Synthesis of α-Substituted Cyclobutane β-Keto Esters

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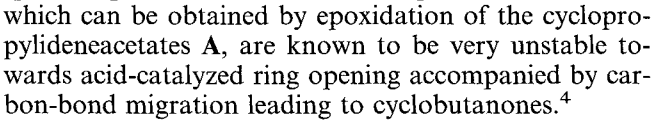
The title compounds, α-substituted-β-keto esters **4**, were prepared from suitably substituted cyclopropylideneacetates **2** by epoxidation and Wagner–Meerwein rearrangement. The highly strained oxaspiro[2.2]pentane intermediate **3** was isolated.

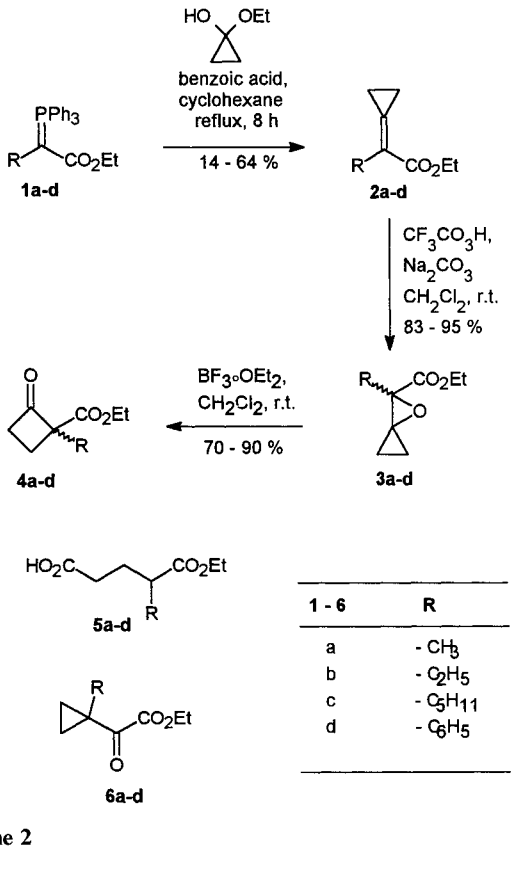
Our previous studies used chiral β-keto esters as valuable intermediates in the EPC (enantiomeric pure compounds)-synthesis of natural products.[1] In this study we looked for synthetic pathways to obtain cyclobutane derivatives of type **D** (Scheme 1). Alkylation of cyclobutanone β-keto esters **C** is not suitable because of the propensity of these compounds towards retro-Dieckmann reaction. Existing methods for the preparation of highly substituted cyclobutanones proceed via formal [1,2]-sigmatropic rearrangements of suitably substituted 1-oxaspiro[2.2]pentanones.[2,3] Strained epoxides such as **B**, which can be obtained by epoxidation of the cyclopropylideneacetates **A**, are known to be very unstable towards acid-catalyzed ring opening accompanied by carbon-bond migration leading to cyclobutanones.[4]



Scheme 1

We now report the preparation of previously unknown α-substituted cyclobutane β-keto esters **4a–d**, following the route outlined in Scheme 2. Cyclopropylideneacetates **2a–d** were synthesized by Wittig reaction of cyclopropanone hemiacetal with the phosphonium ylides **1a–d**. Ylides **1a–b** and **1d** were prepared by the method described by Spitzner et al.,[5] ylide **1c** was prepared by 'trans-ylidation'.[6] Due to the electron deficient character of the double bond of **2a–d**, epoxidation was carried out first by using hydrogen peroxide/sodium hydroxide. However, the expected alkyl-substituted 2-oxocyclobutanecarboxylate **4** could not be isolated. The only compound isolated was the succinic acid derivative **5**, the product of the retro-Dieckmann reaction. Similarily, epoxidation employing *tert*-butyl hydroperoxide/sodium hydroxide was unsuccessful, only starting material **2** could be recovered.

Using trifluoroperacetic acid,[7] epoxidation and rearrangement took place and the cyclobutanones **4a–d** could be isolated in only moderate yields. To suppress unwanted, acid-catalyzed side reactions, sodium carbonate was added to buffer the solution.[8] This time oxidation of the double bond occurred smoothly within 10 minutes. Unexpectedly no rearrangement took place, allowing the isolation of the strained epoxides **3a–c** in excellent yields.



Scheme 2

The epoxides **3a–c** were quite stable and could be stored for several weeks without decomposition at 0°C. The same reaction conditions were employed for **2d** (R = Ph). In this case the epoxide proved to be rather unstable and in situ rearrangement took place, preventing the isolation of the epoxide **3d**.

