1,2-ISOPROPYLIDENE D-GLYCERALDEHYDE AS A CHIRAL SYNTHON FOR γ-BUTYROLACTONE

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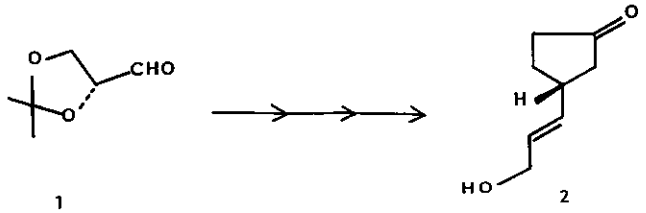
Abstract——1,2-Isopropylidene D-glyceraldehyde (3) is shown to be a useful and inexpensive chiral starting material for a synthesis of γ-butyrolactones (8), (10) and (12) which are potential intermediates for secologanin and sesquiterpene lactones.

In a recent deveolpment on the total synthesis of optically active natural products, 1,2-isopropylidene D-glyceraldehyde (1)[1] has been used as a chiral synthon for a number of biological active compounds such as prostaglandins[2], brefeldin A[3], ipsdienol[4], prestalotin[5] and leukotriene A_4[6]. We have shown, in a previous paper[7], 3(S)-[3-hydroxy-1(E)-propylenyl]cyclopentanone (2) derived from 1 was a potential intermediate leading to antirhine and brefeldin A.



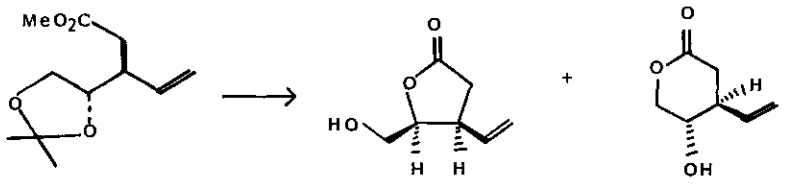
1 2

In our continuous efforts on the synthesis of natural products, secologanin and sesquiterpene lactones, we required a synthesis of the γ-butyrolactone possessing an appropriate substituent at C_3 and C_4. Here we wish to report our successful results.

The aldehyde (3)[1] was treated with methoxycarbonylmethylenetriphenylphosphorane to give 4a, $[\alpha]_D$ + 37.7°(c = 0.29, $CHCl_3$)[8] and 4b, $[\alpha]_D$ + 101.4° (c = 0.29, $CHCl_3$) as a mixture (55 : 45) in 64.1 % yield. Diisobutylaluminum hydride reduction of 4a followed by ortho-ester Claisen rearrangement[9] of the resultant allyl alcohol (5a), $[\alpha]_D$ + 26.7°(c = 0.21, $CHCl_3$) provided a separable mixture of (6), $[\alpha]_D$ + 24.0° (c = 0.20, $CHCl_3$) and (7), $[\alpha]_D$ + 12.7° (c = 0.22, $CHCl_3$) from (E)-olefinic ester (4a) in 22.4 and 10.4 % overall yield, respectively. Similarly, (Z)-olefinic ester (4b) was converted to (6) and (7) in 28.2 and 10.5 % yield, respectively.

Since 3(S) and 3(R)-methyl esters (6) and (7) are in our hand, lactonization was examined under several conditions and the results were summarized in the following Table.

