Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 6088–6114

New synthetic technology for the construction of *N*-hydroxyindoles and synthesis of nocathiacin I model systems

K. C. Nicolaou,[a,b,*] Anthony A. Estrada,[a,b] Graeme C. Freestone,[a] Sang Hyup Lee[a] and Xavier Alvarez-Mico[a]

[a]*Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States*
[b]*Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, United States*

Received 12 January 2007; revised 7 March 2007; accepted 12 March 2007
Available online 16 March 2007

Abstract—A new synthetic method providing expedient access to a wide range of polyfunctionalized *N*-hydroxyindoles (**IV**) is reported. These unique constructs are assembled by nucleophilic additions to in situ generated α,β-unsaturated nitrones (**III**) through carbon–carbon and carbon–heteroatom bond formation. The new synthetic technology was applied to the synthesis of nocathiacin I (**1**) model systems (**2** and **3a–c**) containing the *N*-hydroxyindole structural motif.

1. Introduction

Nocathiacin I (**1**, Fig. 1), a complex thiopeptide antibiotic isolated from *Nocardia* sp. (ATCC-202099) and the fungus *Amicolaptosis* sp., exhibits remarkably potent in vitro and in vivo activity against Gram-positive bacteria.[1–3] One of the most striking structural motifs within the molecular framework of nocathiacin I (**1**) is the *N*-hydroxyindole moiety that carries the oxygen ether linkage and bridges the 15-membered depsipeptide ring with the 10-membered macrolide system of the molecule.[4] Challenged by the daunting structure of nocathiacin I (**1**) and intrigued by the rarity of its *N*-hydroxyindole structural motif in nature and the relative scarcity of methods for its assembly,[5] we initiated a program directed toward the development of synthetic technologies for the generation of substituted *N*-hydroxyindoles suitable for potential applications to complex molecule construction.

In this article, we describe a detailed account of our investigations in this area that culminated in a general method for the synthesis of highly substituted *N*-hydroxyindoles (**IV**, Scheme 1)[6] from readily available aromatic precursors and a variety of nucleophiles through the trapping of in situ generated α,β-unsaturated nitrones and the application of the developed technology to the construction of certain nocathiacin I (**1**) model systems such as **2** and **3a–c** (Fig. 1).[7]

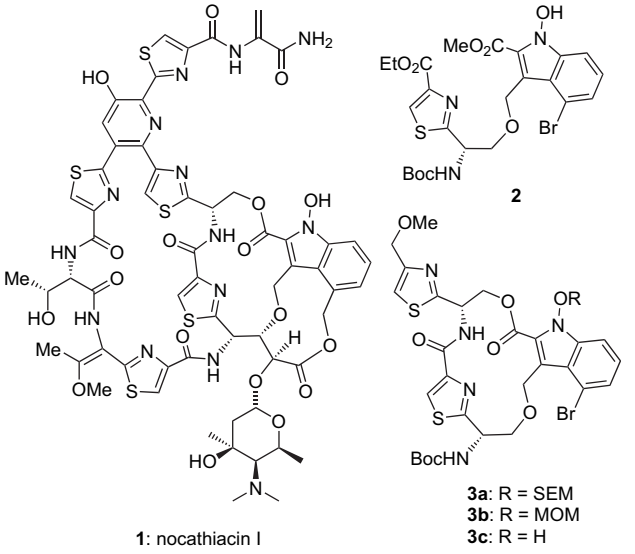
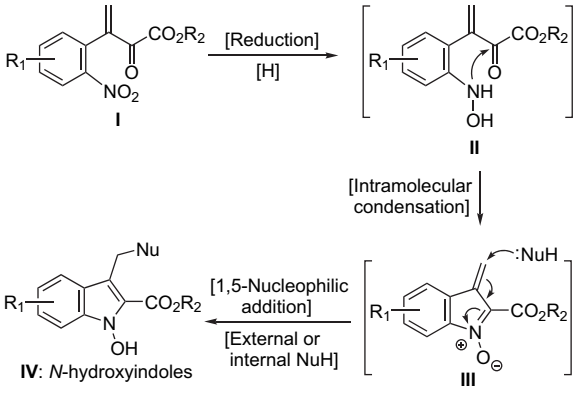


Figure 1. Structures of nocathiacin I (**1**) and *N*-hydroxyindole model systems **2** and **3a–c**. SEM, 2-(trimethylsilyl)ethoxymethyl; MOM, methoxymethyl.

Keywords: *N*-Hydroxyindole; Nitrone; Nocathiacin I; Nucleophilic addition; Synthetic methods.
* Corresponding author. Tel.: +1 858 784 2400; fax: +1 858 784 2469; e-mail: kcn@scripps.edu

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.072



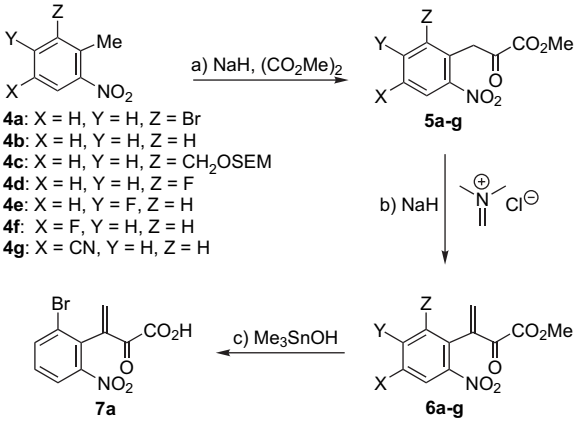
Scheme 1. General route for the construction of 3-substituted *N*-hydroxyindoles (**IV**).

