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# *Synthesis of Novel Disulfide Containing Macrocyclic Diacylglycerols*

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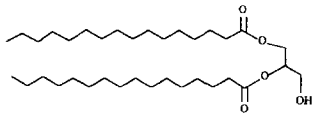
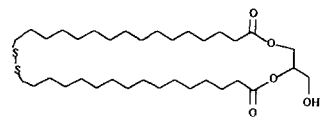
***Abstract:*** *New diacylglycerols (2-4) containing intramolecular disulfide linkages between pendant acyl chains were synthesized. Due to the differences in the location of disulfide units, the present method allows synthesis of macrocycles that vary in sizes.*

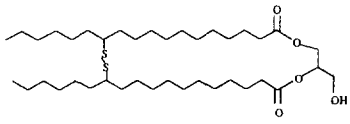

Diacylglycerol (DAG), **1** and its derivatives represent important endogenous membrane active components.[1] In addition, DAGs are potent Protein Kinase C activators[2] and also modulate the activities of cellular Phospholipase $A_2$.[3] Previous studies have shown that selected structural modifications in DAGs lead to pronounced changes in their membrane associated enzymic properties in vitro.[4] However, towards this end, so far no macrocyclic DAGs have been examined. Moreover, lipids with macrocyclic structure are currently receiving a lot of attention due to their apparent architectural similarity with the lipids present in archaebacteria.[5] The presence of macrocycle in lipids of thermophilic bacteria are also believed to be important for their sustenance in extreme temperatures.[6] Due to our interest in the development of membranes with high thermal stability[7,8] and also to examine the specific role of macrocyclic DAG's, we sought to synthesize macrocylic systems that could be incorporated in membranes. Herein we describe a convenient synthesis of three novel macrocyclic DAG analogues (**2-4**), in which the disulfide connector *intramolecularly* joins the two hydrocarbon chains at various positions.



