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Synthetic studies toward spiroleucettadine

Jonah J. Chang, Bryan Chan and Marco A. Ciufolini*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1

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Abstract—Synthetic hydroxydienone precursors to spiroleucettadine and to an isomer thereof resist cyclization to the orthoamide-type functionality present in the proposed structure of the natural product.

In 2004, Crews and collaborators described a noteworthy marine alkaloid, which they termed spiroleucettadine and to which they assigned structure **1** (Fig. 1) on the basis of spectroscopic and chiroptical evidence.[1] The substance displays antibiotic activity and a highly novel architecture that renders it a prime candidate for synthetic work. A noteworthy feature of **1** is a *trans*-fused 1-hydroxy-2-oxa-6,8-diazabicyclo[3.3.0]octane core that sustains an unusual orthoamide-type functionality. We estimate that this system contains no less than 14 kcal/mol (MM+)[2] more strain energy than the *cis*-fused analog, **4**. As shown in Figure 2, the orthoamide-type functionality would be expected to promote facile equilibration of the natural product with **2** and **3**, through reversible release of either a C–O or a C–N bond. Either **2** or **3** could then recyclize to form the less energetic **4**. In a like vein, the hypothetical species **3** might cylize to spiroleucettadine isomers **5** (*cis* or *trans*). Yet, the published spectra of the natural product clearly show the presence of a single compound, implicating a significant preference for structure **1** over isomers **5**, despite the lack of obvious factors favoring such a bias. In a recent paper, Danishefsky and Li describe results that

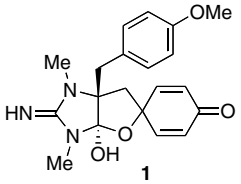

Figure 1. Proposed structure of spiroleucettadine.

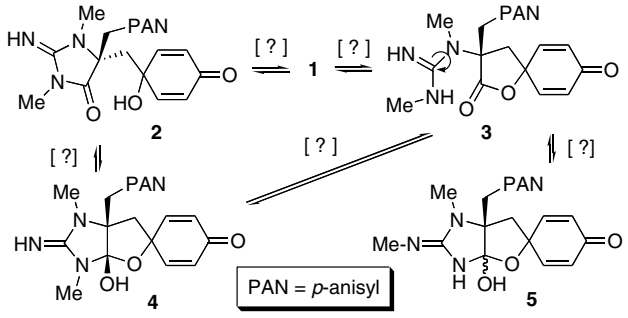

Figure 2. Possible isomerization pathways for **1**.

'invite caution' regarding the structure of **1**.[3] In particular, the Columbia researchers determined that the imino *N*-BOC derivative of **2** shows no apparent inclination to cyclize to an orthoamide. This prompts us to disclose observations of our own that (i) are in complete accord with the foregoing, (ii) reveal that the precursor to **5** also exists exclusively as the open form, and (iii) cast doubt on the viability of the species depicted as **2**.

The study described herein ignores issues of absolute stereocontrol, focusing exclusively on structural questions. Consonant with principles expounded in Ref. 3, our approach also centered on a Wong-type[4] oxidative spirocyclization of **6** and in situ hydration of the presumed intermediate **8**, leading directly to (±)-**1** (Fig. 3). Thus, deprotonation of tyrosine derivative **9**[5] and alkylation of the corresponding enolate with bromide **16**[6] furnished **10**. Cleavage of the BOC group set the stage for N-guanidylation with reagent **17**.[7] Unexpectedly, this step proceeded with concomitant cleavage of the methyl ester, providing acid **12**, arguably due to inadvertent introduction of moisture.

* Corresponding author. Tel.: +1 604 822 2419; fax: +1 604 822 8710; e-mail: ciufi@chem.ubc.ca

