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Synthesis of Novel Exocyclic Allenes with a Norbornene Fragment

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Abstract—*N*-Substituted amino acids with a norbornene fragment were synthesized by the direct fusion of amino acids with endic anhydride at 150°C. The synthesized compounds were used for one-pot synthesis of novel stable allenes with an exocyclic cumulene group derived from 1-phenyl-3-(triphenylphosphoranylidene)-pyrrolidine-2,5-dione has been carried out.

Keywords: allenes, norbornenes, exocyclic allenoates, Arndt–Eistert reaction, phosphorus ylides, amino acids, endic anhydride

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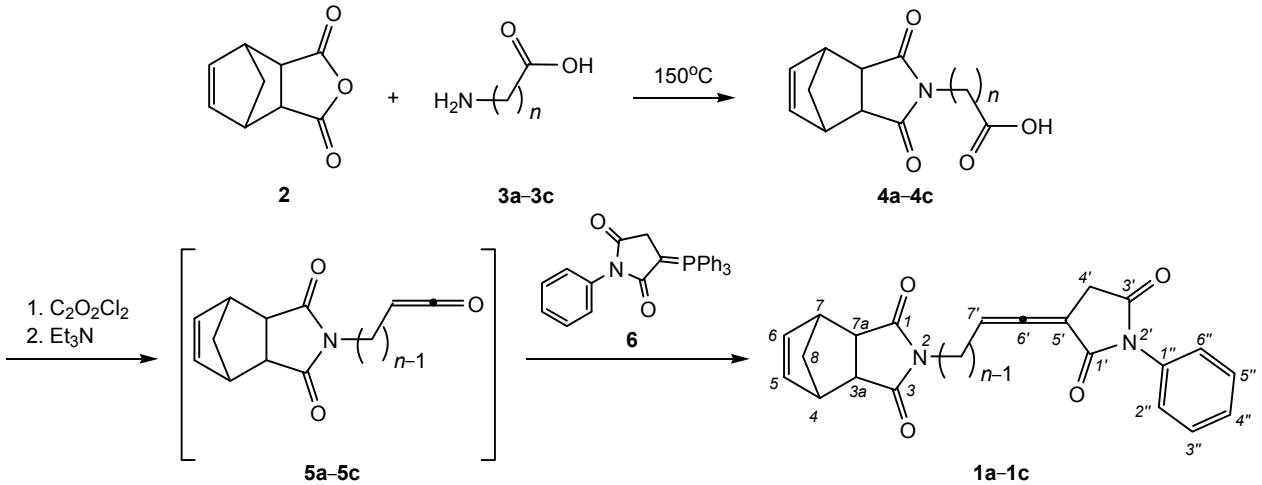
Over the past years, significant advances have been made in the synthesis of functionalized allenes and study of their chemical properties of [1–3]. The enhanced reactivity of allenes makes it possible to synthesize, on their basis, various hardly accessible functionally substituted unsaturated linear and cyclic organic compounds [4–6], which are promising drug precursors [7–11]. In this respect, the most promising are keto-stabilized allenes as accessible and stable compounds. In this paper, we describe the synthesis of a new type of stable allenes having an exocyclic cumulene group.

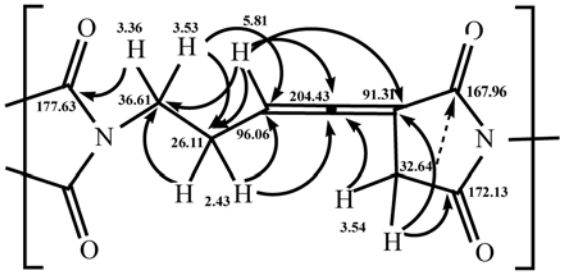
Allenes **1a–1c** were synthesized from *N*-substituted amino acids **4a–4c** and 1-phenyl-3-(triphenylphosphoranylidene)pyrrolidine-2,5-dione **6**. Amino acids **4a–4c** were prepared by directly fusing endic anhydride with amino acids **3a–3c** at 150°C in yields of 75%, 68%, and 75%, respectively. Further on amino acids **4a–4c** were converted into chlorides by refluxing with excess oxalyl chloride in anhydrous methylene chloride, which were reacted with trimethylamine to obtain ketenes **5a–5c**. The latter react with compound **6** to form exocyclic allenes **1a–1c** in yields of 70, 80, and 78%, respectively (Scheme 1).

Scheme 1.



n = 3 (**a**), 4 (**b**), 5 (**c**).

