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# BORON TRIFLUORIDE-CATALYZED OXIDATION OF GLYCAL ESTERS: AN EFFECTIVE AND MILD METHOD FOR THEIR CONVERSION INTO α,β-UNSATURATED LACTONES[1)]

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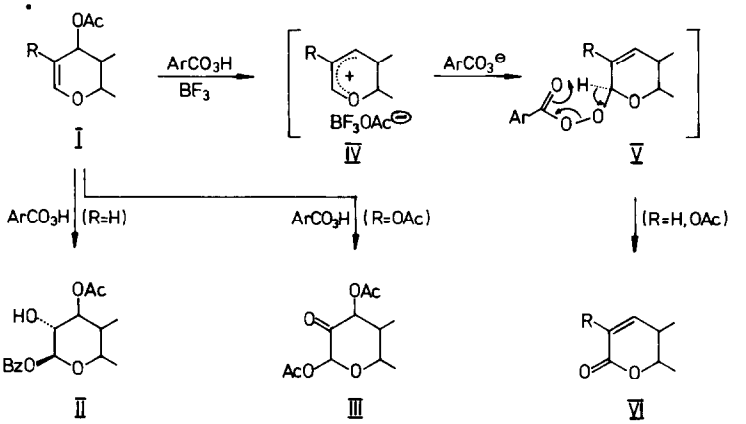
An effective, one-step procedure for conversion of glycal and 2-acyloxyglycal esters to 2,3-unsaturated lactones has been developed, involving $BF_3$-induced removal of the allylic acyloxy function and oxidation with m-chloroperbenzoic acid or pyridinium chlorochromate.

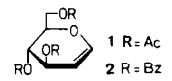
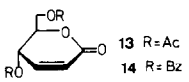
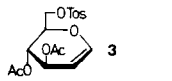
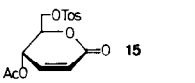
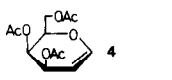
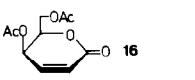
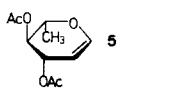
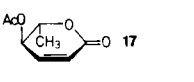
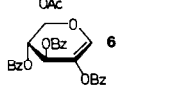
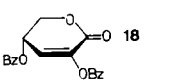
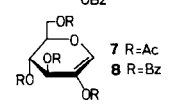
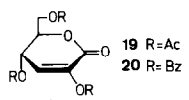
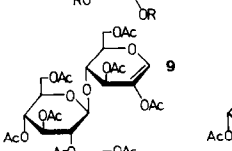
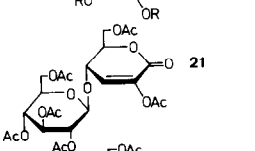
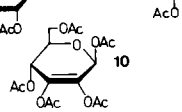
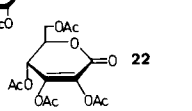
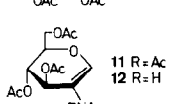
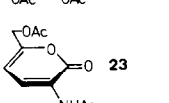
Glycal esters I (R = H), on perbenzoic acid oxidation, yield 1-O-benzoyl-glycoses of type II due to opening of the intermediate epoxide by the benzoic acid generated[2)], whilst 2-acyloxyglycal esters I (R = OAc) are converted into peracyl-glycos-2-uloses III via a C-2 → C-1-acyloxy shift that follows oxidation[3)]. In the presence of a Lewis acid catalyst such as boron trifluoride, the peroxidation of either glycal ester I (R = H or OAc) takes an entirely different course, affording in excellent yields α,β-unsaturated lactones of type VI[4)].




Mechanistically, the oxidative elimination I → VI is initiated by $BF_3$-induced removal of the allylic acyloxy function to form the allylcarboxonium ion IV[5)], is continued by nucleophilic attack of the peroxyacid anion solely at C-1 — as expected from a "hard" nucleophile[6)] — and is concluded by the fragmentation V → VI as indicated by the arrows[7)].

