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GLYCEROLIPIDS I. SYNTHESIS OF D AND L MONO - AND POLYUNSATURATED 1,2-DIGLYCERIDES via GLYCEROL CARBONATES

Francis R. Pfeiffer, Suzanne R. Cohen,
Karlene R. Williams and Jerry A. Weisbach

Research and Development Division
Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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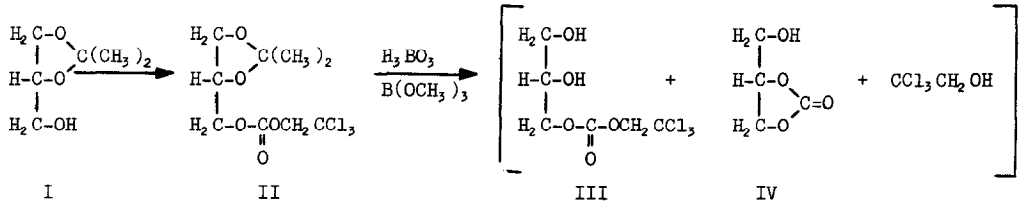
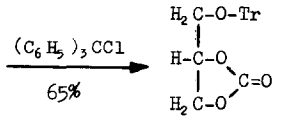
Traditionally, the synthesis of optically active glycerolipids starts with inexpensive, commercially available D-mannitol and proceeds via well documented pathways[1,2] to 2,3-O-isopropylidene-D-glycerol (I). A correspondingly simple approach into the enantiomeric series via L-mannitol is precluded by the relative inaccessability of the starting polyol.[3] In order to circumvent this difficulty, alternative procedures have been devised[4,5] which are partially satisfactory. We now describe a simple, stereoselective pathway to both the sn-glycerol 1,2 and 2,3-diacylates[6] via acyclic and cyclic glycerol carbonates. In the past, unavailability of sufficiently versatile protecting groups in glyceride synthesis has led to the evolution of special procedures for the preparation of unsaturated or mixed-acid 1,2-diglycerides[2,7-9]; there are no direct methods for the synthesis of optically active 1,2-diglycerides containing mono - and/or polyunsaturated acyl groups. Adaptation of the new protecting group, 2,2,2-trichloroethoxycarbonyl,[10] to glyceride chemistry now provides facile entry into the optically active, unsaturated 1,2-diglyceride series. Removal of the CCl_3CH_2OCO group (Zn, HOAc, 25°) causes little or no isomerization of the 1,2-diglycerides to the thermodynamically more stable 1,3-diglycerides.[11] These transformations establish sn-glycerol 1,2-isopropylidene-3-(2,2,2-trichloroethyl) carbonate (II) as a common precursor of choice for all enantiomeric glycerol derivatives, particularly for saturated and unsaturated "mixed-acid" 1,2-diglycerides.

Glycerol Carbonates - Recently, Gigg and Gigg[12,13] prepared glycerol vicinal carbonates IV and VII as precursors in the synthesis of phospholipids; sn-glycerol 2,3-carbonate (IV) was obtained via a lengthy sequence by degradation of 1,3:2,5:4,6-tri-O-methylene-D-mannitol.[12] The

enantiomer VII was prepared by a separate route from sn-glycerol 3-benzyl ether.[13] In contrast, we obtained IV and VII, as described below, in two and three steps, respectively, from the common acyclic carbonate precursor II. The cyclic carbonates IV and VII were best isolated as their trityl derivatives V and VIII. Alkaline hydrolysis of V and VIII provide L-and D-1-trityglycerol,[12,13] well documented starting materials for the synthesis of either mono- or diglycerides.[14-16]

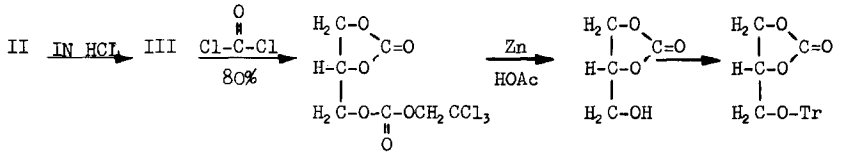


I II III IV



V

Upon reaction of I with 2,2,2-trichloroethyl chloroformate[10] in the presence of pyridine, the carbonate II, bp 130° (0.03 mm); nmr ($CHCl_3$) δ 4.81 (s, 2, $\underline{CH_2}CCl_3$); $[\alpha]_D^{25}$ - 1.5° (C 0.87, $CHCl_3$), was obtained in 85% yield. Treatment of II with boric acid in trimethyl borate (70°, 30 min) cleaved the isopropylidene group[17] with the formation of a mixture of the acyclic carbonate III and the cyclic carbonate IV. The crude product obtained from the boric acid hydrolysis of II was treated with trifluoroacetic anhydride and glc analysis indicated a mixture of 74.3% of III and 25.7% of IV.[18] The crude reaction product was tritylated with one mole of trityl chloride in pyridine (60°) to give the trityl ether V, in 65% yield, mp 217-219°; $[\alpha]_D^{25}$ +19.1°(C 1.675, $CHCl_3$)[reported $[\alpha]_D^{23}$ + 19.6° (C 0.85, $CHCl_3$)].[12] Cyclization of III to IV by direct heating gave extensively racemized glycerol 1,2-carbonate.

