Stereoselective Oxidation of Fusidic Acid Derivatives by the Corey Oxidation Procedure

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The Corey oxidation procedure (treatment with *N*-chlorosuccinimide–dimethyl sulphide complex, then triethylamine) was applied to a series of fusidic acid derivatives. Stereoselective oxidation of the C-3 hydroxy-group can be accomplished. The reagent is highly sensitive to steric and electronic effects; for example successful oxidation of the second hydroxy-group at C-11 is dependent on the nature of the 16-substituent. Unexpectedly, the 16β-hydroxy-substrate (3) is quantitatively lactonised under these conditions. The reactivity of the 16-hydroxy-groups is discussed.

(17*Z*)-METHYL 16β-ACETOXY-11α-HYDROXY-3-OXO-FUSIDA-17(20),24-DIEN-21-OATE (1) was required for study. Partial oxidation of the readily available methyl fusidate [1] (2) seemed the simplest route. However, stereoselective oxidation of multifunctional compounds is a perennial problem.[2] Indeed, oxidation of compound (2) with the Jones reagent [3] or by the Moffatt procedure [4] resulted in either simultaneous oxidation at C-3 and C-11 or side-chain degradation. Oppenauer oxidation [5] under a variety of conditions was ineffective. The oxidation method of Corey and Kim [6] was then employed, although its stereoselectivity (if any) was unknown. The required product (1) was isolated in 85% yield when methyl fusidate (2) was treated with 1 equiv. of reagent.† The

† Better yields were obtained with the *N*-chlorosuccinimide–dimethyl sulphide complex [6] than with the methyl phenyl sulphide–chlorine complex.[7]

[1] W. O. Godtfredsen, S. Jahnsen, H. Lorck, K. Roholt, and L. Tybring, *Nature*, 1962, **193**, 108; W. O. Godtfredsen, 'Fusidic Acid and Some Related Antibiotics,' Copenhagen, 1967, p. 11.

[2] See, for example, E. R. H. Jones, G. D. Meakins, J. Pragnell, W. E. Müller, and A. L. Wilkins, *J.C.S. Perkin I*, 1974, 2376.

[3] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2555.

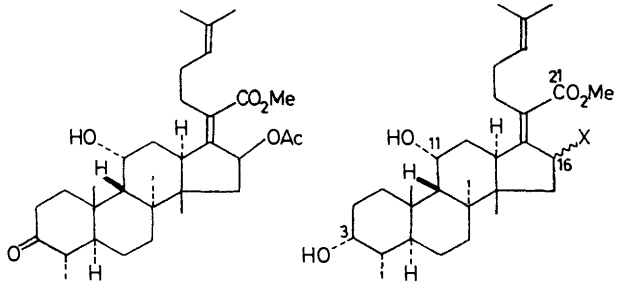
[4] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965 **87**, 5670.

[5] C. Djerassi, *Org. Reactions*, 1951, **6**, 207.

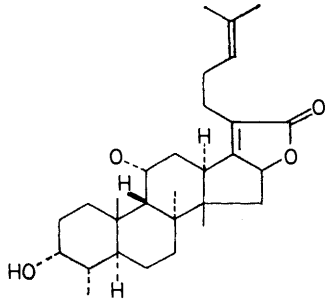
[6] E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, 1972, **94**, 7586.

[7] E. J. Corey and C. U. Kim, *J. Org. Chem.*, 1973, **38**, 1233.

only contaminant in the crude product was unchanged ester (2). Treatment of the ester (2) with an excess (2.2 mol. equiv.) of reagent led to exclusive formation of the 3,11-dione. A more detailed investigation of the stereochemistry of this method was then undertaken.



(1) (2) X = β-OAc (3) X = β-OH (4) X = α-OH



(5)

The effects on the substrates (3)—(5) of 1 equiv. and of an excess of the Corey reagent were studied. The reactions of the lactone (5) followed the same course as those of the ester (2). Oxidation at C-3 occurred exclusively when 1 equiv. of reagent was used. With an excess of oxidant, the 3,11-dione was the only product. By contrast, the triol (4) underwent oxidation at C-3 only, even when an excess of reagent was used. This oxidation method therefore is strongly influenced by steric and electronic factors, which should further extend its synthetic potential. Treatment of the triol (3) with an excess of reagent (4.0 equiv.) led to the lactone (5) (12%), the 3-oxo-analogue of the lactone (5) (65%), and an incompletely characterised chloro-compound (5%). No dione was formed. The structure of the 3-oxo-lactone was confirmed by comparison with samples synthesised from the lactone (5) and from methyl (17*Z*)-11α,16β-dihydroxy-3-oxofusida-17(20),24-dien-21-oate.

