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Protein Kinase C Modulators. Indolactams. 1. Efficient and Flexible Routes for the Preparation of (–)-Indolactam V for Use in the Synthesis of Analogs.

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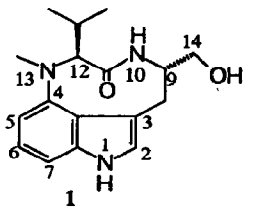
Abstract: Three syntheses of the protein kinase C activator, (–)-indolactam V, are described and are compared for their potential utility in the preparation of ILV analogs. In one route the 4-amino functionality is introduced regiospecifically during the construction of the indole portion and enantiomeric control is achieved by the alkylation of the amine with a triflate derived from D-valine. One of the routes affords racemic ILV from which (–)-ILV is obtained by the first reported resolution of an indolactam.

Protein kinase C (PKC) plays a crucial role in signal transduction for a variety of biologically active substances which modulate cellular functions and proliferation.[1,2] The number and complexity of the cellular responses in which PKC has been implicated are considerable and continues to grow. PKC comprises a ubiquitous family of enzymes with the eleven known isotypes thought to provide divergent paths for signal transduction.[2] The discovery of isotype-selective modulators (activators or inhibitors) of PKC is an important goal of pharmacological research.[3] Such modulators would undoubtedly be valuable tools for the characterization of the functions of these PKC isotypes and would serve as leads for the development of novel pharmaceuticals.

In general, the PKCs require phospholipid and variable, additional cofactors for their full activation. The group A isotypes, α, β_I, β_{II} and γ, are activated by μM Ca^{2+} and by 1,2-*sn*-diacylglycerols (DAG) which bind specifically to the enzyme.[2] The group B PKCs, δ, ε, η and θ, are insensitive to Ca^{2+} but are activated by DAG. The least well understood are the group C isotypes, ζ and $\iota(\lambda)$, which are insensitive to both Ca^{2+} and DAG, and PKCμ, which does not appear to fit well in any of the above groups.[4]

Compounds other than DAG have been demonstrated to activate group A and group B PKCs by binding at the DAG regulatory site. Among these are a structurally diverse group of compounds, including diterpenes (phorbol diesters), indolactams (teleocidin), polyacetate-derived aplysiatoxins and macrocyclic lactones (bryostatin), known collectively as "phorboids". It is among these phorboids that the search for PKC-specific, isotype-selective modulators has shown the most promise.[3]



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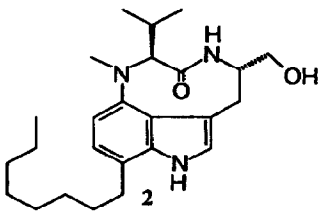

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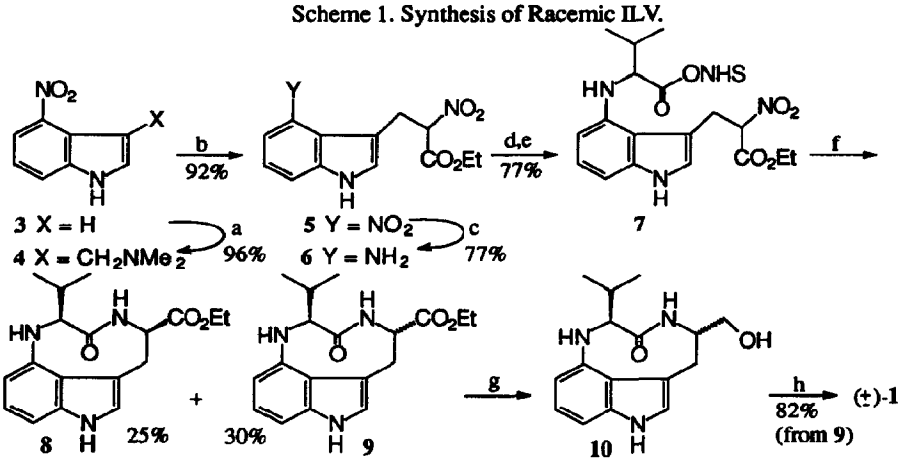
(–)-Indolactam V (ILV) (1) is the structural core common to the teleocidin family of phorboids and has been the target of a variety of synthetic studies.[5] Many derivatives, homologs and analogs of ILV have been prepared.[3a,6] However, since only in the cases of ILV and (–)-7-octylindolactam V (2) has the effect on specific PKC isotypes been reported,[3b] little is known about isotype selectivity in the indolactam series and,

indeed, much of the existing structure activity relationship (SAR) information needs to be interpreted with great caution.[7] In order to rationally explore the isotype-selective SAR of the indolactams, a synthesis of ILV was required which would efficiently provide material for further derivatization and would also be flexible enough to allow other homologs, derivatives and stereoisomers to be readily prepared. Three such synthetic schemes have been in routine use in this laboratory.

