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The synthesis of substituted (4*S*)-4-(hydroxymethyl)imidazolidin-2-ones as novel protein kinase C modulators

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Abstract

The total synthesis of substituted (4*S*)-4-(hydroxymethyl)imidazolidin-2-ones from D-serine methyl ester is described. The key step in the synthesis is a reductive amination reaction which is brought about using titanium(IV) isopropoxide and sodium cyanoborohydride, followed by the cyclization to urea using triphosgene after deprotection.

Protein kinase C (PKC) is a ubiquitous diacylglycerol (DAG) activated signal transducing enzyme system that plays important roles in cell growth, differentiation, apoptosis, ion channel modulation, neurotransmitter release, neuronal plasticity, and tumor promotion.[1] Compounds that selectively modulate certain PKC isozymes cannot only serve as important tools in the elucidation of their physiological roles, but also hold promise in the development of novel therapeutics for the treatment of human diseases, such as cancer and Alzheimer's dementia.[2] However, few isozyme-selective activators have been reported, although several isozyme-selective inhibitors have been developed in the past few years.[3] Various natural products like the teleocidins, as well as analogs of indolactam V (ILV) bearing a hydrocarbon appendage at the 7-position of the indole ring have been shown to function as DAG mimics, and to activate PKC at low concentrations.[4] The synthesis and structure–activity relationships of ILV and its analogs still continue to fascinate both synthetic and medicinal chemists (Fig. 1).[5]

With the aid of molecular modeling based on the X-ray crystal structure of the CRD2 domain of PKCδ in complex with phorbol 13-acetate,[6] our group has reported the design, synthesis, and biological activities of certain pyrrolidone derivatives **1** as a class of novel PKC modulators.[7] In further pursuit of these five-membered ring analogs as PKC activators, we focussed on the isopropyl group in template **1**. From our molecular modeling studies (Fig. 2),[8] we found that

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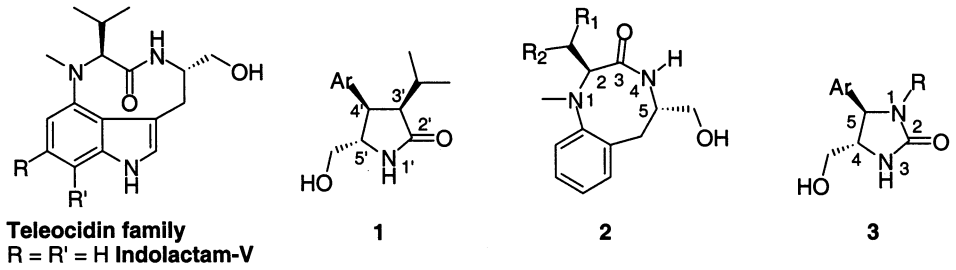


Figure 1.

there is still some space existing between the isopropyl group of compound **1** and the PKC residue Leu254. When C-3′ in these pyrrolidone analogs is replaced by a nitrogen atom, an improved interaction between the isopropyl group of the 'flattened' imidazolidinone **3** and Leu254 is observed, suggesting that a possibly improved PKC binding affinity might result. The hydrogen bonding network and hydrophobic interactions between the aromatic ring and Pro241 remain intact for these new analogs. A further distinct advantage of the urea analogs derives from the removal of one chiral center, which simplifies their chemical synthesis. Moreover, these analogs provide us with the opportunity to maximize interaction with the cell membrane in two ways, this being that an appropriate hydrocarbon appendage can be introduced at either a site on the aromatic ring (as was done for **1**) or at N-1. A recent publication has shown that 2-alkylated benzolactams **2** with a C8–C14 hydrocarbon appendage achieve a PKC binding affinity comparable to that of phorbol 12,13-dibutyrate (PDBu).[9] Thus, in analogy to this work, we postulated that the introduction of suitable hydrocarbon residues to the N-1 might offer a means of further improving upon PKC affinity, as well as providing means for achieving isozyme selectivity. Herein, we disclose chemical routes to these (4*S*)-4-(hydroxymethyl)imidazolidin-2-ones **3**.

