Synthesis of Furanomycin Derivatives by Gold-Catalyzed Cycloisomerization of α-Hydroxyallenes

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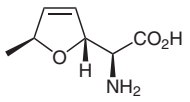
Abstract: The novel furanomycin analogues **8** and **17** were synthesized as mixture of two diastereomers using the gold-catalyzed cycloisomerization of α-hydroxyallenes as the key step. Compared to the traditional use of stoichiometric amounts of silver salts, gold catalysis is much more efficient for the cyclization of highly functionalized substrates.

Key words: allenes, amino acids, cycloisomerization, furanomycin, gold catalysis

The nonproteinogenic α-amino acid (+)-furanomycin (**1**, Figure 1) is one of very few natural products containing a 2,5-dihydrofuran ring. It was first isolated in 1967 by Katagiri et al.[1] from *Streptomyces threomyceticus* and it is one of the smallest antibiotic natural products, inhibiting bacterial protein synthesis by mimicking isoleucine.[2] Due to its activity and moderate chemical complexity, several syntheses of furanomycin[3] and derivatives thereof[4] have been disclosed, often using sugars as the starting material.



(+)-furanomycin (**1**)

Figure 1

By taking advantage of the high reactivity and axial chirality of allenes,[5] we have recently established an efficient and stereoselective synthesis of 2,5-dihydrofurans by gold-catalyzed cycloisomerization of α-hydroxyallenes.[6] This reaction takes place with axis-to-center chirality transfer and was subsequently expanded to the corresponding gold-catalyzed cyclization of β-hydroxyallenes,[7] α-/β-aminoallenes,[7,8] and α-sulfanylallenes[9] to afford five- or six-membered heterocycles. The utility of the method was also demonstrated by the first total synthesis of the β-carboline alkaloids (–)-isocyclocapitelline and (–)-isochrysotricine.[10] Even though furanomycin shows a rather narrow structure–activity relationship,[2] we became interested in the synthesis of unusual amino acids of this type, which may find use in artificial peptides; this would further broaden the scope of the gold-catalyzed cyclization of functionalized allenes.

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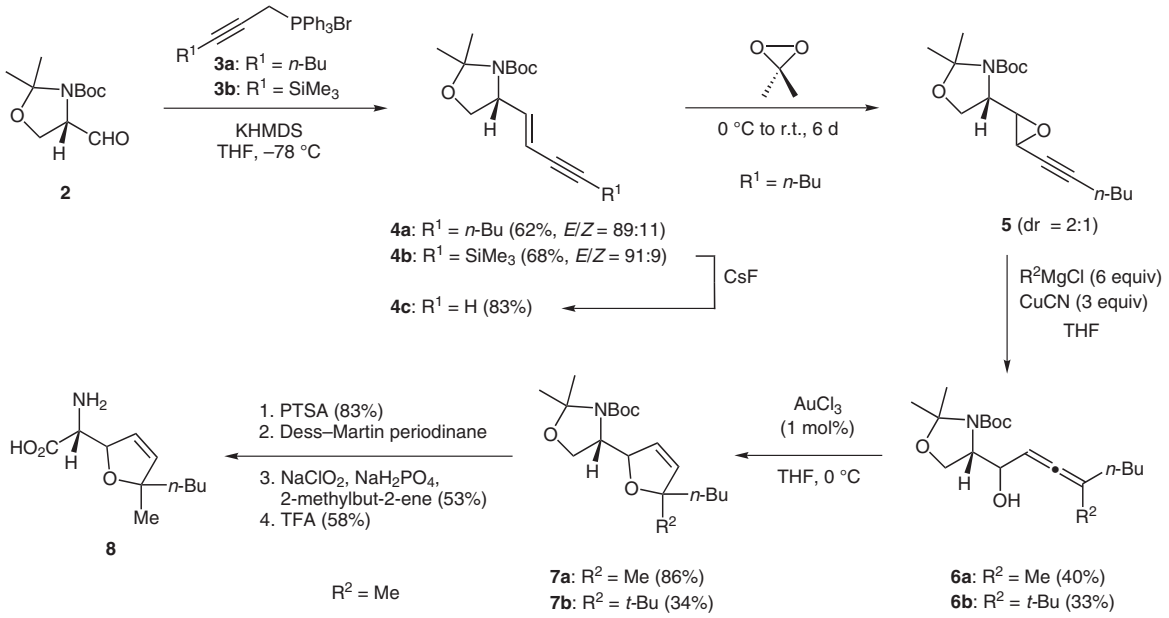
Van Brunt and Standaert[3d] have reported an enantioselective synthesis of (+)-furanomycin (**1**) from Garner's aldehyde (*R*)-**2**, using the silver-mediated cyclization of a chiral α-hydroxyallene, which was prepared by S_N2'-reduction of propargyl silyl ether with lithium aluminum hydride. Our approach, on the other hand, takes advantage of the copper-mediated S_N2'-substitution of propargyloxiranes, which provides a versatile and reliable access to α-hydroxyallenes.[6–11] Thus, Garner's aldehyde (*S*)-**2**[12] was subjected to Wittig alkenation with the propargylphosphonium salts **3a**,**b** to give the conjugated enynes **4a**,**b** in 62% and 68% yield, respectively and with good *trans* selectivity (Scheme 1). The use of the corresponding propargylphosphonates was less effective in terms of both yield and selectivity. Smooth desilylation of **4b** was achieved with cesium fluoride in acetonitrile–water[13] to give **4c** in 83% yield, whereas other fluoride sources (*n*-$Bu_4NF{\cdot}3\ H_2O$, THF or $KF{\cdot}2\ H_2O$, DMF) or strongly basic conditions (KOH, MeOH, reflux)[14] were less effective. Unfortunately, the enynes **4** were very unreactive towards common double bond oxidizing agents (MCPBA; OsO_4, NMO; $RuCl_3$, $NaIO_4$); the only exception is the reaction of **4a** with an excess of dimethyldioxirane (DMDO)[15] for six days, which afforded the labile propargyloxirane **5** as a 2:1 mixture of diastereomers. The next step, the copper-mediated S_N2' substitution of **5** with three equivalents of a magnesium cyanocuprate, provided the desired α-hydroxyallenes **6a**,**b** in 40% and 33% yield, respectively, over two steps. The excess of cuprate is necessary due to deactivation by coordination of the reagent to the heteroatoms of the substrate.

For the formation of the 2,5-dihydrofuran by cycloisomerization of the α-hydroxyallene **6a**, gold(III) chloride in tetrahydrofuran[6d] was identified as the best precatalyst, affording the dihydrofuran **7a** in 86% yield. Just 1 mol% of the gold catalyst was sufficient for complete conversion of **6a**; in contrast to this, the silver-mediated hydroxyallene cyclization used in the synthesis of (+)-furanomycin required stoichiometric amounts of silver nitrate.[3d] Low temperature (0 °C) is necessary to avoid acetal cleavage by the gold salt, which was also observed with prolonged reaction times and less coordinating solvents like dichloromethane. Not surprisingly, the sterically demanding *tert*-butyl-substituted allene **6b** reacted more sluggishly and gave the dihydrofuran **7b** in only 34% yield, accompanied by several side products. The final steps to the amino acid were carried for **7a** and followed well-established procedures:[3,4] *N*,*O*-acetal cleavage with 4-toluenesulfonic



Scheme 1 Synthesis of the furanomycin derivative **8** by gold-catalyzed cycloisomerization of α-hydroxyallene **6a**

acid, two-step oxidation using Dess–Martin periodinane[16] and sodium chlorite in buffered solution,[17] and finally cleavage of the Boc group with trifluoroacetic acid. Purification of the crude product by ion exchange chromatography gave the new furanomycin derivative **8** as a 2:1 mixture of diastereomers (accompanied by small amounts of a third isomer).

Due to the lack of reactivity of the enynes **4**, we did not pursue a diastereoselective synthesis of the propargyloxirane **5** or related allene precursors. Rather, we turned our attention to enynes bearing the oxazolidine ring at the triple bond instead of the double bond. Again starting from Garner's aldehyde **2**, we employed the well-known Corey–Fuchs homologation[18] to obtain the dibromoalkene **9** in good yield (80%, Scheme 2). Here, the use of 4 equivalents of triphenylphosphine (instead of 2 equiv as described by Reginato et al.[19]) gave reproducible results. The Stille coupling[20] of **9** with tributylvinyltin according to a procedure described by Shen and Wang[21] furnished the desired enyne **10** in 49% yield. The presence of copper iodide as a co-catalyst is essential, otherwise complete decomposition takes place.[22] However, the allene synthesis

Biographical Sketches

Jörg Erdsack was born in Halle an der Saale in 1977. He studied chemistry in Magdeburg and Jena and obtained his Diploma from Friedrich-Schiller-Universität Jena in 2005. Since 2005, he has been a Ph.D. student in Prof. Krause's group in Dortmund. His research focuses on the application of homogeneous gold catalysis for the synthesis of biologically active target molecules.

