Tetrahedron Letters, Vol. 34, No. 27, pp. 4313-4316, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

SYNTHESIS OF TWO RIGID DIACYLGLYCEROL ANALOGUES HAVING A PERHYDRO FURO[3,4-*b*]FURAN BIS-γ-BUTYROLACTONE SKELETON. 2.

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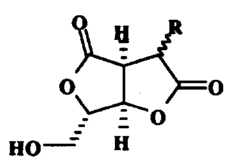
Abstract: The stereoselective synthesis of two rigid diacylglycerol analogues starting from L-arabinose is described. The construction of the desired bicyclic bis-butyrolactone structure was accomplished via intramolecular radical cyclization. Both compounds (**3a** and **3b**) showed poor binding affinity for PK-C.

The mechanism of activation of protein kinase C (PK-C) by diacylglycerol (DAG) is a highly stereospecific process.[1] The molecular superposition of the rather flexible DAG molecule on the rigid template of the pharmacologically equivalent and more potent phorbol ester suggests that there is an "active" conformation of the glycerol backbone that is recognized by PK-C.[2] We have previously identified two active DAG analogues (compounds **1** and **2**) in which the glycerol backbone forms part of a γ-lactone ring.[3,4] More recently, we have investigated an even more complex system in which the glycerol backbone is extended over two fused γ-lactone rings, as in compound **4**.[5] In this communication, we wish to report the synthesis of another set of similar, isomeric bis-γ-butyrolactones that can be rationally derived from the active monolactones **1** and **2**. These target structures were conceived with the intention of restricting rotation of the exocyclic acyl group in **1** and **2** by connecting it back to the lactone ring (see arrows) to produce a bis-lactone system represented by structure **3**.



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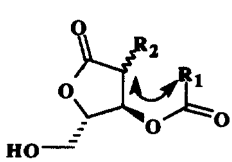
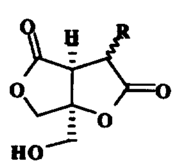


1, $R_1 = C_{13}H_{27}$, $R_2 = H$

2, $R_1 = CH_3$, $R_2 = C_{12}H_{25}$



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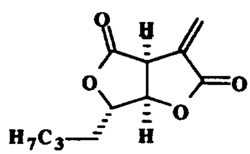


