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

Jeewoo Lee, Joseph J. Barchi, Jr., and Victor E. Marquez*
Laboratory of Medicinal Chemistry, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH, Bethesda, Maryland 20892, U.S.A.

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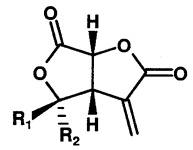
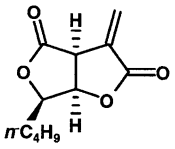
A very efficient method for the construction of a new bis-γ-lactone system constructed on a cyclopenta[1,2-*c*:3,4-*c'*]perhydrodifuran scaffold was developed from cyclopentadiene and methyl (S)-(*Z*)-4,5-*O*-isopropylidene-pent-2-enoate.

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.[1,2] 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.[3,4] The latter compounds can indeed function as DAG surrogates and bind to the DAG target, protein kinase C (PK-C), with micromolar affinities.[3,4] Since in all of 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.



1, R_1 = H, R_2 = C_2H_5



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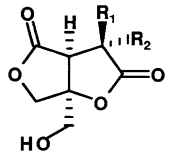
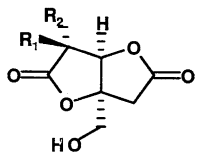
2, R_1 = H, R_2 = *n*-C_8H_{17}

3, R_1 = *n*-C_8H_{17}, R_2 = H



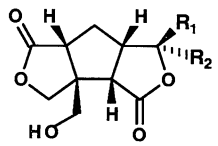
4, R_1 = H, R_2 = *n*-$C_{11}H_{23}$

5, R_1 = *n*-$C_{11}H_{23}$, R_2 = H



6, R_1 = H, R_2 = *n*-$C_{12}H_{25}$

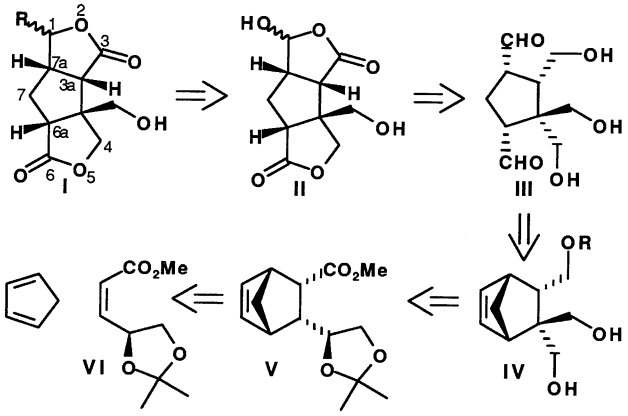
7, R_1 = *n*-$C_{12}H_{25}$, R_2 = H



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

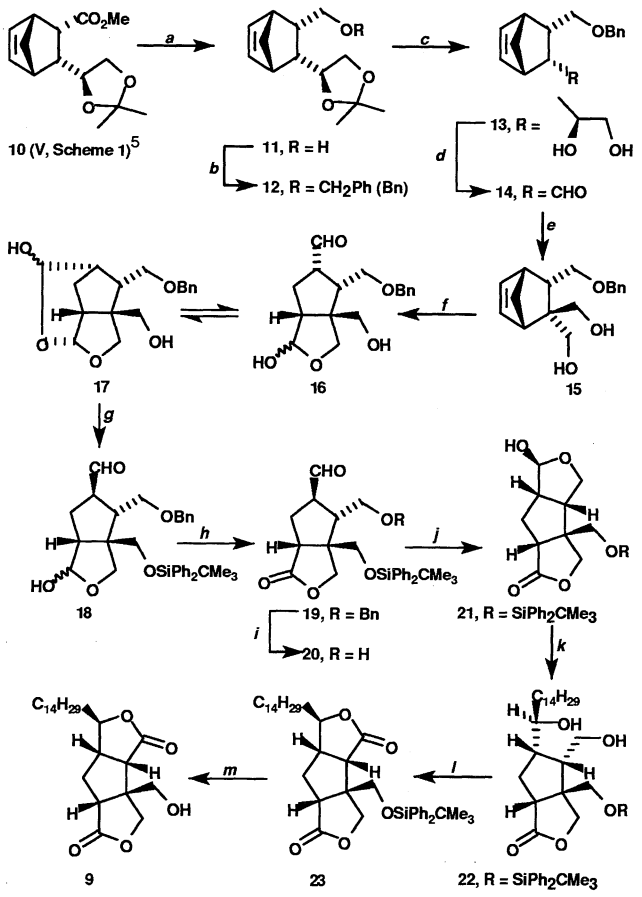
9, R_1 = *n*-$C_{14}H_{29}$, R_2 = H

Scheme 1.



