Tetrahedron Letters,Vol.22,No.48,pp 4871-4872,1981 0040-4039/81/484871-02$02.00/0
Printed in Great Britain 

# STEREOSELECTIVE REDUCTION OF 3-KETO GIBBERELLIN ACIDS TO 3β-OLS USING K-SELECTRIDE WITH $KH_2PO_4$ BUFFER

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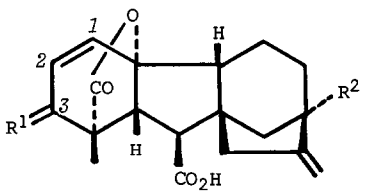
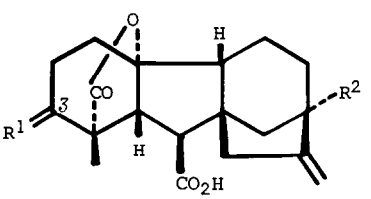
*SUMMARY:* $KH_2PO_4$ buffered K-Selectride gives with 3-keto gibberellin acids, borates which are reduced stereoselectively to 3β-ols.

In connection with our structure-activity studies[2] and syntheses of gibberellins,[3] we required a simple solution to the perennial problem of efficiently converting the available C19-gibberellins $A_3$ [(1), gibberellic acid] and $A_7$ (2),[4] into their respective 1,2-dihydro analogues $A_1$ (5) and $A_4$ (6). Early approaches[5] employing selective hydrogenation of the Δ (1) bond often lead to hydrogenolysis of the allylic lactone. This problem has been solved by more recent procedures[6] based upon conjugate hydride-reduction of the readily derived $\Delta^1$-3-one methyl esters, *e.g.* of acid (4), but the un-natural 3α-(equatorial)-hydroxy esters, *c.f.* (9), are mainly obtained as a consequence of final hydride-delivery to C(3) along the less hindered β-vector.

To probe the feasibility of inducing an α-attack of hydride at C(3), and hence generating 3β-(axial)-alcohols, we treated the 3-keto-$A_4$ *acid* (8)[7,10] in THF with potassium tri-*sec*-butylborohydride (K-Selectride)[11] in the expectation that an initial rapid reaction with the β-carboxylic acid group would generate a borate complex which, because of steric interference and Coulombic repulsion, should then disfavour reagent approach to C(3) along the β-vector. In the event, this K-Selectride reduction of (8) stereoselectively gave gibberellin $A_4$ (6)[8,10] in $\geqslant$ 90% yield with ∿ 4% 3-epi-$A_4$ (9).[8,10] It is of mechanistic and preparative significance that in a similar reduction using lithium tri-*sec*-butylborohydride which forms less bulky lithium carboxylates,[12] 3-epi-$A_4$ (9) was now the major product, ∿ 80%, with $A_4$ (6) formed in only ∿ 17% yield.




| | $R^1$ | $R^2$ |
|---|---|---|
| (1) | βOH, αH | OH |
| (2) | βOH, αH | H |
| (3) | O | OH |
| (4) | O | H |




| | $R^1$ | $R^2$ |
|---|---|---|
| (5) | βOH, αH | OH |
| (6) | βOH, αH | H |
| (7) | O | OH |
| (8) | O | H |
| (9) | βH, αOH | H |

For the direct conversion of $A_3$-ketone (3)[7,10] into $A_1$ (5)[3,10] and $A_7$-ketone (4)[7,10] into $A_4$ (6) using K-Selectride, a proton source was needed which would decompose *in situ* the intermediate enol borate from an initial 1,4-addition of hydride, to unmask the respective ketones (7) and (8) for the final 1,2-reduction. We found that powdered, anhydrous, $KH_2PO_4$ not only fulfilled this requirement but also served to buffer the reaction mixture without rapidly destroying the K-Selectride.[13] Thus, under prescribed conditions (see below), (3) and (4) were reduced in $\geqslant$ 95% yield and with $\geqslant$ 95% stereoselectively to the respective 3β-(axial)-hydroxy gibberellins, $A_1$ (5) and $A_4$ (6).

We expect that the profound stereochemical influence of borane complexation on the reduction of 3-keto gibberellin acids, and the compatibility of $KH_2PO_4$ with K-Selectride, will find wider synthetic applications.

*General Procedure - K-Selectride-$KH_2PO_4$ Reduction:*

K-Selectride in THF (0.5 M, 0.8 ml, 0.4 mmol) was added during 5 min under $N_2$ to a stirred solution [(3) requires initial warming to 50°] of the 3-keto gibberellin acid (0.1 mmol) in THF (1 ml) at -70°, containing dry, powdered, $KH_2PO_4$ (82 mg, 0.6 mmol). The mixture was brought to -30° during 30 min then to 0° during 90 min after which no ketone remained (TLC, quench -70°). The cooled (-10°) mixture was treated with aq. $KH_2PO_4$ (20%, 0.1 ml), the pH adjusted to ∿ 3 ($H_3PO_4$, 10%) and $CH_2Cl_2$ (12 ml) added. The dried ($Na_2SO_4$), concentrated, mixture was quickly chromatographed (Silica act. 3, 6 mm X 50 mm, eluant as for TLC[10]) to give: non-polar borane, then $\geqslant$ 90% 3β-hydroxy and ∿ 4% 3α-hydroxy gibberellin acids.

