Pergamon

Tetrahedron Letters, Vol. 37, No. 24, pp. 4255-4258, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00810-6

Unexpected C-Arylation of a Gibberellin: A Cautionary Note on the Radical Deoxygenation of Homoallylic Secondary Alcohols

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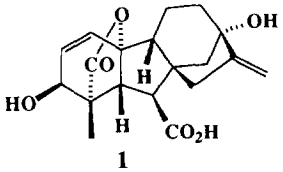
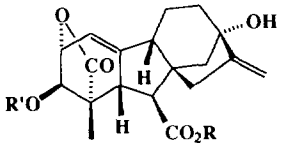
Abstract: Aryl 3-O-thionocarbonates (**7a-c**), upon treatment with tributyltin hydride and a catalytic amount of AIBN in benzene at reflux, do not undergo deoxygenation as expected, but instead afford the 10-arylated-*bis*-γ-lactones (**8a-c**) in high yields.

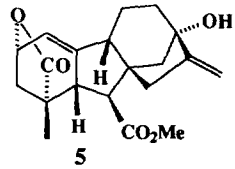
In our ongoing investigations directed towards the confirmation of assignments of provisional structures to new gibberellins ("GAs"),[1] we regarded lactone **5** as a key intermediate in the construction of 2β-hydroxy C_{20}-GAs.[2,3] The 19,2-γ-lactone **2** is readily formed in high yield by treatment of gibberellic acid (GA_3) (**1**) with 0.01M NaOH[4,5] and so all that was required was an acceptable procedure for the removal of the 3β-hydroxy group. The radical-mediated deoxygenation of secondary alcohols *via* their thiocarbonyl-derivatives (the Barton-McCombie reaction) has enjoyed extensive use since its inception in 1975.[6] The mild conditions and operational simplicity of this two step procedure have resulted in its successful application to some of the most demanding molecular frameworks.[7] Such a conversion was envisioned by Beale *et al.*, but they were unable to prepare the xanthate derivative **4** and ultimately adopted a more circuitous approach.[8,9]



1

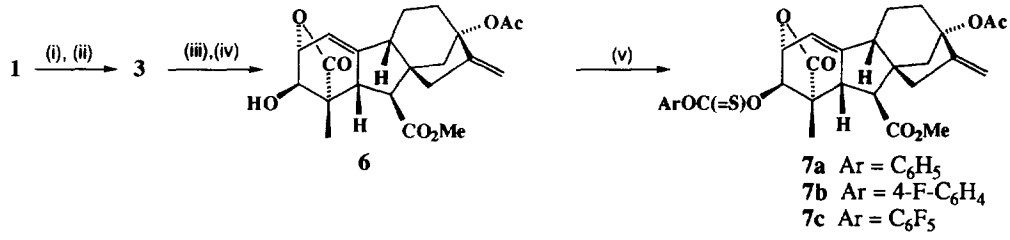


2 R = H R' = H
3 R = Me R' = H
4 R = Me R' = C(=S)SMe



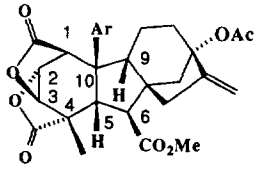
5

After experiencing difficulties in duplicating the Bristol synthesis of **5**, we elected to revisit the more direct approach and prepared the phenyl thionocarbonate derivative **7a** with a view to studying its deoxygenation.[10-12] The preparation of **7a**[13] from gibberellic acid (**1**) is depicted in **Scheme 1**. The use of trifluoroacetic acid to induce isomerisation of the lactone function in **1** (or 1-methyl ester) is more convenient and efficient than the literature procedure for preparing **3**.[5] After blocking reaction at the 13-hydroxyl by acetylation of both hydroxyls in **3** followed by selective hydrolysis of the 3-acetate function to give **6**, treatment with phenyl chlorothionoformate smoothly afforded the desired substrate **7a** for the radical deoxygenation reaction.



Scheme 1 *reagents and conditions:* (i) MeI, K_2CO_3, acetone (92% yield); (ii) CF_3CO_2H (10 eq), 20°C, 45 min.; (iii) Ac_2O (10 eq), Et_3N (10 eq), DMAP (0.1 eq), CH_2Cl_2, 20°C, 24h, (64%, 2 steps); (iv) K_2CO_3 (2.5 eq), $KHCO_3$ (0.7 eq), MeOH-H_2O, 20°C, 5 min., (89%); (v) ArOC(=S)Cl (2 eq), Et_3N (3 eq), DMAP (1 eq), CH_2Cl_2, 20°C, 3h, (98%).

