Synthetic Approach towards the Sex Pheromone of the Female Oleander Scale *Aspidiotus Nerii*

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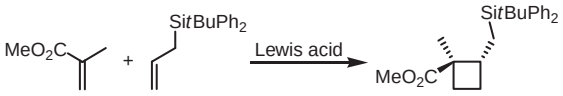
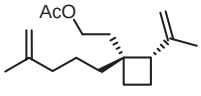
We report a synthetic approach to the sex pheromone of the female oleander scale *Aspidiotus nerii* using our Lewis acid promoted [2 + 2] cycloaddition of allylsilanes in combination with the modified Fleming–Tamao oxidation.

Four-membered carbocyclic rings represent a comparatively rare structural feature of natural products. Nevertheless, a variety of naturally occurring cyclobutanes has been isolated.[1] Although, many strategies have been developed, the construction of cyclobutanes remains a synthetic challenge due to the strained ring system. The most widely used procedures include photochemically induced [2 + 2] cycloadditions of alkenes, thermally induced [2 + 2] cycloadditions of alkenes and ketenes, and cyclization reactions.[1]



Scheme 1. Lewis acid promoted [2 + 2] cycloaddition of allylsilanes.

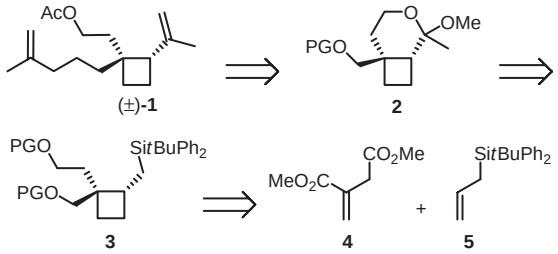
We developed a novel method for the construction of cyclobutanes by Lewis acid promoted [2 + 2] cycloaddition of allylsilanes and acrylic esters (Scheme 1).[2] This method found diverse applications in organic synthesis.[3] The resulting silyl–methyl-substituted cyclobutanes could be functionalized by using a modified Fleming–Tamao oxidation developed in our laboratories.[4,5] This protocol can be applied to the conversion of even highly hindered silyl groups to the corresponding alcohols (e.g.: triphenylsilyl, *tert*-butyldiphenylsilyl, and di(*iso*-propyl)-phenylsilyl). The Lewis acid promoted [2 + 2] cycloaddition followed by the modified Fleming–Tamao oxidation was exploited for the total synthesis of the monoterpenoid alcohol fragranol.[2d]



1 (–)-Oleander scale pheromone

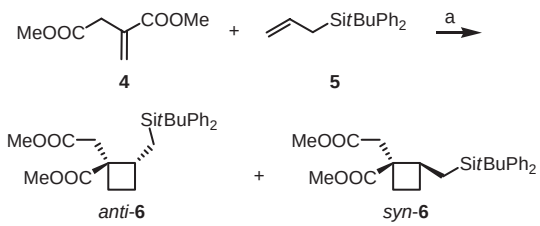
Figure 1. Natural isomer of the oleander scale pheromone **1**.

Using our method, we describe a preliminary synthetic study[6] directed towards the total synthesis of the sex pheromone of the female oleander scale *Aspidiotus nerii* (Figure 1). The oleander scale *Aspidiotus nerii* is a highly polyphagous insect in southern Europe and attacks many economically important plants, e.g. olives and citrus trees, as well as ornamental plants like oleander.[7] Its activity weakens the plant and causes severe fruit deformation. The flying males are attracted by the immobile females through a pheromone, which has been isolated first in 1998.[8] The structure has been assigned based on the spectroscopic data. The relative and absolute configuration of the natural product was assigned by total synthesis and led to 2-[(1*R*,2*S*)-1-(4-methylpent-4-enyl)-2-(prop-1-en-2-yl)-cyclobutyl]ethyl acetate (**1**), which was confirmed by its bioactivity in subsequent field trials.[9] A second synthesis provided racemic **1** and an advanced intermediate for an enantioselective approach.[10]



Scheme 2. Retrosynthetic analysis.

Our projected synthesis of racemic oleander scale pheromone (±)-**1** is based on a construction of the four-membered ring by a Lewis acid promoted [2 + 2] cycloaddition of dimethyl itaconate (**4**) and allyl-*tert*-butyldiphenylsilane (**5**) (Scheme 2). Subsequent reduction of the ester groups leads to the protected diol **3** containing the required hydroxyethyl side chain at C-1. The silylmethyl side chain at C-2 should be converted to the *iso*-propenyl group via Fleming–Tamao oxidation and cyclization to the acetal **2**. The steric hindrance caused by the quaternary center should allow a differentiation of the two hydroxyalkyl side chains and thus, a selective chain extension of the hydroxymethyl group.



Scheme 3. Reagents and conditions: a) 1. $TiCl_4$, CH_2Cl_2, 25 °C, 10 min; 2. **5**, reflux, 10 d, 96% (ratio of *anti*-**6**:*syn*-**6** = 2:1).

