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THE EFFICIENT CONSECUTIVE β-CARBOXYLATION AND α-ALKYLATION OF CYCLIC α,β-ENONES; A NEW ROUTE TO SARKOMYCIN

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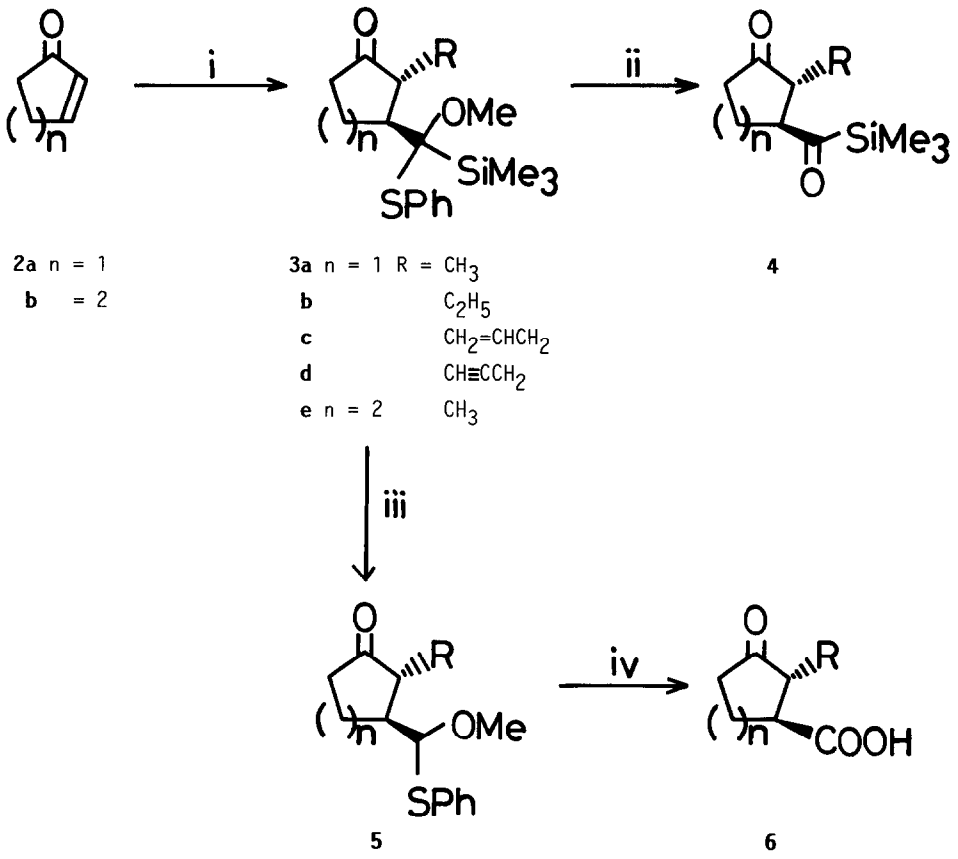
Abstract. Sequential one-pot introduction of a carboxy group equivalent and an alkyl group at the respective β- and α-positions of cyclic enones has been achieved through a 1,4-addition reaction of [methoxy(phenylthio)(trimethylsilyl)methyl]lithium followed by direct trapping of the resulting enolate with alkyl halides. The present method proved to be applicable to a simple synthesis of sarkomycin.

The 1,4-addition of various nucleophiles to cyclic α,β-enones constitutes one of the most versatile reactions in natural product syntheses.[1] Of special importance is the development of effective methods for the reaction with 2-cyclopentenone derivatives due to their occurrence in diverse natural products. The synthetic value should be raised further if the consecutive introduction of electrophiles at the α-position of the resulting enolates was realized; actually, electrophiles such as aldehydes or some Micheal acceptors have been incorporated successfully. However, there have appeared a few precedented examples of the vicinal double alkylation. Organocopper reagents resulted in α,β-dialkylation of 2-cyclohexenone,[2,3] but α'-alkylation was accompanied in the case of 2-cyclopentenone.[3] Exceptionally, α-methylation was realized with the trityllithium-generated enolate of 5,5-dimethyl-2-cyclohexene-1-one.[4] The 1,4-addition reaction with lithium salts of bis(methylthio)(trimethylsilyl)methane and its trimethylstannyl analog has been reported to provide a mixture of α- and α'-alkylation products.[5] These drawbacks have been overcome occasionally by transmetalation of the intermediary enolates.[6,7]

In continuing studies on synthetic applications of methoxy(phenylthio)methane[8] and its silylated derivative,[9] we have succeeded, by use of [methoxy(phenylthio)(trimethylsilyl)-methyl]lithium (**1**), in realizing exclusive one-pot α,β-dialkylation of α,β-enones. Moreover, this is the directed sequential introduction of a carboxy group equivalent and an alkyl group[10] which has enabled us to develop a new route for sarkomycin.[15]

As shown in Scheme I, treatment of 2-cyclopentenone (**2a**) with 2 equiv of **1**[9,16,17] in the presence of HMPA (10 equiv) at -78 °C for 2 h and subsequently with alkyl halides (2.4 equiv) for 30 min in THF at -40 °C afforded the desired α,β-disubstituted cyclopentanones **3** in good yields except for the reaction with ethyl iodide (Table 1). 2-Cyclohexenone (**2b**) reacted similarly. Presence of HMPA proved to be crucial for the 1,4-addition as well as the alkylation which proceeded smoothly without recourse to transmetallation.[17] The trimethylsilyl group in **1** also plays an important role since methoxy(phenylthio)methyllithium resulted in the exclusive 1,2-addition. The present reaction is regiospecific in that neither equilibration to α'-isomer nor 1,2-adducts are detected. Particularly noteworthy is that the resulting enolate can survive even at 0 °C since the yields of the dialkylation products did

Scheme I



2a n = 1
b = 2

3a n = 1 R = CH_3
b C_2H_5
c CH_2=$CHCH_2$
d CH≡CCH_2
e n = 2 CH_3

4

5

6

(i) $(CH_3O)(PhS)(Me_3Si)CLi$ (**1**) (2 equiv), HMPA (10 equiv), THF, -78 °C, 2 h, RX (2.4 equiv), -40 °C, 30 min (ii) $NaIO_4$ (1.5 equiv), dioxane-H_2O (8:2), rt, 3 h (iii) Bu_4NF (1.25 equiv), DMF-H_2O (5:1), rt, 1 h (iv) CrO_3 (3 equiv), H_2SO_4-acetone, rt, 1 h.