2. Results and discussion

2.1. Synthetic technology development

Based on certain precedents,[5c–g] our general strategy for the construction of *N*-hydroxyindoles, shown in Scheme 1, was devised to take advantage of the ready availability of aromatic nitro compounds as starting materials and the perceived propensity of α,β-unsaturated nitrones to enter into reactions with suitable nucleophiles and give stable adducts. Thus, it was envisioned that reduction of nitro ketoesters **I** under appropriate conditions should produce hydroxylamines **II**, which were expected to undergo facile intramolecular condensation to afford the α,β-unsaturated nitrones **III**, whose existence in the presence of suitable nucleophiles should be transient, leading through 1,5-addition reactions, to *N*-hydroxyindoles **IV**.[8] Having defined the general cascade for the projected synthesis of *N*-hydroxyindoles, the synthesis of the starting nitro ketoesters, the exploration of conditions for their reduction, and the range of capable nucleophiles to be employed in this scheme became the first objectives of the investigation.

Scheme 2 summarizes the synthesis of nitro ketoesters **6a–g** and nitro ketoacid **7a**, which were required for the present



Scheme 2. Synthesis of nitro ketoesters **6a–g** and acid **7a**. Reagents and conditions: (a) NaH (4.0 equiv) $(CO_2Me)_2$ (5.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 12 h, **5a** (60%), **5b** (60%), **5c** (85%), **5d** (80%), **5e** (75%), **5f** (75%), **5g** (65%); (b) NaH (1.1 equiv), THF, 0 °C, 1 h; then $CH_2{=}N^+Me_2Cl^-$ (3.0 equiv), 25 °C, 12 h, **6a** (80%), **6b** (67%), **6c** (98%), **6d** (74%), **6e** (55%), **6f** (75%), **6g** (50%); (c) Me_3SnOH (3.0 equiv), 1,2-DCE, 80 °C, 20 min, 77%. DMF, *N*,*N*-dimethylformamide; DCE, 1,2-dichloroethane.

studies. Thus, reaction of the corresponding nitrotoluene compound with excess dimethyl oxalate in the presence of NaH in DMF at 0–25 °C furnished ketoesters **5a–g** in yields ranging from 60 to 85%.[9] Exposure of each of these compounds to Eschenmoser's salt in the presence of NaH in THF at 0–25 °C then led to the desired α,β-unsaturated ketoesters **6a–g** in 50–98% yield.[10,11] The α,β-unsaturated ketoacid **7a** was prepared from methyl ester **6a** through the action of Me_3SnOH in 1,2-dichloroethane at 70 °C (77% yield), as standard hydrolysis methods resulted in decomposition, as alluded to in a previous communication from our laboratories.[12]

The desired generation and trapping of the α,β-unsaturated nitrones was achieved under two sets of experimental conditions. Scheme 3 depicts the first procedure (method A) for this cascade sequence involving activated zinc [Zn] (prepared from zinc dust, 1,2-dibromoethane and TMSCl) as the reducing agent as demonstrated with nitro ketoester **6a**.[13] Thus, refluxing zinc dust with 1,2-dibromoethane in THF, followed by cooling to 25 °C (refluxing/cooling process repeated three additional times) and subsequent addition of TMSCl, followed by a mixture of aqueous 1 N NH_4Cl and **6a** resulted in the formation of *N*-hydroxyindoline **9** (56% yield) and hydroxylactam **14** (10% yield). The structure of the latter compound was unambiguously proven by X-ray crystallographic analysis (see ORTEP structure, Scheme 3).[14] These results can be rationalized by envisioning ring closure within the structure of the initially formed hydroxylamine (**8**) leading to *N*-hydroxylamine tertiary alcohol **9** (path A, Scheme 3) on one hand, and 1,4-addition of NH_3 to the starting material **6a** followed by a lactamization/enolization sequence within the initially formed aminoketoester **13** to generate compound **14** (path B, Scheme 3) on the other. Tertiary alcohol **9** exhibited high reactivity, especially upon exposure to acidic conditions that resulted in the loss of a molecule of water, generating a reactive species presumed to be the α,β-unsaturated nitrone **10**, whose isolation proved elusive. The presence of the α,β-unsaturated nitrone **10** was supported by its trapping with a variety of nucleophiles. Thus, reaction of **9** with benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) in DME at 40 °C in the presence of *p*TsOH led to the formation of *N*-hydroxyindoles **11** (55% yield) and **12** (90% yield), respectively. These reactions are presumed to proceed either directly from **9** by S_N2'-type displacement, or by 1,5-addition to the initially formed nitrone (**10**), or through both of the potential mechanistic pathways. It is interesting to note that the isolation of *N*-hydroxyindoles **11** and **12** stands in contrast to the observations of Myers and Herzon in which their initially formed products from 1,5-nucleophilic additions to a sterically congested α,β-unsaturated nitrone proved too labile for isolation, rapidly reverting back to their components instead.[5d]

In search of a more direct and convenient access to the desired *N*-hydroxyindoles from the same starting materials, an alternative experimental procedure was explored and optimized as summarized in Scheme 4 and Table 1. According to this method (method B), nitro ketoester **6a** was treated with $SnCl_2\cdot 2H_2O$ (2.2 equiv) in the presence of benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) and 4 Å molecular sieves in DME at 40 °C for 1–1.5 h, conditions that