Studies Relating to the Synthesis of the Immunosuppressive Agent FK-506: Coupling of Fragments via a Stereoselective Trisubstituted Olefin Forming Reaction Sequence

Summary: The asymmetric synthesis of FK-506 fragments is reported that illustrates a method for the preparation of one of the trisubstituted olefins within the macrolide.

Sir: The ability of the recently discovered macrolide antibiotic FK-506 to suppress immune systems in vitro and in vivo has focused attention on this compound as a biological probe of the immune response and as a candidate or lead structure for use in clinical allotransplantation. As part of our efforts to develop a synthetic program in this area,[1] we sought access to aldehydes of general structure **1** and a method to couple these fragments to sulfone **2** with the eventual formation of trisubstituted olefin **3**, a substructure of the natural product (Figure 1). Herein we describe two syntheses of aldehydes related to fragment **1** and a reaction sequence that delivers the olefin targets **3** in a stereoselective fashion.

The synthesis of the C_{22}–C_{27} fragment of FK-506 is shown in Scheme I. The conversion of (−)-quinic acid into the enantiomerically homogeneous (4*S*)-cyclohexenones **4a** and **4b** was recently reported in the context of a total synthesis of compactin.[2] While both **4a** and **4b** have been used in this project, the sequence starting with **4b** has thus far proven to be more suitable.

The synthesis of the more highly homologated aldehydes **15** and **16** is illustrated in Scheme II. The formulation of this target structure takes into consideration the constitution and stereochemistry of the C_{20}–C_{27} chain of FK-506. The central feature of the synthesis is the method of preparation of the threo, or anti, aldol product **10**. The combination of two reaction processes provides access to compounds of this structure in high yield and with substantial material processing without resort to chiral auxiliaries or chiral starting materials. The catalytic asymmetric hydrogenation of the β-keto ester **9** was performed with use of 1% $Ru_2Cl_4[(S)\text{-binap}]_2$ in 90% yield when performed on a decagram scale.[4] Although the stereogenic center in the resultant β-hydroxy ester will later be returned to a nonstereogenic, trigonal center in the target FK-506, this site served to control absolute stereogenicity at other sites of the C_{20}–C_{27} fragment through substrate-controlled reaction processes. For example, the Fráter–Seebach alkylation[5] of the dianion of the reduction product with allyl bromide provided **10** in 85% yield when performed in 10:10:1 THF/Et_2O/HMPA and LDA prepared from lithium/styrene.

Reduction of hydroxy ester **10** with $LiAlH_4$ followed by oxidative cyclization with 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-dicarbonitrile (DDQ) provided the benzylidene acetal **11** (PMP = *p*-methoxyphenyl). Iodoetherification with iodine/$NaHCO_3$, opening of the acetal with diisobutylaluminum hydride, and oxidation with the Dess–Martin periodinane reagent[6] gave aldehyde **12**, in which the side-chain allyl has been masked as an iodo ether (4:1 mixture of iodomethyl diastereomers). The stereochemical outcome of addition reactions of substituted allylstannane reagents to chiral aldehydes related to **12** has been investigated by Keck and co-workers.[7] In accord with these studies, we found the chelation-controlled addition of triphenylcrotylstannane (as a 1:1 cis/trans mixture) was achieved with use of stannic chloride at −78 °C to provide the alcohol **13** in 60% yield and a regioisomeric crotyl addition product in 20% yield, which was readily separated by silica gel chromatography. The anti 1,3-diol relationship of **13** was ascertained by analysis of NOEDS of a PMP acetal obtained from **13** upon reaction with DDQ. The assignment of the well-precedented syn 1,2-selectivity in the addition was supported by NMR derived coupling constants of a subsequently obtained cyclic derivative (**16**).

