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Tetrahedron Letters 45 (2004) 6051–6053
Tetrahedron Letters

Studies toward the synthesis of roseophilin: lactam formation and Wittig/aldol methodology

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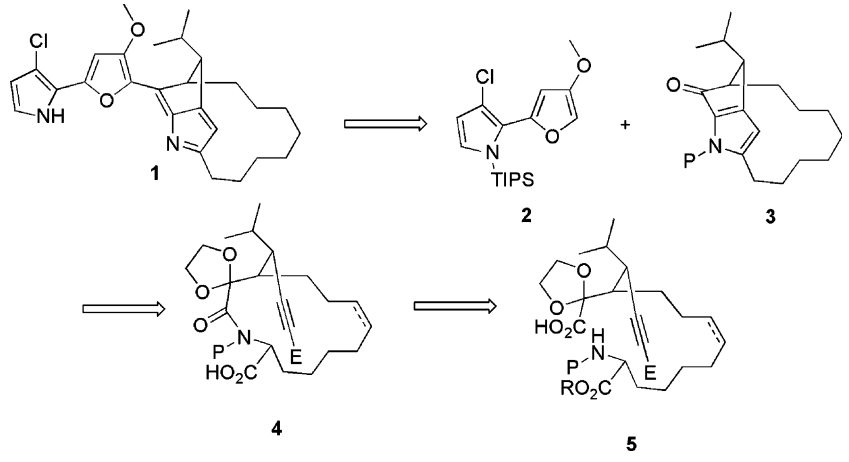
Received 29 April 2004; revised 27 May 2004; accepted 2 June 2004
Available online 25 June 2004

Abstract—In this communication, we introduce our retrosynthetic approach to the synthesis of roseophilin. An interesting, new Wittig/aldol methodology is described. Also discussed is macrocyclization of an azide acid to form an unsaturated lactam.

In 1992, Hayawa, Kawakami, and Seto isolated roseophilin (**1**) from the culture broth of *Streptomyces griseoviridis*. The hydrochloride salt of the pentacyclic compound showed submicromolar cytotoxicity in vitro against K562 human erythroid leukemia and KB human epidermoid carcinoma cell lines.[1] The antitumor agent **1** possesses a unique structure consisting of a strained macrotricyclic core attached to a substituted pyrrolefuran moiety. The unusual nature of the structure coupled with its antitumor characteristics make roseophilin an attractive synthetic target and a lead structure in the search for cancer drugs. This is supported by the magnitude of synthetic efforts reported to date.[2–13]

Our first obvious retrosynthetic cut disconnects the furanpyrrole moiety **2** from the macrotricyclic core **3** (Scheme 1). In the first reported total synthesis of roseophilin, Fürstner and Weintritt obtained **1** through



Scheme 1. Retrosynthetic analysis of roseophilin.

Keywords: Wittig; Aldol; Roseophilin; Lactam; Cyclization.
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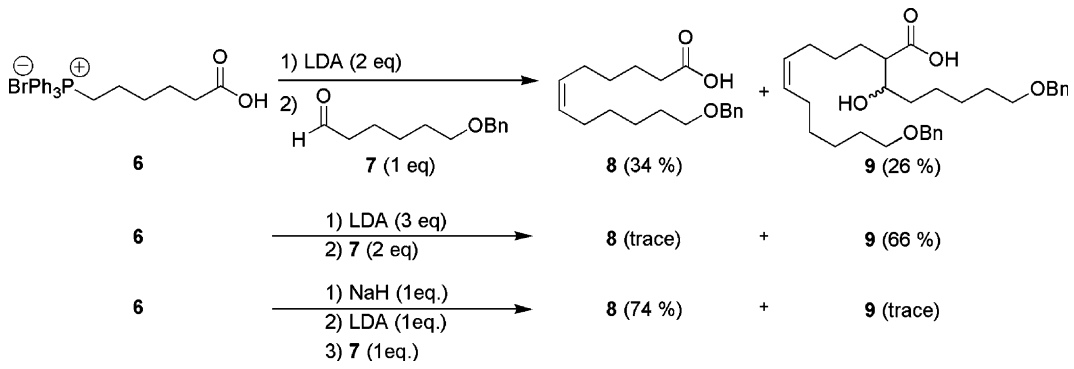
doi:10.1016/j.tetlet.2004.06.013

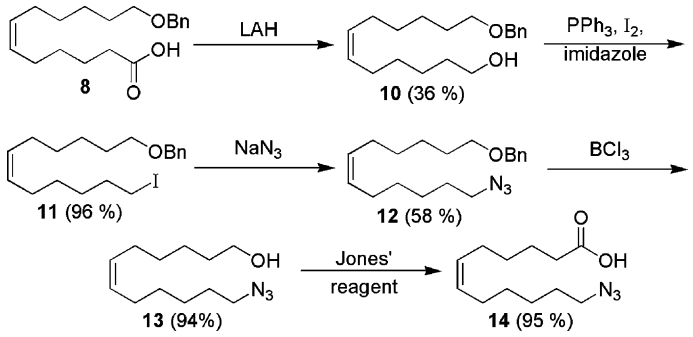


Scheme 2. Wittig/aldol.