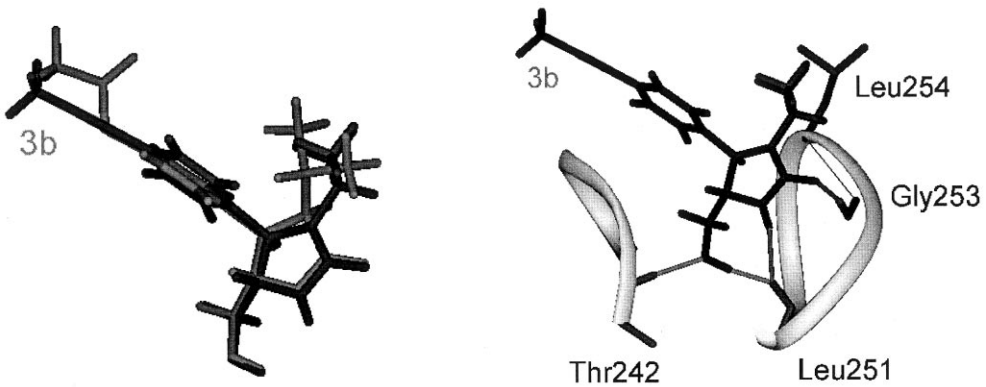
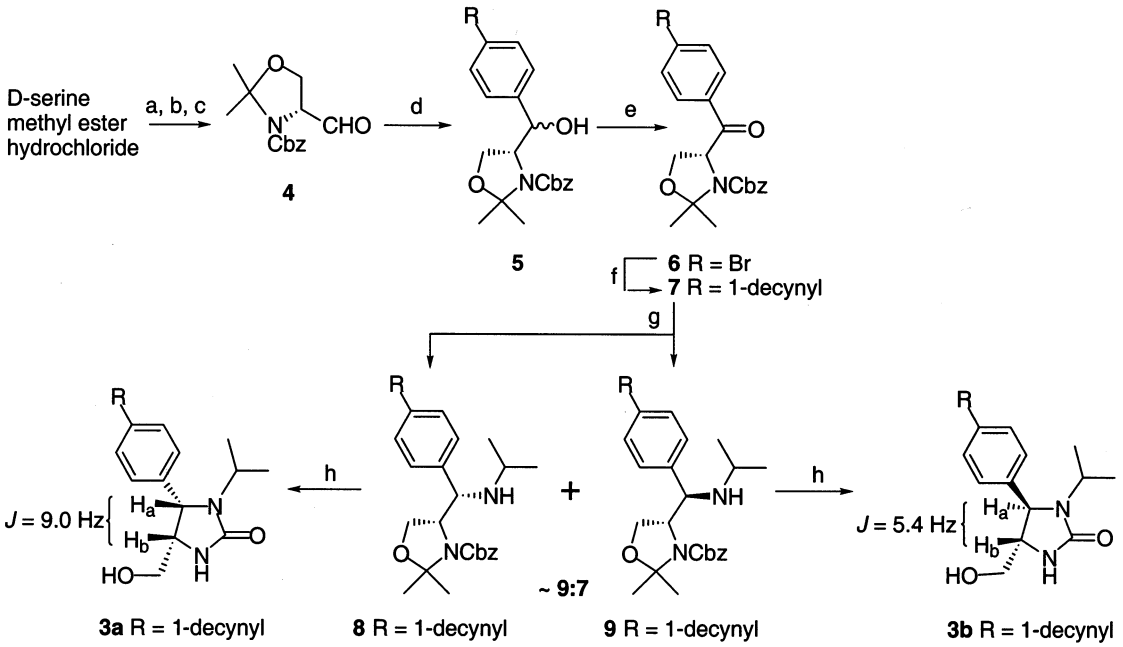


Figure 2. Molecular modeling studies for **3b**. Left: overlay of compounds **1** and **3b**. Right: the overall features of the binding model for compound **3b** in complex with PKCδ CRD2

Using similar procedures as reported earlier,[10,11] the Cbz-protected aldehyde **4** was obtained starting from D-serine methyl ester (Scheme 1). Treatment of the amino aldehyde **4** with *p*-bromophenylmagnesium bromide at −78°C gave the alcohol **5** as a mixture of diastereoisomers. Perruthenate-catalyzed oxidation of the resulting secondary alcohol furnished the ketone **6**.[12] The side chain on the phenyl ring was introduced by coupling the bromide with 1-decyne

