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Total Synthesis of Herboxidiene/GEX 1A

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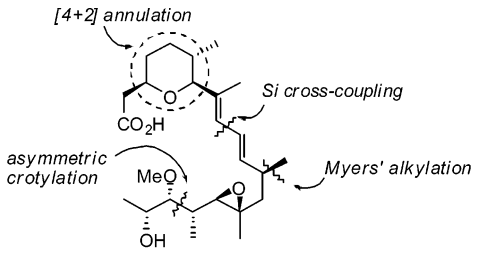
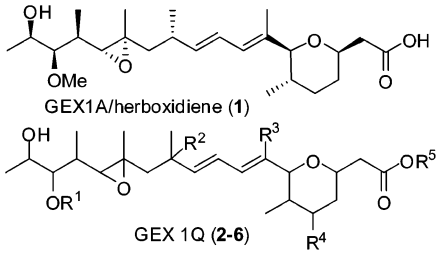
ABSTRACT



A convergent enantioselective synthesis of herboxidiene/GEX 1A (1) is described that features a double stereodifferentiating crotylation, [4 + 2] annulation, and a silicon-based sp^2–sp^2 cross-coupling to assemble the conjugated diene.

Herboxidiene/GEX 1A (**1**), a secondary metabolite originally isolated from *Streptomyces* sp. A7847, displayed selective phytotoxicity against a range of broadleaf annual weeds while remaining harmless to coplanted wheat.[1] In a search for new antitumor agents, **1** was reisolated from a fermentation culture broth with five other structurally related GEX 1 members (**2**−**6**, Figure 1).[2] While several members of this family showed potent cytotoxicity (IC_{50} values ranging from 3.7 nM to 0.99 μM) against several human tumor cell lines in vitro, GEX 1A is the only one possessing antitumor activity in vivo. The entire family of GEX 1 compounds displayed cytotoxicity via up-regulating luciferase reporter gene expression as well as inducing both G1 and G2/M arrest in human tumor cell line WI-38.[3] The stereochemical assignment of **1** was obtained through a combination of degradation studies, partial synthesis, and crystallographic analysis.[4] The class of natural products possesses several synthetically challenging structural features, including the trisubstituted tetrahydropyran core, the conjugated diene moiety, and the polyoxygenated side chain. Two total syntheses and several synthetic approaches toward herboxidiene/GEX 1A have recently been published.[5]

Herein, we describe a convergent enantioselective synthesis of herboxidiene/GEX 1A (**1**) that makes use of



GEX 1Q1 (**2**): R^1=Me; R^2=H; R^3=Me; R^4=OH; R^5=H
GEX 1Q2 (**3**): R^1=Me; R^2=OH; R^3=Me; R^4=H; R^5=H
GEX 1Q3 (**4**): R^1=Me; R^2=H; R^3=Me; R^4=H; R^5=glucuronide
GEX 1Q4 (**5**): R^1=Me; R^2=H; R^3=CH_2OH; R^4=H; R^5=H
GEX 1Q5 (**6**): R^1=OH; R^2=H; R^3=Me; R^4=H; R^5=H

Figure 1. Structures of GEX 1 family members (**1**−**6**).

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(3) Sakai, Y.; Tsujita, T.; Akiyama, T.; Yoshida, T.; Mizukami, T.; Akinaga, S.; Horinouchi, S.; Yoshida, M.; Yoshida, M. *J. Antibiot.* **2002**, *55*, 863.
(4) Edmunds, A. J. F.; Trueb, W.; Oppolzer, W.; Cowley, P. *Tetrahedron* **1997**, *53*, 2785.

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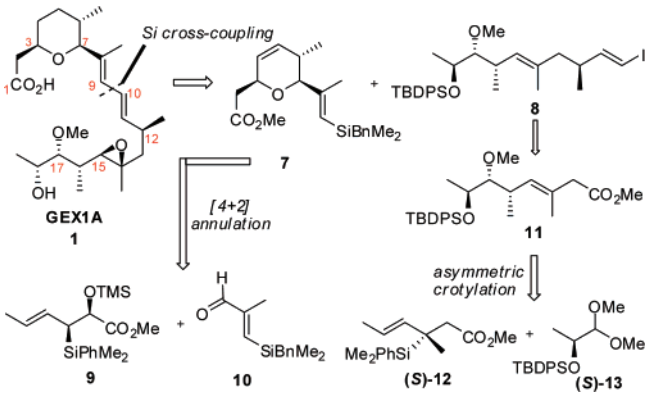
organosilane-based bond construction methodology in three crucial ways (Scheme 1). The first disconnection at C9−

