Reaction of β-Heteroatom-Substituted α,β-Unsaturated Acylsilanes with Ketone Enolates: A New [3 + 2] Annulation Based on Brook Rearrangement

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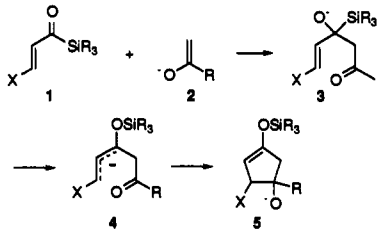
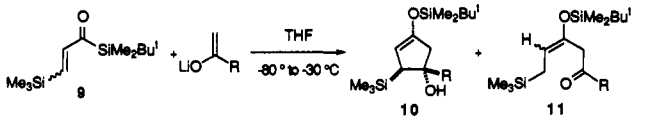
The cyclopentane ring system is found in a variety of biologically important natural products and theoretically interesting molecules, and an increasing number of annulation techniques for five-membered carbocycles have been developed in recent years.[1] Among these, [3 + 2] annulation[2,3] is a particularly attractive and logical approach which permits the rapid construction of functionalized cyclopentanes. Many of the [3 + 2] annulation techniques reported to date require the use of activated olefins having electron-withdrawing or -donating groups in the two-carbon unit. We envisaged that ketone enolates **2** would serve as two-carbon components in [3 + 2] annulation when reacted with β-heteroatom-substituted α,β-unsaturated acylsilanes **1**[4] according to the tandem process expressed in Scheme I. Thus, nucleophilic attack of enolate **2** on acylsilane **1** followed by Brook rearrangement[5,6] in the adduct **3** would generate a delocalized allylic anion (**4**) which should undergo cyclization to yield **5**. For the success of the proposed annulation, the choice of an appropriate heteroatom (X) to facilitate the 3- to 4-silyl migration would be crucial. Here we describe preliminary results from our study of this new annulation strategy employing trimethylsilyl and phenylthio as the X group in **1**.

Scheme I

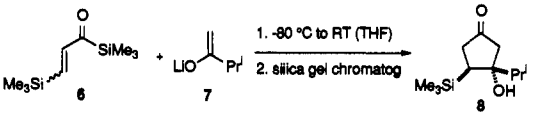


Scheme II



acylsilane 9	Li-enolate R	yield (%) 10	11
(Z)	i-Pr	51	21
(E)	i-Pr	14	63
(Z)	Et	48	16
(E)	Et	17	43
(Z)	n-Pr	55	22
(E)	n-Pr	11	57

Our initial experiment was performed with (*Z*)-(β-(trimethylsilyl)acryloyl)trimethylsilane (**6**)[7] by treating it in THF at −80 °C to room temperature with the lithium enolate of 3-methyl-2-butanone (**7**) generated with LDA. From this reaction we could isolated the cyclopentanone derivative **8** as a single isomer in 12% yield after silica gel chromatography (stereochemistry was determined by X-ray analysis).[8]



We then turned to the use of the *tert*-butyldimethylsilyl derivative **9** to isolate the silyl enol ether intermediate **5** and also to obtain further insight concerning the reaction course (Scheme II). Thus, lithium enolate **7** (generated with LTMP) was added to a THF solution of (*Z*)-**9** (0.02 M) at −80 °C, and the mixture was allowed to warm to −30 °C over 1 h to afford cyclopentenyl silyl ether **10** (R = *i*-Pr) in 51% yield as a single stereoisomer, along with β-silyloxy-β,γ-unsaturated ketone **11** (R = *i*-Pr) (21%, mixture of *E*/*Z* = 1:1.4).[9] The acyclic byproduct **11** could be produced by intra- and/or intermolecular protonation of the Brook rearrangement product **4**. When the annulation reaction was carried out with higher concentrations and/or at temperatures higher than −30 °C, considerably lower yields of both **10** and **11** were obtained. On the other hand, when the isomeric acryloylsilane (*E*)-**9** was subjected to the same annulation reaction, there was obtained exactly the same yield of cyclopentenol **10** as from (*Z*)-**9**, but the uncyclized byproduct **11** was produced to a large extent (**10**/**11** = 18:82). This remarkable trend in the product ratio depending on the geometry of the vinylsilane was observed in the case of annulation reactions with 2-butanone as well as with 2-pentanone (Scheme II). The observation that the acyclic byproduct **11** was produced in the reactions of both (*E*)- and (*Z*)-**9** in greatly varying proportions seems to be inconsistent

