Pergamon

Tetrahedron Letters 43 (2002) 8607–8609

TETRAHEDRON LETTERS

Hydroformylation of glycals using a rhodium(I)(acac)$(CO)_2$ catalyst

Mohindra Seepersaud,[a] Mika Kettunen,[b] Adnan S. Abu-Surrah,[c] Wolfgang Voelter[d] and Yousef Al-Abed[a,d,*]

[a]*The Picower Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030, USA*
[b]*Department of Inorganic Chemistry, University of Helsinki, FIN-00014 Helsinki, Finland*
[c]*Department of Chemistry, Hashemite University, Zarqa 13115, Jordan*
[d]*Physiologisch-chemisches Institut der Universität, D-72076 Tübingen, Germany*

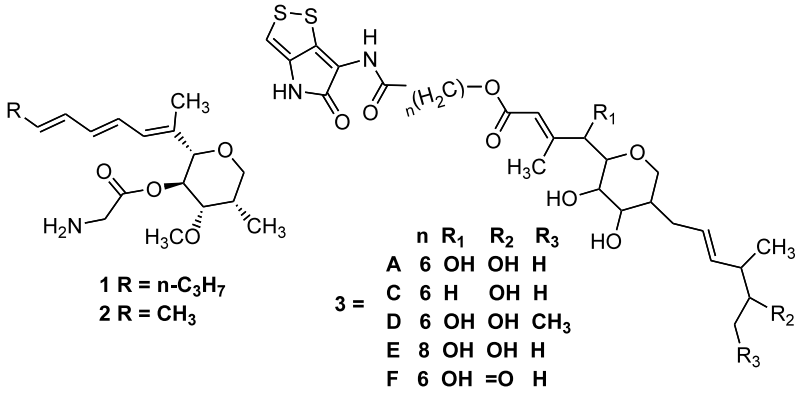
Received 19 February 2002; accepted 6 September 2002

Abstract—The hydroformylation of glycals was achieved using Rh(I)(acac)$(CO)_2$ catalyst. For glucals, the C-2 formyl pyran was the major product whilst for galactal an equimolar mixture of the C-2 and C-1 regioisomers were observed.

C-Branched sugars are essential components in several antibiotics[1] and also key structural subcomponents in many natural products.[2] Members of this group include the polyenes, Restrictin **1** and Lanomycin **2** which have received attention because of their inhibition of P_{450} lanosterol C_{-14} demethylase and the Thiomarinols D–G **3**, which were recently isolated and have demonstrated potent antimicrocidal activity.[3] These classes of compounds are characterized by the presence of a pyran ring which is deoxygenated at C-1 and alkylated at C-2.

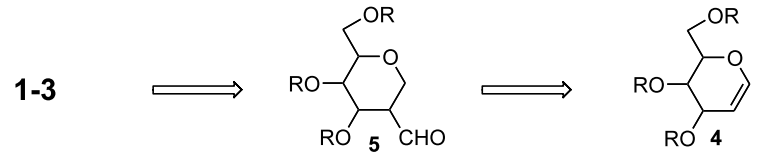
Logical retrosynthetic analysis suggests that a direct route to the pyranose template could involve the regioselective hydroformylation of glycals **4** to their corresponding C-2 intermediates **5**. Intermediate **5** has the necessary functionality at the C-2 position to allow for conversion to target **1**–**3** (Scheme 1).

Since its initial description in 1968 by Evans, Osborn and Wilkinson,[4] hydroformylation of alkenes by homogenous rhodium catalysts has attracted the attention of researchers to functionalization of complex molecules.[5] To date, there are only a few reports on hydroformylation of glycals.[6,7] We recently synthesized carba-D-fructofuranose via a hydroformylation of a functionalized cyclopentene.[8] Utilizing the catalyst Rh(acac)$(CO)_2$ under similar reaction conditions, glycals gave a mixture of the C-1 formyl 2-deoxy C-glycoside and the corresponding C-2 formyl pyran.[9] Thus hydroformylation of tri-*O*-benzyl-D-glucal **6** gave the



* Corresponding author. E-mail: yalabed@nshs.edu

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02059-2



Scheme 1.

formyl adducts **7**:**8** in ratio of 8:92.[7] Use of the corresponding acetyl protected glucal **9** gave similar results. The 3,4-di-*O*-acetyl-6-deoxy glucal **12** gave only the C-2 formyl product **14**. However, tri-*O*-benzyl-D-galactal **15** was quantitatively hydroformylated to give a 1:1 mixture of formyl compounds **16** and **17** (Scheme 2).

