

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

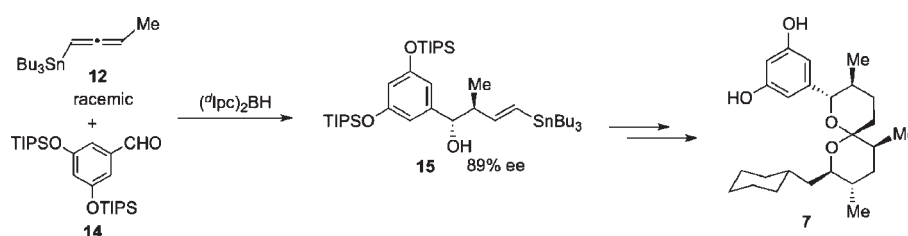
Huikai Sun, Jason R. Abbott, and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States

roush@scripps.edu

Received March 30, 2011

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 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 hydroxyketone **19a** and an application of the stannyl-crotylboration reaction recently developed in our laboratory.⁴

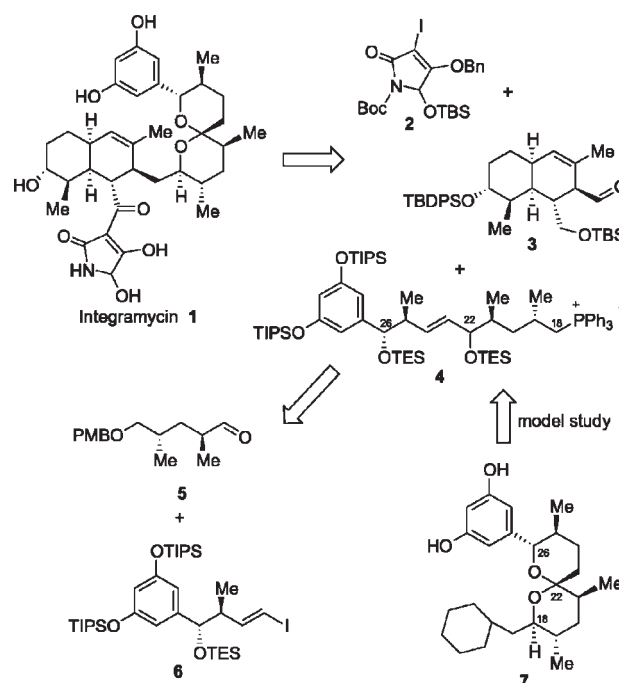


Figure 1. Retrosynthetic analysis of integramycin (**1**) and the model C(18)–C(35) spiroketal unit (**7**).

(1) Singh, S. B.; Zink, D. L.; Heimbach, B.; Genilloud, O.; Teran, A.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. C. *Org. Lett.* **2002**, *4*, 1123.

(2) (a) Craigie, R. *J. Biol. Chem.* **2001**, *276*, 23213. (b) Esposito, D.; Craigie, R. *Adv. Virus Res.* **1999**, *52*, 319.

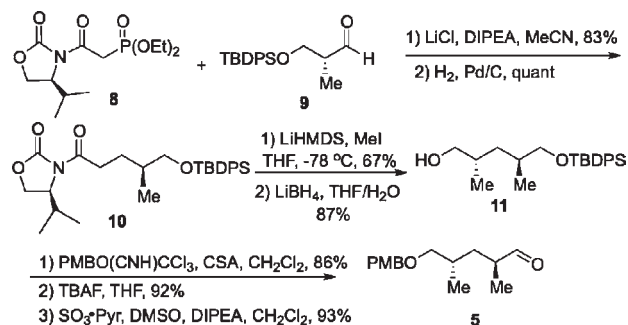
(3) (a) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1355. (b) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569.

(4) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744.

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 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 conditions,⁹ provided aldehyde **5** in excellent overall yield.

Scheme 1. Synthesis of Aldehyde **5**



The enantioconvergent, enantioselective stannyl-crotyl-boration 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 (^dIpc)₂BH (1.9 equiv) at -20 °C.¹¹

(5) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(6) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2162.