Subsequent epoxide ring opening of **3a–c** was best achieved by employing boron trifluoride etherate.[9] Stirring at room temperature for 12 hours gave excellent yields of rearranged cyclobutanones **4a–c**. The alternative product **6** of this Wagner–Meerwein like rearrangement was not observed. With dilute hydrochloric acid (5%) or aqueous citric acid (10%) no detectable ring opening of the epoxides **3a–c** was observed.

In summary, we have devised a concise pathway for the synthesis of α-substituted cyclobutane β-keto esters **4a–d**. In addition, we have isolated the 1-oxaspiro-[2.2]pentanes **3a–c**, which can be of synthetic use. Reports of synthetic applications will be published in due course.

All reagents were of commercial origin and used without further purification. Reactions were routinely carried out in purified sol-

Table. Physical and Spectroscopic Data of Compounds **2–4**

Product[a]	Yield (%)	bp (°C)/Torr	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
2a	64	60/12	1.12 (t, J = 7.5, 3H, CH_3), 1.20–1.40 (m, 2H, CH_2), 1.30 (t, J = 7.1, 3H, CH_3), 2.30–2.50 (m, 2H, CH_2), 4.20 (q, J = 7.1, 2H, OCH_2)	2.28 (CH_2), 6.21 (CH_2), 14.71 (CH_3), 17.23 (CH_3), 60.53 (OCH_2), 118.31 (C=), 137.77 (C=), 167.91 (C=O)
2b	57	75/12	1.12 (t, J = 7.5, 3H, CH_3), 1.20–1.40 (m, 2H, CH_2), 1.30 (t, J = 7.1, 3H, CH_3), 2.30–2.50 (m, 2H, CH_2), 4.20 (q, J = 7.1, 2H, OCH_2)	2.58 (CH_2), 4.98 (CH_2), 13.47 (CH_3), 14.68 (CH_3), 24.97 (CH_2), 60.41 (OCH_2), 123.96 (C=), 136.80 (C=), 167.67 (C=O)
2c	25	60/1.0	0.90 (m, 3H, CH_3), 1.10–1.70 (m, 10H, CH_2), 1.30 (t, J = 7.1, 3H, CH_3), 2.43 (m, 2H, CH_2), 4.21 (q, J = 7.1, 2H, OCH_2)	2.70 (CH_2), 5.48 (CH_2), 14.38 (CH_3), 14.71 (CH_3), 22.85 (CH_2), 28.67 (CH_2), 31.58 (CH_2), 31.98 (CH_2), 60.42 (OCH_2), 122.86 (C=), 137.36 (C=), 167.78 (C=O)
2d	14	80/1.0	1.39 (t, J = 7.1, 3H, CH_3), 1.40–1.71 (m, 2H, CH_2), 4.36 (q, J = 7.1, 2H, OCH_2), 7.22–7.71 (m, 5H_{arom})	4.55 (CH_2), 5.47 (CH_2), 14.76 (CH_3), 61.03 (OCH_2), 123.89 (C=), 127.73, 128.41, 128.66 (CH_{arom}), 136.91 (C=), 140.22 (C=), 167.29 (C=O)
3a	86		0.89–1.40 (m, 4H, CH_2), 1.31 (t, J = 7.1, 3H, CH_3), 1.69 (s, 3H, CH_3), 4.25 (q, J = 7.1, 2H, OCH_2)	2.87 (CH_2), 3.98 (CH_2), 14.58 (CH_3), 17.39 (CH_3), 60.55 (C-epoxide), 61.97 (OCH_2), 65.22 (C-epoxide), 170.71 (C=O)
3b	95		1.03 (t, J = 7.5, 3H, CH_3), 1.12–1.41 (m, 4H, CH_2), 1.26 (t, J = 7.1, 3H, CH_3), 1.75–1.85 (m, 1H, CH_2), 2.15–2.25 (m, 1H, CH_2), 4.19 (q, J = 7.1, 2H, OCH_2)	2.54 (CH_2), 2.63 (CH_2), 8.37 (CH_3), 13.99 (CH_3), 24.10 (CH_2), 61.20 (OCH_2), 63.51 (C-epoxide), 63.71 (C-epoxide), 169.73 (C=O)
3c	85		0.8–0.95 (m, 3H, CH_3), 0.96–1.63 (m, 13H, CH_2, CH_3), 1.64–1.82 (m, 1H, CH_2), 2.10–2.32 (m, 1H, CH_2), 4.82–4.38 (m, 2H, OCH_2)	3.22 (CH_2), 3.32 (CH_2), 14.28 (CH_3), 14.63 (CH_3), 22.81 (CH_2), 24.59 (CH_2), 31.56 (CH_2), 32.12 (CH_2), 61.83 (OCH_2), 63.90 (C-epoxide), 64.25 (C-epoxide), 170.49 (C=O)
4a	93		1.20 (t, J = 7.1, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.70–2.00 (m, 1H, CH_2), 2.53–2.71 (m, 1H, CH_2), 2.99–3.32 (m, 2H, CH_2), 4.15 (q, J = 7.1, 2H, OCH_2)	14.41 (CH_3), 18.80 (CH_3), 23.44 (CH_2), 45.49 (CH_2), 61.77 (OCH_2), 69.82 (C_{quart}), 170.51 (CO-ester), 204.98 (CO-ketone)
4b	90		0.95 (t, J = 7.4, 3H, CH_3), 1.29 (t, J = 7.1, 3H, CH_3), 1.70–2.10 (m, 3H, CH_2), 2.51–2.72 (m, 1H, CH_2), 3.01–3.22 (m, 2H, CH_2), 4.23 (q, J = 7.1, 2H, OCH_2)	9.38 (CH_3), 14.56 (CH_3), 20.28 (CH_2), 26.66 (CH_2), 44.95 (CH_2), 61.80 (OCH_2), 75.57 (C_{quart}), 169.72 (CO-ester), 205.15 (CO-ketone)
4c	90		0.95 (t, J = 7.4, 3H, CH_3), 1.29 (t, J = 7.1, 3H, CH_3), 1.70–2.10 (m, 3H, CH_2), 2.51–2.72 (m, 1H, CH_2), 3.01–3.22 (m, 2H, CH_2), 4.23 (q, J = 7.1, 2H, OCH_2)	14.30 (CH_3), 14.56 (CH_3), 20.73 (CH_2), 22.74 (CH_2), 24.73 (CH_2), 32.16 (CH_2), 33.51 (CH_2), 44.99 (CH_2), 61.87 (OCH_2), 75.13 (C_{quart}), 169.76 (CO-ester), 205.15 (CO-ketone)
4d	17		1.24 (t, J = 7.1, 3H, CH_3), 2.42–3.45 (m, 4H, CH_2), 4.19 (q, J = 7.1, 2H, OCH_2), 7.15–7.56 (m, 5H_{arom})	14.40 (CH_3), 22.81 (CH_3), 45.22 (CH_2), 62.52 (OCH_2), 78.10 (C_{quart}), 127.03, 128.22, 128.99 (CH_{arom}), 169.03 (C=O-ester), 201.97 (C=O-ketone)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.29.

