Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 5059-5062, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00936-8

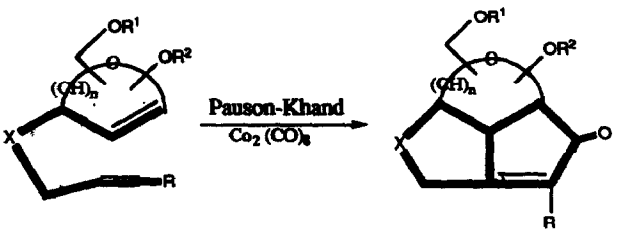
The Pauson-Khand Reaction on Carbohydrate Templates.I. Synthesis of Bis-Heteroannulated-Pyranosides

José Marco-Contelles

Instituto de Química Orgánica General, CSIC, Juan de la Cierva, 3. 28006-Madrid, Spain.

Abstract: The Pauson-Khand reaction on the carbohydrate derived precursors **1-5** is reported. The resulting bis-heteroannulated pyranosides **6-10** have been obtained in moderate yields. These enantiomerically pure, densely functionalized carbocycles are attractive advanced intermediates for the sytnthesis of complex natural products.

In the last years an increased attention has been devoted to the metal (Pd, Zr, Cr) catalyzed cycloisomerization of enynes.[1] In particular, the cobalt-mediated cyclization (Pauson-Khand reaction) of 1-hepten-6-ynes is one of the best methods for cyclopentenone construction.[2] Very recently, an efficient and useful asymmetric version[3] (*chiral auxiliary control*) of this reaction has been reported. Previous to this work, Magnus[4a] and Mulzer[4b] have described the enantiospecific Pauson-Khand cyclization of some acyclic, enantiomerically pure compounds (*chiral substrate control*). The use of chiral catalysts in this process is also known.[5]

