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Total Synthesis of a Pyrrole Lactone Alkaloid, Longanlactone

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Keywords: Total synthesis / Alkaloids / Nitrogen heterocycles / Lactones / Amino acids

The first asymmetric total synthesis of the natural pyrrole lactone longanlactone has been achieved. The key reactions, a Barbier propargylation and a Paal–Knorr pyrrole synthesis, have provided easy access to the target natural product from L-aspartic acid in six steps and 31 % overall yield. The C-4 epimer of the natural product and propionyllonganlactone have also been prepared by this strategy.

Introduction

The seeds of the longan (*Dimocarpus longan*) tree are used as a traditional medicine in China for the treatment of various diseases and they are a rich source of antioxidant compounds.[1] A new natural pyrrole lactone, longanlactone, was isolated from the chloroform extracts of longan seeds by Zheng and co-workers in 2012[2]. On the basis of spectroscopic data, the structure of this natural lactone was determined as **1a**, which exemplifies a *cis* relationship between the C-2 pyrrole and C-4 propargyl units. Compared with the other two known pyrrole lactone alkaloids, (–)-funebrine **2** and (–)-funebral **3**, which contain a 2-formylpyrrole group on the lactone ring, longanlactone has a unique structural feature with 2-acetylpyrrole and propargyl motifs on the lactone ring (Figure 1).[3,4] To date, no synthesis has been reported for longanlactone, and the biological properties of **1** have not been investigated. The above observations and the insufficient natural supply from the seeds (3 mg from 10.5 kg of seeds) combined with our interest in the synthesis of alkaloids[5] have prompted us to focus our attention on the total synthesis of **1a**. Herein, we report the first asymmetric total synthesis of longanlactone (**1a**) along with its C-4 epimer **1b** and propionyl analogue.

The synthesis of small-molecule natural products plays a significant role in the expansion of chemistry as well as in the discovery of new bioactive compounds through the generation of natural-product-like libraries.[6] Therefore, we planned a strategy for the synthesis of longanlactone in a flexible way, which will allow the synthesis of various analogues of the natural product. The retrosynthetic analysis is delineated in Scheme 1. Accordingly, we planned the acetyl pyrrole ring construction of longanlactone **1a** through a

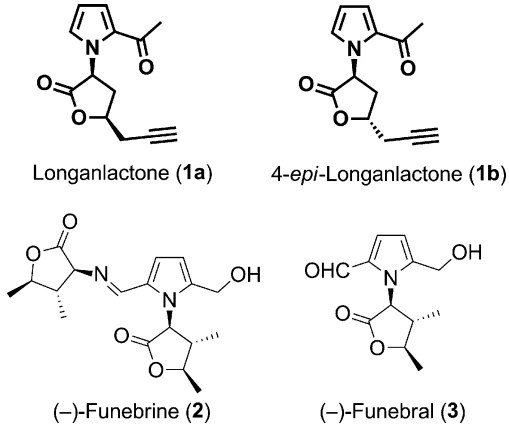
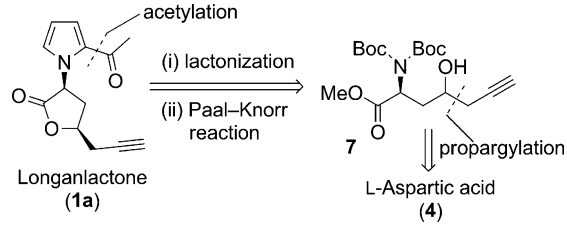


Figure 1. Structures of pyrrole lactone alkaloids.

Paal–Knorr pyrrole formation from the aminolactone generated in situ generated from alcohol **7**, followed by acetylation. To this end, the desired alcohol **7** was envisaged from commercially available L-aspartic acid with stereoselective propargylation as the key step.



Scheme 1. Retrosynthetic analysis of longanlactone (**1a**).

