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Stereoselective Synthesis of a Model C(18)–C(35) Spiroketal Fragment of Integramycin

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Abstract

A highly stereoselective synthesis of a model C(18)–C(35) spiroketal unit (7) of integramycin has been accomplished via an enantioselective stannyl-crotylboration reaction and an *N*-iodosuccinimide-mediated spiroketalization of 19a.

Integramycin (**1**, Figure 1) is an HIV-1 integrase inhibitor that was isolated from an *Actinoplanes* species by Singh and coworkers in 2002.¹ Integrase is a critical enzyme for the process by which reverse-transcribed viral DNA is inserted into the host chromosomal DNA, an essential step for HIV replication.² Integramycin inhibits the third step of the integration process, specifically strand transfer of the proviral DNA into the host cell DNA, with an IC₅₀ value of 4.0 μM. Integramycin (**1**) contains a *cis*-octahydronaphthalene core unit with spiroketal and acyl tetramic acid containing side chains.

In spite of several reported synthetic studies,³ the total synthesis of integramycin has not been accomplished. As part of our ongoing studies on the synthesis of integramycin, we report herein a highly stereoselective synthesis of a model C(18)–C(35) spiroketal unit **7**. Key steps of this synthesis include an *N*-iodosuccinimide (NIS)-mediated spiroketalization of the 1-hydroxy-9-en-5-one **19a** and an application of the stannyl-crotylboration reaction recently developed in our laboratory.⁴

Our retrosynthetic analysis of integramycin (**1**) is outlined in Figure 1. We envisioned that the natural product should be accessible by coupling of tetramic acid intermediate **2**, *cis*-octahydronaphthalene carboxaldehyde **3**, and Wittig reagent **4**. Retrosynthetic disconnection

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via Internet at <http://pubs.acs.org>.

of the C(22)–C(23) bond in **4** gives aldehyde **5** and vinyl iodide **6**, substrates for a Nozaki-Hiyama-Kishi coupling reaction.

Our synthesis commenced with the Horner-Wadsworth-Emmons reaction⁵ of the known β -keto phosphonate **8**⁶ and aldehyde **9**,⁷ followed by Pd-catalyzed hydrogenation of the resulting olefin to give imide **10** (Scheme 1). Diastereoselective α -methylation of **10** was performed by using LiHMDS as the base under Evans' asymmetric alkylation conditions.⁸ Reductive removal of the oxazolidinone unit by treatment of the alkylated product with NaBH₄ afforded primary alcohol **11**. Finally, protection of the primary hydroxyl group of **11** by treatment with p-methoxybenzyl trichloroacetimidate, followed by removal of the TBDPS group with TBAF and oxidation of the resulting primary alcohol under Parikh-Doering reaction conditions⁹ provided aldehyde **5** in excellent overall yield.

The enantioconvergent, enantioselective stannylcrotylboration reaction⁴ recently developed in our laboratory can be used to synthesize a variety of highly enantiomerically enriched γ -stannyl homoallylic alcohols by treating racemic allenylstannane **12**¹⁰ (Scheme 2) with (Ipc)₂BH followed by addition of an aldehyde. For the present synthesis, we employed TIPS-protected 3,5-dihydroxybenzaldehyde **14** (1.0 equiv) in the reaction with the highly enantiomerically enriched crotylborane **13**, formed in situ by treating **12** (2.0 equiv) with (*d*Ipc)₂BH (1.9 equiv) at –20 °C.¹¹ This afforded γ -stannyl homoallylic alcohol **15** in 81% yield and 89% ee with 7.9:1 *anti:syn* ratio (Scheme 2). Protection of the newly formed hydroxyl group as a TES ether and subsequent treatment with I₂ to effect iodine-tin exchange gave vinyl iodide **6**. Coupling of **5** and **6** by using the Nozaki-Hiyama-Kishi reaction¹² provided an inseparable mixture of the allylic alcohols and unreacted aldehyde **5**. Treatment of this mixture with TESOTf enabled **16** (as a mixture of diastereomers) to be isolated in 83% yield over the two steps. Removal of the PMB ether with DDQ generated **17**, which was subsequently converted into the primary iodide by treatment with I₂ and PPh₃. Finally, treatment of the iodide with excess of PPh₃ in benzene at reflux furnished the phosphonium salt **4**.