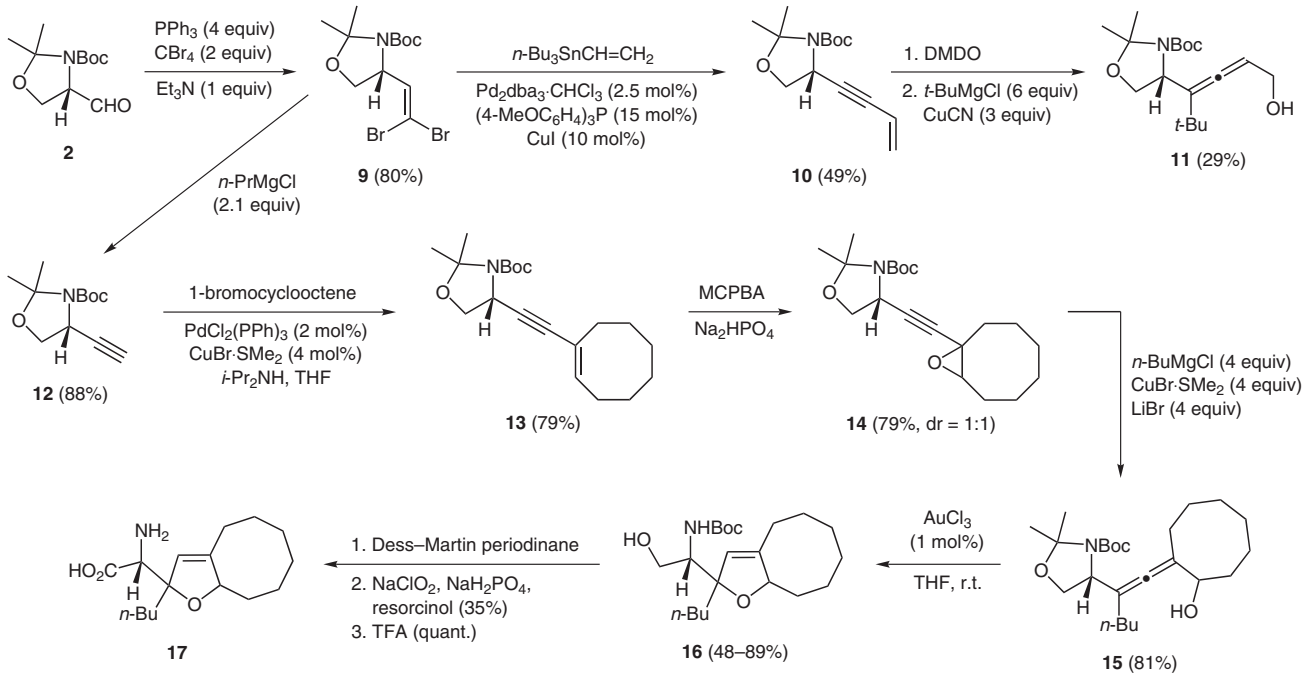
Norbert Krause obtained his Ph.D. in 1986 at the Technical University of Braunschweig and was a Postdoctoral Fellow at the ETH Zürich (Switzerland) and Yale University (New Haven, USA). He obtained his Habilitation for Organic Chemistry at the Technical University of Darmstadt in 1993, he became Associate Professor at Bonn University in 1994, and later Full Professor at Dortmund University in 1998. His research in organometallic and allene chemistry has been recognized through the award of the Heinz-Maier-Leibnitz-Preis (1991), a Heisenberg scholarship (1994), and a 'Japan Society for the Promotion of Science (JSPS) Fellowship' (2003). He is member of the Editorial Board of the European Journal of Organic Chemistry (since 2006) and was Guest Professor at the Université Catholique de Louvain (Louvain-la-Neuve, Belgium) in 2007.

by epoxidation of **10** with dimethyldioxirane and treatment of the crude propargyloxirane with *tert*-butylcyanocuprate was rather unrewarding, affording the desired α-hydroxyallene **11** in only 29% yield over two steps. Extensive variation of the copper reagent and the reaction conditions did not improve this result.

In order to render the enyne more electron rich and thus more susceptible to epoxidation, we next prepared the allene precursor **13** bearing an endocyclic double bond. The required alkyne **12** was obtained in 88% yield by treating dibromoalkene **9** with a slight excess of propylmagnesium chloride,[23] a procedure that avoids ring degradation, which is observed when butyllithium is used as the base.[19] With this protocol in hand, the synthesis of **12** starting from **2** was achieved in high yield on a multigram scale, which, in our hands, is more convenient than the one-step homologation with the Bestmann–Ohira reagent.[24] The Sonogashira coupling[14,25] of **12** with 1-bromocyclooctene in tetrahydrofuran as solvent[26] proceeded smoothly to afford the enyne **13** in 79% yield. As expected, epoxidation of **13** is very facile, taking place even upon exposure to air; accordingly, the reaction of **13** with 3-chloroperbenzoic acid is fast (complete conversion after 3 h at 0 °C) and furnished oxirane **14** (1:1 mixture of diastereomers) in 79% yield.

The conversion of propargyloxirane **14** into α-hydroxyallene **15** was first carried out as in Scheme 1 using a magnesium cyanocuprate, but this afforded a mixture of four diastereomers, indicating epimerization of the allene by the copper reagent.[11] The use of phosphines or phosphites as an additive prevented the epimerization,[11] but separation of the product from the additive was difficult. Application of iron catalysis as described by Fürstner and Mendez[27] also failed because of insufficient reactivity of the substrate **14**. Finally, stereoselective allene formation was achieved by using equimolar amounts of butylmagnesium chloride, copper bromide–dimethyl sulfide complex, and lithium bromide.[28] This afforded the desired allene **15** as a 1:1 mixture of two diastereomers. Again, an excess of the cuprate is necessary to ensure complete conversion of the substrate.

The cycloisomerization of **15** in the presence of 1 mol% of gold(III) chloride in tetrahydrofuran proceeded smoothly and in high yield (89%) on a 20-mg scale to afford the bicyclic dihydrofuran **16** with concomitant acetal cleavage. On a larger scale (150 mg of **15**), however, the yield dropped to 48%. The following oxidation of the primary alcohol to the carboxylic acid was difficult. Treatment of the crude aldehyde (obtained by oxidation of **16** with Dess–Martin periodinane[16]) with sodium chlorite in the presence of 2-methylbut-2-ene[17] similar to the sequence shown in Scheme 1 gave the Boc-protected amino acid in low yield (<20%) and with unsatisfactory purity. Problems with the oxidation step in the synthesis of unsaturated amino acids are not uncommon.[23b,29] Other oxidation methods[30,31] did not solve the problem; for example, the reaction of **16** with pyridinium dichromate in *N*,*N*-dimethylformamide[4b,31] stopped at the aldehyde stage. Further experiments with sodium chlorite as the oxidizing agent revealed that a somewhat higher yield of the carboxylic acid (35% over 2 steps) can be achieved by using resorcinol[32] instead of 2-methylbut-2-ene as a scavenger for electrophilic chlorine. Gratifyingly, the final cleavage of the Boc group with trifluoroacetic acid took place without problem to afford the bicyclic furanomycin derivative **17** as a 1:1 mixture of diastereomers. We are now investigating the diastereoselective epoxidation of enyne **13** in



Scheme 2 Synthesis of the bicyclic furanomycin derivative **17** by gold-catalyzed cycloisomerization of α-hydroxyallene **15**

order to obtain the amino acid **17** in diastereo- and enantiomerically pure form.