Table Lactonization of 3 (R)-methyl ester (6) under acidic conditions



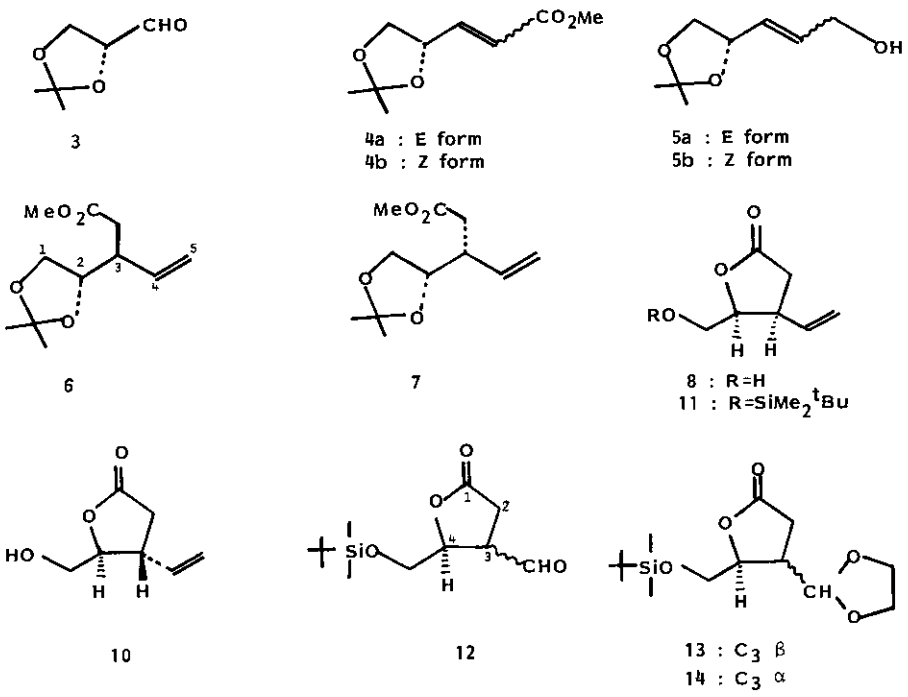
6 8 9

Reaction conditions				Products	Yield (%)
Solvent	Acid	Temp	Time	γ-Lactone (8) : δ-Lactone (9)	
MeOH	30 % H_2SO_4	60	30 min	only γ-lactone	58.7
MeOH	10 % H_2SO_4	r.t.	2 h	77 : 23	81.3
MeOH	10 % H_2SO_4	0°	3 h	57 : 43	60.1
MeOH	P-TsOH	r.t.	2 h	83 : 17	80.0
MeOH	P-TsOH	0°	2 h	84 : 16	48.3
THF	10 % H_2SO_4	r.t.	2 h	89 : 11	35.3
THF	10 % H_2SO_4	0	2 h	55 : 45	20.7

As can be seen in Table, a treatment of 6 under relatively mild conditions produced always a mixture of γ and δ-butyrolactone (8 and 9), whereas a treatment of 6 under a restricted condition (30 % H_2SO_4, MeOH, 60°, 30 min) afforded exclusively γ-butyrolactone (8) in 58.7 % yield, Under this condition, none of the δ-lactone (9) could be detected. Interestingly, trans-γ-butyrolactone (10), $[\alpha]_D$ + 81.6° (c = 0.13, $CHCl_3$) was easily obtained from 7 (10 % H_2SO_4, MeOH, r.t., 3 hr) in 88.4 % yield. Protection of the primary alcohol of 8 as tert-butyldimethylsilyl ether[10] (93.4 %) and subsequent cleavage of the double bond[11] of 11, $[\alpha]_D$ + 13.9° (c = 0.23, $CHCl_3$), provided the aldehyde (12) as a diastereoisomeric mixture at C-3 position (approximately 1 : 1). This labile aldehydes were protected as acetal without purification to give a mixture of syn and anti-type γ-butyrolactones (13) and (14) (approximately 1 : 1), $[\alpha]_D$ + 21.4° (c= 0.28, $CHCl_3$), in 40.8 % overall yield from 11. Similarly, anti-type γ-butyrolactone (10) was also converted to 14, $[\alpha]_D$ + 18.2° (c=0.11, $CHCl_3$), in 40 % overall yield.

Thus, we have achieved the enantioselective synthesis of γ-butyrolactone derivatives in both of syn and anti forms which can be potential intermediates leading to a variety of natural products having α-methylene-γ-butyrolactone moiety. Furthermore, our supposed synthetic route was applied to (S)-glyceraldehyde[12], a useful intermediate leading to eudesmane sesquiterpene lactones and avenaciolide

Scheme 2



could also be obtained. According to this stragegy, enantioselective syntheses of secologanin sesquiterpene lactones are under investigation.

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