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Protein Kinase C Modulators. Indolactams. 2.[1] Alkylation of 4-Nitroindole by Grignard Reagents. Synthesis of (–)-7-OctylindolactamV.

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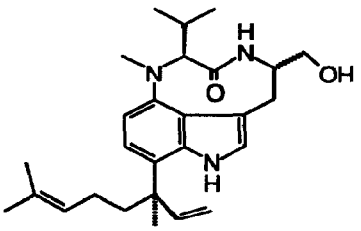
Abstract: A method for the C-alkylation of 4-nitroindole at the 5 and 7 positions by alkyl Grignard reagents has been developed. The 4-nitro-7-octylindole thus prepared has been used as a starting material for the synthesis of the lyngbyatoxin analog, (–)-7-octylindolactam V.

Lyngbyatoxin A (**1**), a very potent skin irritant and activator of protein kinase C (PKC), is a 7-alkyl-substituted indolactam V.[2] (–)-7-Octylindolactam V[3] (OctILV) (**2**) has been introduced as a readily available analog of lyngbyatoxin A for use in the study of PKC activation.[4] OctILV reportedly does not demonstrate PKC isotype selectivity;[4] however, its potency as an agonist makes it a useful starting point for modifications aimed at the development of isotype-selective agonists or antagonists.



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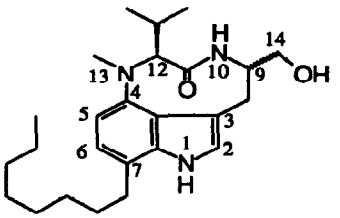


2

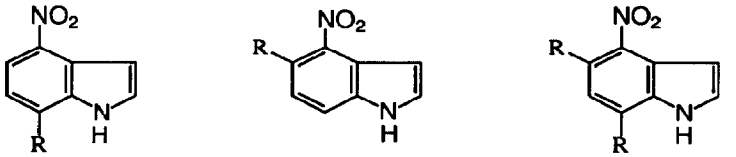
The first preparation of **2** was as part of a series of 7-alkyl substituted indolactam V (ILV) derivatives and it was most convenient to prepare it from ILV itself.[3] However, since only one specific member of the series is required for further SAR studies, it should be more efficient to introduce the octyl group earlier in the synthetic scheme.[5] Such an early introduction would also offer more opportunities to prepare analogs and derivatives containing what is potency-conferring lipophilic moiety, the 7-octyl group. As reported in the previous paper in this series,[1] 4-aminoindole and 4-nitroindole are useful starting materials for convenient and efficient synthetic routes to indolactams. 4-Amino- (or 4-nitro-) 7-octylindole should then be a useful starting point for the synthesis of **2**.

During an earlier study on the synthesis of ILV,[6] the preparation of 4-nitroindolylmagnesium bromide was attempted via treatment of 4-nitroindole (4-NI) with ethylmagnesium bromide.[7] Under a wide variety of conditions the major products were complex and did not appear to result from the 4-nitroindolylmagnesium salt but from the addition of the ethyl group to the 4-NI. Similar observations had been previously reported in the case of 5-nitroindole (5-NI) as well as other nitroaromatics and heteroaromatics.[8] For example, treatment of 5-NI with 3 equivalents of *n*-butylmagnesium bromide followed by an oxidative work-up (aq. $KMnO_4$) afforded a 66% yield of 4-butyl-5-nitroindole.[9] The studies by Bartoli[8] suggested that in the case of 4-NI the

alkyl groups should be directed to the 5 and 7 positions to approximately the same extent.

In the presence of copper(I) iodide this alkylation was reported to afford ring-alkylated aminoaromatics in good yield while minimizing N-alkylated products.[10] In the present case, treatment of 4-NI with octylmagnesium chloride in the presence of CuI gave a complex mixture from which was isolated small amounts of the expected 4-amino-5-octylindole and 4-amino-7-octylindole along with 4-N-octylamino-5-octylindole, 4-N-octylamino-7-octylindole, 4-N-(8'-hexadecyl)aminoindole and other unidentified products. The aminooctylindoles appeared to have limited stability and readily formed polar, colored products.

Bartoli found that oxidative decomposition of the intermediate nitronates regenerated nitroaromatics[8] which were anticipated to be much more stable. Lead(IV) tetraacetate was found to be a convenient and useful oxidizing agent in the present case.[8] Thus, an excess of *n*-octylmagnesium chloride in THF was added to a solution of 4-NI in THF and after a few minutes a solution of $Pb(OAc)_4$ in methylene chloride containing acetic acid was added. Two major products could be detected by their visible yellow spots on tlc.[11] Separation and purification of these products was achieved by preparative liquid chromatography. Elemental analysis and mass spectrometry confirmed that these products were indeed nitrooctylindoles. The NMR spectra suggested that the more mobile isomer was 4-nitro-7-octylindole (**3a**) while the other was 4-nitro-5-octylindole (**4a**).[12] This assignment was confirmed by the conversion of **3a** into 7-octylindolactam V (see below). From some reaction mixtures small amounts of 5,7-dioctyl-4-nitroindole (**5a**) were also obtained.



