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

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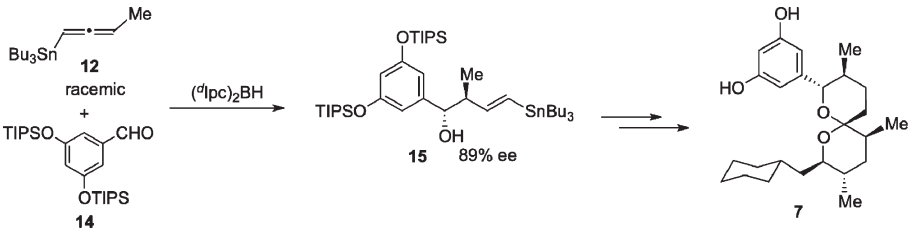
ABSTRACT



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 co-workers 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 IC_{50} 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 hydroxyketone **19a** and an application of the stannyl-crotylboration reaction recently developed in our laboratory.[4]

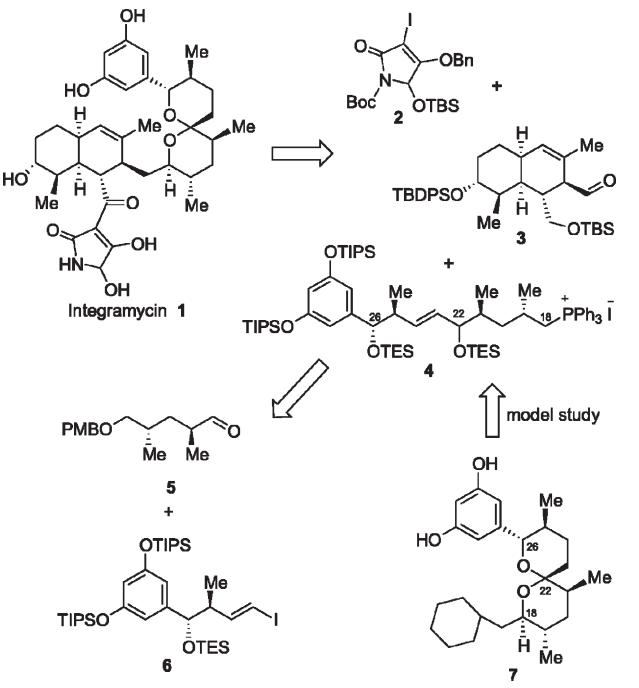


Figure 1. Retrosynthetic analysis of integramycin (**1**) and the model C(18)–C(35) spiroketal unit (**7**).

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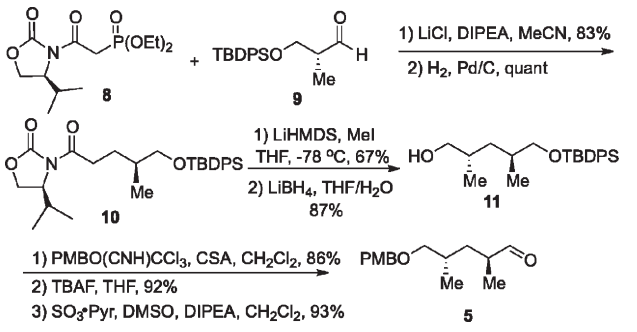
Our retrosynthetic analysis of integramycin (**1**) is outlined in Figure 1. We envisioned that the natural product should be accessible by coupling of tetramic acid intermediate **2**, *cis*-octahydronaphthalene carboxaldehyde **3**, and Wittig reagent **4**. Retrosynthetic disconnection of the C(22)−C(23) bond in **4** gives aldehyde **5** and vinyliodide **6**, substrates for a Nozaki−Hiyama−Kishi coupling reaction.

