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Synthesis of the C16–C35 Fragment of Integramycin Using Olefin Hydroesterification as a Linchpin Reaction

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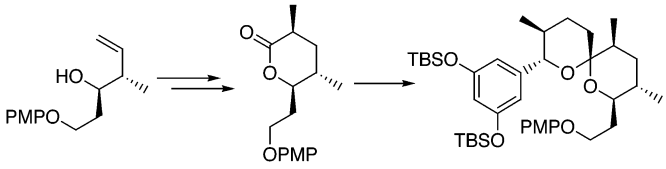
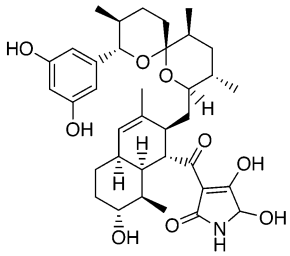
ABSTRACT



The spiroketal unit of the HIV-integrase inhibitor integramycin has been prepared in an efficient and convergent manner. Key steps in this sequence include the use of ruthenium-mediated hydroesterification reactions of homoallylic alcohols and silyl ethers, and a C,O-dianionic addition into a lactone provides the spiroketal while minimizing protecting group manipulations.

Cellular infection by HIV-1 requires the viral genome to be incorporated into the host DNA through a process that is mediated by the enzyme HIV integrase.[1] Since integrase is not present in human cells, its inhibition has been postulated to be an attractive complement for AIDS therapy. Indeed, Merck scientists have demonstrated that integrase inhibitors suppress HIV-1 cellular infection.[2] While the inhibitors used in this study are structurally relatively simple and are readily synthesized, the ability of HIV to acquire drug resistance has led to an aggressive search for new lead targets. Singh and co-workers recently reported[3] that integramycin, isolated from *Actinoplanes* extracts, inhibits the integrase-mediated strand transfer process with an IC_{50} value of 4 μM. In addition to its biological activity, integramycin presents several intriguing synthetic challenges by virtue of the structurally disparate spiroketal and *cis*-decalin fragments. In this Communication, we report our efforts on a stereoselective and convergent synthesis of the C16−C35 spiroketal fragment of integramycin that highlights the utility of a ruthenium-catalyzed hydroesterification reaction.



Integramycin

To minimize protecting group manipulations, we envisioned spiroketal unit **1** as arising (Figure 1) from the union of a C,O-dianion (**2**) with a lactone (**3**).[4] Both **2** and **3** can be accessed through asymmetric aldehyde crotylation reactions that employ the same (*E*)-crotylmetallic reagent (**4**).

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

(2) Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schlief, W.; Blau, C.; Miller, M. D. *Science* **2000**, *287*, 646.

(3) 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.

(4) (a) Cohen, T.; Tong. S. *Tetrahedron* **1997**, *53*, 9487. (b) Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.

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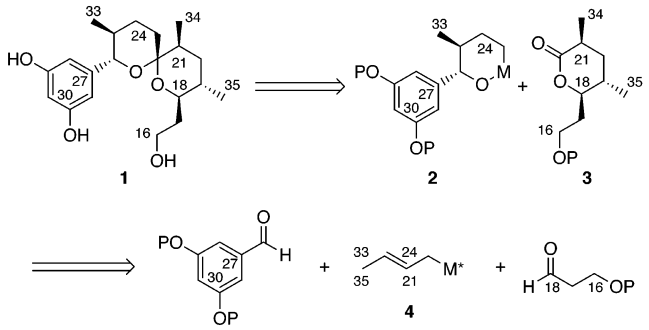
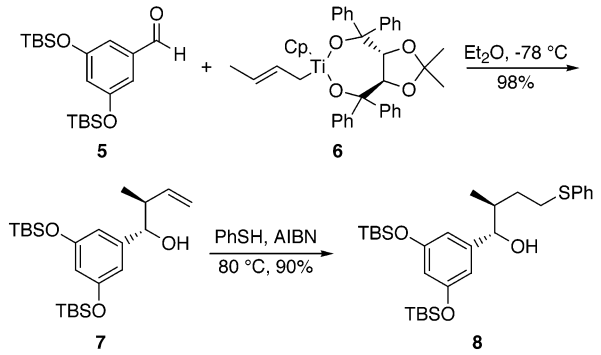


Figure 1.

