

A Stereoselective Synthesis of (+)-Herboxidiene/GEX1A

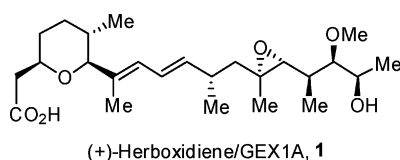
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ABSTRACT



A stereoselective synthesis of (+)-herboxidiene is described. The convergent synthesis utilized a Suzuki cross-coupling reaction to assemble the key segments. The synthesis of the functionalized tetrahydropyran ring utilized an Achmatowicz reaction as the key step. The synthesis of the C10–C19 segment was accomplished using Brown's crotylboration, asymmetric alkylation, and a stereoselective allylic chlorination reactions.

Researchers at Monsanto (USA) isolated herboxidiene (**1**, Figure 1) from *Streptomyces chromofuscus* in 1992.¹ It displayed highly potent and selective phytotoxicity against a myriad of broad leaf weeds over coplanted wheat.¹ Subsequently, in 2002, Yoshida and co-workers isolated six structurally related compounds, including GEX1 from a culture broth of *Streptomyces sp.*² One of the compounds, GEX1A was identified as herboxidiene (**1**), and it was shown to reduce plasma cholesterol by up-regulating the gene expression of low-density lipoprotein receptors.³ Furthermore, it induced both G1 and G2/M cell cycle arrest in a human normal fibroblast cell line, WI-38.⁴ The initial structural assignment of herboxidiene was carried out by chemical degradation and spectroscopic studies.⁵ Ultimately, the first total synthesis by Kocienski and co-workers⁶ confirmed the relative and absolute configuration of her-

boxidiene/GEX1A (**1**). Important biological properties, low abundance, and the interesting structural features of **1** led to considerable interest in its synthesis and biological studies. Subsequently, three other total syntheses were accomplished by Banwell, Panek, and Forsyth.⁷ Edmonds and co-workers reported simplified aromatic hybrids of **1** with interesting herbicidal activity.⁸ Herein we report an asymmetric synthesis of (+)-herboxidiene that can be amenable to analog preparation.

Our retrosynthesis of (+)-herboxidiene (**1**) is shown in Figure 1. We planned to utilize a Suzuki cross-coupling reaction similar to Murray and Forsyth^{7c} to attach the vinyl iodide **2** and boronate **3** at a late stage in the synthesis. The functionalized tetrahydropyran ring **2** could be constructed from furfural derivative **4** via oxidative Achmatowicz rearrangement followed by reduction of the resulting hemiketal. The boronate segment **3** could be derived from cross-metathesis of olefin **5** and vinyl pinacol boronate. Olefin **5** would be obtained by asymmetric alkylation with allylic

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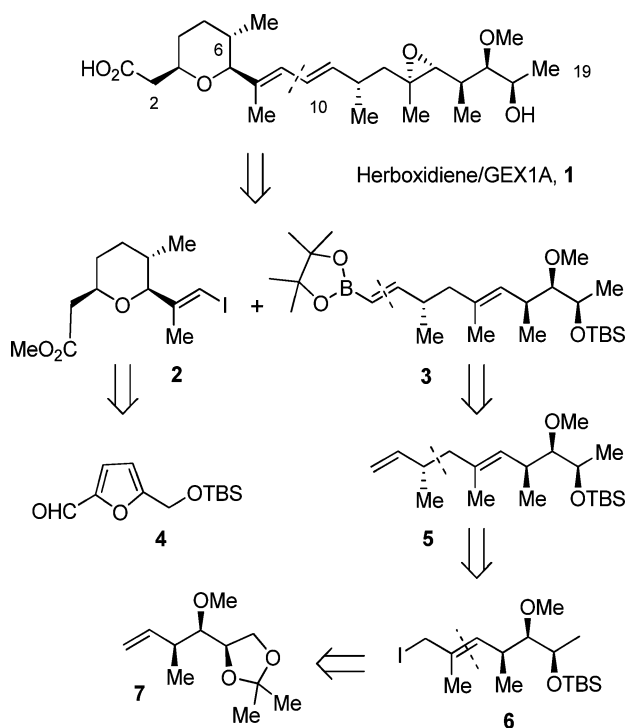