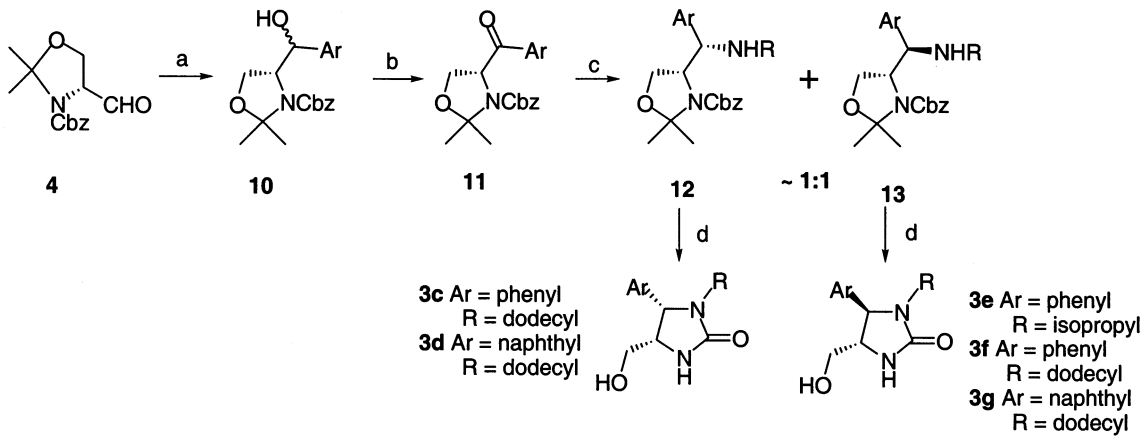
under the catalysis of $PdCl_2(PPh_3)_2$ and CuI. The resulting ketone **7** was then converted into an imine with isopropylamine in the presence of titanium(IV) isopropoxide as catalyst,[13] and the derived imine was converted to amine by reduction with sodium cyanoborohydride. The corresponding amines **8** and **9** were obtained in a ratio of 9:7. These two isomers can be separated by careful flash column chromatography. After deprotection by transketalization with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at reflux, the resulting products were treated directly with triphosgene in 1,4-dioxane/water in the presence of Na_2CO_3 to yield the desired compounds **3a** and **3b** in 28% and 35% yield, respectively.[14]



Scheme 1. *Reagents and conditions*: (a) Et_3N, CbzCl, $CHCl_3$, rt, 24 h, 97%; (b) PPTS, 2,2-dimethoxypropane, toluene, 70°C, overnight, then reflux, 92%; (c) DIBAL-H, dry toluene, −78°C, 2 h, 87%; (d) *p*-BrPhMgBr, THF, −78°C, 82%; (e) NMO, 4 Å MS, TPAP, CH_2Cl_2/CH_3CN, rt, overnight, 85%; (f) $PdCl_2(PPh_3)_2$, CuI, 1-decyne, Et_3N/DMF, 80°C, 6 h, 70%; (g) (i) isopropylamine, $Ti(O\text{-}iPr)_4$, rt, 6 h; (ii) $NaCNBH_3$, EtOH, rt, 16 h, **8**: 48%, **9**: 37%; (h) (i) $BF_3{\cdot}Et_2O$, 1,2-ethanedithiol, dry CH_2Cl_2, reflux, 6 h; (ii) triphosgene, dioxane/H_2O, Na_2CO_3, rt, 1 h, **3a**: 28%, **3b**: 35%

The absolute configuration of the stereocenters present in **3a** and **3b** were assigned based upon an analysis of their ^1H NMR spectra and in accordance with their derivation from D-serine. In the proton NMR spectrum of **3a**, the resonance corresponding to the benzylic proton H_a was observed as a doublet with a coupling constant of 9.0 Hz, indicating a *cis* relationship to H_b. Similarly, the ^1H NMR signal corresponding to the benzylic proton of **3b** was observed as a doublet with a coupling constant of 5.4 Hz, indicating a *trans* substitution pattern.

In the same manner as described above, aldehyde **4** was treated with either phenylmagnesium bromide or naphthylmagnesium bromide to provide the corresponding alcohol **10** (Scheme 2), which was converted to ketone **11** by a perruthenate-catalyzed oxidation reaction. The ketone **11** was reacted in turn with isopropylamine or dodecylamine in the presence of titanium(IV) isopropoxide, followed by the reduction with sodium cyanoborohydride to give a mixture of the amines **12** and **13** in a ratio of about 1:1. Finally, the protecting group of each of the amines **12** and **13** was removed by a hydrogenation reaction in the presence of 20% $Pd(OH)_2/C$ as catalyst,



Scheme 2. *Reagents and conditions*: (a) ArMgBr, THF, −78°C; (b) NMO, 4 Å MS, TPAP, CH_2Cl_2/CH_3CN, rt, overnight; (c) (i) RNH_2, Ti(O-*i*-Pr)$_4$, rt, 6 h; (ii) $NaCNBH_3$, EtOH, rt, 16 h; (d) (i) H_2, 20% $Pd(OH)_2/C$, MeOH, 1 atm, rt, 30 min; (ii) triphosgene, dioxane/H_2O, $NaHCO_3$, rt, 1 h

followed by treatment with triphosgene and $NaHCO_3$ to give the desired cyclic ureas **3c**–**3g**[15] in a yield of 25–40% from **12** and **13**, respectively.