In summary, we have developed new pathways towards unconventional furanomycin derivatives based on the gold-catalyzed cycloisomerization of α-hydroxyallenes derived from conjugated enynes. Compared to the traditional use of stoichiometric amounts of silver salts, gold catalysis is much more efficient even for the highly functionalized substrates examined here. The low reactivity of the enynes **4** and **10** towards double bond oxidizing agents prevented a stereoselective synthesis of the corresponding furanomycin derivatives; in contrast to this, the facile epoxidation of enyne **13** suggests that a completely stereoselective synthesis of furanomycin analogues of the type **17** should be possible. These results demonstrate that homogeneous gold catalysis is a highly useful tool for the preparation of complex target products, and we are currently pursuing further applications of this method.

Melting points were determined with a Reichert thermovar melting point apparatus and are uncorrected. IR spectra were obtained with a Nicolet Avatar 320 FT-IR spectrophotometer either as KBr pellets or as a liquid film between NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX 400 or a Bruker DRX 500 spectrometer using the signals of the undeuterated solvent as the standard. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$: δ = 7.26 for protons, δ = 77.0 for carbon atoms; C_6D_6: δ = 7.27 for protons, δ = 128.0 for carbon atoms; DMSO-d_6: δ = 2.50 for protons, δ = 39.7 for carbon atoms; CD_3OD: δ = 3.31 for OH-proton, δ = 49.05 for carbon atoms; D_2O: δ = 4.81 for protons). Carbon atoms were assigned with APT experiments. The products bearing a Boc group often show broadened and/or duplicated peaks in NMR spectra due to slow conformational inversion. In diastereomeric mixtures, the peaks of the main isomer were assigned with an asterisk (*) if possible. FAB MS spectra were measured with a JEOL JMS-SX102A mass spectrometer, ESI spectra with a LTQ ORBITRAP equipped with a Hypersil gold column (diameter 50 × 1 mm, particle size 1.9 μm). Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Diastereomeric ratios were determined on an AS800 (CE Instruments) gas chromatograph equipped with a CP-SIL-5CB column (low bleed 30 m, 0.32 mm ID, DF 0.25 μm) with helium as carrier gas if not otherwise noted. All reactions were carried out under an argon atmosphere in oven-dried glassware. THF was distilled from Na/benzophenone, CH_2Cl_2 and DMF were distilled from CaH_2 prior to use. TLC plates were visualized by immersion in a soln of alkaline permanganate [$KMnO_4$ (2 g), Na_2CO_3 (10 g), H_2O (200 mL)], followed by heating. Silica gel (particle size 0.035–0.070 mm) and Florisil (60–100 mesh) were purchased from ACROS. Grignard reagents were titrated with salicylaldehyde phenylhydrazone according to the procedure of Love and Jones.[33] Tris(4-methoxyphenyl)phosphine was purchased from Aldrich and was recrystallized from acetone–MeOH (1:1) prior to use. CBr_4 was recrystallized from anhyd EtOH prior to use. The $AuCl_3$ stock soln were prepared by dissolving the gold salt in the appropriated volume of anhyd MeCN in a dry Schlenk tube under argon and cooling with ice. DOWEX 50W-X8 cation exchange resin was purchased from Fluka.

tert-Butyl (*R*)-2,2-Dimethyl-4-(oct-1-en-3-ynyl)oxazolidine-3-carboxylate (4a)

In a 50-mL Schlenk tube equipped with a magnetic stirrer bar, a suspension of (hept-3-ynyl)triphenylphosphonium bromide[34] (**3a**, 496 mg, 1.13 mmol, 1.3 equiv) in anhyd THF (10 mL) was cooled to 0 °C under argon. With stirring, 0.5 M KHMDS in toluene (2.27 mL, 1.13 mmol, 1.3 equiv) was added dropwise to give an orange-red soln. After 5 min the mixture was cooled to –78 °C and a soln of **2**[12b] (200 mg, 0.87 mmol, 1.0 equiv) in anhyd THF (2 mL) was added slowly by syringe on the inner surface of the flask. The mixture was allowed to warm to r.t. overnight (~12 h). It was diluted with Et_2O and sat. aq NH_4Cl (10 mL) was added dropwise. The organic phase was separated, the residue was diluted with H_2O and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 93:7) to give enyne **4a** (166 mg, 62%) as a mixture of isomers (*E*/*Z* 89:11, GC). For analytical purposes, small samples of the pure isomers were obtained by repeated column chromatography.

(*E*)-4a

Colorless oil; R_f = 0.45 (isohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ +190.4 (*c* 0.99, $CHCl_3$).

IR (film): 2978, 2934, 2872, 2210 (C≡C), 1700, 1478, 1456, 1383, 1313, 1254, 1176, 1096, 1056, 853, 770 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.91 (dd, *J* = 7.3 Hz, 15.7 Hz, 1 H), 5.57 (d, *J* = 15.7 Hz, 1 H), 4.30 (br d, 1 H), 4.00 (dd, *J* = 6.2, 9.0 Hz, 1 H), 3.70 (dd, *J* = 2.2, 9.0 Hz, 1 H), 2.31 (t, *J* = 6.0 Hz, 2 H), 1.49–1.37 (m, 19 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.0 [N*C*O$_2$C(CH$_3$)$_3$], 140.5, 111.1, 110.8 [3 HC=CH], 93.0, 92.9 [2 *C*(CH$_3$)$_2$], 79.3 [*C*(CH$_3$)$_3$], 91.2, 78.8, 78.3 [3 C≡C], 67.2, 67.0 [2 OCH$_2$], 58.3, 58.1 [2 CHN], 30.2 [CH$_2$], 27.9 [C(*C*H$_3$)$_3$], 27.1, 26.1, 24.3, 23.3 [4 C(*C*H$_3$)$_2$], 21.3, 18.2 [2 CH$_2$], 13.4 [CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_3$: 308.2226; found: 308.2198.

(*Z*)-4a

Colorless oil; R_f = 0.54 (isohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ +174.3 (*c* 0.79, $CHCl_3$).

IR (film): 2978, 2934, 2872, 2210 (C≡C), 1701, 1456, 1382, 1366, 1253, 1176, 1096, 1056, 852, 769 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 5.81 (t, *J* = 9.2 Hz, 1 H), 5.55 (d, *J* = 10.0 Hz, 1 H), 5.06 (br s, 1 H), 3.99 (t, 1 H), 3.67 (br d, *J* = 7.2 Hz, 1 H), 2.25 (t, *J* = 5.9 Hz, 2 H), 1.84–1.36 (m, 19 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 152.0 [N*C*O$_2$C(CH$_3$)$_3$], 142.3, 110.3 [2 HC=CH], 96.0 [*C*(CH$_3$)$_2$], 94.4 [C≡C], 79.4 [*C*(CH$_3$)$_3$], 77.3 [C≡C], 68.6 [OCH$_2$], 57.2 [CHN], 31.1 [CH$_2$], 28.6 [C(*C*H$_3$)$_3$], 26.8, 24.2 [2 C(*C*H$_3$)$_2$], 22.2, 19.5 [2 CH$_2$], 13.7 [CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_3$: 308.2226; found: 308.2201.

tert-Butyl (*R*)-2,2-Dimethyl-4-(4-trimethylsilylbut-1-en-3-ynyl)oxazolidine-3-carboxylate (4b)

In a 50-mL Schlenk tube equipped with a magnetic stirrer bar, a suspension of (trimethylsilylpropargyl)triphenylphosphonium bromide (**3b**)[35] (1.19 g, 2.62 mmol, 1.5 equiv) in anhyd THF (15 mL) was cooled to 0 °C under argon. With stirring, 0.5 M KHMDS in toluene (5.24 mL, 2.62 mmol, 1.5 equiv) was added dropwise to give a reddish-brown soln. After 5 min the mixture was cooled to –78 °C and a soln of **2**[12b] (400 mg, 1.74 mmol, 1.0 equiv) in anhyd THF (5 mL), was added slowly by syringe on the inner surface of the flask. The mixture was kept at –78 °C for 30 min and then gradually warmed with careful TLC monitoring to avoid partial desilylation due to the strong basic conditions. After complete consumption of the starting material at –40 °C and 2 h, the mixture

was poured quickly into stirred aq phosphate buffer (pH 7, 40 mL). Workup was carried out as for **4a**, and purification by column chromatography (silica gel, isohexane–EtOAc, 93:7) gave of (*E*)-**4b** (347 mg, 62%) and (*Z*)-**4b** (35 mg, 6%).

(*E*)-4b

Colorless solid; mp 48–49 °C; R_f = 0.27 (isohexane–EtOAc, 93:7).

$[\alpha]_D^{20}$ –121.0 (*c* 0.62, $CHCl_3$).

