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Stereospecific synthesis of 9-substituted benzolactam-V8 from L-tyrosine via regioselective aromatic nitration

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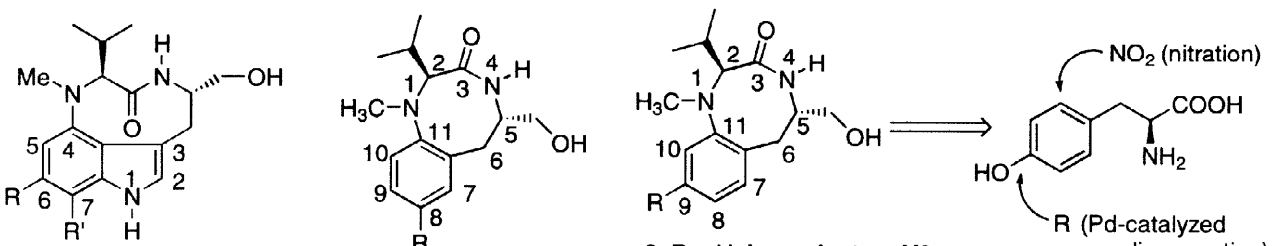
Abstract: A new protocol for the synthesis of 9-substituted benzolactam-V8, a class of potent protein kinase C activators, from L-tyrosine through regioselective aromatic nitration, is described.

Key words: benzolactam-V8; aromatic nitration; protein kinase C.

Teleocidins are a family of natural products possessing strong tumor-promoting activities with a core structure of indolactam V.[1] Since their activation of protein kinase C (PKC) was acknowledged in the late 1970s, total synthesis of the teleocidins and their analogues to determine their active conformation and to discover good isozyme-selective PKC modulators has been an area of interest.[2-4] Kozikowski[3] and Endo[4] first reported benzolactams as indolactam analogues, and Endo found that 9-decyl benzolactam-V8 **5** was a potent PKC activator similar to teleocidins.[4] The side chain at 9-position of **5** was important for activating PKC because benzolactam-V8 **3**, without a side chain, demonstrated poor activity for PKC.[4] As it had been reported that in the phorbol family, different side chains might lead to different isoform-selectivity,[5] we realized that **3** could be a new core structure for pursuing isoform-selective PKC modulators by varying the side chains. In a previous paper,[6] we reported that 8-decynyl benzolactam-V8 **1** exhibited improved isozyme selectivity in activating PKC compared with 8-decyl benzolactam-V8 **2**. The compound **1** also showed isoform-selectivity (for PKCβ) in down-regulating PKC and anti-tumor activity that indolactam V did not have.[6] This progress prompted us to synthesize 9-decynyl benzolactam-V8[7] **4** to contrast the isoform-selectivity differences in regulation of PKCs.

Scheme I



Teleocidin family
R = R' =H, **Indolactam V**

1: R = $-C{\equiv}C-C_8H_{17}$-n
2: R = $C_{10}H_{21}$-n

3: R = H, **benzolactam-V8**
4: R = $-C{\equiv}C-C_8H_{17}$-n
5: R = $C_{10}H_{21}$-n

As shown in Scheme I, we envisaged that L-tyrosine was a good starting material for synthesizing **5**, because the 4'-hydroxy group of L-tyrosine could be used to introduce a decynyl group by a palladium catalyzed coupling reaction.[8] The key problem was how to input a nitro group at the 2'-position of L-tyrosine which would allow us to build the lactam ring

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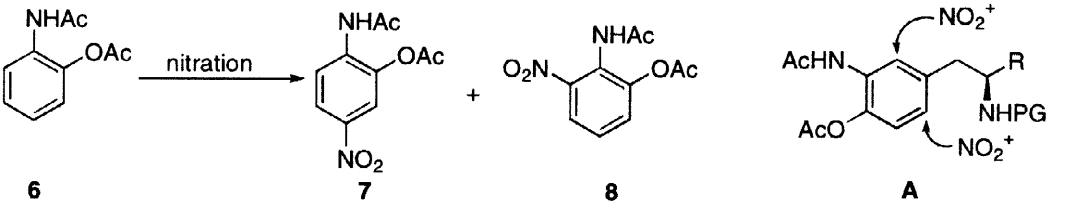
according to our early strategy.[6] It is obvious that direct nitration of L-tyrosine would give the wrong orientation and the electronic distribution on the benzene ring of L-tyrosine must be changed to fit our desired direction. Nitration[9] of **6** producing a mixture of **7** and **8** indicated that we could obtain our desired product by nitration of **A** followed by elimination of the acetamide group on the benzene ring.

