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STEREOSELECTIVE SYNTHESIS OF BICYCLO[3.3.0] OCT-1-EN-3-ONE DERIVATIVES

F. Camps, J. Coll, J.M. Moretó and J. Torras

Departament de Química Orgànica Biològica, C.I.D. (C.S.I.C.)
C/ Jordi Girona, 18-26
08034-Barcelona (Spain)

Summary: Intramolecular carbonylative cyclization of either E or Z-9-methoxy-2-nonen-7-ynyl bromide promoted by $Ni(CO)_4$ afforded the same isomer of 4-(methoxycarbonylmethyl)-2-(methoxymethyl)bicyclo[3.3.0]oct-1-en-3-one in 43-50% yields with a relative trans-configuration of H-4 and H-5 protons.

Recently, we have described a straightforward synthesis of methylenomycin B[1] by modification of a previously reported $Ni(CO)_4$ promoted carbonylative cycloaddition of olefins and acetylenes.[2] In this context, we anticipated that the intramolecular version of this reaction might be also valuable for the preparation of bicyclopentanoid intermediates in natural product synthesis, as an alternative way to other related cyclization processes, such as those promoted by $Co_2(CO)_8$[3] (Pauson-Khand reaction) or Cp_2ZrCl_2.[4]

In the present communication we report on the feasibility of this process for the synthesis of bicyclo[3.3.0]oct-1-en-3-one derivatives. In addition, the preservation of the original stereochemistry of the enyne double bond on both Z and E isomers along the carbonylative cyclization has also been studied.

As depicted in Scheme 1, the selected enynes E and Z-9-methoxy-2-nonen-7-ynyl bromide (1E and 1Z) were synthesized by conventional procedures. For 1E, the required stereochemistry of the double bond was secured by $LiAlH_4$ reduction of the acetylene function of the propargyl alcohol 4;[5] while for 1Z the corresponding Z-double bond was reached by catalytic hydrogenation of the triple bond of a protected derivative in the presence of Lindlar catalyst. In both cases, the allylic alcohol (5E and 5Z) was converted into the corresponding bromide by a sequential one pot treatment with trifluoroacetic anhydride and dry lithium bromide in a 1:1 THF:HMPT mixture.[6] Further purification of the reaction product by flash-chromatography using 1:1 ethyl acetate:n-hexane as eluant afforded the pure enynes.

1E.- IR (neat) : 2920 (br,s), 1710 (m), 1655 (w), 1450 (m), 1110 (s), 960 (s), 900 (m) cm^{-1}

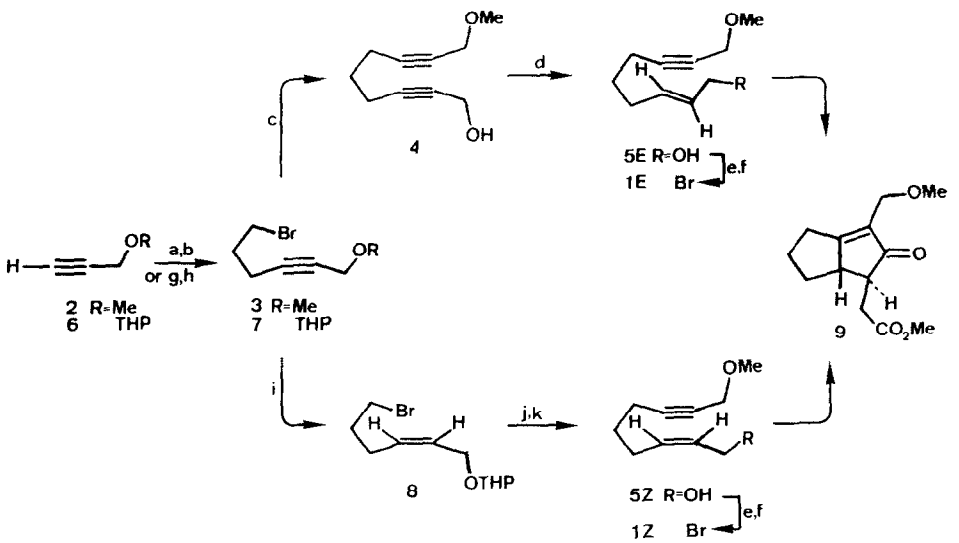
^1H NMR ($CDCl_3$) δ : 1.4-1.8 (c, 2H), 1.9-2.4 (c, 4H), 3.3 (s, 3H) 3.90 (d, J=6 Hz, 2H), 4.05 (t, J=2 Hz, 2H), 5.7-5.9 (c, 2H).