Three of the major synthetic problems which must be addressed in relation to ILV are: the regiospecific introduction of the amino group at the 4-position of the indole; the control of the stereochemistry at C-12 in the valine portion; and, the introduction of the three-carbon fragment at the 3-position with control of the stereochemistry at C-9. These problems have been solved in many ways and with varying degrees of success.[5] The synthetic schemes we have used provide solutions to those problems amalgamated with the flexibility necessary for analog preparation.

The route shown in Scheme 1 produced racemic ILV with the control of the amine regiochemistry being achieved by use of the readily available 4-nitroindole (**3**).[8] The regioselective introduction of the three-carbon fragment was achieved by nucleophilic addition of ethyl nitroacetate to 4-nitrogramine (**4**)[9] affording **5** and taking advantage of the relatively electron-deficient nitroindole. Selective reduction of the aromatic nitro group by catalytic hydrogenation afforded **6** on a 100 g scale.

Scheme 1. Synthesis of Racemic ILV.



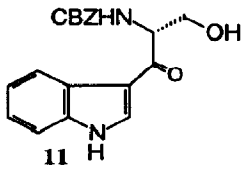
a) CH_2NMe_2Cl, HOAc; b) $O_2NCH_2CO_2Et$, ClC_6H_5; c) H_2, Pd-C, EtOH; d) $(CH_3)_2CHC(O)CO_2H$, $NaBH_3CN$, DMF; e) N-hydroxysuccinimide, DCC, CH_3CN; f) H_2, Raney-nickel, MeOH; g) $LiBH_4$, THF; h) CH_2O, $NaBH_3CN$, CH_3CN.

From **5** the route paralleled that developed independently by Masuda *et al.*[5c] with some differences in reagents, conditions and exact sequence. The valine fragment was introduced without direct stereochemical control by reductive alkylation of **6**.[5a] The single-step reduction of the aliphatic nitro group of **7** and lactamization to form **8** and **9** was difficult to optimize but hydrogenation with a large ratio of Raney-nickel catalyst to substrate was found to provide the best yields. The proper relative stereochemistry at C-9 and C-12 was established by epimerization of **8** to **9**. Several solvents and bases were studied in an effort to maximize the rate of the epimerization while minimizing the decomposition to an unknown polar side product. The rates of epimerization in absolute ethanol at room temperature for various carbonates were: $Li_2CO_3 << K_2CO_3 < Cs_2CO_3$. The best yields, 60% **9** and 35% **8** were obtained with treatment with a large excess of K_2CO_3 in ethanol for 3 hr.

The reductive methylation of **10** avoided the harsher conditions (methyl iodide/methanol/$NaHCO_3$/ reflux/60 h) used in other syntheses[5a] but appears to be unique to formaldehyde since attempts to prepare analogs by the use of other aldehydes were unsuccessful. This milder method could also used on **8** and **9** without the epimerization noted with methylation in the presence of base.[5c]

The first resolution of racemic ILV (or any of the indolactams) to be reported was achieved here by conversion to the diastereomeric (R)-1-(1'-naphthyl)ethylcarbamates [(R)-1-(1'-naphthyl)ethylisocyanate/ dibutyltin dilaurate/DMAP], chromatographic separation and reduction ($SiHCl_3/Et_3N$) of the carbamates to afford **1** and (+)-indolactam V in >99.8% optical purity. The structure and stereochemistry of the carbamate of **1** was established by chromatographic comparison with the (R)-1-(1'-naphthyl)ethylcarbamate of authentic (–)-ILV. The "side product" of this synthetic route, (+)-indolactam V, has potential utility in pharmacological assays as a negative control for **1**. The overall yield of **1** was 9% in 11 steps including resolution.

The second route we have utilized was originally developed by Kogan *et al.*[5d] The regio- and stereochemistry of the three-carbon fragment was established by the use of L-tryptophan methyl ester as a starting material in the preparation of **11**. The presence of the carbonyl in **11** was necessary to control the regiochemistry of the introduction of the amine function. In these laboratories, the yield in the sequence **11** to **12** (thallation, azide displacement and hydride reduction)[5d] has been difficult to control and in ten attempts ranged from 0-60% (normally 35-45%).



