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

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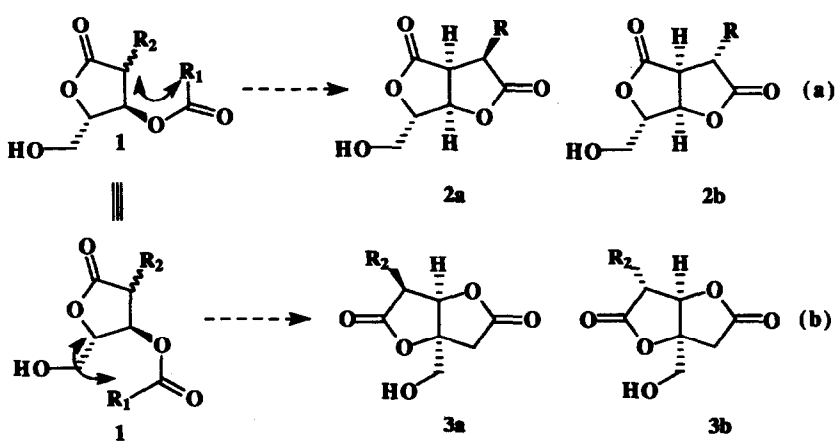
Abstract: The stereoselective synthesis of two new bis-γ-butyrolactones starting from 1,2:5,6-di-O-isopropylidene-α-D-allofuranose was completed in 22 steps. One of the isomers (**3a**) showed very good binding affinity towards protein kinase C.

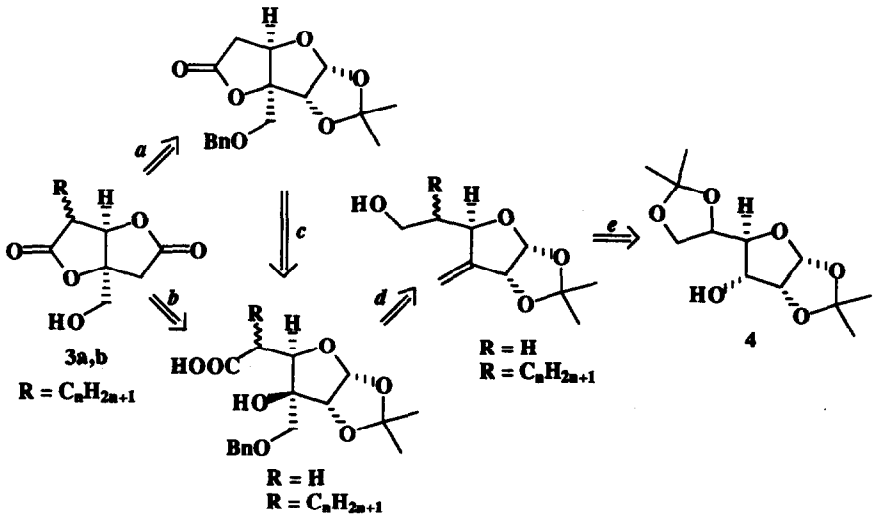
In the preceding communication[1] we examined the protein kinase C (PK-C) binding affinity of two isomeric bis-γ-butyrolactones (**2a,b**) that were synthesized as rigid diacylglycerol (DAG) analogues. These compounds were conceived to restrict the freedom of rotation about the O-acyl bond by incorporating the acyl moiety as part of a second lactone ring (Scheme 1a). In performing this connection, the R_1 and R_2 groups were integrated into a single long alkyl R substituent. Despite the good PK-C binding affinity displayed by the progenitor monolactones **1**,[2,3] in which either R_1 or R_2 represent long alkyl chains, neither resulting bicyclic structure, **2a** or **2b**, showed good binding affinity towards PK-C.[1] In this communication, we wish to report the synthesis and PK-C binding affinity of a new set of bis-γ-butyrolactones (**3a,b**) that can be envisioned as resulting from a different mode of restricting the freedom of rotation of the acyl chain (Scheme 1b).

