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A Stereoselective Synthesis of (+)-Herboxidiene/GEX1A

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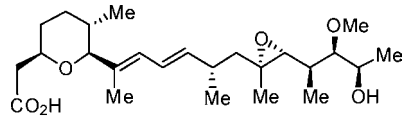
ABSTRACT



(+)-Herboxidiene/GEX1A, **1**

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-workers[6] confirmed the relative and absolute configuration of herboxidiene/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

(1) Isaac, B. G.; Ayer, S. W.; Elliott, R. C.; Stonard, R. J. *J. Org. Chem.* **1992**, *57*, 7220–7226.

(2) (a) Sakai, Y.; Yoshida, T.; Ochiai, K.; Uosaki, Y.; Saitoh, Y.; Tanaka, F.; Akiyama, T.; Akinaga, S.; Mizukami, T. *J. Antibiot.* **2002**, *55*, 855–860. (b) Sakai, Y.; Tsujita, T.; Akiyama, T.; Yoshida, T.; Mizukami, T.; Akinaga, S.; Horinouchi, S.; Yoshida, M. *J. Antibiot.* **2002**, *55*, 863–872.

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(6) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995–1001.

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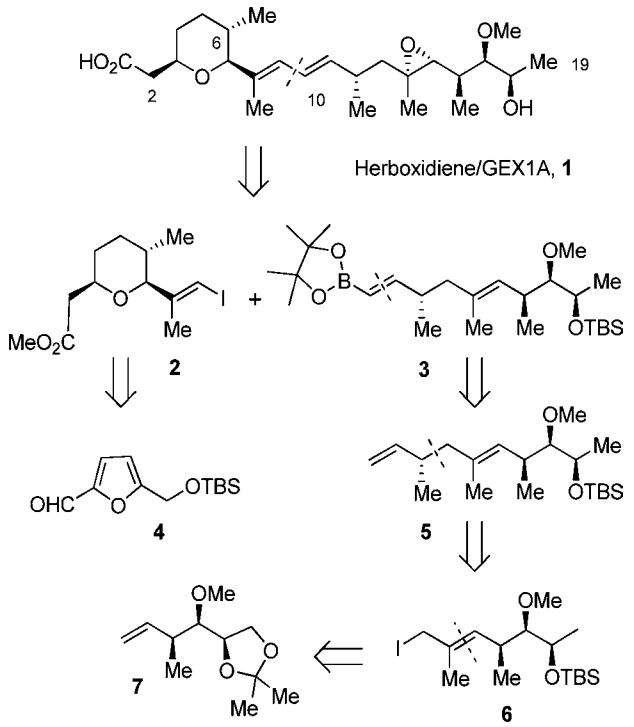


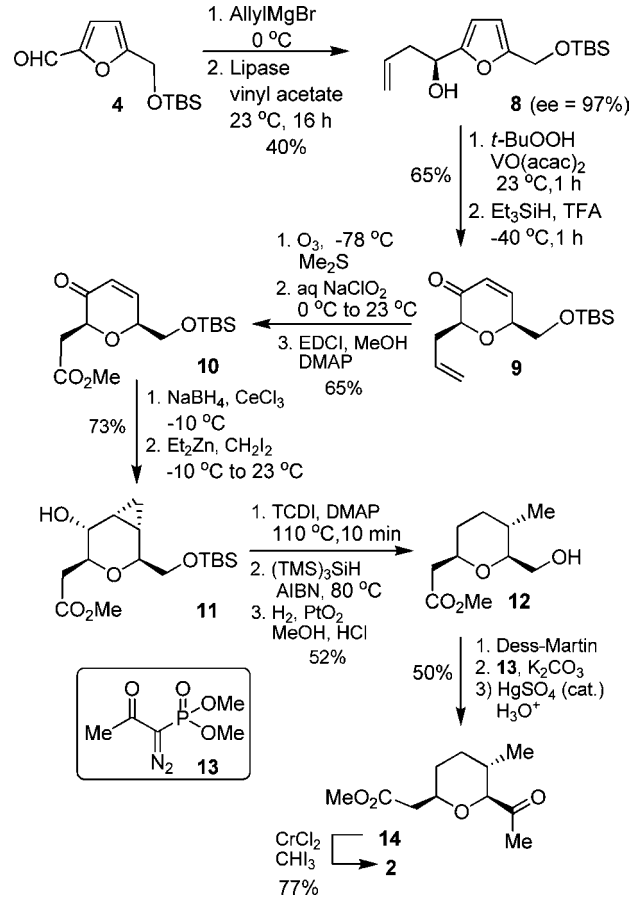
Figure 1. Retrosynthesis of (+)-herboxidiene.