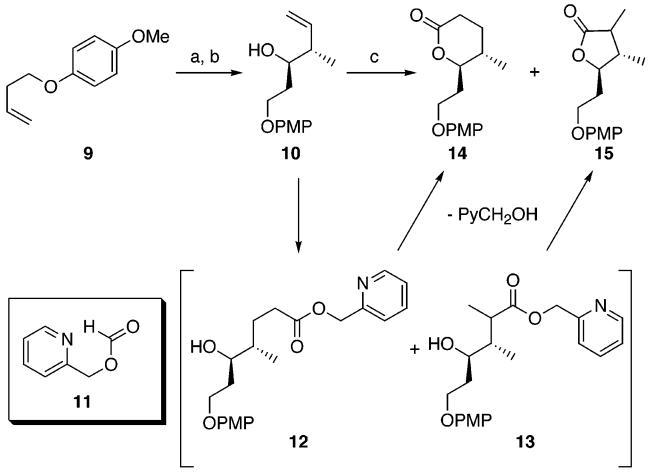
Access to the C23−C33 unit proceeded through an asymmetric crotylation of the known[5] aldehyde **5**. Preparing homoallylic alcohol **7** (Scheme 1) with high enantio- and

Scheme 1



diastereocontrol, however, proved to be somewhat more difficult than expected. For example, the addition of Brown's pinene-derived crotylborane[6] to **5** provided **7** in satisfactory yield and enantiomeric purity but in a relatively low 2.3:1 ratio of anti to syn diastereomers. Employing (*E*)-crotyltrichlorosilane in the presence of Denmark's nucleophilic bis-phosphoramide catalyst[7] was attractive in that it completely solved the diastereoselectivity problem and required only 5 mol % of the chiral source. The enantioselectivity of the addition, however, was somewhat diminished, in accord with literature precedent for (*E*)-silanes. Hafner's crotyltitanium taddolate **6**[8] proved to be a superior reagent for this transformation, providing **7** in 92% ee with essentially complete diastereocontrol and in excellent yield. Heating **7** in PhSH with AIBN provided sulfide **8**, which serves as a progenitor of a nucleophilic C23−C33 fragment.

Scheme 2 [a]



[a] Reagents and conditions: (a) O_3, MeOH, −42 °C, then Me_2S, 56%. (b) **6**, Et_2O, −78 °C, 96%, 85% ee. (c) **11**, $Ru_3(CO)_{12}$, 135 °C, then HOAC, THF, H_2O, 85 °C, **14**: 53%, **15**: 18%.

The synthesis of the C16−C22 fragment (Scheme 2) began from known[9] PMP-protected butenol **9**. Ozonolytic cleavage followed by the addition of **6** provided homoallylic alcohol **10** in 96% yield and in a respectable 85% ee. Given that the separation of **7** and **10** was expected to be facile on the basis of their significantly different polarities, we subjected a mixture of **5** and **9** to simultaneous crotylation with **6**. This experiment showed that the additions proceed independently, providing the homoallylic alcohols with yields and stereoselectivities that are comparable to each individual reaction while eliminating one workup and chromatographic separation.

Converting **10** to a δ-lactone requires the formal addition of formic acid across the olefin. While numerous efficient multistep or multireagent protocols have been devised to achieve this objective,[10] we were intrigued by the possibility of conducting this transformation more directly through the use of the metal-mediated hydroesterification reaction that was recently reported[11] by Chang and co-workers. Thus, heating **10** in an excess (3−5 equiv) of pyridylmethyl formate (**11**) with $Ru_3(CO)_{12}$ (5 mol %) initially provided ester **12**, which cyclized to yield lactone **14** in a moderate 40% yield. Noncyclized **12** and its formate ester were also observed in the reaction mixture. These products converged to the desired lactone upon adding HOAc, THF, and H_2O to the crude reaction mixture and heating to 85 °C. This one-pot protocol improved the yield of **14** to 53%. In consideration of the relatively inexpensive source of ruthenium employed for the

(5) Prepared in three steps from commercialy available 3,5-dihydroxybenzoic acid. (a) Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354. (b) Lupton, J. M.; Hemingway, L. R.; Samuel, I. D. W.; Burn, P. L. *J. Mater. Chem.* **2000**, *10*, 867. (c) Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. *Carbohydr. Res.* **1997**, *301*, 95.

(6) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(7) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

(8) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(9) Prepared in one step from commercially available 3-buten-1-ol. Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805.

(10) For examples, see: (a) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *4*, 459. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (c) Wuts, P. G.; Obrzut, M. L.; Thompson, P. A. *Tetrahedron Lett.* **1984**, *25*, 4051. (d) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066.