3 **4** **5**

a: R = $CH_3(CH_2)_7$- b: R = $(CH_3)_3C$- c: R = C_2H_5 d: R = C_6H_5

A wide variety of reaction conditions were investigated and are summarized in the Table. In contrast to expectations from Bartoli's studies,[8] in almost all cases where THF was the solvent, **4a** was the major product. When ether was used the reaction was much slower (the 4-NI was not very soluble) and the yields were lower; however, **3a** was the major product. Attempts at changing the ratio to favor **3a** in THF or to increase the yield of **3a** in ether by the use of various additives (e.g., HMPA, LiH or NaH) were unsuccessful. Furthermore, it appeared that either **3a** or one or more of the intermediates in its formation were unstable to some of the oxidative workup conditions (Entry 2). The use of minimal acetic acid and low temperatures during work-up appear to provide the best isolated yields of **3a** especially on the larger scales. The sample procedure presented below represents the best conditions for obtaining reproducible, maximum yields of **3a** but as can be seen from the Table, other variants gave similar results.

Treatment of 4-NI with *tert*-butylmagnesium bromide under similar conditions afforded a 23% yield of **3b**, a 11% yield of **4b** and a 4.5% yield of **5b**. The structures were assigned by analogy with the NMR spectra of **3-5a**.[12] The 5-*t*-butyl substituted nitroindoles are somewhat unstable in air (solutions of the purified products turned from yellow to green) which may explain the lower yields of **4b**. While no other types of organometallic reagents were used in this study, alkylation of 4-NI was not noted during an earlier investigation with *tert*-butyllithium.[6]

Treatment of 4-NI with ethylmagnesium bromide under these conditions afforded a 49% yield of a mixture of **3c** and **4c** which could not be efficiently separated on a preparative scale. However, the mixture was estimated by NMR to contain **3c** and **4c** in a 1:2 ratio. Very small yields (1-2%) of diethyl-4-nitroindole isomers and variable yields (0-10%) of 5- or 7-ethyl-2- or 3-bromo-4-nitroindoles were also obtained.

Phenylmagnesium bromide was much less reactive in this alkylation. Partial alkylation was achieved by allowing the reaction mixture to stir for 30 minutes at room temperature before quenching with $Pb(OAc)_4$ which afforded **3d** (7%) and **4d** (2%) along with 2-bromo-4-nitroindole (16%) and a recovery of 47% of the 4-NI.

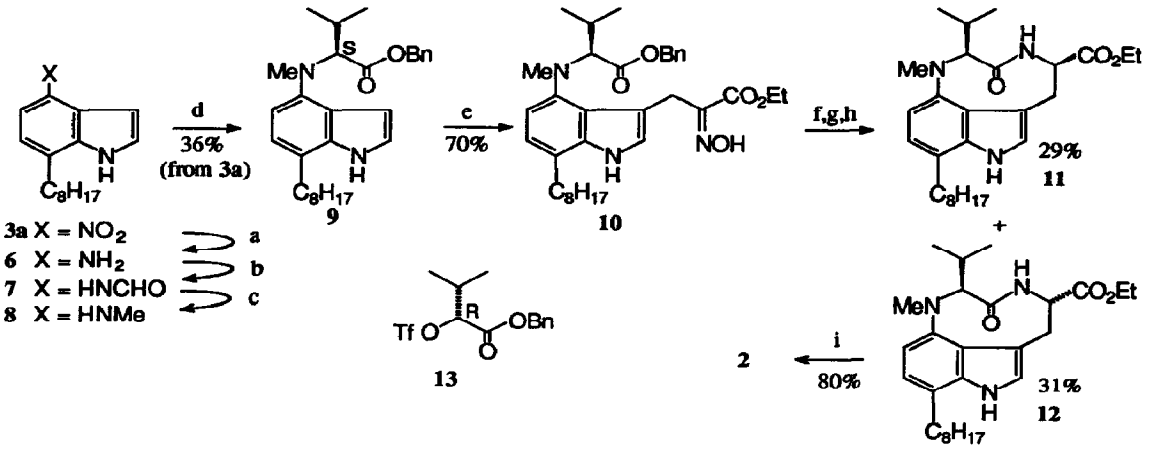
Table. Conditions and Yields for the Addition of *n*-Octylmagnesium Chloride to 4-Nitroindole.