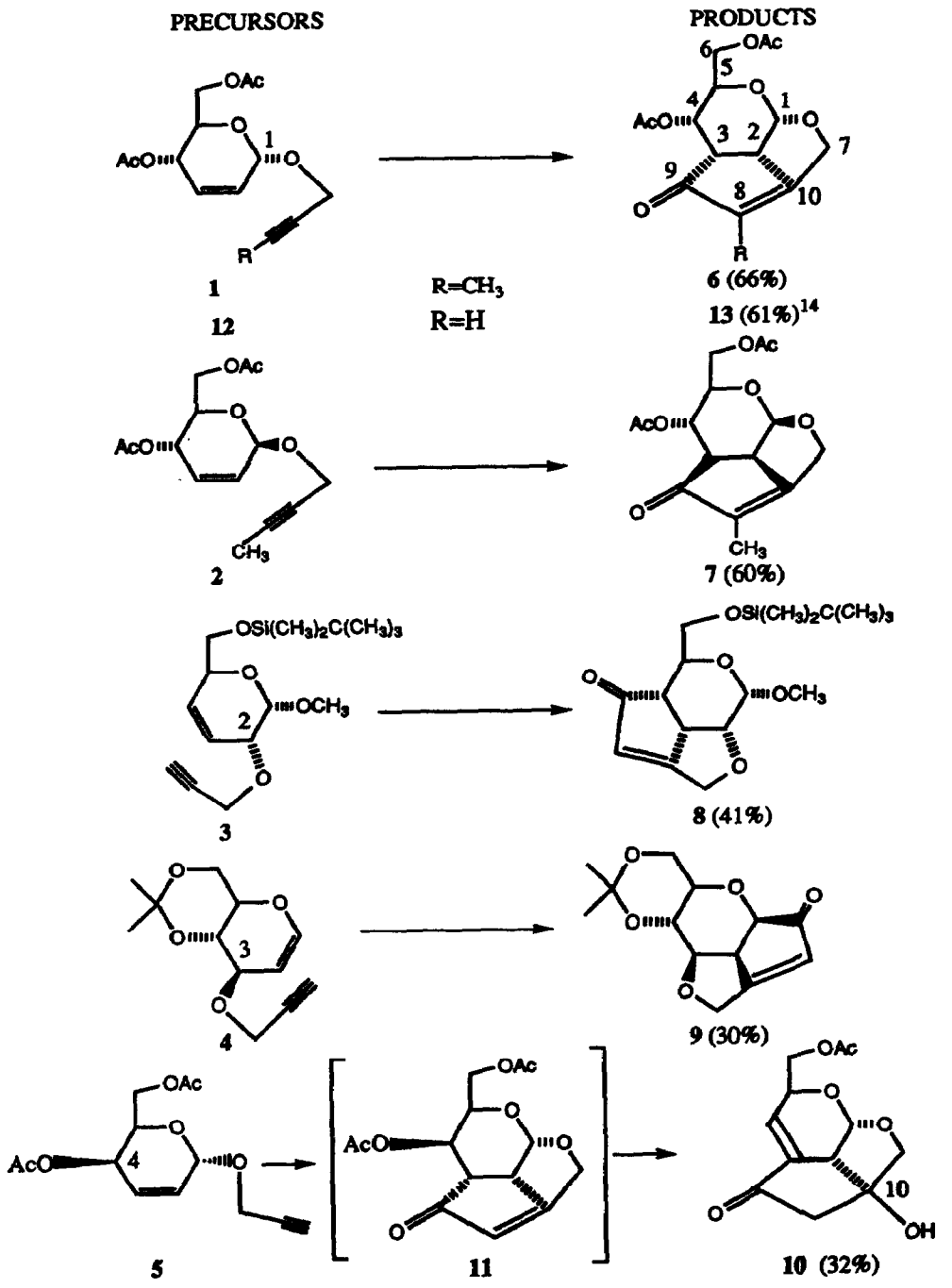


I (X=O, NR^3, CR^4R^5; n=1,2) II

Scheme I

It is well known that the carbohydrate core provides excellent rigid stereochemical and rich functional bias for the rapid assembly of polycyclic molecules.[6] To our knowledge, *the cobalt-mediated cyclization of suitable enynes incorporated in pyranoid (or furanoid) sugar templates,[7] as shown in Scheme I, has never been described.* In this process a synthetically versatile and highly functionalized bis-(hetero)-annulated pyranose[8] should result, with at least, two new stereocenters (C1, C2 in compound II, see Scheme I). The stereochemical outcome of the reaction will depend on the absolute configuration of the carbon where the propargylic branch is attached, the reaction conditions and the stability of the final products. In this Letter we disclose our preliminary results in this subject.

Scheme II. Cobalt-mediated cyclization of precursors 1-5



The D-*glucose* derived 1,6-enyne precursors **1**[9]-**4** and the D-*galacto* derivative **5** have been prepared by known or standard methods.[10] The *O*-propargylic moiety has been conveniently located at carbons C1-C4, around the pyran ring. In the exploratory experiments with compound **1**, it became soon evident that the cobalt complex readily decomposed to the desired cyclopentenone **6**[10] in good yield (66%), upon treatment with N-methyl morpholine N-oxide (NMO).[11] The thermal induced transformation [4] afforded the same compound in a slower reaction and lower yield (20%). Then, the above conditions were routinely used with the other precursors.[12] In Scheme II we show the structures and yields of the resulting fused cyclopentenones. Several points deserve some comments: 1.º The moderate overall yield in the Pauson-Khand reaction is compensated for by the efficiency of the 'one-pot' process and the highly functionalized final products obtained, which are difficult to synthesize by other methodologies; 2.º The observed vicinal coupling constants in the ^{1}H NMR spectra of products **6**-**10**[10] [**6**: $J_{1,2}$= 6.2 Hz, $J_{2,3}$= 6.7 Hz; **7**: $J_{1,2}$= 6.3 Hz, $J_{2,3}$=6.6 Hz, $J_{3,4}$= 8.7 Hz; **8**: $J_{1,2}$= 5.2 Hz, $J_{2,3}$= 9.1 Hz, $J_{3,4}$= 6.6 Hz; **9**: $J_{1,2}$= 5.1 Hz, $J_{2,3}$= $J_{3,4}$= 8.4 Hz] allow us to secure that the the absolute configurations at the carbons where the fused-cyclopentenone are anchored are determined by the stereochemistry of the carbon linked to the *O*-propargyl branch. It means that the carbonylative acetylenic insertion always takes place from the same side where the propargyl moiety is located. This observation has an additional value and will allow us in the future the design of selected target molecules; 3.º The cyclization of precursor **4** is particularly interesting because it gives a stereocontrolled C-glycosyl derivative in a 'one -pot' reaction and complements with advantages other reported free radical based strategy for a similar transformation;[13] 4.º The formation of the anomalous product **10** from D-*galacto* precursor **5** was surprising and can be accounted to the presence of an acetate at C4 in axial position, the mild basic conditions and the acidity of H3 in the presumed intermediate **11** (Scheme II); after acetate elimination and β-hydroxylation promoted by the excess of NMO present in the medium, compound **10** should result; [10,14] the absolute configuration at C10 could not be established.

