ORGANIC LETTERS

2002
Vol. 4, No. 19
3243−3245

Stereoselective Total Synthesis of Dihydrocorynantheol

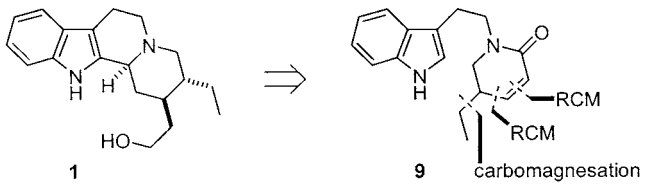
Alexander Deiters and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

sfmartin@mail.utexas.edu

Received July 4, 2002

ABSTRACT



A stereoselective synthesis of the indole alkaloid dihydrocorynantheol (1) from indole-3-acetic acid has been achieved by a sequence involving 9 as a key intermediate. The synthesis of the unsaturated lactam ring in 9 highlights a series of catalytic organometallic reactions featuring two ring-closing metatheses and a zirconocene-catalyzed carbomagnesation. Since no protecting groups were used, the present synthesis of 1 is exceedingly concise, consisting of only eight distinct operations.

We have had a longstanding interest in applying ring-closing metathesis (RCM) as a key reaction for the construction of nitrogen heterocycles and the frameworks of alkaloid natural products.[1] Indeed, our use of an RCM reaction to fabricate the ABCE ring system of manzamine A represents one of the first applications of such processes to complex molecule synthesis.[1a] That RCM is a powerful reaction in natural product synthesis is amply evident from the numerous applications of this general transformation that have appeared since Grubbs first showed that functionalized α,ω-dienes served as substrates for such ring closures.[2,3]

We now report the use of RCM reactions in an exceedingly short synthesis of the archetypal corynantheine alkaloid dihydrocorynantheol (**1**). Indole alkaloids of the corynantheine group have attracted interest over the years because members exhibit antiparasitic, antiviral, and analgesic activity.[4] Dihydrocorynantheol (**1**) was first isolated from the bark of *Aspidosperma marcgravianum* Woodson (Apocynaceae) in 1962.[5] Since its discovery, **1** has been a popular target for the application of new synthetic methods, and there are a number of partial[6] and total syntheses of **1**.[7] Syntheses of enantiomerically pure **1** have employed either an intermediate

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10.1021/ol026470a CCC: $22.00
Published on Web 08/23/2002

derived from the chiral pool,[7f] a chiral auxiliary,[7g] or a resolution step.[7h]

The key bond disconnections in our retrosynthetic analysis of dihydrocorynantheol (**1**) are summarized in Figure 1. We

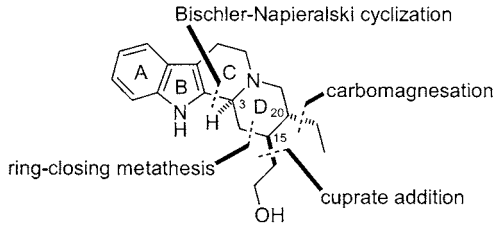
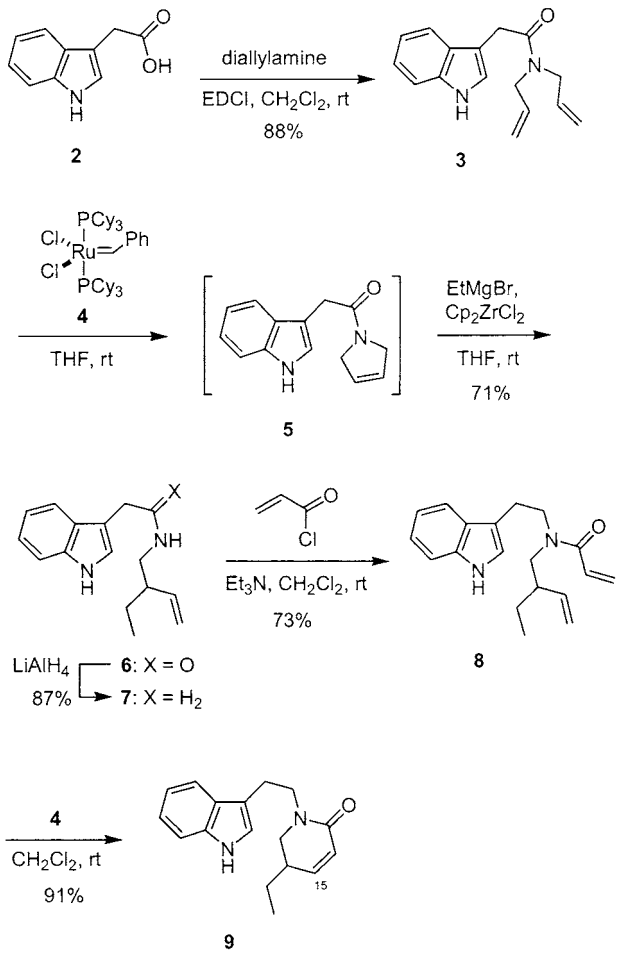


Figure 1. Dihydrocorynantheol (**1**): key bond disconnections.

planned to use a Bischler−Napieralski cyclization to form the tetracyclic skeleton from a suitable ABD precursor. To complement this classical ABD → ABCD approach, we envisioned a novel strategy for constructing the functionalized piperidine D-ring by a conjugate addition of an organocuprate to an α,β-unsaturated lactam that would in turn be prepared by a RCM reaction. The substrate for this RCM would be assembled via a zirconocene-catalyzed carbomagnesation of a double bond,[8,9] a reaction that has only once been applied in natural product synthesis,[10] although not to the synthesis of an alkaloid. Because this reaction sets the stereocenter at C(20), use of a chiral catalyst would enable a facile enantioselective synthesis of **1**.[11]