Scheme II

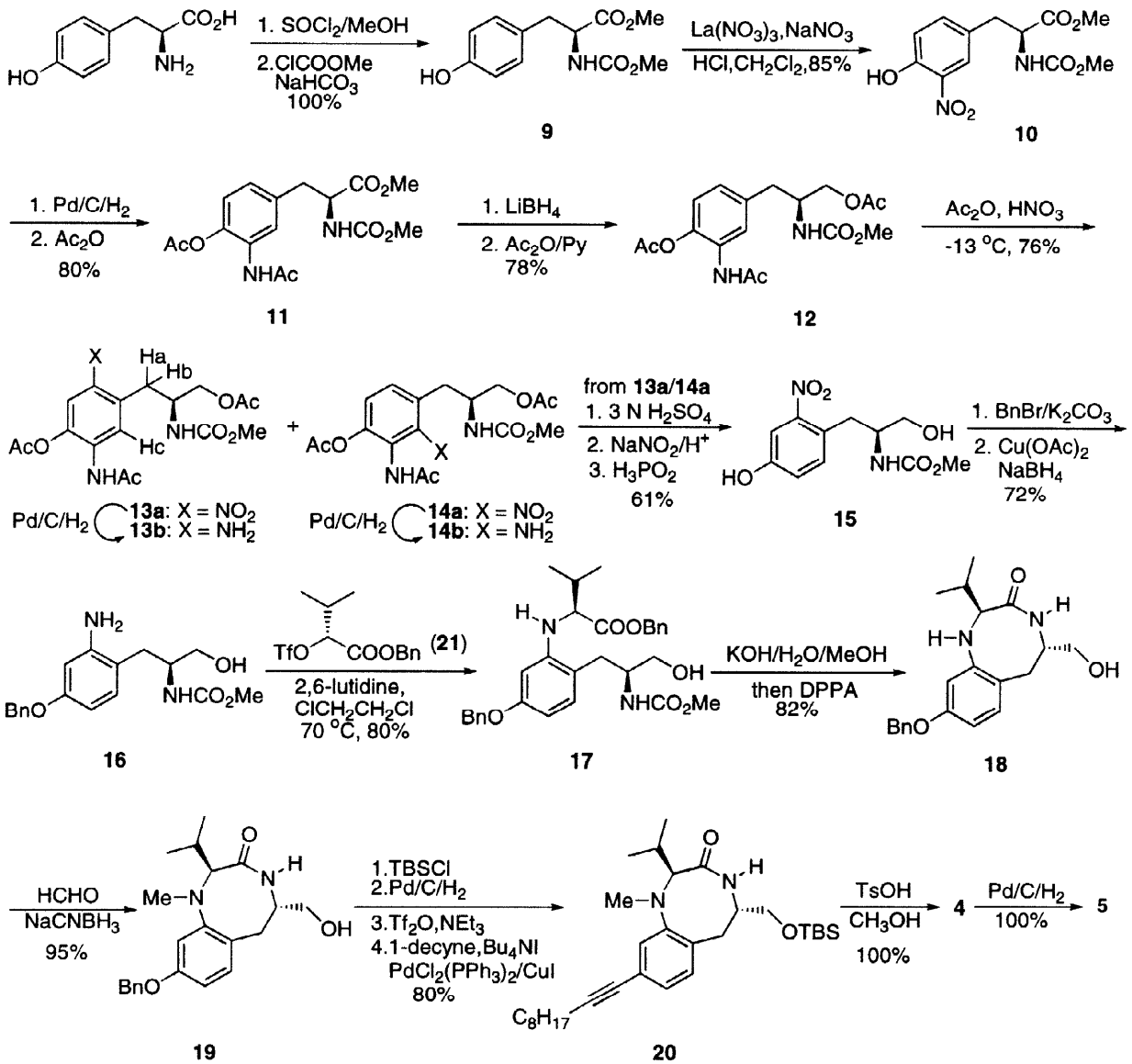


6 **7** **8** **A**

The detailed synthesis is outlined in Scheme III. We prepared **9** quantitatively by esterification of L-tyrosine with thionyl chloride in methanol and protection of the amino group with methyl chloroformate in an aqueous $NaHCO_3$ solution. By using $La(NO_3)_3$ as a phase transfer catalyst, and $NaNO_3$/HCl as the nitration reagent,[10] nitration of **9** was achieved under mild conditions to give **10** in high yield. Reduction of the nitro group of **10** by hydrogenation catalyzed by Pd/C and then protection with an acetyl group afforded **11** in 80% yield. Reduction of the amino ester group of **11** to the corresponding amino alcohol using $LiBH_4$ followed by treatment with Ac_2O produced **12** in 78% overall yield. Initial attempts to nitrate **12** using conc. HNO_3/Ac_2O at 0 °C was found to give a complex mixture of products, while on lowering the reaction temperature to -13 °C we found the formation of two major separable products in a 1/1 ratio with a total yield of 76%. The peaks in the ^1H NMR spectra of **13a** and **14a** are all very broad, which did not enable the determination of the orientation of the nitro group. Fortunately, both reduction products **13b** and **14b** gave clear ^1H NMR spectra to allow us to determine the orientation. The structure of **14b** was confirmed by its ^1H NMR spectrum in which clear doublets at 6.64 and 7.17 were observed, while the structure of **13b** was confirmed by its NOESY spectrum in which the marked NOE between Ha, Hb and Hc was observed. This result was in agreement with our initial proposal. After confirming of the structures of both products, we repeated the nitration of **12** and the mixture was used directly for the next step, without separation. Treatment of the mixture with 3 N H_2SO_4 at 70 °C removed the acetyl groups. The resultant aniline salt was subjected to diazotization and then reduction with H_2PO_2 at 70 °C to afford a single nitro compound **15** in 61% overall yield. Thus, we succeeded in controlling the regioselectivity of aromatic nitration of the L-tyrosine derivative. This methodology may be useful for preparing 2'-substituted tyrosine derivatives which could be valuable for peptidomimetics. Protection of phenol **15** with benzyl bromide and then reduction[11] of the nitro group with $Cu(OAc)_2/NaBH_4$ yielded aniline **16**, which could react with triflate **21** to give **17** according to the known procedure.