Recent synthetic applications of the dealkoxycarbonylation reaction. Part 2. Dealkoxycarbonylations of β-keto esters, α-cyanoesters and related analogues

A. Paul Krapcho

Department of Chemistry, University of Vermont, Burlington, VT 05405 USA
E-mail: A.Paul.Krapcho@uvm.edu

Abstract
In Part 2, the synthetic applications of dealkoxycarbonylations of β-keto esters, α-cyano esters and related activated esters will be reviewed for the period 1981 to the middle of 2006. In Part 1, the dealkoxycarbonylations of malonate esters were reviewed for this same period.

Keywords: Dealkoxycarbonylations, decarbalkoxylations, Krapcho, β-keto esters, α-cyano esters, activated esters

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1. Introduction

In Part 1, the synthetic applications of the dealkoxycarbonylations of malonate esters were presented. In Part 2, the synthetic applications of the dealkoxycarbonylations of β-keto esters, α-cyano esters and related activated ester derivatives will be illustrated with selected examples. The literature search covers the period 1981 through mid 2006 and complements our prior review.1
2. Ketones

2.1. From monosubstituted β-keto esters

2.1.1. Water alone

As noted in our previous review, dealkoxycarbonylations of mono substituted β-keto esters (or the corresponding enols) can be effected on heating in DMSO and water without the addition of salts. Additional examples of this methodology have been reported.

Treatment of cis-1a (n = 1) with DMSO and water (150°C, 15 h) led to cis-2a (68%, n = 1), the product from the decarbomethoxylation of the β-keto ester moiety. Analogue cis-1b (n = 2) in DMSO and water (140°C, 2 h) afforded cis-2b (80%).

\[
\begin{align*}
\text{Me}_2\text{C} &= \text{CO}_2\text{Me} \\
\text{H} &= \text{H} \\
\text{Me}_2\text{C} &= \text{CO}_2\text{Me} \\
\text{a, n} &= 1; \text{b, n} = 2
\end{align*}
\]

In routes to several sex pheromones of the peach fruit moth and the Douglas fir tussock moth, decarbomethoxylations of several long chain β-keto esters were investigated. Treatment of 3a,b,c with DMSO and water (150°C, 3.5 h) led to the products 4a,b,c in yields of 80%.

\[
\begin{align*}
\text{Me(CH}_2\text{)}_x\text{C} &= \text{CO}_2\text{Et} \\
\text{CH}_2\text{CH}_2\text{C} &= \text{C(CH}_2\text{)}_y\text{Me} \\
\text{a, x} &= 7, y = 5; \text{b, x} = 8, y = 5; \text{c, x} = 9, y = 4
\end{align*}
\]

Brief microwave irradiation of mono-alkylated β-ketoesters at 160-200 °C in wet DMF induced smooth and selective decarboalkoxylations. For example, treatment of 5 with DMSO and water (160°C, 3 min) under microwave irradiation led to 6 (89%).

\[
\begin{align*}
\text{EtO}_2\text{C} &= \text{O} \\
\text{Me} &= \text{Me} \\
\text{Me} &= \text{Me} \\
\text{OPG} &= \text{Si}(-\text{Pr})_2(\text{CH}_2\text{CH}_2\text{C}_8\text{H}_{17})
\end{align*}
\]

The deethoxycarbonylation of 7a,b in wet DMSO (reflux, 4 h) afforded 8a (44%) or 8b (66%), respectively.
The demethoxycarbonylation of enantiomer 9 in DMSO and water (155°C, 2.5 h) led to the enantiomeric tricycle 10 (92%).6

2.1.2. Water-salts
2.1.2.1. From alkyl, aryl, heterocyclic and heteroaryl substituted open chain substrates. A number of optically active acetoacetates were alkylated on a solid support (Al₂O₃, t-BuOH) with alkyl bromides and the products subjected to dealkoxycarbonylations using LiCl in DMSO. For example, derivative 11 led to 12 with an optical purity of 13% (S-configuration).7

Keto ester 13 on treatment with DMSO, NaCl and water (70°C, 12 h) led to (+)-14 in good yield. This intermediate was easily converted into the alkaloid (+)-pinidine.8