In summary, the present article outlines an efficient means for constructing the urea analogs of our previously disclosed pyrrolidone-based PKC activators. As some of these pyrrolidones have been shown to possess useful biological activity in blocking tumor growth in vivo, these ureas will also be of interest to study for their PKC activity. The urea analogs are particularly valuable from the standpoint of their greater ease of synthesis, which derives from the deletion of one chiral center. A comprehensive report on the biological activity of these ureas will be published in due course.

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14. Compound **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, $J=7.8$ Hz, 2H), 7.26 (d, $J=7.8$ Hz, 2H), 4.79 (d, $J=9.0$ Hz, 1H), 4.75 (br s, 1H), 4.00 (m, 1H), 3.87 (m, 1H), 3.19 (m, 2H), 2.41 (t, $J=7.2$ Hz, 2H), 1.59 (m, 2H), 1.45 (m, 2H), 1.30 (br s, 8H), 1.25 (d, $J=6.6$ Hz, 3H), 0.90 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 14.09, 19.37, 20.33, 20.82, 22.63, 28.67, 28.91, 29.09, 29.17, 31.81, 45.35, 56.40, 59.97, 63.27, 79.96, 91.36, 124.20, 127.56, 131.61, 136.64, 162.48. Compound **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, $J=8.1$ Hz, 2H), 2.28 (d, $J=8.1$ Hz, 2H), 5.61 (s, 1H), 4.43 (d, $J=5.4$ Hz, 1H), 3.89 (m, 1H), 3.67 (m, 1H), 3.53 (m, 3H), 2.40 (t, $J=7.2$ Hz, 2H), 1.60 (m, 2H), 1.44 (m, 2H), 1.29 (br s, 8H), 1.17 (d, $J=6.9$ Hz, 3H), 0.86 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 14.10, 19.39, 19.65, 21.29, 22.65, 28.69, 28.92, 29.10, 29.18, 31.83, 45.35, 60.08, 61.02, 63.45, 80.00, 91.21, 124.12, 126.91, 131.99, 141.31, 162.01.
15. Compound **3c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 3H), 7.22 (dd, $J=2.1$, 7.8 Hz, 2H), 5.44 (s, 1H), 4.83 (d, $J=9.0$ Hz, 1H), 4.02 (m, 1H), 3.53 (m, 1H), 3.16 (m, 2H), 2.64 (m, 2H), 1.39 (t, $J=6.9$ Hz, 2H), 1.21 (m, 20H), 0.88 (t, $J=6.9$ Hz, 3H). Compound **3d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (m, 3H), 7.51 (m, 4H), 5.74 (d, $J=9.3$ Hz, 1H), 5.25 (s, 1H), 4.23 (dt, $J=4.2$ Hz(d), 9.3 Hz(t), 1H), 3.66 (m, 1H), 3.12 (m, 1H), 2.92 (m, 1H), 2.75 (m, 1H), 1.78 (br s, 1H), 1.43 (m, 2H), 1.20 (m, 20H), 0.87 (t, $J=6.9$ Hz, 3H). Compound **3e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 5H), 5.58 (s, 1H), 4.46 (d, $J=5.7$ Hz, 1H), 3.90 (m, 1H), 3.69 (m, 1H), 3.56 (m, 3H), 1.20 (d, $J=6.6$ Hz, 3H), 0.86 (d, $J=6.9$ Hz, 3H). Compound **3f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H), 5.06 (s, 1H), 4.46 (d, $J=6.0$ Hz, 1H), 3.72 (m, 1H), 3.59 (m, 2H), 3.41 (m, 1H), 2.65 (m, 2H), 1.36 (m, 2H), 1.22 (m, 20H), 0.88 (t, $J=6.9$ Hz, 3H). Compound **3g**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (m, 3H), 7.54 (m, 4H), 5.54 (d, $J=5.1$ Hz, 1H), 4.70 (s, 1H), 3.50–3.90 (m, 5H), 2.73 (m, 1H), 1.42 (m, 2H), 1.90 (m, 20H), 0.87 (t, $J=6.9$ Hz, 3H).