The mechanism of this lactonisation was briefly investigated. When the triol (3) was treated with 1 equiv. of *N*-chlorosuccinimide–dimethyl sulphide complex and no triethylamine was added, complete conversion into the lactone (5) occurred. No reaction of the triol (3) occurred, under the otherwise standard conditions, with either (*a*) triethylamine alone, (*b*) dimethyl sulphide, then triethylamine, or (*c*) *N*-chlorosuccinimide, then triethylamine. Since the methoxycarbonyl group is not attacked when an excess of reagent is used with the substrates (2) and (4), it seems most likely that lactone formation from (3) occurs by initial attack by the *N*-chlorosuccinimide–dimethyl sulphide complex on the C-16 hydroxy-group. The formation of an intermediate complex of the ester (3) which is converted into the lactone (5) only during work-up seems probable, since (3) does not yield a dione with an excess of reagent whereas (5) does.

That lactone formation did not ensue from the reaction of the ester (4) follows from the known resistance, for steric reasons, of the corresponding acid to undergo lactonisation under acidic conditions. The acid corresponding to the ester (3) undergoes spontaneous lactonisation at pH < 5.0.[8]

The resistance of the 16α- and 16β-allylic hydroxy-groups in (3) and (4) to replacement by chlorine under these conditions was unprecedented.[7,9] An unsuccessful attempt was made to replace the 16α-hydroxy-group of (4) by either chlorine or bromine by the literature method.[9] It seems probable that carbocation formation (apparently a prerequisite for hydroxy-group replacement [7,9]) is inhibited at C-16 by the methoxycarbonyl group.

EXPERIMENTAL

N.m.r. spectra were obtained for solutions in $CDCl_3$ at 60 MHz. I.r. spectra were recorded for KBr discs. Optical rotations were recorded for solutions in chloroform at ambient temperature with a Perkin-Elmer 141 polarimeter.

Methyl fusidate (2), (17*Z*)-methyl 3α,11α,16α-trihydroxyfusida-17(20),24-dien-21-oate (4), and 3α,11α-dihydroxyfusida-17(20),24-dien-16β,21-olactone (5) were synthesised from fusidic acid,[1] according to the method of Godtfredsen and Vangedel.[8b]

Synthesis of (17Z)-*Methyl* 3α-11α,16β-*Trihydroxyfusida*-17(20),24-*dien*-21-*oate* (3).—To a solution of methyl fusidate (2) (1.0 g) in methanol (10 ml) was added 2N-sodium hydroxide (5 ml). The solution was refluxed for 2 h. After cooling the methanol was removed under vacuum. The solid was suspended in ether (75 ml) and water (15 ml). Dilute hydrochloric acid was added dropwise with cooling and stirring to pH 5—5.5. The two phases were then clear. The ether layer was separated, washed, and dried. Ethereal diazomethane was then added until a yellow colour persisted. The ether was removed and the crude product was crystallised from acetonitrile to yield the pure ester (3) (0.71 g, 77%), m.p. 168—169° (lit.,[8b] 168—168.5°), $[\alpha]_D$ ±0° (Found: C, 73.5; H, 9.8. Calc. for $C_{30}H_{48}O_5$: C, 73.7; H, 9.9%); $\nu_{max.}$ 3 480, 1 685, and 1 610 cm^{-1}; $\lambda_{max.}$ 232 nm (ε 9 020); τ 4.90br (1 H, t, *J* 5 Hz, 24-H), 5.20br (1 H, t, 16-H), 5.40 (2 H, s, disappears after D_2O addition, 2 × OH), 5.62 (1 H, m, 11-H), 6.28 (3 H, s, CO_2Me), 6.82 (1 H, m, 13-H), 8.32 (3 H, s, 27-H_3), 8.40 (3 H, s, 26-H_3), 8.62 (3 H, s,

[8] (*a*) W. S. Murphy and S. S. Welankiwar, unpublished results; (*b*) see also, W. O. Godtfredsen and S. Vangedal, *Tetrahedron*, 1962, **18**, 1029.

[9] E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339.