The silyl ether of **13** was converted to the allylic alcohol **14** by the indicated two-step sequence. Vinyl Grignard addition proceeded with a modest level of "Cram"-type selectivity when performed in methylene chloride to provide a 3:1 mixture of readily separable stereoisomers (major isomer depicted). The stereochemistry of the major product was assigned by subsequent conversion of **14** to a compound derived from **16**. The details of these

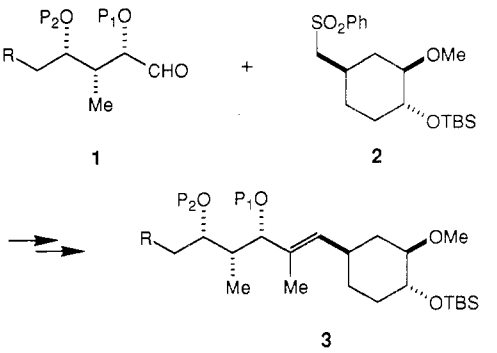
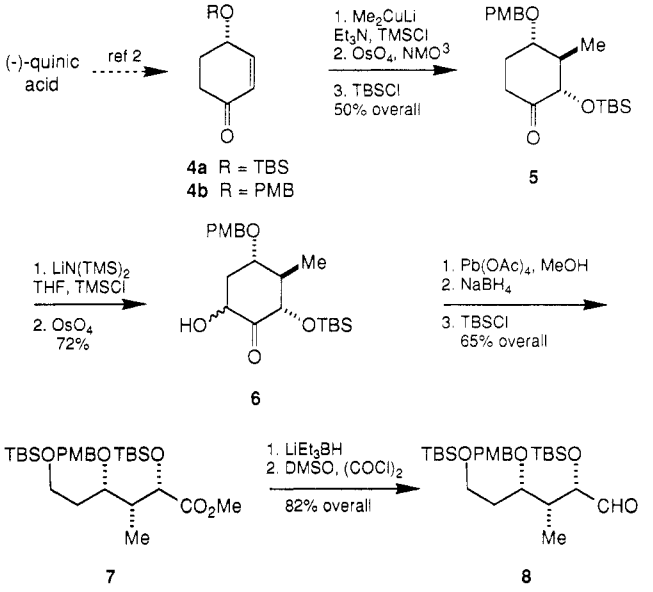


Figure 1.

