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Total Synthesis of GEX1A

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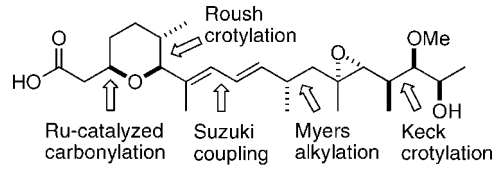
ABSTRACT



GEX1A

An efficient and readily modifiable synthesis of GEX1A/herboxidiene/TAN-1609 (1) was developed. This modular synthesis featured a Suzuki coupling to install the conjugated diene and a Ru-catalyzed lactonization and Roush crotylation to construct the functionalized tetrahydropyran moiety. Myers' alkylation, cross-metathesis, and Keck crotylation were employed for assembly of the biologically essential side-chain domain.

GEX1A (**1**, also known as herboxidiene and TAN-1609) is an interesting microbial natural product that was first described in the primary literature in 1992 by Isaac and co-workers.[1] Thereafter, the absolute configuration of **1** was reported by a group at Novartis in 1997.[2] GEX1A induces an array of diverse xenobiotic responses that include herbicidal activity,[1] activation of the LDL receptor,[3] an increase of G1 and G2 cell phase population,[4–6] and antitumor activity in numerous cell lines.[4–6] Recent publications characterized naturally occurring GEX1A analogues that replicate several of these biological responses.[5,6] However, the cellular mechanisms and modes of action of **1** and its cogeners remain to be elucidated. The provision of GEX1A and structural varaints and derived cellular probes should enable studies to accomplish this.

Two initial synthetic entries to the GEX1A architecture were reported by Kocienski and Banwell, respectively. Kocienski[7] described the first total synthesis of **1** in 1999, whereas Banwell[8] elaborated upon this benchmark in reporting a formal total synthesis in 2000. Edmunds[9] subsequently published the syntheses of simpler, non-natural analogues of **1**, whereas Panek published a signature silane-based total synthesis of **1** in 2007.[10]

The combination of enticing structural features, ammenable to convergent assembly, and opportunities to enable further chemical biology studies compelled us to develop a flexible synthetic entry to this unique class of natural products.[11]

Our synthetic plan for **1** focused on the construction of the diene via a Suzuki coupling of vinyl iodide **2** and vinyl boronate **3** (Scheme 1).[12] Disconnection of the C1−C2 acetate and the C8 vinyl iodide of **2** revealed lactone **4** (Scheme 2). A Ru-catalyzed carbonylation of homoallylic alcohol **5** was designed

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(1) Isaac, B. G.; Ayer, S. W.; Elliott, R. C.; Stonard, R. J. *J. Org. Chem.* **1992**, *57*, 7220.
(2) Edmunds, A. J. F.; Trueb, W.; Oppolzer, W.; Cowley, P. *Tetrahedron* **1997**, *53*, 2785.
(3) Koguchi, Y.; Nishio, M.; Kotera, J.; Omori, K.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **1997**, *50*, 970.
(4) Horiguchi, T.; Shirasaki, M.; Tanida, S. *Takeda Kenkyushoho* **1996**, *55*, 149.
(5) Sakai, Y.; Yoshida, T.; Ochiai, K.; Uosaki, Y.; Saitoh, Y.; Tanaka, F.; Akiyama, T.; Akinaga, S.; Mizukami, T. *J. Antibiot.* **2002**, *55*, 855.
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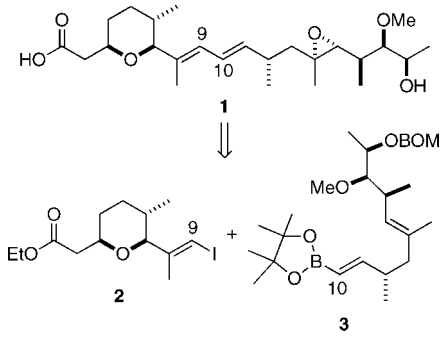
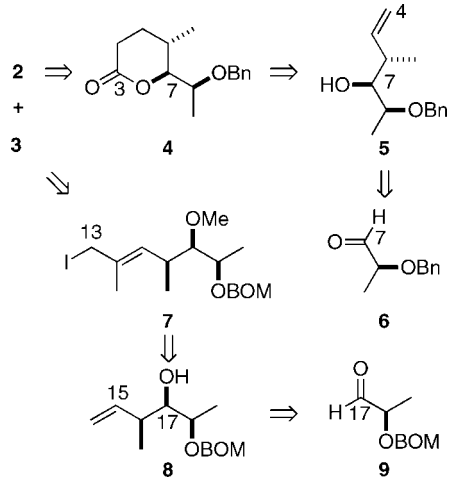
Scheme 1. Major Retrosynthetic Dissection



