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SYNTHESIS OF THE BENZOFURAN ANALOGUE OF ILV, A NEW PROTEIN KINASE C (PKC) ACTIVATOR

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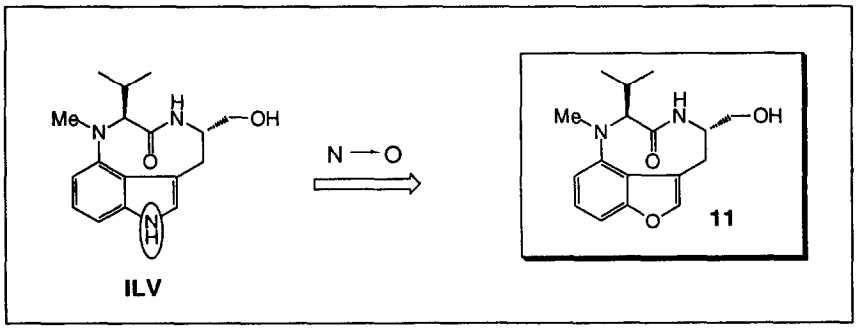
Abstract: In order to probe the effect of small structural changes on the PKC activity of the natural product indolactam V (ILV), a synthesis of its benzofuran analogue was developed. This compound was found to be similar in its activity to ILV, exhibiting a K_i of 17.3 ± 3.7 nM in the displacement of [^{3}H]PDBU from PKCα.

Protein kinase C (PKC), a growing family of enzymes comprised of at least ten isoforms, is a ubiquitous signal transducing enzyme that plays a crucial role in a host of cellular processes including growth and differentiation.[1] The discovery of isoform-selective activators and inhibitors (modulators) of PKC undoubtedly has the potential to define more clearly the respective functional roles of each of these isoforms in intact cells.[2] As part of a continuing effort directed to the exploration of the structure-activity relationships (SAR) of the teleocidin family, indole alkaloids possessing potent PKC activating properties,[3] we became interested in the synthesis of compound **11**, the benzofuran analogue of indolactam V (ILV), in order to explore the effect of this subtle structural change on PKC activity.



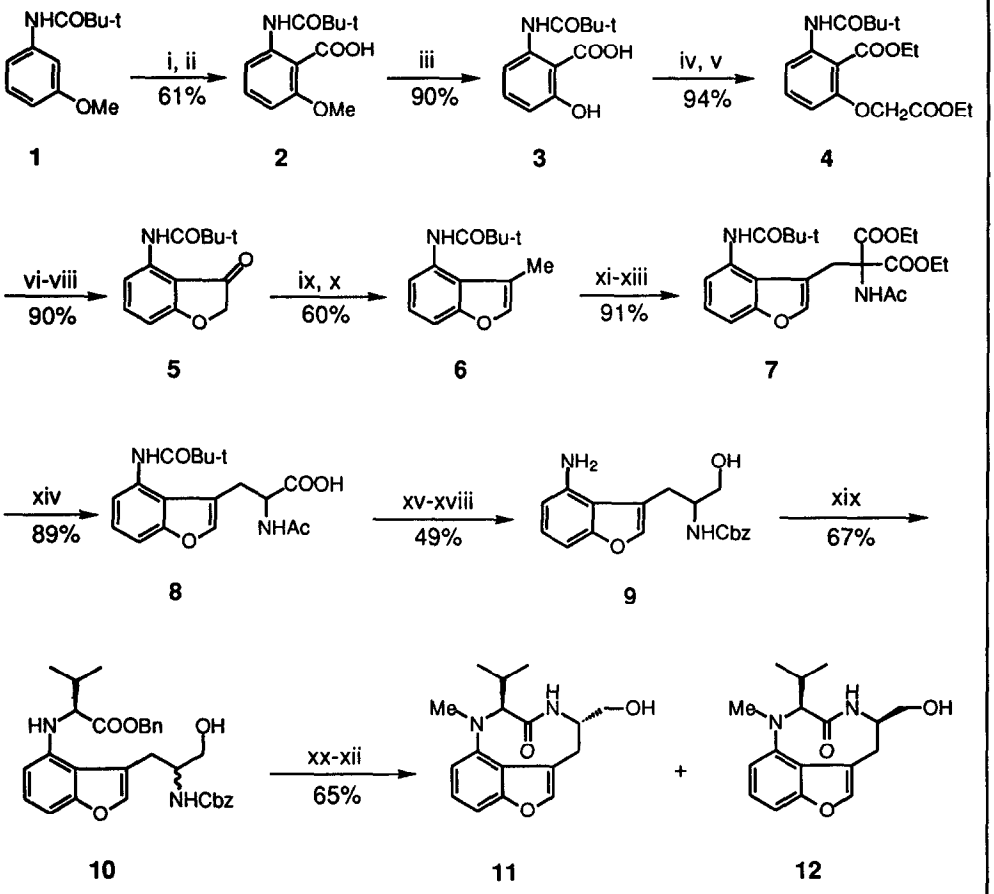
Because of the differences in the chemistry of indoles versus benzofurans we were unable to make use of the synthetic methods that had already been worked out for the preparation of ILV and its congeners. Methods of elaboration involving the use of gramine chemistry,[4] electrophilic

reactions at the C-3 position of the heterocycle,[3a-b, 5] or naturally occurring starting materials such as tryptophan were thus inappropriate.[6] Accordingly, the development of different protocols was required to construct a benzofuran nucleus bearing suitable substitution at the C-3 and C-4 positions for elaboration to the oxygen analogue.

