Organic LETTERS

ACS Editors' Choice

Letter

pubs.acs.org/OrgLett

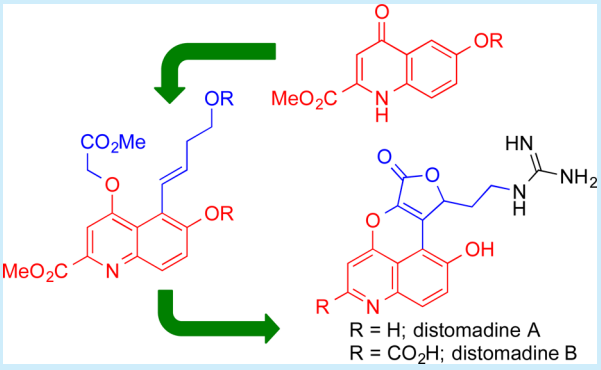
Total Synthesis of (±)-Distomadines A and B

Alexandre E. R. Jolibois, William Lewis, and Christopher J. Moody*

School of Chemistry, University Park, University of Nottingham, Nottingham NG7 2RD, U.K.

Supporting Information

ABSTRACT: The total synthesis of distomadines A and B, two structurally unique tetracyclic quinolines, is described. The route features a three-step process to access the pyranoquinoline butenolide rings via a Suzuki cross coupling of a 5-bromo-4-methoxycarbonylmethoxyquinoline with a vinyl boronate, followed by an α-ketohydroxylation and double cyclization by intramolecular aldol condensation and lactonization. Subsequent manipulation of the side chain to introduce the guanidine fragment completed the synthesis of distomadine B, whereas the distomadine A congener resulted from decarboxylation of a late-stage intermediate.



As part of our ongoing studies into the synthesis of structurally unique heterocyclic natural products,[1−3] we developed an interest in the distomadines, isolated from the New Zealand ascidian *Pseudodistoma aureum* by Copp and co-workers.[4] Although distomadine B was isolated in a 1:1 admixture with 2′-deoxyadenosine, the structure of the A congener was fully elucidated by NMR spectroscopy, although the absolute stereochemistry remained unknown. These unusual structures possess a unique tetracyclic core that comprises a pyrano[2,3,4-*de*]quinoline fused to a butenolide (Figure 1), and only one compound has been reported which possesses a similar pyranoquinoline core, a synthetic compound related to the aaptamine alkaloids.[5] The 2-quinolinecarboxylic acid present in distomadine B is also quite uncommon in marine natural products,[6−8] although the first example, 3,4-dihydroxyquinoline-2-carboxylic acid, was isolated from *Aplysina aerophoba* in the early 1970s.[9] Kynurenic and xanthurenic acid are two of the best known examples of 2-quinolinecarboxylic acid natural products (Figure 1), although distomadine B is the most complex isolated to date. We now report the first syntheses of these unusual heterocyclic natural products.

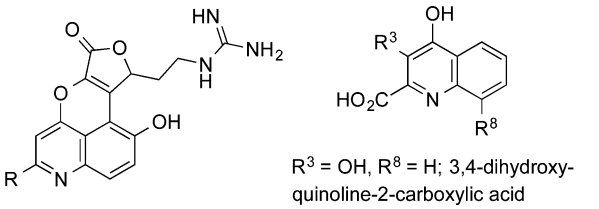
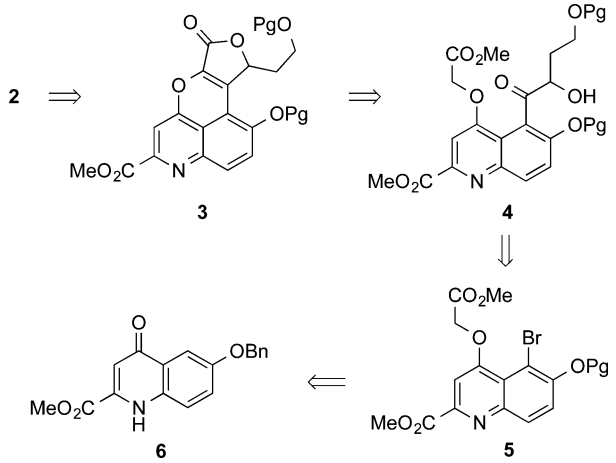


Figure 1. Structures of distomadines A and B and kynurenic and xanthurenic acids.

