Pergamon

Tetrahedron Letters 42 (2001) 4317–4319

TETRAHEDRON LETTERS

Synthesis of 7-methoxybenzolactam-V8 using aminomercuration as a key reaction

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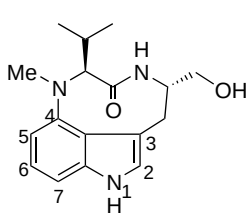
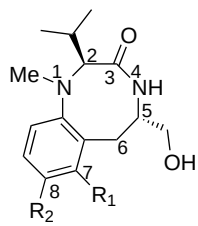
Received 28 March 2001; accepted 30 April 2001

Abstract—7-Methoxybenzolactam-V8 was synthesized using a short synthetic route that employs aminomercuration as a key reaction.

Protein kinase C (PKC) is a ubiquitous signal transducing enzyme system that plays a marked role in diverse cellular processes including regulation of ion channels, neurotransmitter release, growth and differentiation, apoptosis, and neuronal plasticity.[1] This complex enzyme system serves to mediate numerous signals originating from the induction of lipid hydrolysis. The discovery of isozyme-selective activators and inhibitors (modulators) of protein kinase C (PKC) is crucial to both dissecting the role of the individual isozymes in physiological and pathophysiological processes and to manipulating these pathways. It has been our objective to synthesize analogs of the tumor-promoting substance indolactam V (ILV, **1**) or of its structurally simpler mimic benzolactam-V8 (**2**), and to assess the ability of these new compounds to modulate the various isozymes of PKC as well as to examine the effects of such agents on cellular growth and differentiation.[2] Toward this goal we have recently shown that introduction of a methoxy substituent at the C7-position of 8-(1-decynyl)benzolactam-V8 leads to compound **5**, which retains potency at PKCα, PKCδ and PKCε.[3] We have recently reported the synthesis of compounds **4** and **5** using two different synthetic routes.[3,4] The first synthetic route (14 steps, 4.2% overall yield)[3] employs the alkylation of a Schiff's base derived from *tert*-butyl glycinate under phase transfer conditions. This method suffers from poor selectivity. The second approach[4] uses a diastereoselective Strecker reaction to generate the phenylalanine fragment and is a lengthy route with 22 steps and 2.1% overall yield. The total synthesis of benzolactam-V8 analogs depends mainly on the effective construction of the eight-membered lactam ring. The 1-decynyl group at the C8-position, which is important for biological activity, can be introduced easily in the final stage as reported previously.[3] Our continued quest to find a simple synthetic route for the preparation of 7-Methoxybenzolactam (**4**) lead to the present synthetic approach.



Indolactam V (**1**)



R_1 = H, R_2 = H, **Benzolactam-V8** (**2**)
R_1 = H, R_2 = ≡—C_8H_{17}-*n* (**3**)
R_1 = OMe, R_2 = H (**4**)
R_1 = OMe, R_2 = ≡—C_8H_{17}-*n* (**5**)

The sequence began with the introduction of an allyl group in an *ortho* position to the hydroxy group using the Claisen rearrangement (Scheme 1). Thus, 3-nitrophenol (**6**) was transformed into its allyl ether **7** using allyl bromide and potassium carbonate in refluxing acetone in 98% yield. Compound **7** was subjected to Claisen rearrangement in *ortho*-dichlorobenzene at 150°C for 6 h to give a mixture of products **8** and **9** in a 1:1 ratio in 38% yield, which were separated by column chromatography. Several attempts to improve the yield under different reaction conditions[5] were not successful. Higher temperature and longer reaction times gave only polymerized products. Nevertheless, the starting materials are readily accessible, and satisfactory

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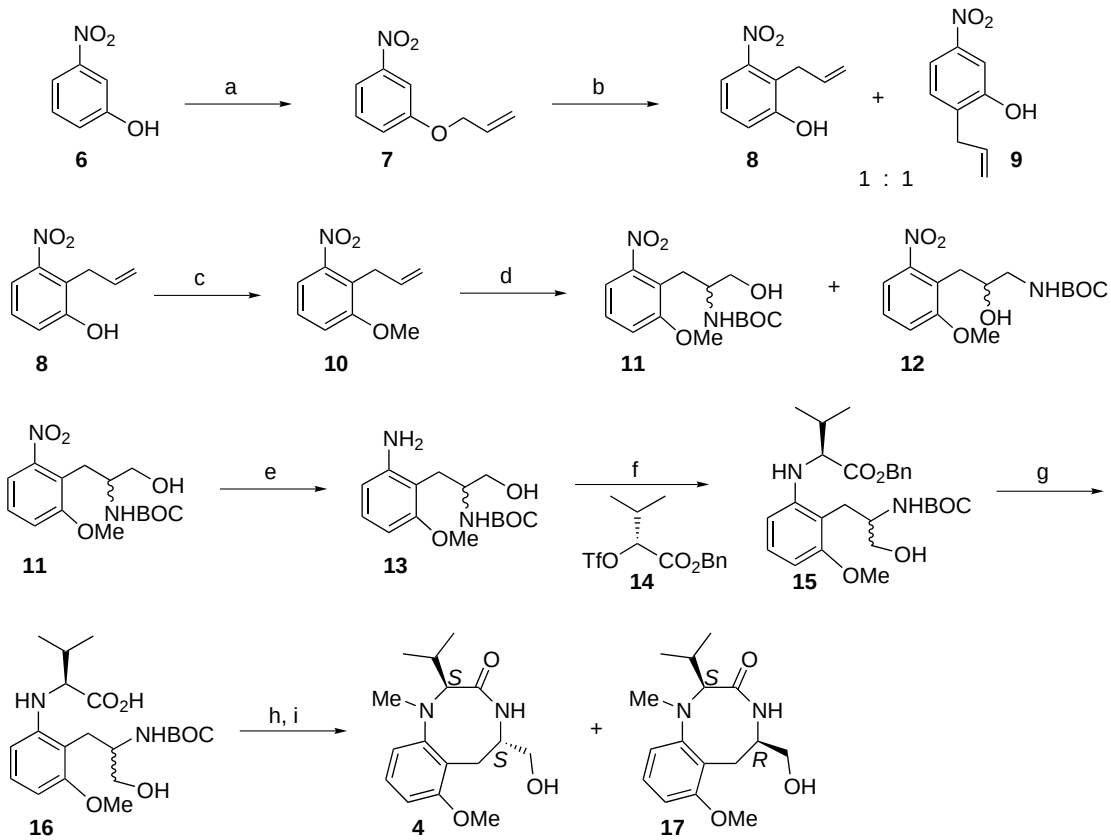
PII: S0040-4039(01)00747-X



