Synthesis of Functionalized Furan Derivatives by Hydroxyalkylation of Methyl 2-Siloxycyclopropanecarboxylates

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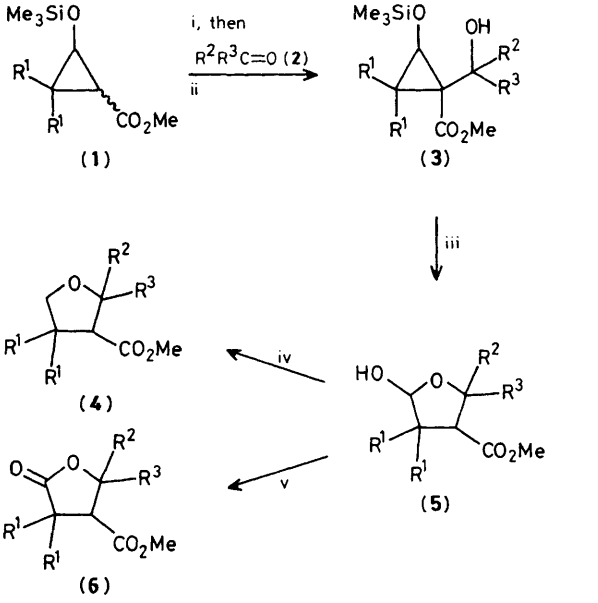
A variety of methyl tetrahydrofuran-3-carboxylates (**4**) or the 5-oxo analogues (**6**) are available in good overall yield by deprotonation of cyclopropanes (**1**), addition of carbonyl compounds, ring cleavage, and reductive or oxidative work-up, respectively.

We have recently demonstrated that deprotonation–alkylation[1] of easily accessible[2] methyl 2-siloxycyclopropanecarboxylates [*e.g.* (**1**) and (**7**)] markedly broadens the scope for preparation of a variety of synthetically valuable 4-oxoalkanoate derivatives.[3] Reactions of carbonyl compounds with ester enolates generated from (**1**) should lead to promising trifunctional products suitable for subsequent transformations. Paquette has recently reported the hydroxyalkylation of methyl cyclopropanecarboxylate,[4] and we now report our own results in this field.

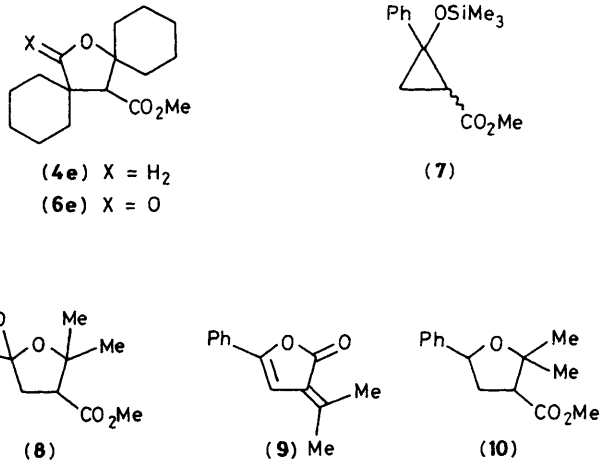
The enolates obtained from (**1**) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C smoothly add to aldehydes or ketones (**2**) (90 min; −78 °C) to give adducts (**3**). However, in only the minority of cases could the adducts (**3**) be isolated in reasonable yield [(**3a**): 64%; (**3e**): 51%] since these alcohols easily suffer ring opening and desilylation delivering (**5**). Deliberate and complete cyclopropane cleavage may be achieved by fluoride reagents ($NEt_3 \cdot 3HF$ or, preferably, NBu_4F, THF). It is of advantage to use the resulting γ-lactols (usually mixture of stereoisomers) as crude material transforming them by removal of the anomeric centre either into methyl tetrahydrofuran-3-carboxylates (**4**) ($HSiEt_3$; $BF_3 \cdot OEt_2$; CH_2Cl_2; 4 h; −78 to 20 °C), or into the 5-oxo analogues (**6**) [pyridinium chlorochromate (PCC); CH_2Cl_2; 3—5 days; 20 °C] (Scheme 1).

