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Synthesis of 7-Substituted Benzolactam-V8s and Their Selectivity for Protein Kinase C Isozymes

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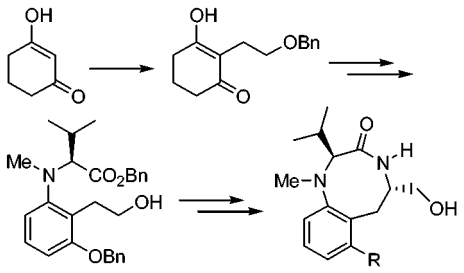
ABSTRACT



Condensation of L-valine benzyl ester toluenesulfonic acid salt with a substituted cyclohexadione followed by aromatization with the assistance of NBS provides an *N*-aryl L-valine benzyl ester. This intermediate is converted into 7-substituted benzolactam-V8s using an asymmetric Strecker reaction as the key step. The target molecules show a different pattern of isozyme selectivity relative to the 8-substituted benzolactam-V8s.

Protein kinase C (PKC), comprised of at least eleven isozymes, plays an important role in signal transduction pathways, mediating signals that orginate from the induction of lipid hydrolysis.[1] These isozymes exhibit a distinct pattern of tissue-specific expression and play diverse roles in both physiological and pathophysiological processes.[1,2] To clarify the biological roles of the individual isozymes, isozyme-specific modulators of PKC are required.[1,2] In the past two decades, both academic and industrial research has been directed to the discovery of PKC modulators possessing such selectivity. To date, several isozyme-selective inhibitors of PKC have been discovered.[3] However, few isozyme-selective activators have been reported.[4] During studies aimed at elucidating the structure−activity relationships (SARs) of the teleocidins, a group of natural products that are potent but relatively nonselective PKC activators, the simplified analogue benzolactam-V8 **1a**[5,6] was found to be a potent PKC activator.[6b] In previous studies we have demonstrated that compound **2a**, a benzolactam-V8 analogue with an acetylene

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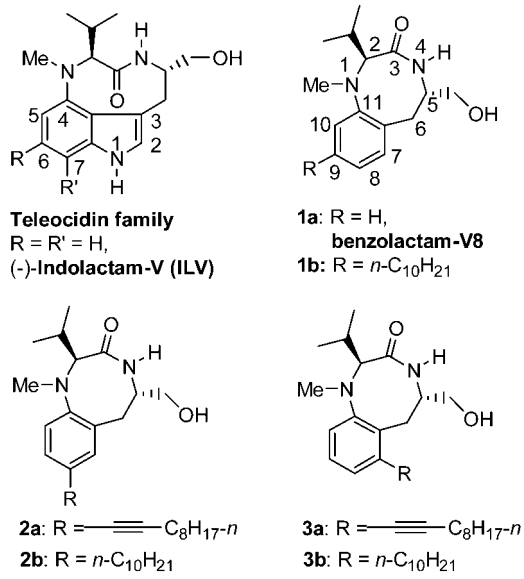
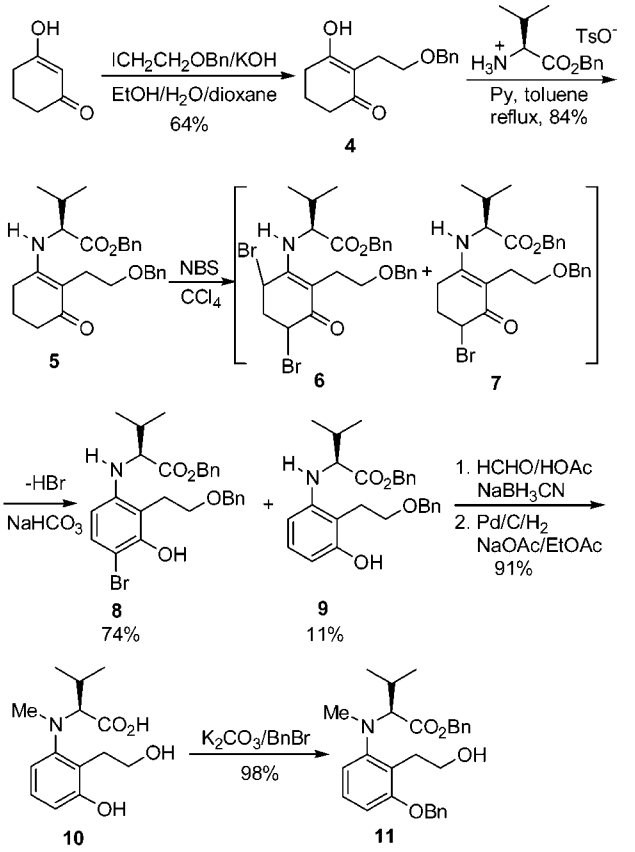