Results and Discussion

The synthesis of the key intermediate, alcohol **7**, is outlined in Scheme 2. Firstly, L-aspartic acid was subjected to $SOCl_2$ in MeOH under reflux to afford the diester, which was subsequently treated with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of triethylamine in tetrahydrofuran (THF)

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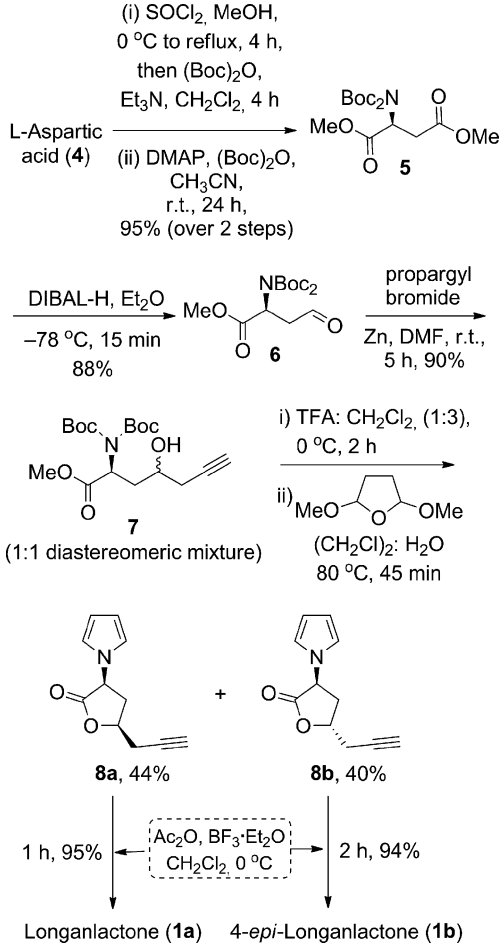
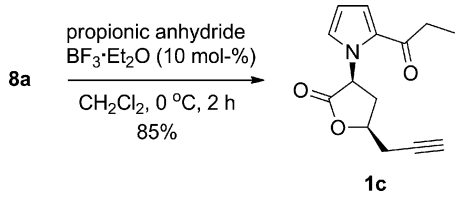
and 4-dimethylaminopyridine (DMAP) in acetonitrile to provide the di-Boc-protected ester **5** in 95% yield over two steps. The selective reduction of the diester **5** with diisobutylaluminum hydride (DIBAL-H) in Et_2O at –78 °C provided the aldehyde **6** in 88% yield.[7] Our initially attempted enantioselective propargylation of **6** with allenylboronate in the presence of a chiral phosphoric acid was unsuccessful.[8,9] Therefore, we decided to proceed with the Zinc-mediated Barbier propargylation[10] of aldehyde **6**, which gave the alcohol **7** as an inseparable diastereomeric mixture (1:1) in 90% yield. Next, the deprotection of the Boc groups, ester hydrolysis, and lactonization reactions were achieved by treatment of the alcohol **7** with trifluoroacetic acid (TFA/CH_2Cl_2, 1:3) at 0 °C to afford the aminolactone, which under Paal–Knorr conditions with 2,5-dimethoxytetrahydrofuran[11] in dichloroethane/water at 80 °C provided a mixture of pyrrole lactones **8a** and **8b** (four steps in one pot). This mixture was separated by silica gel column chromatography to give **8a** (44%) and **8b** (40%) in pure form. The relative configurations of 2-H and 4-H were confirmed as *cis* in **8a** and *trans* in **8b** by NOE experiments.[12] Finally, towards the natural longanlactone, the C-2 acetylation of pyrrole lactone **8a** was performed with Ac_2O in the presence of different Lewis acid catalysts such as $AlCl_3$, $ZnCl_2$, $FeCl_3$, and $BF_3{\cdot}Et_2O$.[13] Among these, $BF_3{\cdot}Et_2O$ in dichloromethane at 0 °C was found to be the best and gave **1a** in 95% yield. The spectroscopic data of the target molecule **1a** (^1H and ^{13}C NMR spectroscopy, NOE measurements, mass spectrometry, and IR spectroscopy) were in full agreement with those reported for natural longanlactone. The specific rotation observed for synthetic **1a**, $[\alpha]_D^{25} = –9.2$ ($c = 1$, acetone), was also comparable with the reported value for the natural product {$[\alpha]_D^{25} = –9.0$ ($c = 0.2$, acetone)}. Hence, the structure and absolute configuration of natural longanlactone, which were proposed on the basis of spectroscopic analyses, were confirmed to be **1a**. It is worth mentioning that the present strategy offers an access to sufficient quantities of the natural product. The acetylation of **8b** afforded 4-*epi*-longanlactone (**1b**, in 94% yield), which was also fully characterized by ^1H and ^{13}C NMR spectrometry, mass spectrometry, and IR spectroscopy.



