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SYNTHESIS OF TWO RIGID DIACYLGLYCEROL ANALOGUES HAVING A BIS-BUTYROLACTONE SKELETON

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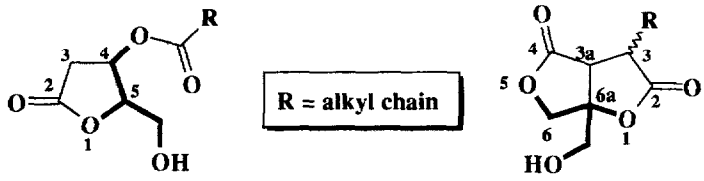
Abstract: The stereoselective synthesis of two rigid diacylglycerol analogues starting from protected D-apio-L-furanose (apiose) is described. The construction of the desired bis-butyrolactone bicyclic structure was accomplished via an intramolecular radical cyclization.

Protein kinase C (PK-C) is an enzyme that plays a critical role in cell signal transduction after it is physiologically activated by the binding of the *S*-enantiomer of a diglyceride [(*S*)-DAG] to its regulatory domain.[1] It has been established that various tumor promoters, such as phorbol esters and aplysiatoxins, also activate PK-C with a binding affinity that greatly exceeds that of (*S*)-DAG.[2,3] The molecular superposition of (*S*)-DAG on the structure of these tumor promoters suggests the existence of several possible "active" (*S*)-DAG conformations capable of binding to PK-C.[2,3] In a search for these "active" conformations, we previously synthesized and studied a series of isomeric γ-lactones (**A**) as rigid (*S*)-DAG analogues.[4] Now, we wish to report the synthesis of two new rigid (*S*)-DAG analogues (**B**) in which the glycerol backbone (highlighted) is extended into two fused γ-lactone rings. In theory, if the correct rigid rotamer of (*S*)-DAG is found, it is expected to bind more tightly to PK-C due to a favorable, smaller entropy decrease relative to the more flexible (*S*)-DAG.

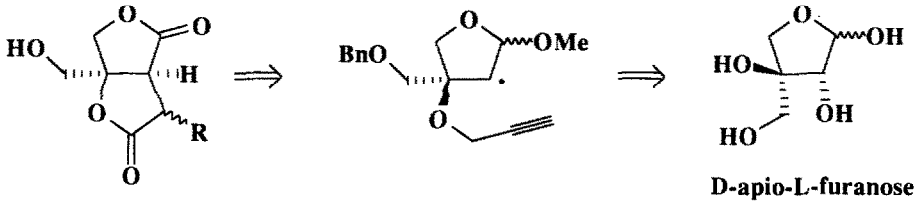


A **B**

These new targets contain a bis-γ–butyrolactone motif found in several antifungal natural products such as avenaciolide, isoavenaciolide and canadensolide.[5-7] In addition, the molecules have striking structural similarities to the *cis*-6-oxabicyclo[3.3.0]oct-3-en-2-one system of the marine natural products didemnenones[8] and the lactam-lactone antitumor antibiotic neooxazolomycin.[9]

In the monolactone **A**-type series, the most active compounds demand the *S* configuration at C-5.[4] Therefore, a similar configuration was sought for the **B**-type bicyclic lactone at C-6a. Both 3a*S*,6a*S*,3*S* and 3a*S*,6a*S*,3*R* isomers were selected as targets.

Retrosynthetic analysis suggested the use of the sugar apiose as a chiral building block with the desired stereochemistry. The key step was envisioned to proceed via a radical-mediated *exo-dig* intramolecular cyclization.[10]

