Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1489-1492, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00046-9

Substrate Dependent Intramolecular Pauson - Khand Reaction of Carbohydrate exo-Methylene Derivatives. Unexpected formation of fused "[4.1.0] bicycloheptene - pyranose" tricyclic product.

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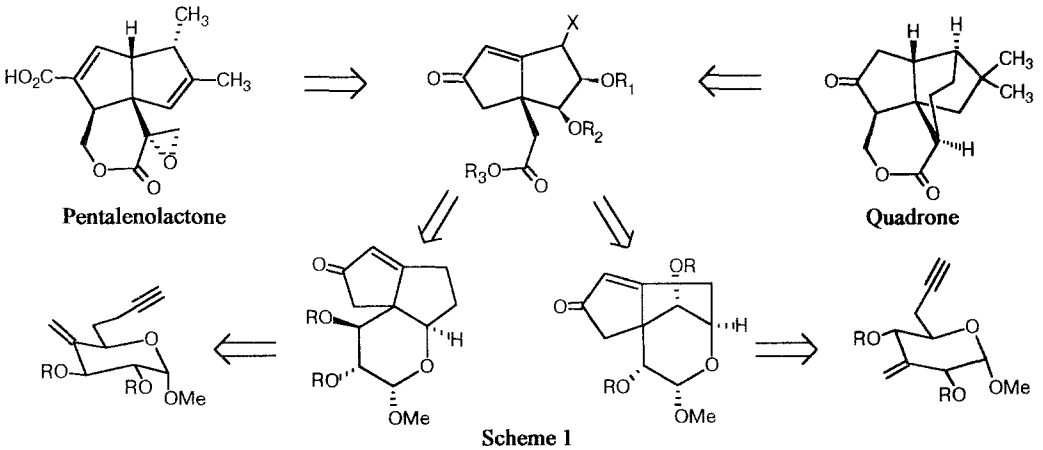
Abstract: *Attempted Pauson-Khand cyclisation of exo- methylene carbohydrate enynic substrates is described. 3-Exo methylene derivative cyclises to give a normal Pauson-Khand product while cyclisation of a 4-exo methylene analog follows a previously unreported pathway to give fused "[4.1.0] bicycloheptene - pyranose" tricyclic product.*

Intramolecular dicobaltoctacarbonyl mediated cyclisation of 1,6-enynes (Pauson-Khand reaction, PKR) proved to be a powerful tool to construct di- and polyquinane-like compounds.[1] Adaptation of this methodology to carbohydrate-derived substrates was first reported in 1994 when successful PKR of a series of O-propargylated unsaturated sugar derivatives with endo positioned double bond were announced.[2a]

The latter report prompted us to investigate the cyclisation of carbohydrate derived enynic substrates with the double bond being an exo substituent in various positions of sugar ring and the tether contained carbon atoms only.[2b] If such a transformation proceeds successfully expeditious route to stereoselective construction of annulated "diquinan-pyranoses", and in turn densely functionalized [3.3.0] bicyclooctenone derivatives with side chain growing up from quaternary carbon atom, could be developed (Scheme 1).

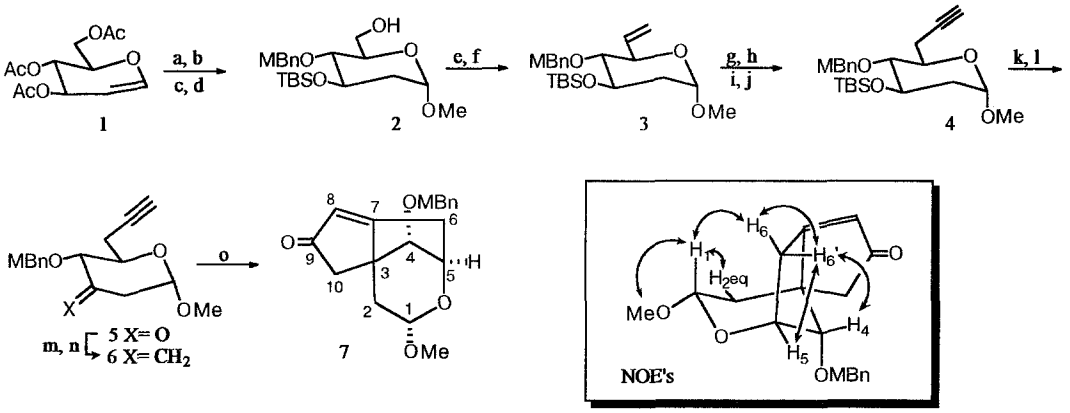


Scheme 1

This carbon assembly can be recognized retrosynthetically as the core of natural sesquiterpenoids pentalenolactone and quadrone and therefore intramolecular Pauson-Khand cyclisation, of properly functionalized 3- or 4- exo methylenated pyranosides, could be regarded as a viable approach to the stereocontrolled synthesis of complex triquinane-type natural compounds[3] from carbohydrates.[4] In this

