EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200384

First Total Synthesis of the Pyrrolizidine Alkaloid Amphorogynine C through Intramolecular Azide–Olefin Cycloaddition

Irene de Miguel,[a] Marina Velado,[a] Bernardo Herradón,[a] and Enrique Mann*[a]

Keywords: Total synthesis / Alkaloids / Cycloaddition / Natural products / Azides

The first total synthesis of the natural alkaloid amphorogynine C is reported (2.9 % overall yield in 20 steps). The key steps include a Claisen–Johnson rearrangement and an intramolecular azide–olefin cycloaddition, followed by a reduction of the resulting imine. The construction of the pyrrolizidine skeleton was achieved by an alkoxide-mediated lactone ring opening and subsequent cyclization of a conveniently functionalized bicyclic amine. Finally, the proposed structure of amphorogynine C was confirmed by single-crystal X-ray diffraction analysis.

Introduction

Because of their diverse structures and biological activities, pyrrolizidine alkaloids have attracted considerable synthetic interest during the previous decades.[1] In 1998, four new pyrrolizidine alkaloids were isolated by Païs and coworkers from the New Caledonian plant *Amphorogynine spicata*.[2] This class of compounds, named amphorogyinines A, B, C, and D (**1**–**4**, Figure 1) are characterized by a double substitution pattern at the C-1 and C-6 positions of the bicyclic pyrrolizidine core. Prior to this work, two syntheses of amphorogynine A (**1**)[3,4a] and one total synthesis of amphorogynine D (**4**)[4b] were described. Herein, we report the first synthesis of amphorogynine C (**3**).

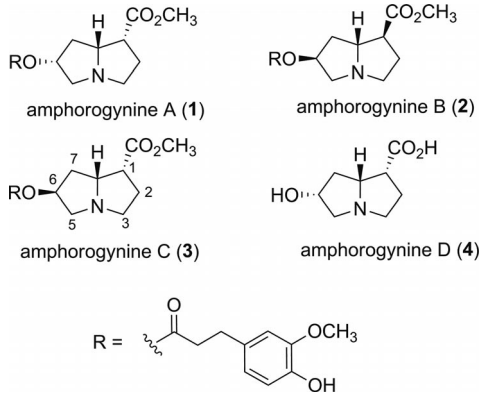


Figure 1. Chemical structures of amphorogynines A–D.

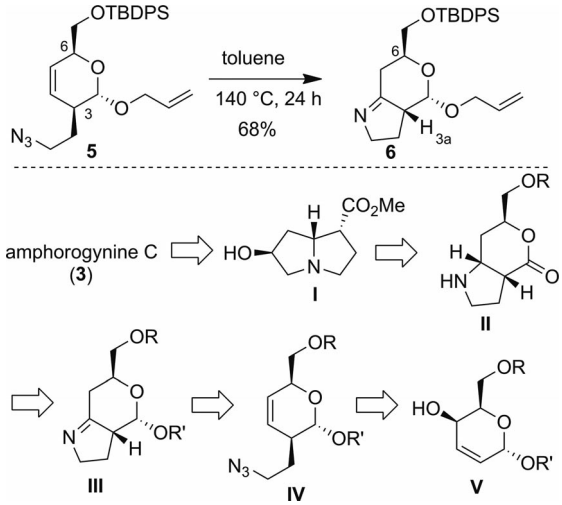
[a] Instituto de Química Orgánica General, CSIC,
Juan de la Cierva 3, 28006 Madrid, Spain
E-mail: mann@iqog.csic.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200384.

Results and Discussion

In connection with our ongoing interest in the application of 1,3-dipolar azide–olefin cycloadditions to the syntheses of nitrogen-containing heterocycles and natural alkaloids,[5] we prepared azidoalkene **5**. When this compound was heated at 140 °C in toluene (sealed tube), the corresponding imine **6** was formed, with total epimerization occurring at the C-3a position [Scheme 1 (top)]. A close inspection of the structure of compound **6** revealed that two of the stereogenic centers already present in this molecule, C-3a and C-6, have the same configuration as C-1 and C-6 of amphorogynine C (Figure 1). In addition, imine **6** already contains all of the carbon and nitrogen atoms (with the exception of the methoxy group of the carboxylate functionality) present in the bicyclic core of **3**. With these considerations in mind, the preparation of amphorogynine C was approached according to the retrosynthetic correlation summarized in Scheme 1 (bottom). The preparation of the 1-azabicyclo[3.3.0]octane **I** could be achieved by opening the lactone and subsequent cyclization of a conveniently functionalized derivative of bicyclic amine **II**. Intermediate **II** would result from a stereoselective reduction of the imine group, which would allow for the construction of the third stereogenic center present in amphorogynine C and subsequent oxidation of the anomeric position of **III**. This key intermediate might be secured by an intramolecular 1,3-dipolar azide–olefin cycloaddition of azidoalkene **IV**. This derivative of 3,6-dihydro-2*H*-pyran should be obtainable from allylic alcohol **V** by employing a Claisen–Johnson rearrangement as the key step.

