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USE OF A THERMALLY STABLE, OPTICALLY ACTIVE NITRILE OXIDE IN THE SYNTHESIS OF A LYNGBYATOXIN A INTERMEDIATE

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Abstract: The synthesis of a homochiral nitrile oxide from a baker's yeast reduction product and its use in the preparation of a lyngbyatoxin A intermediate are detailed.

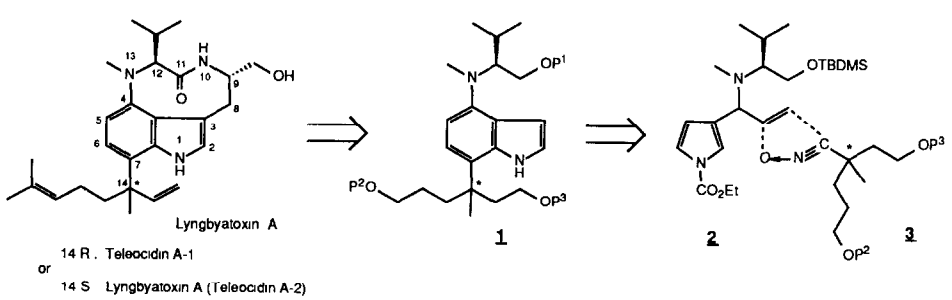
The lyngbyatoxins (also designated teleocidin A-1 and A-2) represent an unusual class of inflammatory and vesicatory substances[1] which are related structurally to the tetracyclic nine-membered lactam ring bearing compounds, the teleocidins[2] and the olivoretins.[3] The structures including the absolute stereochemistries of the olivoretins and the teleocidins have been ascertained through a combination of X-ray and spectral analysis as well as chemical degradations and synthesis.

These indole alkaloids have attracted considerable attention among biologists, for like the phorbol esters they are able to bind to and to activate protein kinase C.[4] This enzyme system is considered to play a key role in the cascade of events involved in signal transduction and thus in the elicitation of intracellular responses induced by external agents (e.g., drugs and hormones).[5]

In continuation[6] of our research aimed at the synthesis of the lyngbyatoxins with the ultimate intention of discovering an inactivator of protein kinase C, we report herein a method for introducing the chiral quaternary carbon center present in the substituent borne by the 7-position of the indole ring. In this effort, the synthesis of a thermally stable, optically active nitrile oxide was achieved whose ^{1}H NMR, IR, and $[\alpha]_D$ were recorded.

As shown in the accompanying retrosynthetic analysis, our strategy which is based upon a new condensed ring heterocycle synthesis described previously by us,[6,7] requires that we react a suitably constituted nitrile oxide **3** hosting a chiral quaternary carbon center with the pyrrole bearing dipolarophile **2**.

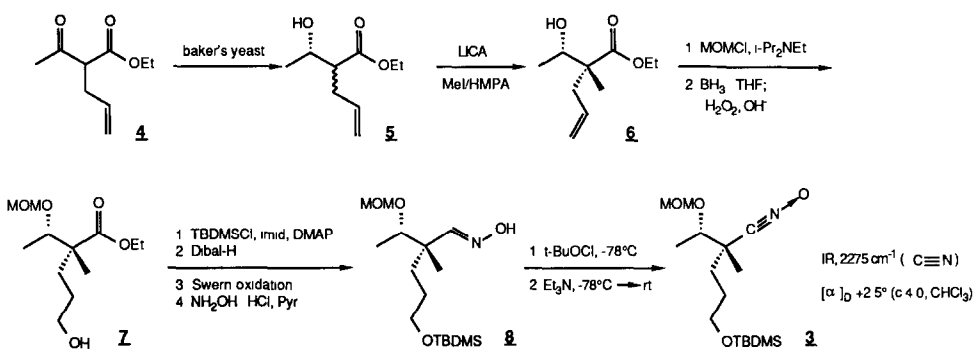
Scheme 1. A Retrosynthetic Analysis of Lyngbyatoxin A



The synthesis of the pyrrole **2** from pyrrole-3-carboxaldehyde and valine has been described previously.[6] The synthesis of the requisite nitrile oxide was to depend on a report published by Frater concerning the high enantioselectivity found in the reduction of the carbonyl group of α-alkylated β-keto esters using baker's yeast.[8] Thus, the allylated ethyl acetoacetate **4** was reduced to **5** and the resulting diastereomeric mixture treated with lithium isopropylcyclohexylamide followed by methyl iodide/HMPA to provide **6** (~97:3 mixture of diastereomers). Next, the hydroxyl group was protected as its MOM ether, and the double bond hydroborated to provide the alcohol **7** on oxidative workup. After silylation of the newly introduced alcohol, the ester was converted to aldehyde and oxime formation brought about (Scheme 2).

While many attempts were made to convert oxime **8** to the corresponding nitrile oxide using halogenating agents like NCS and NBS,[9] only Steven's procedure[10] proved successful. The oxime was thus reacted with *t*-butyl hypochlorite in methylene chloride at -78°C and the resulting bright blue solution treated with triethylamine. The desired dipole **3** could be isolated in pure form and its ^{1}H NMR, IR, and rotation recorded. This sterically

Scheme 2. Synthesis of an Optically Active Nitrile Oxide



hindered species could be stored at refrigerator temperatures indefinitely.[11] On reacting **3** with the dipolarophile **2**, the isoxazoline **9** was isolated (79% overall yield from the oxime) as a 2.5:1 mixture of diastereomers (Scheme 3).

