Tetrahedron Letters 50 (2009) 3182–3184

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Unexpected decarbonylation during an acid-mediated cyclization to access the carbocyclic core of zoanthenol

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ARTICLE INFO

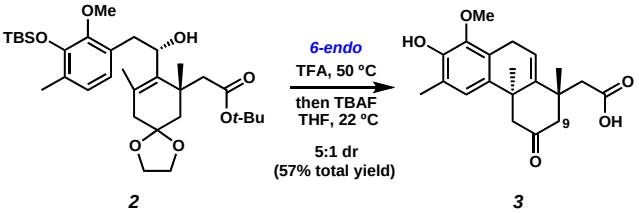
Article history:
Received 17 January 2009
Accepted 21 January 2009
Available online 29 January 2009

ABSTRACT

An unusual loss of CO was observed during a key cyclization event in efforts toward the total synthesis of zoanthenol. The synthesis of the cyclization precursor and a proposed mechanism for decarbonylation are detailed.

Zoanthenol (**1**) is a member of the zoanthamine family of marine alkaloids. In addition to their complex, polycyclic structural framework, the zoanthamines display a range of biological activities including anti-osteoporotic activity in ovariectomized mice, inhibition of inflammation in mouse ears, cytotoxicity against murine leukemia cells, broad-spectrum antibacterial activity, and inhibition of human platelet aggregation.[1] The only completed total syntheses of molecules in this family targeted norzoanthamine, and were published by Miyashita et al.[2] and more recently by Kobayashi and co-workers[3] (Fig. 1).

Recently, we described an acid-mediated 6-endo S_N'-type cyclization to construct the carbocyclic core of zoanthenol.[4] In the event, allylic alcohol **2** was converted smoothly to tricycle **3** upon treatment with neat trifluoroacetic acid at 50 °C (Eq. 1). While tricycle **3** initially seemed well disposed to complete the synthesis, our efforts to install the all-carbon quaternary stereocenter at C(9) were unsuccessful. Anticipating that the remote C(9) quaternary stereocenter would not alter the stereochemical outcome of the acid-mediated cyclization, our retrosynthetic analysis was revised to incorporate its synthesis prior to the key cyclization step.

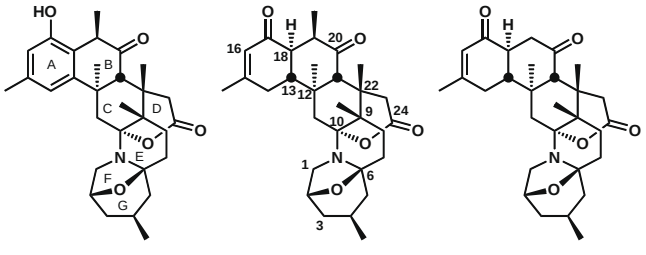


2 **3** (1)

Thus, our revised retrosynthetic analysis begins with the simplification of zoanthenol (**1**) to tricycle **4** (Scheme 1). Disconnection at the B–C ring junction via retro-acid-mediated cyclization reveals allylic alcohol **5**, which could be accessed from benzylic Grignard **6** and enal **7**. Enal **7** was envisioned to be accessible from triol **8**.[5]

Beginning from triol **8**, it was anticipated that treatment with anhydrous copper(II) sulfate in acetone[6] would selectively afford acetonide **9** (Scheme 2). In the event, a mixture of acetal products **9** and **10** was formed. A similar competition between the formation of six- and seven-membered ring acetals had been observed previously.[7] Fortunately, the seven-membered acetal (**9**) can be isomerized to the desired acetonide in 50% conversion and with 100% mass recovery, which allows access to synthetically useful quantities of acetonide **10**. Our next goal was to homologate the primary alcohol by one carbon. Thus, olefin **10** was hydrogenated to give **11**, which in turn was activated by mesylation, and was displaced with KCN to form nitrile **12**. Given the challenging nature of S_N2 chemistry at neopentyl centers,[8] we were delighted to observe good yields in the homologation sequence.

Desilylation of **12** with TBAF in THF at 40 °C revealed a secondary alcohol, which was quantitatively converted to ketone **13** under Swern oxidation conditions (Scheme 3). The methylation of ketone **13** was accomplished by reverse dropwise addition of the enolate solution into methyl iodide at −35 °C to afford the desired methyl ketone **14** in 78% yield. Methyl ketone **14** was then enolized and trapped with Tf_2NPh to give enol triflate **15** in 97% yield. Stille



Zoanthenol (1) *Zoanthamine* *Norzoanthamine*

Figure 1.