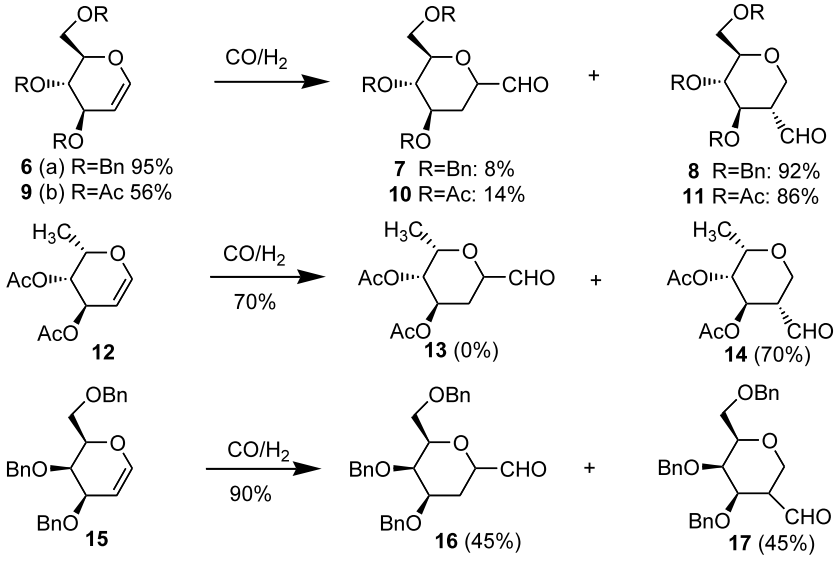
The regioselectivity of formyl addition depends on the following factors; polarization of the olefin, relative stability of the alkyl-metal complexes, the difficulty of producing the β-elimination process in conformationally rigid substrates, and the ratio between the rates of formation of the acyl-metal intermediates.[7b] Our results indicate that there is a general tendency to hydroformylate at the C-2 position. Of note, galactal where C3, C4 and C5 positions are *syn* gave 45% of the C-1 formyl regioisomer compared to its glucal counterpart (0–14%). It seems that this difference in stereochemistry at the C-4 position influences some of the above 'factors' to favor the C-1 formylation. Thus for galactal, the hydroformylation represents a direct entry into the 2-deoxy-C-glycosides **5**. For all the C-2 regioisomers obtained, we observed minimal elimination suggesting an anti addition to the C-3 substituent. Also no hydrogenation products were observed. The reaction proceeds under neutral conditions and does not need the addition of auxiliary ligands such as PPh_3 or P(*O*-*o*-$^tBuC_6H_4)_3$.[10] Of note, the use of the $Co_2(CO)_8$ under the same reaction conditions gave no reaction.[6]

The regiochemistry of our products was established by comparison to the available literature.[7b] In general, key chemical shift differences exist between the C-1 and C-2 formyl diastereomers. In ^1H NMR spectra the presence of a ABq, at 3.4 ppm and the absence of any signals upfield to this are indicative of the formyl group at C-2. In ^{13}C NMR, the presence of an additional signal in the 50–60 ppm region and the absence of a signal upfield to this indicates C-2 formyl attachment.[9]

At present, an extension of this methodology using external chiral ligands is underway in an attempt to direct the regiochemistry to C-1 formyl glycosides.[10] Overall, using the above catalyst, we have demonstrated an efficient and versatile one carbon extension of glycals which allows access to a variety of novel synthetic intermediates for antifungal and antibiotic agents.

Acknowledgements

M.K. and A.S.A. would like to thank Fortum OY for financial support. Y.A. also would like to thank the Humboldt Foundation for the research fellowship.



Scheme 2.