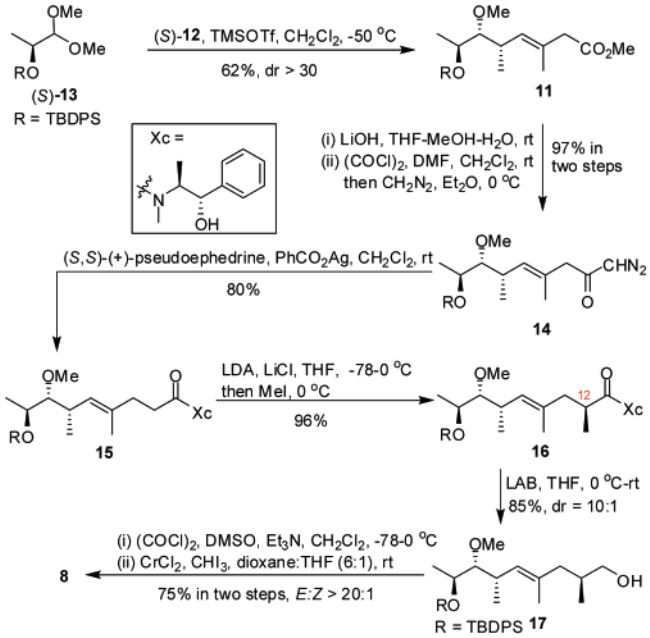
Scheme 1. Retrosynthetic Analysis of Herboxidiene/GEX 1A (**1**)



C10 leads to a functionalized pyran core and an oxygenated side chain. We anticipated using a silicon-assisted sp^2-sp^2 cross-coupling for the union of intermediates **7** and **8**. In this plan, the conjugated (*E*,*E*)-diene could be accessed with high levels of selectivity. Dihydropyran **7** could be obtained from *syn*-silane reagent **9** and the silyl-substituted methacrolein **10** utilizing our stereoselective [4 + 2] annulation strategy.[6] Further, we hoped that side chain **11** could be rapidly constructed from silane reagent (*S*)-**12** and α-silyloxy acetal (*S*)-**13**.

Synthesis of the C10−C19 fragment was initiated with a double-stereodifferentiating crotylation[7] based on the use of a newly developed crotylsilane reagent (*S*)-**12** that bears a fully substituted stereocenter (Scheme 2).[8] Since the C18 hydroxyl would be properly configured for a directed epoxidation later in the synthesis, we chose (*S*)-silyloxy acetal **13** as the crotylation electrophile.[9] Thus, a matched crotylation between (*S*)-**12** and (*S*)-**13** promoted by TMSOTf provided the desired syn homoallylic ether **11** containing a trans-trisubstituted olefin in 62% yield and high diastereoselectivity (dr >30:1). When subjected to Arndt−Eistert conditions[10] **11** was converted to diazoketone **14** in 97% yield

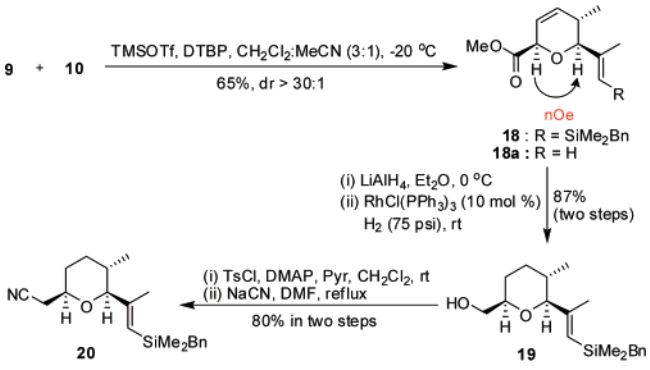
Scheme 2. Synthesis of C10−C19 Fragment **8**



over two steps. Rearrangement of **14** followed by trapping of the ketene with (+)-pseudoephedrine gave the homologated amide **15** in 80% yield. At this stage, the C12 methyl-bearing stereocenter was introduced with high selectivity using Myers' pseudoephedrine-derived auxiliary[11] and afforded **16** in 96% yield. The magnitude of diastereoselectivity of the alkylation was determined to be >10:1 after reductive removal of the auxiliary using lithium amidotrihydroborate (LAB).[12] The resulting primary alcohol **17** was then oxidized to the corresponding aldehyde under Swern conditions,[13] which was subjected to Takai iodoolefination to give the (*E*)-vinyl iodide **8** (*E*/*Z* > 20:1, 75% yield).[14]

The short sequence required for the elaboration of the *cis*-2,6-*trans*-5,6-tetrahydropyran core is summarized in Scheme 3. A TMSOTf-promoted [4 + 2] annulation between *syn*-

Scheme 3. Synthesis of C1−C9 Fragment **20**



crotylsilane **9** and (*E*)-vinylsilyl aldehyde **10**[15] provided *cis*-2,6-dihydropyran **18** in 65% yield and with high selectivity

(5) Total synthesis, see: (a) Blakemore, P. R.; Kocieński, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955. (b) Banwell, M.; McLeod, M.; Premraj, R.; Simpson, G. *Pure Appl. Chem.* **2000**, *72*, 1631. Diastereomeric synthesis, see: (c) Smith, N. D.; Kocieński, P. J.; Street S. D. A. *Synthesis* **1996**, 652. Fragment synthesis, see: (d) Banwell, M. G.; Bui, C. T.; Simpson, G. W.; Watson, K. G. *Chem. Commun.* **1996**, 723. (e) Banwell, M. G.; Bui, C. T.; Hockless, D. C. R.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1261. (f) Banwell, M. G.; Bui, C. T.; Simpson, G. W. *J. Chem. Soc. Perkin Trans. 1* **1998**, 791. SAR studies, see: (g) Edmunds, A. J. F.; Arnold, G.; Hagmann, L.; Schaffner, R.; Furlenmeier, H. *Med. Chem. Lett.* **2000**, 1365.