Scheme 2. Synthesis of longanlactone (**1a**) and its epimer **1b**.

To demonstrate the possibility of acylation reactions of **8a** towards various analogues, the reaction of **8a** with propionic anhydride in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane was performed and afforded the corresponding propionyllonganlactone **1c** in 85% yield (Scheme 3).



Scheme 3. Synthesis of propionyllonganlactone (**1c**).

Conclusions

The first asymmetric total synthesis of the natural pyrrole lactone, longanlactone, was accomplished in six steps and in 31% overall yield from L-aspartic acid. The key features of the strategy are the access to a new pyrrole lactone from a natural amino acid and the successful exploitation of a Barbier propargylation as well as a Paal–Knorr reaction for the natural product synthesis. The present approach is applicable for scale-up and also handy for the syntheses of diversified analogues through (1) the reaction of **6** with different Grignard reagents and (2) acylation reactions of **8a**. We are actively pursuing the synthesis of various analogues of longanlactone and their biological evolution, progress toward which will be reported in due course.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded with samples in $CDCl_3$ and [D_6]acetone with 300 or 500 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. FTIR spectra were recorded with a Perkin–Elmer 683 infrared spectrophotometer; samples were neat or thin films in KBr. Optical rotations were measured with an Anton Paar MLP 200 modular circular digital polarimeter by using a 2 mL cell with a path length of 1 dm. Low-resolution MS were recorded with an Agilent Tech-

nologies LC-MSD trap SL spectrometer. All reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade EtOAc and hexanes for column chromatography were distilled before use. THF, when used as a reaction solvent, was freshly distilled from sodium benzophenone ketyl. Column chromatography was performed with silica gel (60–120 mesh) packed in glass columns. All reactions were performed under N_2 in flame- or oven-dried glassware with magnetic stirring.

Dimethyl (2*S*)-2-[bis(*tert*-butyloxy)amino]butane-1,4-dioate (5): To a suspension of L-aspartic acid (**4**) (4.0 g, 30.07 mmol) in methanol (25 mL) at 0 °C under nitrogen, thionyl chloride (3.2 mL, 45.11 mmol) was added dropwise over 15 min. The reaction mixture was warmed to room temperature and heated to reflux for 4 h. The solution was concentrated in vacuo to give a colorless oil. To this crude oil, hexane was added, and the mixture was stirred for 10 min. Then, the hexane was decanted, and this procedure was repeated two more times to afford a solid compound. To this solid in dichloromethane (60 mL) at 0 °C under nitrogen, triethylamine (8.4 mL, 60.15 mmol) and $(Boc)_2O$ (9.80 g, 45.11 mmol) were added dropwise. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was washed with water (100 mL) and brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was used for the next step without further purification. To a stirred solution of the *N*-Boc amino ester (7.3 g, 27.96 mmol) and DMAP (665 mg, 5.59 mmol, 0.2 equiv.) in dry CH_3CN (50 mL) was added $(Boc)_2O$ (6.59 g, 30.76 mmol, 1.1 equiv.) at room temp. The reaction became slightly red with gas evolution. The mixture was stirred for 2 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (3.2 g, 13.98 mmol, 0.5 equiv.) was added, and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude product was then diluted by the addition of ice cold water (50 mL) and ether (50 mL); the organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried with Na_2SO_4, and the organic solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 95:05) to give **5** (9.17 g, 95%) as a solid, m.p. 57–58 °C. $[\alpha]_D^{20}$ = –61.5 (*c* = 2.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3032, 2989, 1791, 1750, 1698, 1370, 1249, 1142 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.44 (d, *J* = 6.8 Hz, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 3.24 (dd, *J* = 16.5, 6.8 Hz, 1 H), 2.72 (dd, *J* = 16.4, 6.8 Hz, 1 H), 1.49 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.9, 170.1, 151.4, 83.4, 54.7, 52.4, 51.8, 35.5, 27.8 ppm. MS (ESI): *m*/*z* = 362 $[M + H]^+$.