As shown in Table 1, aliphatic as well as aromatic aldehydes and ketones can be employed; even sluggish electrophiles like benzophenone can be added. Enolization of the carbonyl component obviously does not play a role and the total yields of (**4**) and (**6**) obtained over three steps are satisfactory. With aldehydes the end products are mixtures of *cis*- and *trans*-isomers as expected. The dispiro compounds (**4e**) and (**6e**) are depicted to demonstrate their genesis from cyclohexane carbaldehyde, glycine, and cyclohexanone.

The substitution pattern in the cyclopropane portion may also be flexible as illustrated by (**7**), in which position 3 is unsubstituted.[6] Deprotonation, addition of acetone, and subsequent treatment with MeOH–HCl delivers the acetal (**8**) (66%), whereas work-up under dehydrating conditions (*p*-$MeC_6H_4SO_3H$; C_6H_6; 5 h; 80 °C) affords the unsaturated compound (**9**) (46%).[6] The usual procedure and reduction ($HSiEt_3$, $BF_3 \cdot OEt_2$), on the other hand, provides (**10**) (44%; *cis* : *trans* = 1 : 1).



Scheme 1. *Reagents:* i, LDA; ii, NH_4Cl; iii, F^-; iv, Et_3SiH, $BF_3 \cdot Et_2O$; v, PCC.



Transformations of methyl 2-siloxycyclopropanecarboxylates *via* their enolates to different furan derivatives underline the particular synthetic potential for preparation of five-membered heterocycles[8] accessible by ring cleavage of this type of cyclopropane. Further stereoselective substitution reactions replacing the hydroxy function in γ-lactols like (**5**) by

† *E.g.* (**3a**): m.p. 78—79 °C; ^1H n.m.r. ($CDCl_3$): δ 3.66 (s, 3H, CO_2Me), 3.55 (s, 1H, 2-H), 1.62 (s, 1H, OH), and 1.40, 1.35, 1.32, and 1.03 (4s, 3H each, 4 Me); i.r. (CCl_4): 3610 (OH), 1735, and 1720 cm^{-1} (CO_2Me); (**5a**): m.p. 50—52 °C; ^1H n.m.r. (C_6H_6): δ 4.96 (s, 1H, 5-H), 3.70 (s, 3H, CO_2Me), 3.25 (s, 1H, 3-H), and 1.68, 1.50, 1.42, and 1.34 (4s, 3H each, 4 Me); i.r. (CCl_4): 3605, 3400 (OH), and 1745 cm^{-1} (CO_2Me); (**4a**): b.p. 100 °C at 0.02 Torr; ^1H n.m.r. ($CDCl_3$):δ 3.64 (s, 3H, CO_2Me), 3.53 (br. s, 2H, 5-H), 2.52 (s, 1H, 3-H), and 1.36, 1.30, 1.18, and 1.11 (4s, 3H each, 4 Me); i.r. (CCl_4): 1740 cm^{-1} (CO_2Me); (**6a**): b.p. 90 °C at 0.02 Torr; ^1H n.m.r. ($CDCl_3$): δ 3.70 (s, 3H, CO_2Me), 2.93 (s, 1H, 3-H), and 1.52, 1.50, 1.38, and 1.33 (4s, 3H each, 4 Me); i.r. (CCl_4): 1780 (C=O) and 1750 cm^{-1} (CO_2Me).

Table 1. Synthesis of compounds (**4**)—(**6**).[a]

	(**1**)	(**2**)		% Yield		
Entry	$R^1{}_2$	R^2	R^3	(**5**)	(**4**)	(**6**)
a	Me_2	Me	Me	48	43	67
b	Me_2	Ph	Ph	46	40 (88[b])	70 (80[b])[f]
c	Me_2	H	Me	—	61[c]	52[d]
d	Me_2	H	Ph	21	79[e]	57[e]
e	$-[CH_2]_5-$	$-[CH_2]_5-$		—	48	51
f	$-[CH_2]_5-$	H	Me	—	—	51[d]

[a] Non-optimized yields of isolated products after recrystallization or Kugelrohr distillation based on (**1**); all compounds provide characteristic spectra† and satisfactory elemental analyses. [b] Based on (**5**). [c] *cis* : *trans* 1:3. [d] *cis* : *trans* 1:1. [e] *cis* : *trans* 2:3. [f] Ref. 7.

C-nucleophiles should broaden the scope of this general approach and will be reported in due course.

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