The isolated compounds were identified by spectral methods. Thus, the IR spectra of allenes **1a–1c** display a characteristic medium absorption band of medium intensity at ~1950 cm^{-1}, associated with stretching vibrations of the double bond. The characteristic allene proton signal in the ^1H NMR spectrum is observed at δ_H 5.8 ppm. The ^{13}C NMR spectrum contains characteristic signals of the allene carbon atoms at δ_C 91.3 and 96.1 ppm, as well as a downfield signal (δ_C 204.4 ppm) of the quaternary carbon atom. Further evidence for the structure of allenes **1a–1c** was obtained by 2D HSQC and HMBC experiments. The most important HMBC interactions in allene **1a** are presented in the figure.



1a

Significant correlations in the HMBC spectra of compound **1a**.

Thus, exocyclic allenes containing a norbornane fragments were prepared for the first time by the reaction of *N*-substituted amino acids with 1-phenyl-3-(triphenylphosphoranylidene)pyrrolidine-2,5-dione.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR-Prestige-21 FTIR spectrophotometer in thin films or mineral oil. The NMR spectra were obtained on a Bruker-AM 500 spectometer at 500.13 (^1H) and 125.76 (^{13}C) MHz, internal reference TMS. For correct assignment of the NMR spectra of the reaction products, homonuclear and heteronuclear 2D correlation spectroscopy experiments (COSY, NOESY, HSQC, and HMBC) were used. Reaction progress was monitored by TLC on Sorbfil PTSKh-AF-A plates, the spots were visualized by exposure to UV light or iodine vapor, or by spraying the plates with a ninhydrin developer followed by heating at 100–120°C. The mass spectra were obtained on a Shimadzu LCMS-2010EV system in the APCI mode. Elemental analysis was performed on a EURO EA-3000 CHN analyzer. The melting points were measured on a Boetius hot stage. The reaction products were isolated by column chromatography on a Chemapol silica gel (40/100 and 100/160 μm).

Synthesis of *N*-substituted amino acids 4a–4c (*general procedure*). Endic anhydride, 10 mmol, and amino acid (10 mmol) were thoroughly ground in a porcelain mortar and then fused on an oil bath at 150°C for 1 h. After cooling, the reaction mixture was cooled to room temperature, dissolved in pure acetone, and subjected to column chromatography (eluent anhydrous acetone) to isolate the reaction product.

4-(1,3-Dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindol-2(3*H*)-yl)butanoic acid (4a). Yield 0.057 g (75%). Thick yellow oil. IR spectrum (mineral oil), ν, cm^{-1}: 725, 1229, 1571, 1681, 1736, 1762, 3294. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 d (1H^a, C^8H_2, *J* 8.7 Hz), 1.61 d (1H^b, C^8H_2, *J* 8.7 Hz), 1.69 m (2H, $C^{3'}H_2$), 2.17 m (2H, $C^{2'}H_2$), 3.18 s (2H, $C^{3a,7a}H$), 3.32 m (4H, $C^{4,7}H$, $C^{4'}H_2$), 6.02 m (2H, $C^{5,6}H$), 11.1 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 22.84 ($C^{3'}H_2$), 31.22 ($C^{2'}H_2$), 37.63 ($C^{4'}H_2$), 44.79 ($C^{3a,7a}H$), 45.62 ($C^{4,7}H$), 52.18 (C^8H_2), 134.4 ($C^{5,6}H$), 176.85 ($C^{1'}$=O), 177.83 ($C^{1,3}$=O). Found, %: C 62.66, H 6.09, N 5.63. $C_{13}H_{15}NO_4$. Calculated, %: C 62.64; H 6.07; O 25.27; N 5.62. *M* 249.26.

5-(1,3-Dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindol-2(3*H*)-yl)pentanoic acid (4b). Yield 1.78 g (68%), white crystals, mp 118°C. IR spectrum (mineral oil), ν, cm^{-1}: 720, 1230, 1551, 1692, 1713, 3435. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.42–1.56 m (1H^a, C^8H_2, 4H, $C^{3',4'}H_2$), 1.70 d (1H^b, C^8H_2, *J* 8.8 Hz), 2.31 t (2H, $C^{2'}H_2$, *J* 7.3 Hz), 3.22 s (2H, $C^{3a,7a}H$), 3.31 t (2H, $C^{5'}H_2$, *J* 7.4 Hz), 3.35 s (2H, $C^{4,7}H$), 6.06 s (2H, $C^{5,6}H$), 10.64 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 21.80 ($C^{3'}H_2$), 27.03 ($C^{4'}H_2$), 33.31 ($C^{2'}H_2$), 37.78 ($C^{5'}H_2$), 44.84 ($C^{3a,7a}H$), 45.68 ($C^{4,7}H$), 52.22 (C^8H_2), 134.42 ($C^{5,6}H$), 177.9 ($C^{1,3}$=O), 178.93 ($C^{1'}$=O). Found, %: C 63.89, H 6.54, N 5.33. $C_{14}H_{17}NO_4$. Calculated, %: C 63.87; H 6.51; O 24.31; N 5.32. *M* 263.29.