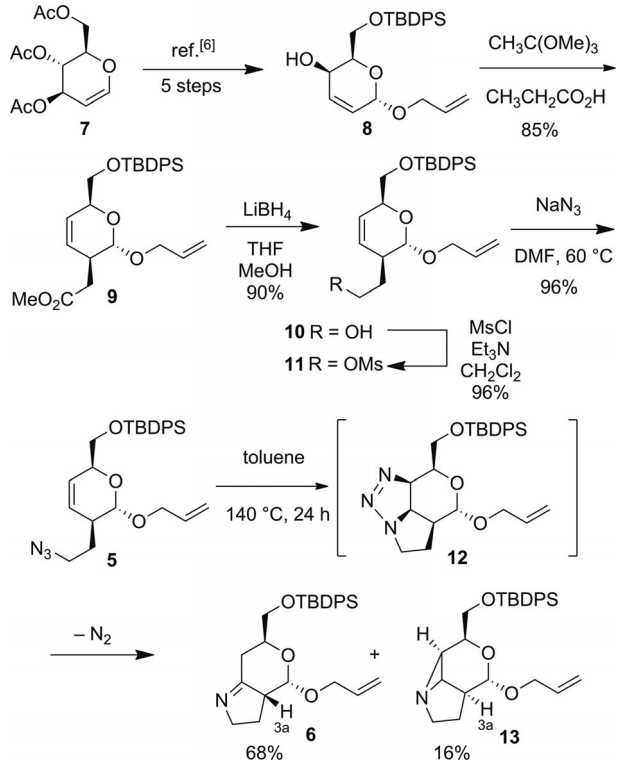
The synthesis of the key imine **6** is outlined in Scheme 2. The requisite starting material, allylic alcohol **8** was prepared on a multigram scale in five steps from commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**7**) according to a method previously reported by our group.[6] The Claisen–Johnson rearrangement was accomplished by heating to re-



Scheme 1. Key transformation of azide **5** into imine **6** (top), and retrosynthesis of amphorogynine C (**3**) (bottom).

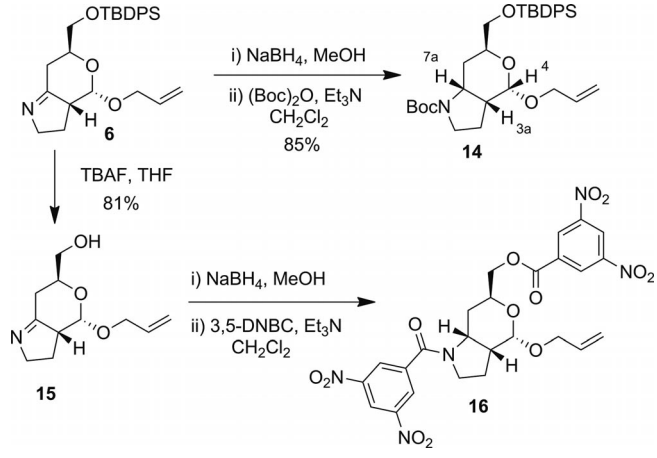
flux compound **8** in trimethyl orthoacetate in the presence of propanoic acid. This gave the corresponding γ,δ-unsaturated ester **9** as the only product in excellent yield (85%). Furthermore, the reaction took place in a completely stereoselective way, as is expected for such suprafacial allylic rearrangements. The reduction of **9** with lithium borohydride ($LiBH_4$) furnished alcohol **10** (90% yield), and that, in turn, was treated with methanesulfonyl chloride in the presence of triethylamine to give methanesulfonate **11** in quantitative yield (96%). Compound **11** was converted into **5** by treatment with sodium azide (95% yield). With azidoalkene **5** in hand, we focused our attention on its conversion to the key intermediate **6**. Under thermal conditions, azides react with olefins through a 1,3-dipolar cycloaddition to form 1,2,3-Δ^2-triazolines[7] that – unlike their aromatic analogues (1,2,3-triazoles) – are generally not isolable and evolve after nitrogen loss to the corresponding imines.[8] In particular, the intramolecular azide–olefin cycloaddition reaction (IAOC) has found broad application in the syntheses of complex molecules.[8,9] Upon heating of azidoalkene **5** at 140 °C in toluene (sealed tube), a readily separable mixture of imine **6** (68% yield) and aziridine **13** (16% yield) was obtained. As anticipated, because of the configurationally labile nature of the enaminic C-3a position of **6**, a total epimerization took place at this center (see below). On the other hand, such an epimerization was not observed in aziridine **13**, because equilibration was not possible in this case. The use of other solvents such as DMF (*N*,*N*-dimethylformamide) and methanol or the employment of microwave heating resulted in lower yields and more complex mixtures of products. Furthermore, all attempts to decrease the amount of aziridine **13** by modifying the temperature and reaction times were unsuccessful, leading to similar ratios but lower yields.

As shown in Scheme 3, the reduction of imine **6** with sodium borohydride ($NaBH_4$) in the presence of methanol and the in situ protection of the generated amine with di-



Scheme 2. Synthesis of key imine **6**.

tert-butyl dicarbonate afforded intermediate **14** as a single diastereomer. As expected, the reduction of the imine functionality proceeded from the less hindered convex face of bicycle **6**. The relative *syn* stereochemistry between 3a-H, 7a-H, and 4-H was established with the aid of NOE experiments. These assignments were ultimately confirmed by the conversion of imine **6** into compound **16** through deprotection with TBAF (tetra-*n*-butylammonium fluoride), reduction of the resulting imino alcohol **15** with $NaBH_4$, and a subsequent reaction with 3,5-dinitrobenzoyl chloride (3,5-DNBC) in the presence of Et_3N. The structure and relative stereochemistry of amide **16** was determined by single-crystal X-ray diffraction analysis (Figure 2).[10]



Scheme 3. Synthesis of Boc-protected amine **14** and amide **16**.

