Synthesis of 7-methoxybenzolactam-V8 using a diastereoselective Strecker synthesis

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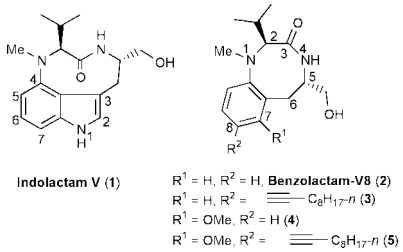
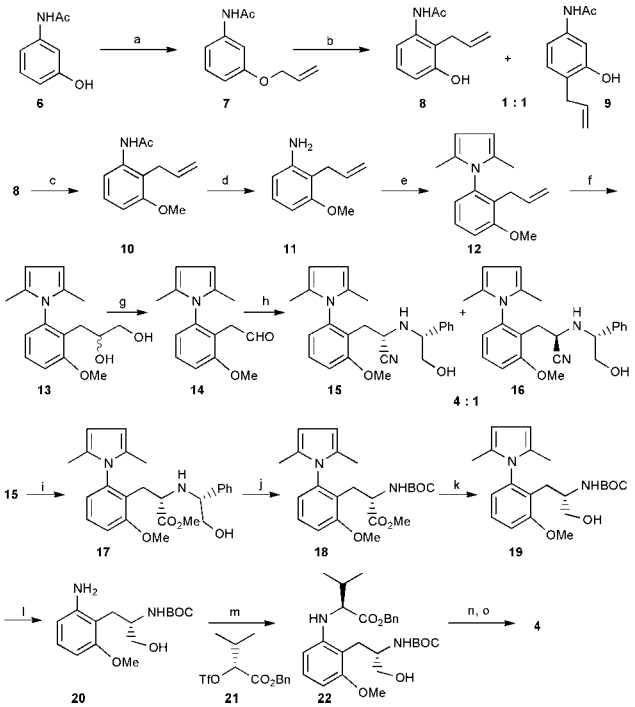
7-Methoxybenzolactam-V8 (4) was synthesized using a diastereoselective Strecker reaction as the key step employing an *ortho*-substituted phenylacetaldehyde and (*R*)-phenylglycinol as the chiral auxiliary.

Protein kinase C (PKC) consists of a growing family of closely related isozymes that mediate a wide range of cellular signal transduction processes.[1] Compounds that are able to selectively modulate the individual PKC isozymes can serve as valuable research tools in the elucidation of their physiological roles. Additionally, such compounds hold promise in the development of novel therapeutics for the treatment of human diseases, such as cancer and Alzheimer's dementia. However, very few isozyme-selective activators have been reported to date. The teleocidins (*e.g.* indolactam V, **1**) are potent PKC activators,



however, they show little selectivity.[2] Endo's group and ours have reported[3] that the benzolactam-V8 derivative **3**, a mimic of the twist-like conformation of indolactam V, is a potent activator of PKC. Recently, our group has shown that introduction of a methoxy substituent at the C7-position of benzolactam-V8 leads to a compound (**5**) that retains potency at PKCα, PKCδ and PKCε.[4] The total synthesis of benzolactam-V8 analogs depends mainly on the effective construction of the 8-membered lactam ring, which in turn depends on an efficient synthesis of a suitably substituted phenylalanine moiety. An improved synthesis of 7-methoxybenzolactam-V8 (**4**) would permit access to further analogs by making use of the heteroatom at the 7-position. We have recently developed the first synthesis of 7-methoxybenzolactam-V8,[4] which makes use of a catalytic asymmetric alkylation. The poor selectivity in this step induced us to explore an alternative approach. In the present communication, we describe a diastereoselective Strecker reaction for the synthesis of the required substituted phenylalanine which after a series of further reactions leads to the title compound **4**.

Our synthetic sequence began with the introduction of an allyl group in the ortho position to the hydroxy group using the Claisen rearrangement. Thus, 3-hydroxyacetanilide (**6**) was transformed into its allyl ether **7** using allyl bromide and potassium carbonate in refluxing acetone in 88% yield (Scheme 1). Compound **7** was subjected to the Claisen rearrangement in refluxing dimethylaniline for 6 h to give a mixture of products **8** and **9** in a 1 : 1 ratio.[5] The required regioisomer **8** was isolated by fractional crystallization and protected as its methyl ether in 82% yield. The *N*-acetyl group in compound **10** was unstable to the conditions of a subsequent nitrile methanolysis step, resulting in the formation of an undesired six-membered lactam.[6] We therefore masked the amine as a 2,5-dimethylpyrrole which can be easily cleaved under mild conditions but is stable to the conditions of acidic nitrile methanolysis. Accordingly, compound **10** was deprotected to give aniline **11**, which on treatment with acetonylacetone in toluene utilizing a Dean–Stark trap for azeotropic water removal gave compound **12** in 72% yield.[7] Compound **12** was converted to the aldehyde in a two step sequence. First, compound **12** on treatment with osmium tetroxide in acetone in the presence of NMO at rt gave diol **13** in 74% yield. Compound **13** was oxidized to the aldehyde **14** using sodium metaperiodate in a 1 : 1 mixture of ^{t}BuOH and H_2O at rt in 69% yield. Compound **14** was now subjected to the Strecker synthesis using (*R*)-phenylglycinol.[8] It is important to note that previously Chakraborty *et al.*[8] reported