IR (KBr): 2975, 2936, 2149 (C≡C), 1697, 1385, 1365, 1253, 1176, 1147, 1116, 1086, 1055, 1023, 988, 850, 781, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.11 (m, 1 H), 5.65 (dd, *J* = 15.7 Hz, 1 H), 4.35 (2 br s, 1 H), 4.03 (m, *J* = 6.6, 8.5 Hz, 1 H), 3.74 (dd, *J* = 8.9 Hz, 1 H), 1.60–1.44 (m, 15 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 151.6 [2 $NCO_2C(CH_3)_3$], 142.5, 142.2, 111.5, 111.3 [4 HC=CH], 102.9, 102.5 [2 C≡C], 95.2, 94.0 [2 $C(CH_3)_2$], 93.6 [C≡C], 80.4, 79.9 [2 $C(CH_3)_3$], 67.6, 67.5 [2 OCH_2], 58.8, 58.7 [2 CHN], 28.3 [$C(CH_3)_3$], 27.2, 26.4, 24.5, 23.5 [4 $C(CH_3)_2$], –0.2 [$Si(CH_3)_3$].

HRMS (FAB): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{28}NO_3Si$: 322.1838; found: 322.1814.

(*Z*)-4b

Colorless solid; mp 48–50 °C; R_f = 0.40 (isohexane–EtOAc, 93:7).

$[\alpha]_D^{20}$ +142.2 (*c* 0.40, $CHCl_3$).

IR (KBr): 2975, 2936, 2149 (C≡C), 1697, 1385, 1365, 1253, 1176, 1147, 1116, 1086, 1055, 1023, 988, 850, 781, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.95 (m, 1 H), 5.55 (d, *J* = 10.8 Hz, 1 H), 4.84 (br m, 1 H), 4.14 (m, 1 H), 3.78 (br m, 1 H), 1.60–1.44 (m, 15 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9 [$NCO_2C(CH_3)_3$], 144.0, 109.8 [2 HC=CH], 100.8, 100.3 [2 C≡C], 94.1 [$C(CH_3)_2$], 79.9 [$C(CH_3)_3$], 68.3 [OCH_2], 56.8 [CHN], 28.5 [$C(CH_3)_3$], 26.5, 23.9 [2 $C(CH_3)_2$], –0.1 [$Si(CH_3)_3$].

HRMS (FAB): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{28}NO_3Si$: 322.1838; found: 322.1814.

***tert*-Butyl (*R,E*)-4-(But-1-en-3-ynyl)-2,2-dimethyloxazolidine-3-carboxylate (4c)**

In a 20-mL round-bottom flask equipped with a magnetic stirrer bar, enyne (*E*)-**4b** (115 mg, 0.36 mmol) was dissolved in MeCN (3 mL) and H_2O (0.1 mL). CsF (162 mg, 1.07 mmol) was added in one portion and the mixture was stirred at r.t. for 2.5 h. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, isohexane–EtOAc, 9:1) to give enyne **4c** (74 mg, 83%) as a colorless oil that darkened upon storage; R_f = 0.77 (isohexane–EtOAc, 4:1).

$[\alpha]_D^{20}$ –66.3 (*c* 1.35, $CHCl_3$).

IR (film): 3293 (C≡CH), 2980, 2936, 2876, 2104 (C≡C), 1697, 1478, 1457, 1385, 1367, 1255, 1207, 1173, 1098, 1059, 953, 852, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.14 (dd, *J* = 7.7, 14.6 Hz, 1 H), 5.61 (dd, *J* = 15.4 Hz, 1 H), 4.35 (2 br s, 1 H), 4.04 (m, 1 H), 3.75 (dd, *J* = 1.9, 9.0 Hz, 1 H), 2.89 (s, 1 H), 1.60–1.43 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6 [$NCO_2C(CH_3)_3$], 143.5, 143.2, 110.5, 110.3 [4 HC=CH], 94.2, 93.7 [2 $C(CH_3)_2$], 80.5 [C≡C], 80.0 [$C(CH_3)_3$], 78.1 [C≡CH], 67.6, 67.5 [2 OCH_2], 58.8, 58.7 [2 CHN], 28.3 [$C(CH_3)_3$], 27.4, 26.5, 24.6, 23.6 [4 $C(CH_3)_2$].

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{22}NO_3$: 252.1600; found: 252.1577.

Epoxidation of Enynes followed by Copper-Mediated S_N2' Substitution; General Procedure

In a flask equipped with a magnetic stirrer bar, a soln of the enyne (1.0 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (1 mL) was cooled to 0 °C under argon. With stirring, an excess of a freshly prepared soln of DMDO in acetone[15] (0.1 mol/L) was added quickly by syringe. The temperature was kept between 0 °C and r.t. After complete consumption of the starting material (TLC monitoring), the solvent was removed in vacuo. The crude epoxide was used in the next step without delay.

In a Schlenk tube equipped with a magnetic stirrer bar, CuCN (3.0 mmol, 3.0 equiv) was suspended in anhyd THF (15 mL) under argon. After cooling to –30 °C, a soln of the Grignard reagent (3.0 mmol, 3.0 equiv) was added dropwise by syringe and stirring was continued for 30 min. A soln of the propargyloxirane (1.0 mmol, 1.0 equiv) in anhyd THF (5 mL) was added slowly by syringe on the inner surface of the flask; the reaction was monitored by TLC. After 60 min stirring at –30 °C, the soln was allowed to warm up slowly to 0 °C. After complete conversion of the starting material, sat. aq NH_4Cl (3 mL) was added dropwise, the cooling bath was removed, and the mixture was stirred at r.t. for 30 min. The suspension was diluted with Et_2O and filtered through a small pad of silica gel. The filtrate was washed with H_2O, the aqueous phase was washed with Et_2O (2 ×), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Filtration and evaporation of the solvent gave a crude product that was purified by column chromatography (silica gel).

***tert*-Butyl (4*S*)-4-(1-Hydroxy-4-methylocta-2,3-dienyl)-2,2-dimethyloxazolidine-3-carboxylate (6a)**

According to the general procedure, enyne **4a** (3.3 g, 10.2 mmol) was epoxidized with DMDO (190 mL, ca. 19 mmol) for 6 d; during this time, the mixture was concentrated twice carefully at r.t. and was treated with freshly prepared DMDO (200 mL, ca. 20 mmol) again. Reaction of the crude oxirane (3.3 g) with MeMgCl (21.5 mL, 61.2 mmol, 22 wt% in THF) and CuCN (2.74 g, 30.6 mmol) afforded α-hydroxyallene **6a** (1.37 g, 40%) as a yellow oil; mixture of diastereomers (dr = 2:1) together with a small amount of a third diastereomer (5–10%, by NMR analysis); R_f = 0.36 (isohexane–EtOAc, 85:15).

IR (film): 3467 (br, OH), 2977, 2960, 2933, 2874, 1967 (C=C=C), 1698, 1386, 1366, 1257, 1174, 1097, 849, 808, 767 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 5.39 (br d, 1 H), 4.52 (br m, 1 H), 4.22 (br m, 1 H), 3.95 (br d, 1 H), 3.82 (dd, *J* = 6.5, 8.7 Hz, 1 H), 1.98–1.46 (m, 24 H), 0.99 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 201.1 [C=*C*=C], 152.1 [$NCO_2C(CH_3)_3$], 101.9, 101.5 [2 HC=C=C_q], 94.5 [$C(CH_3)_2$], 93.1, 92.1 [2 H*C*=C=C_q], 80.4, 79.5 [2 $C(CH_3)_3$], 72.5, 72.2 [2 CHOH], 65.2 [OCH_2], 63.1, 61.8 [2 CHN], 34.0, 33.9, 30.0, 29.9 [4 CH_2], 28.3 [$C(CH_3)_3$], 26.8, 25.1 [2 $C(CH_3)_2$], 22.7 [CH_2], 19.0 [CH_3], 14.2 [CH_3].

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{34}NO_4$: 340.2488; found: 340.2478.

***tert*-Butyl (4*S*)-4-(4-*tert*-Butyl-1-hydroxyocta-2,3-dienyl)-2,2-dimethyloxazolidine-3-carboxylate (6b)**

The crude propargylic oxirane **5** (222 mg, prepared as in the synthesis of **6a**) was treated with *t*-BuMgCl (2.7 mL, 4.3 mmol, 20 wt% in THF) and CuCN (194 mg, 2.16 mmol) to give α-hydroxyallene **6b** (91 mg, 33%) as a yellow oil; mixture of diastereomers (dr = 2:1; NMR analysis); R_f = 0.56 (isohexane–EtOAc, 4:1).