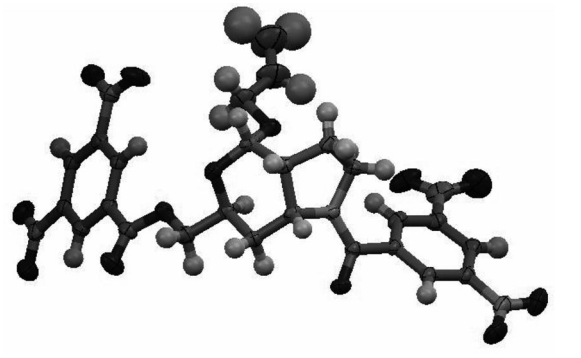
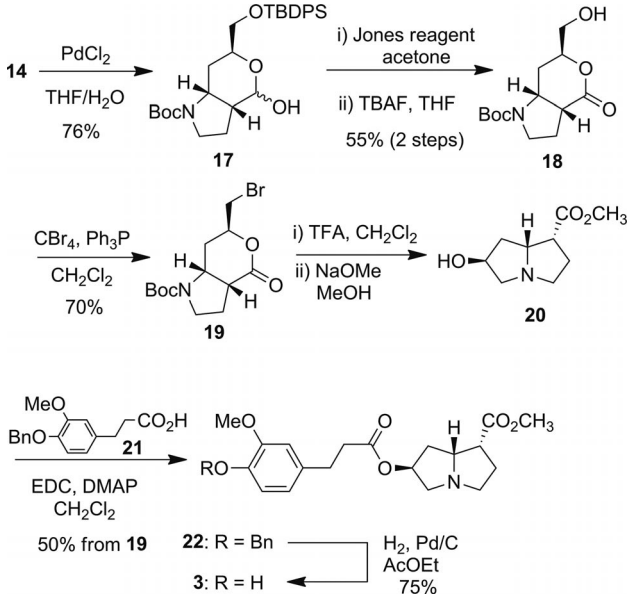


Figure 2. X-ray structure of amide **16**.

With the three stereocenters required for the synthesis of the amphorogynine C skeleton already installed, we turned our attention to the formation of the pyrrolizidine core. Treatment of compound **14** with palladium chloride[11] in a mixture of THF/H_2O (9:1) afforded lactol **17** in moderate yield (Scheme 4). The oxidation of **17** to the corresponding bicyclic lactone **18** proved to be one of the most problematic steps in the synthesis. Although PCC (pyridinium chlorochromate), Dess–Martin periodinane, MnO_2, and TPAP (tetra-*n*-propylammonium perruthenate) were unsuccessful in promoting the oxidation,[12] resulting in the recovery of unaltered starting material, exposing **17** to Jones reagent[13] and subsequent treatment of the crude material with TBAF (see Exp. Sect.) provided **18** in a 55% combined yield. The treatment of the alcohol **18** with carbon tetrabromide in the presence of triphenylphosphane delivered the corresponding bromide **19** (70% yield). After some experimentation, we found that exposing compound **19** to trifluoroacetic acid and subsequent treatment with freshly prepared sodium methoxide afforded hydroxypyrrolizidine **20**, which was immediately esterified with the *O*-benzylated derivative of the hydroferulic acid **21**[14] to afford **22** as single diastereoisomer with an overall yield of 50% (3 steps). Finally, the elimination of the benzyl group by catalytic hydrogenation (H_2, Pd/C) cleanly afforded amphorogynine C (**3**) in 75% yield. The physical and spectroscopic data (^1H and ^{13}C NMR) obtained for the synthetic material are in agreement with those previously reported in the literature.[2,15]



Scheme 4. Completion of total synthesis.

Finally, slow concentration of a methanol solution of **3** afforded crystals suitable for X-ray diffraction analysis (Figure 3).[10] Because the synthetic route from tri-*O*-acetyl-D-glucal is unambiguous with total stereocontrol, it confirms the structure of amphorogynine C proposed by Païs and coworkers[2].

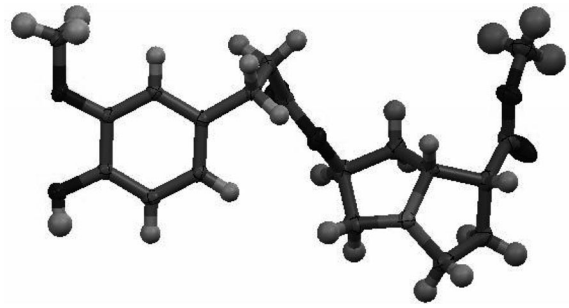


Figure 3. X-ray structure of amphorogynine C (**3**).

Conclusions

The first total synthesis of natural amphorogynine C was achieved. The key steps include an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene and subsequent reduction of the resulting imine to the corresponding amine. Finally, the proposed structure of amphorogynine C was confirmed by single-crystal X-ray diffraction analysis.

Experimental Section

General Methods: When it was appropriate, the reactions were carried out under argon, by using dry solvents and anhydrous conditions, unless it was stated otherwise. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Dry dichloromethane (DCM), tetrahydrofuran (THF), DMF, toluene, and diethyl ether were obtained by passing the previously degassed solvents through activated alumina columns. The reagents purchased were of the highest commercial quality and used without further purification, unless otherwise stated. Flash column chromatography was performed by using silica gel (60 Å pore size, 40–63 μm, Merck) or deactivated alumina (Brockmann I, Sigma-Aldrich). The reactions were monitored by thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). Detection was performed by using UV light and by charring the plate at ca. 150 °C, after dipping it into an aqueous solution of potassium permanganate ($KMnO_4$), an ethanolic solution of phosphomolybdic acid (PMA), or an ethanolic solution of ninhydrin. The yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous material, unless otherwise stated. The NMR spectroscopic data were recorded with Varian Unity-500, Inova-400, Mercury-400, and Inova-300 instruments and are calibrated by using the residual undeuterated solvent as an internal reference. The abbrevi-

ations used to explain multiplicities are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. High-resolution mass spectra (HRMS) were recorded with an Agilent 6520-Accurate-Mass LC/MS Q-TOF mass spectrometer. IR experiments were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were performed with a Perkin–Elmer 241 MC polarimeter.

