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Synthesis of a Rigid Diacylglycerol Analogue Having a Bis-γ-butyrolactone Skeleton Separated by a Cyclopentane Ring

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A very efficient method for the construction of a new bis- γ -lactone system constructed on a cyclopenta[1,2-c:3,4-c']perhydrodifuran scaffold was developed from cyclopentadiene and methyl (S)-(Z)-4,5-O-isopropylidenepent-2-enoate.

The bis-γ-lactone skeleton common to some natural products, such as ethisiolide (1), isoavenaciolide (2), avenaciolide (3) and canadensolide (3), have attracted the attention of chemists and pharmacologists alike due to their biological activity. I.2 In our own laboratory, we have recently synthesized several related bis-γ-lactones (i.e, 4-7) as molecular scaffolds for the construction of rigid diacylglycerol (DAG) analogues. In the latter compounds can indeed function as DAG surrogates and bind to the DAG target, protein kinase C (PK-C), with micromolar affinities. In these structures the two lactone rings are contiguous, we decided to investigate the synthesis of bis-γ-lactones separated by a spacer ring.

The first example of such an effort is represented by the attempted synthesis of the cyclopenta[1,2-c:3,4-c']perhydrofuran analogues (8 and 9) which were designed as PK-C agonists by additionally attaching to the molecule a hydroxymethyl substituent and a lipophilic alkyl chain.

9, $R_1 = n - C_{14}H_{29}$, $R_2 = H$

The retrosynthetic analysis of templates I/II via the polyfunctional cyclopentane III is outlined in Scheme 1. This intermediate was envisioned to originate from the chiral norbornene IV which, in turn, was expected to come from the Diels-Alder adduct V derived from cyclopentadiene and the chiral methyl (Z)-pentenoate ester VI. The cycloaddition was expected to proceed with the anticipated syn-endo diastereoselectivity where the cyclopentadiene approaches the dienophile VI from the same side as the allylic oxygen function.5 Indeed, as shown in Scheme 2, the optically pure syn-endo adduct 10 was readily prepared.⁵ Because of its susceptibility to epimerization,6 the ester group in 10 was reduced and protected as a benzyl ether (compound 12). The isopropylidene group of 12 was then removed and the resulting diol 13 was cleaved with sodium metaperiodate to give aldehyde 14. Aldol condensation of 14 with excess formaldehyde, followed by an in situ Cannizaro reaction gave the bis-hydroxymethyl derivative 15 in excellent yield.7 Osmium tetroxide cleavage of the double bond in 15 produced a transient dialdehyde which cyclized immediately to an equilibrium mixture of hemiacetals 16 and 17. The first intramolecular cyclization automatically fixed the stereochemistry of the hydroxymethyl group at the bridgehead because the proximal aldehyde reacted only with the hydroxymethyl group on the same side of the cyclopentane ring. Further reaction of one epimer of hemiacetal 16 with the second aldehyde group gave the tricyclic hemiacetal 17. Treatment of the 16/17 mixture under basic conditions with tert-butylchlorodiphenylsilane accomplished both protection of the primary alcohol and epimerization of the second aldehyde function to give 18 as a single product.8 Since hemiacetal formation from the convex face of the molecule is impossible, the stereochemistry of the aldehyde function had to be "up" as indicated. Oxidation of 18 to lactone 19 was uneventful and removal of the benzyl ether protection gave hydroxy-aldehyde 20. Formation of this product confirmed the stereochemistry of the free aldehydebearing carbon which was subsequently re-epimerized in the

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Scheme 2.

Reagents: a. LiAlH₄, Ether, -10 °C. b. PhCH₂Br, NaH, n-Bu₄NI, THF (92% from 1). c. 1N HCl, THF. d. NaIO₄, Ether-H₂O (93% from 3). e. HCHO, NaOH, THF, 48 h (98%). f. OsO₄, 4-Methylmorpholine N-oxide (NMO), NaIO₄, acetone-H₂O. g. Me₃CSiPh₂Cl, Et₃N, DMAP, CH₂Cl₂, 5 days (62% from 6). h. Tetrapropylammonium perruthenate, NMO, CH₂Cl₂ (92%). i. H₂, Pd/C, AcOH-MeOH (96%). j. DBU, CH₂Cl₂, 24 h (100%). k. n-C₁₄H₂₉MgCl, THF, -10 °C (40%). l. (PPh₃)₃RuCl₂, benzene, 60 °C, 5 days (95%). m. n-Bu₄NF, THF (94%).

presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give hemiacetal 21 as a single isomer ($J_{1,7a} = 0$ Hz). The side chain was finally introduced by a Grignard reaction with tetradecylmagnesium chloride to give 22 as a single diastereoisomer. Selective oxidation of the primary alcohol in 22 was accomplished with tris(triphenylphosphine)-ruthenium (II) chloride⁹ which led to the desired bis- γ -lactone 23. The stereochemistry of the alkyl chain in 23 was

delineated by NÓE difference experiments. 10 Irradiation of H1 caused enhancement only at the α -CH₂ of the alkyl chain (4.2%) and at the H7_{endo} proton (3.8%). When the α -CH₂ was irradiated, a similar effect was seen for

H1, as well as a small effect on H7a (3 %). Moreover,

irradiation at H7a caused moderate enhancements at H3a (7.8%) and H7_{exo} (5.7%), but only a small enhancement at H1 (3.3%). The observed NOE between the *trans* H1/H7a system is not unusual since the distance between these two protons was shown to be 3.01 Å in the AM1 minimized structure. Irradiation of any of H3a, H7a, or H7_{exo}, caused the complementary enhancements of their partner protons on the *exo* (convex) face of the tricyclic skeleton. As expected, H1 was not affected by perturbations at H3a and H7_{exo}. Final removal of the silyl group in **23** gave the target compound **9**.11

The stereochemistry at the carbon bearing the $n-C_{14}H_{29}$ alkyl chain in 9 is probably determined at the stage of the Grignard addition of 21, which is controlled by the severe convex-concave nature of the molecule. No amount of the diastereoisomer 8 was detected.

Compound 9 showed less binding affinity for PK-C than all the contiguous bislactones 4-7.

References and Notes

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- 7 The intermediate aldol condensation product could be isolated and it was shown to be the *exo* product.
- 8 This reaction required 5 days for completion.
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- 10 One-dimensional NOE difference spectroscopy was performed on compound 9 in CDCl₃ at 500 MHz on Bruker AMX500 spectrometer using the standard Bruker pulse sequence NOEMUL and using multiple irradiation sites for each multiplet. Relevant parameters are as follows: irradiation time, 5 sec; relaxation delay, 10 sec; temperature, 299 K; number of scans, 8; number of cycles, 16. Percentages were measured as the difference in integral intensity of the enhanced resonance between a control spectrum (with the decoupler set to a blank region ca 200 Hz down-field of the lowest field doublet at C4) and a spectrum where a particular multiplet was irradiated. Errors in measurements are estimated at ±2%.
- 11 Compound 9: white solid, mp 92 °C; $[\alpha]_D^{24} = -30.71^\circ$ (c 0.14, CHCl₃); IR (KBr) 3440 (OH), 1770 (C=O); ¹H NMR (CDCl₃) δ 0.87 (distorted t, 3 H, CH₃), 1.25 and 1.60 (multiplets, 26 H, $(-\text{CH}_2)_{13}$ –), 2.17 (dt, J = 14.2, 3.3 Hz, 1H, H-7_{endo}), 2.37 (dt, J = 14.2, 8.3 Hz, 1 H, H-7_{exo}), 2.82 (m, 1 H, H-7a), 3.10 (m, 2 H, H-3a, H-6a), 3.71 (AB q, J = 10.4 Hz, 2 H), 4.10 (dd, J = 12.9, 6.0 Hz, 1 H, H-1), 4.24 (d, J = 10.3 Hz, 1 H, H-4), 4.62 (d, J = 10.3 Hz, 1-4'); ¹³C NMR (CDCl₃) δ 14.12, 22.68, 25.04, 29.29, 29.35, 29.41, 29.48, 29.69, 31.91, 33.12, 36.21, 48.00, 48.68, 51.50, 65.75, 69.82, 85.43, 176.23, 178.41; FAB MS m/z (relative intensity) 409 (MH+, 100). Anal. Calcd for C₂₄H₄₀O₅: C, 70.55; H, 9.87. Found: C, 70.38; H, 9.85.