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Stereoselective synthesis of substituted ketopyranose subunits of polyketide natural products by intramolecular alkoxycarbonylation of δ-alkynyl alcohols

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Abstract

Upon treatment with 5 mol% $Pd(MeCN)_2Cl_2$ in methanol containing 1.1–1.5 equiv. of *p*-benzoquinone under 1 atm of CO, δ-hydroxy alkynes are converted to methyl ketopyranosides with excellent stereoselectivity. The reaction proceeds by sequential intramolecular alkoxypalladation of the alkyne followed by CO insertion and methanolysis, then an ensuing Pd^{+2}-catalyzed 1,4-addition of methanol to the intermediate conjugated ester. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; cycloadditions; pyrans; palladium and compounds.

Substituted ketopyranose moieties occur as subunits in a number of cytotoxic polyketide natural products of interest as potential antitumor agents. Some representative partial structures are shown in Fig. 1.[1–3]

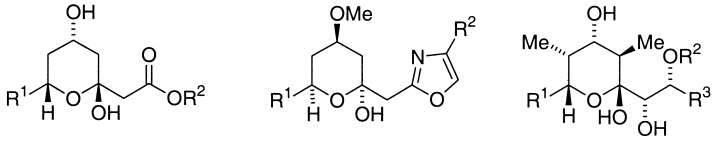

Figure 1. Ketopyranose subunits of polyketide natural products

Synthetic access to such subunits has typically involved addition of lithiated acetic esters to δ-lactones[4] or acid-catalyzed cyclization of δ-hydroxy ketones.[5–7] In recent years a number of reports on the Pd^{+2}-catalyzed stereoselective alkoxycarbonylation of δ-hydroxy alkenes, leading to substituted tetrahydropyrans, have appeared.[8] We reasoned that an analogous cyclization of

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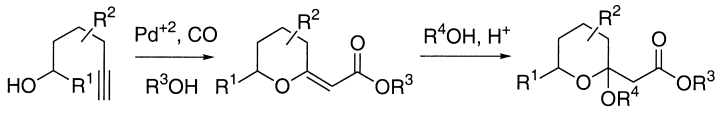
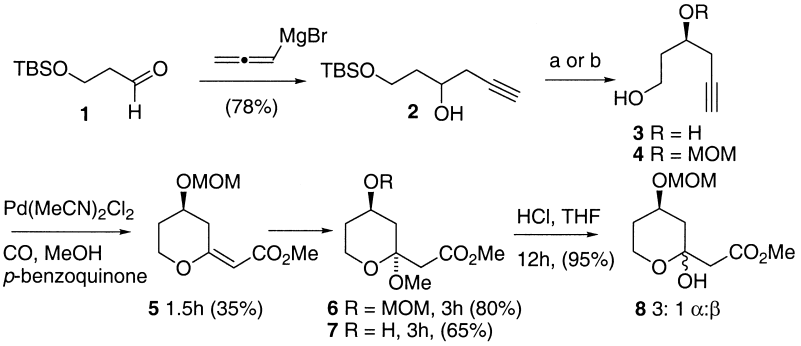
δ-hydroxy alkynes might provide ready access to the aforementioned ketopyranose substructures along the lines of Eq. (1).[9]



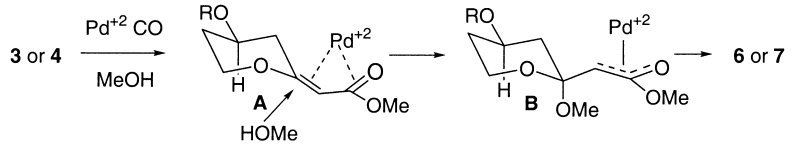
(1)

A prototype system was readily assembled along the lines of Scheme 1 through addition of allenylmagnesium bromide to aldehyde **1** and subsequent desilylation to afford diol **3**. Alternatively, adduct **2** was converted to the MOM ether followed by desilylation to alcohol **4**. Exposure of **4** to 1 mol% $Pd(MeCN)_2Cl_2$ in MeOH under an atmosphere of CO with 1.2 equivalents of *p*-benzoquinone as the Pd(0) reoxidant[10] afforded the unsaturated ester **5** in 35% yield after 1.5 h. If the reaction was allowed to proceed for 3 h with 5 mol% of catalyst, the methyl pyranoside ester **6** was isolated in 80% yield. Treatment of the unsaturated ester **5** with methanolic PPTS for several hours afforded recovered starting material. However, resubjecting **5** to the Pd^{+2} reaction condition gave rise to pyranoside **6**. The hydroxy pyranoside **7** could be similarly obtained from alcohol **3**. Hydrolysis of pyranoside **6** with 0.2 M HCl in THF[11] afforded the pyranose **8** as a 3:1 mixture of diastereomers in near-quantitative yield (Scheme 1).