Figure 1. Structures of the teleocidin family and substituted benzolactam-V8s.

side chain at the 8-position, shows some selectivity for classical isozymes, while its analogue **2b** with a saturated side chain is less potent.[7] On the basis of this finding and results from molecular modeling, we believed that it would be valuable to examine the isozyme selectivity of the 7-substituted benzolactam-V8s **3**. Herein we report a novel method for the synthesis of these compounds together with their PKC binding profile. As outlined in Scheme 1, our synthesis started with construction of the *N*-aryl L-valine moiety using an unprecedented condensation/oxidative aromatization strategy. Accordingly, alkylation of 1,3-cyclohexanedione with ICH_2CH_2OBn mediated by KOH in a mixture of ethanol, water, and dioxane provided **4** in 64% yield. These reaction conditions were found to be essential for minimizing the generation of products of *O*-alkylation. The diketone **4** was condensed with L-valine benzyl ester toluenesulfonic acid salt under the action of pyridine in refluxing toluene to afford enamine **5**.[10] Aromatization of **5** was required next in order to generate the *N*-aryl L-valine ester intermediates. After a number of failed attempts that included MnO_2 oxidation and dehydrogenation by Pd/C, we soon found that bromination of **5** with 2 equiv of NBS was effective. This bromination reaction may involve the formation of compounds **6** and **7** as intermediates, which undergo elimination of HBr assisted by $NaHCO_3$ to produce aryl bromide **8** in 74% yield together with a small amount of **9**. When only 1 equiv of NBS was used, this reaction gave **9** as the major product, but the overall yield was lower. Next, the mixture of **8** and **9** was subjected to a reductive amination reaction with $HCHO/NaBH_3CN$ to introduce a *N*-methyl group. Removal of the extraneous bromine atom by Pd/C-catalyzed hydrogenolysis yielded the *N*-aryl amino acid **10** in 91% yield. The overall yield from **4** to **10** was 65%. Next, the hydroxyl and carboxyl group of **10** were protected by treatment with BnBr under the action of potassium carbonate to provide **11**. Chiral HPLC analysis of **11** indicated that its enantiomeric purity was ~98%, which implies that little if any racemization had occurred during the condensation or aromatization steps. The present chemistry thus provides an efficient method for gaining access to optically pure *N*-aryl α-amino acids from optically pure α-amino acids, compounds which represent the core structures of a number of biologically important molecules.[11]

Scheme 1



Next, Dess−Martin oxidation of **11** produced the aldehyde **12**, which was subjected to an asymmetric Strecker reaction with (*R*)-phenylglycinol and trimethylsilyl cyanide in methanol to deliver a separable mixture of diastereomers **13** and

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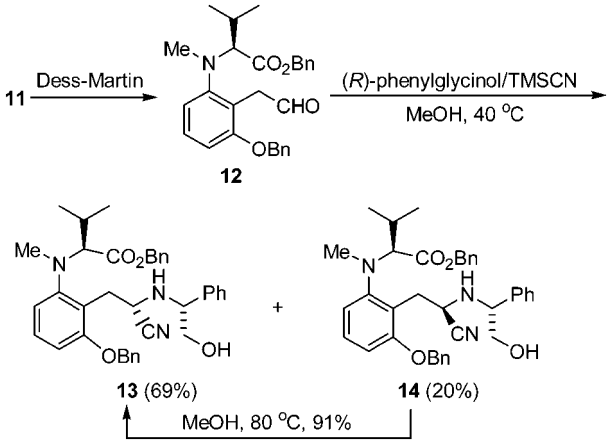
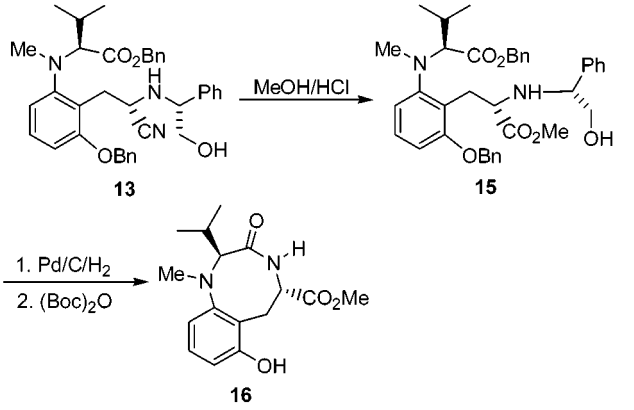
14 (Scheme 2).[12] The undesired isomer **14** was converted to thermodynamically stable **13** by heating it in methanol at 80 °C.

