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A NEW METHOD FOR THE SYNTHESIS OF [3]-CUMULENES AND ENEYNECUMULENES RELATED TO NEOCARZINOSTATIN CHROMOPHORE

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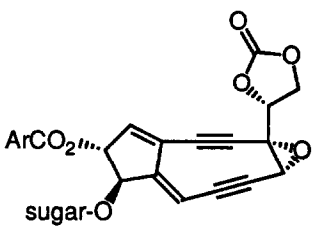
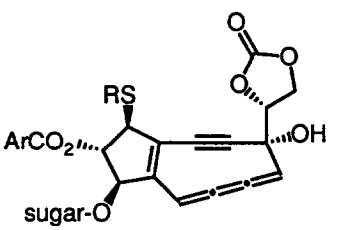
Summary: *A convenient method for the synthesis of [3]-cumulenes based on a Horner-Emmons type reaction of allenyldiphenylphosphine oxides with aldehydes or ketones has been described. A facile two-step synthesis of eneynecumulenes has been accomplished by this method.*

Neocarzinostatin chromophore (NCS-Chr) is a new class of antitumor antibiotics with an unusual cycloalkendiyne structure and a remarkably high DNA-cleaving activity.[1] The mechanism of its DNA-cleaving process proposed by Myers et al.,[2] involves the generation of a biradical species through a Bergman type cycloaromatization of the eneynecumulene **1**. In connection with our studies on the action mechanism of NCS,[3] we disclosed that non-strained acyclic eneyneallenes undergo extremely facile cycloaromatization to generate a biradical species which causes cleavage of double stranded DNA under mild conditions.[4,5] In an extension of these studies, we became interested in the biradical forming process of more closely related system, eneynecumulenes.

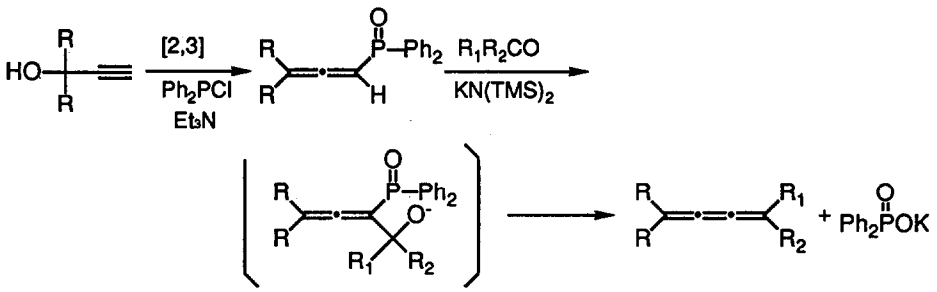


NCS-Chr

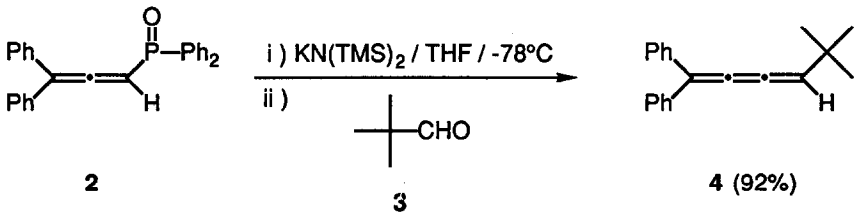


1

While existing synthetic methods for [3]-cumulenes (1,2,3-butatrienes) include i)1,4-elimination of various types of substituted acetylenes,[6] ii) coupling of metal-methylenecarbenoids,[7] vinyl-copper derivatives[8] or vinyl-borane precursors[9] and iii) a Wittig phosphacumulene strategy,[10] vast majority of the previous methods are not useful for the synthesis of unstable, highly conjugated and partially substituted eneynecumulenes. A more convenient and versatile method for the construction of [3]-cumulene structure under milder conditions is apparently necessary. We now wish to report a convenient and general method for the synthesis of [3]-cumulenes based on a Horner-Emmons type reaction using allenyldiphenylphosphine oxides[11] in combination with aldehydes or ketones which can be successfully utilized for the synthesis of a variety of eneynecumulenes.