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(2) (a) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Freming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 239–270. (b) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlight*; VCH: Weinheim, 1991; pp 96–104. (c) Boger, D. L.; Brotherton-Pleiss, C. E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 147–219. (d) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77–151. (e) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (f) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

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(7) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949–960.

(8) The same [3 + 2] annulation using **1** (X = Ph, *t*-Bu) has independently been studied at MIT by Danheiser and Nowick, Nowick, J. S. Ph.D. Dissertation, Massachusetts Institute of Technology, 1989. The authors thank Professor R. L. Danheiser for providing us with this information.

(9) The olefinic geometry of the silyl enol ether was assigned on the basis of ^1H and ^{13}C NMR,[6] and the *E*/*Z* ratios were variable.

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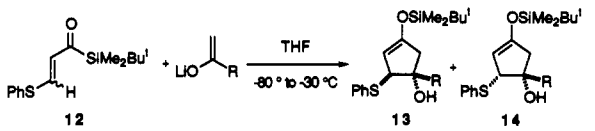
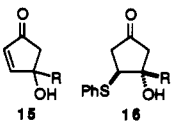
Scheme III



Li enolate	yield (%)			
R	13	14	15	16
i-Pr	55	19	77	79
Et	70	5	70	83
n-Pr	74	7	77	87
n-octyl	71	8	66	73



with the annulation mechanism via the delocalized allylic anion species **4**. Studies on the mechanism will be the subject of further investigations.

We next investigated the [3 + 2] annulation reaction of the β-(phenylthio)acryloyl silane **12**.[10] Treatment of **12** as an *E*/*Z* mixture (1:7.6) with the enolate derivative of 3-methyl-2-butanone under conditions similar to those used for the silyl counterpart **9** afforded diastereomeric cyclopentenols **13** (R = *i*-Pr, 55%) and **14** (R = *i*-Pr, 19%), with stereochemistry determined on the basis of X-ray analysis of the major product **13**. In contrast to the foregoing annulation with **9**, only a trace amount of uncyclized product corresponding to **11** was produced regardless of the concentration of the reactants. More importantly, the ratio of **13** to **14** was unaffected by the *E*/*Z* ratio of the three-carbon unit **12**.[11] The same results were realized in the reactions with the enolates derived from primary alkyl methyl ketones (Scheme III), except for the predominant formation of the *syn*-R/PhS isomers **13** (>90:10). These results suggest that the annulation of **12** with methyl ketone enolates proceeds via the delocalized allylic anion **4** (Scheme I).

The cyclopentanols **13** thus obtained are expected to serve as intermediates in the synthesis of highly functionalized cyclopentanones of biological interest. Toward this end, we first investigated desilylation of these compounds by conventional reagents. Treatment of **13** with TBAF yielded cyclopentenone **15** by desilylation and concomitant β-elimination of the phenylthio group, whereas under acidic conditions using HF in aqueous MeCN, the thio group could be retained affording **16** (Scheme III).

With ready access to 4-alkyl-4-hydroxy-2-cyclopentenones, we examined the synthesis of the reported structure of the chromomoric acid D-II methyl ester **20**,[12,13] which is an analog of the antitumor marine prostanoid clavulones.[14] The [3 + 2] annulation protocol conducted using the β-(phenylthio)acryloyl silane (**12**)

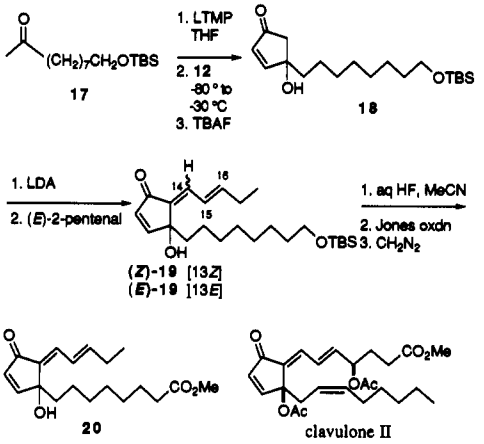
(10) The acylsilane **12** was prepared from 1-(*tert*-butyldimethylsilyl)-1-(1-ethoxyethoxy)-1,2-propadiene according to the procedure of Reich and co-workers[7] for the corresponding β-phenylselenenyl derivative.