IR (film): 3470 (br, OH), 2963, 2933, 2873, 1954 (C=C=C), 1700, 1477, 1459, 1390, 1377, 1366, 1255, 1206, 1174, 1103, 1088, 1067, 849 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 5.51 (br d, 1 H), 4.63 (br d, 1 H), 4.25 (br s, 1 H), 4.09 (br m, 1 H), 3.83 (br m, 1 H), 1.99 (br m, 2 H), 1.74–1.46 (m, 19 H), 1.17 (d, 9 H), 1.04 (dt, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 200.0 [C=*C*=C], 153.9, 151.9 [2 N*C*O$_2$C(CH$_3$)$_3$], 116.4 [HC=C=*C*$_q$], 96.0, 95.2 [2 H*C*=C=C$_q$], 94.4 [*C*(CH$_3$)$_2$], 80.2, 79.7 [2 *C*(CH$_3$)$_3$], 72.2, 71.3 [2 CHOH], 64.9, 64.4 [2 OCH$_2$], 62.9, 62.0 [2 CHN], 33.8, 31.0, 29.6 [3 CH$_2$], 28.3 [C(*C*H$_3$)$_3$], 27.2, 26.9, 26.9, 26.8, 24.9, 24.9 [6 CH$_2$/CH$_3$], 23.0 [C(*C*H$_3$)$_3$], 14.3 [CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{40}NO_4$: 382.2957; found: 382.2942.

tert-Butyl (4*S*)-4-(5-Butyl-5-methyl-2,5-dihydrofuran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (7a); Typical Procedure

A soln of α-hydroxyallene **6a** (74 mg, 0.23 mmol) in THF (4 mL) was cooled to 0 °C and treated with 0.165 M $AuCl_3$ in MeCN (14 μL, 1 mol%). The mixture was stirred at 0 °C for 2 h, diluted with EtOAc, and filtered through a short plug of Celite. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, isohexane–EtOAc, 9:1) to give dihydrofuran **7a** (64 mg, 86%) as a pale yellow oil; mixture of diastereomers (dr = 2:1; NMR analysis); R_f = 0.40, 0.43 (PE–EtOAc, 9:1).

IR (film): 2974, 2934, 2873, 1700, 1479, 1456, 1385, 1365, 1257, 1176, 1083, 1052, 850, 770, 732 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 6.07–5.88 (m, 1 H), 5.70–5.53 (m, 1 H), 5.39–5.05 (m, 1 H), 4.50–3.94 (m, 2 H), 3.79 (m, 1 H), 1.90–1.74 (m, 24 H), 0.89 (m, 3 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 152.7, 152.2 [2 N*C*O$_2$C(CH$_3$)$_3$], 134.5, 134.3, 134.2 [3 HC=CH], 94.4, 93.8 [2 *C*(CH$_3$)$_2$], 90.5, 90.2 [2 C$_q$], 86.6, 85.6 [2 CH], 79.5 [*C*(CH$_3$)$_3$], 66.0, 65.1 [2 OCH$_2$], 62.0 [CHN], 41.5, 41.4, 41.4 [3 CH$_2$], 28.5, 28.4 [2 C(*C*H$_3$)$_3$], 28.0, 27.5, 27.4, 27.3, 27.2, 26.8, 26.8, 26.6, 26.6, 25.4, 24.8, 23.5, 23.1[13 CH$_2$/CH$_3$], 14.3 [CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{34}NO_4$: 340.2488; found: 340.2482.

tert-Butyl (4*S*)-4-(5-Butyl-5-*tert*-butyl-2,5-dihydrofuran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (7b)

According to the synthesis of **7a**, reaction of α-hydroxyallene **6b** (300 mg, 0.79 mmol) with 0.165 M $AuCl_3$ in MeCN (48 μL, 1 mol%) gave dihydrofuran **7b** (102 mg, 34%) as a colorless solid; mixture of diastereomers (dr = 2:1; NMR analysis); R_f = 0.86 (isohexane–EtOAc, 9:1).

IR (KBr): 2974, 2934, 2873, 1691, 1478, 1387, 1254, 1176, 1121, 1083, 1049, 850 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 6.32–5.99 (m, 1 H), 5.56–5.41 (m, 1 H), 4.93 (m, 1 H), 4.50–4.01 (m, 2 H), 3.81 (m, 1 H), 1.87–1.43 (m, 21 H), 1.06 (m, 12 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 152.7, 152.2 [2 N*C*O$_2$C(CH$_3$)$_3$], 130.4, 129.7 [2 HC=CH], 98.5, 98.2 [2 C$_q$], 94.4, 93.8 [2 *C*(CH$_3$)$_2$], 88.1, 87.6 [2 CH], 79.5 [*C*(CH$_3$)$_3$], 66.3, 65.5 [2 OCH$_2$], 61.5 [CHN], 39.6 [*C*(CH$_3$)$_3$], 33.0 [CH$_2$], 28.6 [C(*C*H$_3$)$_3$], 28.3, 27.8 [2 C(*C*H$_3$)$_3$], 28.1 [CH$_2$], 26.7, 26.0 [2 C(*C*H$_3$)$_3$], 25.8 [C(*C*H$_3$)$_3$], 23.7 [CH$_2$], 23.0 [C(*C*H$_3$)$_3$], 14.6, 14.5 [2 CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{40}NO_4$: 382.2957; found: 382.2961.

(2*R*)-2-Amino-2-(5-butyl-5-methyl-2,5-dihydrofuran-2-yl)acetic Acid (8)

In a round-bottom flask equipped with a magnetic stirrer bar, a soln of **7a** (738 mg, 2.17 mmol) and *p*-TsOH·H_2O (41 mg, 0.22 mmol, 0.1 equiv) in MeOH (20 mL) was stirred at r.t. overnight. Sat. aq $NaHCO_3$ (5 mL) was then added and the mixture was concentrated under reduced pressure and partitioned between H_2O (20 mL) and EtOAc (50 mL). The organic phase was separated and the aqueous layer was washed with EtOAc (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated to give the crude hydroxycarbamate (540 mg, 83%, 2:1 mixture of diastereomers together with a small amount of a third isomer), which was used directly in the next step. For analytical purposes, a small amount was purified by column chromatography (silica gel, isohexane–EtOAc, 3:2); colorless oil; R_f = 0.48 (isohexane–EtOAc, 3:2).

IR (film): 3444, 2964, 2933, 2873, 1701, 1502, 1457, 1391, 1366, 1247, 1172, 1048, 856, 827, 779, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.71 (m, 2 H), 5.15–4.87 (m, 2 H), 3.89–3.63 (m, 3 H), 2.99 (br s, 1 H), 1.57 (m, 2 H), 1.43*/1.40 (2 s, 9 H), 1.30–1.22 (m, 7 H), 0.88 (m, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 156.1 [N*C*O$_2$C(CH$_3$)$_3$], 136.0, 135.5, 127.1, 126.7 [4 C=C], 90.6, 90.6 [2 C$_q$], 86.8, 85.6 [2 CH], 79.0, 78.8 [2 *C*(CH$_3$)$_3$], 64.7, 62.8 [2 OCH$_2$], 55.9, 54.1 [2 CHN], 41.2, 41.2 [2 CH$_2$], 28.4 [C(*C*H$_3$)$_3$], 27.2, 27.1, 25.7, 25.5 [4 CH$_2$], 23.5, 23.5 [2 CH$_3$], 14.3, 14.3 [2 CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{30}NO_4$: 300.2175; found: 300.2204.

In a Schlenk tube equipped with a magnetic stirrer bar, a soln of the hydroxycarbamate (300 mg, 1.0 mmol) in anhyd CH_2Cl_2 (8 mL) was cooled to 0 °C. With vigorous stirring, Dess–Martin periodinane[16] (555 mg, 1.3 mmol) was added in one portion. After 1 h, TLC monitoring indicated complete consumption of the starting material. The mixture was diluted with Et_2O (10 mL) and treated with sat. aq $NaHCO_3$ (5 mL), sat. aq $Na_2S_2O_3$ (5 mL), and Et_2O (10 mL). After a few min with stirring at r.t., the biphasic mixture became clear. The organic phase was separated and the aqueous layer was washed with Et_2O (3 × 15 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ and brine and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude aldehyde, which was used in the next step without delay.