6-(1,3-Dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindol-2(3*H*)-yl)hexanoic acid (4c). Yield 2.07 g (75%), yellow oil. IR spectrum (mineral oil), ν, cm^{-1}: 725, 1227, 1552, 1695, 1731, 3273. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.19–1.57 m (1H^a, C^8H_2, 6H, $C^{3',4',5'}H_2$), 1.66 d (1H^b, C^8H_2, *J* 7 Hz), 2.23 t (2H, $C^{2'}H_2$, *J* 7.3 Hz), 3.17 s (2H, $C^{3a,7a}H$), 3.24 t (2H,$C^{6'}H_2$, *J* 7.4 Hz), 3.31 s (2H, $C^{4,7}H$), 6.03 s (2H, $C^{5,6}H$), 10.98 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 24.12 ($C^{4'}H_2$),

26.18 ($C^{3'}H_2$), 27.35 ($C^{5'}H_2$), 33.77 ($C^{2'}H_2$), 37.99 ($C^{6'}H_2$), 44.8 ($C^{3a,7a}H$), 45.61 ($C^{4,7}H$), 52.15 ($C^{8}H_2$), 134.33 ($C^{5,6}H$), 177.95 ($C^{1,3}$=O), 178.51 ($C^{1'}$=O). Found, %: C 64.98, H 6.93, N 5.03. Calculated $C_{15}H_{19}NO_4$ (*M* 277.32), %: C 64.97; H 6.91; O 23.08; N 5.05.

Synthesis of allenes by the Wittig reaction (*general procedure*). A five-fold excess of oxalyl chloride was added to a suspension of 1 g of acid in 10 mL of anhydrous methylene chloride. The mixture was left to stand overnight and then the solvent and excess oxalyl chloride were removed on a rotary evaporator. The resulting chloride was further reacted without purification. Triethylmine was added dropwise to a solution of an equimolar amount of methyl (triphenylphosphoranylidene)acetate in CH_2Cl_2. The resulting solution was cooled to–5°C, and a cold solution of *N*-substituted amino acid chloride was slowly added dropwise to it. The reaction mixture was stirred for 2 h, after which the solvent was removed, and the residue was subjected to column chromatography (eluent petroleum ether–ethyl acetate, 4 : 1) to isolate the reaction product.

2-[4-(2,5-Dioxo-1-phenylpyrrolidin-3-ylidene)but-3-en-1-yl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (1a). Yield 1.09 g (70%), yellow oil. IR spectrum, ν, cm^{-1}: 724, 1166, 1377, 1456, 1653, 1767, 1952. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.53 d (1H^a, $C^{8}H_2$, *J* 8.6 Hz), 1.69 d (1H^b, $C^{8}H_2$, *J* 8.6 Hz), 2.43 s (2H, $C^{8'}H_2$), 3.26 s (2H, $C^{3a,7a}H$), 3.35 m (4H, $C^{4,7}H$ and $C^{9'}H_2$), 3.54 br.m (2H, $C^{4'}H_2$), 5.81 s (1H, =$C^{7'}$H), 6.08 m (2H, $C^{5,6}H$), 7.32 s (2H, $C^{3'',5''}H$), 7.32 s (1H, $C^{4''}H$), 7.46 s (2H, $C^{2'',6''}H$). ^{13}C NMR spectrum, δ, ppm: 26.11 ($C^{8'}H_2$), 32.64 ($C^{4'}H_2$), 36.61 ($C^{9'}H_2$), 44.62 ($C^{4,7}H$), 45.47 ($C^{3a,7a}H$), 51.92 ($C^{8}H_2$), 91.31 (=$C^{5'}$), 96.06 (=$C^{7'}$H), 126.26 ($C^{3'',5''}H$), 128.41 ($C^{4''}H$), 128.84 ($C^{2'',6''}H$), 131.77 ($C^{1''}$), 134.19 ($C^{5,6}H$), 167.96 ($C^{1'}$), 172.13 ($C^{3'}$), 177.63 ($C^{1,3}$=O), 204.43 (=C=). Found, %: C 71.14; H 5.17, N 7.20. $C_{23}H_{20}N_2O_4$. Calculated, %: C 71.12; H 5.19; O 16.48; N 7.21. *M* 388.42.