Scheme 1. (a) TBAF, THF (86%); (b) MOMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2 (99%); TBAF, THF (79%)

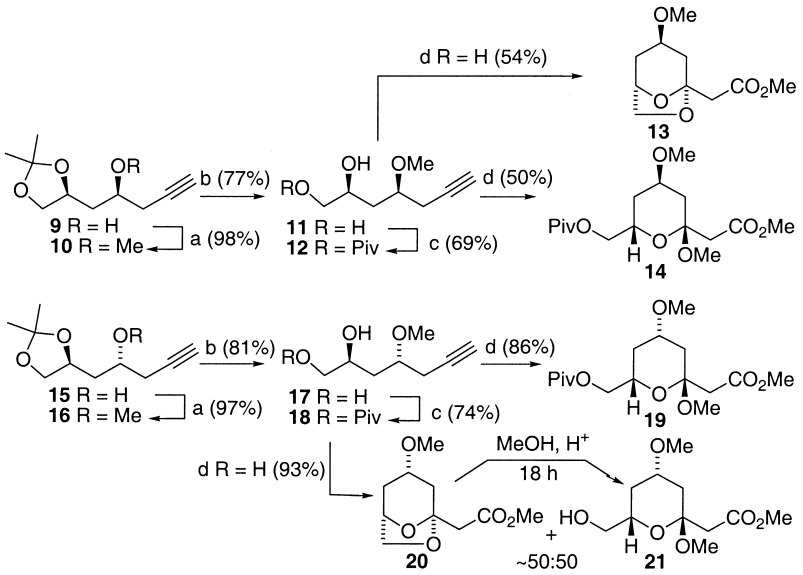
The foregoing observations suggest that hydrocarbonylation is a stepwise process involving an initial 6-*exo*-dig reaction leading to intermediate **A** which undergoes a kinetically controlled methanolysis in a second step to yield **B**, as illustrated in Eq. (2). The stereochemistry of pyranosides **6** and **7** is assigned accordingly.



(2)

A further probe of the methodology, with possible applications to subunits of acutyphycin and phorboxazole, (Fig. 1) is summarized in Scheme 2. Thus addition of allenylmagnesium bromide to the known acetonide of (*S*)-3,4-dihydroxybutanal[12] afforded a separable mixture of diastereomers **9** and **15**.[13] The stereochemistry of these adducts was assigned on the basis of the ^1H NMR

spectra of the *O*-methyl mandelic esters.[14] The methyl ethers **10** and **16** were subjected to acetonide hydrolysis and selective pivalate formation leading to the secondary alkynols **12** and **18**. Each of the four δ-hydroxy acetylenes **11**, **12**, **17** and **18** were subjected to the Pd^{+2}-catalyzed hydrocarbonylation conditions whereupon the indicated methyl ketopyranosides **13**, **14**, **19**, **20** and **21** were isolated in the indicated yields. Interestingly, the 1,3-*syn* hydroxy ether **11** afforded the bridged ether **13** as sole product whereas the 1,3-*anti* isomer **17** gave a mixture of bicyclic and monocylic adducts **20** and **21**.[5,15] Treatment of the former with methanolic *p*-toluenesulfonic acid resulted in near quantitative conversion to the latter in support of the stereochemical assignment.

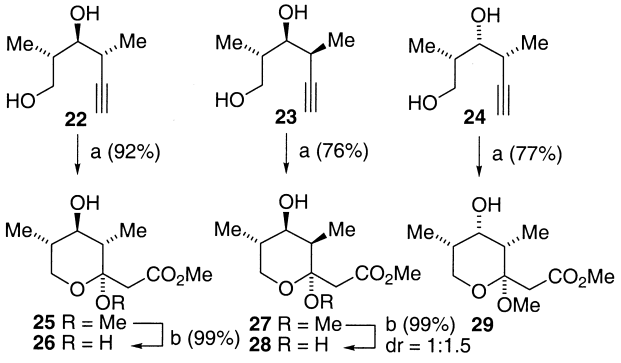


Scheme 2. (a) NaH, Mel, 15-C-5; (b) PPTS, MeOH; (c) PivCl, Et_3N, DMAP, CH_2Cl_2; (d) 5 mol% $Pd(MeCN)_2Cl_2$, CO, MeOH, *p*-benzoquinone, 3–12 h

An application of the methodology to ketopyranosides of the type found in apoptolidin was also explored. The starting materials for this study, alkynols **22**–**24**, were prepared through addition of enantioenriched allenylstannane (*syn* isomer **22**) and allenylzinc (*anti* isomers **23** and **24)** reagents to (*S*)-2-methyl-3-ODPS propanal.[16] In all cases the cyclizations proceeded smoothly to afford the methyl glycosides **25**, **27** and **29** as sole products (Scheme 3). Subsequent hydrolysis of glycosides **25** and **27** led to the keto pyranoses **26** and **28**, the latter as a 1.5:1 mixture of anomers. Molecular mechanics calculations indicate that the α- and β-anomers of pyranose **28** are of comparable energy.[17] These findings provide additional indirect support for a kinetically controlled cyclization-addition pathway.

