

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

Tetsuji Kametani*

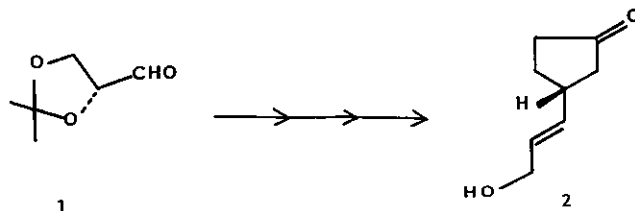
Hoshi College of Pharmacy, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Toshio Suzuki, Masahiro Nishimura, Etsuko Sato and Katsuo Unno

Department of Pharmacy, Akita University Hospital, Hondo, Akita 010, Japan

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 development 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 prostaglandins², brefeldin A³, ipsdienol⁴, prestatin⁵ and leukotriene A₄⁶. We have shown, in a previous paper⁷, 3(S)-[3-hydroxy-1(E)-propylenyl]cyclopentanone (2) derived from 1 was a potential intermediate leading to antirrhine and brefeldin A.

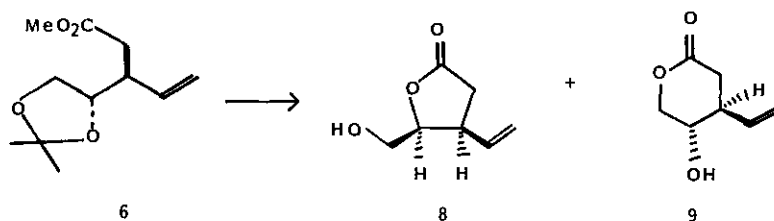


In our continuous efforts on the synthesis of natural products, secologanin and sesquiterpene lactones, we required a synthesis of the γ -butyrolactone possessing an appropriate substituent at C₃ and C₄. Here we wish to report our successful results.

The aldehyde (3)¹ was treated with methoxycarbonylmethylenetriphenylphosphorane to give 4a, $[\alpha]_D + 37.7^\circ$ ($c = 0.29$, CHCl₃)⁸ and 4b, $[\alpha]_D + 101.4^\circ$ ($c = 0.29$, CHCl₃) as a mixture (55 : 45) in 64.1 % yield. Diisobutylaluminum hydride reduction of 4a followed by ortho-ester Claisen rearrangement⁹ of the resultant allyl alcohol (5a), $[\alpha]_D + 26.7^\circ$ ($c = 0.21$, CHCl₃) provided a separable mixture of (6), $[\alpha]_D + 24.0^\circ$ ($c = 0.20$, CHCl₃) and (7), $[\alpha]_D + 12.7^\circ$ ($c = 0.22$, CHCl₃) 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.

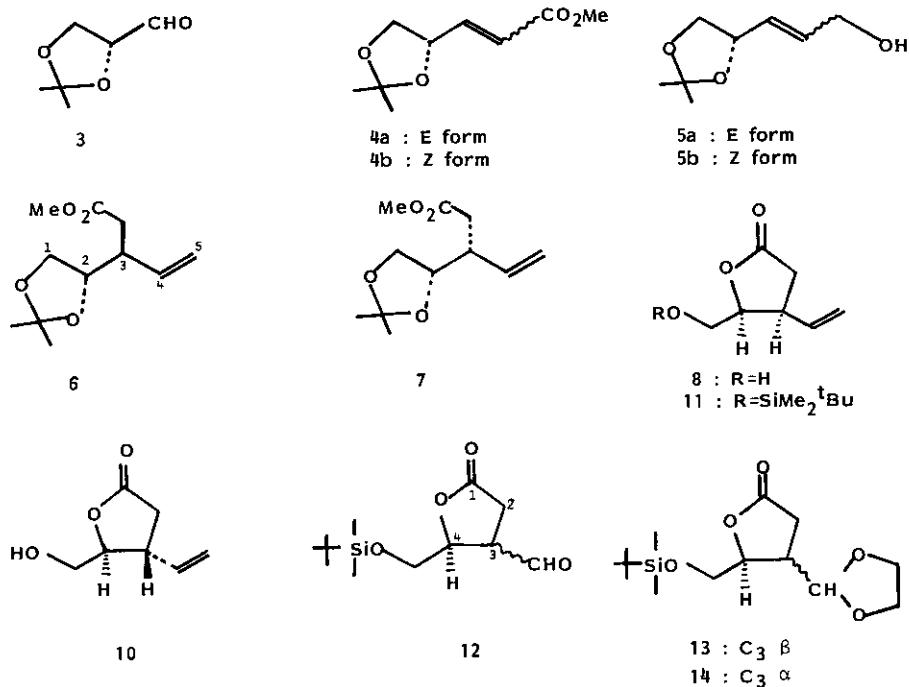
Table Lactonization of 3 (R)-methyl ester (6) under acidic conditions



