Natural Product Synthesis with Unnatural Results: Characterization of a Novel Fused Imidazolidinone Tetrahydropyrroloindole Ring System by Long-Range ^{1}H-^{15}N 2D-NMR

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Synthetic efforts towards the indole alkaloid natural product roquefortine C resulted in the formation of an unknown intermediate. Elucidation of the structure of this molecule relied on the use of long-range ^{1}H-^{15}N 2D-NMR. Computational predictions were used to facilitate the location of weak responses in long-range ^{1}H-^{13}C HMBC spectra. These methods provided conclusive evidence that this compound possessed a novel tetracycle. The complete ^{1}H, ^{13}C, and ^{15}N chemical shift assignments of this unique fused imidazolidinone tetrahydropyrroloindole derivative are reported.

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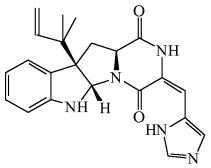
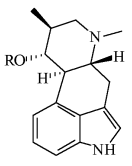
Introduction.

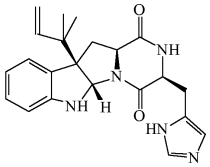
Roquefortine C (**1**) has been isolated as a fungal metabolite of *Penicillium roqueforti* strains along with three other related alkaloids, roquefortines A (**2**), B (**3**), and D (**4**) [1-3]. *Penicillium roqueforti* is of particular interest from an agricultural and food chemistry standpoint, as it is the essential fungus used in the production of Roquefort cheese, as well as numerous other varieties of blue-veined cheeses [4]. The ambiguous neurotoxic properties of this alkaloid [2,5,6] stimulated interest in its synthetic preparation. To this end, copper catalyzed amidation of vinyl bromide **5** (Scheme 1) was envisioned as leading to formation of the requisite diketopiperazine ring **6** [7-8]. However, initial analysis of the product of this reaction by 1D NMR, IR, and mass spectrometry indicated that the product was a structural isomer of the desired compound. Based on mechanistic considerations, the alternative structure **7** was proposed. The high degree of heteroatom substitution in this compound made analysis solely by conventional ^{1}H and ^{13}C NMR methods difficult. Confirmation of the structure of this cyclization product was achieved through concerted interpretation of one and two-dimensional NMR data including homonuclear GCOSY, direct heteronuclear RDSQC [9-11], and heteronuclear long-range ^{1}H-^{13}C [12] and ^{1}H-^{15}N GHMBC data [13,14].



1 (C)



2 (A) R = Ac
3 (B) R = H

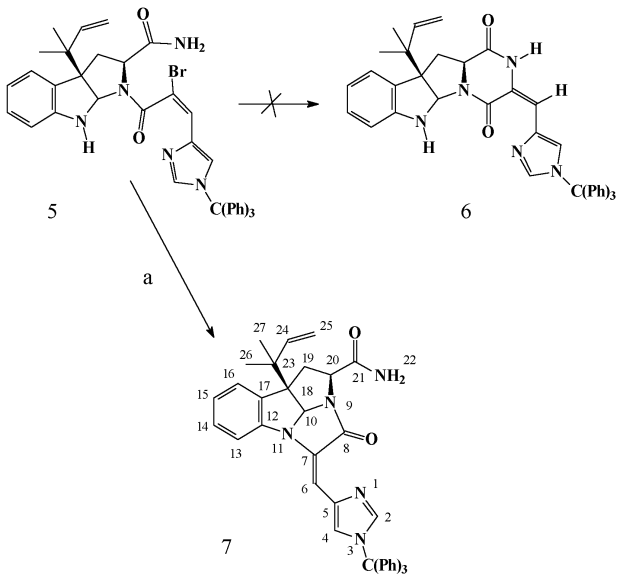


4 (D)

Results and Discussion.