To check whether the chiral center present in the nitrile oxide was playing a role in the diastereofacial selection observed, **3** was also reacted with allyl benzyl ether. Not unexpectedly, a ~55:45 mixture of diastereomeric isoxazolines **10** resulted indicating that little π-facial control is exerted by the nitrile oxide **3** itself.[12]

To carry the diastereomeric isoxazolines **9** on further, a variety of protecting group modifications were required, for the hydroxy ketone formed directly from **9** by N-decarboethoxylation and N-O bond cleavage failed to undergo cyclization to the desired indole. Eventually, we cleaved the MOM and silyl ether protecting groups from **9** by HCl/MeOH treatment. The primary alcohol groups of the resulting triol were then selectively resilylated (TBDMSCl) and the *N*-carboethoxy group removed by base treatment. The isoxazoline ring was then hydrogenated in the standard way to provide the diol **12** as a chromatographically separable mixture of isomers.

Scheme 3. Reactions of the Optically Active Nitrile Oxide 3

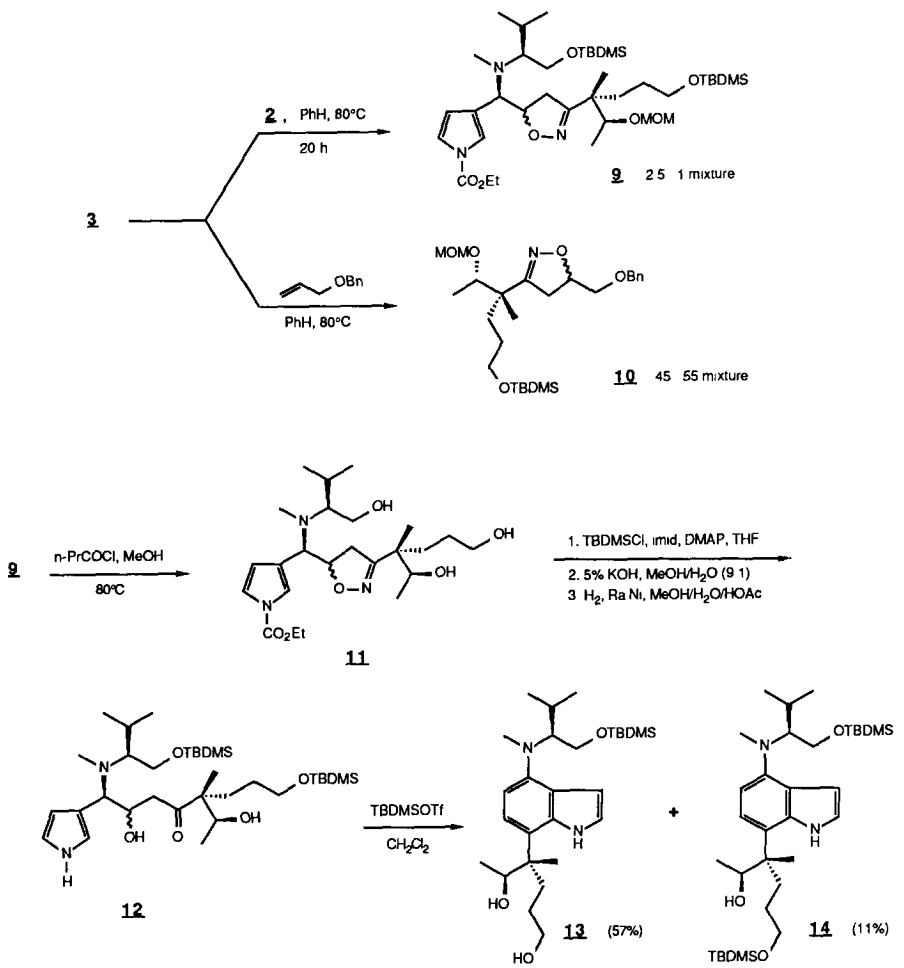


Table 1. A comparison of the ^{13}C NMR data for **13** and lyngbyatoxin A

Carbon atom	C_2	C_4	C_5	C_6	C_{7a}	C_3	C_{3a}	C_7
Chemical shifts for **13**	120.0	145.2	103.2	119.3	136.3	121.2,	119.6,	107.3
Chemical shifts for lyngbyatoxin A	120.7	146.2	106.1	119.7	137.2	121.4,	118.4,	114.1

With this material we were finally able to test the indolization reaction. Unfortunately, $Zn(OTf)_2$, $Mg(OTf)_2$, and TMSOTf all led to decomposition of **12**. However, use of TBDMSOTf[13] as the catalyst furnished two indolic products in 68% total yield from the "major" isomeric hydroxy ketone. The "minor" hydroxy ketone could be cyclized to some extent as well, but more unidentifiable side products resulted. The two indolic products resulting from the cyclization reaction were identified by ^1H NMR analysis to be the mono-silyl ether **13** (57%) and the bis-silyl ether **14** (11%). The former compound could be resilylated to provide **14.** The ^{13}C-NMR chemical shifts observed for the indolic carbon atoms of **13** are nearly identical to those reported for lyngbyatoxin A. The mass spectra of both **13** and **14** failed to give a parent ion but instead exhibited strong (M^+-CH_3CHO) peaks, a consequence presumably of a facile McLafferty rearrangement.

In summary, the present work has led to the preparation of a 4,7-disubstituted indole in which the substituent at the 4-position corresponds to the 11-13 portion of lyngbyatoxin A, while the substituent at the 7-position is properly constituted to give rise to the linalyl fragment of this natural product. The (3+2)-cyclocondensation chemistry thus provides an effective way of utilizing the "chiral pool" in the chiral-specific elaboration of a fused ring heterocycle.[14]

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