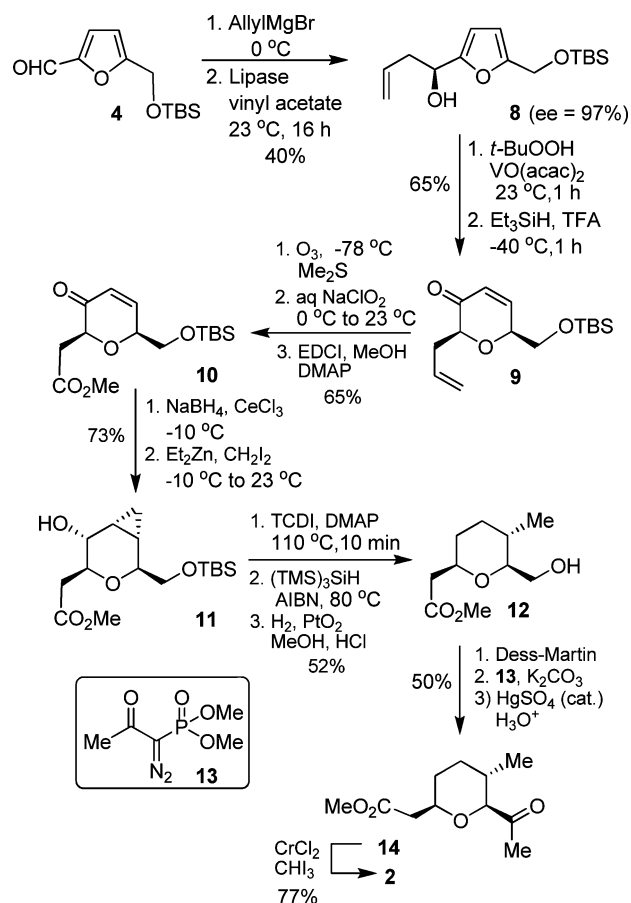
Figure 1. Retrosynthesis of (+)-herboxidiene.

iodide **6**, which can be obtained from an asymmetric crotylboration with an appropriate aldehyde.

The synthesis of vinyl iodide **2** (Scheme 1) commenced by treatment of aldehyde **4**⁹ with allylmagnesium bromide followed by lipase resolution of the resulting homoallylic alcohol to provide **8** in 40% yield and 97% *ee* (by Mosher ester analysis). The absolute stereochemistry of **8** was predicted based upon the Kazlauskas model.¹⁰ Ultimately, it was confirmed through its conversion to (+)-herboxidiene. Reaction of alcohol **8** with *t*-BuOOH in the presence of a catalytic amount of VO(acac)₂ resulted in a rearranged hemiketal.¹¹ The resulting hemiketal was reduced according to the procedure developed by Kishi and co-workers¹² to afford enone **9** in 65% yield, over two steps.

Our synthetic plan then required installation of the 6(*S*)-methyl-bearing stereocenter. This was achieved by selective ozonolysis of the terminal olefin of **9** using Sudan Red 7B¹³ as an indicator. The resulting aldehyde was oxidized with NaClO₂ to the corresponding acid which was esterified to methyl ester **10**. Reduction of **10** with NaBH₄ in the presence of CeCl₃·7H₂O in a mixture (1:1) of CH₂Cl₂ and MeOH at −10 °C yielded the allylic alcohol as a single diastereomer.¹⁴

Scheme 1. Synthesis of Tetrahydropyran Segment 2



Directed cyclopropanation of the resulting allylic alcohol with Et₂Zn and CH₂I₂ at −10 °C to 23 °C furnished cyclopropane derivative **11** as a single diastereomer (by ¹H NMR).¹⁵

