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Stereocontrolled [4+2]-Annulation Accessing Dihydropyrans: Synthesis of the C1a-C10 Fragment of Kendomycin

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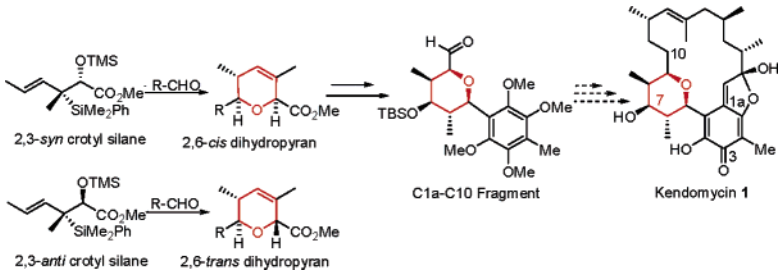
ABSTRACT



Development of new organosilane reagents bearing *C*-centered chirality where the stereocenter is fully substituted, and their use in the stereocontrolled synthesis of *cis*- and *trans*-dihydropyrans containing a trisubstituted olefin is described. The reagents participate in Lewis acid promoted [4+2]-annulations providing useful levels of selectivity with both aliphatic and aromatic aldehydes. A stereoselective synthesis of the C1a-C10 fragment of kendomycin (1) is also described.

Functionalized pyrans are important subunits of biologically active compounds, serving as common structural motifs of natural products and precursors to chemically diverse *C*-glycosides.[1] Much of their chemistry has been extensively reviewed.[2] Examples of complex natural products bearing pyran subunits include the phorboxazoles,[3] lasonolide A,[4] callipeltoside,[5] and spongistatin 1.[6] Accessing anomeric-linked aliphatic and aromatic pyran systems in a stereocontrolled manner would be a useful contribution to the field of synthesis. Approaches previously documented for the construction of dihydropyran ring systems include palladium mediated reactions,[7] ring closing metathesis (RCM),[8] radical cyclization,[9] cationic cyclization,[10] Prins cyclization,[11] hetero-Michael additions,[12] and hetero-Diels−Alder reaction path-

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(12) (a) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662. (b) Siliphaivanh, P.; Crimmins, M. T. *Org. Lett.* **2003**, *5*, 4641. (c) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226.

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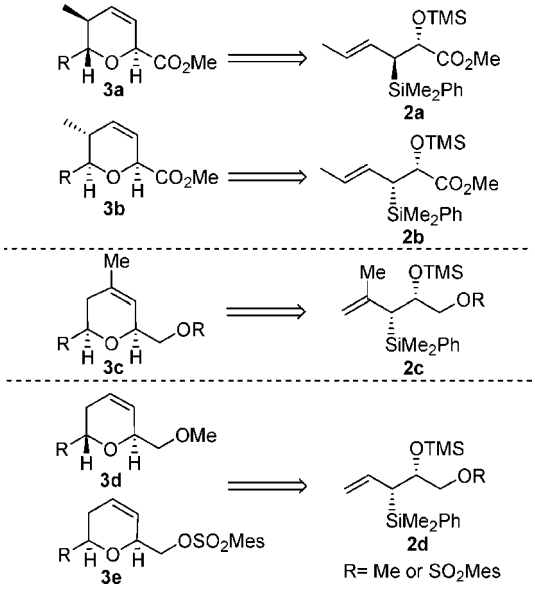
ways.[13] Several of these methods constitute efficient pathways and high levels of selectivity for the formation of 2,6-*cis*-dihydropyrans. However, access to the complimentary 2,6-*trans*-dihydropyrans remains underdeveloped.[14]

We have described the use of chiral silanes **2a**−**d** in [4+2]-annulations leading to the preparation of functionalized dihydropyrans.[15] These reagents access pyrans of the general structure **3a**−**e** illustrated in Scheme 1.

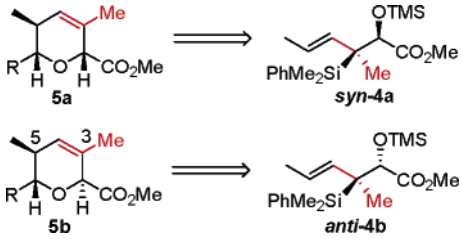
Scheme 1. Chiral Crotyl and Allyl Silanes in [4+2]-Annulations



Herein, we describe the synthesis of dihydropyrans with high diastereo- and enantioselectivity from silanes **4a** and **4b** bearing a quaternary center at the carbon bearing the silyl group.[16] The described methodology will then be utilized in the synthesis of the C1a-C10 fragment of kendomycin **1**.