(*S*)-Methyl 2-[Di(*tert*-butoxycarbonyl)amino]-4-oxobutanoate (6): To a stirred solution of the dimethyl ester **5** (6 g, 16.6 mmol) in dry Et_2O (50 mL, 0.1 M) was added dropwise DIBAL-H (12.36 mL, 25% in toluene, 19.28 mmol, 1.1 equiv.) at –78 °C. The reaction mixture was stirred for 15 min at the same temperature and quenched with H_2O (2 mL, 7 equiv.). The mixture was stirred for 30 min and then warmed to 0 °C; Na_2SO_4 was added, and the mixture was filtered through a pad of Celite. The solvent was evaporated, and the crude product was purified by silica gel column chromatography to afford **6** (4.84 g, 88%) as an oil. $[\alpha]_D^{20}$ = –54.5 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3022, 2988, 1791, 1749, 1698, 1370, 1267, 1142 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.76 (s, 1 H), 5.50 (dd, *J* = 6.8, 6.6 Hz, 1 H), 3.71 (s, 3 H), 3.38 (dd, *J* = 17.0, 6.9 Hz, 1 H), 2.82 (dd, *J* = 17.0, 6.8 Hz, 1 H), 1.48 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.3, 170.2, 151.6, 83.6, 52.8, 52.5, 44.9, 27.9 ppm. MS (ESI): *m*/*z* = 332 $[M + H]^+$.

Methyl (2*S*)-2-[Di(*tert*-butoxycarbonyl)amino]-4-hydroxyhept-6-ynoate (7): To a solution of **6** (1 g, 3.0 mmol) and propargyl bromide (0.32 mL, 4.2 mmol) in *N*,*N*-dimethylformamide (DMF, 10 mL) was added zinc (273 mg, 4.2 mmol), and the reaction mixture was stirred for 5 h. Saturated NH_4Cl (10 mL) solution was added, and the compound was extracted with ethyl acetate (2 X 15 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo to afford the crude oil, which was purified by column chromatography, eluted with hexanes/EtOAc (80:20) to give **7** (1 g, 90%) in a 1:1 ratio of inseparable diastereomers; the identity of the obtained product was confirmed by NMR spectroscopy. IR (KBr): $\tilde{\nu}$ = 3031, 2979, 1781, 1756, 1611, 1370, 1249, 1122 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.09 (t, *J* = 5.9 Hz, 1 H), 5.04 (dd, *J* = 5.0, 9.7 Hz, 1 H), 4.07–3.99 (m, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.33–3.28 (m, 1 H), 2.59–2.45 (m, 3 H), 2.43–2.36 (m, 2 H), 2.29–2.36 (m, 2 H), 2.07 (t, *J* = 2.5 Hz, 1 H), 2.04 (t, *J* = 2.5 Hz, 1 H), 1.50 (s, 36 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.3, 171.2, 152.3, 151.9, 83.7, 83.3, 80.6, 80.3, 71.0, 70.5, 67.7, 66.6, 55.6, 55.3, 52.3, 52.2, 37.3, 36.5, 27.9, 27.8, 27.2, 26.9 ppm. MS(ESI): *m*/*z* = 394 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{29}NO_7Na$ $[M + Na]^+$ 394.1841; found 394.1854.

(3*S*,5*R*)-5-(Prop-2-yn-1-yl)-3-(1*H*-pyrrol-1-yl)dihydrofuran-2(3*H*)-one (8a): Di-Boc compound **7** (0.8 g, 2.3 mmol) was dissolved in dichloromethane/TFA (1:1, 10 mL) in a 50 mL flask, and the mixture was then cooled to 0 °C. The reaction mixture was stirred for 2 h at same temperature. The mixture of solvents was evaporated under reduced pressure to afford a thick red oil. Dichloroethane (10 mL) and water (10 mL) were added to the above crude mixture, followed by 2,5-dimethoxytetrahydrofuran (0.45 mL, 3.5 mmol). The resulting solution was stirred for 45 min at 80 °C. The solution was diluted with water (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 × 25 mL) and saturated NaCl solution (1 × 25 mL) and dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the obtained crude product was purified by silica gel column chromatography to afford a separable mixture of the two diastereomers **8a** (179 mg, 44%) and **8b** (163 mg, 40%) as brown solids, m.p. 147–149 °C. $[\alpha]_D^{20}$ = –8.3 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3127, 2922, 2854, 1777, 1490, 1322, 1175, 1020, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.76 (t, *J* = 2.1 Hz, 2 H), 6.25 (t, *J* = 2.1 Hz, 2 H), 4.99 (dd, *J* = 12.3, 9.0 Hz, 1 H), 4.65 (ddd, *J* = 16.0, 10.6, 5.1 Hz, 1 H), 2.97 (ddd, *J* = 13.0, 8.9, 3.4 Hz, 1 H), 2.79–2.74 (m, 2 H), 2.53 (ddd, *J* = 12.5, 10.2, 2.6 Hz, 1 H), 2.14 (t, *J* = 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.3, 119.8, 109.5, 77.2, 73.8, 72.2, 58.0, 35.1, 24.5 ppm. MS(ESI): *m*/*z* = 190 $[M + H]^+$. HRMS (ESI): calcd. for $C_{11}H_{11}NO_2Na$ $[M + Na]^+$ 212.0687; found 212.0692.