We initially focused on synthesizing distomadine B (**2**), anticipating that distomadine A could be accessed by a late-stage decarboxylation. We also planned to introduce the guanidine during the final stages from a protected alcohol **3**. The butenolide could be formed by a one-step aldol-condensation−lactonization from the corresponding α-ketol **4**, which could be accessed by oxidation of an alkene, available via a Suzuki− Miyaura cross-coupling between the 5-bromoquinoline **5** and the corresponding alkenylboronic ester as outlined in Scheme 1.

The synthesis began with the known 6-benzyloxy-4-quinolone **6**, previously prepared via a modified Conrad−

Scheme 1. Retrosynthesis Analysis of Distomadine B (Pg = Protecting Group)

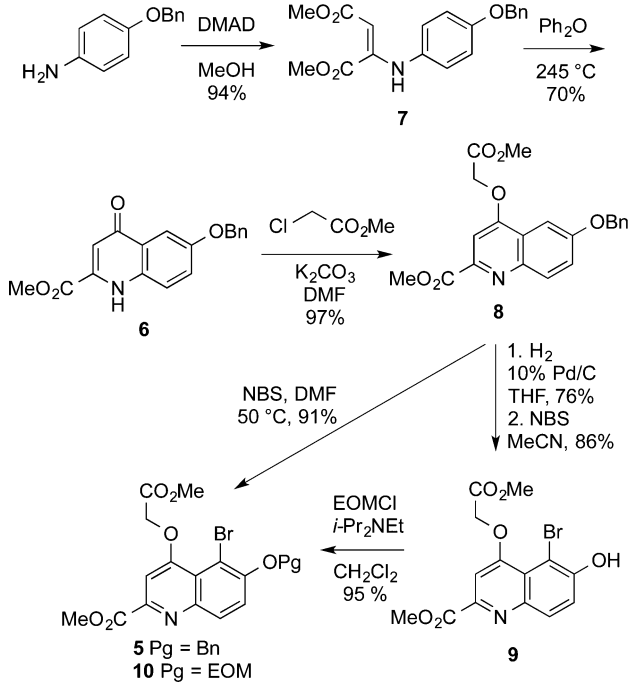


Received: December 12, 2013
Published: February 8, 2014

   dx.doi.org/10.1021/ol403598k | *Org. Lett.* 2014, 16, 1064−1067

Limpach reaction[10] from the commercially available 4-benzyloxyaniline hydrochloride. Thus, aza-Michael addition to dimethyl acetylenedicarboxylate (DMAD), followed by heating in diphenyl ether at 245 °C, afforded the 4-quinolone **6** in 70% yield. Alkylation with methyl chloroacetate followed by bromination with NBS in DMF gave the desired 5-bromoquinoline **5** in excellent yield (Scheme 2).

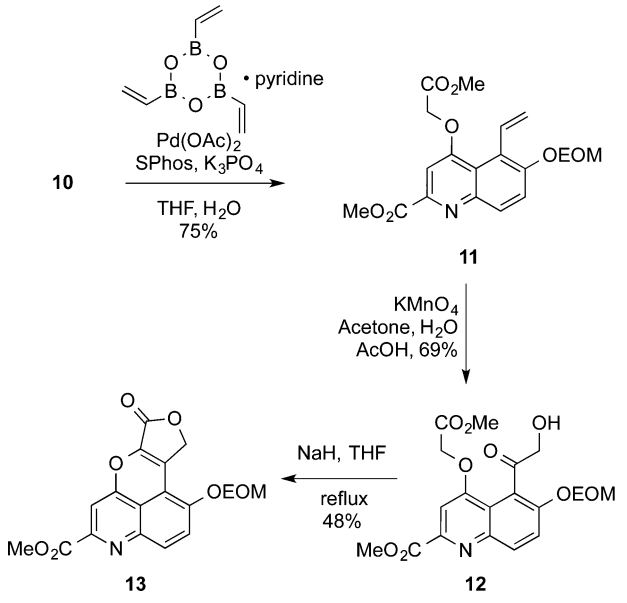
Scheme 2. Synthesis of 5-Bromoquinolines 5 and 10