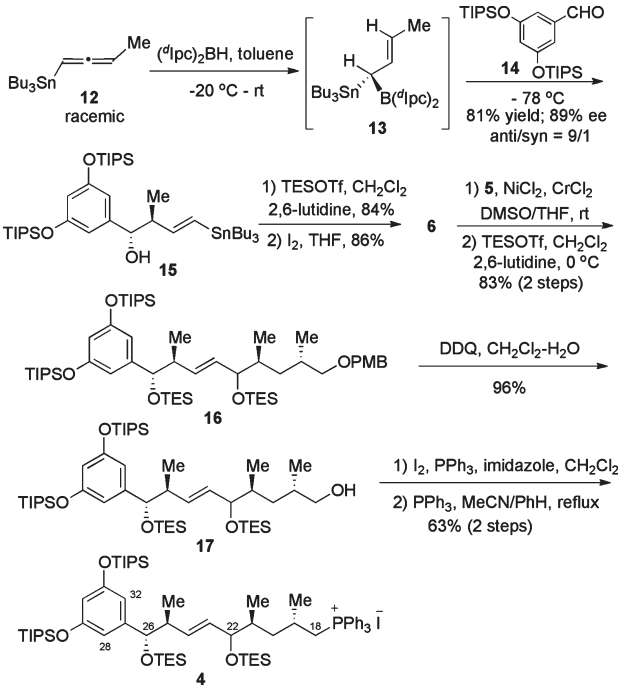
Our synthesis commenced with the Horner−Wadsworth−Emmons reaction[5] of the known β-keto phosphonate **8**[6] and aldehyde **9**,[7] followed by Pd-catalyzed hydrogenation of the resulting olefin to give imide **10** (Scheme 1). Diastereoselective α-methylation of **10** was performed by using LiHMDS as the base under Evans' asymmetric alkylation conditions.[8] Reductive removal of the oxazolidinone unit by treatment of the alkylated product with $NaBH_4$ afforded primary alcohol **11**. Finally, protection of the primary hydroxyl group of **11** by treatment with *p*-methoxybenzyl tricholoroacetimidate, followed by removal of the TBDPS group with TBAF and oxidation of the resulting primary alcohol under Parihk−Doering reaction conditions,[9] provided aldehyde **5** in excellent overall yield.

Scheme 1. Synthesis of Aldehyde **5**



The enantioconvergent, enantioselective stannyl-crotylboration reaction[4] 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 $(^dIpc)_2BH$ (1.9 equiv) at −20 °C.[11]

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



This afforded γ-stannyl homoallylic alcohol **15** in 81% yield and 89% ee with a 9:1 *anti*/*syn* ratio (Scheme 2). Protection of the newly formed hydroxyl group as a TES ether and subsequent treatment with I_2 to effect iodine−tin exchange gave vinyliodide **6**. Coupling of **5** and **6** by using the Nozaki−Hiyama−Kishi reaction[12] 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 I_2 and PPh_3. Finally, treatment of the iodide with an excess of PPh_3 in benzene at reflux furnished the phosphonium salt **4**.

We next turned to the task of forming the spiroketal unit stereoselectively. Cyclohexanecarboxaldehyde 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 isomerization[13] 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

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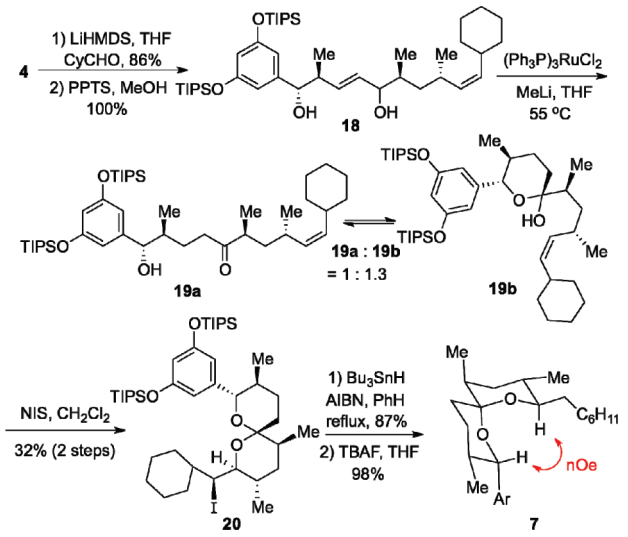
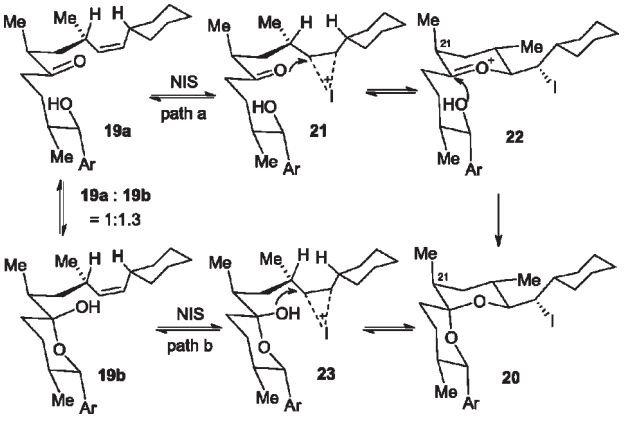
Scheme 3. First Generation Synthesis of Spiroketal **7**