Preparatively, the one-step conversion I → VI simply involves treatment of the glycal ester with 1:1 molar equivalents of m-chloroperbenzoic acid in dichloromethane in the presence of boron trifluoride[8)], is best conducted with initial cooling (e.g. -10°C → ambient temperature) and is essentially complete within 15 - 30 min. In this form, the reaction is applicable to a variety of allylic substrates, the apparent generality being amply illustrated by the conversion of glycal esters 1 - 9 into enlactones (13 - 17) or enol-lactones (18 - 21) in equally satisfactory yields (cf. Table).

Table. $BF_3$-catalyzed Oxidation of Glycal Esters with m-Chloroperbenzoic Acid[a)]

| Educt[b)] | Product[c)] | Yield[d)] | m.p. (°C) b.p. (°C/mm) found | m.p. (°C) b.p. (°C/mm) reported (ref.) | $[\alpha]_D$ in $CHCl_3$ (°) found (c=1) | $[\alpha]_D$ in $CHCl_3$ (°) reported (ref.) |
|---|---|---|---|---|---|---|
|  1 R=Ac 2 R=Bz |  13 R=Ac 14 R=Bz | 69<br>74 | 135/0.1<br>syrup | 160/0.3 (19)<br>syrup | +128<br>+195 | +129 (19)<br>+193 |
|  3 |  15 | 78 | 92-93 | — | + 92 | — |
|  4 |  16 | 81 | 135/0.1 | 160/0.3 (19) | -347 | -350 (19) |
|  5 |  17 | 89 | 110/0.5 | 73/0.01 (17) | -179 | -160 (17) |
|  6 |  18 | 78 | 134-135 | — | + 79 | — |
|  7 R=Ac 8 R=Bz |  19 R=Ac 20 R=Bz | 67<br>91 | 110/0.1<br>110-111 | —<br>111-112 | +109<br>+104 | +108 (21)<br>+105 (22) |
|  9 |  21 | 87 | 130-131 | 128-129 | + 28 | + 27.9 (21) |
|  10 |  22 | 85 | syrup | — | +165 | — |
|  11 R=Ac 12 R=H |  23 | 83 | 151 | 154 (23) | — | — |

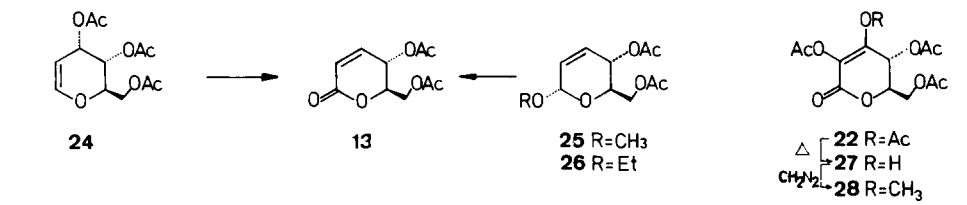
a) The preparative procedure involved addition of the oxidant (1.1 molar equiv. of m-chloroperbenzoic acid, 90% commercial product) to a cooled (-10 to 0°C) solution of glycal ester in dichloromethane, and, subsequently, of $BF_3$-etherate (~ 1 molar equiv.), followed by warming to room temperature. After 15 - 30 min total reaction time (TLC monitoring with 10:1 to 5:1 mixtures of dichloromethane/ethyl acetate; carmine-red spots for the enelactones on charring with sulfuric acid), the mixture is poured on satd. $NaHCO_3$ solution containing 5 - 10 mg $Na_2S_2O_3$, followed by extraction with dichloromethane, washing and concentration to a syrup which is either crystallized, subjected to short-path vacuum distillation, or purified by elution from a silica gel column with 9:1 to 5:1 ratios of dichloromethane/ethyl acetate.