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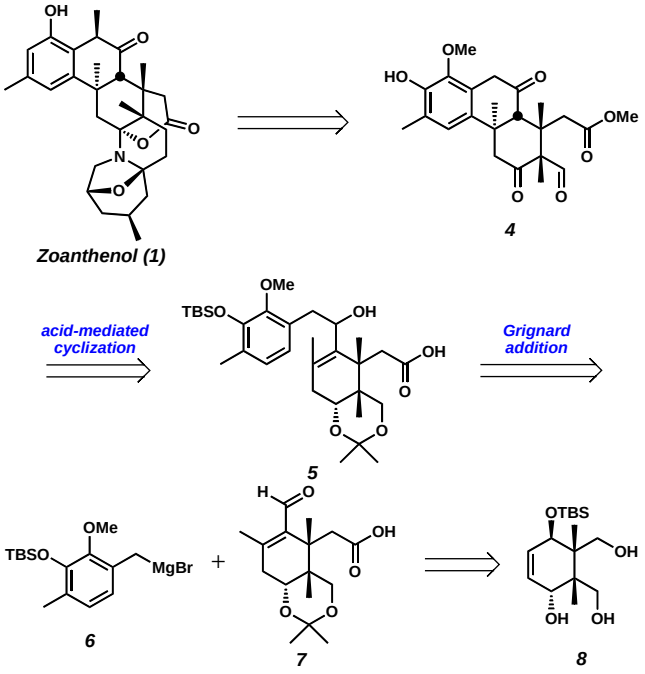
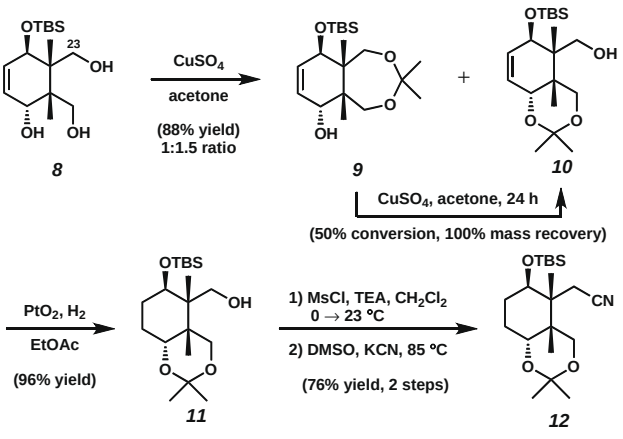
doi:10.1016/j.tetlet.2009.01.121



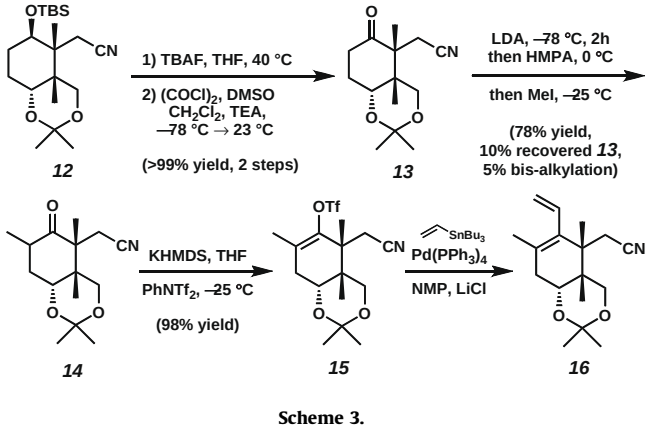
Scheme 1.

coupling with vinyl tributylstannane proceeded smoothly to provide diene **16**.

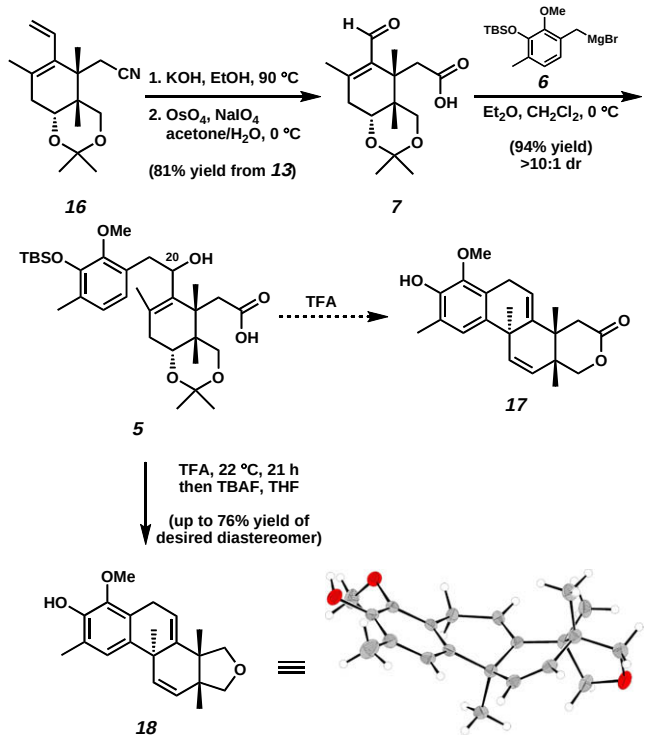
Nitrile **16** was then converted to enal **7** by hydrolysis of the nitrile to the corresponding carboxylic acid followed by oxidative cleavage of the terminal olefin (Scheme 4). Addition of Grignard reagent **6** to a solution of enal **7** provided allylic alcohol **5** in 94% yield and with a greater than 10:1 diastereomeric ratio. Given our experience with this type of cyclization, we anticipated formation of tetracycle **17** upon treatment with neat TFA at ambient temperature. To our delight, we observed the formation of a new cyclized compound displaying the desired relative stereochemistry at C(12). However, we were surprised to find that there were no signals in the ^{13}C NMR and IR spectra corresponding to the lactone functionality that we expected in the desired product (**17**). We tentatively assigned the observed product as **18**. Indeed, X-ray diffraction data obtained from a single crystal confirmed both the desired relative stereochemistry and the formation of a tetrahydrofuran ring.



