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# ON THE FORMATION OF THE 1,2-ACETONIDE OF (+), (-), AND (±) 1,2,4-BUTANETRIOL AND ITS CORRESPONDING ALDEHYDE

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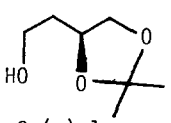
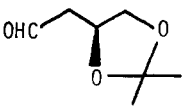
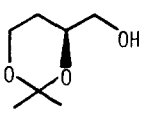
Summary The acetonides 1 and 3 are components of a 9 1 equilibrium established during their formation

The acetonides 1 and 2, in enantiomeric or racemic form, have been utilized by a number of laboratories[1] for total synthesis yet an impurity 3 present to the extent of 10% has gone unnoticed The acetonide alcohol 1 has been prepared by either starting with S(-)[1a-c] or


S-(-)-1

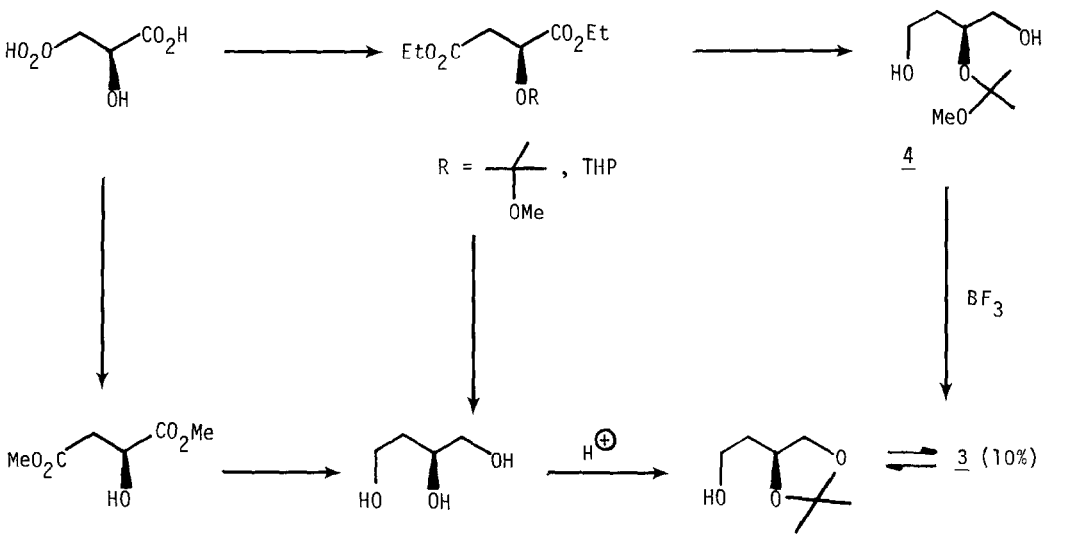

S-(+)-2


S-3

R(+)[1d] malic acid (leading to R-(+)-1), esterification, protection of the 2-hydroxyl, reduction, and acidic cyclization (Scheme 1) Although each of the routes in Scheme 1 is smoothly reproducible and represents fine synthetic procedures to reach 1, the cyclization step to the acetonide, contrary to these reports, all lead to a mixture of 1 and the 6-membered acetonide 3 Furthermore, Nakanishi[1c] made an attempt to exclude 3 as a by-product of the cyclization by nmr shift studies and concluded there was no 6-membered acetonide present Unfortunately, the wrong shift reagent was utilized which was not able to discern the presence of 3

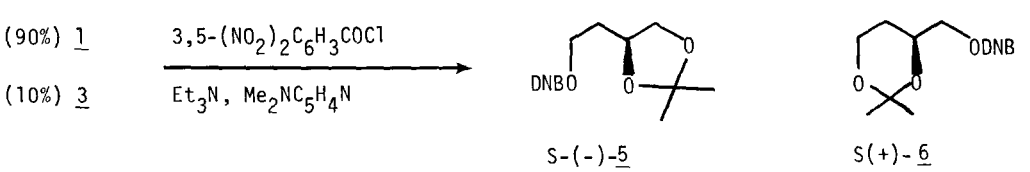
During the course of a program aimed at the total synthesis of griseoviridin[2], we required a quantity of (-)-1 and (+)-2 and on repeating the synthesis[1a] of (-)-1 found that treatment of the diol 4 with $BF_3 \cdot Et_2O$ for 2 h gave a mixture of 2 to 3 in a ratio of 2 1 Further treatment of the mixture with $BF_3$ for extended periods of time with the original acid