Ester 9: A mixture of alcohol **8** (5.0 g, 11.8 mmol) and trimethyl orthoacetate (22.1 mL, 118 mmol) was heated to 100 °C, and then propionic acid (0.09 mL, 1.18 mmol) was added. The mixture was stirred at 140 °C for 72 h. (The MeOH formed during the reaction was eliminated periodically with a rotary evaporator.) The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 9:1). Ester **9** (4.82 g, 85%) was obtained as a colorless viscous oil. $[\alpha]_D^{25}$ = +29.5 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H), 7.41 (m, 6 H), 5.93 (dddd, *J* = 17.2, 10.4, 6.2, 5.2 Hz, 1 H), 5.79 (m, 2 H), 5.29 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H), 5.18 (ddd, *J* = 10.4, 1.7, 1.3 Hz, 1 H), 4.80 (s, 1 H), 4.26–4.20 (m, 2 H), 4.06 (ddd, *J* = 13.0, 6.2, 1.3 Hz, 1 H), 3.73 (m, 2 H), 3.67 (s, 3 H), 2.60 (m, 1 H), 2.48 (dd, *J* = 16.1, 8.1 Hz, 1 H), 2.36 (dd, *J* = 16.1, 6.6 Hz, 1 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 135.8, 134.4, 133.6, 129.8, 127.8, 127.0, 126.0, 117.4, 98.2, 69.5, 68.6, 66.3, 51.8, 37.8, 35.8, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3048, 2931, 2858, 1739, 1647, 1590, 1473, 1428, 1391, 1361, 1267, 1113, 1027, 933, 823, 794, 740, 702 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{40}NO_5Si$ $[M + NH_4]^+$ 498.2670; found 498.2668.

Alcohol 10: Lithium borohydride (272 mg, 12.5 mmol) was added to a solution of compound **9** (2.0 g, 4.16 mmol) in anhydrous THF (10 mL) at 0 °C. Then, MeOH (1 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and then at room temperature for another 4 h. The mixture was cooled again to 0 °C and the reaction quenched by the addition of H_2O. The MeOH was evaporated, and the residue was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 8:2) to provided compound **10** (1.69 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ = +51.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (m, 4 H), 7.40 (m, 6 H), 5.94 (dddd, *J* = 17.2, 10.4, 6.2, 5.2 Hz, 1 H), 5.85 (m, 1 H), 5.75 (m, 1 H), 5.28 (ddd, *J* = 17.2, 1.6, 1.5 Hz, 1 H), 5.19 (ddd, *J* = 10.4, 1.6, 0.9 Hz, 1 H), 4.88 (s, 1 H), 4.23 (m, 2 H), 4.05 (ddd, *J* = 12.9, 6.3, 1.1 Hz, 1 H), 3.80–3.59 (m, 4 H), 2.33 (m, 1 H), 2.19 (br. s, 1 H), 1.73 (m, 2 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 134.4, 133.6, 129.8, 127.8, 126.7, 126.0, 117.5, 99.5, 69.3, 68.5, 66.3, 59.9, 36.9, 35.9, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3048, 2931, 2859, 1473, 1428, 1187, 1113, 1031, 823, 740, 703 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{36}NaO_4Si$ $[M + Na]^+$ 475.2275; found 475.2262.

Mesylate 11: Et_3N (0.74 mL, 5.30 mmol) was added to a solution of alcohol **10** (1.0 g, 2.21 mmol) in CH_2Cl_2 (30 mL) at 0 °C, followed by the dropwise addition of MsCl (0.22 mL, 2.88 mmol) dissolved in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 8:2) to afford compound **11** (1.124 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = +47.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 4 H), 7.41 (m, 6 H), 5.93 (dddd, *J* = 17.2, 10.3, 6.3, 5.2 Hz, 1 H), 5.82 (m, 2 H), 5.29 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H), 5.20 (ddd, *J* = 10.3, 1.7, 1.3 Hz, 1 H), 4.78 (s, 1 H), 4.26 (m, 4 H), 4.05 (ddd, *J* = 12.9, 6.3, 1.6 Hz, 1 H), 3.75 (m, 2 H), 2.97 (s, 3 H), 2.31 (m, 1 H), 1.96 (td, *J* = 13.9, 6.9 Hz, 1 H), 1.83 (td, *J* = 13.9, 6.3 Hz, 1 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 134.3, 133.6, 129.8, 127.8, 127.4, 125.6, 117.6, 98.6, 69.6, 68.5, 67.5, 66.2, 37.6, 35.7, 33.0, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3032, 2931, 2858, 1736, 1647, 1589, 1473, 1428, 1359, 1176, 1114, 1030, 958, 823, 796, 742, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{38}NaO_6SSi$ $[M + Na]^+$ 553.2051; found 553.2046.

Azide 5: Mesylate **11** (800 mg, 1.51 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (10 mL). Sodium azide (980 mg, 15.1 mmol) was added, and the mixture was heated at 60 °C for 2 h. Then, the solvent was removed in vacuo. The residue was dissolved in water, and the resulting solution was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 85:15) to yield **5** (691 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ = +67.2 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (m, 4 H), 7.40 (m, 6 H), 5.92 (dddd, *J* = 17.2, 10.2, 6.3, 5.2 Hz, 1 H), 5.79 (m, 2 H), 5.28 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H), 5.19 (ddd, *J* = 10.3, 1.7, 1.3 Hz, 1 H), 4.75 (s, 1 H), 4.22 (m, 2 H), 4.05 (ddd, *J* = 12.8, 6.3, 1.3 Hz, 1 H), 3.73 (m, 2 H), 3.32 (m, 2 H), 2.23 (m, 1 H),1.71 (m, 2 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 134.4, 133.7, 129.8, 127.8, 127.0, 125.9, 117.5, 98.8, 69.5, 68.5, 66.4, 49.0, 36.7, 32.6, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3048, 2931, 2859, 2096, 1473, 1462, 1428, 1362, 1261, 1187, 1114, 1033, 823, 702 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{35}N_3NaO_3Si$ $[M + Na]^+$ 500.2340; found 500.2316.