Scheme 1. *Reagents and conditions*: (a) allyl bromide, K_2CO_3, acetone, reflux, 98%; (b) *o*-dichlorobenzene, 150°C, 6 h, 38%; (c) MeI, K_2CO_3, acetone, 87%; (d) i. $Hg(NO_3)_2$, $BocNH_2$, CH_2Cl_2, reflux, 24 h, ii. aq. NaCl, rt, 3 h, (iii) $NaBH_4$, O_2, DMF, 43% for three steps; (e) H_2, Pd/C, EtOH, overnight, 85%; (f) 2,6-lutidine, 1,2-dichloroethane, 74%; (g) H_2, Pd/C, EtOH, quantitative; (h) i. *N*-hydroxysuccinimide/DCC, CH_2Cl_2, ii. trifluoroacetic acid, then $NaHCO_3$, EtOAc, 68% for two steps; (i) HCHO, $NaCNBH_3$, AcOH, CH_3CN, reflux, 86%.

quantities of the intermediate **8** were obtained without difficulty. Compound **8** was protected as its methyl ether **10** in 87% yield.

The addition of different carboxamides and related compounds such as urethane to olefins using mercury(II) nitrate is well documented in the literature. This sequence provides a general method for the Markovnikov functionalization of alkenes. Compound **10** on treatment with $Hg(NO_3)_2$ and *tert*-butylcarbamate in refluxing dichloromethane for 24 h gave the organomercuric nitrate, which on treatment with aqueous sodium chloride provided the organomercuric chloride.[6,7] This intermediate on reaction with sodium borohydride in dimethylformamide saturated with molecular oxygen gave alcohols **11** and **12** in a 4:1 ratio in 43% yield over the three steps.[8] Steric factors may be the reason for formation of the anti-Markovnikov product **12**. The amino alcohols **11** and **12** were easily separated by column chromatography. Compound **11** on catalytic hydrogenation gave the aniline **13** in 85% yield. Aniline **13** was reacted with the D-valine derived triflate[9] **14** to give compound **15** in 74% yield as a mixture of two diastereoisomers. Compound **15** on hydrogenation gave the carboxylic acid **16** in quantitative yield, which was subsequently converted to the eight-membered lactam using the active ester method as reported previously.[2a] The two isomers were easily separated at this stage and were individually subjected to reductive *N*-methylation using HCHO–$NaCNBH_3$–HOAc to give compounds **4** and **17** in good yield.[10] The stereochemistry of **4** and **17** was confirmed by comparing their optical rotations and NMR spectra with those of (2*S*,5*S*)- and (2*S*,5*R*)-7-methoxybenzolactam-V8.[3,4]

In conclusion, an improved synthesis of 7-methoxybenzolactam-V8 which makes use of an aminomercuration reaction has been reported. This synthesis, which is relatively short with 13 steps, gives an improved overall yield (5.1%), and can be used to prepare a variety of C7-substituted analogs.

Acknowledgements

The author is grateful to Professor Alan P. Kozikowski for his guidance and encouragement. Financial support from the National Institutes of Health (CA 79601) is highly appreciated.

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10. Compound **4**: $[\alpha]_D^{22}$ −276 (*c* 0.9, $CHCl_3$), lit:[3] $[\alpha]_D^{22}$ −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. Compound **17**: $[\alpha]_D^{22}$ −154 (*c* 0.45, $CHCl_3$), lit:[3] $[\alpha]_D^{22}$ −159 (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, s), 7.12 (1H, t, $J=8.1$ Hz), 6.77 (1H, d, $J=8.0$ Hz), 6.57 (1H, d, $J=8.0$ Hz), 3.88–3.74 (4H, m), 3.69–3.62 (1H, m), 3.34 (1H, d, $J=15.1$ Hz), 3.15 (2H, d, $J=11.8$ Hz), 2.93 (3H, s), 2.52 (1H, dd, $J=14.9$, 6.3 Hz), 2.46–2.34 (1H, m), 0.93 (3H, d, $J=6.3$ Hz), 0.86 (3H, d, $J=6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 20.3, 27.3, 32.3, 34.6, 55.6, 55.7, 65.9, 70.8, 105.2, 114.7, 127.1, 158.3, 174.4.