It was thought that 5-bromoquinoline **5** would then participate in Suzuki–Miyaura cross-coupling, but this gave poor results, possibly due to steric hindrance by the benzyloxy protecting group in addition to the *peri*-substituent at C-4. As a result, it was envisioned that deprotection, followed by installation of a smaller protecting group, could improve the yield of the cross-coupling. Deprotection of the benzyl ether **8** followed by bromination with NBS in acetonitrile afforded **9**, which was protected as the ethoxymethyl ether **10**. The Suzuki–Miyaura cross-coupling was initially attempted using trivinylboroxine as a model for the requisite terminal alkene (Scheme 3). Thus, reaction of **10** and vinyl boroxine pyridine complex using $Pd(OAc)_2$ and SPhos[11] gave coupled product **11** in 75% yield. Oxidation of the alkene with $KMnO_4$ in acetone, water, and acetic acid[12] allowed access to the α-ketol **12** in good yield, allowing us to attempt a model butenolide formation. Previous syntheses of butenolides have been reported by condensation between dimethyl malonate and α-hydroxy ketones with sodium hydride or sodium methoxide.[13,14] The cyclization of model α-ketol **12** with sodium hydride afforded the desired butenolide **13** in 48% yield, X-ray crystallographic analysis of which confirmed the tetracyclic structure (Figure 2).

In proceeding with our synthesis toward distomadine B, it was first necessary to synthesize a suitable boronic ester to be used as a coupling partner in the Suzuki–Miyaura reaction. Due to the harsh conditions of the formation of the butenolide, a benzyloxymethyl (BOM)-protected alcohol was selected for the side chain. But-3-yn-1-ol was protected with BOMCl and

Scheme 3. Synthesis of the Model Tetracyclic Core of Distomadine B



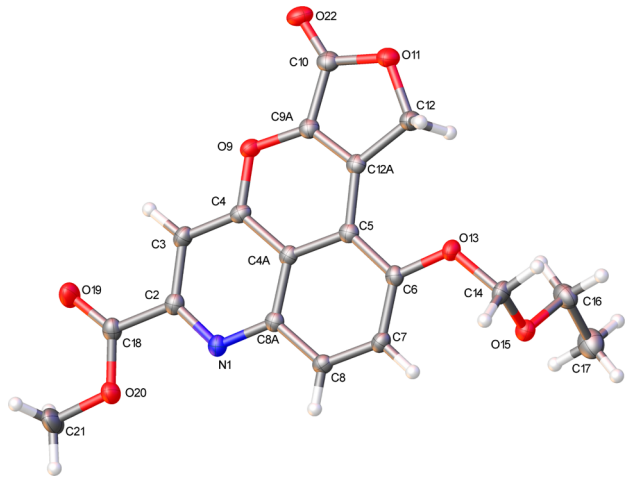


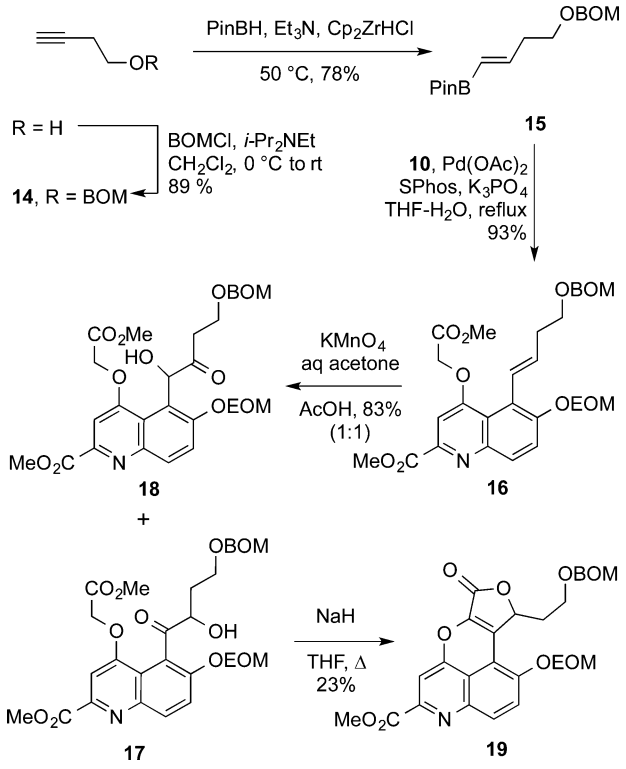
Figure 2. X-ray crystal structure of tetracyclic pyrano[2,3,4-*de*]-quinoline **13**.