^{13}C NMR ($CDCl_3$) δ : 18.07 (t), 27.67 (t), 30.95 (t), 32.97 (t), 57.31 (q), 60.15 (t), 76.4 (s), 86.34 (s), 127.23 (d), 135.4 (d).

1Z.- IR (neat) : 2920 (br,s), 1740 (m), 1645 (w), 1450 (m), 1100 (s), 905 (m), 715 (m) cm^{-1}

^1H NMR ($CDCl_3$) δ : 1.4-1.8 (c, 2H), 2.0-2.4 (c, 4H), 3.3 (s, 3H), 3.95 (d, J=8 Hz, 2H) 4,05 (t, J=2 Hz, 2H), 5.3-5.9 (c, 2H).

^{13}C NMR ($CDCl_3$) δ : 18.14 (t), 28.04 (t), 31.10 (t), 32.76 (t), 56.82 (q), 59.91 (t), 76.81 (s), 85.96 (s), 127.63 (d), 134.99 (d).



Scheme 1

a) LiBu/THF,-30°C

b) $Br(CH_2)_3Br$, r.t., then reflux 72 h (68%)

c) $LiOCH_2$-C≡C-Li/NH_3-DMSO; 15 h, slow warming from -33°C to r.t. (56%)

d) LAH/THF, -65°; 15 h, slow warming to r.t., then 5 h at 60°C (49%)

e) $(F_3CCO)_2O$/THF, r.t.

f) LiBr/1:1 THF:HMPT, reflux (81%);

g) $LiNH_2/NH_3$,-30°C

h) excess $Br(CH_2)_3Br$/hexane; DMSO; 15 h, slow warming from -33°C to r.t. (38%)

i) H_2,Pd/$CaCO_3$-quinoline hexane 2 h (96%)

j) CH_3OCH_2-C≡C-Li/NH_3-DMSO; 15 h, slow warming from -33°C to r.t. (75%)

k) p-TsOH/MeOH, reflux 2 h (88%).

Application of the carbonylative cyclization to both isomers was as follows: A solution of $Ni(CO)_4$ (0.84 ml, 0.064 mol) in 4 ml of hexane was added dropwise to a solution of **1E** (0.75 g, 0.032 mol) in 15 ml of MeOH and the reaction mixture was kept at 15ºC for 10 hrs. Then the temperature was raised up to 40ºC for 1 hr. Elimination of the excess of $Ni(CO)_4$ was carried out by flushing with nitrogen while the temperature was kept at 40ºC. After solvent evaporation the residue was partitioned between methylene chloride and water. The organic layer was dried and evaporated to give a crude product (700 mg) which was purified by flash chromatography eluting with a 1:1 ethyl acetate:n-hexane mixture to afford 0.38 g (50%) of 4-(methoxycarbonylmethyl)-2-(methoxymethyl)bicyclo[3.3.0]oct-1-en-3-one (**9**).

9.- IR ($CHCl_3$) : 2940 (br, s), 1730 (s), 1705 (s), 1660 (s), 1100 (m) cm^{-1}

^1H NMR ($CDCl_3$) δ: 0.9-1.0 (c, 1H), 1.7-2.15 (c, 3H), 2.2-3.0 (c, 6H), 3.25 (s, 3H), 3.6 (s, 3H), 4.0 (s, 2H).

^{13}C NMR ($CDCl_3$) δ: 25.44 (t), 25.66 (t), 30.71 (t), 33.37 (t), 49.99 (d), 51.43 (q), 51.94 (d), 58.43 (q), 64.93 (t), 131.55 (s), 172.53 (s), 185.47 (s), 208.16 (s).

Anal. calcd. for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65,63; H, 7,48.

The trans relative stereochemistry of H-4 and H-5 protons was ascertained from the observed 3.1 Hz value for de $J_{H-4,H-5}$ coupling constant in the corresponding 400 MHz ^1H NMR spectrum in good agreement with data reported recently for other bicyclo[3.3.0]oct-1-en-one derivatives[7].

Starting from **1Z**, we obtained a similar yield of a compound which spectroscopically and chromatographically proved to be identical to **9**. This result would suggest that the isomerization of the π-allyl nickel complex takes place previous to triple bond coordination, given the low syn-anti rotational energy barrier through the corresponding σ-allyl bond as it has been reported for other allyl complexes[8]. Similar failures in maintaining the stereochemistry of the allylic double bond have also been reported by Semmelhack et al.[9-11] in attempted intramolecular cycloadditions of π-allyl nickel complexes onto aldehydes in approaches directed to the synthesis of several natural products.

On the other hand, as it has been reported recently in closely related reactions, the possible beneficial influence of chelating heteroatoms in the enyne concerning the stereoselectivity control in this intramolecular cyclization will be further investigated.

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