New Access to 7-Membered Heterocyclic C-Glycosides by the Cyclo-Addition-Ring-Expansion (CARE)-Reaction

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Dedicated to Professor Alan R. Katritzky, on the occasion of his 70th birthday.

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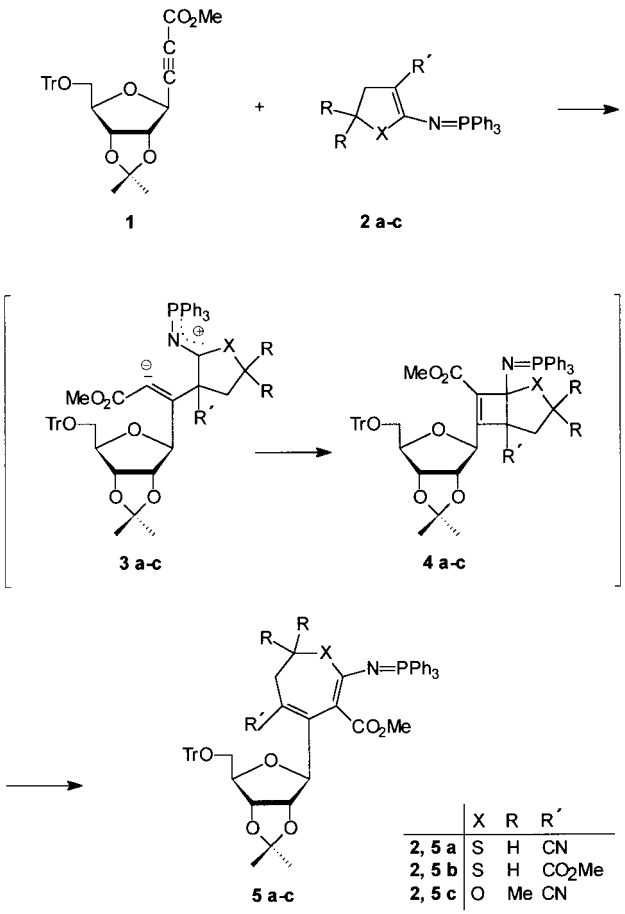
Abstract: CARE-reaction of methyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate **1** and methyl 4(*R*)-4,5-*O*-isopropylidene-2-pentynecarboxylate **10** leading to 7-membered heterocyclic C-glycosides is reported.

Several naturally occurring and synthetic heterocyclic C-glycosides exhibit strong biological activities (anti-cancer, anti-virus, antibiotic). The synthesis of a first example, pseudocytidine,[1] has been reported by Fox *et al.*[2] in 1975.

Now, we want to describe a novel class of C-glycosides containing a 7-membered heterocyclic base. In this course, we have modified the CARE (**C**yclo-**A**ddition-**R**ing-**E**xpansion)-reaction[3] which has served as a useful access to 7- and 8-membered heterocyclic ring systems. For this purpose, heterocyclic β-enaminonitriles and -esters have been protected at their 2-amino function by phosphorylation with dihalotriphenylphosphoranes.[4] Subsequent reaction with acetylenic esters gave stepwise thermal [2+2]-cycloaddition, followed by ring enlargement (5→7; 6→8) leading to the correspondent enlarged ring systems. Due to their enaminoester moiety these are capable of several subsequent cyclization reactions.[5]

In the present case, the acetylenic esters that had been used in former investigations (e.g. diethyl acetylenedicarboxylate or ethyl propiolate), were firstly replaced by methyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (**1**).[6] Upon reaction with the β-enaminonitriles and -esters (**2 a-c**) in dry acetonitrile we obtained the ring enlarged C-glycosides **5 a-c** (Scheme 1).[7] Due to the instability of these iminophosphoranes towards hydrolysis under acidic conditions, purification had to be carried out on neutral aluminum oxide. Thereby, the heteroatoms and substituents of **2 a-c** play a decisive role on the reaction rate to a more or less polarized enamine double bond.[3f]



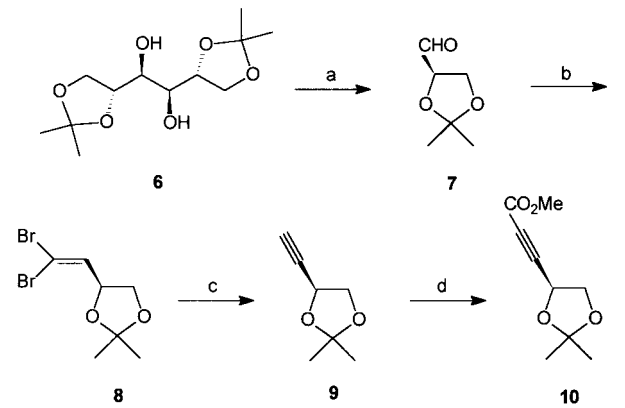
Scheme 1

Another important chiral building block for the synthesis of many biologically active compounds is D-glyceraldehyde[8] and its derivatives such as (+)-3,4-*O*-isopropylidenebutyne **9**,[9] which are easily accessible from 1,2:5,6-di-*O*-isopropylidene-D-mannitol **6**. We developed a smooth carboxylation of **9** using methyl chloroformate in dry THF[10] for obtaining a suitable new precursor **10** for the CARE-reaction.