vents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 200 instrument ($CDCl_3$ as solvent and TMS as an internal reference). ^{13}C NMR multiplities were determined by the DEPT-135 method. Elemental analyses were obtained from the Microanalytical Laboratory of this University.

Ethyl 2-Cyclopropylidenealkanoates 2a–d; General Procedure:
A stirred cyclohexane solution (150 mL) of ylide **1** (13 mmol), 1-ethoxycyclopropanol (10 mmol)[10] and benzoic acid (1 mmol) was refluxed for 8 h. The solvent was removed in vacuo and the residue was treated with pentane (3 × 20 mL), unsoluble Ph_3PO and benzoic acid were filtered, and the combined organic phases concentrated in vacuo. Further purification was achieved by Kugelrohr distillation (Table).

Ethyl 2-Alkyl-1-oxaspiro[2.2]pentane-2-carboxylates 3a–c; General Procedure:
H_2O_2 (85%, 0.52 mL, 21.4 mmol) was added to an ice cooled solution of trifluoroacetic anhydride (5.8 g, 27.5 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred for 30 min. After warming up to 20°C, a solution of alkene **2** (7.1 mmol) and Na_2CO_3 (2.27 g, 21.4 mmol) in CH_2Cl_2 (15 mL) was added. After the exothermic reaction had subsided, the solution was refluxed for 15 min. The cooled solution was washed with sat. aq Na_2CO_3 (30 mL), sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The reaction product was analytically pure (Table).

Ethyl 2-Alkylcyclobutanone-2-carboxylates 4a–c; General Procedure:
$BF_3 \cdot OEt_2$ (0.45 mL, 5.3 mmol) was added to a solution of spiro compound **3** (3.5 mmol) in Et_2O (10 mL) at 20°C. After stirring overnight the solution was washed with H_2O (2 × 15 mL), dried (Na_2SO_4) and concentrated in vacuo. The products were analytically pure (Table).

Ethyl 2-Phenylcyclobutanone-2-carboxylate (4d):
This compound was prepared according to the general procedure described for **3a–c**. The oily residue, which resulted after evaporation of the solvents, was purified by chromatography on silica gel (hexane/EtOAc 9:1) to afford **4d** as a colourless oil (Table).

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