In a round-bottom flask equipped with a magnetic stirrer bar, the crude aldehyde was dissolved in a mixture of *t*-BuOH (6 mL) and 2-methylbut-2-ene (15 mL) and was cooled to 0 °C. With vigorous stirring, a soln of $NaClO_2$ (339 mg, 3.0 mmol, 80%, technical grade) and NaH_2PO_4·H_2O (414 mg, 3.0 mmol) in H_2O (2.5 mL) was slowly added dropwise by syringe over 30 min. The mixture became yellow and was allowed to stir at r.t. overnight. The reaction was quenched with sat. aq $NaHCO_3$ and was extracted with hexanes (2 × 25 mL). The aqueous layer was mixed with Et_2O and cooled to 0 °C. With stirring, 1 M HCl was added dropwise to adjust the pH to 2–3. The organic phase was separated and the residue was washed with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated to give the Boc-protected amino acid (165 mg, 53%) as a colorless oil; R_f = 0.43 (isohexane–EtOAc–AcOH, 8:2:1).

IR (film): 3446 (br), 2972, 2873, 1715, 1505, 1456, 1368, 1245, 1167, 1102, 1058, 1024, 907, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H), 5.91 (dd, *J* = 2.0, 6.0 Hz, 1 H), 5.71 (d, *J* = 6.0 Hz, 1 H), 5.19 (d, *J* = 8.2 Hz, 1 H), 5.07 (d, *J* = 4.8 Hz, 1 H), 4.46 (m, 1 H), 1.58 (m, 2 H), 1.48–1.41 (m, 10 H), 1.29–1.24 (m, 6 H), 0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 [COOH], 155.2 [N*C*O$_2$C(CH$_3$)$_3$], 137.2, 137.0, 125.2, 124.3 [4 HC=CH], 91.8, 91.4 [2 C$_q$], 85.2, 84.4 [2 CH], 80.4, 79.9 [2 *C*(CH$_3$)$_3$], 56.9 [CHN], 41.0, 40.8 [2 CH$_2$], 28.3 [C(*C*H$_3$)$_3$], 26.9, 26.7 [2 CH$_2$], 25.5, 25.4 [2 CH$_3$], 23.1, 23.1 [2 CH$_2$], 14.0 [CH$_3$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_5$: 314.1967; found: 314.1947.

In a round-bottom flask equipped with a magnetic stirrer bar, a soln of the Boc-protected amino acid (56 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C. TFA (1 mL) was added, and the soln was stirred at r.t. for 2 h. Evaporation of the solvent under reduced pressure gave the crude amino acid, which was purified by passing through a column of Dowex 50W-X8. Elution with 10% aq NH_4OH gave **8** (22 mg, 58%) as a colorless oil that became a solid upon storage; mixture of diastereomers (dr = 2:1) together with small amount of a third isomer (NMR analysis).

IR (film): 3438 (br), 3075 (br), 2960, 2933, 2872, 1631, 1502, 1468, 1384, 1203, 1181, 1137, 1048, 831, 722 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 6.20* (dd, *J* = 2.1, 6.1 Hz)/6.16 (dd, *J* = 2.1, 6.2 Hz, 1 H), 5.80 (d, *J* = 6.0 Hz)/5.63* (d, *J* = 6.1 Hz, 1 H), 5.34*/5.27 (2 br s, 1 H), 3.98* (d, *J* = 4.1 Hz)/3.83 (d, *J* = 4.0 Hz, 1 H), 1.64 (m, 2 H), 1.35–1.28 (m, 9 H), 0.87 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 170.9 [COOH], 139.7*, 138.7, 121.4*, 123.5 [4 HC=CH], 92.8*, 92.9 [2 C_q], 82.2*, 82.8 [2 CH], 56.7*, 57.3 [2 CHN], 40.2*, 40.1 [2 CH_2], 26.3*, 26.4 [2 CH_2], 23.6*, 24.2 [2 CH_3], 22.6*, 22.6 [2 CH_2], 13.3 [CH_3].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}NO_3$: 214.1443; found: 214.1424.

tert-Butyl (*R*)-4-(2,2-Dibromovinyl)-2,2-dimethyloxazolidine-3-carboxylate (9)

In a 3-necked 500-mL flask equipped with a magnetic stirrer bar and N_2 inlet, a soln of Ph_3P (32.0 g, 122 mmol, 4.0 equiv) in anhyd CH_2Cl_2 (200 mL) was cooled to 0 °C under argon. With stirring, CBr_4 (20.5 g, 61.8 mmol, 2.0 equiv) was added slowly in small portions to give an orange-red soln. After 15 min, the mixture was cooled to –78 °C and a soln of **2**[12b] (7.0 g, 30.5 mmol, 1.0 equiv) and Et_3N (3.1 g, 30.6 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (20 mL) was added slowly by syringe. The mixture was allowed to warm to r.t. overnight, poured into pentane (500 mL), and the resulting suspension was stirred for 30 min. The precipitate was filtered off and the solvent was evaporated. The residue was treated with isohexane (200 mL), the suspension was stirred vigorously for 20 min and filtered again. The collected residue was dissolved in a small amount of CH_2Cl_2 and an excess of pentane was added. After filtration, this process was repeated once more. The combined filtrates were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, isohexane–EtOAc, 93:7) to give dibromide **9** (9.4 g, 80%) as a colorless solid (mp 55 °C), which should be stored under argon to avoid decomposition. The spectroscopic data were in full agreement with those reported in the literature.[19b]

tert-Butyl (*R*)-4-(But-3-en-1-ynyl)-2,2-dimethyloxazolidine-3-carboxylate (10)

In a Schlenk tube equipped with a Star Head magnetic stirrer bar, dibromide **9** (50.0 mg, 0.130 mmol), tris(4-methoxyphenyl)phosphine (4.6 mg, 0.013 mmol), and tributyl(vinyl)tin (43.0 mg, 40 μL, 0.137 mmol) were dissolved in anhyd DMF (1.3 mL) under argon, and the soln was degassed with 3 freeze-pump–thaw cycles. Freshly distilled *i*-Pr_2NEt (25.2 mg, 34 μL, 0.195 mmol) was added, followed by Pd_2dba_3·$CHCl_3$ (3.0 mg, 0.003 mmol) and CuI (2.5 mg, 0.013 mmol). The tube was sealed with a stopper and was stirred at 80 °C in a preheated oil bath. After 12 h the mixture was cooled to r.t., diluted with Et_2O (10 mL), and filtered through a short plug of Celite [rinsing with Et_2O (10 mL)]. The filtrate was stirred for 5 h with an aq alkaline KF soln [sat. aq KF (20 mL) + concd NH_4OH (2 mL)]. The organic phase was separated and the aqueous layer was washed with Et_2O (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 93:7) to give enyne **10** (16.0 mg, 49%) as a pale yellow oil; R_f = 0.58 (isohexane–EtOAc, 9:1).

$[\alpha]_D^{20}$ –123.1 (*c* 2.69, $CHCl_3$).

IR (film): 2980, 2936, 2874, 2220 (C≡C), 1704, 1478, 1456, 1382, 1264, 1246, 1174, 1132, 1092, 1056, 864, 846, 770, 723, 672 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (dd, *J* = 11.1, 17.5 Hz, 1 H), 5.60 (d, *J* = 17.3 Hz, 1 H), 5.45 (d, *J* = 10.9 Hz, 1 H), 4.67 (br d, 1 H), 4.02 (m, 2 H), 1.61 (s, 3 H), 1.48 (br s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5 [N*C*$O_2C(CH_3)_3$], 127.1 [HC=*C*H_2], 116.8 [H*C*=CH_2], 94.3, 93.9 [2 *C*$(CH_3)_2$], 88.7 [C≡C], 80.8 [C≡C], 80.2 [*C*$(CH_3)_3$], 68.7 [OCH_2], 49.0 [CHN], 28.4 [C(*C*$H_3)_3$], 27.0, 25.8, 25.2, 24.4 [4 C(*C*$H_3)_2$].