context we decided to investigate the cyclisation of model 3- and 4-exo methylene substituted D-glucose derivatives bearing tethered acetylenic function in place of hydroxymethyl substituent.

Intramolecular PKR of 3-exo methylene substituted carbohydrate enynic substrate was studied with the 2-deoxy sugar derivative **6** prepared through a synthetic sequence starting with stereoselective methoxymercuration of D-glucal[5] (Scheme 2). The crucial methylenation of the 2-deoxy ulose **5** was conveniently accomplished via cerium chloride mediated addition of trimethylsilylmethyl lithium[6] followed by thionyl chloride induced silanol elimination.[7] Note that when we had tried to apply the same protocol to the substrate bearing 4,6-O-methoxybenzylidene protection to introduce exo methylene substituent at earlier steps, competitive formation of a byproduct (presumably allylic silane with 3,4-endo positioned double bond) substantially lowered the yield.

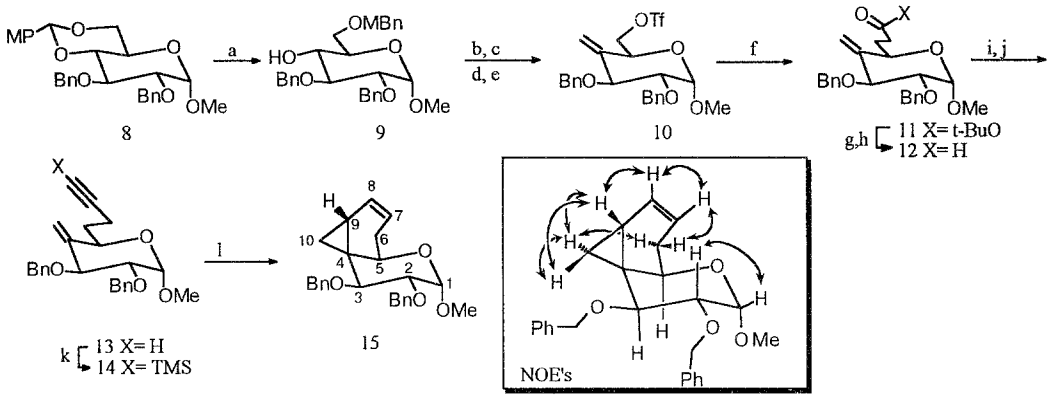


Scheme 2: a) Ref. 5; b) $MPCH(OCH_3)_2$, Dowex 50X 8 H^+/DMF, 73%, on two steps; c) TBSCl, ImH/DMF; d) DIBAL-H/DCM, -40°C→0°C, 90% on two steps; e) $(COCl)_2$-DMSO, then Et_3N/DCM, -60°C, 90%; f) Ph_3PCH_3Br, n-BuLi/THF, -40°C then 12 h RT, 84%; g) 9-BBN/THF, 0°C, then NaOH 30 % H_2O_2, 96%; h) $(COCl)_2$-DMSO, then Et_3N/DCM -60°C;i) Ph_3P, CBr_4/DCM; j) n-BuLi/THF, -78°C→RT, 64% on three steps; k) $Bu_4NF{\cdot}3H_2O$/THF, 85%; l) $(COCl)_2$-DMSO, then i-Pr_2NEt/DCM -60°C, 90%; m) Bu_3SnCH_2TMS, n-BuLi, $CeCl_3$/THF -78°C; n) $SOCl_2$, Py/DCM, 0°C 1 h, 73% on two steps; o) $Co_2(CO)_8$/0.2 M toluene soln 1h rt, then dilute to 0.02M 1 atm CO +110°C 2h, 30%.