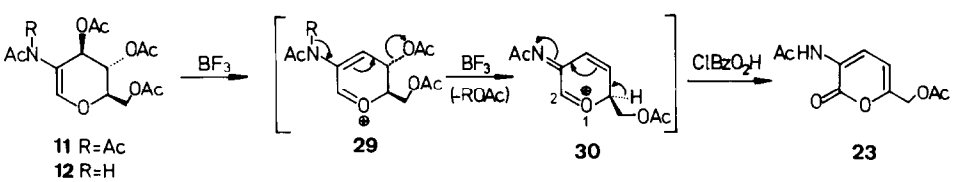
b) Origin of educts 1, 4 and 5: *Methods Carbohydr. Chem.* 2, 405, 409 (1963). — 2: I. Lundt, C. Pedersen, *Acta Chim. Scand.* 20, 1369 (1966). — 3: T. Maki, S. Tejima, *Chem. Pharm. Bull. Jpn.* 15, 1367 (1967). — 6 - 8: R.J. Ferrier, G.H. Sankey, *J. Chem. Soc. C* 1966, 2339. — 9: K. Maurer, *Ber. Dtsch. Chem. Ges.* 63, 30 (1930). — 10: ref. 3. — 11, 12: N. Pravdić, I. Franjić-Mihalić, B. Danilov, *Carbohyar. Res.* 45, 302 (1975).

c) Values for combustion analysis and/or molecular weights (MS-FD spectra) are as expected. $^1$H-NMR data reported for 13[19], 14[13], 16[19], 17[17], 19[21], 20[22] and 21[21] correlated satisfactorily with those we obtained. — $^1$H-NMR for new compounds ($CDCl_3$, 300 MHz, δ-values, proton numbering according to pyran nomenclature):
15: 6.78 (dd, 1H, H-4), 6.06 (d, 1H, H-3), 5.52 (dq, 1H, H-5), 4.63 (dt, 1H, H-6), 4.30 and 4.24 (two 1H-q, 7-$H_2$), 2.48 (s, 3H, tosyl-$CH_3$), 2.12 (s, 3H, Ac), $J_{3,4}$ = 10.0, $J_{3,5}$ = 1.7, $J_{4,5}$ = 2.9, $J_{5,6}$ = 8.0, $J_{6,7}$ = 4.0, $J_{7,7'}$ = 11.3 Hz.
18: 6.85 (dd, 1H, H-4), 5.77 (spt, 1H, H-5), 4.82 (q, 1H, 6-H), 4.74 (q, 1H, 6'-H), $J_{4,5}$ = 6.0, $J_{4,6'}$ = 1.3, $J_{5,6}$ = 3.2, $J_{5,6'}$ = 2.3, $J_{6,6'}$ = 12.9 Hz.
22: 5.68 (d, 1H, H-5), 4.70 (dt, 1H, H-6), 4.46 (q, 1H, H-7) 4.36 (q, 1H, H-7'), 2.11, 2.18, 2.22 and 2.27 (four 3H-s, 4 Ac), $J_{5,6}$ = 13.0, $J_{6,7}$ = 3.8, $J_{6,7'}$ = 2.5, $J_{7,7'}$ = 12.9 Hz.
23: 8.23 (d, 1H, H-4), 8.04 (s, 1H, NH), 6.34 (d, 1H, H-5), 4.85 (s, 2H, $CH_2$), 2.22, 2.12 (two 3H-s, 2 Ac), $J_{4,5}$ = 7.3 Hz.

d) The reactions are invariably quantitative as indicated by TLC; the yields refer to isolated pure product, i.e. after crystallization, distillation or chromatographic purification.

Glycal esters epimeric at C-3, or allylic rearrangement products thereof, yield the same α,β-unsaturated lactone, as expected from elaboration of identical carboxonium ion intermediates of type IV under $BF_3$-catalysis. Accordingly, the glucal 1, the allal 24[9], or the hexenopyranosides 25 and 26[10] exclusively yield the enelactone 13. Similarly, the dehydrosugar 10 is converted into the 2,3-endiollactone 22, a pyranoid derivative of D-erythro-ascorbic acid, which was characterized as a uniform, stable syrup (cf. Table). Upon distillation, however (150°C/0.5 mm), the acetyl group vinylogous to the lactone carbonyl is lost to give triacetate 27 (syrup, $[\alpha]_D^{22} = +195°$, chloroform, 69%), its structure following from an intense red color with ferric chloride and its ready O-methylation to 28 with diazomethane.