Entry	Solvent	Reaction Temp.	Additive	Quench Temp.	% 3a	% 4a
1	THF	0°C	—	RT	21	33
2[b]	THF	0°C	—	RT	4	27
3	THF	0°C	—	0°C	27	44
4	ether	0°C→RT	—	RT	21	14
5	ether	RT	HMPA	0°C	19	13
6	THF	0°C	HMPA	0°C	31	41
7	THF	0°C	LiH	0°C	15	23
8	THF	0°C	HMPA	0°C	24	21
9	THF	0°C	HMPA	-22°C	23	34
10	THF	-21°C	HMPA	-22°C	27	38
11	THF	-65°C	HMPA	-65°C	24	36

[a] Entries 1-7 were with 1 mmol of 4-NI. Entries 8-11 were with 6 mmol of 4-NI.
[b] A larger excess of acetic acid was used during the work-up.

Compound **3a** was converted to OctILV (**2**) in 6.2% overall yield using a reaction sequence (see Scheme) analogous to that used for the preparation of ILV.[1] Thus, **3a** was reduced to 4-amino-7-octylindole (**6**) which, because of the question of stability noted earlier, was immediately converted to the formamide **7**. The reduction of the formamide and alkylation with the Kogan triflate, **13**,[14] afforded **9** in 36% overall yield from **3a**. The Gilchrist alkylation, lactam formation and reduction proceeded as described for indolactam V.[1] The identity of **2** was established by chromatographic comparison with a sample prepared by the octanoylation of indolactam V 14-*O*-acetate with octanoyl chloride/$AlCl_3$ followed by reduction ($LiAlH_4/AlCl_3$).[3,15]

Scheme. Synthesis of (–)-7-Octylindolactam V.



a) H_2, Pd-C; b) AcOCHO, THF; c) BH_3-Me_2S, THF, 60°C; d) **13**, 2,6-lutidine, $ClCH_2CH_2Cl$, 95°C; e) $BrCH_2C(=NOH)CO_2Et$, Na_2CO_3, CH_2Cl_2; f) Al(Hg), wet THF; g) H_2, Pd-C, (+)-camphorsulfonic acid; h) HOBT, BOP, N-methylmorpholine, dimethylacetamide; i) $LiBH_4$, THF.

Derivatives and stereoisomers of **2** and of 5-octylindolactam V (starting from **4a**) have been prepared. The abilities of these derivatives to modulate the activity of specific PKC isotypes will be reported separately.

Alkylation Procedure: A solution of 1.01 g (6.22 mmole) of 4-nitroindole[16] in 60 mL of THF and 2.5 mL of hexamethylphosphoramide was cooled in a salt-ice bath (-21°C) under nitrogen. To this solution, 14 mL (28 mmole) of 2M octylmagnesium chloride in THF was added at a moderate rate. After the mixture had stirred for 15 min, a solution, prepared by dissolving 2.9 g of lead(IV) tetraacetate in 25 mL of methylene chloride containing 0.6 mL of acetic acid, was added at a moderate rate. After 5 min the reaction mixture was removed from the cooling bath. Then, 45 min later 1.5 mL of ethylene glycol was added. About 1 hr later the reaction mixture was filtered and the residue washed with methylene chloride and water. The organic layer was separated, washed with saturated aq. sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to preparative liquid chromatography [silica; hexane/methylene chloride/ ethyl acetate (68:30:2)] to afford, in order of elution, 102 mg (4.2% yield) of **5a**, 464 mg (27% yield) of **3a** and 657 mg (38.5% yield) of **4a**.

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11. Compounds **3a** and **4a** could be distinguished as separate spots on silica tlc only when the developing solvent contained ethyl acetate, e.g., hexane/ethyl acetate (50:50).
12. The NMR spectrum (400 MHz; $CDCl_3$) of 4-NI had signals at δ8.06, 7.79 and 7.25 which were assigned to H-5, H-7 and H-6 respectively by analogy with nitrobenzene.[13] The spectrum of **3a** showed two doublets (J=8Hz) at δ8.09 and 7.06 which were assigned to H-5 and H-6 respectively. The spectrum of **4a** also showed doublets (J=8Hz) at δ7.49 and 7.09 which were assigned as H-7 and H-6. The upfield shift in the H-7 signal of **4a** as compared to 4-NI was assumed to be due to a forced rotation of the nitro group out of coplanarity with the ring by the adjacent bulky group. However, the H-6 signal was upfield in both **3a** and **4a** which originally cast some doubt on the assignments.
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15. The overall yield of **2** from ILV averaged about 30% using this sequence.
16. Prepared by a modified Bergman-Sand procedure.[17] N,N-dimethyl N'-(2-methyl-3-nitrophenyl)formamidine was prepared by heating 2-amino-6-nitrotoluene in dimethylformamide dimethylacetal. Treatment of the formamide with potassium ethoxide/diethyl oxalate[17] in THF afforded an overall yield of 71% 4-nitroindole.
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