With cyclisation precursor **6** in hand we have initially attempted annulation to be carried out with anhydrous N-methyl morpholine N-oxide (NMO) but only oxidation products were isolated from the reaction mixture (cf. Ref. 2a). The condition of choice was found to be the thermal induced reaction. When a toluene solution of $\mathbf{Co_2(CO)_6}$·**6** complex was heated at 110°C for 2h, with CO passing throughout the reaction mixture (see below), the desired tricyclic compound **7**[8a] was isolated in 30 % yield along with some recovered starting material. NOE's measured for **7** unambiguously confirmed the spatial proximity of H-1 and H-6_{exo} located on the convex face of [3.3.0] bicyclooctenone and H-6_{endo} and H-4, H-5 located on the concave.

Preparation of 4-exo methylene derivative **13** was launched with reductive acetal ring opening of the known dibenzyl ether **8**[9] (Scheme 3). Oxidation - methylenation sequence followed by selective removal of 6-O-methoxybenzyl protection and triflation of the resulting primary alcohol ultimately gave stable triflate **3**. Triflate displacement with lithium *tert*-butyl acetate in THF-HMPA[10] provided a chain-elongated derivative **4** in 70 % yield after chromatography. Finally, routine alkynylation, according to the Corey-Fuchs protocol,[11] applied to the aldehyde **12** furnished the desired enynic substrate.

Attempts to trigger the annulation of **13** with tertiary amines N-oxides were unsuccessful. Regeneration of unchanged starting material from preformed $Co_2(CO)_6$·**13** complex was the only outcome when NMO in THF-CH_2Cl_2 was used,[12] while oxidation was the principal reaction pathway in the case of trimethyl amine N-oxide - oxygen system.[13]



Scheme 3: a) $NaBH_3CN,CF_3CO_2H$/DMF, MS 3Å 12 h RT, 81%; b) $(COCl)_2$-DMSO, then Et_3N/DCM -60°C; c) Ph_3PCH_3Br, n-BuLi/THF, -40°C then 12 h RT, 90% on two steps; d) CAN/CH_3CN-H_2O; e) Tf_2O, Py/DCM,-78°C→ 0°C, 90% on two steps; f) LDA, t-BuOAc/THF-HMPA, -78°C, 70%; g) LAH/THF, 0°C ,h) $(COCl)_2$-DMSO, then Et_3N/DCM -60°C; 89% on two steps; i) Ph_3P, CBr_4/DCM; j) n-BuLi/THF, -78°C→RT, 77% on two steps; k) n-BuLi/THF then TMSCl -78°C, 82%; l) $Co_2(CO)_8$/0.2 M toluene soln 1h RT, then dilute to 0.02M, 1 atm CO +110°C 3h, 61%.

Being tested as a last resort, thermal PKR resulted in the formation of a slightly more polar new product. After the reaction mixture was worked-up with NMO[3c] to remove cobalt residues and chromatographed, homogeneous material was obtained in 36% yield. This was increased almost two-fold when the reaction was performed in carbon monoxide atmosphere (slow bubbling of CO throughout the reaction mixture). The result of structural proof was astonishing.[8b] Indeed, the MS showed the molecular peak with m/z 392 (i.e. revealed the absence of carbonyl group), while the ^{1}H-NMR homodecoupling experiment supported by ^{1}H-^{13}C COSY and ROESY trials clearly indicated the presence of intact pyranose nuclei fused to [4.1.0] bicycloheptene carbon framework with the double bond positioned between C7 and C8.

Faced with the unprecedented cyclisation pathway of the enynic substrate **13** we tried to explore structural factors that probably govern this process. We presumed initially that the tether is too short to ensure the transition state of normal geometry in the case of **13**. However, no homogeneous products were isolated from the pilot thermal cyclisation of homologous substrate with one carbon longer tether. Similarly, when the silylated analog of **13** was brought into thermal cyclisation only slow decomposition of intermediate $Co_2(CO)_6$·**14** complex to the mixture of unidentified products resulted.

In conclusion, pronounced dependence of substrate structure upon the reaction course of Pauson - Khand cycloaddition is observed for the first time. We have successfully prepared annulated "[3.3.0] bicyclooctenone-sugar" derivative from the monocyclic precursor with the double bond being the 3-exo substituent and acetylenic function at C-7 under the thermal Pauson-Khand reaction. In contrast, attempted cyclisation of 4-exo methylene substrate bearing acetylenic group at C-8 does not provide normal Pauson-Khand product but fused "[4.1.0]bicyclohepten-pyranose" derivative was formed via a previously unknown

process. At this time we can speculate only that carbenoid species[14] could be plausible reactive intermediates in this cyclisation, meanwhile further experimentation is needed to confirm or reject this hypothesis.