The elucidation of the structure of the unknown cyclization product began with the acquisition of GCOSY data that were used to subgroup resonances into individual spin systems. Association of individual proton resonances with their respective directly bound carbons was achieved *via* an RDSQC experiment. Long-range ^{1}H-^{13}C connectivities from a GHMBC experiment were then used to begin to link together the substructural fragments. This task was somewhat challenging due to the overlap of the intense correlations from the triphenylmethyl substituent with weaker responses in the aromatic region of the GHMBC spectrum.

Scheme 1



(a) CuI (0.1 eq), *N*,*N*'-dimethylethylenediamine (0.2 eq), K_2CO_3 (2 eq), dioxane, 100 °C, 14 hrs, 74%.

Protons resonating at 7.18 and 7.49 ppm did not exhibit a correlation to a ^{13}C nucleus in the RDSQC spectrum, suggesting that these signals were likely NH resonances. In the case of the desired product **6**, the NH resonances would be on different nitrogen atoms (N-11 and N-22) and could be differentiated based on their observed long-range correlations in the ^{1}H-^{13}C GHMBC data acquired. In the case of compound **7**, both protons would be bound to the primary amide nitrogen (N-22) and would be expected to exhibit similar long-range carbon correlations. Restricted rotation in the case of primary amide groups leading to anisochronous protons is not uncommon and may be invoked to explain the relatively small difference in the chemical shifts of the two NH protons. Given the potential problems that could be caused by response overlap in the ^{1}H-^{13}C GHMBC spectrum, the acquisition of a long-range ^{1}H-^{15}N GHMBC spectrum parameterized allow for observation of $^{1}J_{NH}$ direct correlation responses was seen as an attractive source of additional structural information.

Long-range ^{1}H-^{15}N GHMBC data (Figure 1) were acquired with the $^{1}J_{NH}$ delay set for 1 KHz rather than ~90 Hz to allow for improved observation of the one-bond responses. Using this approach, the protons resonating at 7.18 and 7.49 ppm were both correlated to the same nitrogen resonating at 107.5 ppm as ~90 Hz doublets. This observation is consistent with the structure of compound **7**, in which restricted rotation of the primary amide NH_2 gives rise to the observed anisochronous proton shifts. More importantly, the ^{1}H-^{15}N GHMBC spectrum shown in Figure 1 also displayed a response correlating the H-6 vinyl proton at 6.92 ppm to the indole N-11 resonance at 111.8 ppm, an interaction which would be expected for compound **7** but not likely for the diketopiperazine **6**.

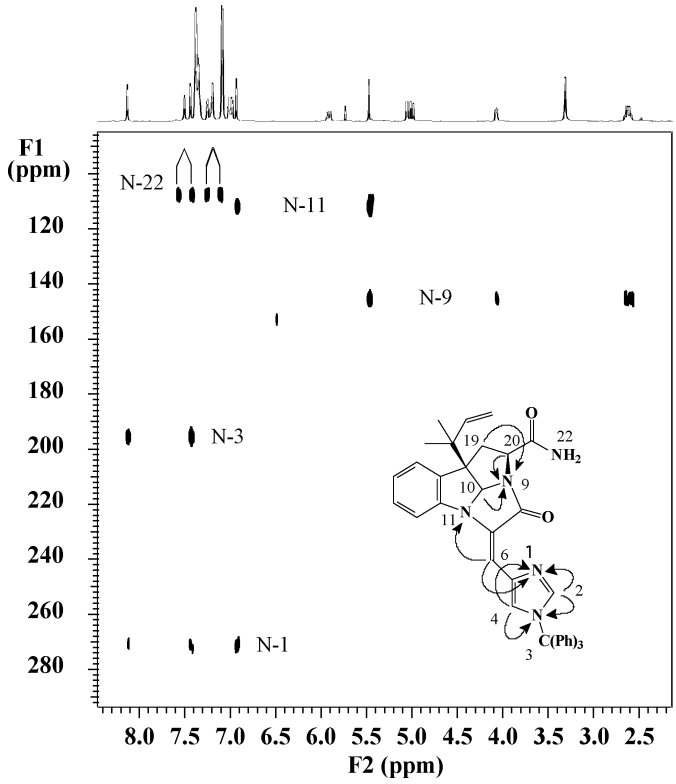


Figure 1. Long-range ^{1}H-^{15}N GHMBC spectrum of **7** optimized for 6 Hz recorded overnight in d_6-dimethylsulfoxide.