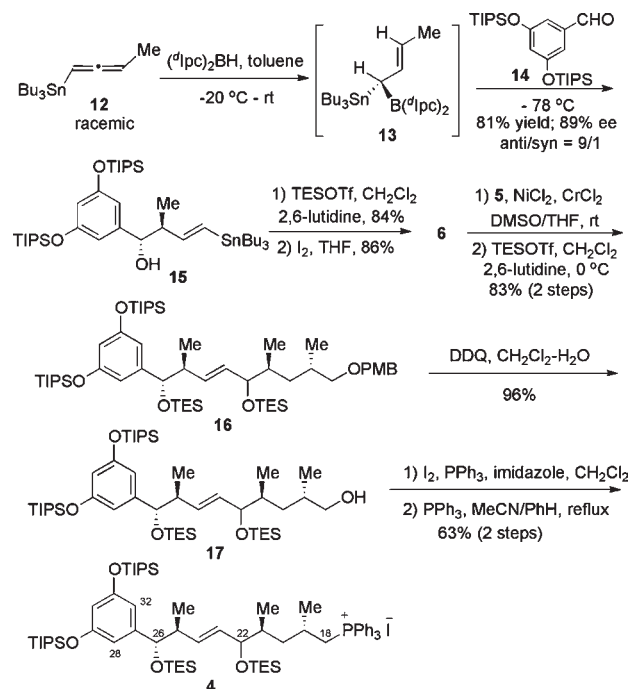
(7) Johns, B. A.; Grant, C. M.; Marshall, J. A. *Org. Synth.* **2002**, *79*, 59.

(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(9) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175.

(10) Marshall, J. A.; Chobanion, H. *Org. Synth.* **2005**, *82*, 43.

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 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 an excess of PPh₃ in benzene at reflux furnished the phosphonium salt **4**.

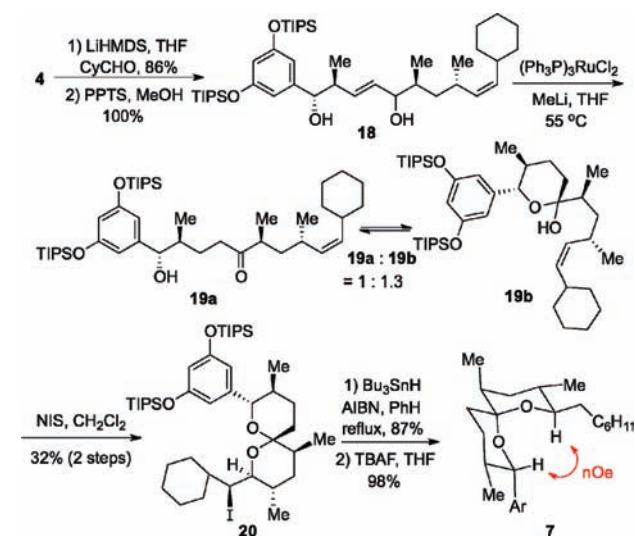
We next turned to the task of forming the spiroketal unit stereoselectively. Cyclohexanecarboxaldehyde was used as a model substrate in the Wittig reaction with **4**, which provided the (*Z*)-olefinic product in 86% yield (Scheme 3). Removal of both TES protecting groups by treatment with PPTS in MeOH then afforded diol **18**. A ruthenium-mediated olefin 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

(11) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

(12) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

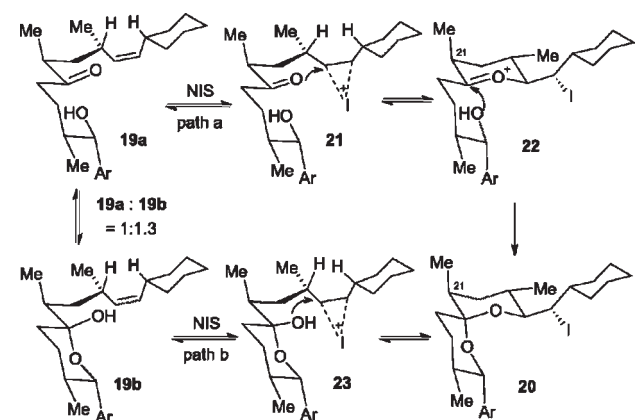
(13) Uma, R.; Davies, M. K.; Crevisy, C.; Gree, R. *Eur. J. Org. Chem.* **2001**, 3141.