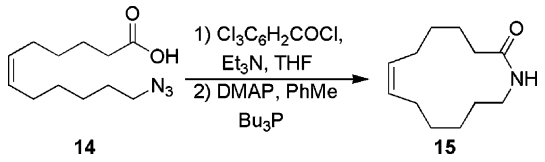
condensation of the two segments **2** and **3**.[7] We envisioned delivery of ketopyrrole **3** using 1,3-dipolarcycloaddition methodologies on the amino acid **4**. Unlike all other synthetic efforts to obtain compound **3**, we chose to investigate macrocyclization via connecting two polar end groups tethered by an aliphatic chain. Considering the hydrophobic nature of the tether, we surmised that coiling of cyclization precursors such as **5** in polar protic solvents would promote macrocyclization. Also, *cis*-unsaturation in the aliphatic tether, where the dashed line in compounds **4** and **5** denote the site of unsaturation, could deliver substrates that have a propensity for intramolecular reactivity. We now report the formation of macrolactams as well as an interesting Wittig/aldol methodology (Scheme 2) we observed while generating *cis*-olefins.

During the formation of *cis*-olefins for macrocyclization studies, an interesting observation was made. The use of LDA to generate the carboxylate anion and ylide of Wittig salt **6** followed by addition of aldehyde **7** led to the formation of a significant amount of side product (Scheme 2). Isolation and characterization of this side product led to the realization that the Wittig reaction was occurring efficiently giving enoic acid **8**, but an aldol reaction[14] was taking place simultaneously, generating the enol acid **9**. We performed the standard Wittig reaction, and an aliquot was taken after addition of 0.25 equiv of the aldehyde and the Wittig/aldol product **9** was already observed. We concluded that the LDA was basic enough to generate the ylide as well as the carboxylate dianion. Further investigation into this process led to an ability to either optimize or inhibit the Wittig/aldol pathway. By increasing the number of equivalents of LDA from two to three and increasing the number of equivalents of aldehyde from one to two, we were able to solely produce the Wittig/aldol product **9**. Suppression of this pathway was accomplished by forming the carboxylate anion with sodium hydride, thereby generating the more ionic sodium carboxylate as opposed to the lithium carboxylate. Formation of the sodium carboxylate decreases the acidity of the protons alpha to the carboxylic acid. Therefore, upon addition of 1 equiv of LDA, the ylide is generated instead of the carboxylate dianion. Using this methodology, the major product is the *cis*-olefin **8**, and the aldol product is no longer observed.

With the ability to either solely produce benzyl ether acid **8** or functionalized ether acids such as **9**, we proceeded to investigate lactam formation. After disappointing initial attempts to form 13-membered lactams from simple amino acids employing peptide coupling reagents, we chose to cyclize an azide acid, which was shown to deliver macrolactams by Vilarrasa and coworkers.[15] The cyclization precursor was generated from the unsubstituted Wittig product **8**. First, reduction of the acid **8** generated the benzyl ether alcohol **10** with the low yield attributed to benzyl ether cleavage. The alcohol was then converted to the iodide,[16] and the iodide was displaced with azide[17] ion to generate the masked amine **12**. Benzyl ether cleavage followed by oxidation of the resultant alcohol **13** generated the cyclization precursor **14** (Scheme 3).



Scheme 3. Formation of azide acid.



Scheme 4. Macrolactamization.

Following the work of Vilarrasa and co-workers[15] we produced lactam **15** (Scheme 4). High dilution conditions were followed as well as generation of the anhydride that is used in Yamaguchi lactonization[18] protocols. Unlike Yamaguchi lactonization, tributylphosphine was introduced to the cyclization flask; tributylphosphine unmasks the amine in situ. We initially formed an unsaturated lactam, and the yield of lactam formation was similar to that reported by Vilarrasa (57%). In the case of azide acid **14**, the *cis*-olefin did not considerably increase the yield, but it also did not interfere with or inhibit lactam formation. The synthesis of **15** establishes an ability to form 13-membered unsaturated lactams, and thus the feasibility of our retrosynthetic analysis.

In conclusion, we have demonstrated the ability to harness the Wittig/aldol reaction in order to generate substituted and unsubstituted *cis*-olefins. We also generated a *cis*-unsaturated lactam following published protocols where the unsaturation did not interfere with the lactamization pathway. These findings should prove beneficial in our efforts to synthesize roseophilin.

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