Alcohol **11** was subjected to Barton's deoxygenation reaction¹⁶ to open the cyclopropane ring to give the corresponding methyl group. Thus, reaction of **11** with thiocarbonyldiimidazole (TCDI) in the presence of 3 equiv of DMAP in toluene at 110 °C for 10 min provided the corresponding imidazole thiocarbonate. Subsequent radical generation with *n*-Bu₃SnH in the presence of AIBN at 80 °C in toluene provided the desired ring-opened product in 38% yield, and a small amount (*ca.* 5%) of starting material was recovered. Interestingly, the use of (TMS)₃SiH at 80 °C in place of *n*-Bu₃SnH improved the yield and the desired ring-opened product was obtained in 54% yield along with a small amount of a deoxygenated cyclopropane derivative (*ca.* 6%). Catalytic hydrogenation of the resulting olefin over PtO₂ followed by treatment with dilute methanolic HCl yielded **12**. Our initial attempt to use 10% Pd/C resulted in a significant epimerization at the ring methyl stereocenter. Oxidation of alcohol **12** with Dess–Martin periodinane¹⁷

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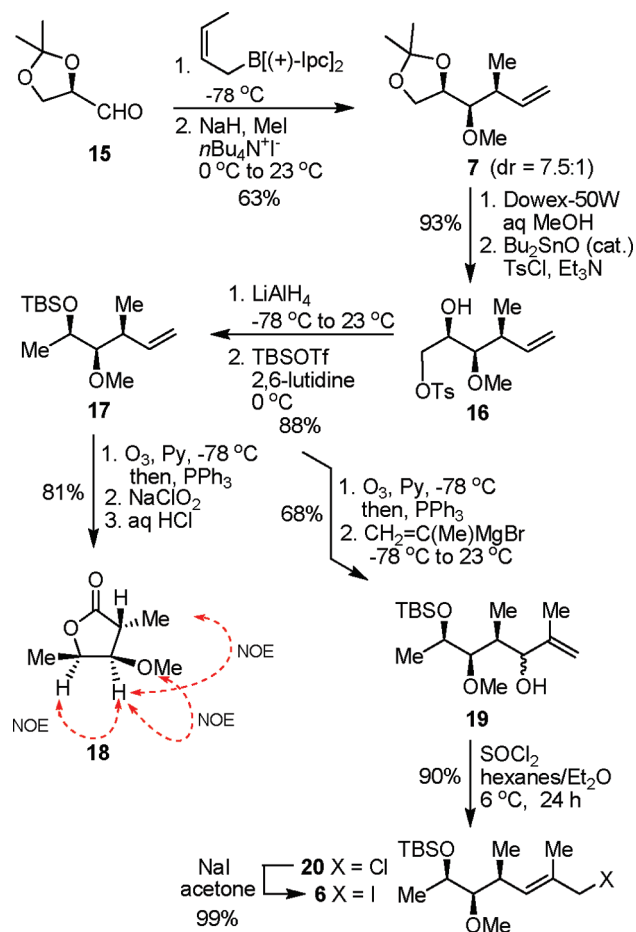
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provided the corresponding aldehyde. Treatment of this aldehyde with the Ohira–Bestmann reagent (**13**)¹⁸ in a methanolic suspension of K₂CO₃ afforded the corresponding alkyne. Exposure of the resulting alkyne to a catalytic amount of HgSO₄ (0.2 equiv) in aqueous THF and acid smoothly transformed the alkyne into ketone **14** in good yield.¹⁹ It was reacted with a mixture of CrCl₂ and CHI₃²⁰ in THF to furnish the requisite vinyl iodide **2** in excellent yield and good *E/Z* selectivity (5.7:1, by HPLC analysis).