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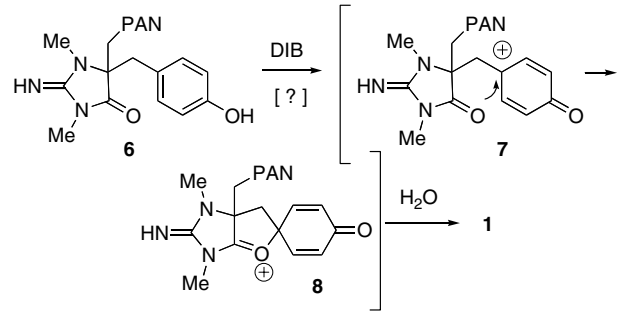
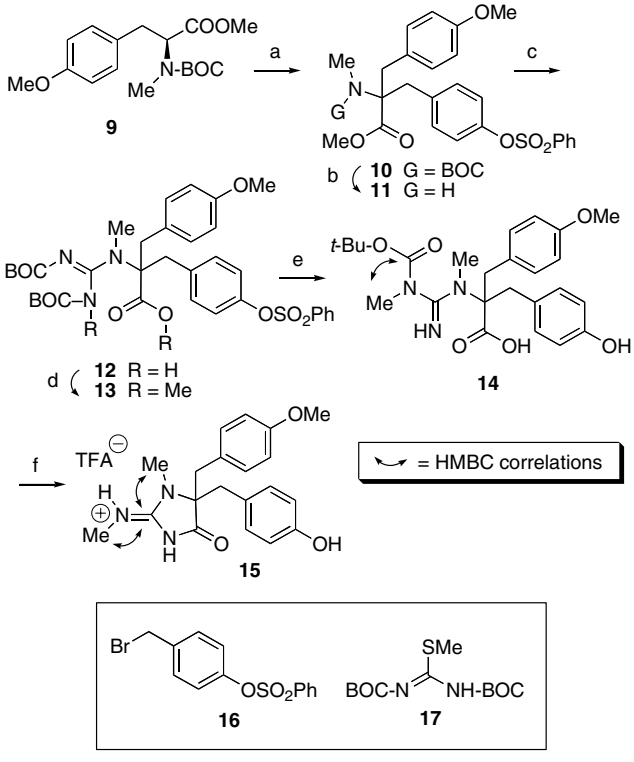


Figure 3. Strategy for the synthesis of **1**.

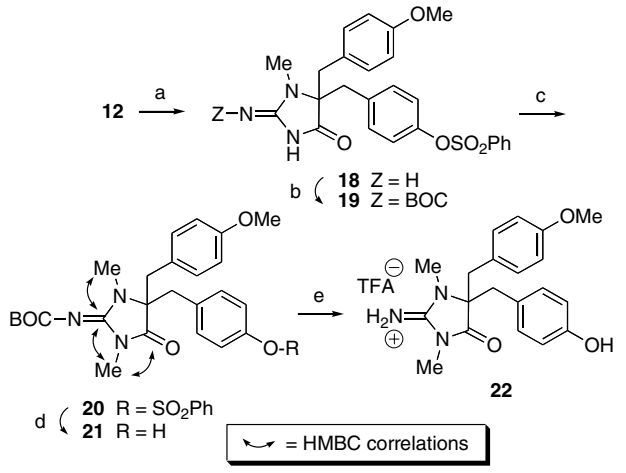
However, ester saponification was inconsequential, in that subsequent treatment of **12** with excess NaH and MeI installed a requisite *N*-methyl substituent and reformed the methyl ester (cf. **13**, Scheme 1). We note that attempts to form **13** directly through reaction of **11** with the *N*-methyl analog of **17**[8] were unsuccessful, necessitating the implementation of the present sequence. Exposure of **13** to KOH induced ester saponification and release of the sulfonyl group, as well as selective cleavage of the BOC group on the imino-type N atom of the guanidine. The structure of the emerging **14** rests upon an HMBC correlation between the H atoms of an *N*-methyl group and the carbonyl carbon of the surviving BOC unit. Treatment of **14** with TFA induced loss of the BOC group and cyclization to **15**. The structural assignment of this material again rests on the presence of strong HMBC correlations between the H atoms of both *N*-methyl substituents and the guanidine carbon (double-headed curved arrows, Scheme 1), but the absence of a correlation with the carbonyl carbon. Thus, the imino-hydantoin ring had formed with the regioisomeric distribution of *N*-methyl groups relative to **1**. Compound **15** served as a precursor to the plausible spiroleucettadine isomer **5**.



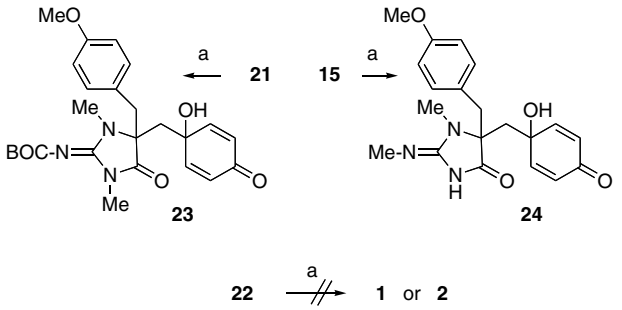
Scheme 1. Reagents and conditions: (a) LDA, THF, −78 °C, 1 h, then **16**, −78 °C, 3 h, 59% (chrom.); (b) 2:1 CH_2Cl_2–TFA, 0 °C, 10 min, 73% (chrom.); (c) **17**, Et_3N, DMF, $HgCl_2$, rt, 12 h, 75% (chrom.); (d) NaH, MeI, DMF, 0 °C to rt, 12 h, 59%; (e) aq KOH, MeOH, reflux, 1 h, 88%; (f) neat TFA, rt, 1 h, 64% (chrom.).