The synthesis of **1** commenced with an EDCI coupling of indole-3-acetic acid (**2**) with diallylamine to give the amide **3** in 88% yield (Scheme 1). Compound **3** was then converted into the homoallylic amide **6** in a novel one-pot sequence in which **3** was first cyclized via a RCM reaction employing Grubbs' catalyst **4** (0.5 mol %) in THF at room temperature

Scheme 1



to provide the amide **5**. Zirconocene dichloride (15 mol %) and EtMgBr (4 equiv) were then simply added to the mixture to induce the requisite carbomagnesation[9] of **5** and a subsequent elimination to deliver **6** in 71% yield from **3**. Significantly, it was not necessary to protect the indole-NH during this conversion. It is possible to perform enantioselective carbomagnesations of cyclic allyl amides using the chiral catalyst (EBTHI)Zr-binol,[11] so there is an opportunity to prepare **6** in enantiomerically pure form although we have not yet examined this possibility. The amide **6** was then reduced to the amine **7** ($LiAlH_4$, Et_2O, rt, 87%), acylation of which with acryloyl chloride in CH_2Cl_2 at room temperature gave **8** (73%) to set the stage for the second RCM reaction. In the event, cyclization of **8** using 5 mol % of **4** delivered lactam **9** in 91% yield.[12]

The lactam **9** is potentially a versatile intermediate for the syntheses of corynantheoid and other indole alkaloids because the α,β-unsaturated carbonyl moiety should enable introduction of a variety of substituents onto the D-ring at C(15) via conjugate addition. However, α,β-unsaturated

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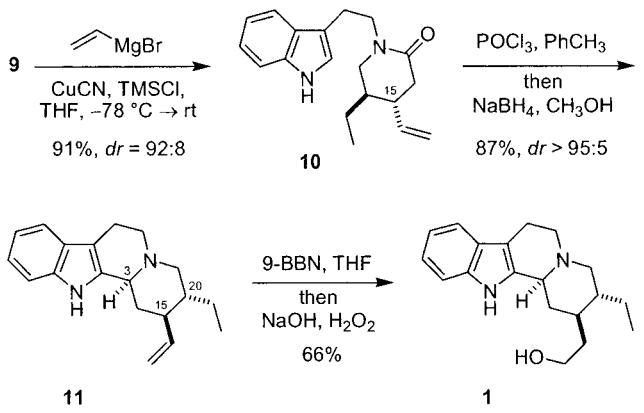
lactams are notoriously poor Michael acceptors[13] and there are relatively few examples of 1,4-additions of organometallic reagents to unsaturated piperidinones.[14] In most of these cases, there is an additional electron withdrawing group on the nitrogen atom and/or in conjugation with the double bond.

After surveying a number of reagents and conditions, we discovered that organocuprates derived from Grignard reagents were superior nucleophiles in conjugate additions to **9**.[15] The reaction of **9** with vinylmagnesium bromide in the presence of stoichiometric amounts of CuCN and trimethylsilyl chloride (TMSCl) proceeded in 91% yield to give an inseparable mixture (dr = 92:8) of **10** and its C(15) epimer (Scheme 2). It is again noteworthy that no protection of the

Scheme 2



indole-NH is required. Use of TMSCl in the 1,4-addition prevented the occurrence of side reactions, presumably by trapping the transient copper enolate generated upon addition of the vinyl cuprate to **9**.

The final assembly of the indoloquinolizidine skeleton was achieved by a Bischler−Napieralski reaction of **10** ($POCl_3$, toluene, 100 °C) followed by stereoselective hydride reduction ($NaBH_4$, CH_3OH, 0 °C) to furnish **11** in 87% yield as the only diastereomer. The relative configurations at C(3), C(15), and C(20) were confirmed by NOE experiments. Regioselective hydroboration of the pendant vinyl group in **11** with 9-BBN in THF at room temperature followed by an oxidative workup (NaOH, H_2O_2, THF, 0 °C) delivered dihydrocorynantheol (**1**) in 66% yield [mp 175−177 °C (lit.[7a] mp 178−180 °C)]. The ^1H and ^{13}C NMR spectra of **1** thus obtained were consistent with those previously reported.[7d,g,h]

In summary, an efficient (19% overall yield), eight-step stereoselective synthesis of dihydrocorynantheol (**1**) has been completed. The synthesis was conducted without any protecting groups and features the extensive application of catalytic organometallic transformations, including two RCM reactions and the first application of an olefin carbomagnesation reaction to alkaloid synthesis. Indeed, the synthesis could be rendered enantioselective by using a chiral catalyst for the carbomagnesation step.

The use of RCM and other organometallic transformations as key steps in the synthesis of alkaloids is being actively pursued in our laboratory, and the results of these studies will be reported in due course.

Acknowledgment. We thank the National Institutes of Health, The Robert A. Welch Foundation, Merck Research Laboratories, and Pfizer, Inc., for their generous support of this research. A.D. gratefully acknowledges a Feodor−Lynen postdoctoral fellowship from the Alexander von Humboldt Foundation.

Supporting Information Available: Experimental procedures, analytical data, and ^1H NMR spectra for **1**, **6**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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