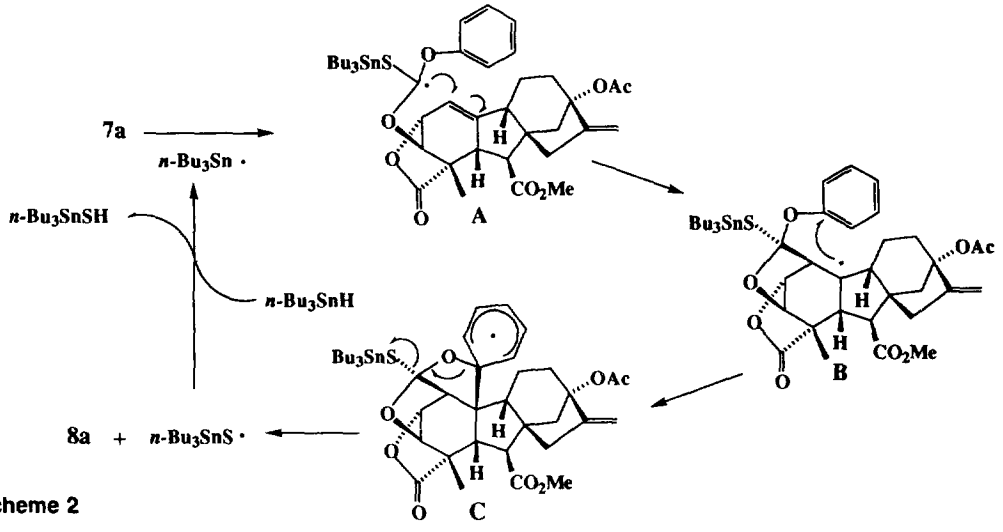
We were surprised to find that treatment of the phenyl thionocarbonate **7a** with Bu_3SnH and AIBN in benzene under reflux for 15 minutes gave a clean conversion to a product that was still highly oxygenated and that had incorporated a phenyl group. Structure **8a** was deduced from consideration of spectroscopic data[14] and ultimately confirmed by single crystal X-ray analysis.[15] The introduction of the aryl group into the 10β-position results in significant downfield shifts for H-5, H-6, H-9 and the 4-methyl group relative to their location in ^{1}H-NMR spectra of standard gibberellins.[1] Of further interest was the observation that all five aromatic protons were anisochronous as a consequence of the restricted rotation of the phenyl substituent.[16] None of the expected 3-deoxy derivative was detected.



8a Ar = C_6H_5 (80%)
8b Ar = 4-F-C_6H_4 (89%)
8c Ar = C_6F_5 (80%)

The formation of **8a** is rationalised as shown in **Scheme 2**. Substituted alkyl radical **A**, the product of tributyltin radical addition to the thiocarbonyl group, undergoes a 5-*exo*-trig cyclisation to generate the bridgehead *tert*-alkyl radical **B**. Intramolecular *ipso*-addition to the aromatic ring then affords the cyclohexadienyl radical **C**.[17] The aromatic ring is regenerated and the γ-lactone functionality set in place through β-fragmentation, ejecting a tributyltin thiyl radical in the process. Repeating the reaction with substoichiometric quantities of Bu_3SnH led to

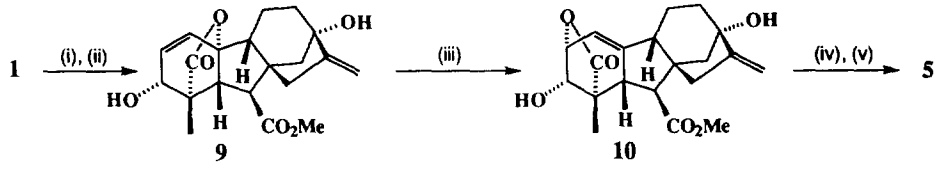
incomplete conversion of starting material **7a**. A plausible candidate for the final propagation step in this efficient chain process involves an S_H2 reaction between the tributyltin thiyl radical and *n*-Bu_3SnH.



Scheme 2

While this interpretation seemed reasonable, the possibility of solvent being incorporated (as the bridgehead phenyl group) could not be completely discounted.[18] In further efforts to obtain **5** we turned to Barton's improved protocols for primary alcohol deoxygenation[19] and prepared the *para*-fluorophenoxy-thionocarbonate **6b** and pentafluorophenoxy-thionocarbonate **6c** derivatives. Exposure to Bu_3SnH and AIBN in benzene under reflux provided none of the anticipated deoxygenation product (**5**) with either of these substrates, the only isolated products being the lactones **8b** and **8c**, respectively. These results indicate that the sequence of events depicted in **Scheme 2** must be especially favourable for derivatives of homoallylic alcohol **3**. Moreover, transfer of the fluoroaromatic residues of substrates **7b** and **7c** into the products **8a** and **8c**, respectively, rules out the possibility of solvent incorporation.