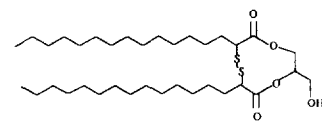

**1**




**2**




**3**



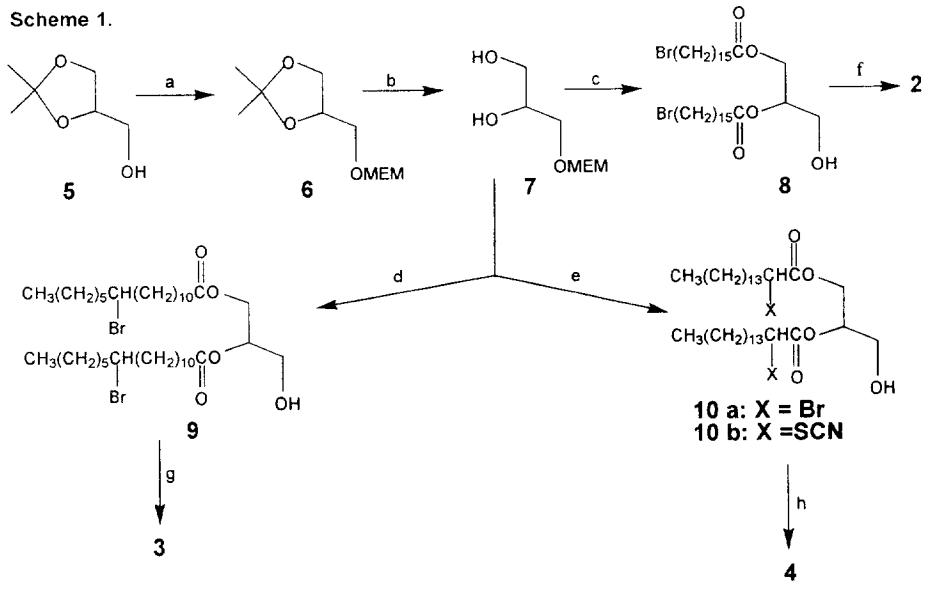

**4**

The overall synthetic routes to different disulfide containing DAGs are summarized in the Scheme 1. First, the MEM ($\beta$-methoxyethoxymethyl) protecting group was introduced into the building block, 1,2-isopropylidene glycerol, **5**, by partial modification of a literature procedure[9] which gave 1,2-isopropylidene-3-methoxyethoxymethylglycerol, **6** as a colorless oil in ~82% yield. The isopropylidene group was then removed by brief stirring **6** with 0.3 equivalent of *p*-toluenesulphonic acid in aqueous MeOH at ambient temperature. After workup, the crude diol was purified by preparative column chromatography (silica gel, 60-120 mesh) and the fractions corresponding to the pure diol, **7**, was concentrated to afford an oily residue (90%). The diol, **7**, was then acylated with two equivalents of appropriate $\alpha,\omega$-bromoalkanoic acid in dry $CCl_4$ upon addition of a solution of 2.2 equivalents of DCC to a mixture of the diol, **7**, the respective acid and DMAP in dry $CCl_4$ at 0 °C and then allowing the reaction to proceed at ambient temperature until tlc indicated no further change. DCU was then filtered and the crude MEM protected dibromoacylglycerols were purified by column chromatography over silica gel. The MEM protecting group from each of these dibromoacyl glyceroethers were then removed by brief treatment with 1.5 equivalents of $TiCl_4$ in dry $CH_2Cl_2$ under nitrogen blankets at 0 °C.[10]

The 1,2-dibromoacylglycerols (**8**,**9**) thus obtained were then converted to the corresponding macrocyclic, disulfide tethered diacylglycerols (**2**,**3**) by adaptation of the methodology developed by Chandrasekaran and coworkers.[11] For the preparation of the intramolecular disulfides **2**,**3** from the corresponding dibromide precursors (**8**,**9**) in the key macrocyclization step, we employed freshly prepared benzyltriethylammonium tetrathiomolybdate, $[(PhCH_2NEt_3)_2MoS_4]$ in DMF as a sulfur transfer reagent. Though the yields in this key step were good to moderate, formation of a single product made the separation of the individual macrocyclic DAGs relatively simpler task.

However, the above reductive dimerization of the dibromo compound **10a**, containing bromide at the $\alpha$-carbon of the carbonyl groups yielded a practically inseparable mixture of the corresponding mono and disulfides. Repetitive chromatographic steps using this complex mixture yielded the desired compound, **4**, in insignificant amounts (<5% yield). To circumvent this problem, we first converted the dibromide **10a**, to the corresponding dithiocyanate **10b**[12] by stirring **10a** with $NH_4SCN$ in acetone at ambient temperature (quantitative yield) to afford a material that readily and cleanly reacted with $[(PhCH_2NEt_3)_2MoS_4]$ to give the desired disulfide ~70% yield. This method thus appears to be particularly useful for the synthesis of the disulfides with $\alpha$-carbonyl function where all the other known methods in literature were found to be inadequate. All the numbered intermediates and the final products were characterized by their IR, $^1$H-NMR, mass spectra.[13]

Scheme 1.




**Reaction Conditions, Reagents and Yields**: (a) 1.5 equiv. each of MEMCl and NaH, dry THF, 0°C, $N_2$, 1.5h, 80%; (b) 0.3 equiv. *p*-TsOH, MeOH-$H_2O$ (1:10 v/v), RT, 2h, 91%; (c) (i) 2.2 equiv. $Br(CH_2)_{15}CO_2H$, 2.2 equiv. DCC, 2.2 equiv. DMAP, dry $CCl_4$, RT, 3-4h, 50%; (ii) 1.5 equiv. $TiCl_4$, dry $CH_2Cl_2$, 0°C, $N_2$, 1h, 80%; (d) (i) 2.2 equiv. $CH_3(CH_2)_5CH(Br)(CH_2)_{10}CO_2H$, 2.2 equiv. DCC, 2.2 equiv. DMAP, dry $CCl_4$, RT, 4h, 87%; (ii) 1.5 equiv. $TiCl_4$, dry $CH_2Cl_2$, 0°C, $N_2$, 1h, 73%; (e) (i) 2.2 equiv. $CH_3(CH_2)_{13}CH(Br)CO_2H$, 2.2 equiv. DCC, 2.2 equiv. DMAP, dry $CCl_4$, RT, 3-4h, 52%; (ii) 1.5 equiv. $TiCl_4$, dry $CH_2Cl_2$, 0°C, $N_2$, 1h, 57%; (f) 2 equiv. $(PhCH_2NEt_3)_2MoS_4$, DMF, RT, 3h, 55%; (g) 2 equiv. $(PhCH_2NEt_3)_2MoS_4$, DMF, RT, 5h, 62%; (h) 2 equiv. $(PhCH_2NEt_3)_2MoS_4$, DMF, RT, 2h, 70%.