Imine 6: In a sealed tube, a solution of compound **5** (300 mg, 0.63 mmol) in toluene (10 mL) was heated at 140 °C for 24 h. The mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to CH_2Cl_2/MeOH, 3%) to afford the desired imine **6** (192 mg, 68%) as a pale yellow, viscous oil and aziridine **13** (45 mg, 16%) as a dark yellow oil. Data for compound **6**: $[\alpha]_D^{25}$ = +110.5 (*c* = 0.88, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (m, 4 H), 7.39 (m, 6 H), 5.86 (dddd, *J* = 17.2, 10.7, 5.9, 4.9 Hz, 1 H), 5.23 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H), 5.14 (ddd, *J* = 10.7, 1.7, 1.3 Hz, 1 H), 5.09 (d, *J* = 4.7 Hz, 1 H), 4.16 (ddd, *J* = 13.3, 4.9, 1.6 Hz, 1 H), 3.94 (m, 3 H), 3.79 (dd, *J* = 10.7, 5.6 Hz, 1 H), 3.72 (m, 2 H), 2.93 (m, 1 H), 2.65 (dd, *J* = 14.0, 2.9 Hz, 1 H), 2.30 (m, 1 H), 1.90 (m, 2 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 135.7, 134.1, 133.5, 129.8, 127.8, 116.9, 98.5, 69.2, 67.7, 66.7, 60.2, 51.6, 34.4, 26.9, 22.8, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3071, 3049, 2956, 2930, 2859, 1663, 1472, 1462, 1428, 1362, 1287, 1136, 1113, 1031, 823, 703 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{36}NO_3Si$ $[M + H]^+$ 450.2459; found 450.2474. Data for aziridine **13**: $[\alpha]_D^{25}$ = +29.9 (*c* = 0.97, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (m, 4 H), 7.40 (m, 6 H), 5.93 (dddd, *J* = 17.2, 10.3, 6.2, 5.2 Hz, 1 H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.20 (dd, *J* = 10.3, 1.6 Hz, 1 H), 4.60 (s, 1 H), 4.34 (td, *J* = 6.2, 2.3 Hz, 1 H), 4.15 (ddt, *J* = 12.9, 5.2, 1.5 Hz, 1 H), 4.01–3.87 (m, 3 H), 3.05 (m, 1 H), 2.81 (m, 2 H), 2.41 (m, 2 H), 2.16 (m, 1 H), 1.81 (m, 1 H), 1.08 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 134.3, 133.5, 129.8, 127.8, 117.6, 98.0, 67.9 (2 C), 64.9, 49.0, 40.2, 38.4, 37.1, 36.6, 26.9, 19.3 ppm. FTIR (neat): $\tilde{\nu}$ = 3071, 3049, 2956, 2931, 2858, 1472, 1463, 1428, 1391, 1362, 1190, 1113, 1089, 1029, 999, 823, 740, 703 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{36}NO_3Si$ $[M + H]^+$ 450.2459; found 450.2478.

Boc-Protected Amine 14: To a solution of **6** (500 mg, 1.11 mmol) in MeOH (25 mL) at 0 °C was added $NaBH_4$ (84 mg, 2.22 mmol).

After 30 min, the mixture was warmed to room temperature and stirred for an additional 1 h. Then, a saturated solution of NH_4Cl (10 mL) was added, and the MeOH was removed under reduced pressure. The resulting residue was diluted with aqueous NaOH (1 N solution, 10 mL), and the mixture was thoroughly extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude amine was dissolved in CH_2Cl_2 (25 mL), and the resulting solution was cooled to 0 °C. Et_3N (0.23 mL, 1.66 mmol) and $(Boc)_2O$ (291 mg, 1.33 mmol) dissolved in CH_2Cl_2 (3 mL) were sequentially added. The mixture was left at 0 °C for 30 min and then at room temperature for 12 h. The solvent was removed under reduced pressure, and the crude oil was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 9:1) to yield **14** (521 mg, 85%) as a colorless oil. $[\alpha]_D^{25}$ = –3.9 (*c* = 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 4 H), 7.38 (m, 6 H), 5.89 (dddd, *J* = 17.2, 10.5, 5.3, 4.9 Hz, 1 H), 5.25 (d, *J* = 17.2 Hz, 1 H), 5.14 (ddd, *J* = 10.5, 1.6, 1.4 Hz, 1 H), 4.95 (d, *J* = 4.9 Hz, 1 H), 4.27 (m, 1 H), 3.96 (m, 3 H), 3.66 (m, 2 H), 3.52 (m, 1 H), 3.42 (m, 1 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.12 (m, 1 H), 1.95 (m, 1 H), 1.79 (m, 1 H), 1.46 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 135.8, 134.8, 133.7, 129.8, 127.8, 116.4, 97.0, 68.5, 67.6, 66.8, 53.4, 47.5, 41.0, 28.0 (2 C), 27.4, 27.1, 24.5, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3050, 2931, 2859, 1811, 1757, 1694, 1474, 1456, 1428, 1393, 1366, 1262, 1211, 1172, 1113, 1034, 824, 741, 703, 613 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{45}NNaO_5Si$ $[M + Na]^+$ 574.2959; found 574.2975.

Imino Alcohol 15: Tetrabutylammonium fluoride trihydrate (320 mg, 1.02 mmol) was added to a solution of **6** (230 mg, 0.051 mmol) in THF (10 mL). The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residual oil was purified by flash chromatography (silica gel, gradient from DCM to DCM/MeOH, 4%) to afford compound **15** (87 mg, 81%) as a yellow oil. $[\alpha]_D^{25}$ = +229.3 (*c* = 1.60, CH_3Cl_3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84 (dddd, *J* = 17.2, 10.6, 5.9, 5.1 Hz, 1 H), 5.22 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H), 5.13 (ddd, *J* = 10.4, 1.6, 1.5 Hz, 1 H), 5.08 (d, *J* = 4.6 Hz, 1 H), 4.14 (ddt, *J* = 13.3, 5.1, 1.5 Hz, 1 H), 3.97–3.84 (m, 3 H), 3.75–3.58 (m, 3 H), 2.91 (m, 1 H), 2.38 (dd, *J* = 13.9, 3.1 Hz, 1 H), 1.88 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 133.9, 117.1, 98.8, 69.1, 67.9, 65.1, 60.1, 51.6, 33.5, 22.8 ppm. FTIR (neat): $\tilde{\nu}$ = 3233, 2914, 2871, 1664, 1461, 1424, 1370, 1344, 1314, 1288, 1132, 1032, 979, 955, 820, 731 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{18}NO_3$ $[M + H]^+$ 212.1281; found 212.1291.