8-Me), 8.88 (3 H, s, 14-Me), 9.02 (3 H, s, 10-Me), and 9.05 (3 H, d, J 6 Hz, 4-Me).

Oxidations. General Procedure.—The procedure involving use of *N*-chlorosuccinimide–dimethyl sulphide complex in methylene chloride with the later addition of triethylamine detailed by Corey and Kim [6] was strictly adhered to. It was necessary to use freshly distilled dimethyl sulphide. Since traces (<2%) of unidentified less polar side products were invariably formed, the crude products were generally purified by preparative t.l.c.

Oxidation of Methyl Fusidate (2).—Methyl fusidate (0.53 g, 1.0 mmol) was treated with oxidant (1.1 mmol) and then triethylamine (2.2 mmol). The crude product (0.51 g) was eluted through a silica gel (15 g) column with ether–petroleum (50 : 50). The first fraction was methyl fusidate (2) (25 mg, 5%). The second was recrystallised from ether–petroleum ether to give white, solid (17Z)-*methyl* 16β-*acetoxy*-11α-*hydroxy*-3-*oxofusida*-17(20),24-dien-21-oate (1) (0.45 g, 85%), m.p. 57—58°, $[\alpha]_D$ +36° (*c* 5.1) (Found: C, 72.6; H, 9.7. $C_{32}H_{48}O_6$ requires C, 72.7; H, 9.2%); $\nu_{max.}$ 3 520, 1 732, 1 718, and 1 685 cm^{-1}; $\lambda_{max.}$ 234 nm (ε 4 172); τ 4.12 (1 H, d, J 9 Hz, 16-H), 4.90br (1 H, t, J 7 Hz, 24-H), 5.62 (1 H, m, 11-H), 6.32 (3 H, s, CO_2Me), 8.0 (3 H, s, OAc), 8.30 (3 H, s, 27-H_3), 8.38 (3 H, s, 26-H_3), 8.68 (3 H, s, 8-Me), 8.82 (3 H, s, 14-Me), 9.02 (3 H, s, 10-Me), and 9.10 (3 H, d, J 6 Hz, 4-Me).

The same procedure but with an excess (3 equiv.) of oxidising agent gave (17Z)-*methyl* 16β-*acetoxy*-3,11-*dioxofusida*-17(20),24-*dien*-21-*oate* as a white solid (from ether–hexane) (80%), m.p. 82—83°, $[\alpha]_D$ +107° (*c* 3.7) (Found: C, 72.5; H, 8.7. $C_{32}H_{46}O_6$ requires C, 73.0; H, 8.8%); $\nu_{max.}$ 1 735, 1 720, 1 715, and 1 685 cm^{-1}; $\lambda_{max.}$ 230 nm (ε 6 525); τ 4.12 (1 H, d, J 8.5 Hz, 16-H), 4.90br (1 H, t, J 7 Hz, 24-H), 6.35 (3 H, s, CO_2Me), 8.0 (3 H, s, OAc), 8.35 (3 H, s, 27-H_3), 8.40 (3 H, s, 26-H_3), and 8.80—9.00 (12 H, 4-, 8-, 10-, and 14-Me).

Attempted Oxidation of the Triol (3).—Treatment of the triol (3) with oxidant (1 equiv.) gave the lactone (5) (90%), m.p. 157—158° (from acetonitrile) (lit.,[8b] 158.5—159.5°), $[\alpha]_D$ +55° (*c* 3.7) (Found: C, 76.2; H, 9.6. Calc. for $C_{29}H_{44}O_4$: C, 76.3; H, 9.7%); $\nu_{max.}$ 3 520, 3 410, 1 740, and 1 690 cm^{-1}; $\lambda_{max.}$ 224 nm (ε 13 700); τ 7.65 (2 H, disappears with D_2O, 2 × OH), 4.92br (1 H, d, J 5 Hz, 24-H), 5.15br (1 H, d, J 6 Hz, 16-H), 5.62 (1 H, m, 11-H), 6.32 (1 H, d, J 3 Hz, 3-H), 6.60 (1 H, m, 13-H), 8.35 (3 H, s, 27-H_3), 8.42 (3 H, s, 26-H_3), 8.52 (3 H, s, 8-Me), 9.05 (3 H, s, 14-Me), 9.10 (3 H, d, J 3 Hz, 4-Me), and 9.20 (3 H, s, 10-Me).