(6) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

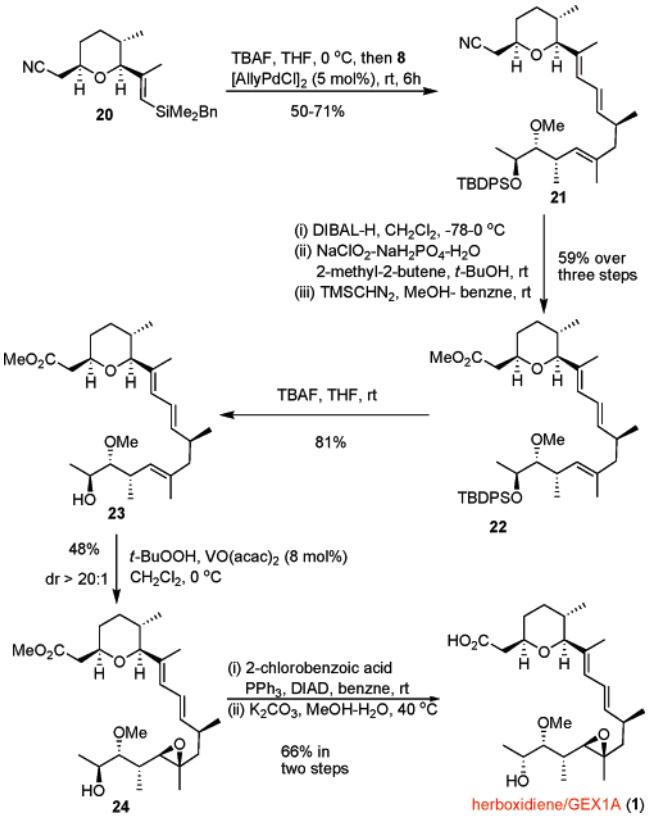
(7) (a) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.

(8) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529.

(9) (*S*)-Silyloxy acetal **13** was prepared in two steps from the commercially available (*S*)-ethyl lactate. See the Supporting Information for details.

(10) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

Scheme 4. Completion of the Total Synthesis of **1**



(dr >30:1).[6] Initially, this annulation was plagued with significant amounts of protodesilylation giving terminal olefin **18a** as the major product. After screening several bases and solvent systems, we learned that with catalytic amounts of 2,6-di-*tert*-butylpyridine (DTBP) and 1.0 equiv of TMSOTf in a mixture of CH_2Cl_2/MeCN (3:1, −20 °C), the reaction proceeded smoothly to provide the desired product in a useful yield. Reduction of **18**, followed by a hydroxyl-directed chemoselective hydrogenation using Wilkinson's catalyst,[16,20a] afforded the tetrahydropyran product **19** in 87% yield over both steps. Alcohol **19** was then converted to a tosylate followed by displacement with sodium cyanide to give the desired nitrile **20**, thereby reconstituting the oxidation state of a carboxylate.

With workable amounts of advanced intermediates **8** and **20** available, we were positioned to carry out the crucial silicon-based sp^2-sp^2 cross-coupling.[17] Preactivation of vinylsilane **20** with 2.2 equiv of TBAF[18] followed by addition of $[AllyPdCl]_2$ and vinyl iodide **8**, the desired product **21** was obtained in a good yield and exclusively as the (*E*,*E*)-diene isomer. Nitrile **21** was then partially reduced to the aldehyde by DIBAL-H. Pinnick oxidation[19] followed by methylation with TMS-stabilized diazomethane provided methyl ester **22** in three steps, 59% yield. Removal of the TBDPS group using TBAF was followed by a directed epoxidation of the bishomoallylic alcohol **23**.[20] As reported, C18 hydroxyl-directed epoxidation, catalyzed by $VO(acac)_2$ gave a single diastereomer in 48% yield.[5a] Inversion of the C18 hydroxyl under modified Mitsunobu conditions[21] and saponification of the resulting diester[5] completed the total synthesis of herboxidiene/GEX 1A (**1**).

In summary, we have described a highly convergent and enantioselective synthesis of herboxidiene/GEX 1A (**1**) in 16 steps from the crotysilane **12**. The construction of pyran fragment and oxygenated side chain and the utility of vinylsilane in the union of **8** and **20** demonstrate the versatility of organosilanes in natural product synthesis. This work also illustrates the use of silicon-based cross-coupling as an alternative to vinylstannane and other more sensitive metal based cross-coupling reactions in complex molecule synthesis.

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Note Added after ASAP Publication. There was an error in Scheme 4 in the version published ASAP July 13, 2007; the corrected version was published July 17, 2007.

Supporting Information Available: Experimental details and new selected spectral for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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