The preparation of the 'correct' isomer of the dimethyl creatinine segment proceeded as delineated in Scheme 2. Thus, TFA treatment of **12** provided **18**, which underwent selective BOC protection at the imino nitrogen to furnish **19**. This intermediate was N-methylated to give **20**, the structural assignment of which again rests upon the diagnostic HMBC correlations indicated with double-headed curved arrows. Full deblocking surrendered compound **22**.

Consistent with the observations of Danishefsky and Li, oxidative attack of **22** with $PhI(OAc)_2$ ('DIB') in hexafluoroisopropanol ('HFIP') furnished an intractable mixture of products. The same outcome obtained upon analogous treatment of **21** or of **15**. However, oxidation of **21** with DIB in aqueous HFIP furnished **23** in a low 8% yield after chromatography (Scheme 3). This material was reasonably stable and it was purified to homogeneity. Consonant with Ref. 3, **23** existed in solution exclusively as the depicted tautomer. The ^{13}C spectrum[9] of **21** exhibited a resonance at 174.4 ppm attributable to the carbonyl group of the creatinine segment. This signal appeared at 175.7 ppm in the ^{13}C spectrum of **23** and it was accompanied by a new carbonyl resonance arising from the dienone at 187.3 ppm.[10] Thus, **23** incorporates an intact creatinine carbonyl, that is, it does not exists as a cyclic orthoamide. Indeed, no signals were apparent near 102 ppm (the chemical shift of the orthoamide carbon in **1**): the ^{13}C spectrum was blank between 113.9 and 79.9 ppm.



Scheme 2. Reagents and conditions: (a) TFA, rt, 15 min, 98%; (b) BOC_2O, $NaHCO_3$, aq dioxane, rt, 12 h, 82% (chrom.); (c) MeI, K_2CO_3, DMF, rt, 15 min, 99%; (d) aq KOH, MeOH, reflux, 1.5 h, 88%; (e) neat TFA, rt, 15 min, 95%.



Scheme 3. Reagents and conditions: (a) $PhI(OAc)_2$, aq $(CF_3)_2CHOH$, rt, 15 min, 8% (chrom.) for **23**; 95% (chrom.) for **24**.

Encouraged by the successful formation of a hydroxy dienone in mixed organic–aqueous media, we subjected **22** to the action of DIB in HFIP/water, in the hope of reaching **1**—or at least its open tautomer **2**. This resulted in formation of a complex mixture of products. An ESI mass spectrum of this crude mixture exhibited a signal at $m/z = 370$, corresponding to the protonated form of **1** or **2**. Unfortunately, all attempts to retrieve the presumed product met with failure.[11]

Spectral data provided as supporting information in Ref. 1 do not seem entirely inconsistent with alternative structure **5** for spiroleucettadine. In an effort to produce **5**, compound **15** was oxidized with DIB in aqueous HFIP. Contrary to previous cases, conversion to dienone **24** occurred efficiently (95%). The NMR spectra of **24** were similar, but by no means identical, to those of **1**. Furthermore, ^{13}C NMR spectroscopy once again ruled out the presence of cyclic orthoamide tautomers. In fact, the spectrum of **15** exhibited a signal at 184.6 (creatinine C=O) whereas **24** displayed resonances at 189.6 (dienone C=O) and 187.6 (intact creatinine C=O).

On a speculative note, the striking contrast between the stability of **24** and the apparent instability of the presumed hydroxydienone arising upon oxidation of **22** raise questions about the viability of intermediates of the type **2**. Analogy with the behavior of an *N*-unprotected dienone intermediate in our synthesis of cylindricines[12] intimates that **2** is readily predisposed to Michael-type polymerization, perhaps accounting for the difficulties we encountered in its isolation.

In conclusion, our results reinforce the cautionary note of Ref. 3 regarding the stability of the orthoamide function of **1**, and by inference, the proposed constitution of the natural product.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and spectral data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.024.

References and notes

1. Ralifo, P.; Crews, P. *J. Org. Chem.* **2004**, *69*, 9025.
2. Calculations were carried out with the Hyperchem® package.
3. Li, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 385.
4. Wong, Y.-S. *Chem. Commun.* **2002**, 686.
5. Belagali, S. L.; Thankamma, M.; Himaja, M. *Indian J. Chem.* **1995**, *34B*, 45.
6. Prepared by NBS bromination of the corresponding toluene (74%). See Supplementary data for details.
7. Cf. Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2002**, *68*, 2300.
8. Obtained by N-methylation (NaH/MeI, THF) of **17**.
9. All NMR spectra discussed herein were recorded in MeOH-d_4 for the purpose of comparison with those of **1**, which were recorded in the same solvent.
10. Our NMR data for **23** are identical to those of Ref. 3.
11. Compound **2** may be prepared in 21% yield by reaction of **22** with $PhI(OCOCF_3)_2$ in moist MeCN (Ref. 3).
12. Cf. the N-unprotected form of compds. **6**–**7** in: Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336.