(11) This stands on the results obtained from separate reactions of pure (*E*)- and (*Z*)-**12**.

(12) Bohlmann, F.; Borthakur, N.; King, R. M.; Robinson, H. *Phytochemistry* **1982**, *21*, 125–127.

(13) For naming of chromomoric acids and synthesis of chromomoric acid D-I methyl ester, see: Liu, Z.-Y.; Chu, X.-J. *Tetrahedron Lett.* **1993**, *34*, 349–352.

Scheme IV



and methyl ketone **17**[15] provided cyclopentenone **18** in 52% overall yield (Scheme IV). Reaction of the lithium enolate of **18** with *trans*-2-pentenal, followed by dehydration of the resulting aldol product, afforded trienone **19** in 58% yield as a separable mixture of 13 *E*/*Z* isomers (1.1:1). The protected octanol side chain of (*E*)-**19** was oxidized to the corresponding carboxylic acid by Jones reagent after desilylation, and then esterification with diazomethane afforded the target molecule **20**[16,17] in 32% overall yield from (*E*)-**19**.

In summary, the newly developed [3 + 2] annulation methodology provides a direct entry to cyclopentenol derivatives bearing useful functionality for further synthetic elaboration. Investigations to clarify the mechanism of the annulation and to define the scope of its application in natural products synthesis are in progress.

Supplementary Material Available: General procedures for the annulation, spectroscopic and analytical characterizations of compounds, and X-ray crystallographic data and ORTEP drawings for compounds **8** and **13** (R = *i*-Pr) (16 pages). Ordering information is given on any current masthead page.

(14) (a) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171–5174. (b) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Ibid.* **1983**, *24*, 1549–1552. (c) Iguchi, K.; Yamada, Y.; Kikuchi, H.; Tsukitani, Y. *Ibid.* **1983**, *24*, 4433–4436.

(15) This compound was prepared from 8-bromo-1-octanol by the three-step sequence: (i) TBSCl, imidazole, DMF, (ii) Mg, Et_2O; MeCHO, (iii) PCC, AcONa, CH_2Cl_2.

(16) IR (neat) 3420, 1735, 1700, 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (3H, t, *J* = 7.6 Hz, H-18), 1.26 (8H, br s), 1.42–1.70 (2H, m), 1.70 (1H, br s, OH), 1.90–2.05 (2H, m), 2.20–2.35 (4H, m, H-2 and H-17), 3.66 (3H, s, OMe), 6.29 (1H, t, *J* = 15.1, 6.6 Hz, H-16), 6.34 (1H, d, *J* = 6.1 Hz, H-11), 6.69 (1H, ddm, *J* = 15.1, 12.0 Hz, H-15), 6.93 (1H, d, *J* = 12.0 Hz, H-14), 7.30 (1H, d, *J* = 6.1 Hz, H-11); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3 (C-18), 26.9 (C-17), 24.7, 25.2, 29.3, 29.9, and 38.7 (C3–C8), 34.3 (C-2), 51.8 (OMe), 80.2 (C-9), 124.4 (C-15), 132.9 (C-14), 135.1 (C-11), 136.8 (C-9), 149.9 (C-16), 161.7 (C-10), 174.6 (C-1), 196.0 (C-12).

(17) The spectral data for synthetic **20** did not coincide with those reported by Bohlmann. Careful comparison with the spectral data reported for the clavulones suggests that the original ^1H NMR assignments made for the mixture of chromomoric acids should be revised. Details will be reported elsewhere.