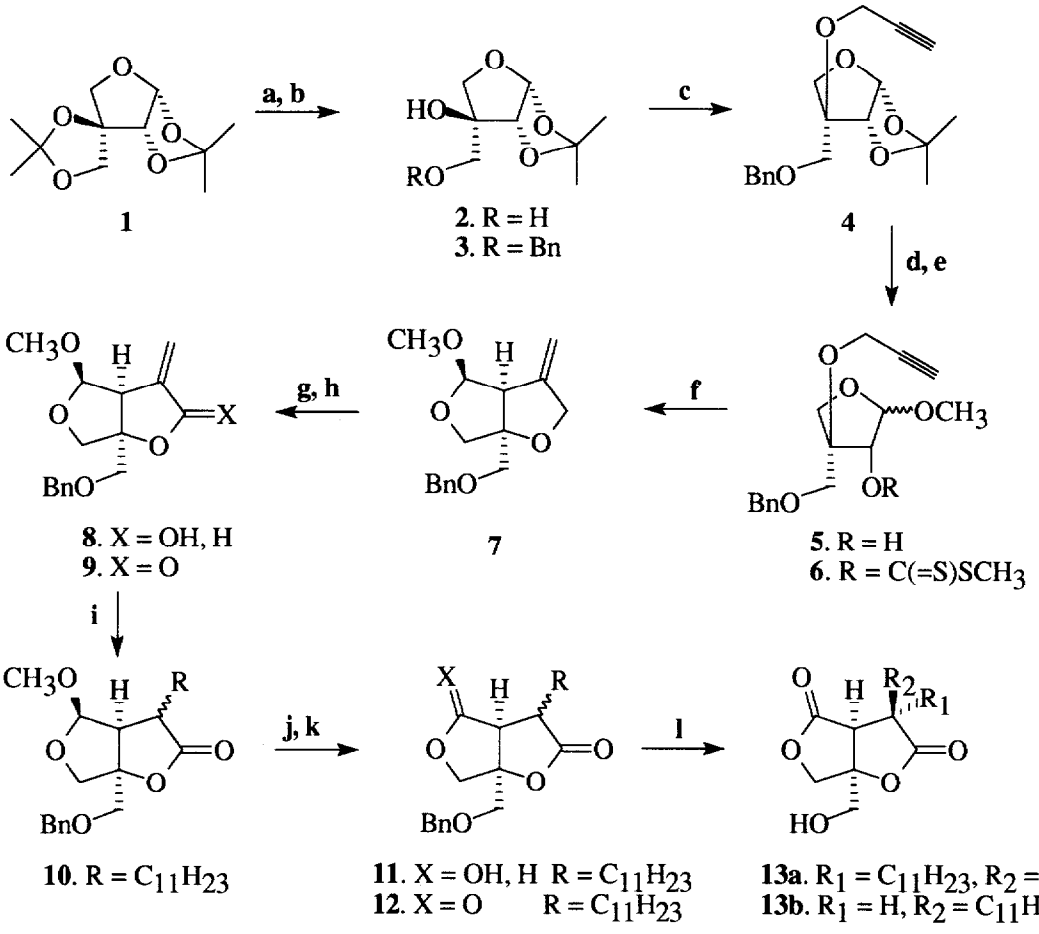


D-apio-L-furanose

1,2:3,5-Di-O-isopropylidene-α-D-*threo*-apiofuranose (**1**)[11] was hydrolyzed under mild conditions to remove the 3,5-O-isopropylidene group (**Scheme**). Selective monobenzylation of the primary alcohol in **2** via the 3,5-O-(dibutylstannylene)-intermediate gave compound **3** in quantitative yield. Reaction of this compound with NaH and propargyl bromide provided the key propargyl ether **4** in excellent yield. This compound, after methanolysis to a 1:1 mixture of anomeric methyl glycosides (**5**) and conversion to the xanthate ester **6**, set the stage for the ensuing intramolecular radical cyclization that provided the bicyclic intermediate **7** with the protected hydroxymethyl substituent at the bridgehead. The radical cyclization constituted the lowest yield step of the entire synthesis (40%). In an attempt to improve the yield of this step, the two diastereoisomers of **6** were separated and individually investigated. The results, however, indicated that while the α-anomer reacted poorly (13% yield), the β-anomer fared only a little better giving a 48% yield; thus, no significant advantage was gained from the separation of anomers. It was interesting to observe that upon cyclization to **7** only a single anomer at C-4 was obtained (probably β, $J_{3a,4}$ = 5.8 Hz). Next, several methods to oxidize the allylic carbon in **7** were investigated. Under refluxing conditions PCC produced extensive decomposition, while Collins reagent overoxidized the substrate giving a mixture of **9** and a product with an extra carbonyl at C-6 that was difficult to separate. To accomplish our goal the oxidation was performed in two steps, first oxidation of **7** to the lactol **8** through the action of SeO_2, and then oxidation to the carbonyl stage by MnO_2 to give **9**. In the following chain elongation step, the copper-catalyzed 1,4-addition of the Grignard $C_{10}H_{21}MgBr$ provided both alkylated products (**10**). The reaction gave a 4:1 mixture in favor of the α-isomer at C-3 as judged by NMR, but the separation was postponed until the end of the synthesis for fear of isomerization during the subsequent steps. Transformation of the remaining acetal proceeded uneventfully after acid hydrolysis and oxidation of the resulting lactol with PCC to give the penultimate intermediate **12**. Removal of the benzyl protection by catalytic hydrogenation gave a ca. 4:1 mixture of **13a/13b** which was separated by column chromatography (silica gel, pet ether/ethyl acetate, 2:1). Thus, the isomer ratio was maintained unchanged since the chain elongation step. The characteristic $J_{3,3a}$ couplings of 3.3 Hz and 10.3 Hz, respectively for compounds **13a** and **13b**, helped corroborate the assignments.[12,13] Results from the inhibition of binding of [^{3}H]phorbol-12,13-dibutyrate to protein kinase C identified only **13b** as an effective inhibitor with a K_i of 22 μM. The biological significance