Scheme 1



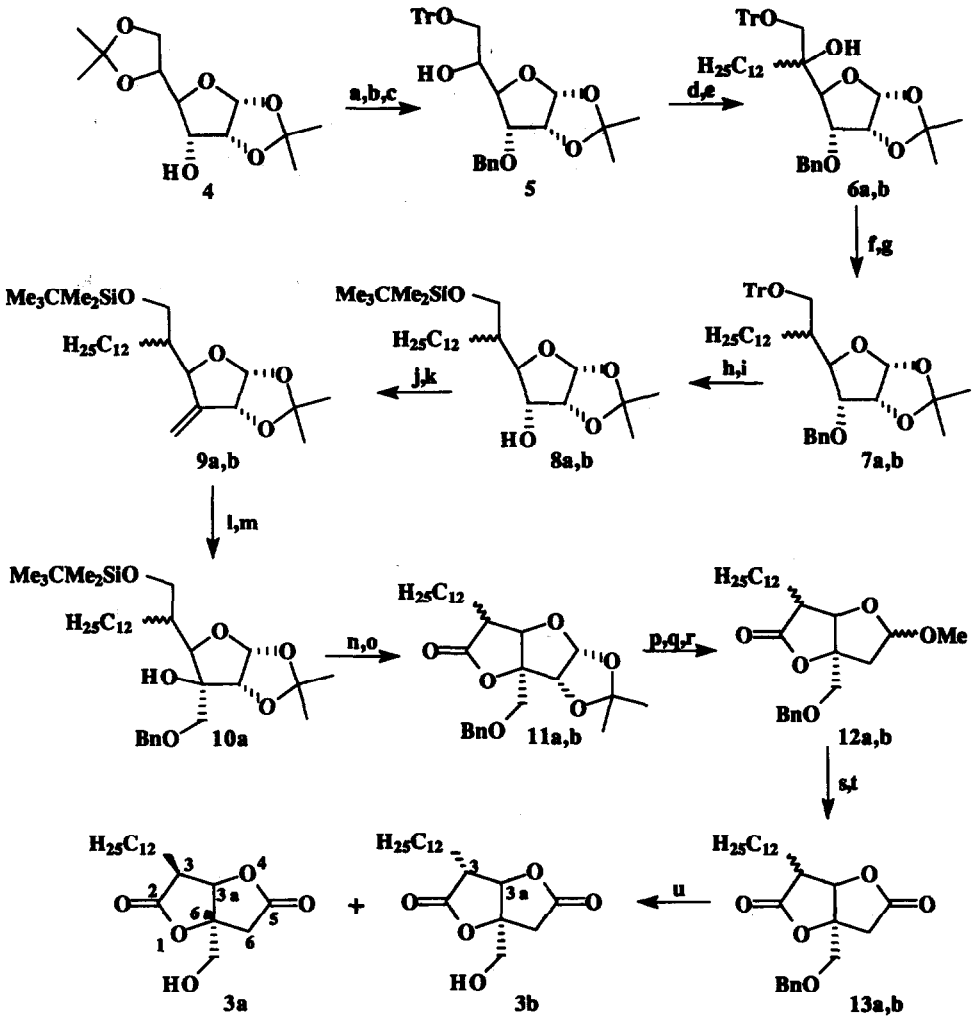
Retrosynthetic analysis of these targets suggested the use of either 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, or the isomeric 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**4**) as chiral building blocks.

For reasons to be discussed later, the allofuranose precursor was preferred. Building of the second lactone ring was envisaged to proceed after appropriate transformations at both C-3 and C-4 positions of the sugar (steps *e* and *d*). Later, for the construction of the alkyl chain R, two options were considered: 1) alkylation of the preformed bicyclic structure (step *a*) or 2) introduction of the alkyl group at an early stage of the synthesis (step *e*, R = C_nH_{2n+1}), followed by lactonization (steps *d* and *b*, R = C_nH_{2n+1}). Although the first approach seemed very attractive, alkylation of the bis-γ-butyrolactone system (LDA, THF, $C_nH_{2n+1}I$, –78 °C) failed due to facile β-elimination of the β-alkoxylactone. The second alternative, although somewhat cumbersome, worked well (Scheme 2). The selection of this route, which required an early alkylation step, convinced us to choose the allofuranose precursor **4** which offered no steric encumbrance on the β-face.



