

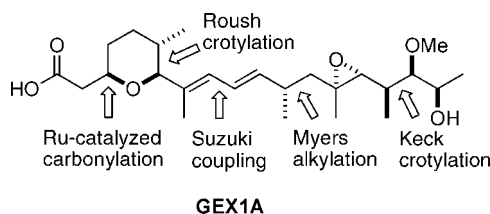
Total Synthesis of GEX1A

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ABSTRACT



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 congeners remain to be elucidated. The provision of GEX1A and structural variants 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. Kocienski⁷ described the first total synthesis of **1** in 1999, whereas Banwell⁸ elaborated upon this benchmark in reporting a formal total synthesis in 2000. Edmunds⁹ 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, amenable 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

[†] GlaxoSmithKline.[‡] The Ohio State University.(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.(6) Sakai, Y.; Tsujita, T.; Akiyama, T.; Yoshida, T.; Mizukami, T.; Akinaga, S.; Horinouchi, S.; Yoshida, M.; Yoshida, T. *J. Antibiot.* **2002**, *55*, 863.(7) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995.(8) Banwell, M.; McLeod, M.; Premaj, R.; Simpson, G. *Pure Appl. Chem.* **2000**, *72*, 1631.(9) Edmunds, A. J. F.; Arnold, G.; Hagmnaa, L.; Schaffner, R.; Furlenmeier, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1365.(10) Zhang, Y.; Panek, J. S. *Org. Lett.* **2007**, *9*, 3141.

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Chemical reaction scheme showing the conversion of compound **1** to compounds **2** and **3**.

Compound **1** is a complex molecule featuring a tetrahydropyran ring, a carboxylic acid group, and a side chain with multiple stereocenters and a terminal vinyl group.

Compound **2** is a similar molecule, but with an ester group and an iodine atom at the terminal position.

Compound **3** is a complex molecule featuring a boron atom, a methoxy group, and a side chain with multiple stereocenters and a terminal vinyl group.

Chemical reaction scheme showing the conversion of 2 and 3 to 4, then to 5, 6, 7, 8, and 9.

2 + 3 $\Rightarrow$ 4 $\Rightarrow$ 5 $\Rightarrow$ 6 $\Rightarrow$ 7 $\Rightarrow$ 8 $\Rightarrow$ 9

Structure 4 is a bicyclic acetal with a benzyl group (OBn) and a methyl group. Structure 5 is a linear molecule with a hydroxyl group (HO), a benzyl group (OBn), and a methyl group. Structure 6 is a linear molecule with a carbonyl group (O), a benzyl group (OBn), and a methyl group. Structure 7 is a linear molecule with a hydroxyl group (OH), a benzyl group (OBOM), and a methyl group. Structure 8 is a linear molecule with a hydroxyl group (OH), a benzyl group (OBOM), and a methyl group. Structure 9 is a linear molecule with a carbonyl group (O), a benzyl group (OBOM), and a methyl group.

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(a) BnTCA, TiOH,
CH₂Cl₂, hexanes
6

(b) LiAlH₄, Et₂O,
0 °C, 77% 2 steps

(c) Swern [O]

(a) KO^tBu, *n*BuLi;
B(OiPr)₃, -78 °C
5

(b) 1 N HCl; (L)-DIPT
(c) **6**, tol., -78 °C
68% 2 steps
> 12:1 dr

Ru₃(CO)₁₂, **11**,
NMO, 135 °C
58% **4** &
19-28% **12**

4 + **12**

11

Ethyl Acetate
 (a) LiHMDS, THF, -78 °C;
 then **4**
 (b) Et₃SiH, BF₃·OEt₂
 CH₂Cl₂, -78 °C,
 72%, 2 steps

13

(a) H₂, 10% Pd/C
 EtOAc, 90%
 (b) DMP, CH₂Cl₂
 NaHCO₃, 95%

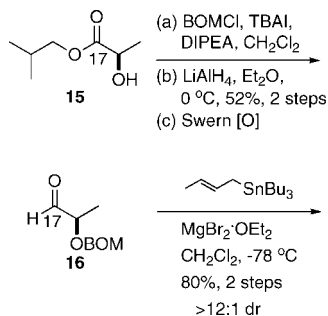
14

CH₃I, CrCl₂
 THF, 57%
 >14:1 E:Z

2

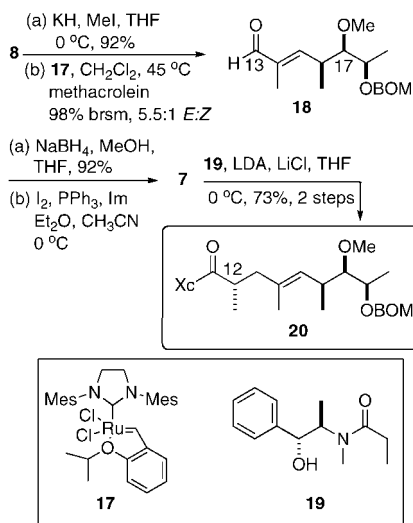
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Scheme 5



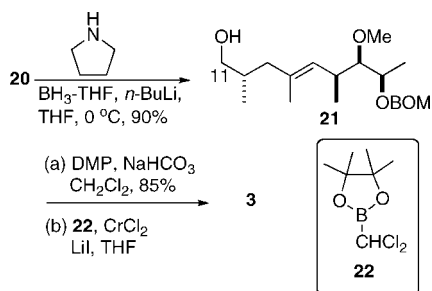
for homologation to aldehyde **18** (Scheme 6).¹⁸ Aldehyde **18** was reduced with NaBH_4 , and iodination of the resultant alcohol gave allylic iodide **7**. The iodide was then reacted with Myers' pseudoephedrine propionate enolate to set the C12 configuration in **20**.¹⁷

Scheme 6



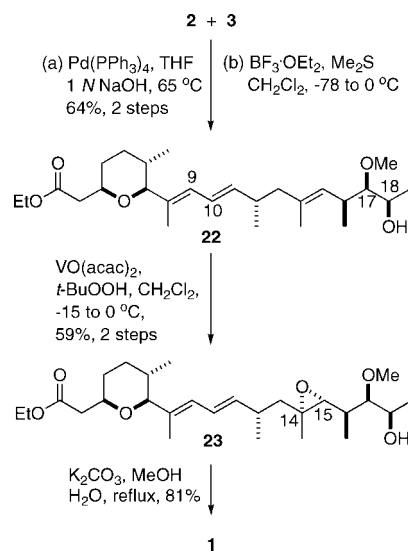
To elaborate the boronate coupling partner, the pseudoephedrine chiral auxiliary of **20** was removed via lithiopyrrolide–borane induced reduction (Scheme 7).^{17a} Oxidation of the resultant

Scheme 7



primary alcohol **21** was best performed with Dess–Martin periodinane. Finally, Takai olefination with the bis-chloroborane 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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