Amide 16: Sodium borohydride (31 mg, 0.81 mmol) was added to a solution of compound **15** (86 mg, 0.41 mmol) in absolute methanol (5 mL) at 0 °C. After 45 min, the reaction was quenched with a saturated NH_4Cl solution, and the resulting mixture was concentrated under reduced pressure. The residue was diluted with aqueous NaOH (1 N solution, 5 mL), and the resulting solution was thoroughly extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. Et_3N (0.23 mL, 1.63 mmol) and 3,5-dinitrobenzoyl chloride (281 mg, 1.22 mmol) were sequentially added. After stirring at room temperature for 8 h, the reaction mixture was quenched with a saturated NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 6:4) to afford compound **16** (48 mg, 19%) as a yellow solid; m.p. 193–195 °C. $[\alpha]_D^{25}$ = +0.09 (*c* = 1.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (t, *J* = 2.1 Hz, 1 H), 9.19 (d, *J* = 2.1 Hz, 2 H), 9.12 (t, *J* = 2.1 Hz, 1 H), 8.76 (d, *J* = 2.1 Hz, 2 H), 6.01 (dddd, *J* = 17.1, 10.6, 5.6, 4.9 Hz, 1 H), 5.36 (ddd, *J* = 17.1, 1.7, 1.6 Hz, 1 H), 5.32 (dd, *J* = 10.6, 1.5 Hz, 1 H), 5.04 (d, *J* = 5.4 Hz, 1 H), 4.50 (d, *J* = 5.6 Hz, 2 H), 4.38 (m, 3 H), 4.07 (m, 2 H), 3.32 (t, *J* = 9.0 Hz, 1 H), 2.73 (m, 2 H), 2.04 (m, 1 H), 1.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 162.4, 148.8, 148.6, 140.3 (2 C), 133.7, 129.6, 128.1, 122.7, 120.4, 117.7, 97.4, 68.7, 68.6, 62.1, 54.8, 52.3, 39.3, 27.0, 26.5 ppm. FTIR (KBr): $\tilde{\nu}$ = 3100, 2922, 1733, 1631, 1543, 1463, 1404, 1345, 1281, 1171, 1079, 1024, 921, 730, 721 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{24}N_5O_{13}$ $[M + H]^+$ 602.1365; found 602.1365.

Lactol 17: Compound **14** (500 mg, 0.91 mmol) was dissolved in THF/H_2O (9:1, 30 mL) at room temperature. Then, $PdCl_2$ (160 mg, 0.91 mmol) was added. After 8 h, additional catalyst (0.2 equiv.) was added, and, after 24 h, more catalyst (0.2 equiv.) was added. After 36 h, the reaction mixture was filtered through a plug of Celite. The filtrate was diluted with water, and the resulting mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 3:7) to afford the lactol **17** (354 mg, 76%) as a mixture of diastereomers (85:15). Data for major diastereomer: $[\alpha]_D^{25}$ = –2.1 (*c* = 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.39 (m, 6 H), 4.94 (d, *J* = 5.0 Hz, 1 H), 4.22 (m, 1 H), 4.08 (d, *J* = 17.4 Hz, 1 H), 3.97 (m, 1 H), 3.91 (m, 1 H), 3.54 (m, 2 H), 2.51 (m, 1 H), 2.33 (m, 1 H), 2.09 (m, 1 H), 2.06 (m, 1 H), 1.84 (m, 1 H), 1.45 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 135.8, 133.7, 129.9, 127.9, 98.0, 72.7, 68.1, 53.2, 47.4, 40.9, 28.8, 27.1 (2 C), 26.6, 24.9, 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3050, 1733, 1694, 1474, 1455, 1428, 1393, 1366, 1334, 1254, 1172, 1148, 1113, 1064, 824, 741, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{40}NO_5Si$ $[M - H]^-$ 510.2681; found 510.2669. Data for minor diastereomer: $[\alpha]_D^{25}$ = –62.0 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.39 (m, 6 H), 4.69 (br. s, 1 H), 4.06 (m, 1 H), 3.99 (m, 1 H), 3.72–3.61 (m, 3 H), 3.59 (m, 1 H), 3.33 (ddd, *J* = 10.6, 8.6, 8.4 Hz, 1 H), 2.17 (m, 1 H), 1.84 (m, 2 H), 1.75 (m, 2 H), 1.46 (s, 9 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 135.8, 133.5, 129.8, 127.8, 95.3, 71.2, 66.9, 54.5, 46.4, 43.9, 28.6, 28.7, 27.0, 26.4 (2 C), 19.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3072, 3050, 1733, 1694, 1474, 1455, 1428, 1393, 1366, 1334, 1254, 1172, 1148, 1113, 1064, 824, 741, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{42}NO_5Si$ $[M + H]^+$ 512.2827; found 512.2858.

Lactone 18: Lactol **17** (180 mg, 0.35 mmol) was dissolved in acetone (10 mL), and some anhydrous magnesium sulfate was added. Then, the solution was cooled to 0 °C, and freshly prepared Jones reagent (2 mL) was added dropwise. After 30 min, the mixture was warmed to room temperature over 1 h. Isopropyl alcohol (5 mL) was then added to destroy the excess Jones reagent, and the mixture was filtered through a small pad of Celite. The solvent was removed in vacuo, and the crude residue was dissolved in a solution of $NaHCO_3$, and the resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was used in the next step without further purification. Tetrabutylammonium fluoride trihydrate (110 mg, 0.35 mmol) was added to a solution of the crude lactone in THF (15 mL). The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 2:8) to afford **18** (52 mg, 55%, 2 steps) as a colorless oil. $[\alpha]_D^{25}$ = –89.3 (*c* = 2.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.47 (m, 1 H), 4.21 (br. s, 1 H), 3.82 (d, *J*

= 11.3 Hz, 1 H), 3.68 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.52 (br. s, 1 H), 3.37 (dt, *J* = 11.1, 7.1 Hz, 1 H), 3.21 (m, 1 H), 2.33 (m, 1 H), 2.27 (m, 1 H), 2.19 (m, 1 H), 1.97 (ddd, *J* = 14.7, 10.5, 4.2 Hz, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 154.5, 77.0, 64.7, 53.6, 46.4, 43.2, 29.6, 28.6 (2 C), 28.1 ppm. FTIR (neat): $\tilde{\nu}$ = 3444, 2976, 2935, 2880, 1732, 1694, 1399, 1367, 1260, 1167, 1096, 1049, 856, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{22}NO_5$ $[M + H]^+$ 272.1492; found 272.1495.