Further analysis of GHMBC data provided further support of structure **7**. The N-11 indoline nitrogen was coupled to the H-10 bridgehead proton resonating at 5.46 ppm. In addition, this H-10 proton showed a two-bond correlation to the N-9 resonance, and the N-9 signal in turn with the H-19 methylene protons resonating at 2.46 ppm and the H-20 methine resonance at 4.05 ppm. The nitrogen resonances of the N-triphenylmethylimidazole were also readily assigned from the data shown in Figure 1. The nitrogen resonating at 271.3 ppm was assigned to the sp^2 hybridized nitrogen N-1 on the basis of correlations to the H-6 vinyl proton resonating at 6.92 ppm as well as the imidazole protons resonating at 7.43 and 8.12 ppm. The triphenylmethyl-bearing sp^3 nitrogen N-3 resonates at 195.3 ppm, upfield of the sp^2 N-1 nitrogen resonance, and was correlated only to the imidazole protons. Correlation to the H-6 vinyl resonance would be across four bonds and would not be expected to exhibit a strong correlation. Observed long-range ^{1}H-^{15}N heteronuclear coupling pathways for **7** are shown in Figure 1.

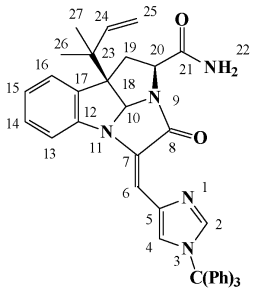
While it was possible to assign nearly all of the carbon resonances of **7**, the carbon at which the carbon-nitrogen bond forming process occurred, C-7, remained unaccounted. As this compound is an unreported ring system, examination of the ^{1}H-^{13}C GHMBC spectrum for this potentially weak signal could be difficult without predefinition of a particular spectral region. To facilitate this process, carbon chemical shift prediction software developed by ACD Laboratories [15] was employed to estimate the chemical shift of C-7. By this method, the calculated shift of the carbon in question was found to be ~118 ppm. A visual search of the GHMBC spectrum centered on 118 ppm afforded a weak correlation from H-10 at 5.46 ppm to a carbon resonance at 126.2 ppm. This carbon was thus assigned as C-7, completing the total spectral assignment of the molecule. Complete ^{1}H, ^{13}C, and ^{15}N chemical shift assignments for **7** are collected in Table 1.

Conclusion.

Long-range ^{1}H-^{15}N correlations were used to unequivocally confirm the structure of the novel tetracycle **7**. ^{13}C prediction software by ACD Laboratories was employed to calculate a chemical shift for the C-7 resonance that allowed a very low-level threshold search in the correct chemical shift range to complete the full NMR spectral assignment. The results indicate that copper catalyzed

Table 1

600 MHz ^{1}H, ^{13}C and ^{15}N Chemical Shift Assignments for **7**



7

Assignment	δ ^{1}H	δ ^{13}C	δ ^{15}N
1	-	-	271.3
2	7.43	138.8	-
3	-	-	195.3
4	8.12	125.1	-
5	-	134.6	-
6	6.92	121.7	-
7	-	126.2	-
8	-	166.7	-
9	-	-	145.4
10	5.46	86.9	-
11	-	-	111.8
12	-	152.6	-
13	6.96	115.0	-
14	7.19	129.6	-
15	7.00	123.9	-
16	7.24	126.5	-
17	-	135.7	-
18	-	41.1	-
19	2.61	42.6	-
20	4.05	58.5	-
21	-	173.5	-
22	7.18, 7.49	-	107.5
23	-	62.5	-
24	5.89	144.3	-
25	4.98, 5.04	114.8	-
26	0.93	22.9	-
27	0.88	23.5	-
28	-	75.6	-
29	-	142.6	-
30	7.08	129.9	-
31	7.35	128.8	-
32	7.33	130.2	-