The synthesis of allylic iodide **6** is shown in Scheme 2. We investigated the double diastereoselection of Brown's

Scheme 2. Synthesis of Allylic Iodide **6**



crotylboration²¹ with (*R*)-isopropylidene glyceraldehyde **15**²² at -78°C . The crude product was directly treated with NaH and methyl iodide to provide **7** in 63% overall yield and good diastereoselectivity (*dr* = 7.5:1). Interestingly, despite

a substrate–reagent mismatch, the high diastereoselectivity of **7** clearly demonstrated that the chiral borane reagent overruled the stereodirecting effect of the α -stereogenic center of **15**. Similar diastereoselection was observed by Armstrong and co-workers²³ with tetrasubstituted borane reagents and Masamune and co-workers with a chiral *Z*-crotyldimethyl borane.²⁴ Removal of the isopropylidene group by exposure of **7** to Dowex-50W in MeOH followed by regioselective tosylation of the resulting diol provided monotosylate **16** in excellent yield.²⁵ The reduction of **16** with LiAlH₄ in THF followed by protection of the resulting alcohol afforded TBS ether **17**. This was converted to γ -lactone **18** in 81% yield over three steps. The ¹H NMR NOE experiments of **18** fully supported the stereochemical assignment of the major diastereomer **7**. Ozonolysis of **17** followed by reaction of the resulting aldehyde with isopropenyl magnesium bromide resulted in a mixture (2.6:1) of alcohols **19**. Treatment of **19** with thionyl chloride at 6°C provided the rearranged allylic chloride **20** as a single isomer (by ¹H NMR). Finkelstein reaction of **20** furnished iodide **6** in excellent yield. The high degree of stereoselection in favor of the *E*-isomer in this allylic chlorination reaction can be explained by an S_Ni process²⁶ through a chair-like six-membered transition state shown in Figure 2. The large

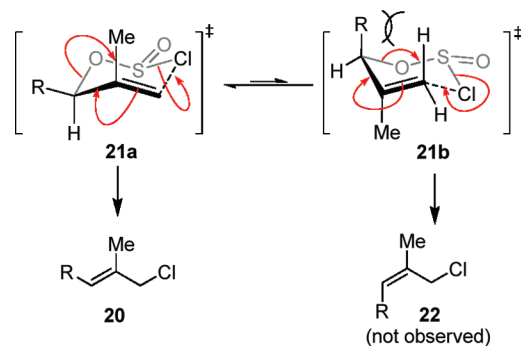


Figure 2. Plausible chlorination transition states for **20**.

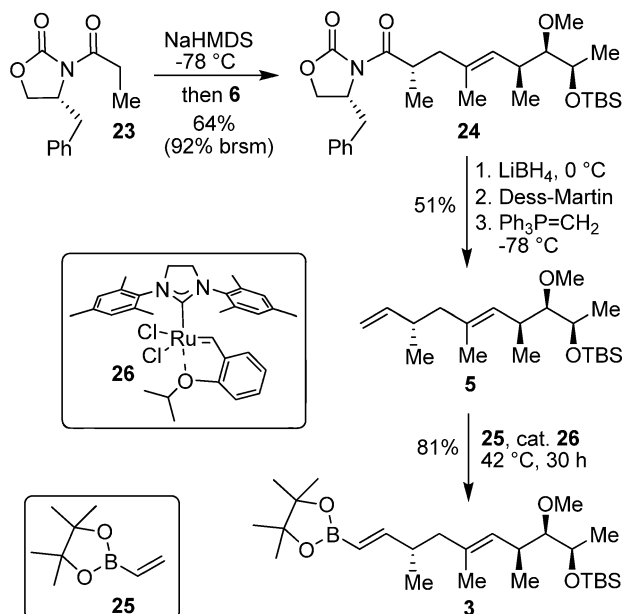
R-group would likely induce a greater 1,3-diaxial interaction in transition state **21b** over **21a**, resulting in **20** as the sole product. The reaction can also proceed through a close ion-pair mechanism as suggested by Cram.²⁷ It is noteworthy to mention that the TBS group was unaffected under the reaction conditions. This was also observed by Paquette and Taylor previously.²⁸

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Synthesis of boronate **3** is shown in Scheme 3. Asymmetric alkylation²⁹ of (*R*)-4-benzyl-3-propionyloxazolidin-