Bromide 19: Lactone **18** (100 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. Carbon tetrabromide (184 mg, 0.56 mmol) and triphenylphosphane (147 mg, 0.56 mmol) were added, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Upon completion, the solvent was removed in vacuo, and the crude residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 7:3) to obtain **19** (90 mg, 70%) as a white solid; m.p. 90–92 °C. $[\alpha]_D^{25}$ = –96.1 (*c* = 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.55 (m, 1 H), 4.19 (br. s, 1 H), 3.52 (m, 3 H), 3.36 (dt, *J* = 11.2, 7.3 Hz, 1 H), 3.23 (m, 1 H), 2.59 (m, 1 H), 2.24 (m, 2 H), 1.93 (ddd, *J* = 14.7, 10.6, 4.0 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 154.4, 74.8, 53.5, 46.4, 43.1, 33.4, 29.5, 28.6 (2 C), 28.0 ppm. FTIR (KBr): $\tilde{\nu}$ = 3449, 2960, 2926, 2854, 2097, 1739, 1694, 1394, 1367, 1260, 1168, 1115, 1042 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{24}N_2O_4Br$ $[M + NH_4]^+$ 351.0903; found 351.0927.

Compound 22: Bromide **19** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (trifluoroacetic acid, 0.5 mL) was added dropwise. The reaction mixture was stirred for 90 min, and then the solvent was removed in vacuo. The crude amine was then dissolved in MeOH (5 mL), and freshly prepared NaOMe (solution in methanol, 1 mL) was added. The reaction was stirred at room temperature for 1 h, and the methanol was eliminated under reduced pressure. The crude residue was dissolved in HCl (5% solution), and the resulting mixture was extracted with diethyl ether (1 × 10 mL). The aqueous layer was basified with NaOH (1 N solution), and the resulting solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to obtain hydroxy ester **20** that was used without further purification. To a solution of the crude hydroxy ester in CH_2Cl_2 (4 mL), *O*-benzyl-protected hydroferulic acid **21** (43 mg, 0.15 mmol), DMAP [4-(dimethylamino)pyridine, 0.24 mg, 0.002 mmol], and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (40 mg, 0.21 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h and then filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to CH_2Cl_2/MeOH, 2%) to afford **22** (34 mg, 50%) as a white solid; m.p. 101–103 °C. $[\alpha]_D^{25}$ = –3.8 (*c* = 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H), 7.33 (m, 2 H), 7.27 (m, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 6.64 (m, 1 H), 5.33 (t, *J* = 5.0 Hz, 1 H), 5.10 (s, 2 H), 4.14 (m, 1 H), 3.84 (s, 3 H), 3.68 (s, 3 H), 3.36 (d, *J* = 12.1 Hz, 1 H), 3.26–3.17 (m, 2 H), 2.88–2.78 (m, 4 H), 2.60 (td, *J* = 8.0, 2.7 Hz, 2 H), 2.14 (m, 1 H), 2.05 (m, 1 H), 1.95 (dd, *J* = 14.2, 7.0 Hz, 1 H), 1.72 (ddd, *J* = 14.2, 10.0, 5.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 172.6, 149.7, 146.6, 137.4, 133.7, 128.6, 127.8, 127.3, 120.1, 114.2, 112.3, 75.8, 71.2, 64.3, 59.9, 56.0, 53.4, 52.0, 46.4, 36.1, 34.2, 30.5, 27.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 3062, 3033, 2951, 2871, 1732, 1606, 1591, 1463, 1455, 1419, 1378, 1262, 1231, 1158, 1139, 1034, 853, 807, 736, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{32}NO_6$ $[M + H]^+$ 454.2224; found 454.2240.

Amphorogynine C (3): Activated Pd/C (10%, 4 mg) was added in a single portion to a solution of **22** (35 mg, 0.077 mmol) in EtOAc (3 mL). The mixture was stirred under H_2 for 2 h. Upon completion, the mixture was filtered through Celite by using several washes of EtOAc to ensure quantitative transfer. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to CH_2Cl_2/MeOH, 3%) to obtain amphorogynine C (**3**, 21 mg, 75%) as a white solid; m.p. 120 °C. $[\alpha]_D^{25}$ = –1.7 (*c* = 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 1.9 Hz, 1 H) 6.65 (dd, *J* = 8.0, 1.9 Hz, 1 H), 5.34 (t, *J* = 4.6 Hz, 1 H), 4.03 (m, 1 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.28 (d, *J* = 11.8 Hz, 1 H), 3.19 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1 H), 3.13 (m, 1 H), 2.87 (m, 1 H), 2.85 (m, 2 H), 2.80 (m, 1 H), 2.58 (t, *J* = 8.5 Hz, 2 H), 2.12 (m, 1 H), 1.99 (m, 1 H), 1.90 (dd, *J* = 14.1, 6.9 Hz, 1 H), 1.68 (ddd, *J* = 14.1, 9.7, 5.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 172.8, 146.7, 144.3, 132.3, 120.9, 114.6, 111.1, 76.3, 64.6, 60.4, 56.0, 53.8, 52.0, 46.7, 36.4, 34.4, 30.7, 27.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 2952, 1732, 1597, 1516, 1452, 1436, 1377, 1275, 1236, 1202, 1156, 1125, 1035, 754 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{26}NO_6$ $[M + H]^+$ 364.1755; found 364.1765.