Hunig's base to afford **14**. The hydroboration of the alkyne was performed by following the reported modification of Srebnik's conditions[15,16] for the Schwartz's reagent catalyzed hydroboration, affording the boronic ester **15** in 78% yield. Suzuki–Miyaura cross-coupling between bromoquinoline **10** and boronic ester **15** with $Pd(OAc)_2$ and SPhos gave **16** in excellent yield. However, the previously employed oxidation with $KMnO_4$ resulted in a mixture (ca. 1:1) of the α-hydroxy ketones **17** and **18**. Attempts to selectively synthesize the desired regioisomer **17** by either selective oxidation of the corresponding diol or by a Rubottom oxidation of an enol ether were unsuccessful. However, treatment of the mixture of α-ketols **17** and **18** with sodium hydride resulted in the tetracyclic core **19** in a moderate 23% yield (Scheme 4).[17]

With access to the tetracyclic core, the synthesis could be completed by introduction of the guanidine and removal of the protecting groups. Deprotection of the BOM group in tetracycle **19** by transfer hydrogenation using formic acid and palladium black gave the deprotected alcohol that could be

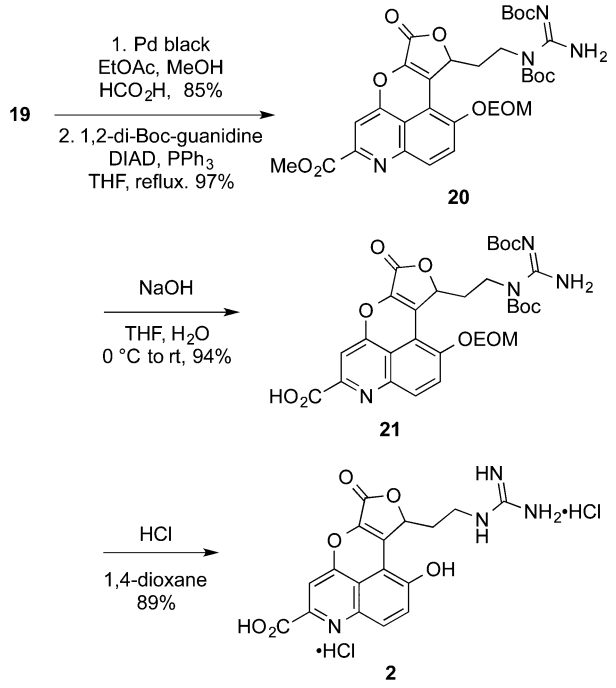
dx.doi.org/10.1021/ol403598k | *Org. Lett.* 2014, 16, 1064–1067

Scheme 4. Synthesis of γ-Butenolide 19 Core of Distomadine B (PinB = 4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)



coupled with 1,2-di-Boc-protected guanidine under Mitsunobu conditions[18] to afford **20** in nearly quantitative yield. Hydrolysis of the ester with NaOH provided the acid **21**, X-ray crystallography confirming the structure (Figure 3). Finally, treatment of the acid **21** with HCl in dioxane gave the dihydrochloride salt of distomadine B in 89% yield (Scheme 5). Although natural distomadine B was only reported as a mixture with 2′-deoxyadenosine, we were able to compare the NMR spectroscopic data with our synthetic sample. Thus, treatment

Scheme 5. Completion of Synthesis of Distomadine B (2)



of the dihydrochloride salt with concentrated ammonia in methanol gave the monohydrochloride salt; ^{1}H NMR in CD_3OD with a drop of concentrated ammonia matched the reported data for the natural product.

