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THE SYNTHESIS OF CONFORMATIONALLY-RESTRICTED DIACYL GLYCEROL ANALOGUES

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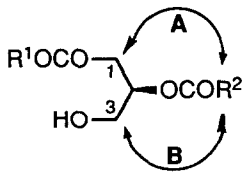
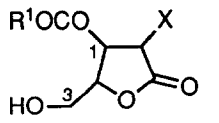
Abstract: A series of conformationally-restricted diacylglycerol analogues have been prepared in homochiral form as potential protein kinase C antagonists using D-ribonolactone and D- and L-2-deoxyribose as starting materials.

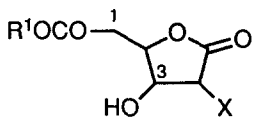
In the preceding paper[1] we reported the preparation of a series of acyclic analogues of intracelluar diacylglycerols (DAG, e.g.**1**) which were screened as potential protein kinase C (PKC) antagonists and as inhibitors of cellular proliferation.[2] As part of the same programme we decided to prepare cyclic DAG analogues in which the 2-acyl unit of diacyl glycerol (**1**) was covalently linked to the 1 or 3 positions of the glycerol backbone [e.g. (**A**) and (**B**), respectively], thereby conferring conformational rigidity to the extremely flexible DAG.



(**1**) $R^1 = CH_3(CH_2)_{16}$
$R^2 = C_5H_{11}(CH{=}CHCH_2)_4(CH_2)_2$



(**A**) X = H or $OCOR^1$



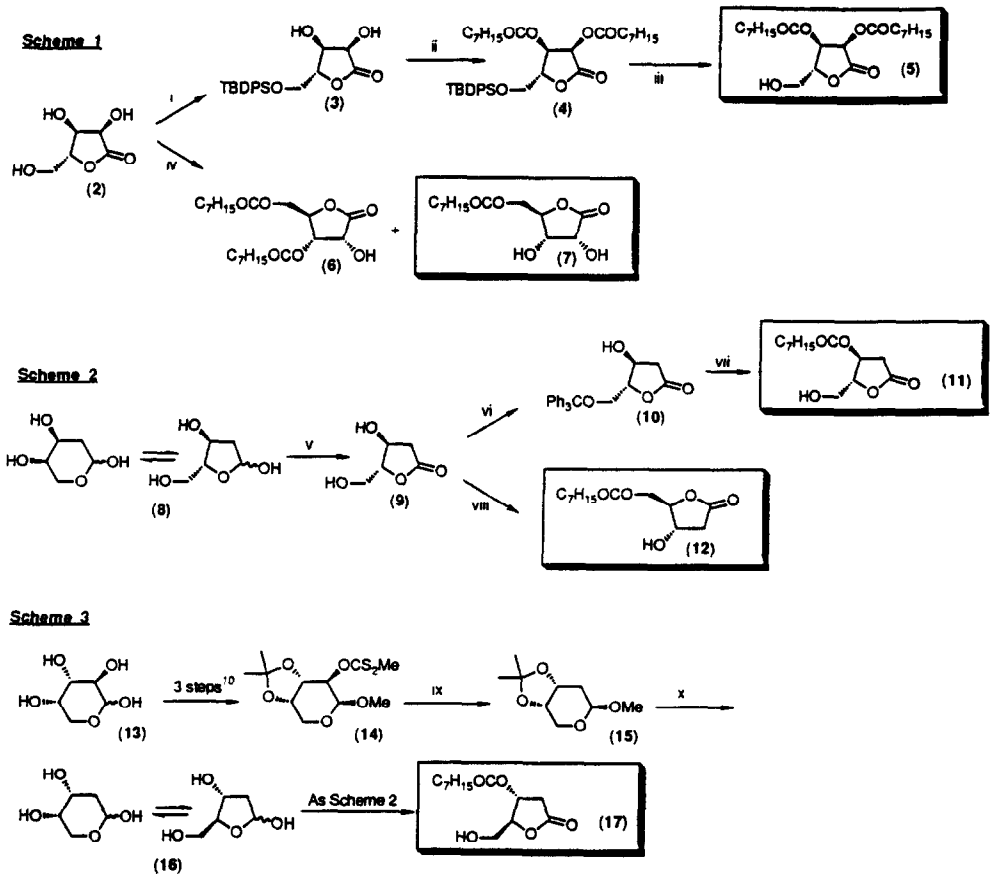
(**B**) X = H or OH

By using furanose sugars as starting materials, the DAG analogues were available in homochiral form.[3] Scheme 1 illustrates the preparation of such compounds commencing with D-ribonolactone (**2**). Selective silylation using $^tBuPh_2SiCl$ and imidazole gave diol (**3**) as a crystalline solid[4] which was treated with octanoyl chloride to give di-acyl derivative (**4**). Desilylation of compound (**4**) was achieved

using aq. HF in acetonitrile[5] to produce the type (**A**) DAG analogue (**5**). Direct acylation at the primary site of D-ribonolactone (**2**) was effected using Rosenthal's procedure,[6] the addition of acyl chloride in dichloromethane to an excess of the alcohol in pyridine at 0°C. This procedure gave the type (**B**) DAG analogue (**7**) along with a small amount of the diacylated derivative (**6**) which could be separated by chromatography on silica. The corresponding deoxy-analogues (**11**) and (**12**) were prepared from 2-deoxy-D-ribose (**8**) by the procedures shown in Scheme 2. Oxidation of deoxyribose (**8**) using aqueous bromine in the presence of calcium carbonate, followed by heating the product at 70°C under vacuum, gave lactone (**9**)[7] which was regioselectively tritylated to produce (**10**) as a crystalline solid. Acylation followed by acidic detritylation using formic acid in ether[8] gave the type (**A**) DAG analogue (**11**). Selective acylation of (**9**) with octanoyl chloride[6] gave direct access to the type (**B**) DAG analogue (**12**).