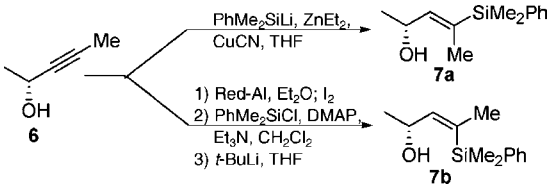
The synthesis of silanes **4a** and **4b** began with the preparation of vinyl silanes **7a** and **7b** (Scheme 3). The synthesis of *E*-vinyl silane used a silyl-zincation of (*R*)-3-pentyn-2-ol **6**[17] employing lithium dimethylphenyl silane,[18]

Scheme 2. New Chiral Crotyl Silanes in [4+2]-Annulation[15]



diethyl zinc, and a catalytic amount of copper(I) cyanide to give **7a** in 90% yield as a single stereoisomer.[19]

Scheme 3. Synthesis of (*E*) and (*Z*)-Vinyl Silanes



The complementary *Z*-vinyl silane **7b** was synthesized in 3 steps from **6**. A regioselective hydroalumination with Red-Al followed by an iodine trap provided an enantiomerically pure vinyl iodide.[20] The alcohol was then protected as the dimethylphenylsilyl ether and subjected to a retro-Brook rearrangement[21] to give **7b** in 3 steps (65% yield).[22] Both the *Z*- and *E*-vinyl silanes can be prepared on a 20 g scale with greater than 99% enantiomeric excess as determined by chiral HPLC.[23]

With both vinyl silanes in hand the remaining steps in the formation of the desired crotyl silanes parallel each other with few variations in yield and procedure for [3,3]-sigmatropic rearrangement (Scheme 4). Substrates for the Claisen rearrangements were prepared through a DCC coupling of (4-methoxybenzyloxy)acetic acid[24] with vinyl silanes depicted in Scheme 2 to give **8a** and **8b**. Treatment with LiHMDS and trapping of the intermediate lithium enolate at −78 °C with TMSCl and warming to room temperature afforded the desired α-alkoxy acids **9a** and **9b**.[25,26] The rearrangement of **8a** gave only one detectable diastereoisomer of the hexanoic acid by NMR. The comple-

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(16) Prior methods required several additional steps to install a methyl group in the 3-position with use of **2a** or **2b**. A more efficient approach would be to introduce the second methyl group prior to annulation as depicted in Scheme 2, transforming **4** into **5**. Representative examples of 3,5-substituted glycosides: (a) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569. (b) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 2299. (c) Czuba, I. R.; Zammit, S.; Rizzacasa, M. A. *Org. Biomol. Chem.* **2003**, *1*, 2044 and references therein.

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(20) Marshall, J. A.; Shearer, B.; Crooks, S. *J. Org. Chem.* **1987**, *52*, 1236.

(21) For recent examples of retro-Brook rearrangement see: Gandon, V.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2000**, *41*, 3053 and references therein.

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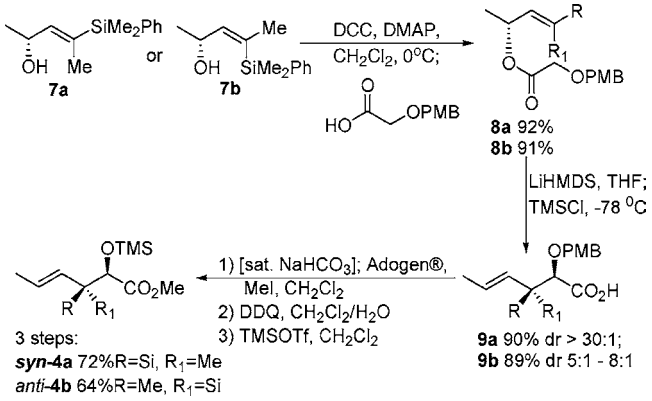
(26) Clark, T.; Panek, J. S. *J. Org. Chem.* **1992**, *57*, 4323.