Oxidation with an excess of the oxidising agent (4.0 equiv.) resulted in three compounds (t.l.c.). The most polar was the lactone (5) (12%). The major component was 11α-*hydroxy*-3-*oxofusida*-17(20),24-*dien*-16β,21-*olactone* (6) (65%), m.p. 112—113° (from ether–petroleum, 1 : 2) (Found: C, 76.4; H, 9.3. $C_{29}H_{42}O_4$ requires C, 76.6; H, 9.3%); $[\alpha]_D$ +85° (*c* 1.7); $\nu_{max.}$ 3 480, 1 750, 1 710, 1 700, and 1 640 cm^{-1}; $\lambda_{max.}$ 235 nm (ε 11 875); τ 4.93br (1 H, d, J 5 Hz, 24-H), 5.12br (1 H, t, J 6 Hz, 16-H), 5.62 (1 H, m, 11-H), 6.35 (1 H, s, disappears with D_2O, 11-OH), 6.60 (1 H, m, 13-H), 8.32 (3 H, s, 27-H_3), 8.40 (3 H, s, 26-H_3), 8.55 (3 H, s, 8-Me), 8.82 (3 H, s, 14-Me), 8.94 (3 H, d, J 6 Hz, 4-Me), and 9.15 (3 H, s, 10-Me).

Insufficient amounts of the third, least polar compound were obtained (5%) to permit full characterisation {m.p. 90—91° (Found: C, 67.8; H, 9.0; Cl, 6.9%); $[\alpha]_D$ +32° (*c* 1.2); $\nu_{max.}$ 3 460, 1 730, 1 715, and 795s cm^{-1}; $\lambda_{max.}$ 232 nm}.

Oxidation of the Triol (4).—Treatment of the triol (4) with 1 equiv. of oxidant resulted in (17Z)-*methyl* 11α-16α-*dihydroxy*-3-*oxofusida*-17(20),24-*dien*-21-*oate* (45%). The yield was increased to 82% when an excess (4.5 equiv.) of reagent was used. The product was a white solid, m.p. 135—136° (Found: C, 73.9; H, 9.4. $C_{30}H_{46}O_5$ requires C, 74.0; H, 9.5%); $[\alpha]_D$ −25.2° (*c* 2.1); $\nu_{max.}$ 3 470br, 1 715, 1 685, and 1 630 cm^{-1}; $\lambda_{max.}$ 235 nm (ε 6 804); τ 4.90br (1 H, t, J 5 Hz, 24-H), 5.25br (1 H, t, 16-H), 5.52 (1 H, d, J 3 Hz, disappears after addition D_2O, 16-OH), 5.62 (1 H, m, 11-H), 6.28 (3 H, s, CO_2Me), 6.60 (1 H, m, 13-H), 7.58br (1 H, s, disappears with D_2O + trace $CF_3{\cdot}CO_2D$, 11-OH), 8.32 (3 H, s, 27-H_3), 8.40 (3 H, s, 26-H_3), 8.62 (3 H, s, 8-Me), 8.88 (3 H, s, 10-Me), 9.0 (3 H, d, J 6 Hz, 4-Me), and 9.26 (3 H, s, 14-Me).

Oxidation of the Lactone (5).—The lactone (5) was treated with 1.2 equiv. of oxidant. The 3-oxo-lactone (63%) was separated from unchanged lactone (5) (18%) by preparative t.l.c. Treatment of the lactone (5) with an excess (4.0 equiv.) of oxidant resulted in 3,11-*dioxofusida*-17(20),24-*dien*-16β,21-*olactone* (78%), m.p. 124—125° (from ether–hexane), $[\alpha]_D$ +105° (*c* 1.6) (Found: C, 76.8; H, 8.7. $C_{29}H_{40}O_4$ requires C, 77.0; H, 8.8%); $\nu_{max.}$ 1 750, 1 705, and 1 700 cm^{-1}; $\lambda_{max.}$ 232 nm (ε 12 510); τ 4.95br (1 H, d, J 5 Hz, 24-H), 5.12 (1 H, d, J 6 Hz, 16-H), 6.60 (1 H, m, 13-H), 8.32 (3 H, s, 27-H_3), 8.40 (3 H, s, 26-H_3), 8.70 (3 H, s, 8-Me), 8.91 (6 H, s, 10- and 14-Me), and 8.94 (3 H, d, J 6 Hz, 4-Me).

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