(3*S*,5*S*)-5-(Prop-2-yn-1-yl)-3-(1*H*-pyrrol-1-yl)dihydrofuran-2(3*H*)-one (8b): M.p. 167–169 °C. $[\alpha]_D^{20}$ = –103 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3032, 2989, 1791, 1750, 1698, 1370, 1249, 1142 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.73 (t, *J* = 2.0 Hz, 2 H), 6.24 (t, *J* = 2.0 Hz, 2 H), 5.17 (t, *J* = 9.2 Hz, 1 H), 4.86 (ddd, *J* = 12.1, 7.9, 4.0 Hz, 1 H), 2.86–2.69 (m, 4 H), 2.14 (t, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.7, 119.6, 109.6, 77.7, 74.9, 72.3, 56.5, 34.1, 25.2 ppm. MS (ESI): *m*/*z* = 212 $[M + Na]^+$.

Longanlactone (1a): To a stirred solution of **8a** (175 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) were added Ac_2O (92 mg, 0.91 mmol) and $BF_3{\cdot}Et_2O$ (10 mol-%) at 0 °C, and the mixture was stirred for 1 h. Water was added to the reaction mixture, which was then extracted with chloroform (2 × 10 mL), dried with sodium sulfate, concentrated under reduced pressure, and purified by column chromatography, eluted with 20% EtOAc in hexane to give product **1a** (200 mg) in 95% yield as white acicular crystals, m.p. 197–199 °C. $[\alpha]_D^{20}$ = –9.2 (*c* = 1.00, acetone). IR (KBr): $\tilde{\nu}$ = 3304, 3141, 2929,

1771, 1642, 1408, 1347, 1197, 1095, 1025, 636 cm^{-1}. ^1H NMR ([D_6]-acetone, 500 MHz): δ = 7.07 (dd, J = 4.0, 1.5 Hz, 1 H), 6.97 (dd, J = 2.6, 1.5 Hz, 1 H), 6.26 (dd, J = 4.4, 2.6 Hz, 1 H), 5.88 (br. s, 1 H), 4.62–4.71 (m, 1 H), 2.97 (ddd, J = 12.3, 9.2, 6.2 Hz, 1 H), 2.89 (ddd, J = 16.7, 5.3, 2.9 Hz, 1 H), 2.82 (ddd, J = 16.7, 7.1, 2.9 Hz, 1 H), 2.46 (s, 3 H), 2.38 (ddd, J = 21.2, 12.4, 2.1 Hz, 1 H), 2.07 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR ([D_6]acetone, 125 MHz): δ = 188.7, 171.8, 130.0, 129.7, 121.4, 109.7, 77.7, 74.3, 71.5, 58.2, 35.5, 27.0, 24.8 ppm. MS (ESI): m/z = 232 $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_{14}NO_3$ $[M + H]^+$ 232.0968; found 232.0965.

4-*epi*-Longanlactone (1b): A similar procedure (as that used for **1a**) was followed starting from **8b**. Reaction time 2 h, white solid (183 mg, 94% yield), m.p. 123–124 °C. $[\alpha]_D^{20}$ = –53.5 (c = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3304, 3141, 2929, 1771, 1642, 1408, 1347, 1197, 1095, 1025, 636 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.08 (dd, J = 4.1, 1.5 Hz, 1 H), 6.94 (dd, J = 2.6, 1.8 Hz, 1 H), 6.24 (dd, J = 4.0, 2.6 Hz, 1 H), 5.60 (t, J = 9.2 Hz, 1 H), 5.02–4.93 (m, 1 H), 2.75 (ddd, J = 8.4, 5.2, 2.4 Hz, 1 H), 2.71–2.60 (m, 3 H), 2.44 (s, 3 H), 2.11 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 188.5, 172.4, 131.3, 129.3, 121.7, 109.2, 78.4, 74.9, 71.7, 57.8, 33.2, 26.6, 25.6 ppm. MS(ESI): m/z = 254 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{13}H_{13}O_3NNa$ $[M + Na]^+$ 254.0787; found 254.0784.