Scheme 1 *Reagents and conditions*: (a) K_2CO_3, allyl bromide, acetone, reflux, 88%; (b) $PhNMe_2$, reflux, 6 h, 84%; (c) K_2CO_3, MeI, acetone, reflux, 82%; (d) 7% HCl, reflux, 2 h, 81%; (e) acetonylacetone, toluene, reflux, 24 h, 72%; (f) OsO_4, NMO, rt, acetone, 74%; (g) $NaIO_4$, t-BuOH–H_2O, rt, 69%; (h) i, (*R*)-phenylglycinol, $CHCl_3$, ii, Me_3SiCN, 0 °C–rt, 10 h, iii, TBAF, 66% for three steps; (i) HCl in ether, MeOH, 0 °C–rt, 48 h, 81% (j) i, $Pb(OAc)_4$, CH_2Cl_2–MeOH (2 : 1), 15 min; ii, 20% $Pd(OH)_2$/C, EtOH, 50 psi of H_2, overnight; iii, BOC_2O, Et_3N, THF, rt, 44% for three steps; (k) $LiBH_4$, THF, 0 °C–rt, 8 h, 96%; (l) NH_2OH·HCl, Et_3N, *i*-PrOH–H_2O, reflux, 24 h, 81%; (m) 2,6-lutidine, 1,2-dichloroethane, 87%; (n) H_2, Pd/C, EtOH, quantitative; (o) i, *N*-hydroxysuccinimide–DCC, CH_2Cl_2, ii, trifluoroacetic acid, then $NaHCO_3$, EtOAc, 82%; iii, HCHO, $NaCNBH_3$, AcOH, CH_3CN, reflux, 87%.

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that the Strecker reaction of phenylacetaldehyde with (*R*)-phenylglycinol gave a 1 : 1 ratio of isomers. The poor selectivity was attributed to steric factors. Compound **14** on reaction with (*R*)-phenylglycinol in chloroform at rt overnight gave the imine which on reaction with Me_3SiCN at rt for 10 h followed by treatment with tetrabutylammonium fluoride gave the amino nitriles **15** and **16** in a 4 : 1 ratio in 66% yield over the three steps. The amino nitriles **15** and **16** were easily separated by column chromatography. The structure of the isomer **15** was confirmed by X-ray crystallography. This compound was subjected to acidic hydrolysis to afford the ester **17** in 81% yield based on recovered starting material. No cyclization product was formed in the hydrolysis reaction, thus supporting our choice of protecting group. Oxidative removal of the phenylglycinol moiety was carried out with lead tetraacetate in CH_2Cl_2–MeOH to give a Schiff's base, which on catalytic hydrogenation over $Pd(OH)_2$/C gave the free amine. The amine was isolated as the BOC-protected intermediate **18**, and the overall yield for the three steps was 44%.

With the substituted phenylalanine fragment in hand, we now needed to add the valine fragment. Compound **18** was reduced to alcohol **19** using $LiBH_4$ in THF in near quantitative yield. The aromatic amino group was unmasked in good yield by refluxing in a solvent mixture of ^iPrOH–H_2O with hydroxylamine hydrochloride and triethylamine. The aniline **20** was reacted with the D-valine derived triflate **21**[9] to give compound **22** in 87% yield. Compound **22** on hydrogenation gave the carboxylic acid in quantitative yield, which was converted to the eight-membered lactam using the active ester method as reported previously.[3b] *N*-Methylation using HCHO–$NaCNBH_3$–HOAc gave 7-methoxybenzolactam **4** in 87% yield.[10]

In conclusion, we report an improved synthesis of 7-methoxybenzolactam-V8 making use of a diastereoselective Strecker synthesis. This compound may serve as an intermediate in the preparation of a variety of C7-substituted benzolactam analogs, which may exhibit better isozyme selectivity.

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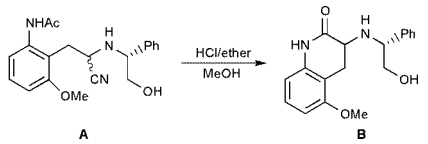
6 Compound **10** after a sequence of reactions as reported in Scheme 1 gave compound **A**, which on acid hydrolysis gave lactam **B**.



A B

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10 Selected data for compound **4**: $[\alpha]_D^{22}$ − 262° (*c* 0.6, $CHCl_3$), lit[4]: $[\alpha]_D^{22}$ − 275° (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, t, *J* = 8.3 Hz), 6.65 (1H, d, *J* = 8.0 Hz), 6.61 (1H, br s), 6.49 (1H, d, *J* = 8.0 Hz), 4.36 (1H, s), 3.80 (3H, s), 3.71 (1H, dd, *J* = 10.9, 4.2 Hz), 3.57 (1H, d, *J* = 8.5 Hz), 3.50 (1H, d, *J* = 9.3 Hz), 3.24 (1H, d, *J* = 17.5 Hz), 2.80 (3H, s), 2.76–2.64 (2H, m), 2.45–2.38 (1H, m), 1.04 (3H, d, *J* = 6.3 Hz), 0.83 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.7, 27.8, 28.2, 34.9, 54.2, 55.6, 66.4, 69.7, 103.4, 112.3, 118.7, 127.3, 157.9, 173.9.