The original objective of deoxygenation was simply achieved as outlined in **Scheme 3** by first epimerising the gibberellin substrate at C-3 so that the 3-subsituent then possessed an equatorial conformation. Thus, the methyl ester of GA_3 (**1**) was treated with LiO*t*-Bu to afford **9**,[20,21] which was isomerised to **10** as for the 3β-epimer. The derived 3-thionocarbonate then smoothly underwent deoxygenation to afford **5** in 74% yield.



Scheme 3 *reagents and conditions:* (i) MeI, K_2CO_3, acetone (92% yield); (ii) LiO*t*-Bu, HO*t*-Bu-THF, 20°C, 4h (90%); (iii) CF_3CO_2H (10 eq), 20°C, 45 min (86%); (iv) ArOC(=S)Cl (2 eq), Et_3N (3 eq), DMAP (1 eq), CH_2Cl_2, 20°C, 3h (79%); (v) *n*-Bu_3SnH (1.75 eq), AIBN, C_6H_6, reflux 35 min (74%).

While competing processes might be anticipated in reactions of thionocarbonates and esters of *primary* alcohols,[22] secondary alcohol derivatives routinely undergo deoxygenation in a very efficient manner. From a practical standpoint, this sequence of events has several notable attributes, including the regio- and stereocontrolled construction of two differentiated carbon-carbon bonds across an unactivated alkene with the introduction of an aryl group into a sterically very hindered location. Work is underway to define the scope and limitations of the process which would appear to have considerable potential for carbocyclic syntheses.

Acknowledgements

We gratefully acknowledge a generous gift of gibberellic acid from Abbott Laboratories.

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11. Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.*, **1983**, *105*, 4059.
12. Barton, D.H.R.; Motherwell, W.B.; Stange, A. *Synthesis*, **1981**, 743.
13. All new compounds exhibited satisfactory spectroscopic data (^{1}H nmr, ^{13}C nmr, FTIR) as well as HRMS and/or elemental analyses.
14. ^{1}H-NMR (500MHz, $CDCl_3$): δ 1.37 (s, 3H, H-18); 1.40 (dd, 1H, *J* = 14.5, 1.4Hz, H-15); 1.74 (m, 2H, H-11, H-12); 1.99 (s, 3H, OAc); 2.25 (m, 3H, H-11, H-14, H-15); 2.36 (m, 2H, H-12, H-14); 2.63 (dd, 1H, *J* = 14.0, 3.6Hz, H-9); 3.30 (d, 1H, *J* = 5.3 Hz, H-1); 3.44 (d, 1H, *J* = 3.6 Hz, H-6); 3.68 (s, 3H, OMe); 3.85 (d, 1H, *J* = 3.6 Hz, H-5); 4.70 (br s, 1H, H-17); 4.78 (d, 1 H, *J* = 6.4 Hz, H-3); 5.00 (d, 1H, *J* = 1.7 Hz, H-17); 5.07 (dd, 1H, *J* = 6.4, 5.3 Hz, H-2); 7.26 (m, 2H, ArH); 7.33 (br t, 1H, *J* = 8.0Hz, ArH); 7.38 (br t, 1H, *J* = 8.0Hz, ArH); 7.84 (br d, 1H, *J* = 7.5Hz, ArH).
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16. Sternhell, S. in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, Jackman, L.M. & Cotton, F.A. eds. Academic Press, New York, 1975, pp 163-201.
17. For such an addition to the aromatic ring to be geometrically possible, an *endo*-orientation of the phenoxy substituent must be adopted in the initial cyclisation at C-1.
18. Reactions of alkyl radicals with benzene are usually slow (Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986; p 212) but have been witnessed before: Camaggi, C.M.; Leardini, R.; Zanirato, P. *J. Org. Chem.*, **1977**, *42*, 1570.
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20. Kirkwood, P.S.; MacMillan, J.; Hutchison, M. *J. Chem. Soc.* **1982**, 707.
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22. An analogous sequence has been reported for the phenyl thionocarbonate of 4-phenyl-3-butenol (M.D. Bachi, M.D.; Bosch, M. *J. Org. Chem.*, **1989**, *54*, 1234). In this case, however, by virtue of the primary nature of the C-O bond, fragmentation (leading to deoxygenation) would be disfavoured relative to cyclisation. Moreover, there are fewer steric constraints and the radical centre is benzylic in the initial cyclised intermediate (equivalent to **B**).

(*Received in UK* 10 *April* 1996; *accepted* 26 *April* 1996)