to provide **4**.[13,14] Resident in **5** is the necessary C6,C7-*anti* stereochemistry installed via crotylation of aldehyde **6**.[15] The Suzuki coupling partner boronate **3** would arise from allylic

Scheme 2. Detailed Retrosynthesis



iodide **7** via the key operations of Myers alkylation and Takai olefination (Scheme 2).[16,17] The trisubstituted (*E*)-olefin of **7** could be obtained by cross metathesis of precursor **8** with methacrolein.[18] Keck crotylation of **9** was recognized to provide the *syn*,*syn*stereochemistry within **8**.[19]

The synthesis of **1** thus began with the assembly of **2**. For this, (*S*)-methyl lactate **10** was converted into aldehyde **6** in

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(14) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 4207.
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(18) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451.
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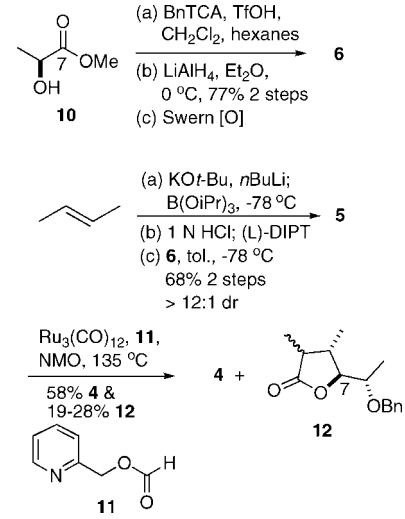
(20) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

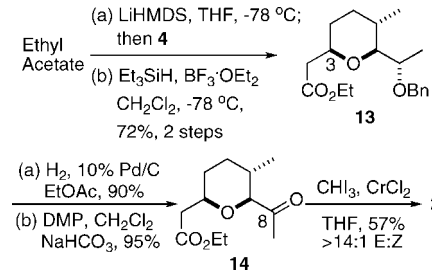
Scheme 3. Preparation of Lactone **4**



three steps (Scheme 3). Lactate derivative **6** was then subjeted to crotylation to furnish the *anti*,*syn* stereochemistry in homoallylic alcohol **5**.[15] Heating alcohol **5** with $Ru_3(CO)_{12}$, NMO, and pyridyl formate **11** primarily yielded the six-membered lactone **4** and lesser amounts of the related five-membered lactone **12**.[14]

The acetate side chain of **2** was installed by addition of the lithium enolate of ethyl acetate followed by reduction of the resultant hemiketal with boron trifluoride etherate and triethylsilane[20] to yield **13** (Scheme 4). Cleavage of the benzyl ether

Scheme 4



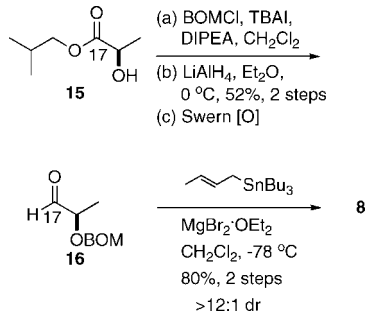
of **13** and oxidation of the resultant alcohol provided ketone **14**. Finally, Takai olefination of ketone **14** installed the vinyl iodide of **2** in high *E*/*Z* selectivity.[21]

To synthesize boronate **3**, (*R*)-isobutyl lactate **15** was converted into aldehyde **16** (Scheme 5) via a three step sequence similar to that used for the generation of **6**. With **16** in hand, Keck crotylation installed the necessary *syn*,*syn* stereochemistry at carbons 16−18 in intermediate **8**.[19,22]

Next, the C17 methyl ether was formed from **8** and subsequent cross metathesis with methacrolein using the Grubbs−Hoyveda catalyst was found to produce the best results