HRMS (FAB): *m*/*z* [M – H]$^+$ calcd for $C_{14}H_{20}NO_3$: 251.1443; found: 250.1484.

tert-Butyl (4*R*)-4-(1-*tert*-Butyl-4-hydroxybuta-1,2-dienyl)-2,2-dimethyloxazolidine-3-carboxylate (11)

According to the general procedure, treatment of enyne **10** (50 mg, 0.20 mmol) with DMDO (4 mL, ca. 0.4 mmol) at 0 °C for 16 h followed by reaction of the crude propargyloxirane with 1.7 M *t*-BuMgCl in THF (0.7 mL, 1.2 mmol) and CuCN (50 mg, 0.56 mmol) gave α-hydroxyallene **11** (18 mg, 29%) as a pale yellow oil; R_f = 0.43 (isohexane–EtOAc, 4:1).

IR (film): 3455, 2971, 2870, 1960 (C=C=C), 1697, 1478, 1391, 1250, 1207, 1173, 1094, 1067, 938, 853, 807, 770, 555, 517 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 5.37 (br d, 1 H), 4.31 (br s, 1 H), 4.20–4.11 (m, 2 H), 3.88–3.82 (m, 2 H), 3.22 (br s, 1 H), 1.73 (s, 3 H), 1.56 (s, 3 H), 1.49 (s, 9 H), 1.22 (s, 9 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 196.8 [C=*C*=C], 152.5 [N*C*$O_2C(CH_3)_3$], 119.8 [HC=C=*C*$_q$], 98.8 [H*C*=C=C$_q$], 93.5 [*C*$(CH_3)_2$], 80.2 [*C*$(CH_3)_3$], 69.3 [OCH_2], 59.0 [CH_2], 57.3 [CHN], 33.6 [*C*$(CH_3)_3$], 30.0, 28.3 [C(*C*$H_3)_3$], 26.4, 25.0 [2 C(*C*$H_3)_2$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{32}NO_4$: 326.2331; found: 326.2304.

tert-Butyl (*R*)-4-Ethynyl-2,2-dimethyloxazolidine-3-carboxylate (12)

In a 3-necked 500-mL flask equipped with a magnetic stirrer bar and an N_2 inlet, a soln of dibromide **9** (15.8 g, 41.0 mmol) in anhyd THF (80 mL) was cooled to 0 °C under argon. With stirring, 1.7 M *n*-PrMgBr in THF (51 mL, 86.7 mmol, 2.1 equiv) was added slowly by cannula. The mixture was stirred for 30 min at 0 °C and quenched by dropwise addition of sat. aq NH_4Cl (100 mL). After dilution with Et_2O (50 mL) and H_2O, the organic phase was separated and the aqueous layer was washed with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 93:7) to give alkyne **12** (8.1 g, 88%). The spectroscopic data were in full agreement with those reported in literature.[19c]

tert-Butyl (*R*)-4-[(Cyclooct-1-enyl)ethynyl]-2,2-dimethyloxazolidine-3-carboxylate (13)

In a 50-mL Schlenk tube equipped with a magnetic stirrer bar, $PdCl_2(PPh_3)_2$ (0.174 g, 0.25 mmol) and CuBr·SMe_2 (0.102 g, 0.50 mmol) were suspended in anhyd THF (50 mL) under argon. Freshly distilled 1-bromocyclooctene[36] (2.34 g, 12.4 mmol) and freshly distilled *i*-Pr_2NH (3.96 g, 39.1 mmol) were added, and the tube was sealed with a rubber septum. With stirring, a soln of alkyne **12** (2.94 g, 13.1 mmol) in anhyd THF (15 mL) was added slowly over 30 min. The deep green suspension became yellow and was stirred at r.t. for 16 h, after which TLC monitoring indicated complete consumption of the starting material. The solvent was evaporated, the residue was taken up in isohexane–EtOAc (1:1) and filtered through a thin pad of silica gel. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, isohexane–

EtOAc, 93:7) to give enyne **13** (3.27 g, 79%) as a pale yellow oil that should be stored under argon at –20 °C to avoid air epoxidation; R_f = 0.25 (isohexane–EtOAc, 93:7).

$[\alpha]_D^{20}$ –110.0 (*c* 1.02, $CHCl_3$).

IR (film): 2979, 2929, 2853, 1704, 1451, 1384, 1263, 1245, 1174, 1144, 1097, 1084, 1059, 841 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.03 (t, *J* = 8.3 Hz, 1 H), 4.61 (br s, 1 H), 4.00 (m, 2 H), 2.26 (t, 2 H), 2.14 (br m, 2 H), 1.62–1.48 (m, 23 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6 [$NCO_2C(CH_3)_3$], 137.5, 123.2 [2 C=C], 94.2 [$C(CH_3)_2$], 84.9, 84.5 [2 C≡C], 80.0 [$C(CH_3)_3$], 69.0 [OCH_2], 49.1 [CHN], 29.9, 29.7 [2 CH_2], 28.4 [$C(CH_3)_3$], 28.3, 26.9, 26.3 [3 CH_2], 25.8 [$C(CH_3)_2$], 25.7 [CH_2], 24.6 [$C(CH_3)_2$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}NO_3$: 334.2382; found: 334.2356.

tert-Butyl (4*R*)-2,2-Dimethyl-4-[(9-oxabicyclo[6.1.0]nonan-1-yl)ethynyl]oxazolidine-3-carboxylate (14)

In a 250-mL round-bottom flask equipped with a magnetic stirrer bar, enyne **13** (1.83 g, 5.49 mmol) was dissolved in CH_2Cl_2 (75 mL) and $Na_2HPO_4 \cdot 2\,H_2O$ (1.96 g, 11.0 mmol) was added in one portion. The stirred mixture was cooled to 0 °C, MCPBA (2.37 g, 11.0 mmol, ca. 70%) was added in one portion and the mixture was stirred at 0 °C for 3 h. The reaction was quenched by addition of sat. aq Na_2SO_3 (100 mL) and the biphasic mixture was stirred at r.t. for 30 min. The organic phase was separated and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$), and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 85:15) to give oxirane **14** (1.51 g, 79%) as a pale yellow oil; mixture of diastereomers, 1:1; R_f = 0.51 (isohexane–EtOAc, 85:15).

IR (film): 2977, 2931, 2863, 1704, 1458, 1379, 1263, 1174, 1086, 1059, 928, 843, 770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.56 (m, 1 H), 3.98 (m, 2 H), 3.03 (dd, *J* = 10.3, 4.1 Hz, 1 H), 2.15 (m, 2 H), 1.74–1.31 (m, 25 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 [$NCO_2C(CH_3)_3$], 94.3 [$C(CH_3)_2$], 81.6, 81.4 [2 C≡C], 80.2 [$C(CH_3)_3$], 68.7, 68.5 [2 OCH_2], 63.5, 63.4 [2 CH], 53.6 [C_q], 48.5 [CHN], 30.5, 30.4 [2 CH_2], 28.4 [$C(CH_3)_3$], 27.0, 26.3, 26.0 [3 CH_2], 25.9 [$C(CH_3)_2$], 25.7, 25.1 [2 CH_2], 24.3 [$C(CH_3)_2$].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}NO_4$: 350.2331; found: 350.2369.

tert-Butyl (4*R*)-4-{1-[(2-Hydroxycyclooctylidene)methylene]pentyl}-2,2-dimethyloxazolidine-3-carboxylate (15)

Anhyd LiBr (0.96 g, 11.0 mmol, 4.0 equiv) was transferred into a Schlenk tube equipped with a magnetic stirrer bar. The tube was evacuated and heated with a heat gun. After cooling, the tube was flushed with argon and CuBr·SMe_2 (2.26 g, 11.0 mmol, 4.0 equiv) and anhyd THF (40 mL) were added. The suspension was cooled to –15 °C, *n*-BuMgCl (6.4 mL, 11.0 mmol, 20 wt% in THF–toluene) was added dropwise by syringe and stirring was continued for 30 min. The mixture was cooled to –60 °C and a soln of oxirane **14** (0.96 g, 2.75 mmol, 1.0 equiv) in anhyd THF (10 mL) was slowly added by syringe on the inner surface of the flask. After 15 min, the soln was allowed to warm to 0 °C over 3 h and stirring was continued for 1 h, after which TLC monitoring indicated complete conversion of the starting material. The reaction was quenched by dropwise addition of sat. aq NH_4Cl (8 mL), the cooling bath was removed, and the mixture was stirred for 30 min. The suspension was diluted with Et_2O, filtered through a thin pad of silica gel, and the filtrate was washed with H_2O. The aqueous layer was washed with Et_2O (2 ×), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 85:15) to give α-hydroxyallene **15** (0.91 g, 81%) as a colorless oil; mixture of diastereomers (dr = 1:1) together with a small amount of a third isomer; R_f = 0.47, 0.51 (isohexane–EtOAc, 85:15).