Elaboration of the α-pyrone 23 on $BF_3$-catalyzed oxidation of 2-acetamidoglycal esters 11 and 12 appeared surprising at first, yet is readily rationalized on the basis that the remaining secondary acetoxy group is also allylically displaced (29 → 30) followed by a proton shift either before (arrows in 30) or after attack of the peroxyacid anion at C-2 as expected[6] from a hard base[11], and subsequent fragmentation of type V → VI.

In this $BF_3$-induced eliminative oxidation, the peracid may be replaced by pyridinium chlorochromate (PCC) or chromium trioxide, obviously elaborating the enelactones via chlorochromate or chromate ester intermediates of type V that fragment analogously. However, these reactions are more sluggish, even with excess $BF_3$, hence require longer reaction times or heating, and are not free of side products (TLC). PCC-oxidation in the absence of $BF_3$ yields the corresponding lactones, as shown by the conversion of some glycal ethers into the corresponding 2-deoxyhexenolactones (yields 60 - 70%)[13] or by the essentially quantitative formation of δ-valerolactone and other 6-substituted tetrahydropyran-2-ones from the respective 3,4-dihydropyrans (PCC/dichloromethane, 12 h at 25°C, 85 - 90% isol. yield)[14]. With glycal esters, the lactones formed on (non-$BF_3$-catalyzed) PCC-oxidation can undergo β-elimination to give the enelactones in good yields (78% for 1 → 13, 65% for 2 - 14)[13]. However, to effect β-elimination, extensive heating is required (17 - 24 h reflux)[13], and side products are detectable on TLC[14]. In comparison thereto, the $BF_3$-mediated oxidation of glycal and 2-hydroxyglycal esters with m-chloroperbenzoic acid is milder (ambient or lower temperature), distinctly faster (15 - 30 min) and free of side products; consequently, it is a considerable improvement over the previous multistep methodology to effect the conversion I → VI[15] and also appears to be more efficient than the available[13,20] one-step procedures.

## REFERENCES AND NOTES


1) Sugar Enolones, XVII. Grateful acknowledgement is made to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this investigation, and to cand.ing. F.D. Klingler for experiments leading to 15. — Part XVI: F.W. Lichtenthaler, P. Jarglis, *Angew. Chem.* 94 (1982), and *Angew. Chem. Suppl.* 1982, in press.

2) C. Tanaka, *Bull. Chem. Soc. Jpn.* 5, 214 (1930); P.A. Levene, A.L. Raymond, *J. Biol. Chem.* 88, 513 (1930); P.A. Levene, R.S. Tipson, *ibid.* 93, 631 (1931).

3) F.W. Lichtenthaler, P. Jarglis, *Chem. Ber.* 113, 489 (1980).

4) Presented in part at the *1st European Symposium on Carbohydrates*, Vienna, Sept. 1981, Abstract b/11.

5) There is ample evidence for such carboxonium ions in the recent literature; see, e.g., K. Heyns, Ja In Park, *Chem. Ber.* 109, 3262 (1976); J. Heyns, R. Hohlweg, *ibid.* 111, 1632 (1978); R.D. Guthrie, R.W. Irvine, *Carbohydr. Res.* 82, 207, 225 (1980).

6) W. Priebe, A. Zamojski, *Tetrahedron* 36, 287 (1980), and literature cited.