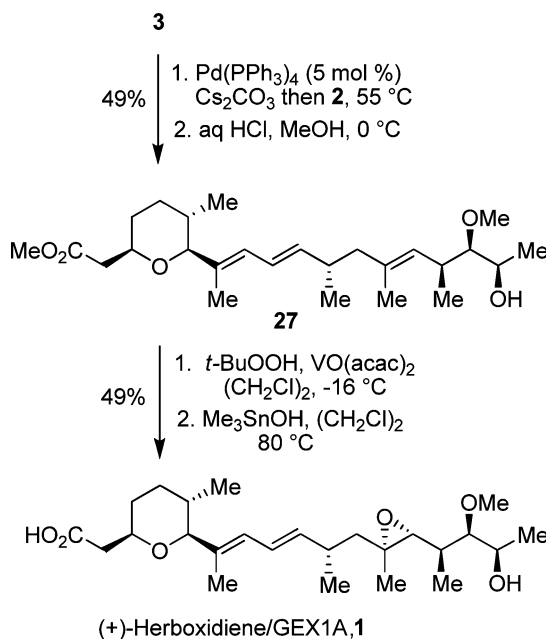
Scheme 3. Synthesis of Boronate **3**



2-one (**23**) with **6** afforded **24** as a single diastereomer in 64% isolated yield. Reductive cleavage of the chiral auxiliary with LiBH_4 furnished the primary alcohol. Dess–Martin oxidation¹⁷ afforded the corresponding aldehyde, which was converted to terminal alkene **5** by a Wittig reaction. Cross-metathesis of the resulting olefin with vinyl pinacol boronate **25** catalyzed by Hoveyda–Grubbs II catalyst **26**³⁰ provided **3** predominantly (*E/Z* selectivity >16:1, by ^1H NMR), in 43% yield, over three steps.

With vinyl iodide **2** and boronate **3** in hand, our synthetic plan was to utilize a Suzuki cross-coupling reaction, previously carried out by Murray and Forsyth.^{7c} As shown in Scheme 4, coupling of **2** and **3** was conducted in the presence of Cs_2CO_3 and $\text{Pd}(\text{PPh}_3)_4$ (5 mol %) at 55 °C to give the corresponding coupled product in 71% yield.³¹ Treatment of this coupled product with dilute methanolic HCl solution at 0 °C gave alcohol **27**. Regio- and stereoselective directed epoxidation of **27** was carried out as described in previous syntheses.⁷ Thus, treatment of **27** with *t*-BuOOH and $\text{VO}(\text{acac})_2$ furnished the corresponding epoxide. Methyl ester hydrolysis with Me_3SnOH using a protocol described by Nicolaou and co-workers³² provided synthetic (+)-**1**. The spectroscopic data of our synthetic (+)-**1** $\{[\alpha]_{\text{D}}^{20} = +4.2$ (*c*

Scheme 4. Completion of (+)-Herboxidiene/GEX1A



0.29, MeOH)} and the synthetic (+)-herboxidiene/GEXA1 $\{[\alpha]_{\text{D}}^{22} = +4.9$ (*c* 0.02, MeOH)} reported by Zhang and Panek^{7b} and $\{[\alpha]_{\text{D}}^{22} = +4.0$ (*c* 0.02, MeOH)} by Murray and Forsyth^{7c} are identical.

In summary, we have accomplished a stereoselective synthesis of (+)-herboxidiene/GEX1A. The synthesis features an Achmatowicz reaction, a lipase resolution, stereoselective construction of the tetrahydropyran ring, and stereoselective installation of the ring methyl group through a radical-promoted opening of a cyclopropane derivative for subunit **2**. Segment **3** utilized Brown's crotylboration of (*R*)-isopropylidene glyceraldehyde as one of the key steps. Interestingly, the product showed high diastereoselectivity despite that there was a substrate–reagent mismatch. These results indicated that the chiral borane reagent overruled the stereodirecting effect of the α -stereogenic center. The synthesis also utilized a highly stereoselective allylic chlorination reaction, asymmetric alkylation, and Suzuki coupling reaction. The present synthesis could be utilized in the synthesis of structural variants of (+)-herboxidiene/GEX1A.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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