Table 1. Yield (%)[a] of **3**, **4**, **5**, and **6**.

RX	n	**3**	**4**[b]	**5**	**6**
CH_3I	1	98	91 (>99)	92	72
C_2H_5I		48	67 (>99)	77	65
CH_2=$CHCH_2Br$		82	73 (95:5)	82	82
CH≡CCH_2Br		95	90 (96:4)	95	70
CH_3I	2	65	83 (>99)	82	54

a Isolated yields after column chromatography on silica gel.

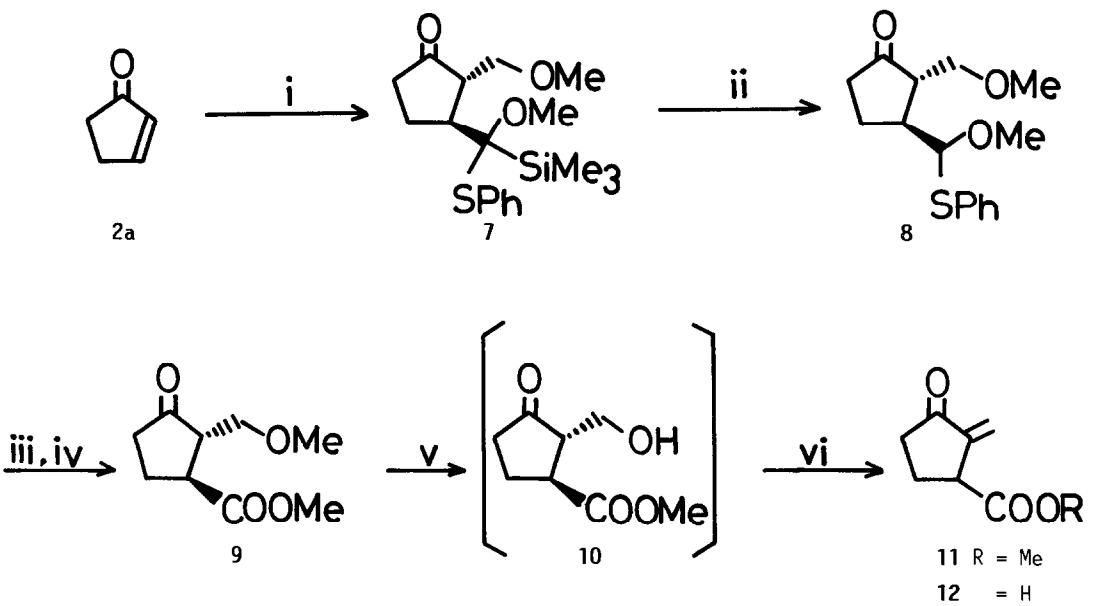
b Values in parentheses: ratio of trans:cis.

not decrease significantly when the alkylation was conducted at this temperature.

The adducts **3** were converted into the acylsilanes **4** on exposure to $NaIO_4$ in dioxane-water.[9] GLC analyses of these compounds revealed the trans/cis isomeric ratio to be more than 95:5. Trasnsformation of **3** to the corresponding carboxylic acids **6** was achieved by desilylation with Bu_4NF followed by the Jones oxidation. The whole results are summarized in Table 1.

The synthetic utility of the present method was exemplified by a novel synthesis of sarkomycin (**12**) (Scheme II). Treatment of **2a** with **1** (2 equiv) in the presence of HMPA (10 equiv) in THF at -78 °C for 2 h and susequently with iodomethyl methyl ether[18] at 0°C for 30 min provided **7** in 71% yield. On desilylation (78%) and the Jones oxidation followed by esterification with diazomathane (69%), **7** was converted to 2-methoxymethyl-3-methoxycarbonyl-cyclopentanone (**9**) via **8**. Treatment of **9** with BCl_3 in dichloromethane afforded the hydroxyketone **10** (95%, crude) which was contaminated by a small amount (ca. 10%) of the dehydrated product **11**. The mixture was conveniently converted to pure **11**[19] by standing on silica gel for 1 h before column chromatographic isolation (5:1 hexane-ethyl acetate, 57% based on **9**), although the analogous isopropyl ester had been dehydrated via the mesylate previously.[20] Hydrolysis of **11** to sarkomycin (**12**) has been achieved already.[19]

Scheme II



(i) **1** (2 equiv), HMPA (10 equiv), THF, -78 °C, 2 h; ICH_2OCH_3 (3 equiv), 0 °C, 30 min (ii) Bu_4NF (1.1 equiv), DMF-H_2O (8:1), rt, 1 h (iii) CrO_3 (3 equiv), H_2SO_4-acetone, rt, 1 h (iv) CH_2N_2 (excess), Et_2O, 0 °C, 1 h (v) BCl_3 (3 equiv), CH_2Cl_2, -10 °C, 4 h (vi) SiO_2.

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