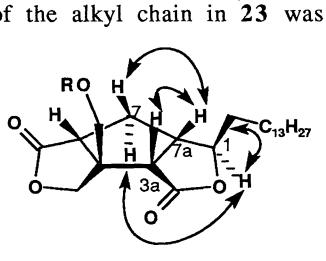
The retrosynthetic analysis of templates **I**/**II** via the polyfunctional cyclopentane **III** is outlined in Scheme 1. This intermediate was envisioned to originate from the chiral norbornene **IV** which, in turn, was expected to come from the Diels-Alder adduct **V** derived from cyclopentadiene 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 aldehyde-bearing carbon which was subsequently re-epimerized in the

Scheme 2.



Reagents: ***a.*** $LiAlH_4$, Ether, –10 °C. ***b.*** $PhCH_2Br$, NaH, *n*-Bu_4NI, THF (92% from **1**). ***c.*** 1N HCl, THF. ***d.*** $NaIO_4$, Ether-H_2O (93% from **3**). ***e.*** HCHO, NaOH, THF, 48 h (98%). ***f.*** OsO_4, 4-Methylmorpholine *N*-oxide (NMO), $NaIO_4$, acetone-H_2O. ***g.*** Me_3CSiPh_2Cl, Et_3N, DMAP, CH_2Cl_2, 5 days (62% from **6**). ***h.*** Tetrapropylammonium perruthenate, NMO, CH_2Cl_2 (92%). ***i.*** H_2, Pd/C, AcOH-MeOH (96%). ***j.*** DBU, CH_2Cl_2, 24 h (100%). ***k.*** *n*-$C_{14}H_{29}MgCl$, THF, –10 °C (40%). ***l.*** $(PPh_3)_3RuCl_2$, benzene, 60 °C, 5 days (95%). ***m.*** *n*-Bu_4NF, 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) chloride[9] which led to the desired bis-γ-lactone **23**. The stereochemistry of the alkyl chain in **23** was delineated by NOE difference experiments.[10] Irradiation of H1 caused enhancement only at the α-CH_2 of the alkyl chain (4.2%) and at the $H7_{endo}$ proton (3.8%). When the α-CH_2 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

1 S. D. Burke, G. J. Pacofsky and A. D. Piscopio, *J. Org. Chem.* **57**, 2228 (1992) and references therein.
2 T. Honda, Y. Kobayashi and M. Tsubuki, *Tetrahedron Lett.*, **31**, 4891 (1990) and references therein.
3 J. Lee, K. Teng and V. E. Marquez, *Tetrahedron Lett.*, **33**, 1539 (1992).
4 J. Lee, V. E. Marquez, A. Bahador, M. G. Kazanietz and P. M. Blumberg, *Tetrahedron Lett.*,**34**, 4317 (1993).
5 a) J. Mulzer, M. Kappert, G. Huttner and I. Jibril, *Tetrahedron Lett.*, **26**, 1631 (1985); b) R. Casas, T. Parella, V. Branchadell, A. Oliva, R. M. Ortuño and G. Guingant, *Tetrahedron*, **48**, 2659 (1992).
6 a) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, **20**, 399 (1979); b) R. Casas and R. M. Ortuño, *Tetrahedron Asymm.*, **3**, 1205 (1992).
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.
9 H. Tomioka, K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **22**, 1605 (1981).
10 One-dimensional NOE difference spectroscopy was performed on compound **9** in $CDCl_3$ 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° (c 0.14, $CHCl_3$); IR (KBr) 3440 (OH), 1770 (C=O); ^1H NMR ($CDCl_3$) δ 0.87 (distorted t, 3 H, CH_3), 1.25 and 1.60 (multiplets, 26 H, $(-CH_2)_{13}-$), 2.17 (dt, *J* = 14.2, 3.3 Hz, 1H, $H\text{-}7_{endo}$), 2.37 (dt, *J* = 14.2, 8.3 Hz, 1 H, $H\text{-}7_{exo}$), 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, H-4´); ^{13}C NMR ($CDCl_3$) 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 $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.38; H, 9.85.