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-workers[12] 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 7B[13] as an indicator. The resulting aldehyde was oxidized with $NaClO_2$ to the corresponding acid which was esterified to methyl ester **10**. Reduction of **10** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in a mixture (1:1) of CH_2Cl_2 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 Et_2Zn and CH_2I_2 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 reaction[16] 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*-Bu_3SnH 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*-Bu_3SnH 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 PtO_2 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 periodinane[17]

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(10) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999.
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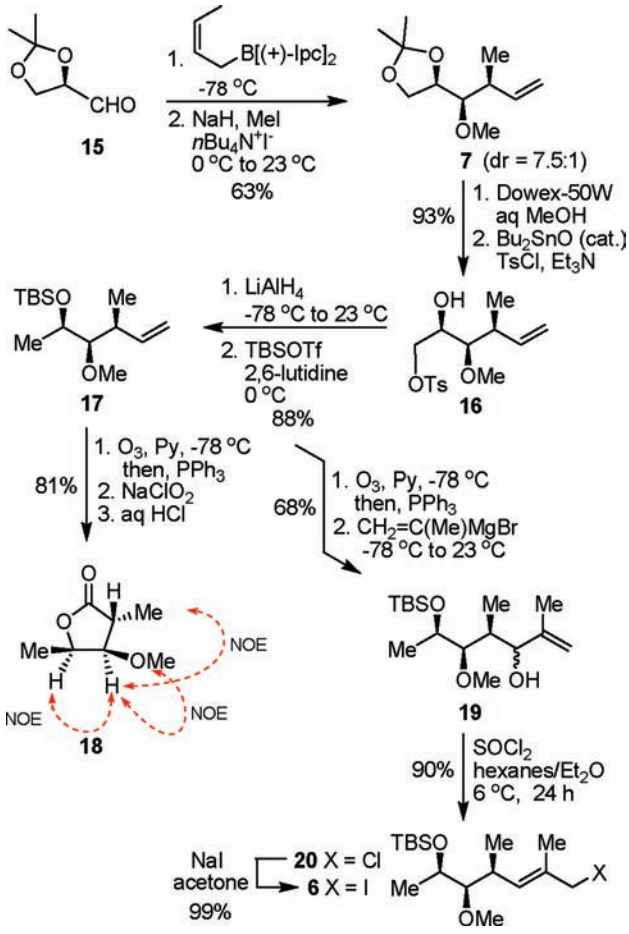
provided the corresponding aldehyde. Treatment of this aldehyde with the Ohira−Bestmann reagent (**13**)[18] in a methanolic suspension of K_2CO_3 afforded the corresponding alkyne. Exposure of the resulting alkyne to a catalytic amount of $HgSO_4$ (0.2 equiv) in aqueous THF and acid smoothly tranformed the alkyne into ketone **14** in good yield.[19] It was reacted with a mixture of $CrCl_2$ and CHI_3[20] 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**



crotylboration[21] 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-workers[23] 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 $LiAlH_4$ 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 ^{1}H 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 ^{1}H 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_N^i process[26] through a chair-like six-membered transition state shown in Figure 2. The large

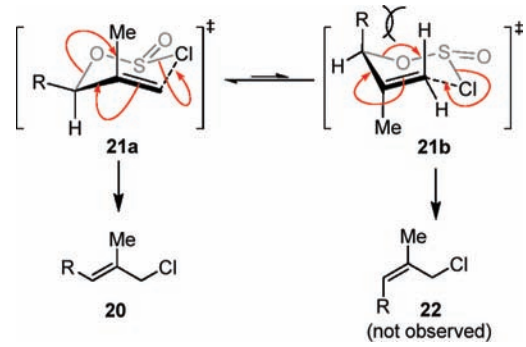


Figure 2. Plausible chlorination transition states for **20**.