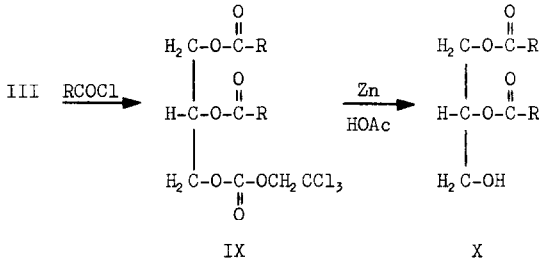


VI VII VIII

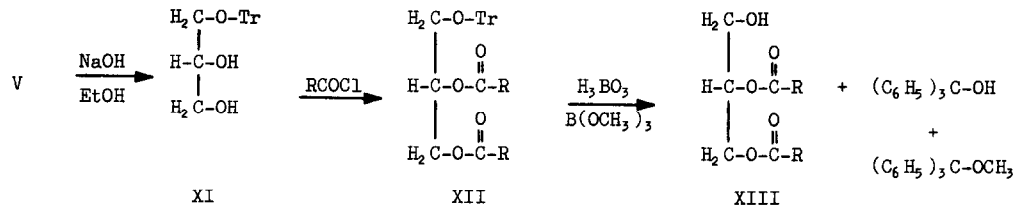
Hydrolysis of II with dilute hydrochloric acid at 25° gave a mixture of 93.5% III and 6.5% IV (as determined by glc analysis of their trifluoroacetates).[18] Treatment of III with phosgene in pyridine afforded about an 80% yield of the acyclic-cyclic carbonate VI, mp 80-82°;

nmr ($CDCl_3$) δ 4.80 (s, 2, $\underline{CH_2}CCl_3$); $[\alpha]_D^{25}$ - 10.5° (C 1.16, $CHCl_3$). The acyclic carbonate group of VI was removed at room temperature (zinc, acetic acid)[10,19] to provide the syrupy VII, isolated and characterized as the crystalline trityl ether VIII, mp 217-219°; $[\alpha]_D^{25}$ - 17.5° (C 3.98, $CHCl_3$) [reported $[\alpha]_D^{23}$ - 17.5° (C 4, $CHCl_3$)][13] (65% yield calculated from VI).

1,2-Diglycerides - Enantiomeric saturated and unsaturated sn-glycerol 1,2 and 2,3-diacylates were synthesized from the common intermediate II; sn-glycerol 1,2-diacylates were efficiently prepared in two steps from the diol III, and the corresponding 2,3-compounds were synthesized in three steps from V. For the preparation of the sn-glycerol 1,2-acylates X, the diol III was treated with two moles of the appropriate acid chloride to afford the diacylated carbonates IX in 60-75% yield after purification by chromatography; chromatographic separations on Florisil were relatively easy due to the large R_f difference between IX and other products. Brief zinc/acetic acid treatment of IX, with R= stearoyl, oleoyl, elaidoyl and linoleoyl moieties, gave the corresponding diglycerides X. Compound X (R= oleoyl moiety) had an optical rotation $[\alpha]_D^{25}$ -1.91° (C 6.2, $CHCl_3$) [reported $[\alpha]_D^{20}$ - 2.8° (C 10, $CHCl_3$)].[14] Thin layer chromatography of the crude products using systems known to separate the 1,2- and 1,3-diglycerides[9,20] showed the presence of only trace amounts of the 1,3-isomers.



Alkaline hydrolysis of V led to diol XI which was acylated to afford XII (R= $C_{17}H_{35}$ or $C_{17}H_{33}$). Detritylation of XII was accomplished with boric acid[13] in trimethyl borate with little or no isomerization, as the intermediate borate ester effectively prevents acyl migration.[2] Compound XII (R= oleoyl moiety) had an optical rotation $[\alpha]_D^{25}$ + 2.14° (C 5.62, $CHCl_3$) [reported $[\alpha]_D^{20}$ + 2.7° (C 11, $CHCl_3$)].[14] Thus, application of known methods of synthesis of diglycerides to these readily prepared, optically active trityl glycerols, now provides direct access to all combinations of acylated 1,2-diglycerides.



XI XII XIII

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