In order to complete the synthesis of distomadine A, the late-stage intermediate **19** was first hydrolyzed to give the acid which then underwent decarboxylation on heating in diphenyl ether at 190 °C to give quinoline **22** in 77% yield over two steps. The structure of the decarboxylated tetracycle **22** was confirmed by X-ray crystallography (Figure 4). Transfer hydrogenation with palladium black and formic acid gave the alcohol **23** that was coupled to 1,2-di-Boc-protected guanidine

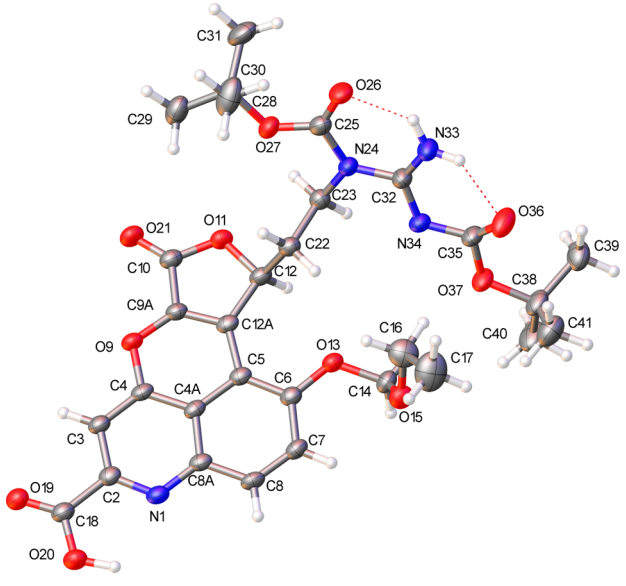


Figure 3. X-ray structure of **21**.

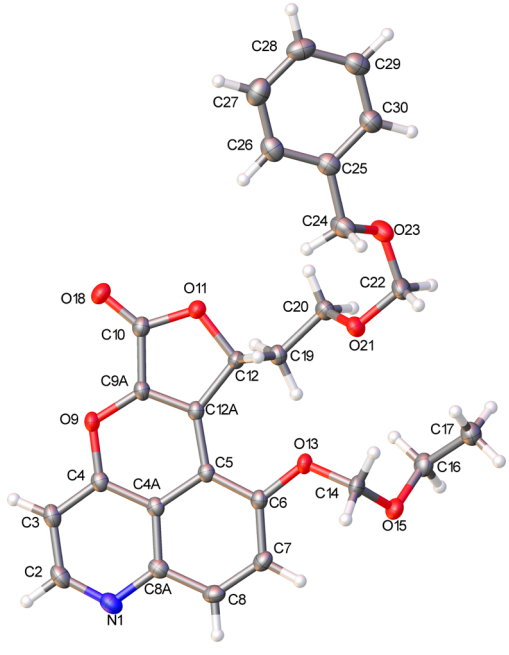
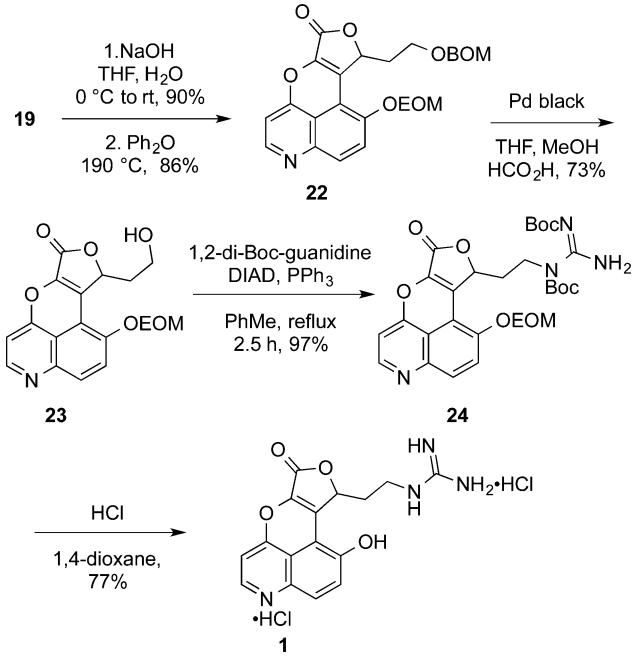