In summary, we have been able to conveniently synthesize three novel macrocyclic DAG analogues (**2-4**), in which the hydrophobic acyl chains are *intramolecularly* connected at various depths. The described procedure does not require high dilution in the macrocyclization steps and due to the differences in the location of the disulfides widely varying sizes of macrocycles could be formed. The versatility of this procedure is also illustrated with the synthesis of different DAGs. To our knowledge, this is the only synthetic strategy[14] that unambiguously gives an intramolecular macrocyclic disulfide from the bromide or thiocyanate in a single step as the sole product.[11,12] This is also the first example of the application of the reagent, $[(PhCH_2NEt_3)_2MoS_4]$[11] to the macrocyclic DAG synthesis. Subsequent synthetic extension towards different glycerophospholipid systems and the elucidation of the precise effects of macrocyclizations of various DAGs on to the activities of Phospholipase $A_2$ are currently underway in our laboratory.

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13. All the compounds exhibited spectral characteristics consistent with their given structures. IR, $^1$H-NMR, mass spectral data for the final compounds are as follows: For **2**, IR (neat):$\nu_{max}$ 3500-3100 (br), 1720 cm$^{-1}$. $^1$H-NMR (200 MHz, $CDCl_3$): $\delta$ 5.11 (1H, *m*, -$CH_2\underline{C}H\underline{C}H_2$-), 4.37-4.1 (2H, *m*, -$C\underline{H}_2$CH), 3.72 (2H, *d*, -$C\underline{H}_2$OH), 2.69 (4H, *t*, 2x-$C\underline{H}_2$-S), 2.31 (4H, *t*, 2x-$C\underline{H}_2$-C=O), 1.25 (52H, br *m*, 2x-$(C\underline{H}_2)_{13}$). FAB-MS m/z 631 ($MH^+$). For **3**, IR (neat):$\nu_{max}$ 3550-3400 (br), 1740 cm$^{-1}$. $^1$H-NMR (200 MHz, $CDCl_3$): $\delta$ 5.1 (1H, *m*, -$CH_2\underline{C}H\underline{C}H_2$-), 4.16-4.1 (2H, complex *m*, -$C\underline{H}_2$CH), 3.68 (2H, *d*, -$C\underline{H}_2$OH), 2.8 (1H, *m*, $\underline{C}$H-S), 2.6 (1H, *m*, $\underline{C}$H-S), 2.16 (4H, *t*, 2x-$C\underline{H}_2$-C=O), 1.25 (56H, br *m*, 2x-[$(C\underline{H}_2)_5$+$(C\underline{H}_2)_9$]), 0.88 (6H, *t*, 2x-$C\underline{H}_3$). LR-MS m/z 686 ($M^+$, 3%), 658(10), 603(1), 404(45), 379(4), 373(4), 339(100), 330(12), 297(10), 281(6), 265 (92), 247(8), 227(6), 185(6), 129(14), 111(18), 97(32), 83(38), 69(35), 57(30), 43(18). For **4**, IR (neat): $\nu_{max}$ 3600-3100 (br), 1730 cm$^{-1}$. $^1$H-NMR (200 MHz, $CDCl_3$): $\delta$ 5.22 (1H, *m*, -$CH_2\underline{C}H$ $CH_2$-), 4.66-3.7 (4H, complex *m*), 3.4-3.23 (2H, *m*, $\underline{C}$H-S), 1.25 (52H, br *m*, 2x-$(C\underline{H}_2)_{13}$), 0.88 (6H, *t*, 2x-$C\underline{H}_3$). LR-MS m/z 630 ($M^+$, 22%), 345(20), 329(18), 311(80), 297(10), 265(18), 255(5), 237(100), 185(4), 148(10), 129(20), 116(12), 97(25), 83(30), 69(26), 57(34), 43(22).
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