(11) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750.

hydroesterification, this method of converting homoallylic alcohols into δ-lactones compares quite favorably to commonly employed olefin metathesis/reduction sequences.

The major byproduct of the hydroesterification reaction (18% yield) was γ-lactone **15**, arising through the intermediacy of branched ester **13**. The formation of **15** contrasts with Chang's observation of nearly exclusive linear product formation from nonfunctionalized alkenes when branching is present at the allylic position. We propose that the branched isomer forms through a competitive hydroxyl-directed pathway that proceeds through intermediate **16** (Figure 2). Compelling precedent for a coordinating group

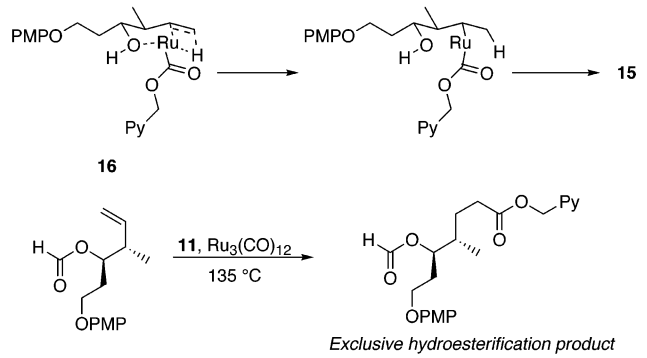


Figure 2.

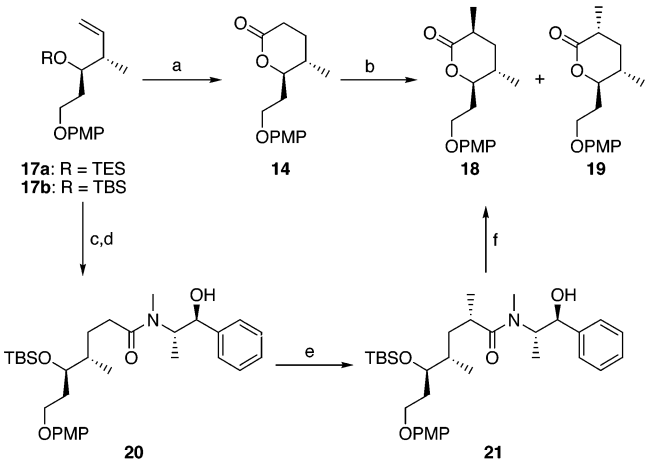
causing a regiochemical reversal in hydrometalation reactions has been provided through the Evans group's studies[12] on metal-catalyzed hydroborations.

To exclude the possibility that the unexpected regioisomer forms from a transesterification reaction between **10** and **11** followed by intramolecular hydroesterification, we subjected the formate ester of **10** to hydroesterification conditions. This reaction, although slower than the parent transformation, provided the linear isomer exclusively, consistent with suppressing the coordinative addition.

To avoid regioselectivity problems, we subjected silyl ether **17a** (prepared in 94% yield by exposing **10** to TESCl and imidazole) to hydroesterification. While the intermediate pyridylmethyl ester, formed exclusively as the linear isomer, could be purified and isolated, we found that stirring the crude reaction mixture in HOAc, THF, and water at room temperature effected silyl ether cleavage and lactonization to form **14** in 68% yield. While requiring one additional step relative to the one-pot lactone synthesis, the increase in efficiency should prove to be useful for homoallylic alcohols that are difficult to access.

Unfortunately, treatment of the enolate of **14** with MeI proceeded with no stereocontrol, providing lactones **18** and **19** in a 1:1 ratio. Although **19** could be epimerized to **18**, the efficiency of the process was insufficient for large-scale

Scheme 3 [a]



[a] Reagents and conditions: (a) **11**, $Ru_3(CO)_{12}$, 135 °C, then HOAc, THF, H_2O, rt, 68%. (b) LDA, THF, −78 °C, then MeI, HMPA, 72% at 72% conversion. (c) **11**, $Ru_3(CO)_{12}$, 135 °C, 80%. (d) (1*S*,2*S*)-pseudoephedrine, NaH, THF, 0 °C, 83%. (e) LDA, LiCl, THF, −78 °C, then MeI, −78 to 0 °C, 91%. (f) Bu_4NF, THF, then *p*-TsOH, 79%.

material throughput. To improve the methylation selectivity, we converted pyridylmethyl ester formed from the hydroesterification of **17b** to pseudoephedrine amide **20** through a variant of Myers' aminolysis conditions[13] (pseudoephedrine, NaH, THF). In accord with Myers' studies, alkylating the lithium enolate of **20** (LDA, LiCl, THF) with MeI provided **21**. Removal of the silyl group of **21** followed in the same flask by acid-mediated lactonization provided **18** in 79% yield.