Reaction conditions				Products	Yield (%)
Solvent	Acid	Temp	Time	γ -Lactone (8) : δ -Lactone (9)	
MeOH	30 % H ₂ SO ₄	60	30 min	only γ -lactone	58.7
MeOH	10 % H ₂ SO ₄	r.t.	2 h	77 : 23	81.3
MeOH	10 % H ₂ SO ₄	0°	3 h	57 : 43	60.1
MeOH	<u>P</u> -TsOH	r.t.	2 h	83 : 17	80.0
MeOH	<u>P</u> -TsOH	0°	2 h	84 : 16	48.3
THF	10 % H ₂ SO ₄	r.t.	2 h	89 : 11	35.3
THF	10 % H ₂ SO 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 % H₂SO₄, 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), [α]_D + 81.6° (c = 0.13, CHCl₃) was easily obtained from 7 (10 % H₂SO₄, MeOH, r.t., 3 hr) in 88.4 % yield. Protection of the primary alcohol of 8 as tert-butyldimethylsilyl ether¹⁰ (93.4 %) and subsequent cleavage of the double bond¹¹ of 11, [α]_D + 13.9° (c = 0.23, CHCl₃), 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), [α]_D + 21.4° (c = 0.28, CHCl₃), in 40.8 % overall yield from 11. Similarly, anti-type γ -butyrolactone (10) was also converted to 14, [α]_D + 18.2° (c = 0.11, CHCl₃), 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)-glyceraldehyde¹², a useful intermediate leading to eudesmane sesquiterpene lactones and avenaciolide

Scheme 2



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

REFERENCES and NOTES

- 1 H. Fischer and E. Baer, *Helv. Chim. Acta*, 1934, 17, 622; E. Baer and H. Fischer, *J. Biol. Chem.*, 1939, 128, 463.
- 2 G. Stork and T. Takahashi, *J. Amer. Chem. Soc.*, 1977, 99, 1275.
- 3 T. Kitahara, K. Mori and M. Matsui, *Tetrahedron Lett.*, 1979, 3021.
- 4 K. Mori, T. Takigawa, and T. Matsuo, *Tetrahedron*, 1979, 35, 933.
- 5 K. Mori, M. Oda, and M. Matsui, *Tetrahedron Lett.*, 1976, 3173.
- 6 J. Rokach, R. N. Young, and M. Kakushima, *Tetrahedron Lett.*, 1981, 22, 979.
- 7 T. Kametani, T. Suzuki, E. Sato, M. Nishimura, and K. Unno, *J. Chem. Soc. Chem. Commun.*, in press.
- 8 Optical rotation was measured with a JASCO-DIP-4 automatic polarimeter.
- 9 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Pertersen, *J. Amer. Chem. Soc.*, 1970, 92, 741; G. Stork and S. Raucher, *J. Amer. Chem. Soc.*, 1976, 98, 1583; G. Stork, T. Takahashi, I. Kawamoto, and T. Suzuki, *J. Amer. Chem. Soc.*,

- 1978, 100, 8272. For a review, see F. E. Ziegler, Acc. Chem. Res., 1977, 10, 227.
- 10 E. J. Corey and A. Verkateswarlu, J. Amer. Chem. Soc., 1972, 94, 6190.
- 11 R. Pappo, D. S. Allen, Jr., R. V. Lemieux, and W. S. Johnson, J. Org. Chem., 1956, 21, 478;
S. H. Graham and A. J. S. Williams, J. Chem. Soc. (C), 1966, 655.
- 12 S. B. Baker, J. Amer. Chem. Soc., 1952, 74, 82; M. E. Jung and T. J. Shaw, J. Amer. Chem. Soc., 1980, 102, 6304.

Received, 18th September, 1981.