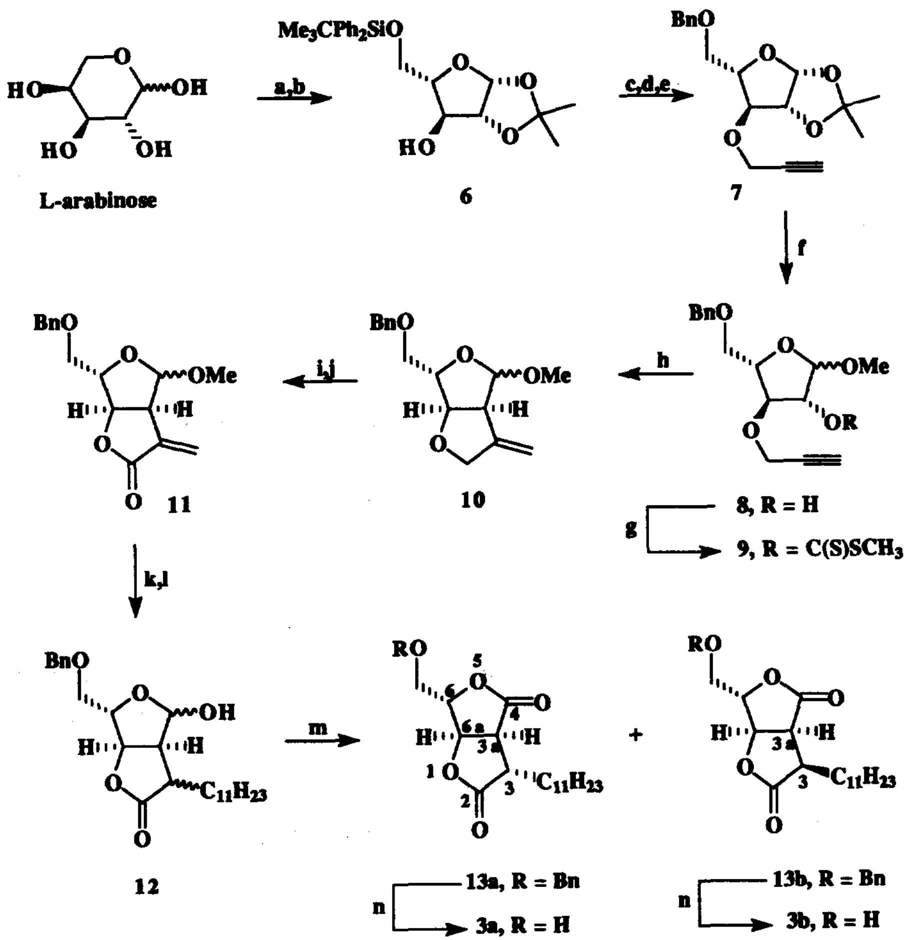
5, **(-)-canadensolide**

We have demonstrated earlier that the stereochemistry of the side chain (R_2) at the β-position of lactone **2** is of little consequence to biological activity, since in both possible orientations the resulting compounds showed equivalent binding affinity towards PK-C.[4] Therefore, a cyclization process leading to the stable cis-fused bis-γ-lactone system of type **3** ought to provide for an adequate orientation of the side chain. The new side chain R in **3** can have two possible orientations resulting in compounds **3a** and **3b** (Scheme) which were selected as target structures for the present study. From a chemical perspective, these compounds are structurally related to the natural product (-)-canadensolide (**5**).[6]

Starting from commercially available L-arabinose, compound **6** was synthesized in two steps according to a literature report[7] (Scheme). Reaction of this compound with NaH and propargyl bromide provided the corresponding propargyl ether. The *t*-butyldiphenylsilyl ether protecting group was replaced by the more robust benzyl ether in two high-yield steps to give key intermediate **7**. Methanolysis of this compound over cation exchange resin provided a 1:1 mixture of anomeric methyl glycosides **8** which was converted to a mixture of xanthate esters **9**. The ensuing radical cyclization proceeded in 56% yield to give the expected *exo-dig* product **10**.[8] An attempted allylic oxidation with CrO_3/pyridine on the newly formed ring gave a mixture of compounds in which the benzyl protecting group was additionally oxidized to a benzoyl moiety. Finally, a successful allylic oxidation to the desired lactone **11** was performed in two steps involving first oxidation to the lactol intermediate with SeO_2, followed by oxidation of the lactol to the lactone with MnO_2. The chain elongation step consisted of using the copper-catalyzed 1,4-addition of the Grignard $C_{10}H_{21}MgBr$ to give a mixture of compounds whose separation was postponed until the following two steps. Transformation of the methyl glycoside to the lactol **12** proceeded uneventfully under acid catalysis and oxidation with pyridinium chlorochromate (PCC) gave a mixture of only two products corresponding, respectively, to the compounds having two different orientations of the side chain. At this stage, the nearly 1:1 mixture of isomers was separated by column chromatography (silica gel, hexane:ethyl acetate, 2:1) and the assignment of their structures was made by ^1H NMR by using the characteristic values of the $J_{3,3a}$ coupling constants. In isomer **13a**, the 1.7 Hz value is consistent with two protons disposed *trans* to each other, whereas in isomer **13b**, the 10.2 Hz value is typical for protons that are in a *cis* relationship. Removal of the O-benzyl protection by catalytic hydrogenation gave the final products which along with most of the critical intermediates were fully characterized.[9,10]

The compounds were evaluated for their ability to inhibit [20-^3H]phorbol-12,13-dibutyrate binding to PK-C. The inhibition curves obtained for these compounds, however, were rather shallow and did not fit to the expected profile typical for a competitive mechanism.[3] Furthermore, there was very little difference in potency between these compounds, which inhibited phorbol ester binding with ID_{50} values of 70 μM (**3a**) and 90 μM (**3b**), respectively. These results stand in stark contrast with those reported earlier for one of the isomers of **4**[5] and with results from another investigation of a similar set of bicyclic compounds that were derived by an alternative mode of fixing the rotatable acyl side chain.[11]