Starting from *N*-pivaloyl-3-methoxyaniline (**1**), this compound was transformed into the acid **2** through a directed *ortho*-metalation reaction.[7] The pivaloyl protecting group was chosen since it was required to survive both strongly acidic and basic conditions that would be encountered later in the synthesis. The methyl group of **2** was removed by using lithium *n*-propylmercaptide in DMF to furnish **3**.[8] Lower yields were obtained when TMSI was employed as the cleavage reagent. Next, the carboxyl group of **3** was converted to its ethyl ester, and the hydroxyl group was coupled with ethyl bromoacetate in ethanol through its sodium salt to produce **4**. This intermediate was subjected to the Dieckmann condensation followed by decarboxylation to afford ketone **5**. To introduce a bromomethyl group at the C-3 position of the heterocycle in order to allow for further elaboration of this appendage, ketone **5** was first reacted with methylmagnesium iodide, and then the resulting tertiary alcohol was dehydrated under acidic conditions to provide the 3,4-disubstituted benzofuran **6** in 60% yield. In this step 30% of the ketone **5** was recovered due apparently to enolate formation. For the same reason MeLi proved to be ineffective for this transformation. The treatment of **6** with NBS in benzene at reflux gave a complex mixture of products in which bromination at the methyl group and the aromatic ring had taken place. The use of three equivalents of NBS was required to achieve complete bromination of the methyl group. The crude products were then coupled directly with sodium diethyl acetamidomalonate, and the resulting mixture was exposed to hydrogen in the presence of Pd/C and triethylamine to effect removal of the ring bromines with formation of diester **7**. Ester saponification with decarboxylation gave **8**. Since further hydrolysis of **8** to remove the nitrogen protecting groups was complicated by lactam ring formation, the carboxylic acid group was first reduced to alcohol **9**. Acidic hydrolysis now proceeded uneventfully to afford a diamine which was converted selectively to intermediate **9** by CbzCl treatment. At this stage the method of Kogan[6b] could be used to complete the synthesis. Thus, the reaction of **9** with benzyl (*R*)-2-[(trifluoromethanesulfonyl)oxy]-3-methylbutanoate[6b] led to **10**, which was deprotected by Pd/C catalyzed hydrogenation and then treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), HOBt, and *N*-methylmorpholine in DMF to afford a mixture of two lactams. The lactam mixture was *N*-methylated and separated to provide **11**[9] ($[\alpha]_D^{22}$ = -183°, *c* 0.53, chloroform) in 33% yield, together with its cis-isomer **12** ($[\alpha]_D^{22}$ = -136°, *c* 0.12, chloroform) in 32% yield.

Compound **11** was evaluated for its ability to inhibit [^{3}H]PDBu binding to purified PKCα employing the same experimental protocol described elsewhere.[10] We found that **11** exhibited nearly identical potency to ILV (K_i = 17.30 ± 3.70 nM compared with 10.96 ± 1.32 nM for ILV), thus clearly demonstrating that an indole NH group is not essential for activity. In view of the present result, the effect of this and related structural changes on isoform selectivity would thus appear to be worthy of exploration.[11]

Scheme I. Synthesis of the Benzofuran Analogue of ILV



Reagents and conditions: i) 2.5 eq *n*-BuLi, THF, 0 °C, 2.5 h; ii) CO_2, 0 °C to rt, 8h; iii) *n*-PrSLi, DMF, 70 °C; iv) $SOCl_2$, EtOH; v) NaOEt, then $BrCH_2COOEt$; vi) NaH, benzene, reflux; vii) 2N NaOH, MeOH, reflux; viii) H_3O^+; ix) CH_3MgI; x) H_3O^+, THF-Et_2O, reflux; xi) NBS, benzene, reflux; xii) $Na[AcHNC(COOEt)_2]$, EtOH; xiii) Pd/C, H_2, Et_3N, EtOAc; xiv) 2N NaOH, MeOH, reflux, then H_3O^+; xv) $SOCl_2$, EtOH; xvi) $NaBH_4$; xvii) 12N HCl/EtOH (1:2), reflux; xviii) 1 eq ClCOOBn, -20 °C to 0 °C; xix) (*R*)-benzyl 2-[(trifluoromethanesulfonyl)oxy]-3-methylbutanoate, 2,6-lutidine, 1,2-dichloroethane, reflux; xx) Pd/C, H_2; xxi) BOP, NMM, HOBt, DMF; xxii) $CH_2O/NaCNBH_3$.

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(9) Compound **11:** IR (KBr) 3378, 2981, 1667, 1568, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) shows the presence of two conformers in the ratio of 1:5.8, δ (major conformer only) 7.33 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.06 (br s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 4.23 (d, J = 8.1 Hz, 1H), 4.20 (m, 1H), 3.75 and 3.56 (d of ABq, A part, J = 3.9, 11.4 Hz, 1H, B part, J = 8.4, 11.4 Hz, 1H), 3.01 (m, 2H), 2.90 (s, 3H), 2.59 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 Hz) δ (major conformer only) 174.0, 158.2, 148.3, 140.4, 125.3, 118.6, 117.7, 109.0, 104.2, 71.6, 64.8, 54.9, 36.0, 32.9, 31.2, 28.4, 21.5, 19.5; HRMS calcd for $C_{17}H_{23}N_2O_3$ ($M + H^+$) 303.171, found 303.170.
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