*Acknowledgements:* We are grateful to Professor L.N. Mander for his generous support and to I.C.I. (UK) for gifts of gibberellins $A_3$ and $A_{4/7}$.

*References and Notes*

1. Visiting Fellow in Chemistry from McMaster University, Hamilton, Ontario, Canada.
2. L.N. Mander, J.V. Turner and B. Twitchin, *Tetrahedron Lett.*, *22*, 3017 (1981).
3. L. Lombardo, L.N. Mander and J.V. Turner, *J. Am. Chem. Soc.*, *102*, 6626 (1980).
4. Gibberellin $A_7$ is isolated with $A_4$ as a mixture, resolvable by HPLC.[10] However, the operations described here for $A_7 \rightarrow A_4$ work on the $A_{4/7}$ mixture equally well.
5. (a) B.E. Cross, R.H.B. Galt and J.R. Hanson, *Tetrahedron*, *18*, 451 (1962); (b) D.F. Jones and P. McCloskey, *J. Appl. Chem.*, *13*, 324 (1963).
6. Reagents used include, (a) $LiBH_4$-THF: I.A. Gurvich, N.S. Kobrina and V.F. Kucherov, *Bull. Acad. Sci. U.S.S.R.*, 1668 (1969); (b) $NaBH_4$-LiBr: M.H. Beale and J. MacMillan, *J.C.S. Perkin 1*, 877 (1980); (c) $NaBH_4$-MeOH: B. Voigt, G. Adams, N.S. Kobrina, E.P. Serebryakov and N.D. Zelinsky, *Z. Chem.*, *17*, 373 (1977); (d) $NaBH_4$-CuCl: Z.J. Duri, B.M. Fraga and J.R. Hanson, *J.C.S. Perkin 1*, 161 (1981); (e) K-Selectride-THF-EtOH: L. Lombardo, L.N. Mander and J.V. Turner, *Aust. J. Chem.*, *34*, 745 (1981).
7. *3-Keto-gibberellins $A_4$ and $A_7$*[8] were made by $CrO_3$ oxidation[6e] of either an $A_{4/7}$ mixture or the separated alcohols;[4] *3-keto-gibberellin $A_3$* (3)[9] was prepared by oxidising gibberellic acid with pyridinium dichromate as for the corresponding methyl ester.[6d]
8. C.D. Aldridge, J.R. Hanson and T.P.C. Mulholland, *J. Chem. Soc.*, 3539 (1965).
9. P.J. Keay, J.S. Moffatt and T.P.C. Mulholland, *J. Chem. Soc.*, 1605 (1965).
10. All gibberellins had characteristics as reported; their purity was established by TLC (Silica; $CH_2Cl_2$:$Et_2O$:MeOH:HOAc, 20:20:1:1; light petrol adjusts Rf) and by HPLC [Waters, μ Bondapak C18, flow rate 4 ml/min; MeOH:$H_2O$, 55:45, 3.6 mM in $H_3PO_4$; (9) 14 min, (2) 15 min, (6) 17 min, (8) 18 min. MeOH:$H_2O$, 32.5:67.5, 3.6 mM in $H_3PO_4$; (3-epi-$GA_1$) 13 min, (1) 14 min, (5) 15 min, (3) 23 min]. Selected data $^1$H-NMR ($CDCl_3$-$d_4$MeOH) δ H 18 [3H, s] and H 6, H 5 [doublets J ∿ 10 Hz]:

| Compounds | (3) | (4) | (5) | (6) | (8) | (9) |
|---|---|---|---|---|---|---|
| H 18 | 1.32 | 1.33 | 1.16 | 1.16 | 1.18 | 1.20 |
| H 6 | 2.86 | 2.92 | 2.62 | 2.64 | 2.78 | 2.76 |
| H 5 | 3.52 | 3.47 | 3.08 | 3.12 | 3.08 | 2.46 |

11. J.M. Fortunato and B. Ganem, *J. Org. Chem.*, *41*, 2194 (1976).
12. H.C. Brown, S.C. Kim and S. Krishnamurthy, *J. Org. Chem.*, *45*, 1 (1980).
13. Several alcohols were tried as a proton source under a variety of conditions but protonation of the enolate was too slow below -30° and above this temperature additional polar products arose. $KH_2PO_4$ is compatible with L-Selectride also.

(Received in UK 18 September 1981)