Acknowledgments: We are very gratefull to Dr. Alexander Shashkov for his help in taking and interpretation 2D NMR spectra. This work is supported by INTAS grant N°93-1450.

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8. a) Compound **7**: syrup $[\alpha]_D$ +57.6 (c= 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.3 and 6.9 (2×m, 4H; Ar*H*), 5.92 (dd, J= 1.7Hz, 1.7Hz, 1H; *H8*), 4.74 (dd, J= 10Hz, 4Hz, 1H; *H1*), 4.7 (d, J= 11Hz, 1H; PhCH*H*O), 4.57 (d, J= 11Hz, 1H; PhCH*H*O),4.57 (dd, J=5Hz, 3Hz, 1H; *H5*), 3.8 (s, 3H; C*H*$_3$O), 3.5 (s, 3H; C*H*$_3$O), 3.31 (bd, J= 3.5Hz, 1H; *H4*), 3.07 (dd, J= 20Hz, 1.7Hz, 1H; *H6*$_{exo}$), 2.65 (ddd, J= 20Hz, 5Hz, 1.7Hz, 1H; *H6*$_{endo}$), 2.51 (dd, J= 12.5Hz, 10Hz, 1H; *H2*$_{ax}$), 2.24 (AB spectrum, 2H; *H10*, *H10'*), 1.4 (bdd, J= 12.5Hz, 4Hz, .5Hz; 1H, *H2*$_{eq}$); ^{13}C NMR (75 MHz, $CDCl_3$): 208.3 (*C9*), 184.2 (*C7*), 159.5 (MeO*Ph*CH$_2$O), 129.6 (MeO*Ph*CH$_2$O), 129.4 (MeO*Ph*CH$_2$O), 126.6(*C8*),114 (MeO*Ph*CH$_2$O), 97.5 (*C1*), 80.0 (*C5*), 75.4 (MeOPh*C*H$_2$O), 70.8 (*C4*), 56.4 (O*C*H$_3$), 53.3 (O*C*H$_3$), 53.2(*C3*), 47.8 (*C6*), 37.9 (*C10*), 31.3 (*C2*).
b) Compound **15**: syrup $[\alpha]_D$ -65.4 (c= 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.25-7.45 (m, 5H; Ar*H*), 5.96 (ddd, J= 10Hz, 5Hz, 2.5Hz, 1H; *H8*), 5.33 (m, J= 10Hz, 6.5Hz, 2.5Hz 1H; *H7*),4.96 (d, J= 11Hz, 1H; PhCH*H*O), 4.8 (d, J= 12Hz, 1H; PhCH*H*O), 4.75 (d, J= 3.5Hz, 1H; *H1*), 4.66(d, J= 12Hz, 1H; PhCH*H*O), 4.58 (d, J= 11Hz, 1H; PhCH*H*O), 4.16 (dd,J= 10Hz, 6.5Hz, 1H; *H5*), 4.15 (d, J= 10Hz, 1H; *H3*), 3.65 (dd, J= 10Hz, 3.5Hz, 1H; *H2*), 3.47 (s, 3H; C*H*$_3$O), 2.24 (ddd, J= 16Hz, 6.5Hz, 6.5Hz, 1H; *H6*), 1.89 (m, J= 16Hz, 10Hz, 2.5Hz, 2.5Hz, 1H; *H6'*), 1.53 (ddd, J= 8.5Hz, 5Hz, 4.5Hz, 1H; *H9*), 1.19 (dd, J= 8.5Hz, 4Hz, 1H; *H10*), .89 (t, J= 4Hz, 4Hz, 1H; *H10'*); ^{13}C NMR (75 MHz, $CDCl_3$): 129.5 (*C8*), 120.6 (*C7*), 100.3 (*C1*), 82.3 (*C2*), 76.9 (*C3*), 75.7 (Ph*C*H$_2$0), 73.8 (Ph*C*H$_2$0), 66.2 (*C5*), 55.7 (O*C*H$_3$), 29.9 (*C4*), 28.1 (*C6*), 15.8 (*C9*), 11.8 (*C10*).
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(*Received in UK* 8 *November* 1995; *revised* 31 *December* 1995; *accepted* 8 *January* 1996)