IR (film): 3467, 2929, 2871, 1961 (C=C=C), 1699, 1678, 1478, 1457, 1385, 1366, 1249, 1206, 1173, 1106, 1059, 865, 847, 808, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.29 (t, *J* = 5.9 Hz, 1 H), 4.05 (m, 1 H), 3.99 (dd, 1 H), 3.88 (dd, 1 H), 2.29 (m, 1 H), 1.97 (m, 4 H), 1.67–1.42 (m, 29 H), 0.87 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 195.1 [2 C=*C*=C], 152.9, 152.2 [2 $NCO_2C(CH_3)_3$], 114.0, 112.6 [2 *C*=C=C], 108.8, 108.3 [2 C=C=*C*], 93.7, 93.6 [2 $C(CH_3)_2$], 80.6, 80.5 [2 $C(CH_3)_3$], 71.1, 70.4 [2 CHOH], 67.5, 66.6 [2 OCH_2], 61.3, 59.3 [2 CHN], 33.7, 32.2, 30.5, 30.1, 29.9, 29.6 [6 CH_2], 28.4, 28.3 [2 $C(CH_3)_3$], 28.0, 28.2, 27.4, 26.7, 25.2, 25.1, 22.5, 22.5, 22.0, 21.9 [10 CH_2/CH_3], 13.9, 13.9 [2 CH_3].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{42}NO_4$: 408.3114; found: 408.3026.

tert-Butyl (1*S*)-1-(2-Butyl-2,4,5,6,7,8,9,9a-octahydrocyclooctа[*b*]furan-2-yl)-2-hydroxyethylcarbamate (16)

In a Schlenk tube with a magnetic stirrer bar, α-hydroxyallene **15** (20 mg, 0.05 mmol) was dissolved in anhyd THF (0.35 mL) under argon. 0.165 M $AuCl_3$ in MeCN (3.0 μL) was added by syringe and the yellow mixture was stirred at r.t. for 3 d. The mixture was diluted with Et_2O (2 mL) and quenched with sat. aq $NaHCO_3$ (2 mL). The organic phase was separated and the residue was washed with Et_2O (3 × 2 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, isohexane–EtOAc, 7:3) to give hydroxycarbamate **16** (16 mg, 89%) as a colorless oil; mixture of diastereomers (dr = 1:1; NMR analysis); R_f = 0.32, 0.36 (isohexane–EtOAc, 7:3).

IR (film): 3452 (br), 2930, 2860, 1699, 1501, 1456, 1390, 1366, 1249, 1173, 1058, 1054, 1030, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.42/5.36 (2 s, 1 H), 5.18 (d, *J* = 8.9 Hz)/5.06 (d, *J* = 9.1 Hz, 1 H), 4.77/4.67 (2 br s, 1 H), 4.05–3.34 (m, 3 H), 2.46 (m, 1 H), 2.07–1.28 (m, 26 H), 0.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 156.1 [2 $NCO_2C(CH_3)_3$], 145.0, 143.9 [2 HC=C_q], 126.0, 125.3 [2 H*C*=C_q], 95.1, 92.5 [2 C_q], 88.0, 87.6 [2 CH], 79.4, 79.0 [2 $C(CH_3)_3$], 63.4, 62.6 [2 OCH_2], 57.5, 55.3 [2 CHN], 37.3, 32.0 [2 CH_2], 28.3 [$C(CH_3)_3$], 28.1, 27.0, 26.8, 26.6, 26.4, 26.2, 26.2, 25.0, 24.9, 23.2, 23.1, 22.3, 22.1 [13 CH_2], 14.0 [CH_3].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{38}NO_4$: 368.2801; found: 368.2792.

(2*R*)-2-Amino-(2-butyl-2,4,5,6,7,8,9,9a-octahydrocyclooctа[*b*]furan-2-yl)acetic acid (17)

The oxidation of **16** (115 mg, 0.31 mmol) in anhyd CH_2Cl_2 (3 mL) with Dess–Martin periodinane[16] (226 mg, 0.53 mmol) was carried out as in the synthesis of **8**; the crude aldehyde was used in the next step without delay.

A soln of the crude aldehyde and resorcinol (45 mg, 0.41 mmol) in dioxane (30 mL) was cooled to 12 °C. With vigorous stirring, a soln of $NaClO_2$ (138 mg, 1.22 mmol, 80%, technical grade) and $NaH_2PO_4 \cdot H_2O$ (168 mg, 1.22 mmol) in H_2O (4 mL) was added dropwise by syringe over 30 min. After 15 min with stirring at 12 °C, the slightly yellow mixture was poured into sat. aq $NaHCO_3$ (15 mL). The biphasic mixture was concentrated to its half volume un-

der reduced pressure. The residue was diluted with H_2O until the precipitate was dissolved. $CHCl_3$ (40 mL) was added and after cooling to 0 °C, 1 M HCl was added dropwise with stirring to adjust the pH to 2–3. The organic phase was separated, and the aqueous layer was washed with $CHCl_3$ (2 ×). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated to give the crude Boc-protected amino acid, which was dissolved up in $CHCl_3$ and put on a column (silica gel). Elution with isohexane–EtOAc (1:1) removed resorcinol and chlorinated byproducts. Further elution with isohexane–EtOAc–AcOH (8:2:1) gave the product, which was coevaporated with toluene (3 × 2 mL) to remove AcOH to give the Boc-protected amino acid (42 mg, 35%) as a colorless oil; mixture of diastereomers (dr = 1:1; NMR analysis); R_f = 0.60, 0.68 (isohexane–EtOAc–AcOH, 8:2:1).

IR (film): 3342 (br), 3059, 2933, 2872, 1713, 1509, 1457, 1393, 1368, 1251, 1163, 1055, 854, 738, 7037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.42 (br s, 1 H), 5.36 (d, *J* = 8.6 Hz)/5.21 (br s, 1 H), 4.83 (br s, 1 H), 4.42 (d, *J* = 8.1 Hz)/4.34 (d, *J* = 8.6 Hz, 1 H), 2.50 (m, 1 H), 2.07 (m, 1 H), 1.94 (m, 1 H), 1.81–1.25 (m, 24 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 [COOH], 155.8, 155.4 [2 $NCO_2C(CH_3)_3$], 145.6 [HC=C_q], 125.0, 124.8 [2 HC=C_q], 92.7, 92.6 [2 C_q], 88.2, 87.5 [2 CH], 79.8 [$C(CH_3)_3$], 59.5 [CHN], 36.6, 31.7, 31.4 [3 CH_2], 28.3 [$C(CH_3)_3$], 28.1, 28.0, 26.7, 26.7, 26.5, 26.2, 26.2, 25.0, 23.0, 22.9, 22.2 [11 CH_2], 14.0 [CH_3].

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{36}NO_5$: 382.2588; found: 382.2588.

Analogous to the synthesis of **8**, treatment of the Boc-protected amino acid (15.7 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) with TFA (0.25 mL) at 0 °C gave amino acid **17** (12.3 mg, quantitative yield); mixture of diastereomers (dr = 1:1; NMR analysis). This was purified by filtration through a small column (Florisil, MeOH) to give a yellow oil, which became a solid upon storage.

IR (film): 3383 (br), 2930, 2860, 1720, 1614, 1385, 1210, 1161, 1047, 757 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 5.48 (br s, 1 H), 4.78/4.72 (2 br s, 1 H), 4.52/4.40 (2 s, 1 H), 3.82/3.74 (2 s, 1 H), 2.53 (m, 1 H), 2.11–1.34 (m, 18 H), 0.91 (t, *J* = 6.1 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 175.4, 174.9 [2 COOH], 147.0, 146.3 [2 HC=C_q], 127.6, 126.2 [2 HC=C_q], 93.9, 93.7 [2 C_q], 89.2, 88.5 [2 CH], 63.0, 62.6 [2 CHN], 38.6, 36.5, 32.9, 32.5, 29.4, 29.3, 28.3, 27.9, 27.8, 27.6, 27.1, 27.0, 26.1, 24.3, 24.3, 23.6, 23.5 [17 CH_2], 14.5, 14.5 [2 CH_3].

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{28}NO_3$: 282.2069; found: 282.2065.

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