Propionyllonganlactone (1c): To a stirred solution of **8a** (50 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was added propionic anhydride (50 mg, 0.40 mmol) and $BF_3{\cdot}Et_2O$ (10 mol-%) at 0 °C, and the mixture was stirred for 2 h. Water was added to the reaction mixture, which was then extracted with dichloromethane (2 × 5 mL), dried with sodium sulfate, concentrated under reduced pressure, and purified by column chromatography, eluted with 15% EtOAc in hexanes to give product **1c** (55 mg) in 85% yield as a white solid, m.p. 210–212 °C. $[\alpha]_D^{20}$ = 57 (c = 0.26, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3275, 3131, 2921, 1771, 1650, 1413, 1216, 1193, 1029, 742, 662 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.06 (dd, J = 4.1, 1.5 Hz, 1 H), 6.96 (dd, J = 2.6, 1.7 Hz, 1 H), 6.25 (dd, J = 4.9, 2.6 Hz, 1 H), 5.94 (br. s, 1 H), 4.64–4.71 (m, 1 H), 2.94–3.71 (m, 1 H), 2.79–2.80 (m, 4 H), 2.34 (ddd, J = 22.1, 12.0, 10.0 Hz, 1 H), 2.07 (t, J = 2.7 Hz, 1 H), 1.18 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.2, 171.9, 129.6, 129.2, 120.3, 109.5, 77.8, 74.2, 71.6, 58.1, 35.7, 32.1, 24.8, 8.9 ppm. MS (ESI): m/z = 268 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_3$ $[M + Na]^+$ 268.0944; found 268.0948.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all compounds.

Acknowledgments

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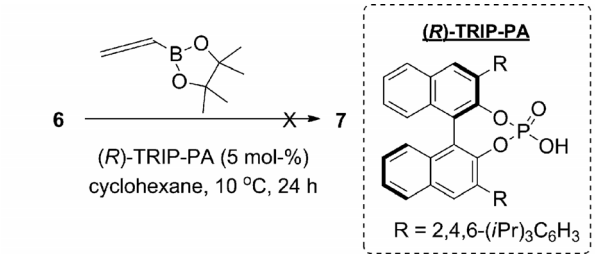

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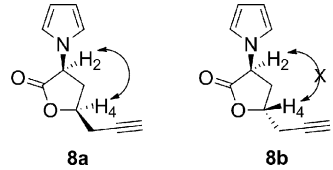
[13] The results of C-2 acetylation of **8a** (1 mmol) with Ac_2O (1 mmol) in CH_2Cl_2 in the presence of various Lewis acids to give **1a** are as follows: a) $AlCl_3$ (10 mol-%), room temp., 9 h, 86% yield of **1a**; b) $ZnCl_2$ (10 mol-%), room temp., 24 h, 54%; c) $FeCl_3$ (10 mol-%), room temp., 24 h, 36%; d) $BF_3{\cdot}Et_2O$ (10 mol-%), 0 °C, 1 h, 95%.



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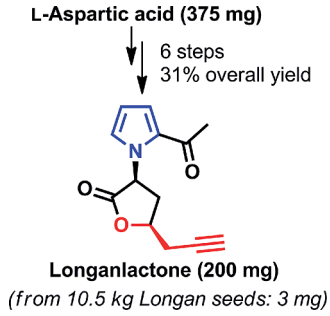
Total Synthesis

The first total synthesis of a new pyrrole lactone alkaloid, longanlactone, along with its C-4 epimer is achieved from the natural amino acid L-aspartic acid with a Barbier-type propargylation and a Paal–Knorr pyrrole synthesis as key steps.



Keywords: Total synthesis / Alkaloids / Nitrogen heterocycles / Lactones / Amino acids