2-[5-(2,5-Dioxo-1-phenylpyrrolidin-3-ylidene)-pent-4-en-1-yl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (1b). Yield 1.22 g (80%), orange oil. IR spectrum, ν, cm^{-1}: 724, 1161, 1362, 1456, 1661, 1761, 1973. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.49 d (1H^a, $C^{8}H_2$, *J* 8.5 Hz), 1.58 m (2H, $C^{9'}H_2$), 1.65 d (1H^b, $C^{8}H_2$, *J* 8.5 Hz), 2.12 m (2H, $C^{8'}H_2$), 3.19 s (2H, $C^{3a,7a}H$), 3.32–3.36 m (4H, $C^{4,7}H$ and $C^{10'}H_2$), 3.58 br m (2H, $C^{4'}H_2$), 5.91 s (1H, =$C^{7'}$H), 6.03 m (2H, $C^{5,6}H$), 7.31 s (2H, $C^{3'',5''}H$), 7.26 s (1H, $C^{4''}H$), 7.46 s (2H, $C^{2'',6''}H$). ^{13}C NMR spectrum, δ, ppm: 24.91 ($C^{9'}H_2$), 26.40 ($C^{10'}H_2$), 32.99 ($C^{8'}H_2$), 37.30 ($C^{4'}H$), 44.88 ($C^{4,7}H$), 45.68 ($C^{3a,7a}H$), 52.21 ($C^{8}H_2$), 95.26 (=$C^{5'}$), 98.78 (=$C^{7'}$H), 126.43 ($C^{3'',5''}H$), 128.55 ($C^{4''}H$), 129.08 ($C^{2'',6''}H$), 132.13 ($C^{1''}$), 134.42 ($C^{5,6}H$), 168.53 ($C^{1'}$), 172.68 ($C^{3'}$), 177.63 ($C^{1,3}$=O), 204.45 (=C=). Found, %: C 71.61; H 5.53, N 6.96. $C_{24}H_{22}N_2O_4$. Calculated, %: C 71.63; H 5.51; O 15.90; N 6.96. *M* 402.44.

2-[6-(2,5-Dioxo-1-phenylpyrrolidin-3-ylidene)-hex-5-en-1-yl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (1c). Yield 1.16 g (78%). Yellow oil. IR spectrum, ν, cm^{-1}: 730, 1192, 1377, 1436, 1695, 1768, 1948. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.41 d (1H^a, $C^{8}H_2$, *J* 8.6 Hz), 1.49 m (4H, $C^{9',10'}H_2$), 1.65 d (1H^b, $C^{8}H_2$, *J* 8.6 Hz), 2.13 s (2H, $C^{8'}H_2$), 3.18 s (2H, $C^{3a,7a}H$), 3.31 m (4H, $C^{4,7}H$, $C^{11'}H_2$), 3.55 br.m (2H, $C^{4'}H_2$), 5.88 m (1H, =$C^{7'}$H), 6.05 m (2H, $C^{5,6}H$), 7.26 s (2H, $C^{3'',5''}H$), 7.33 s (1H, $C^{4''}H$), 7.45 s (2H, $C^{2'',6''}H$). ^{13}C NMR spectrum, δ, ppm: 25.68($C^{9'}H_2$), 26.78 ($C^{10'}H_2$), 30.91 ($C^{8'}H_2$), 33.00 ($C^{4'}H_2$), 37.84 ($C^{11'}H_2$), 44.86 ($C^{4,7}H$), 45.71 ($C^{3a,7a}H$), 52.21 ($C^{8}H_2$), 94.34 (=$C^{5'}$), 99.31 (=$C^{7'}$H),126.57 ($C^{3'',5''}H$), 128.53 ($C^{4''}H$), 129.06 ($C^{2'',6''}H$), 132.10 ($C^{1''}$), 134.36 ($C^{5,6}H$), 168.39 ($C^{1'}$), 172.56 ($C^{3'}$), 177.71 ($C^{1,3}$=O), 204.65 (=C=). Found, %: C 72.12; H 5.81, N 6.71. $C_{25}H_{24}N_2O_4$. Calculated, %: C 72.10; H 5.81; O 15.37; N 6.73. *M* 416.47.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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