We next turned to the task of forming the spiroketal unit stereoselectively. Cyclohexane carboxaldehyde was used as a model substrate in the Wittig reaction with **4**, which provided the (*Z*)-olefinic product in 86% yield (Scheme 3). Removal of both TES protecting groups by treatment with PPTS in MeOH then afforded diol **18**. A ruthenium-mediated olefin isomerization¹³ selectively converted the allylic alcohol **18** to the saturated ketone **19a** without scrambling the *Z* olefin in the substrate. Ketone **19a** was obtained as a 1 : 1.3 mixture with the corresponding hemiacetal isomer **19b**, along with 10–20% of unidentified inseparable impurities. This impure product mixture was used in the following spiroketalization experiments. Among several reagents¹⁴ that have been reported to mediate the oxidative spiroketalization of hemiacetal-alkene (or keto-alcohol-alkene) substrates, we elected to use NIS in our experiments. We hypothesized that hemiacetal isomer **19b** would undergo cyclization through iodonium ion intermediate **23** (Path b, Scheme 4), with stereochemical control governed by minimization of 1,3-allylic steric interactions.¹⁵ Attack of the hemiacetal hydroxy group in **23** from the top face of the iodonium ion, as indicated in Scheme 4, leads to the doubly anomeric effect stabilized spiroketal **20**. Ketone isomer **19a** could similarly undergo spirocyclization by Path a via oxonium intermediate **22** with the same stereochemical control as in Path b. In the event, treatment of the **19a/19b** mixture with NIS in CH₂Cl₂ at 23 °C for 24 h delivered the desired spiroketal **20** as the predominant product in 32% overall yield from **18**. Some side products were also observed, but could not be isolated in pure form for structural characterization. The iodine substituent was readily cleaved reductively under radical conditions utilizing Bu₃SnH and AIBN. Subsequent treatment of the de-iodinated spiroketal with TBAF in THF provided the model spiroketal **7** in 98% yield.

The efficiency of the NIS-mediated spiroketalization of the **19a/19b** mixture in Scheme 3 was compromised by the presence of impurities deriving from the preceding olefin isomerization step that could not be separated. In order to investigate the NIS-mediated spiroketalization with a pure substrate, an alternative route to the **19a/19b** mixture was developed (Scheme 5). After coupling of **5** with **6** via the Nozaki-Hiyama-Kishi reaction, the secondary alcohol of the allylic alcohol product was protected as a pivaloyl ester, thereby providing **24** in 81% yield. The *E* olefin was reduced by using diimide generated from NBSH (*o*-nitrobenzenesulfonyl hydrazide)¹⁶ in the presence of Et₃N. Reductive cleavage of the PMB ether then provided primary alcohol **25**. Iodination of **25**, followed by treatment with PPh₃, furnished the new C(18)–C(35) fragment **26** in 86% yield. Wittig olefination of cyclohexanecarboxaldehyde and the ylide generated from **26** provided the *Z* olefin product in 89% yield. The pivaloyl group was removed by treatment with DIBAL-H, and then the resulting secondary alcohol was oxidized to afford ketone **27**. Upon removal of the TES protecting group with HOAc and H₂O in THF, the pure **19a/b** mixture (1:1.3 ratio, as before) was obtained in 87% yield. Treatment of pure **19a/b** to NIS in CH₂Cl₂ at 23 °C for 24 h yielded the spiroketal **20** in 68% yield, along with four unidentified minor isomers (10:7:3:3 ratio) that were obtained in 17% combined yield.

In summary, we have developed a synthesis of a model spiroketal fragment **7** of integramycin. This synthesis was facilitated by use of the highly stereoselective stannyl-crotylboration reaction recently developed in our laboratory,⁴ that was used to synthesize the vinylstannane intermediate **15**. The spiroketal was established by a stereoselective NIS-mediated spirocyclization of **19a/b** that provided the C(18)–C(35) fragment **20**. Further progress on the synthesis of integramycin will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Retrosynthetic Analysis of Integrgramycin (1) and the Model C(18)–(35) Spiroketal Unit (7).

Scheme 1.
Synthesis of Aldehyde **5**

Scheme 2.
Synthesis of the C(18)–C(35) Fragment **4**

Scheme 3.
First Generation Synthesis of Spiroketal **7**

Scheme 4.
Stereoselective NIS-Mediated Spiroketalization

^aNBSH = *o*-nitrobenzenesulfonylhydrazide

Scheme 5.
Second Generation Synthesis of Spiroketal **20**

^aNBSH = *o*-nitrobenzenesulfonylhydrazide