Scheme



Reagents and Conditions: **a.** Me_3CPh_2SiCl/imidazole, DMF, 60 °C 2 h (55%). **b.** $CuSO_4/H_2SO_4$, acetone, rt 24 h (70%). **c.** Propargyl bromide, NaH, imidazole (cat), THF, rt 5 h (86%). **d.** Bu_4NF, THF, rt 2 h (88%). **e.** BnBr, NaH, Bu_4NI, THF, rt 8 h (98%). **f.** H^+–Resin, MeOH, Δ, 3 h (95%). **g.** NaH, CS_2, MeI, DMF, rt (94%). **h.** Bu_3SnH/azobis(isobutyronitrile), toluene, 90 °C (56%), **i.** SeO_2, dioxane, 80 °C 0.5 h (68%). **j.** MnO_2, CH_2Cl_2, rt 1h (100%). **k.** $C_{10}H_{21}MgBr$/CuCl, ether, –40 °C 1h (80%). **l.** HCl, AcOH-H_2O-THF, 90 °C 20 h (90%). **m.** PCC, CH_2Cl_2, rt 1 h (86%). **n.** H_2, Pd/C, MeOH, rt 2h (96%).

References and Notes

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9. Compound **3a**, white solid, mp 89 °C; $[\alpha]_D{}^{24}$ –17.8° (c 0.55, $CHCl_3$); IR (KBr) 3480 (OH) and 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ5.12 (d, $J_{3a,6a}$ = 6.6 Hz, 1 H, H_{6a}), 4.72 (m, 1 H, H_6), 4.05 (br d, J_{gem} = 12.1 Hz, 1 H, CH*H*OH), 3.90 (br d, J_{gem} = 12.1 Hz, 1 H, C*H*HOH), 3.26 (dd, $J_{3a,6a}$ = 6.6, $J_{3,3a}$ = 1.8 Hz, 1 H, H_{3a}), 2.87 (m, 1 H, H_3), 1.15-1.95 (m, 20 H, CH_2's), 0.85 (distorted triplet, 3 H, CH_3); ^{13}C NMR δ 176.29, 176.16, 83.77, 79.94, 62.51, 46.76, 43.25, 31.89, 31.77, 29.69, 29.57, 29.49, 29.31, 29.03, 26.66, 22.67, 14.10; FAB MS *m/z* (rel intensity) 327 (MH^+, 100). Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.00; H, 9.28.
10. Compound **3b**, white solid, mp 82 °C; $[\alpha]_D{}^{24}$ –16.4° (c 0.72, $CHCl_3$); IR (KBr) 3568 (OH), 1785 and 1761 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ5.09 (d, $J_{3a,6a}$ = 6.1 Hz, 1 H, H_{6a}), 4.67 (m, 1 H, H_6), 4.04 (dd, J_{gem} = 12.2, $J_{H,OH}$ = 2.1 Hz, 1 H, CH*H*OH), 3.88 (br d, J_{gem} = 12.2 Hz, 1 H, C*H*HOH), 3.58 (dd, $J_{3a,6a}$ = 6.1, $J_{3,3a}$ = 10.3 Hz, 1 H, H_{3a}), 2.88 (m, 1 H, H_3), 2.15 (br s, 1 H, OH), 1.15-1.90 (m, 20 H, CH_2's), 0.85 (distorted triplet, 3 H, CH_3); ^{13}C NMR δ 175.58, 173.17, 82.85, 79.55, 62.44, 43.76, 41.55, 31.89, 29.61, 29.57, 29.32, 28.03, 25.99, 22.66, 14.09; FAB MS *m/z* (rel intensity) 327 (MH^+, 100). Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.16; H, 9.27.
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(Received in USA 26 March 1993; accepted 12 May 1993)