of these results will be discussed elsewhere.

Scheme



Reagents and Conditions: **a.** AcOH-H_2O (2:1), 3 days, rt (70-80%). **b.** $(Bu_3Sn)_2O$, toluene, reflux 4h; then BnBr, Bu_4NBr, 80° C, 12 h (100%). **c.** Propargyl bromide, NaH, DMF, rt 16 h (95%). **d.** HCl, MeOH-THF, rt 2 days (92%). **e.** NaH, CS_2, MeI, DMF (94%). **f.** Bu_3SnH, AIBN, toluene, reflux 1 h (40%). **g.** SeO_2, dioxane, 80° C, 0.5 h (72%). **h.** MnO_2, CH_2Cl_2, rt 2 h (100%). **i.** $C_{10}H_{21}MgBr$, CuCl, -40° C, ether (70%). **j.** HCl, AcOH-H_2O, 80° C, 14 h (85%). **k.** PCC, CH_2Cl_2, rt 30 h (95%). **l.** 10% Pd/C, MeOH, AcOH (cat.), 40 psi , 4 h (95%).

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References and Notes

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12. Compound **13a**, white solid, mp 95.5° C; $[\alpha]_D^{24}$ +24.8° (c 1.6, $CHCl_3$); IR (KBr) 3426.9, 1781.9 and 1750.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (d, 1 H, J = 11.2 Hz, H-6α), 4.39 (d, 1 H, J = 11.2 Hz, H-6β), 3.91 (br d, 1 H, J = 11 Hz, CHHOH), 3.79 (br d, 1 H, J = 11 Hz, CHHOH), 3.12 (d, 1 H, J = 3.3 Hz, H-3a), 2.89 (m, 1 H, H-3), 2.70 (br s, 1 H, OH), 1.20-2.05 (m, 20 H, CH_2's), 0.88 (distorted triplet, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.6 (s), 175.7 (s), 88.4 (s), 73.1 (t), 63.9 (t), 46.9 (d), 44.8 (d), 31.9 (t), 31.6 (t), 29.6 (t), 29.5 (t), 29.4 (t), 28.9 (t), 27.4 (t), 22.7 (t), 14.1 (q); FAB MS *m/z* (relative intensity) 327 (MH^+, 100); Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.13; H, 9.22.
13. Compound **13b**, white solid, mp 65.5° C; $[\alpha]_D^{24}$ +20.0° (c 0.45, $CHCl_3$); IR (KBr) 3448.0, 1793.8 and 1746.87 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.47 (d, 1 H, J = 11.1 Hz, H-6α), 4.29 (d, 1 H, J = 11.1 Hz, H-6β), 3.95 (d, 1 H, J = 12 Hz, CHHOH), 3.84 (d, 1 H, J = 12 Hz, CHHOH), 3.42 (d, 1 H, J = 10.3 Hz, H-3a), 3.11 (m, 1 H, H-3), 2.18 (br s, 1 H, OH), 1.20-1.90 (m, 20 H, CH_2's), 0.88 (distorted triplet, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.9 (s), 172.2 (s), 87.8 (s), 71.5 (t), 63.6 (t), 44.5 (d), 42.6 (d), 31.9 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.1 (t), 26.2 (t), 22.7 (t), 14.1 (q); FAB MS *m/z* (relative intensity) 327 (MH^+, 100); Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.53; H, 9.13.

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