Scheme I



(1) See accompanying papers and references cited therein.
(2) Danishefsky, S.; Simoneau, B. *Pure Appl. Chem.* In press. The transformation of quinic acid to (*S*)-4-hydroxycyclohexenone on multigram scales was originally achieved by Drs. James Audia and Louise Boisvert of these laboratories.
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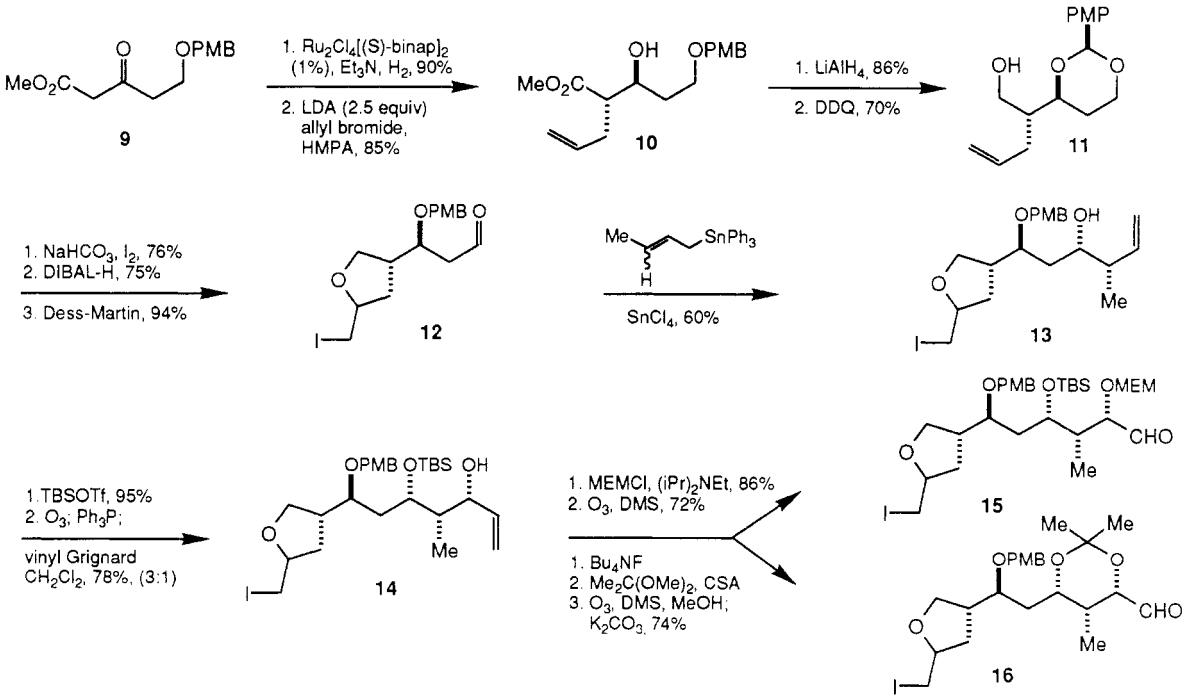
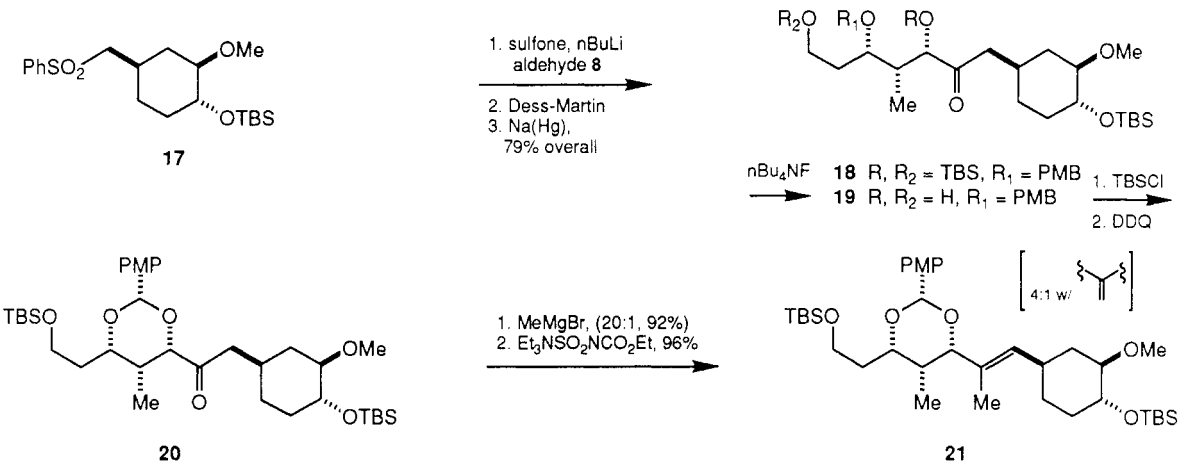
Scheme II



Scheme III



transformations will be described in a subsequent report. The methoxyethoxymethyl (MEM) ether of **14** was oxidized to the aldehyde **15**, a compound that is suitable for coupling by the method outlined below. Alternatively, the allyl alcohol **14** could be converted to the acetal **16** with >20:1 selectivity by the method of "ancillary stereocontrol"[8] as depicted in Scheme II. Analysis of the spin–spin coupling constants of **16** provided support for the syn-stereochemical relationships of this cyclic derivative.

A representative coupling sequence that serves to join these aldehyde substrates with the sulfone **17** (whose synthesis is described in an accompanying paper) is shown in Scheme III. Lithiation of **17** (nBuLi, −78 °C) and addition to aldehyde **8** gave rise to a diastereomeric mixture of β-hydroxy sulfones in good yield. Oxidation with the Dess–Martin reagent[6] provided the α-sulfonyl ketone, which was desulfonylated with sodium amalgam to provide the ketone **18** in 79% overall yield. Protecting-group interchange as shown in Scheme III delivered the cyclic acetal **20**. The addition of methylmagnesium bromide proceeded in excellent yield and with a high level of facial selectivity. The resultant tertiary alcohol was found to undergo elimination with the Burgess reagent[9] to provide the *E*-trisubstituted olefin **21**[10] and the methylidene isomer in a 4:1 ratio. Several related systems have been investigated and found to undergo elimination under these conditions with similar levels of stereoselectivity and positional selectivity. Application of these methods to the synthesis of FK-506 is under investigation.