The β-keto ester 15 on heating in DMF, NaCl and water (reflux, 72 h) led to 16 (88%), which was converted into a octahydropyrrolopyrrolizine-2-(1H)-one.9
The decarbomethoxylation of 17 using DMSO, LiCl and water (reflux, 10 min) led to the C-2 symmetrical ketone 18 (94%). This intermediate could be readily transformed into the corresponding enantiomeric spiroketal on treatment with aqueous acetic acid.\textsuperscript{10}

The decarbomethoxylation of 19 with DMSO, LiCl, and water (190\textdegree C, 40 min) provided the C\textsubscript{2}-symmetric ketone 20 (3\textit{E},5\textit{S},9\textit{S},10\textit{E}) (96%). This ketone on asymmetric syn- dihydroxylation and acid catalysis led to a mixture of dioxa[5,5]undecane and dioxa[4,5]decane.\textsuperscript{11}

A number of \(\omega\)-alkenyl ketones have been prepared by deethoxycarbonylation of the appropriate \(\beta\)-keto esters. For example, treatment of 21 with DMF and LiBr (195-200\textdegree C, 3 d) led to 22 (67%).\textsuperscript{12}

Treatment of 23 (isomeric mixture) with DMSO, NaCN (90\textdegree C, 22 h) led to 24 (70%) as an isomeric mixture. This intermediate was used in the synthesis of estrone derivatives.\textsuperscript{13}
The deethoxycarbonylation of 25 was accomplished using DMSO, LiCl and water (160°C, 24 h) to yield 26 (83%). This was converted into an acerogenin-type diaryl heptanoid holding an endocyclic biaryl ether bond.14

The chemoselective demethoxycarbonylation of the β-keto ester 27 was accomplished by treatment with DMSO, NaCl and water (125°C, 24 h) to afford optically active 28 (78%), which in a subsequent series of steps could be converted into (-)-virantmycin.15

In a pathway to racemic chrysolic acid, the deethoxycarbonylation of 29 with DMSO, NaCN and water (140-150°C, 10 h) led to intermediate 30 (60%).16

Treatment of 31 with DMSO, NaCl and water (135°C, 8 h) led to 32 (82%), isolated as the HCl salt.17
Treatment of keto ester 33 with DMSO, NaCl and water (150°C, 2 h) led to ketone 34 (70%).

The enantiomeric β-keto ester 35 on treatment with DMF, NaCl and water (reflux, 9 h) led to the de-t-butoxycarbonylated pyrrolidine 36-(3R) (92%). The stability of the BOC group under the reaction conditions is of particular note.

Treatment of β-keto ester 37 with DMSO, NaCl and water (135°C, 2 h) led to 38 (80%). This intermediate was converted into 1,6-dideoxyojirimycin (a polyhydroxy piperidine) in a series of subsequent steps.

A mixture of enol 39 and the corresponding β-keto ester in DMSO, NaCl and water (150-160°C, 5 h) afforded the flavanoid 40 (89%).
The deethoxycarbonylation of 41 was accomplished by heating in DMSO, NaCl and water (150-160°C, 8 h) to afford 42 (42%).

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{Ph} \\
\text{O} \\
\text{O} \\
\text{Ph} \\
\text{41} \quad \rightarrow \\
\text{42}
\end{array}
\]

The synthesis of (-)-secodaphniphylline (44) (44%, 99.6% ee) has been accomplished by heating β-keto ester 43 with NaCN in DMSO containing a few drops of water (150°C, 2 h).

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{MeO}_2\text{C} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{HN} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{HN} \\
\text{43} \quad \rightarrow \\
\text{44}
\end{array}
\]

Treatment of 45 (and the enol tautomer) with DMSO, NaCl and water (150°C, 5 h) led to the ethyl thiazole-5-carboxylate 46 (47%).