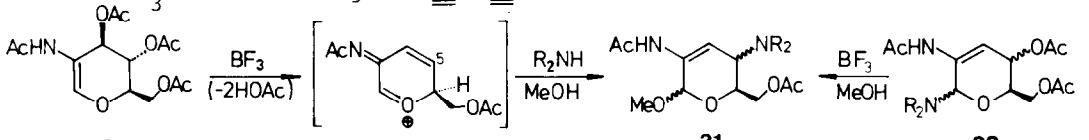
7) A similar fragmentation was observed in the one-step conversion of furanoid lactols into lactones with m-chloroperbenzoic acid/$BF_3$-etherate: P.A. Grieco, T. Oguri, Y. Yokoyama, *Tetrahedron Lett.* 1978, 419.

8) When using 1-1.1 molar equivalents of boron trifluoride etherate the reactions are invariably complete within 15-30 min; catalytic amounts, as e.g. 0.05-0.1 molar equiv., also induce the conversion yet reaction times at room temperature have to be increased (8-10 h) for completion.

9) M. Haga, S. Tejima, *Carbohydr. Res.* 34, 214 (1974).

10) R.J. Ferrier, N. Prasad, *J. Chem. Soc. C* 1969, 570.

11) Soft bases, such as N-heterocycles, would correspondingly be expected to preferentially attack at the "soft" carbocationic site, i.e. at C-5 in intermediates of type 30. This appears to be the case, since the formation of the 4-theophyllinyl-glycosides of the type 31 on $BF_3$-catalyzed fusion of 12 with theophylline (= $R_2NH$) and subsequent quenching with methanol[12a] is readily understood via such mechanistic rationalizations, as is the $BF_3$-induced rearrangement 32 → 31[12b].




**12** **30** **31** **32**

12) (a) Kojić-Prodić, B. Danilov, N. Pravdić, *Carbohydr. Res.* 52, C7 (1976); N. Pravdić, B. Danilov, *ibid.* 97, 31 (1981). — (b) N. Pravdić, *ibid.* 97, 45 (1981).

13) P. Rollin, A. Sinay, *Carbohydr. Res.* 98, 139 (1981).

14) P. Jarglis, Techn. Hochschule Darmstadt, unpublished results.

15) The multistep procedures used for the conversion of glycal esters of type I (R = H) into their enelactones invariably involved preparation of the allylic rearrangement products. The transformations 1 → 13 and 2 → 14 for example, were effected by addition of HCl, hydrolysis of the unsaturated 1-chloride majorily formed, and DMSO/$SO_3$-oxidation[16] direct addition of water and subsequent oxidation with $CrO_3$[17] (28 % for the two steps). Alternate procedures involved conversion into 2,3-unsaturated 2-oxopropyl glycosides and subsequent photolysis[18] (18 % for 1 → 13), proceeded via hexenopyranosides of type 26, $MoO_3$-catalyzed hydrogen peroxide oxidation and quenching of the 1-hydroperoxides formed with acetic anhydride[19] (overall yields for 1 → 13 and 4 → 16 < 30 %).

16) S. Lesage, A.S. Perlin, *Can. J. Chem.* 56, 2889 (1978).

17) K.H. Hollenbeak, M.E. Kuehne, *Tetrahedron* 30, 2307 (1974).

18) C. Bernasconi, L. Cottier, G. Descotes, G. Rémy, *Bull. Soc. Chim. Fr.* 1979, 332.

19) J. Mieczkowski, J. Jurczak, M. Chmielewski, A. Zamojski, *Carbohydr. Res.* 56, 180 (1977).

20) The oxidation of 1 with oxygen/palladium chloride/copper nitrate affords an approximate 1:3-mixture of lactone and α,β-unsaturated lactone 13, which can be separated (yields: 11 and 33 %, resp.): M. Gouedard, F. Gaudemer, A. Gaudemer, *Bull. Soc. Chim. Fr.* 1973, 577.

21) D.M. Mackie, A.S. Perlin, *Carbohydr. Res.* 24, 67 (1972).

22) R.M. de Lederkremer, M.I. Litter, L.F. Sala, *Carbohydr. Res.* 36, 185 (1974).

23) M. Bergmann, L. Zervas, E. Silberkweit, *Ber. Dtsch. Chem. Ges.* 64, 2428 (1931).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