The starting 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**4**) was prepared from the corresponding α-D-glucofuranose derivative according to published methodology.[4] The next three steps: benzylation of the 3-hydroxyl group, opening of the 5,6-O-isopropylidene ring, and selective tritylation of the resulting primary 6-hydroxyl group were performed in a combined yield of 65%. Oxidation of the free secondary alcohol in **5** with pyridinium chlorochromate (PCC), followed by Grignard addition of $C_{12}H_{25}MgBr$, produced the expected mixture of diastereoisomers (**6a,b**). Throughout the ensuing steps isomers were not separated until the end of the synthesis. Radical deoxygenation of the newly generated tertiary alcohol proceeded uneventfully via the xanthate intermediate to give **7a,b**. Removal of the O-benzyl group with Na in liquid ammonia cleaved also the trityl group to give an intermediate which was then selectively protected as a *t*-butyldimethylsilyl ether derivative (**8a,b**). Oxidation of **8a,b** with pyridinium dichromate (PDC) was followed by a Wittig reaction to form the methylene compound **9a,b** which was regiospecifically cis-hydroxylated with OsO_4 from the less hindered β-face. The resulting diol intermediate was then selectively monobenzylated via the 3,5-O-(dibutylstannylene) derivative to give the advanced intermediate **10a,b**. At this point, lactonization was achieved, in one step, via oxidation of the unmasked primary alcohol. Most

Scheme 2



Reagents and Conditions: **a**. BnBr, NaH, Bu_4NI, THF, rt 2h. **b**. 0.06 *N* HCl/MeOH, 55 °C 2h. **c**. TrCl, pyridine/DMF, rt 12 h (65% steps **a-c**). **d**. PCC, 4Å mol. sieves, rt 1.5 h (98%). **e**. $C_{12}H_{25}MgBr$, ether, –10 °C -> rt (85%). **f**. NaH, CS_2, MeI, DMF, 80 °C (75%). **g**. Bu_3SnH/azobis(isobutyronitrile), toluene, Δ 1h (82%). **h**. Na, liq.NH_3/THF (90%). **i**. Me_3CPh_2SiCl, NEt_3, DMAP, CH_2Cl_2, rt 12 h (95%). **j**. PDC, AcOH 4Å mol. sieves, CH_2Cl_2, rt 1h (98%). **k**. $Me(PPh_3)Br$, BuLi, THF, –10 °C -> rt (84%). **l**. OsO_4, 4-Methylmorpholine *N*-oxide, aq. acetone, rt 12 h (92%). **m**. i. $(Bu_3Sn)_2O$, toluene, Δ 4 h. ii. BnBr, Bu_4NBr, 80 °C 24 h (98%). **n**. Bu_4NF, THF, rt 0.5 h (98%). **o**. PCC, 4Å mol sieves, CH_2Cl_2, rt 1h (96%). **p**. H^+—Resin, MeOH, Δ 12 h (95%). **q**. NaH, CS_2, MeI, THF, rt (93%). **r**. Bu_3SnH/azobis(isobutyronitrile), toluene, Δ 1 h (66%). **s**. HCl, AcOH-H_2O-THF, 90 °C 4 h (96%). **t**. PCC, CH_2Cl_2, rt 1 h (98%). **u**. H_2, Pd/C, MeOH, rt 2 h (94%).