[6] The next step was the construction of the 8-membered lactam ring. At this time we wanted to develop a new procedure for cyclization because we felt that the previous method[4,6] was not efficient. After some experimentation, we found that DPPA was a suitable coupling reagent for this purpose with much higher yield. Accordingly, **17** was hydrolyzed with 2 N KOH at 70 °C to remove the protecting groups of the amino and carboxylic acid groups, and then neutralized with HCl, concentrated, and dried over P_2O_5. Without any separation, this mixture was directly treated with DPPA and Et_3N in DMF to afford benzolactam **18** in 82% overall yield. It was notable that the previous procedure gave only about 50% overall yield in similar transformations. Finally, we finished our synthesis of **4**[12] by the following conversions: 1) methylation of **18** with HCHO and $NaCNBH_3$ to gave **19**; ii) protection of hydroxy group with TBSCl and imidazole in DMF; iii) removing the benzyl group by hydrogenation followed by transforming the

resultant phenol into its triflate; iv) coupling the triflate with 1-decyne under the catalysis of $PdCl_2(PPh_3)_2$, CuI and Bu_4NI[8]; v) removal of the silyl group by TsOH/MeOH. The overall yield for these transformations was 76%. Further hydrogenation of **4** in EtOAc gave compound **5**, which was identical in all respects with those reported.[4]

Scheme II



In summary, we have found a convenient and stereospecific route to 9-substituted benzolactam-V8 by using L-tyrosine as the chiral pool. The overall yield of **4** from L-tyrosine was 8.8%. Synthesis of other analogues based on this protocol and their biological evaluation as isoform-selective PKC modulators are underway in our group and the results will be reported in due course.

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12. Selected date for **4**: $[\alpha]_D^{19}$ = -140.6 (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 1.3 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.51 (m, 1H), 3.95 (br s, 1H), 3.71 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.53 (dd, *J* = 10.6, 9.1 Hz, 1H), 3.09 (dd, *J* = 17.0 Hz, 7.8 Hz, 1H), 2.79 (s, 3H), 2.74 (m, 1H), 2.51 (m, 1H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.60 (m, 2H), 1.45 (m, 2H), 1.29 (m, 8H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H).