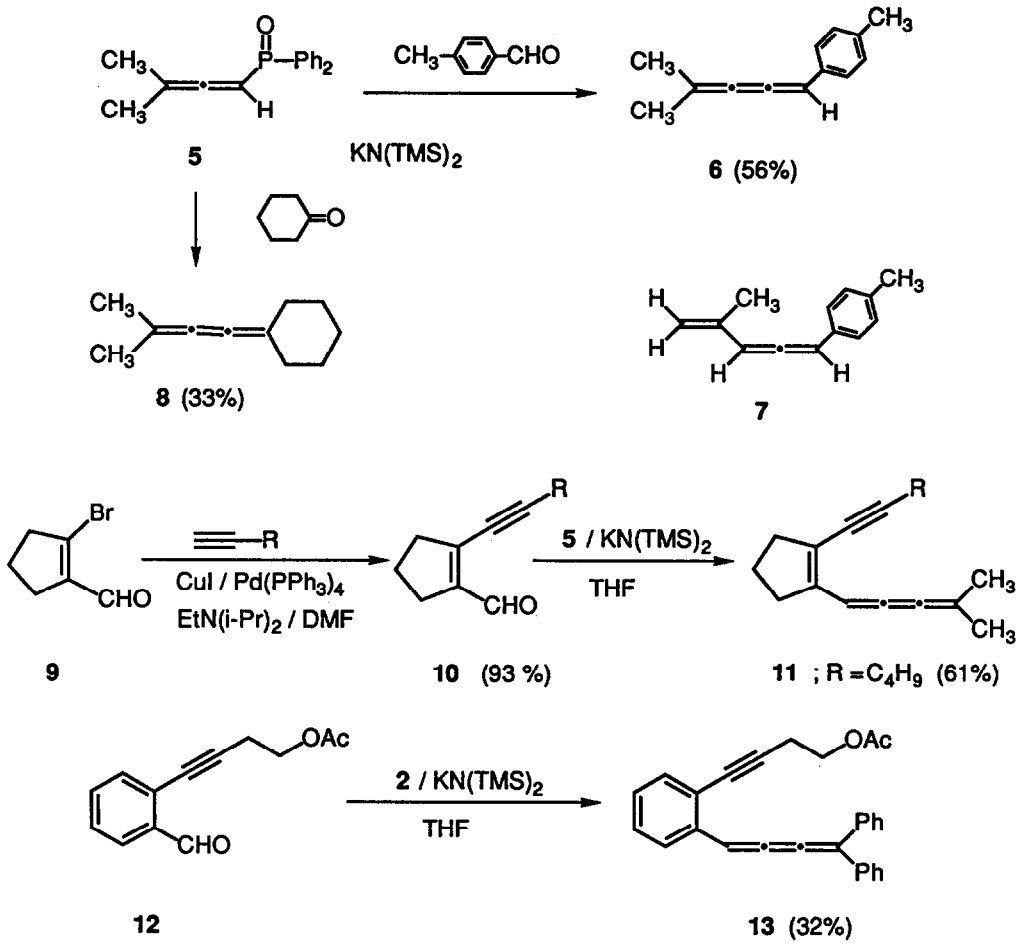
Allenyldiphenylphosphine oxide **2** is readily available from propargyl alcohol and chlorodiphenylphosphine (Et_3N / hexane/ -78 °C to 0 °C) via [2,3]-sigmatropic rearrangement.[4a,6] When $KN(TMS)_2$ (1 equiv, 0.5 M toluene solution) was added to the solution of **2** in THF at -75 °C, the reaction mixture turned from colorless to red. To the red solution was added aldehyde **3** (1 equiv) at -78 °C, and the solution was stirred at -78 °C for 1 h and then at 15 °C for 15 min. Extractive workup followed by flash column chromatography (Florisil) using cold hexane as eluent gave **4** (92%).