Several groups have established that only DAGs with the natural *sn*-1,2-substitution pattern activate PKC.[9] Analogues (**7**) and (**12**) are *sn*-1,2-isomers whereas (**5**) and (**11**) are *sn*-2,3-isomers. For comparison purposes, we therefore prepared the enantiomeric version of lactone (**11**), i.e. compound (**17**), as shown in Scheme 3. For this sequence we required 2-deoxy-L-ribose (**16**). This compound has been prepared previously[7,10] but we utilised the route from L-arabinose (**13**) shown in Scheme 3.[11] The key step involved the Barton deoxygenation[12] of xanthate (**14**) using tri-n-butyltin hydride and AIBN in boiling toluene. Acid-catalysed deprotection of product (**15**) was achieved using Amberlite IR120(H) in refluxing aqueous THF, removal of the resin by filtration and freeze-drying of the filtrate affording 2-deoxy-L-ribose (**16**). The remaining steps in the synthesis of (**17**) were identical to those used in the enantiomeric series as shown in Scheme 2.

Using the testing procedures described in the preceding paper,[1] we have found that compounds (**5**), (**6**), (**7**) and (**11**) do not activate PKC. However, we have no data as yet to establish whether or not the compounds are capable of inhibiting PKC in assays where it has been activated by OAG (see preceding paper[1]). In cell culture studies (see preceding paper[1]), compound (**12**) was found not to significantly affect (either stimulate or inhibit) the growth of HL60 cells at concentrations up to 10^{-4} M whereas a reduction in growth of *ca.* 20% was observed with compound (**11**) at 10^{-4} M.



Reagents (TBDPS = $^{t}BuPh_2Si$)

(i) TBDPSCl, imidazole, DMF (66%)
(ii) $C_7H_{15}COCl$, py (79%)
(iii) aq. HF, CH_3CN (65%)
(iv) $C_7H_{15}COCl$, py, CH_2Cl_2, 0°C [(**7**), 53%; (**6**), 12%]
(v) Br_2, H_2O, $CaCO_3$
(vi) Ph_3CCl, py, 4-DMAP [34% from (**8**)]
(vii) as ii (59%) then HCO_2H, ether (64%)
(viii) as (iv) [37% from (**8**)]
(ix) Bu_3SnH, toluene, AIBN (66%)
(x) Amberlite IR-120(H), aq. THF (1:1), 93% unpurified yield

Acknowledgements

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References and notes

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