likely, the transiently formed cyclic hemiacetal was immediately oxidized *in situ* to the lactone **11a,b**. To complete the synthesis, removal of the acetonide group, followed by a second radical deoxygenation gave **12a,b**. Hydrolysis of this methyl glycoside and oxidation to the corresponding lactol gave a mixture of the desired bis-γ-butyrolactone **13a,b**. Finally, removal of the O-benzyl protection and chromatographic separation of the isomers (silica gel, hexane:ethyl acetate, 1:1) gave the two targets **3a** and **3b**.[5,6] The obtained ratio of **3b/3a** = 3 reflects the kind of selectivity obtained during the Grignard alkylation step performed earlier in the synthesis. As before, characterization of each isomer was possible by examining the value of the $J_{3,3a}$ coupling constant.[5,6]

Evaluation of these compounds for their ability to inhibit [20-^{3}H]phorbol-12,13-dibutyrate binding to PK-C indicated that isomer **3a** was an excellent competitive inhibitor with a K_i of 6.1 μM, while the corresponding isomer **3b** had an ID_{50} of greater than 100 μM. Compound **3a** is the most potent inhibitor of all of the bis-γ-butyrolactones examined to date in our laboratory.

References and Notes

1. Lee, J.; Marquez, V. E.; Lewin, N. E.; Blumberg, P. M. *Tetrahedron Lett.* previous communication.

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3. Lee, J.; Marquez, V. E.; Lewin, N. E.; Kazanietz, M. G.; Bahador, A.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* in press.

4. Sowa, W.; Thomas, H. S. *Can. J. Chem.* **1966**, *44*, 836.

5. Compound **3a**, mp 84.5 °C; $[\alpha]_D^{24}$ +68.6° (c 0.22, $CHCl_3$); IR (KBr) 3496 (OH) and 1773 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 5.06 (d, $J_{3,3a}$ = 5.7 Hz, 1 H, H_{3a}), 4.03 (dd, J_{gem} = 11.9, $J_{H,OH}$ = 4.2 Hz, 1 H, C*H*HOH), 3.82 (dd, J_{gem} = 11.9, $J_{H,OH}$ = 4.8 Hz, CH*H*OH), 2.97 (m, 1 H, H_3), 2.87 (d, J_{gem} = 18.6 Hz, 1 H, $H_{6\alpha}$), 2.74 (d, J = 18.6 Hz, 1 H, $H_{6\beta}$), 2.30 (br s, 1 H, OH), 1.15-1.95 (m, 22 H, CH_2's), 0.86 (distorted triplet, 3 H); ^{13}C NMR δ 175.87, 172.25, 87.64, 81.90, 63.82, 45.30, 36.50, 31.90, 29.69, 29.64, 29.61, 29.53, 29.35, 27.59, 24.91, 22.68, 14.11; FAB MS *m/z* (rel intensity) 341 (MH+, 100). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.48. Found: C, 66.50; H, 9.44.

6. Compound **3b**, mp 91 °C; $[\alpha]_D^{24}$ +22.7° (c 0.65, $CHCl_3$); IR (KBr) 3447 (OH) and 1774 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.85 (d, $J_{3,3a}$ = 1.6 Hz, 1 H, H_{3a}), 3.96 (dd, J_{gem} = 11.9, $J_{H,OH}$ = 5.0 Hz, 1 H, C*H*HOH), 3.77 (dd, J_{gem} = 11.9, $J_{H,OH}$ = 6.0Hz, CH*H*OH), 2.91 (d, J_{gem} = 19.0 Hz, 1 H, $H_{6\alpha}$), 2.78 (d, J = 19.0 Hz, 1 H, $H_{6\beta}$), 2.81 (m, 1 H, H_3), 2.12 (br s, 1 H, OH), 1.15-1.95 (m, 22 H, CH_2's), 0.86 (distorted triplet, 3 H); ^{13}C NMR δ 175.99, 172.47, 87.57, 84.36, 64.32, 47.93, 36.25, 31.89, 29.61, 29.57, 29.49, 29.32, 28.98, 28.79, 27.57, 22.67, 14.09; FAB MS *m/z* (rel intensity) 341 (MH+, 100). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.48. Found: C, 66.39; H, 9.39.

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