References

1. (a) Chapleur, Y.; Chetien, F. In *Preparative Carbohydrate Chemistry*; Hannesian, S., Ed.; Marcel Dekker: New York, 1997; p. 207; (b) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69; (c) Fraser-Reid, B.; Burgey, C. S.; Vollerthun, R. *Pure Appl. Chem.* **1998**, *70*, 285; (d) Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57; (e) Hanessian, S. In *Total Synthesis of Natural Products. The 'Chiron' Approach*; Pergamon Press: Oxford, 1983.
2. For some recent examples, see: (a) Sasaki, M.; Inoue, M.; Takamatsu, K.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9399; (b) Fernandez Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991; (c) Horita, K.; Nagasawa, M.; Sakarai, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1199; (d) Bamba, M.; Nishikawa, T.; Isobe, M.; *Tetrahedron* **1997**, *53*, 16287; (e) Shimura, T.; Komatsu, C.; Matsumura, M.; Shimada, Y.; Ohta, K.; Mitsunobu, O. *Tetrahedron Lett.* **1997**, *38*, 8341; (f) Sin, N.; Kallmerton, J. *Tetrahedron Lett.* **1996**, *37*, 5645.
3. (a) Tsukuda, T.; Umeda, I.; Masubuchi, K.; Shirai, M.; Shimma, N. *Chem. Pharm. Bull.* **1993**, *41*, 1191; (b) Jendrzejewski, S.; Ermann, P. *Tetrahedron Lett.* **1993**, *34*, 615; (c) Kang, S.; Min Kim, C. *Synlett* **1996**, 515; (d) Shiozawa, H.; Shimada, A.; Takahashi, S. *J. Antibiot.* **1997**, *50*, 449.
4. Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc.* **1968**, 3133.
5. (a) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 7658; (b) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285; (c) Kollar, L.; Sandor, P. *J. Organomet. Chem.* **1993**, *445*, 257; (d) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145; (e) Lapidus, A. L.; Priudze, I. G.; Korneyeva, G. A.; Vartanyan, M. M.; Rodin, A. P.; Slivinskii, Y. V.; Dolidze, A. V.; Loktev, S. M. *Neftekhimiya* **1993**, *33*, 102; *Petrol. Chem.* **1993**, *33*, 91.
6. Rosenthal, A. *Adv. Carbohydr. Chem.* **1968**, *23*, 59.
7. (a) Polo, A.; Claver, C.; Castillon, S.; Ruiz, A.; Bayon, J. C.; Real, J.; Mealli, C.; Massi, D. *Organometallics* **1992**, *11*, 3525; (b) Fernandez, E.; Ruiz, A.; Claver, C.; Castillon, S. *Organometallics* **1998**, *17*, 2857.
8. Seepersaud, M.; Kettunen, M.; Abu-Surrah, A. S.; Repo, T.; Voelter, W.; Al-Abed, Y. *Tetrahedron Lett.* **2002**, *43*, 1793.
9. A solution containing the dicarbonylacetylacetonato rhodium (0.035 g, 0.14 mmol), toluene (70 mL) and the olefin **15** (3.0 g, 1.2 mmol) were placed in a 300 mL mechanically-stirred steel autoclave (equipped with a gas entrainment impeller) which was then charged with carbon monoxide (50 bar) and hydrogen (50 bar). The reaction mixture was stirred at 100°C for 48 h. At the end of this period, the remaining gases were vented off and the solvent was evaporated to furnish the crude aldehydes **16**/**17** in 1:1 ratio and 90% yield with R_fs 0.30 and 0.4 (25% EtOAc:PE), respectively. Selected spectroscopic data are as follows; Compound **16**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.25 (m, 2H), 3.45–3.61 (m, 3H), 3.80 (m, 3H), 4.35 (t, $J=7.5$ Hz, 1H), 4.42–4.62 (m, 6H), 4.89 (m, 1H), 7.3 (m, 15H), 9.75 (s, 1H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 25.4, 68.9, 70.8, 73.2, 73.6, 74.0, 74.9, 75.6, 127.5, 127.8–128.7 (several signals), 138.0, 138.2, 138.5, 203.8. MS (ES) m/z (M+K$^+$), 485 (base peak), 181. Compound **17**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.46 (ABq, $J=8.9$ Hz, $\Delta\delta=0.10$ ppm, 2H), 3.59 (m, 3H), 3.80 (dd, $J=2.2$, 8.4 Hz, 1H), 4.00 (d, $J=2.2$ Hz, 1H), 4.13 (d, $J=7.0$ Hz, 1H), 4.47 (ABq, $J=11.9$ Hz, $\Delta\delta=0.08$ ppm, 2H), 4.60 (ABq, $J=11.4$ Hz, $\Delta\delta=0.22$ ppm, 2H), 4.76 (ABq, $J=11.6$ Hz, $\Delta\delta=0.31$ ppm, 2H), 7.3 (m, 15H), 9.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 50.1, 65.6, 69.2, 71.3, 71.5, 73.7, 74.7, 77.8, 79.2, 127.9–128.7 (several signals), 137.4, 137.8, 138.4, 202.8. MS (ES) m/z (M+Na$^+$), 469 (base peak), 181.
10. (a) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413; (b) Casey, C. P.; Paulsen, E. L.; Beuttenmueller, E. W.; Proft, B. R.; Petrovich, L. M.; Matter, B. A.; Powell, D. R. *J. Am. Chem. Soc.* **1997**, *119*, 11817.