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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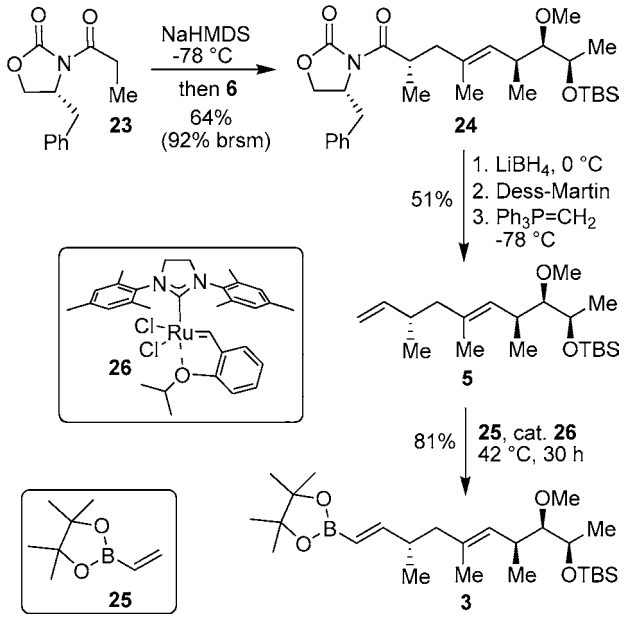
Synthesis of boronate **3** is shown in Scheme 3. Asymmetric alkylation[29] of (*R*)-4-benzyl-3-propionyloxazolidin-

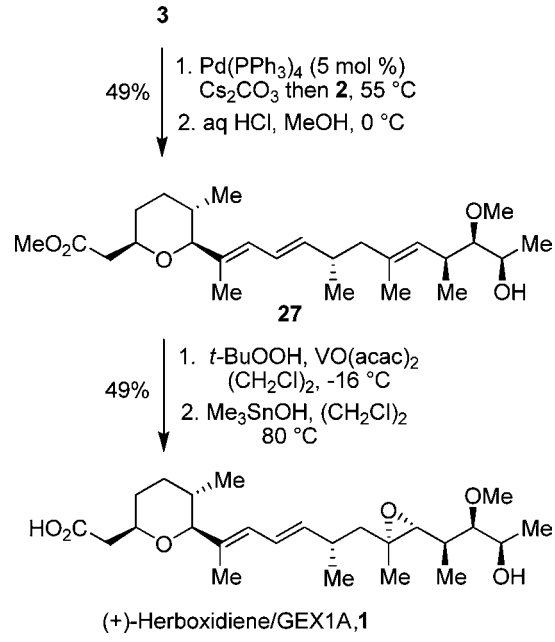
Scheme 3. Synthesis of Boronate **3**



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 oxidation[17] 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 ^{1}H 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 $Pd(PPh_3)_4$ (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 $VO(acac)_2$ furnished the corresponding epoxide. Methyl ester hydrolysis with Me_3SnOH using a protocol described by Nicolaou and co-workers[32] provided synthetic (+)-**1**. The spectroscopic data of our synthetic (+)-**1** {$[\alpha]_D^{20} = +4.2$ (*c* 0.29, MeOH)} and the synthetic (+)-herboxidiene/GEXA1 {$[\alpha]_D^{22} = +4.9$ (*c* 0.02, MeOH)} reported by Zhang and Panek[7b] and {$[\alpha]_D^{22} = +4.0$ (*c* 0.02, MeOH)} by Murray and Forsyth[7c] are identical.

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



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 ^{1}H 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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