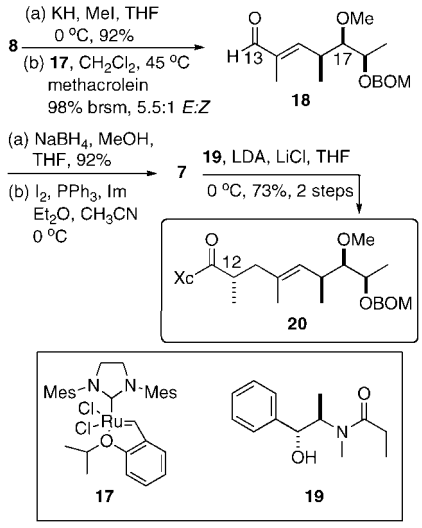
(21) Takai, K.; Nitta, K.; Utimeto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(22) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

Scheme 5



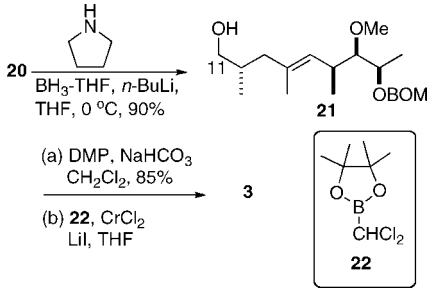
for homologation to aldehyde **18** (Scheme 6).[18] Aldehdye **18** was reduced with $NaBH_4$, and iodination of the resultnt alcohol gave allylic iodide **7**. The iodide was then reacted with Myers' pseudoephedrine propionate enolate to set the C12 configuration in **20**.[17]

Scheme 6



To elaborate the boronate coupling partner, the pseudoephedrine chiral auxiliary of **20** was removed via lithiopyrrolidide−borane induced reduction (Scheme 7).[17a] Oxidation of the resultant

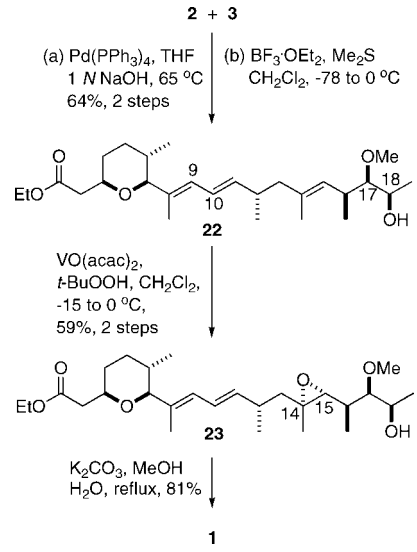
Scheme 7



primary alcohol **21** was best performed with Dess−Martin periodinane. Finally, Takai olefination with the bis-chloroborolane installed vinyl boronate **3** ready for the Suzuki coupling.[16]

The complete carbon skeleton of **1** was ultimately assembled via a successful palladium-mediated Suzuki coupling (Scheme 8).[12] Boron trifluoride-mediated cleavage of the BOM acetal

Scheme 8. Completion of the Total Synthesis of **1**



masking the C18 hydroxyl required careful control of reaction temperature. When the reaction was performed at 0 °C, the C17 methyl ether also suffered cleavage. Initiating the reaction at −78 °C and gradually warming to 0 °C led to selective cleavage of the BOM acetal without scission the methyl ether. Thereafter, the C14,15 oxirane was regio- and stereoselectively installed via an established vanadyl−oxo epoxidation to produce epoxide **23** with only a small amount of the undesired C14,15 diastereomeric epoxide produced.[8] Finally, saponification of the ester yielded carboxylic acid **1**, the spectroscopic data of which matched those previously reported.[1,7]

This total synthesis of GEX1A was completed in a longest linear sequence of 16 steps (26 total steps) and a 3.4% overall yield from methyl lactate. This improves upon the statistical efficiencies of the previously reported total syntheses of GEX1A.[7,8] It also offers an additional platform for the generation of probes to elucidate the cellular targets and mechanism(s) of action of GEX1A and congeners.

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Supporting Information Available: Experimental procedures, characterization data, and NMR and spectra for **1**−**5**, **7**, **8**, **13**, **14**, **16**, **18**, **22**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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