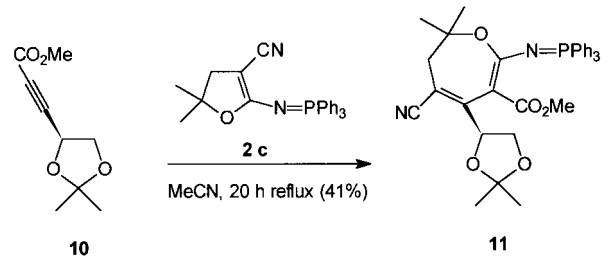
The resulting D-glyceraldehyde derivative **10** is of high optical purity and undergoes CARE-reaction with **2c** as expected under similar conditions as the ribose derivative **1**.[7]

The yield of **11** (41%) is higher compared with **5 a-c** (< 20%). This leads to the conclusion that the sterical demand of the protected ribose **1** influences the formation rate of **5 a-c**. Nevertheless, due to the instability of the iminophosphorane group in **11** towards hydrolysis, considerable loss during the chromatographic purification, even on neutral aluminum oxide, is observed.

In order to get a higher amount of a CARE-product comparable to **11**, any attempt of the hydrolysis of the iminophosphorane group using acetic acid, diluted HCl or H_2SO_4 failed. Another approach is the cyclization reaction of the phosphorylated β-enaminonitrile chromophore in **11** using an isocyanate[3c,d,11] as e.g. phenylisocyanate

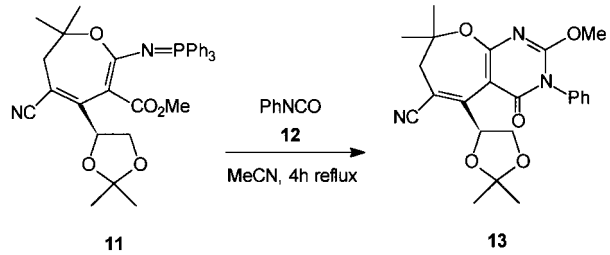


Scheme 2: a) $NaIO_4$ (2 eq), CH_2Cl_2, H_2O, RT (82%). b) CBr_4 (1.3 eq), PPh_3 (2.6 eq), NEt_3 (1 eq), CH_2Cl_2, 0 - 15°C (75%). c) EtMgBr (2 eq), THF, 25 -30°C (71%). d) cf. ref. 9.



Scheme 3

12. A first example **13** of this versatile reaction type[4b] was characterized by HRMS and further investigations are in progress.



Scheme 4

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(7) Typical procedure: the acetylenic compound **10** (240 mg, 1.3 mmol) and the iminophosphorane **2 c** (520 mg, 1.3 mmol) in dry acetonitrile (15 ml) were heated under reflux for 20 h (controlled by TLC). The solvent was removed *in vacuo*. Purification of the residue by column chromatography on neutral aluminum oxide (n-hexane/ethyl acetate 2:1 as eluent) gave **11** (310 mg, 41%). Analytical data of compound **11**: Anal. Calcd. For: $C_{34}H_{35}O_5N_2P_1$ C: 70.14; H: 6.06; N: 4.81. Found: C: 69.74; H: 5.99; N: 4.39. HRMS (EI): (m/z) calcd. for $C_{34}H_{35}O_5N_2P_1$ $(M)^+$ 582.2283; Found: 582.2284. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 0.68 (s, 3H, Oxepine CH_3), 0.71 (s, 3H, Oxepine CH_3), 1.28 (s, 3H, isopr.CH_3), 1.42 (s, 3H, isopr.CH_3), 2.30 (d, 2H, Oxepine CH_2), 3.62 (s, 3H, OCH_3), 3.65 (t, 1H, J=7.8 Hz, OCH_2-), 4.13 (t, 1H, J=7.2 Hz, OCH_2-), 4.76 (t, 1H, J=7.5-7.8 Hz, OCH-), 7.7-7.8 (m, 15H, Ph).

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(10) Methyl 4(*R*)-4,5-*O*-isopropylidene-2-pentyne carboxylate **10**: (+)-3,4-*O*-isopropylidenebutyne **9** (500 mg, 3.96 mmol), was dissolved in 10 ml THF and the solution was cooled to -50°C. BuLi (2.5 ml of a 1.6 M solution in n-hexane, 3.96 mmol) was added and the solution was warmed up to 0°C. Then, the mixture was again cooled to -35°C and a solution of $ClCO_2Me$ (750 mg, 7.92 mmol) in 10 ml dry THF was added within 30 min. After 1h at -35°C, the solvent was removed *in vacuo* and the residue diluted in 20 ml $CHCl_3$, washed with H_2O and dried ($MgSO_4$). Purification by column chromatography on silica gel (n-hexane/ethyl acetate 5:1 as eluent) gave **10,** 550 mg (75 %). Analytical data of **10**: Anal. Calcd. For: $C_9H_{12}O_4$ C: 58.69; H: 6.57. Found: C: 58.61; H: 6.54. MS (EI): (m/z) 183.1 $(M-H)^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.98 (dd, 1H, J=5.4, 8.4 Hz, OCH_2-), 4.14 (dd, 1H, J=6.5, 8.4 Hz, OCH_2-), 4.75 (dd, 1H, J=5.4, 6.5 Hz, OCH-).

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