Figure 4. X-ray crystal structure of decarboxylated tetracycle **22**.

dx.doi.org/10.1021/ol403598k | Org. Lett. 2014, 16, 1064−1067

to give **24** in nearly quantitative yield. Finally, **24** was treated with HCl in dioxane to give the dihydrochloride salt of distomadine A (**1**) in 77% yield (Scheme 6). Treatment with

Scheme 6. Completion of the Synthesis of Distomadine A (1)



concentrated ammonia gave material whose ^{1}H and ^{13}C NMR spectra in CD_3OD were identical with a sample of the authentic natural product, although the ^{13}C NMR data appeared to be concentration dependent.[19]

In summary, we have achieved the first total syntheses of distomadines A and B in 14 steps (3.5% yield) and 13 steps (5.6% yield), respectively, with key intermediate structures being confirmed by X-ray crystallography. The pivotal steps of the syntheses are the construction of the butenolide by Suzuki cross-coupling, oxidation of the resulting alkene, and the intramolecular aldol lactonization sequence. The syntheses confirm the unusual tetracyclic pyranoquinoline structure of the natural products.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures, copies of ^{1}H and $1^{3}C$ NMR spectra, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: (+44)115 846 8500. E-mail: c.j.moody@nottingham.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Nottingham for funding and Drs Brent Copp and Norrie Pearce (University of Auckland) for copies of NMR spectra of the distomadines and a sample of natural distomadine A.

■ REFERENCES

(1) Nawrat, C. C.; Moody, C. J. *Org. Lett.* **2012**, *14*, 1484−1487.
(2) Carbone, A.; Lucas, C. L.; Moody, C. J. *J. Org. Chem.* **2012**, *77*, 9179−9189.
(3) George, I. R.; Lewis, W.; Moody, C. J. *Tetrahedron* **2013**, *69*, 8209−8215.
(4) Pearce, A. N.; Appleton, D. R.; Babcock, R. C.; Copp, B. R. *Tetrahedron Lett.* **2003**, *44*, 3897−3899.
(5) Abbiati, G.; Doda, A.; Dell'Acqua, M.; Pirovano, V.; Facoetti, D.; Rizzato, S.; Rossi, E. *J. Org. Chem.* **2012**, *77*, 10461−10467.
(6) Yin, S.; Boyle, G. M.; Carroll, A. R.; Kotiw, M.; Dearnaley, J.; Quinn, R. J.; Davis, R. A. *J. Nat. Prod.* **2010**, *73*, 1586−1589.
(7) Molinski, T. F.; Faulkner, D. J. *Tetrahedron Lett.* **1988**, *29*, 2137−2138.
(8) de Silva, E. D.; Miao, S.; Andersen, R. J.; Schultz, L. W.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 2917−2920.
(9) Fatorusso, E.; Forenza, S.; Minale, L.; Sodano, G. *Gazz. Chim. Ital.* **1971**, *101*, 104−105.
(10) Borza, I.; Kolok, S.; Galgóczy, K.; Gere, A.; Horváth, C.; Farkas, S.; Greiner, I.; Domány, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 406−409.
(11) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.
(12) Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520−521.
(13) Orduña, A.; Zepeda, L. G.; Tamariz, J. *Synthesis* **1993**, 375−377.
(14) Tyvorskii, V. I.; Kukharev, A. S.; Kulinkovich, O. G.; De Kimpe, N.; Abbaspour Tehrani, K. *Tetrahedron* **1998**, *54*, 1801−1808.
(15) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127−3128.
(16) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202−1203.
(17) Although only isomer **17** can lead to the correct product, in principle isomers **17** and **18** may interconvert under the basic reaction conditions. Isomer **18** was not recovered from the reaction mixture.
(18) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977−980.
(19) The NMR sample necessarily now contains NH_4Cl, although the effect of NH_4Cl concentration on chemical shift was not investigated.