A possible catalytic cycle for these alkoxycarbonylation reactions is presented in Fig. 2. It should be noted that the protons produced in the addition steps are consumed by *p*-benzoquinone in the course of catalyst regeneration thereby ensuring a weakly acidic reaction environment. In contrast, when $CuCl_2$ is used to reoxidize the Pd(0) in such reactions, two moles of HCl are formed.

These results demonstrate the potential use of homopropargylic alcohol adducts such as **22**–**24**[16] for the synthesis of ketopyranose-containing polyketide natural products of the type illustrated in Fig. 1. The methodology is noteworthy for its high degree of stereocontrol and the mild reaction conditions.



Scheme 3. (a) 5 Mol% $Pd(MeCN)_2Cl_2$, CO, MeOH, *p*-benzoquinone, 3 h; (b) HCl, THF, 12 h

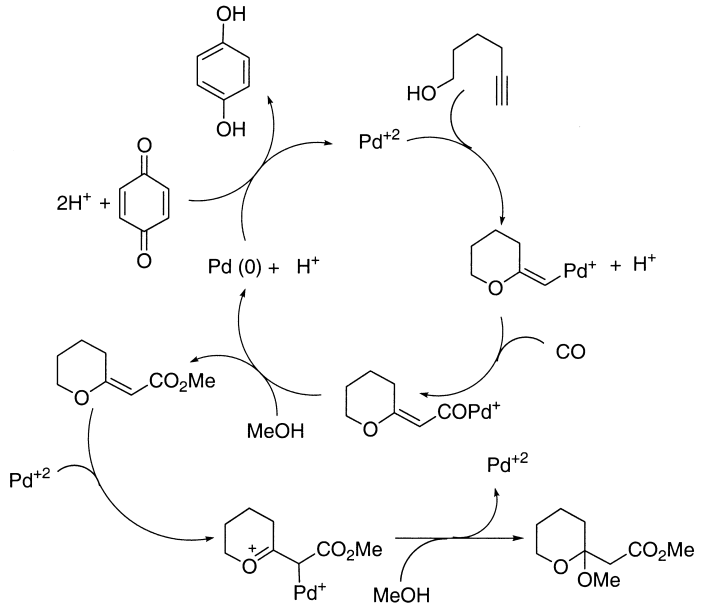


Figure 2. Catalytic cycle for alkoxycarbonylation-alcohol addition to δ-hydroxy alkynes (the ligands are not shown)

Representative experimental procedure. Pyranosides **20** and **21**: A stream of CO was passed over a solution of diol **17** (133 mg, 0.84 mmol) in MeOH (6 mL) for 1 min. A balloon of CO was affixed and stirring was started. After 5 min, sublimed *p*-benzoquinone (120 mg, 1.10 mmol) and $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.042 mmol) were added in one portion. The solution became bright yellow immediately upon dissolution. After 15 min the color of the solution changed to light orange. After 3.5 h the solution was concentrated affording a black solid. Dilution with CH_2Cl_2 (100 mL) afforded a yellow solution that was washed three times with 1N NaOH (10 mL) and once with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by chromatography on 5% Et_3N-deactivated silica gel (50% EtOAc/hexanes-100% EtOAc), affording 83 mg (45%) of the bridged compound **20** and 98 mg (48%) of methyl glycoside **21**[15] as light yellow oils. Equilibration of the bridged compound **20** with *p*-TsOH and methanol at rt for 18 h afforded an additional 90 mg of **21** (90% combined yield). Methyl Glycoside **21**:[5] R_f 0.37

(EtOAc); $[\alpha]_D = +65.0$, (*c* 0.92, $CHCl_3$); IR 3466, 2942, 1745 cm^{-1}; ^1H NMR δ 1.19 (q, $J = 12.0$ Hz, 1H), 1.44 (dd, $J = 11.4$, 12.9 Hz, 1H), 1.89–1.95 (m, 1H), 2.04 (br, 1H), 2.36 (ddd, $J = 2.1$, 4.8, 12.9 Hz, 1H), 2.60 (d, $J = 13.8$ Hz, 1H), 2.79 (d, $J = 13.8$ Hz, 1H), 3.24 (s, 3H), 3.33 (s, 3H), 3.59–3.80 (m, 4H), 3.68 (s, 3H); ^{13}C NMR δ 32.4, 39.4, 41.7, 47.9, 51.8, 55.6, 65.6, 70.1, 72.6, 99.4, 169.4. Bridged Glycoside **20**: R_f 0.55 (EtOAc); $[\alpha]_D = -38.4$ (*c* 1.4, $CHCl_3$); IR 2963, 1745 cm^{-1}; ^1H NMR δ 1.85–2.19 (m, 4H), 2.76 (s, 2H), 3.29 (s, 3H), 3.56 (td, $J = 4.2$, 1.0 Hz, 1H), 3.69 (s, 3H), 3.74 (d, $J = 6.3$ Hz, 1H), 4.18 (d, $J = 6.3$ Hz, 1H), 4.53 (br, 1H); ^{13}C NMR δ 32.3, 37.2, 43.0, 51.8, 56.5, 68.6, 72.9, 73.4, 104.7, 169.4.

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