Scheme 4. Preparation of Chiral Crotyl Silanes



mentary **9b** was unfortunately obtained as a 5:1 to 8:1 mixture of *anti*:*syn* diastereomers, which may be separated at a later stage. Esterification with the phase transfer catalyst Adogen[27] in the presence of iodomethane followed by the deprotection of the PMB group gave a free α-hydroxy ester. The alcohol may then be protected as a TMS ether to complete the synthesis of both the *syn*- and *anti*-crotyl silanes (5 steps, 60% **4a**; 56% **4b**, respectively) from **7a** and **7b**.

Once a practical method was developed for the preparation of **4a** and **4b**, we turned our attention toward exploring their utility in [4+2]-annulations with a number of different aldehydes (Table 1). On exposure to TMSOTf (0.05 M CH_2Cl_2 at −50 °C) the desired dihydropyrans 2,6-*cis* **11a** (from **4a**) and 2,6-*trans* **11b** (from **4b**) were obtained respectfully.

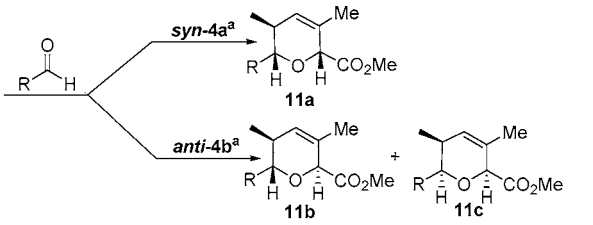
Aromatic and conjugated aldehydes (entries 1−5 and 6) gave the corresponding pyrans with useful yields and high levels of diastereoselectivity. The lower yield observed for entry 5 was a result of competitive deprotection of a single acetonide group on the aromatic aldehyde. Aldehydes containing multiple heteroatoms (chelatable centers) also performed well under the described conditions (entries 2 and 5).

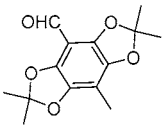
Aliphatic aldehydes (entries 7 and 8) showed slightly lower levels of diastereoselectivities with **4a**.[28] Interestingly the [4+2]-annulation utilizing **4b** with aliphatic aldehydes (entries 7 and 8) gave a 2,6-*cis* 5,6-*cis* relationship (**11b**) suggesting a mechanistic crossover in the stereochemical course of the annulation.

The utility of these crotyl silanes in complex molecule synthesis is documented in the synthesis of the C1a-C10 fragment of kendomycin **1** (Scheme 5).

Compound **1** was isolated from two different *Streptomyces* species as described in the patent literature.[29] More recently this substance was re-isolated from *Streptomyces violaceoruber* (strain 3844-33C) in connection with a chemical

Table 1. Application of **4a**/**4b** in the [4+2]-Annulation Reaction



entry	aldehyde	yield[b]	11a[c,d]	yield[b]	11b:11c[c,d]
1	Benzaldehyde	92	>30:1	92	>20:1
2	2, 5-Dimethoxy benzaldehyde	86	>30:1	80	>20:1
3	4-Chlorobenzaldehyde	89	>30:1	87	>20:1
4	2-Napthylaldehyde	84	>30:1	88	>20:1
5[e]		63	>30:1	45	2:1
6	Crotyl aldehyde	61	>30:1	67	>15:1
7	Propionaldehyde	91	>15:1	72	1:3
8	Cyclohexane carboxaldehyde	72	>15:1	79	1:5

[a] Typical experiment was run in CH_2Cl_2 (0.05M), using 1 to 1.3 equiv of aldehyde in the presence of TMSOTf (0.3 equiv). [b] All yields are based on isolated product after chromatography. [c] Relative stereochemical assignments were determined by nOe experiments. [d] The ratio of products is determined by ^1H NMR. [e] See the Supporting Information.

screening program to detect new metabolites from actinomycetes.[30] The highly substituted tetrahydropyran core of **1** makes for an attractive target for this methodology. Presently there is one reported total synthesis[31] and multiple reports of synthetic approaches.[32]

Use of silane *ent*-**4a** in the [4+2]-annulation with the highly substituted aromatic aldehyde **12b** gave the desired 2,5-*syn*-dihydropyran **13** in 85% isolated yield (dr >30:1). The epoxidation of the resulting trisubstituted double bond with 1,1,1-trifluoro dimethyl dioxirane in acetonitrile at −20 °C gave epoxide **14** with an α:β > 12:1 and 93% yield. Oxirane ring opening occurred with elimination of the intermediate β-methoxy ester in the presence of potassium carbonate in methanol and gave the secondary alcohol **15**.