2 **3** **4** (92%)

Alkyl-substituted [3]-cumulenes **6** and **8** were prepared from **5** by a simialr procedure. While these products were stable in solution at ambient temperature under nitrogen, evaporation to dryness or exposure to silica gel resulted in a gradual decomposition to give polymeric products. These air sensitive [3]-cumulenes (**4**, **6**, **8**) are best handled in dilute solution under nitrogen and were fully characterized by IR (in the region of 1960-2070 cm^{-1}), ^{13}C NMR (δ 138-156) and mass spectroscopy.[12] It is worthwhile to note here that methyl-substituted [3]-cumulene **6** gradually rearranged in $CDCl_3$ at room temperature to give allene **7** (85% after 5 h).

Eneynecumulene **11**, an acyclic model of **1**, was prepared by following sequence. Coupling of 2-bromocyclopentenecarboxaldehyde **9** with 1-hexyne in DMF ($Pd(Ph_3)_4$ / CuI / diisopropylethylamine) gave **10** (93%). Addition of $KN(TMS)_2$ (1 equiv) to allenyldiphenylphosphine oxide **5** in THF at -78 °C followed by dropwise addition of aldehyde **10** at -78 °C provided **11** in 61% yield after separation by flash column chromatography (Florisil) using cold hexane as eluent. Eneynecumulene **13** was also prepared from **12** via a similar route. The structures of **11** and **13** were confirmed by spectroscopic data.[12] These eneynecumulenes were relatively stable in dilute solution under nitrogen at ambient temperature.



In conclusion, a facile two-step synthesis of acyclic eneynecumulenes has been accomplished for the first time. This method, though not proven here, should be amenable to the preparation of cyclic eneynecumulenes as well. Further studies in this line and the biradical-forming reaction of these eneynecumulenes associated with DNA cleavage are in progress in our laboratory.[13]

References and Notes

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12. Selected spectral data follow. **4;** ^{1}H NMR (C_6D_6) δ 1.18 (s, 9 H), 5.73 (s, 1 H), 7.27-7.38 (m, 6 H), 7.48-7.55 (m, 4 H); ^{13}C NMR (C_6D_6) δ 120.7, 122.8, 154.7, 161.2; IR (CCl_4) 1960 cm^{-1}. **6;** ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 1.80 (s, 3 H), 2.30 (s, 3 H), 5.94 (m, 1 H), 7.07 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 92.7, 117.2, 137.8, 142.7. **8;** ^{1}H NMR (C_6D_6) δ 1.33 (m, 2 H), 1.47 (m, 4 H), 1.78 (s, 3 H), 1.79 (s, 3 H), 2.27 (t, J = 6 Hz, 4 H); ^{13}C NMR (C_6D_6) δ 107.4, 115.8, 152.0, 155.4; IR (CCl_4) 2070 cm^{-1}. **11;** ^{1}H NMR (C_6D_6) δ 0.77 (t, J = 6.7 Hz, 3 H), 1.20-1.50 (m, 4 H), 1.64 (m, 2 H), 1.90 (s, 3 H), 1.96 (s, 3 H), 2.24 (t, J = 6.7 Hz, 2 H), 2.58 (m, 4 H), 6.96 (s, 1 H); ^{13}C NMR (C_6D_6) δ 98.2, 100.2, 116.0, 123.2, 128.4, 146.5, 153,1, 158.2; IR (CCl_4) 2048 cm^{-1}. **13;** ^{1}H NMR (C_6D_6) δ 1.67 (s, 3 H), 2.38 (t, J = 6.7 Hz, 2 H), 3.99 (t, J = 6.7 Hz, 2 H), 6.82 (m, 1 H), 6.95 (m, 1 H), 7.06 (m, 6 H), 7.42 (m, 1 H), 7.50 (s, 1 H), 7.60 (m, 4 H), 7.81 (m, 1 H); ^{13}C NMR (C_6D_6) δ 107.7, 123.2, 155.0, 155.5.
13. This work was supported by Grant-in-Aid for Priority Research from Ministry of Education.

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