Scheme 1




catalyst (trace) gave the equilibrium mixture of 1 and 3 as 9 1 This ratio did not change after prolonged reaction time The 60 MHz spectrum showed a barely visible shoulder at δ1 45 downfield from the two closely packed singlets for 1 at δ1 39 and 1 43 When this mixture was treated with 20 mole percent of $Eu(hfc)_3$[3], a chiral shift reagent, a new pair of doublets emerged which represent 10% of 3 The methyl singlets for 1 and 3 remained intact and of equal heights indicating there was probably no enantiomeric material present, only the two isomeric acetonides Similarly (±)-1,2,4-butanetriol was subjected to acid-catalyzed (TsOH)[1c] conditions in the presence of acetone and likewise gave a 9 1 ratio of (±)-1 to (±)-3 Thus, both routes to 1 were accompanied by contamination by the six-membered acetonide 3

The mixture of 1 and 3 could only be purified by preparing the 3,5-dinitrobenzoates 5 and 6 and recrystallization from absolute ethanol (3x) to give pure ester 5 [41%, mp 62 5-63 0, 99 9% pure by hplc, μ-porosil, 8% THF-Hexane, $[\alpha]_D$-13 7° (1 5, $CHCl_3$), CH analysis]



The isomeric acetonide 6 was recovered using radial preparative TLC (Chromatotron [96 5% purity by hplc, mp 92 5-93 0 $[\alpha]_D$ + 14 4° (1 3, $CHCl_3$), CH analyses] Regeneration of pure 1 was accomplished in 83% yield using $K_2CO_3$-methanol (59 5 gr 5, 36 gr $K_2CO_3$, 1 2 l anhydrous methanol) and stirring the pink solution for 18 h at 23° Distillation, after filtration and concentration, gave 21 3 gr of 1, bp 55-61° (0 05 mm), $[\alpha]_D$ - 2 23° (9 8, MeOH), 99 9% purity by hplc Furthermore, the $[\alpha]_D$ value and shift reagents confirmed this level of purity over several different runs

That 1 and 3 were truly part of an equilibrium mixture formed in the cyclization of 1,2,4-butanetriol was shown by subjecting 99 9% pure 1, obtained from the dinitrobenzoate esters, to $BF_3 \cdot Et_2O$ in chloroform (25°, 3 h) and once again generating the 9 1 mixture of 1 and 3 This was disclosed by using the $Eu(hfc)_3$ reagent Oxidation of pure 1 ([α]-2 23°) to the aldehyde 2 was accomplished with the modified Collins procedure[4] and gave, after distillation, 60% pure 2 [$[\alpha]_D$ + 16 5°, bp 57° (3 mm), 100 MHz pmr 9 80 (t, 1 J = 8, 6 Hz), 2 74 (m,2), 1 41 (s,3), 1 37 (s,3)] Also present after distillation was a higher boiling fraction, suggested, but not characterized by Mori[1d] as the ester derived from oxidation of the hemi-acetal of 1 and 2 This was confirmed by isolation and characterization [bp 135° (1 mm), ir (film) 1730 $cm^{-1}$, m/e 273, (-$CH_3$ of acetonide)] and could be reduced ($LiAlH_4$, THF) back to the alcohol, 1 for further use Reduction of the purified aldehyde, (+) or (±)-2 to (+) or (±)-1 gave material which was completely free of the isomeric acetonide 3 as shown by $Eu(hfc)_3$ studies previously mentioned However, the 9 1 mixture of 1 and 3, oxidized with the Collins reagent gave an aldehyde which failed to reveal the 9 1 mixture present using various chiral LISR reagents Thus, the aldehydes are insensitive to this technique Yet, reduction to the corresponding alcohols and examination by LISR reagents clearly indicate the presence of the mixture

In summary, the various rotations for 1 and 2 in the literature should be ignored since they contain ∿10% of the 6-membered acetonides and only through LISR studies, followed by purification as described above can those acetonides be reached in a high state of purity It is also of interest to note that since the ratio of 1 to 2 during the cyclization gave a 67 33 mixture after 2 h and a 90 10 mixture after 20 h, that the 6-membered acetonide is undoubtedly the kinetic product while the 5-membered acetonide is the thermodynamic product

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