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



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**. 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 CH₂Cl₂ at 23 °C for 24 h delivered the desired spiroketal

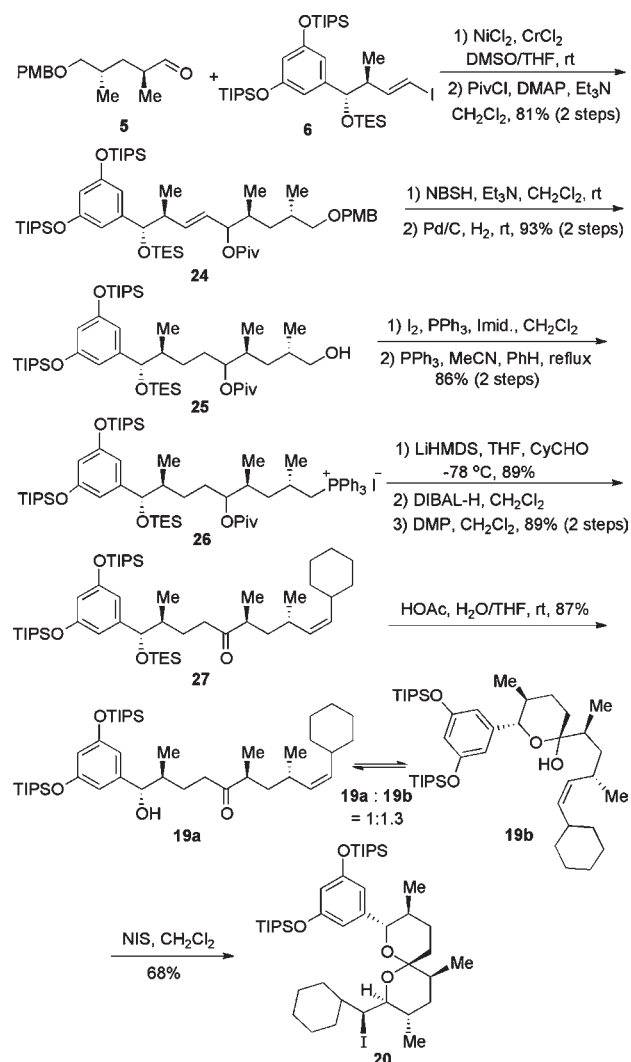
Scheme 4. Stereoselective NIS-Mediated Spiroketalization



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 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 Et₃N.

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



^aNBSH = *o*-nitrobenzenesulfonylhydrazide.

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 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 H₂O 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 CH₂Cl₂ at 23 °C for 24 h yielded the spiroketal **20** in 68% yield, along

(14) (a) Bartlett, P. A.; Mori, I.; Bose, J. A. *J. Org. Chem.* **1989**, *54*, 3236. (b) Kitching, W.; Lewis, J. A.; Fletcher, M. T.; De Voss, J. J.; Drew, R. A. I.; Moore, C. J. *J. Chem. Soc., Chem. Commun.* **1986**, *11*, 855. (c) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063. (d) Perkins, M. V.; Jacobs, M. F.; Kitching, W.; Cassidy, P. J.; Lewis, J. A.; Drew, R. A. I. *J. Org. Chem.* **1992**, *57*, 3365.

(15) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(16) (a) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109. (b) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

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 integracycin. This synthesis was facilitated by use of the highly stereoselective stannyl-crotylboration reaction recently developed in our laboratory⁴ 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 integracycin will be reported in due course.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM026782).

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>.