Coupling of **8** and **18** (Scheme 4) was achieved with Cohen's method. Thus, deprotonation of the hydroxyl group of **8** with *n*-BuLi followed by reductive lithiation of the sulfide with lithium di-*tert*-butylbiphenylide (LDBB)[14] provided a dianion that underwent transmetalation with anhydrous $CeCl_3$.[15] Addition of **18** to the resulting alkylcerium reagent afforded, following an acidic workup, spiroketal **22** in 60% yield. This reaction, however, proved to be somewhat capricious due to technical difficulties associated with preparing the alkylcerium reagent. An exploration of alternate reagents for effecting the transmetalation reaction showed that $MgBr_2$, prepared in situ from 1,2-dibromoethane and Mg metal, promoted spiroketal formation in 56% yield and with greater reproducibility than the alkylcerium addition. The PMP group was removed selectively using ceric ammonium nitrate in wet acetonitrile,[16] yielding **23** in 79% yield. Alcohol **23** is well-suited for subsequent elaboration of the C1−C15 portion of integramycin. Significant overlap in the ^{1}H NMR spectra of the spiroketals precluded their

(12) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. (b) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679.

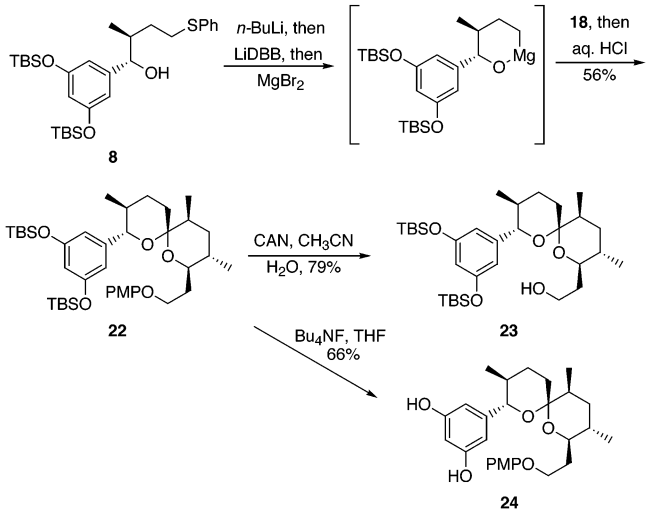
(13) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.

(14) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

(15) Takeda, N.; Imamoto, T. *Org. Synth.* **1998**, *76*, 228.

(16) Fukuyama, T.; Laud, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

Scheme 4



rigorous structural assignment through NOESY analysis. Therefore, we removed the silyl groups from **22** to form **24** as a solid that crystallized as its hydrate. This allowed our stereochemical assignments to be validated by single-crystal X-ray diffraction analysis of the monohydrate of **24** (Figure 3).

We have reported a convergent and stereoselective synthesis of the C16−C35 spiroketal portion of the HIV-integrase inhibitor integramyin that proceeds in 10 steps from commercially available materials (longest linear sequence, 14 steps overall). The sequence highlights the synthetic utility of a recently reported ruthenium-mediated hydroesterification reaction. This process can be used to form lactones directly from homoallylic alcohols in moderate yield or more efficiently from homoallylic silyl ethers after acid treatment. The pyridylmethyl esters that form in this reaction can readily be converted to pseudoephedrine amides, providing opportunities for subsequent diastereoselective operations.

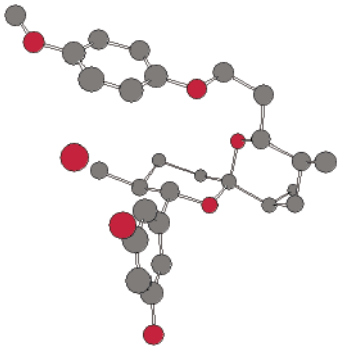


Figure 3. Crystal structure of **24**·H_2O.

These reactions demonstrate, to the best of our knowledge, the first applications of this extremely powerful method of carbon−hydrogen bond activation to the synthesis of functionalized molecules. This sequence also demonstrates the efficiency of C,O-dianioic additions into lactones as a method for producing spiroketals in a single operation without recourse to extensive protecting group manipulations. We are currently developing a sequence for the synthesis of the integramycin C1−C15 decalin system that can be incorporated into the sequence described herein.

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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