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{S} \quad \text{S} \\
\text{S} \\
\text{N} \\
\text{NH}_2 \\
\text{O} \\
\text{Me} \\
\text{CO}_2\text{Et} \\
\text{45} \quad \rightarrow \\
\text{EtO}_2\text{C} \quad \text{S} \quad \text{S} \\
\text{N} \\
\text{NH}_2 \\
\text{46}
\end{array}
\]

**2.1.2.2. From fluoro substituted substrates.** In a general method for the preparation of trifluoromethyl ketones, derivatives 47 on treatment with DMF, LiCl and water (reflux, 2 h) led to the ketones 48 (38-90%).

\[
\begin{array}{c}
\text{F}_3\text{C} \quad \text{R} \\
\text{CO}_2\text{Et} \\
\text{47} \quad \rightarrow \\
\text{F}_3\text{C} \quad \text{R} \\
\text{48}
\end{array}
\]

\[R = \text{n-octyl, benzyl, CH}_2\text{CH}_2\text{Ph, C}_6\text{H}_5\text{CH=CHCH}_2\]
Treatment of 49 with DMSO, NaCl and water (150-160°C, 15 min) led to the loss of a methoxycarbonyl group to afford the fluoro keto ester 50 (32%).26

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
(\text{CO}_2\text{Me})_2 & \quad \text{(H}_3\text{C})_3\text{C} \\
\end{align*}
\]

\[
49 \quad \rightarrow \quad 50
\]

2.1.2.3. From carbocyclic β-keto esters. The β-keto ester 51 on treatment in DMF with LiI (reflux, 2 h) led to 52 (76%), an intermediate used in an attempted approach to the sesquiterpene quadrone.27

A mixture of 53a and 53b was treated with DMSO, LiCl and water (120-130°C, 3 h) to afford a mixture of optically active 54a and 54b (64%, ratio 2.45:1).28

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{OMOM} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{EtO}_2\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{OMOM} \\
\end{align*}
\]

\[
53a + 53b \quad \rightarrow \quad 54a + 54b
\]

Treatment of chiral 55 with DMSO and NaI (100°C, 3 h) led to the (-)-56 (3S, 4S) (89%). This intermediate was subsequented converted into cuparene, laurenene, (-)-α- and (+)-β-cuparenones.29
The synthesis of (+)-58 (69%) was accomplished by heating 57 in DMSO, NaCl and water (165°C, 45 min). This intermediate was converted into (+)-estrone methyl ether.30

Upon heating β-keto ester 59 in DMSO, LiCl and water (190°C, 2 h), the α,β-unsaturated ketone 60 (73%) was obtained. This intermediate was subsequently transformed into cis-jasmone.31

The bis-silylated keto ester 61 on treatment with DMSO, NaCl and water (130-150°C, 3 h) led to the decarbomethoxylated product 62 (86%).32

Treatment of rac-63 with DMSO, LiCl and water (reflux, 5 h) led to rac-64 (40%) which was used in a synthesis of (-)-norgestrel.33
Treatment of 65 with DMSO, NaCl and water (reflux, 5 h) led to a mixture of 66a:66b (69%).

Treatment of 67 with DMSO, LiCl and water (145°C, quickly to room temperature) led to racemic 68 (96%) which was used in a synthesis of racemic silphinene.

Treatment of 69 with DMSO, NaCl and water (150°C, 6 h) afforded (-)-70 (86%) which in a series of steps could be converted into (+)-capnellene.

Treatment of enolic triester 71 with DMSO, NaCl and water (140°C, 2 h) led to keto diester 72 (92%). This was used as an intermediate in the synthesis of tricyclo octane structure.
The demethoxycarbonylation of 73 was accomplished by heating in DMSO, NaCl and water (85°C, 19 h) to afford racemic 74 (62%). This was subsequently converted into the cedrenoid sesquiterpenes racemic α-biotol and β-biotol. Other similar conversions have also been reported.37a Other similar conversions have also been reported.38b,c

Enantiomerically pure 75 on treatment with DMSO and water (155°C, 2.5 h) led to the deethoxycarbonylated ketone 76 (1R,6R) (92%). Attempts to convert this ketone into (+)-papuamine, a pentacyclic alkaloid isolated from a sponge, were not successful.39

Treatment of 77 with DMSO, LiCl and water (120-140°C, 2 h) led to (3aR,7aR)-78 (91%). This ketone was subsequently converted into (+)-grindelic acid in a 10-step sequence.40

The dealkoxycarbonylation of 79 using DMSO, LiCl and water (reflux, 30 min) led to the removal of the protective group with formation of the keto diol 80 (78%).41
Treatment of 81 with N-methylpyrrolidone, LiCl and water (120-125°C, 6 h) led to 82 (70%), used in a synthesis of racemic strigol, a seed germination stimulant.\(^\text{42}\)

\[
\text{81} \xrightarrow{\text{N-methylpyrrolidone, LiCl and water}} \text{82}
\]