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

Acknowledgments

We thank the Spanish Ministry of Economy and Competitivity (Project CTQ2010-19295) for its financial support as well as for the purchase of a QToF-HRMS instrument (Project CTQ2007-28978-E). I. M. (JAE predoc fellowship) and E. M. (I3P contract) thank the Spanish National Research Council (CSIC). We also thank Jose Antonio Romero of Universidad Autónoma of Madrid for assistance with the optical rotation measurements of amphorogynine C.

[1] For reviews on the pyrrolizidine alkaloids, see: a) M. Dreger, M. Stanislawska, A. Krajewska-Patan, S. Mielcarek, P. L. Mikolajczak, W. Buchwald, *Herba Pol.* **2009**, *55*, 127–146; b) W.-M. Dai, Y. Nagao, *Heterocycles* **1990**, *30*, 1231–1261; c) D. J. Robins, *Nat. Prod. Rep.* **1989**, *6*, 221–230.

[2] D. T. T. Huong, M.-T. Martin, M. Litaudon, T. Sévenet, M. Païs, *J. Nat. Prod.* **1998**, *61*, 1444–1446.

[3] H. Yoda, T. Egawa, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 1643–1646.

[4] a) C. Roche, P. Delair, A. E. Greene, *Org. Lett.* **2003**, *5*, 1741–1744; b) C. Roche, K. Kadlecíková, A. Veyron, P. Delair, C. Philouze, A. E. Greene, *J. Org. Chem.* **2005**, *70*, 8352–8363.

[5] I. de Miguel, B. Herradón, E. Mann, *Adv. Synth. Catal.* **2012**, *354*, 1731–1736.

[6] A. Montero, E. Mann, B. Herradón, *Eur. J. Org. Chem.* **2004**, 3063–3073.

[7] a) L. Wolff, *Justus Liebigs Ann. Chem.* **1912**, *394*, 23–59; b) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–632.

[8] a) S. Bräse, A. Friedrich, M. Gartner, T. Schröder, *Top. Heterocycl. Chem.* **2008**, *12*, 45–115; b) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247–12275; c) C. K. Sha, A. K. Mohanakrishnan in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, pp. 623–629.

[9] For representative examples, see: a) B. W. Q. Hui, S. Chiba, *Org. Lett.* **2009**, *11*, 729–732; b) Y. Zhou, P. V. Murphy, *Org. Lett.* **2008**, *10*, 3777–3780; c) S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho, D. Kim, *J. Org. Chem.* **2007**, *72*, 4886–4891; d) Y. Konda-Yamada, K. Asano, T. Satou, S. Monma, M. Sakayanagi, N. Satou, K. Takeda, Y. Harigaya, *Chem. Pharm. Bull.* **2005**, *53*, 529–536; e) V. Santagada, E. Perissutti,

F. Fiorino, B. Vivenzio, G. Caliendo, *Tetrahedron Lett.* **2001**, *42*, 2397–2400; f) W. H. Pearson, H. Suga, *J. Org. Chem.* **1998**, *63*, 9910–9918; g) J. M. Schkeryantz, W. H. Pearson, *Tetrahedron* **1996**, *52*, 3107–3116; h) R. B. Bennet, J. R. Choi, W. D. Montgomery, J. K. Cha, *J. Am. Chem. Soc.* **1989**, *111*, 2580–2582.

[10] CCDC-872920 (for **16**) and -872921 (for **3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] L. Ban, M. Mrksich, *Angew. Chem.* **2008**, *120*, 3444; *Angew. Chem. Int. Ed.* **2008**, *47*, 3396–3399.

[12] J.-E. Bäckvall (Ed.), *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2004**.

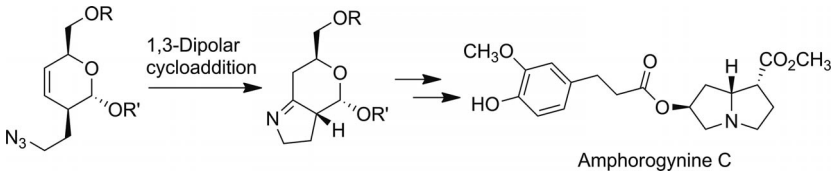
[13] S. Valverde, B. Herradon, R. M. Rabanal, M. Martín-Lomas, *Can. J. Chem.* **1987**, *65*, 339–342; S. Valverde, A. Hernández, B. Herradón, R. M. Rabanal, *Tetrahedron* **1987**, *43*, 3499–3503.

[14] D. Li, B. Zhao, S.-P. Sim, T.-K. Li, A. Liu, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem.* **2003**, *11*, 3795–3805.

[15] Because of the low absolute value of the optical rotation described for amphorogynine C, we measured it at different wavelengths: $[\alpha]_D$ = –1.7 (*c* = 1.3, $CHCl_3$), $[\alpha]_{578}$ = –1.9 (*c* = 1.3, $CHCl_3$), $[\alpha]_{546}$ = –2.3 (*c* = 1.3, $CHCl_3$), $[\alpha]_{465}$ = –1.8 (*c* = 1.3, $CHCl_3$), $[\alpha]_{365}$ = –27.1 (*c* = 1.3, $CHCl_3$). These values are in agreement with the negative sign for the optical rotation reported for the natural compound.[2]

Received: March 27, 2012
Published Online: ■

Pyrrolizidine Alkaloids



Amphorogynine C

The first synthesis of the representative pyrrolizidine alkaloid amphorogynine C is described. The key step includes an intramolecular azide–olefin cycloaddition reaction. The proposed structure of the natural product was confirmed by single-crystal X-ray diffraction analysis.

Keywords: Total synthesis / Alkaloids / Cycloaddition / Natural products / Azides