Scheme 2



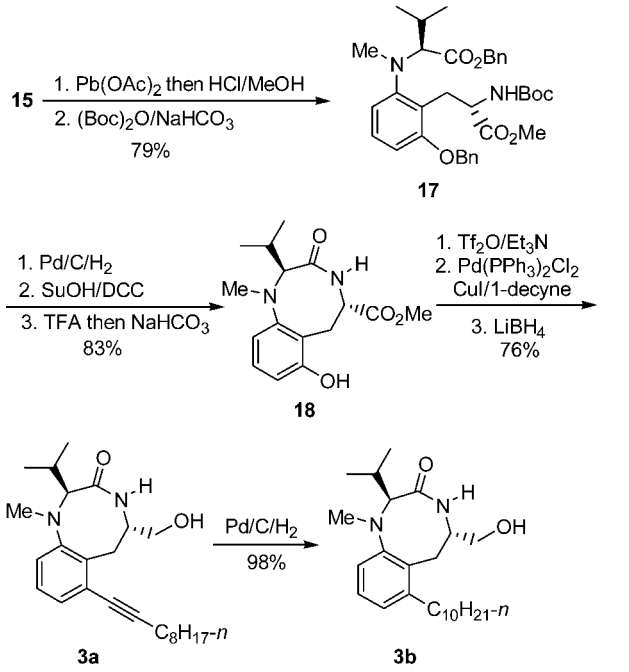
Treatment of **13** with HCl-saturated methanol provided the ester **15**, which was hydrogenated to bring about removal of the benzyl protecting groups to give the corresponding amino acid. Occasionally, we found that the resulting amino acid was cyclized to give the desired lactam **16** under the action of di-*tert*-butyl dicarbonate.[13] However, the lactamization yield (47%) was not so satisfactory (Scheme 3).

Scheme 3



To improve the overall yield of the lactam, an alternative route was explored (Scheme 4). The chiral auxiliary of **13** was subjected to oxidative cleavage,[12a] and the resulting free amine was protected with di-*tert*-butyl dicarbonate to produce **17**. After Pd/C-catalyzed hydrogenation to remove the benzyl

Scheme 4



protecting groups, the acid was transformed to the lactam **18** using the activated ester method.[8,14] Although this route required more steps, the overall yield (65%) from **15** to the lactam was higher.

The target molecule **3a** was obtained from **18** in 76% yield by the following steps: (1) treatment of **18** with trifluoromethylsulfonic anhydride to give the triflate; (2) Pd/CuI-catalyzed coupling of the triflate with 1-decyne;[8,15] and (3) reduction of the ester to the alcohol with lithium borohydride. Finally, hydrogenation of **3a** provided **3b** in 98% yield.

Compounds **3a** and **3b** have been evaluated for their ability to displace phorbol 12,13-dibutyrate (PDBU) binding from recombinant PKCα, PKCβ, PKCγ, PKCδ, and PKCϵ.[7] The K_i values for **3a** and **3b** are summarized in Table 1. For

Table 1. K_i Values for the Inhibition of [^{3}H]PDBu Binding by PKC Activators (nM)

compd	3a	3b	2a[a]	2b[a]
PKCα	4533	513	14.7	46.6
PKCβ	1691	309	17.4	58.2
PKCγ	>10 000	409	40.7	140
PKCδ	2098	169	122	185
PKCϵ	2562	60	142	187

[a] Data taken from ref 7.

comparison, The K_i values of the 8-substituted benzolactam-V8s **2a** and **2b** are also provided. As is apparent, the

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7-substituted benzolactam-V8s display a different isozyme selectivity pattern in comparison to the 8-substituted benzolactam-V8s. Compound **3b** possessing a saturated side chain is more potent than its acetylene-bearing counterpart **3a**, and it shows an 8-fold selectivity for PKCϵ over PKCα. On the other hand, in the 8-substituted series, **2a** with an acetylenic side chain is about 10-fold more selective for PKCα than PKCϵ. A detailed explanation for these subtle differences using computer modeling, as well as the design of more selective compounds based upon this information, is in progress.

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Supporting Information Available: Experimental procedures and characterizations for compounds **4**−**18**, **3a**, and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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