: 332.1862 $[M]^+$; found: 332.1856.

## Acknowledgment

We thank Dr. Peter Mayer at the Ludwig-Maximilians-Universität München for elucidating the X-ray structure of **15**.

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



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