Lewis acid promoted [2 + 2] cycloaddition of dimethyl itaconate (**4**) and allyl-*tert*-butyldiphenylsilane (**5**) afforded the cyclobutanes *anti*-**6** and *syn*-**6** almost quantitatively in a ratio of 2:1 (Scheme 3). Both isomers were separated by chromatography on silica gel (petroleum ether–Et_2O, 20:1). The stereochemistry was assigned based on our previous studies,[2a,2d] using the chemical shifts of the signals for the α-silyl–CH_2 and β-

Table 1. Chemical shifts/ppm of the α-Si–CH_2 and β-Si–CH groups in the ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of **6**

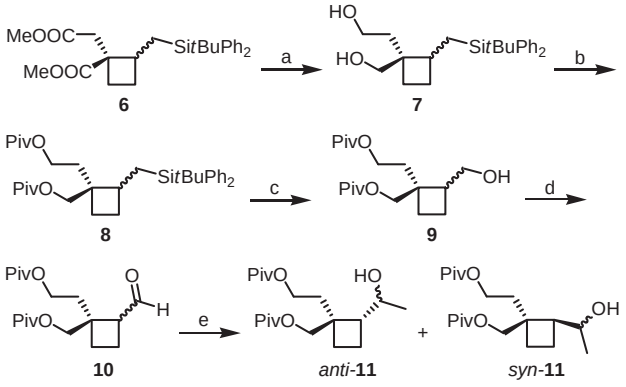
	anti-**6**	*syn*-**6**
α-Si–CH_2	11.49	12.74
β-Si–CH	38.61	40.83

silyl–CH groups in the ^{13}C NMR spectrum (Table 1).

The major diastereoisomer *anti*-**6** has the correct relative configuration required for the synthesis of the natural product. Since the stereogenic center at C-2 can be epimerized at a later stage of the synthesis, either pure *anti*-**6** or pure *syn*-**6**, or the isomeric mixture was used for the following transformations (Table 2). A separation of the anti from the syn isomer is feasible at any stage of our synthetic route.

Table 2. Transformation of the diastereoisomers of cycloadduct **6**

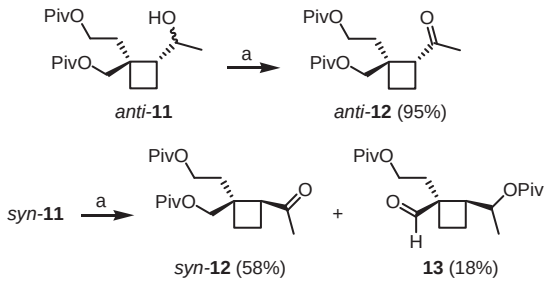
		Isolated yields/%	
		anti series	syn series
a) Reduction	(**6** → **7**)	93	93
b) Pivaloylation	(**7** → **8**)	90	90
c) Fleming–Tamao Oxid.	(**8** → **9**)	36	48
d) PDC Oxidation	(**9** → **10**)	80	82
e) Grignard Addition	(**10** → **11**)	72	72



Scheme 4. Reagents and conditions: a) $LiAlH_4$, THF, 25 °C, 20 h, 93%; b) PivCl, NEt_3, DMAP, CH_2Cl_2, 25 °C, 24–48 h, 90%; c) 1. BF_3·2AcOH, 1,2-$C_2H_4Cl_2$, reflux, 20 h; 2. KF, $NaHCO_3$, H_2O_2, THF–MeOH (1:1), 25 °C, 43 h, 36–48% (two steps); d) PDC, 4 Å molecular sieves, CH_2Cl_2, 25 °C, 5 h, 80–82%.; e) MeMgBr, THF, −10 °C to 25 °C, 4 h, 72%.

Reduction of **6** to the diol **7** followed by esterification provided the dipivalate **8** (Scheme 4). For introduction of the *iso*-propenyl side chain the silylmethyl group at C-2 had to be converted into a hydroxymethyl group. We applied our modified protocol for the Fleming–Tamao oxidation.[5] As shown previously, both phenyl groups at the silicon atom have to be replaced by fluorine to achieve good yields in the oxidation step. The primary alcohol **9** was oxidized to the aldehyde **10** using pyridinium dichromate in the presence of powdered molecular sieves.[11] Addition of methylmagnesium bromide led to the secondary alcohols *anti*-**11** and *syn*-**11**, each as a mixture of diastereoisomers (Scheme 4).

Oxidation of *anti*-**11** with catalytic amounts of TPAP and NMO as the stoichiometric oxidant provided the ketone *anti*-**12** (Scheme 5).[12] Application of the same procedure to the diastereoisomeric *syn*-**11** afforded *syn*-**12** along with the aldehyde **13** as a by-product. The ^{1}H NMR and ^{13}C NMR spectra supported by 2D NMR experiments (COSY, HSQC, HMBC, and NOESY) confirmed the structure of aldehyde **13**, which was obtained as a single diastereoisomer. The formation of this by-product obviously results from an initial intramolecular transesterification reaction prior to oxidation.



Scheme 5. Reagents and conditions: a) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, −10 °C to 25 °C, 4 h.

In conclusion, the Lewis acid promoted [2 + 2] cycloaddition of dimethyl itaconate (**4**) and allyl-*tert*-butyldiphenylsilane (**5**) proceeds in excellent yield. Compound **12** was obtained over 7 steps in 15% overall yield and represents an advanced intermediate for the projected total synthesis of the oleander scale pheromone (±)-**1** which is in progress.

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