In summary, we have described for the first time[15] the cobalt-mediated cyclization of some *O*-branched-chain sugar enynes. These compounds are valuable and advanced intermediates in the synthesis of some natural products. Work directed to this goal is in progress in our laboratory and will be reported in due course.

Acknowledgments. We thank CICYT (PB 90-0078) and Comunidad Autónoma de Madrid (C195/91A) for financial support. JMC thanks Miss Angeles Martínez-Grau for recording some NMR spectra. The author also thanks Dr. Fernández-Mayoralas for useful discussions, and Dr. A. Moyano and Dr. M.A. Pericás for performing some preliminary experiments and their interest in this work.

References and Notes

1. (a) Trost, B.M. *Accounts of Chem. Res.* **1990**, *23*, 34. (b) Negishi, E. in *Comprehensive Organic Synthesis*, Ed. Trost, B.M.; Pergamon: Oxford, 1991, Vol 5, p 1163. (c) Kim, O.K.; Wulff, W.D.; Jiang, N. *J.Org.Chem.***1993**, *58*, 5571.

2. (a) Pauson, P.L. in *Organometallics in Organic Synthesis. Aspects of Modern Interdisciplinary Field*; de Meijere, A.; tom Dieck, H., Eds.; Springer: Berlin, 1987. (b) Schore, N. *Organic Reactions* **1991**, *40*, 1.

3. Verdaguer, X.; Moyano, A.; Pericás, M.A.; Riera, A.; Bernardes, V.; Greene, A.E.; Alvarez-Larena, A.; Piniella, J.F.; *J.Am.Chem.Soc.* **1994**, *116*, 2531, and references cited therein.

4. (a) Magnus, P.; Becker, D.P. *J.Am.Chem.Soc.* **1987**, *109*, 7495. (b) Mulzer, J.; Graske, K.-D.; Kirste, B. *Liebigs Ann.Chem.* **1988**, 891.

5. Bladon, P.; Pauson, P.L.; Brunner, H.; Eder, R. *J.Organometal.Chem.* **1988**, *355*, 449.

6. Ferrier, R.J.; Middleton, S. *Chem.Rev.* **1993**, *93*, 2779.

7. (a) Moufid, N.; Chapleur, Y. *Tetrahedron Lett.* **1991**, *32*, 1799. (b) RajanBabu, T.V.; Nugent, W.A.; Taber, D.F.; Fagan, P.J. *J.Am.Chem.Soc.* **1988**, *110*, 7128. (c) Engelbrecht, G.J.; Holzapfel, C.W. *Tetrahedron Lett.* **1991**, *32*, 2161. (d) Trost, B.M.; Runge, T.A. *J.Am.Chem.Soc.* **1981**, *103*, 759.

8. For the concept and developments of annulated pyranoses or furanoses, see: (a) Fraser-Reid, B.; Tsang, R. in *Strategies and Tactics in Organic Synthesis*, Academic Press Inc: New York, 1989, Vol 2, p 123. (b) Yeung, B.-W.A.; Contelles, J.L.M.; Fraser-Reid, B. *J.Chem.Soc., Chem.Commun.* **1989**, 1160.