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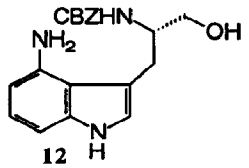

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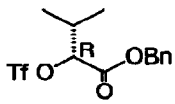

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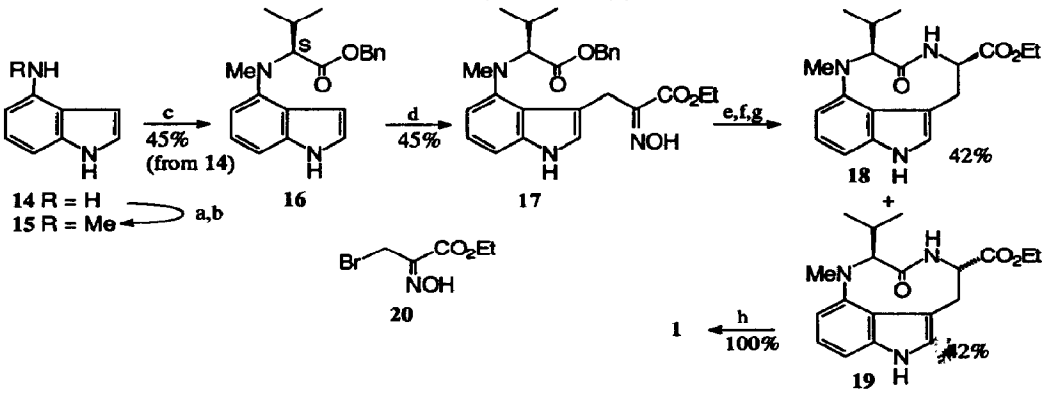
The valine stereochemistry was established from D-valine via triflate **13**. Inversion of the stereocenter during alkylation of the amine **12** established the natural S configuration at C-12. The practical overall yield of **1** was 7-12% in 11 steps. The expected stereospecificity (>99.8%) was confirmed by chromatographic comparison of the (R)-1-(1'-naphthyl)ethylcarbamate to that obtained via Scheme 1. This route is highly stereospecific but has limited flexibility in indole substitution and with regard to stereochemistry.

The third route is presented in Scheme 2. As in Scheme 1 the amine was introduced by the use of a readily available starting material, 4-aminoindole (**14**).[10] The Kogan triflate, **13**, was used to introduce the valine fragment stereoselectively and to establish the correct absolute stereochemistry. In this case, with an electron rich indole, the three-carbon fragment was introduced by means of the electrophilic Gilchrist reagent, **20**.[12] Since this step was more efficient (fewer side-products) when the amine was tertiary, the methyl was introduced at an early stage via formylation/reduction to afford **15**.[13] Other alkyl groups may be introduced at N-13 in a similar fashion. Reduction of the oxime group of **17** followed by lactam formation in the manner of

Scheme 2. Synthesis of (–)-ILV.



a) AcOCHO, THF; b) BH_3-Me_2S, THF, 60°C; c) **13**, 2,6-lutidine, $ClCH_2CH_2Cl$, 95°C; d) **20**, Na_2CO_3, CH_2Cl_2; e) Al(Hg), wet THF; f) H_2, Pd-C, (+)-camphorsulfonic acid; g) HOBT, BOP, N-methylmorpholine, dimethylacetamide; h) $LiBH_4$, THF.

Kogan *et al.*[5d] afforded equal amounts of **18** and **19** which were identified by chromatographic comparison with the racemic forms prepared from **8** and **9** respectively.

As in Scheme 1 the relative stereochemistry at C-12 and C-9 was controlled by epimerization of **18** to **19** which, with the N-methyl present, required more vigorous conditions ($CsCO_3$/THF/65°C; 50% **19** and 48% **18**). That this epimerization does not affect C-12 was demonstrated by a determination of the optical purity to be >99.8% via HPLC analysis of the (S)-1-(1'-naphthyl)ethylcarbamate. The overall yield of **1** was 13% for 9 steps. This route allows the greatest flexibility in the choice of indole substitution, N-13 substitution and stereochemistry and provides the highest yield with the fewest steps.

The combination of these three synthetic routes has allowed the preparation of many analogs of ILV.[14] The synthesis and the PKC isotype selectivity of these analogs will be reported separately.

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