inseparable impurities. This impure product mixture was used in the following spiroketalization experiments. Among several reagents[14] 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**. Hydroxyketone isomer **19a** could similarly undergo spirocyclization by Path a via oxonium intermediate **22** with the same stereochemical control as that in Path b. In the event, treatment of the **19a/19b** mixture with NIS in CH_2Cl_2 at 23 °C for 24 h delivered the desired spiroketal

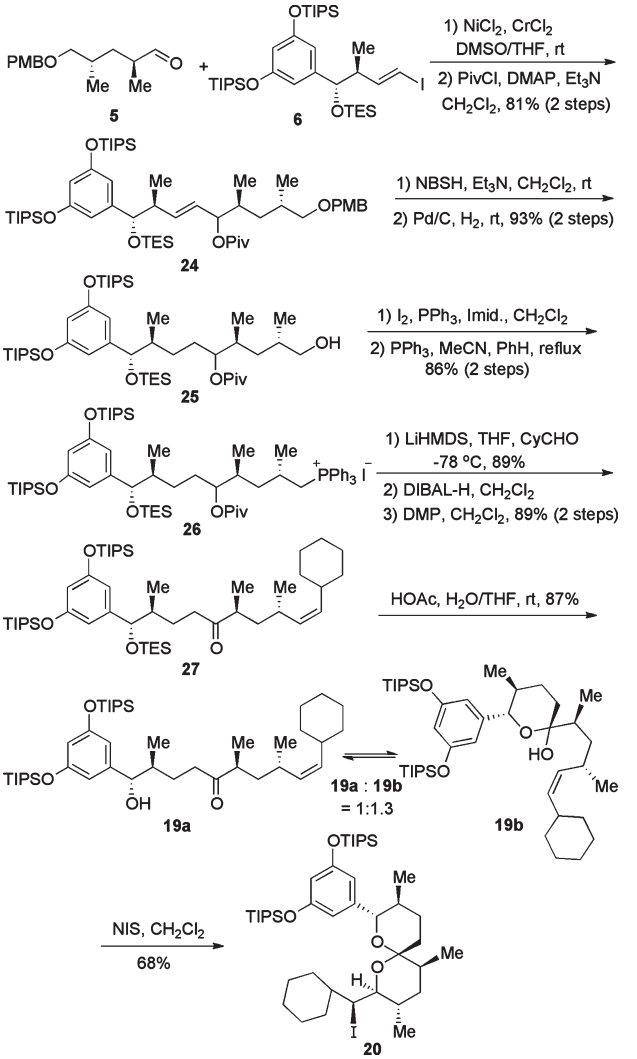
Scheme 4. Stereoselective NIS-Mediated Spiroketalization



20 as the predominant product in 32% overal 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 Bu_3SnH and AIBN. Subsequent treatment of the deiodinated 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 Et_3N.

Scheme 5. Second Genertion Synthesis of Spiroketal **20**[a]



[a] NBSH = *o*-nitrobenzenesulfonylhydrazide.

Reductive cleavage of the PMB ether then provided primary alcohol **25**. Iodination of **25**, followed by treatment with PPh_3, furnished the new C(18)−C(35) fragment **26** in 86% yield. Wittig olefination of cyclohexanecarboxaldehyde with 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 H_2O in THF, the pure **19a**/**b** mixture (1:1.3 ratio, as before) was obtained in 87% yield. Treatment of pure **19a**/**b** with NIS in CH_2Cl_2 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 stannylcrotylboration 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.

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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.

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