9. Jeong, N.; Lee, .Y.; Lee, S.M.; Chung, Y.K.; Lee, S.-G. *Tetrahedron Lett.* **1993**, *34*, 4023.

10. A full account on the preparation of these precursors will be reported elsewhere. All new compounds showed good spectroscopic and analytical data. *Selected data*: **6**{oil; $[\alpha]_D^{25}$ -17 (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (d, $J_{1,2}$= 6.2 Hz, 1 H, H1), 4.97 (dd, $J_{4,3}$= 8.9 Hz, $J_{4,5}$= 10.3 Hz, 1 H, H4), 4.84 (d, *J*= 14.6 Hz, 1 H, H7), 4.59 (d, 1 H, H7'), 4.17 (m, $J_{6,6'}$= 11.7 Hz, $J_{6,5}$= 4.1 Hz,1 H, H6), 4.10 (dd, $J_{6',5}$= 2.7 Hz, 1H, H6'), 3.70 (ddd, 1 H, H5), 3.50 (m, $J_{2,3}$= 6.7 Hz, 1 H, H3), 3.35 (m, 1 H, H3), 2.08, 2.05 (s, s; 3H, 3H; CH_3COO-), 1.82 (br s, C8-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.27 (C9), 172.36 (C10), 170.53, 169.83 (CH_3COO-), 134.66 (C8), 96.28 (C1), 66.64 (C7), 66.19, 65.16 (C4, C5), 62.79 (C6), 45.47, 44.93 (C2, C3), 20.63 (CH_3COO-), 9.1 (CH_3)}; **8**{$[\alpha]_D^{25}$-57 (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (br s, 1 H, H8), 4.78 (d, $J_{1,2}$= 5.2 Hz, 1 H, H1), 4.76 (d, $J_{7,7'}$= 15.8 Hz, 1 H H7), 4.71 (d, 1 H, H7'), 4.33 (dd, $J_{2,3}$= 9.1 Hz, 1 H, H2), 3.91 (dd, $J_{6,6'}$= 11.2 Hz, $J_{6,5}$= 2.2 Hz, 1 H, H6), 3.74 (dd, $J_{6',5}$= 6.7 Hz, 1 H, H6'), 3.48 (ddd, $J_{4,5}$= 10.5 Hz, 1H, H5), 3.41 (m, 1 H, H3), 3.29 (s, 3 H, OCH_3), 2.79 (dd, $J_{4,3}$= 6.6 Hz, 1 H, H4), 0.89, 0.087 [s,s; 9H, 6H; $OSiC(CH_3)_3(CH_3)_2$]; ^{13}C NMR (75 MHz $CDCl_3$) δ: 209.11 (C9), 182.62 (C10), 121.59 (C8), 98.32 (C1), 71.70, 65.48 (C5, C2), 67.42, 64.52 (C6, C7), 55.49 (OCH_3), 47.54, 44.96 (C3, C4), 25.89,18.38, -0.55[$OSiC(CH_3)_3(CH_3)_2$]; **10**{oil; $[\alpha]_D^{25}$ -54 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (t, $J_{4,2}$= $J_{4,5}$= 3.0 Hz, 1 H, H4), 6.11 (d, $J_{1,2}$= 4.8 Hz, 1 H, H1), 4.65 (m, 1H, H5), 4.28 (dd, $J_{6,6'}$= 10.8 Hz, $J_{6,5}$= 4.2 Hz, 1 H, H6), 4.23 (dd, $J_{6',5}$= 5.7 Hz, 1 H, H6'), 3.97 (d, $J_{7,7'}$= 10.2 Hz, 1 H, H7), 3.85 (d, 1 H, H7'), 3.04 (dd, 1 H, H2), 2.70 (s, 2 H, H8), 2.09 (s, 3 H, $COOCH_3$); ^{13}C NMR (75 MHz $CDCl_3$) δ 199.31 (C9), 170.43 (CH_3COO-), 136.83 (C3), 130.13 (C4), 100.46 (C1), 82.13 (C10), 78.26 (C7), 67.80 (C5), 64.45 (C6), 49.62 (C2), 47.14 (C8), 20.62 (CH_3COO-)}.

11. Shambayati, S.; Crowe, W.E.; Schreiber, S.L. *Tetrahedron Lett.* **1990**, *31*, 5289.

12. In a typical experiment, to a solution of the precursor in methylene chloride, cobalt carbonyl (1.1 equiv) was added in one portion at room temperature. The mixture was stirred for ~3 h and then, anhydrous NMO (6.3 equiv) was slowly added and stirred for ~5 h at room temperature. Part of the solvent was removed, the suspension was adsorbed in silica gel and submitted to flash chromatography. Elution with hexane/ethyl acetate mixtures gave pure products.

13. López, J.C.; Fraser-Reid, B. *J.Am.Chem.Soc.* **1989**, *111*, 3450.

14. The formation of compound **10** from precursor **5** is in sharp contrast with the obtention of the *normal* product **13** (61% yield) from the D-*gluco* starting material **12** (see Scheme II) (The author thanks Dr. A. Moyano and Dr. M.A. Pericás for performing this experiment).

15. A report describing the unsuccessful Pauson-Khand reaction on substrates **1**, **12** and similar, has been recently published: Lindsell, W.E.; Preston, P.N.; Rettie, A.B. *Carbohydr. Res.* **1994**, *254*, 311. These results point out the critical effect of the experimental conditions for the decomposition of the hexacarbonyl complexes in the Pauson-Khand reactions; see reference 11 and references cited therein.

(*Received in UK 7 April* 1994; *revised* 9 *May* 1994; *accepted* 12 *May* 1994)