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(10) The assignment of olefin geometry is supported by NOEDS experiments. Details will be provided in a forthcoming paper. Small amounts of the corresponding enol ether ($\Delta^{26,28}$) isomer could also be detected at this stage by high-field NMR analysis.

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Supplementary Material Available: ^{1}H NMR spectra for **8**, **10–16**, **20**, and **21** (19 pages). Ordering information is given on any current masthead page.

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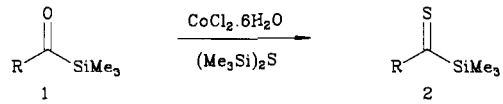
Cobalt(II) Chloride Promoted Thionation of Carbonyl Compounds: A Simple Access to Silyl Thioketones and Thioaldehydes

Summary: The $CoCl_2$-catalyzed reaction of $Me_3SiSSiMe_3$ with acylsilanes and simple aldehydes affords a direct and easy entry to their sulfur analogues.

Sir: Thiocarbonyl containing molecules are versatile synthetic intermediates, which find many applications in the synthesis of complex natural products.[1] Several methods have so far been reported for the formation of such molecules, based on direct conversion of carbonyl derivatives[2] or on pyrolytic[3] and photochemical techniques.[4]

Our long-standing interest in the chemistry of acylsilanes **1** as nucleophilic acylating agents[5] prompted us to focus attention on thioacylsilanes, a closely related but only recently explored[6] class of exotic molecules. We report here that a wide range of acylsilanes reacts with bis(trimethylsilyl) sulfide under mild conditions in the presence of $CoCl_2 \cdot 6H_2O$ as catalyst, affording in high yields the corresponding thiocarbonyl derivatives **2** (Scheme I).

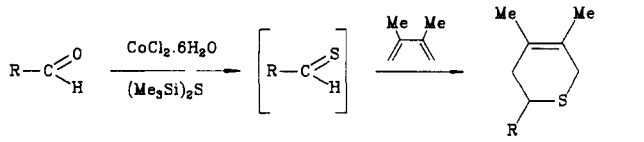
Scheme I



1 2

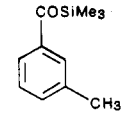
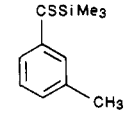
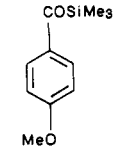
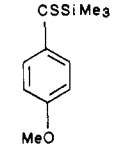
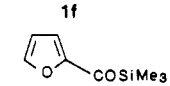
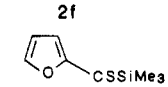
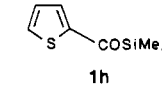
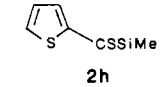
R = Alk, Ar, Het.

Scheme II



3a: R = Ph 94 %
b: R = Thienyl 91 %
c: R = Furyl 88 %

Table I. Synthesis of Thioacylsilanes

entry	acylsilane	product	yield,[a] %
1	$CH_3COSiMe_3$ **1a**	$CH_3CSSiMe_3$ **2a**	30[b]
2	$CH_3(CH_2)_5COSiMe_3$ **1b**	$CH_3(CH_2)_5CSSiMe_3$ **2b**	64
3	$PhCOSiMe_3$ **1c**	$PhCSSiMe_3$ **2c**	92
4	$PhCOSiPh_3$ **1d**	-	
5	 **1e**	 **2e**	74
6	 **1f**	 **2f**	66
7	 **1g**	 **2g**	68
8	 **1h**	 **2h**	59

[a] Yields refer to isolated material. [b] Dimers and trimers were isolated together with the wanted compound.

Thus, treatment of a solution of $CoCl_2 \cdot 6H_2O$ (26.2 mg, 0.112 mmol) and $PhCOSiMe_3$ (50 mg, 0.28 mmol) in 0.5 mL of CH_3CN (RPE Carlo Erba) with a solution of

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