Scheme 2.



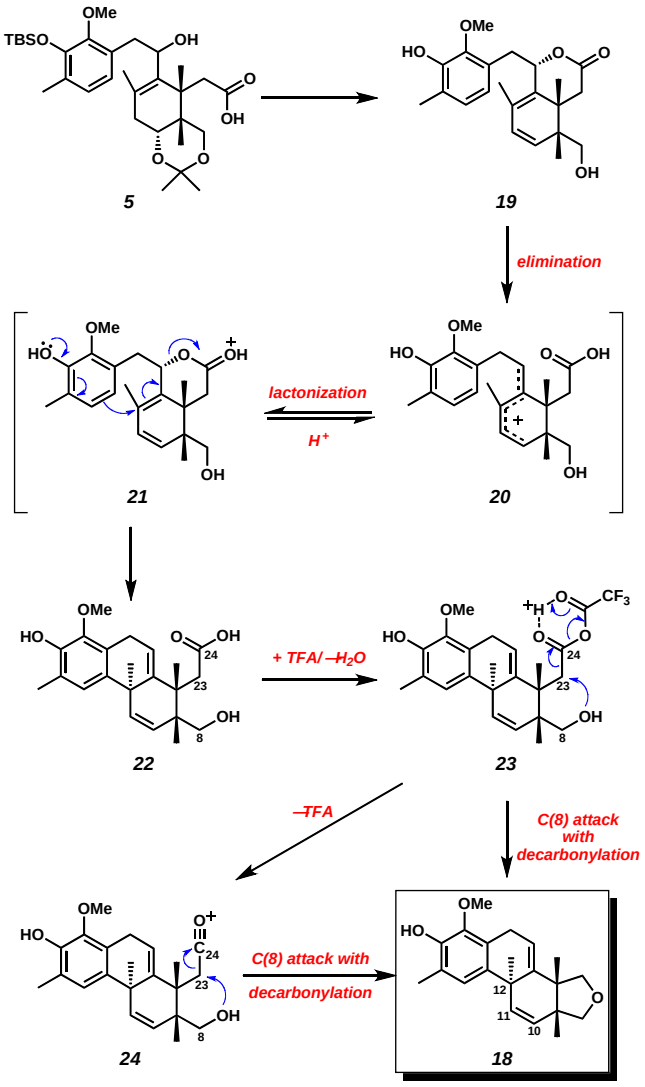
Scheme 3.



Scheme 4.

A potential mechanism by which the observed product may be formed is outlined in Scheme 5. Lactonization and elimination of the C(10) acetal should afford intermediate **19**. Protonation of the lactone carbonyl would induce an equilibrium between highly stabilized carbocation **20** and intermediate **21**. The stability of intermediate **20** likely aids in the formation of the product in the high yields observed.[9] Given the extraordinary selectivities observed for this system, we hypothesized that the cyclization event occurs much more quickly than the C(23)–C(24) bond cleavage and that protonated lactone **21** is the intermediate that undergoes cyclization. Following cyclization, carboxylic acid **22** condenses with an equivalent of TFA to form mixed anhydride **23**. This anhydride may undergo decomposition to form acylium **24**, releasing an equivalent of TFA. The pendant C(8) alcohol would then attack either activated anhydride **23** or acylium **24** to release CO and to form the tetrahydrofuran-containing product **18**.

In summary, we have described an efficient approach to the synthesis of intermediate **3**, highlighted by a challenging S_N2 ni-



Scheme 5.

trile displacement and a highly efficient, stereoselective Grignard addition to access the desired allylic alcohol. The cyclization of this allylic alcohol represents a truly remarkable reaction, wherein a desilylation, acetonide elimination, and CO extrusion all occur in addition to the desired cyclization. These transformations occur in one reaction flask to form the desired diastereomer of a tetracyclic compound possessing three all-carbon quaternary stereocenters in 76% yield. Efforts to apply this approach to a system wherein decarbonylation is not observed are ongoing.

Acknowledgments

The authors wish to thank Novartis (predoctoral fellowship to JLS), the Philanthropic Education Organization (Scholar Award to JLS), the John and Fannie Hertz Foundation (predoctoral fellowship to DCB), and Abbott, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, and Caltech for their generous financial support. The authors acknowledge Dr. Andrew McClory for experimental assistance and helpful discussions. Special thanks to Professor Andrew S. Kende for a stimulating discussion regarding the mechanism in Scheme 5.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.121.

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