(27) Bocchi, V.; Casnati, G.; Dossena, A.; Marchelli, R. *Synthesis* **1979**, 957.

(28) One notable exception involves the use of trimethylacetaldehyde, as only the product from Peterson elimination was observed to give the conjugated diene of **4**. This result was consistent with that observed for crotyl silanes **2a** and **2b** with this particular aldehyde.[14a]

(29) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japanese Patent 08231551, 1996; *Chem. Abstr.* **1997**, *126*, 6553. (b) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japanese Patent 08231553, 1996; *Chem. Abstr.* **1997**, *125*, 326518. (c) Su, M.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. U.S. Patent 5728727, 1998; *Chem. Abstr.* **1998**, *128*, 239489.

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(31) Yaun, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720.

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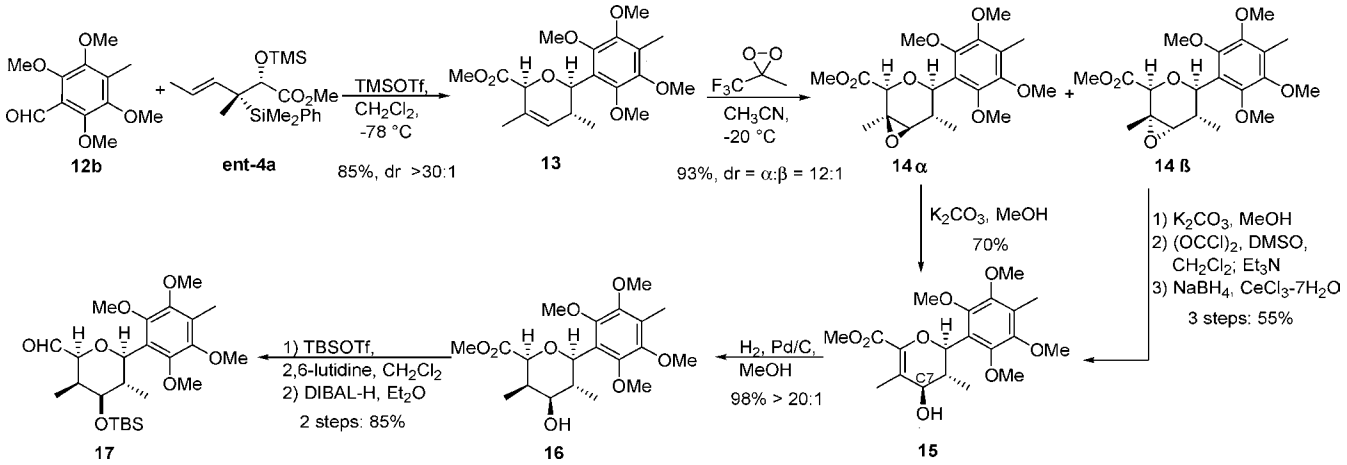
Scheme 5. Synthesis for the C1a-C10 Fragment of Kendomycin



Catalytic hydrogenation of the α,*β*-unsaturated ester completed the installation of the final two stereocenters. The stereochemical course of the reduction is consistent with a sterically controlled approach in a 69% 2 step yield and >20:1 selectivity for **16**. The undesired diastereoisomer **14*β*** could be recycled to give the correct C7 stereochemistry. This was realized with the oxirane ring opening, Swern oxidation of the resulting secondary alcohol, followed by selective Luche reduction[33] to give compound **15** in a 15:1 and 3 step 55% overall yield. Completion of the synthesis required the protection of secondary alcohol in **16** as a TBS ether, followed by DIBAl-H reduction of the methyl ester to give aldehyde **17**.

In conclusion, we have developed a reliable route for the preparation of two new organosilanes bearing a quaternary center on the carbon containing the silicon moiety. The route provides the silanes **4a** and **4b** in multigram quantities (>10 g) in high enantiopurity. These reagents were used in [4+2]-annulations with structurally diverse aldehydes to produce both 2,6-*cis*- and *trans*-dihydropyrans with useful levels of diastereoselectivity. Application in the synthesis of the C1a-C10 fragment of kendomycin has also been described. Further studies on the application of this reagent for complex molecule synthesis will be reported in due course.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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