vinyl amidation led to reaction of the indoline nitrogen to form an imidazolidinone rather than attack by the primary amide to form the desired diketopiperazine. This example is a significant addition to the very limited reports of bifunctional nucleophiles in metal-catalyzed amidation reactions. To the best of our knowledge the only other report in the area of metal-catalyzed amidation reactions involves the selective intermolecular arylation of the amide of 4-aminobenzamide in high yield [8]. Though the intramolecular nature of the reaction presented here may be used to rationalize the results (intermediacy of a six-membered metallocycle versus a seven-membered metallocycle), the general chemoselectivity of this reaction has yet to be fully elucidated.

EXPERIMENTAL

Imidazolidinone-tetrahydropyrroloindole (**7**).

Vinyl bromide **5** (175 mg, 0.238 mmole), cuprous iodide (4.5 mg, 0.024 mmole, 10 mol %), and finely powdered potassium carbonate (66 mg, 0.476 mmole, 2 eq) were added to a thick-walled pressure tube and fitted with a rubber septum. The tube was evacuated and back-filled with argon three times. Dioxane (2 ml) and N-N'-dimethylethylenediamine (5.2 µL, 0.048 mmoles, 20 mol %) were added, and the reaction mixture was flushed with argon and sealed by replacement of the septum with a Teflon screw cap. The reaction was heated to 100 °C for 14 hours then cooled to room temperature, diluted with ethyl acetate (10 ml), filtered through a plug of silica, washed with additional ethyl acetate (10 ml), and the filtrate was then concentrated. The crude product was purified by column chromatography on silica gel to afford **7** (111 mg, 0.176 mmole) as a white foam in 74% yield. R_f 0.48 (5:95 MeOH/CH_2Cl_2); ^{1}H NMR (599.75 MHz, DMSO) See Table 1; IR (neat) 3331, 3170 ($CONH_2$), 1690, 1661, 1472, 1449, 1384; [α]= +21.5 (c=0.55, $CHCl_3$); HRMS (ES) calcd. for $C_{41}H_{38}N_5O_2$ $(M + H)^+$; *m/z* 632.302551, found 632.302684.

NMR Spectra of **7**.

A sample of **7** was prepared by dissolving approximately 5 mg in 150 µL dimethylsulphoxide-d_6 (CIL, 99.996 %) in a 3mm NMR tube (Wilmad). All NMR experiments were performed on a Varian INOVA 600 MHz NMR spectrometer, operating at a proton frequency of 599.75 MHz, and equipped with a Nalorac Z•Spec™ MIDTG-600-3 inverse-detection NMR probe. The 90° pulse lengths were as follows: 5.5 µs at 51 dB (63 dB max) for ^{1}H; 13.8 µs at 59 dB (63 dB max) for ^{13}C; and 28.0 µs at 61 dB (63 dB max) for ^{15}N. Data acquired included a homonuclear GCOSY, multiplicity-edited RDSQC, and both ^{1}H-^{13}C and ^{1}H-^{15}N GHMBC. Heteronuclear shift correlation data were acquired using F_1 spectral windows of from 10-180 ppm for the RDSQC and ^{1}H-^{13}C GHMBC experiments and from 90-300 ppm for the ^{1}H-^{15}N GHMBC experiment. The F_1 spectral windows were digitized by the acquisition of 80, 128, and 96 increments of the evolution times, respectively, for the three experiments.

REFERENCES AND NOTES

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