Treatment of 83 (THF = 2-tetrahydrofuranyl) with DMSO-LiCl, sodium bicarbonate and water (150°C, 3 h) led to racemic product 84 (92%), which was converted into a intermediate for the synthesis of racemic perhydrohistrionicotoxin.\(^\text{43}\)

\[
\text{83} \xrightarrow{\text{DMSO-LiCl, sodium bicarbonate and water}} \text{84}
\]

The demethoxycarbonylation of 85 (and the enol tautomer) with DMSO, LiCl and water (165-170°C, 8 h) led to 86 (67%) in which the tertiary ester was also hydrolyzed to the carboxylic acid.\(^\text{44}\)

\[
\text{85} \xrightarrow{\text{DMSO, LiCl and water}} \text{86}
\]

The demethoxycarbonylation of β-keto ester 87 with DMSO, NaCl and water (150°C, 8 h) led to 88 (88%) which was used in a synthetic pathway to several natural tricyclic sequiterpenes.\(^\text{45}\)

\[
\text{87} \xrightarrow{\text{DMSO, NaCl and water}} \text{88}
\]

The β-keto ester 89 and DMSO, NaCl and water (110°C, 16 h) yielded 90 (72%), which could be converted into other functionalized tricycloundecanes.\(^\text{46}\)
The deethoxycarbonylation of 91 with DMSO, NaCl (70°C, 3 h) led to (-)-92 (73%, for 2 steps with prior CrO₃ oxidation of alcohol to the ketone), a common intermediate utilized in the synthesis of the indole diterpenes (+)-paspalicine and (+)-pasalinine.⁴⁷

Treatment of racemic 93 with DMSO, LiCl and water (170°C, 1.25 h) led to racemic 94 (92%).⁴⁸

Treatment of 95 with DMSO, NaCl and water (150°C) led to 96, used in a synthesis of a racemic capnellene.⁴⁹

The deethoxycarbonylation of 97 with DMSO, MgCl₂ hexahydrate (140°C, 28 h) led to racemic 98 (74%) with the α-trisubstituted ester intact. Ester 98 was utilized in a synthesis of the sequiterpenes cedranediol and cedranoxide.⁵⁰
A 12:1 mixture of 99a and 99b on treatment with DMSO, NaCl and water (reflux, 24 h) led to 100 (S) (83%ee) (59%).

Treatment of 101 with DMSO and water (130°C, 24 h) led to the demethoxycarbonylation product 102 (2S, 1R) (99%) which in a number of steps could be converted into (-)-epibatidine, an alkaloid isolated from the skin of a Ecuadorian frog and exhibiting potent activity as a nonopiate analgesic.

Treatment of optically active 103 with DMSO, NaCl and water (180-185°C, 3.5 h) led to (3S)-104 (79%).

The β-keto ester 105 underwent decarbomethoxylation when treated with DMSO, NaCl and water (150°C, 4.5 h) to yield racemic β-vetivone 106 and racemic epi β-vetivone (1.7:1 ratio) (77%), which could be separated by column chromatography.
The spiro β-keto ester 107 on treatment with DMSO, NaCl and water (130°C, 2 h) led to the (1R,5R) spiro[4,5]decan-7-one (108, 70%).

Treatment of 109 with DMSO and water (115-120°C, 3 h) gave 110 (73%).

Treatment of 111 (and the enolic tautomer) with DMSO, NaCl and water (140°C, 4 h) led to homothujone 112 (as a mixture of α- and β-diastereoisomers in a 10:1 ratio).

Treatment of enol 113 with DMSO, LiCl and water (150°C, 4 h) led to 114 in a quantitative yield, which was utilized in a synthesis of a benzindene prostacyclin analogue.
Treatment of 115 with DMSO, NaCl and water (heat) led to 116 (47%).

\[
\begin{align*}
\text{MeO} & \text{MeO} \\
\text{H} & \text{H} \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et}
\end{align*}
\]

115 116

In a study dealing with thromboxane A\textsubscript{2} analogues, it was reported that treatment of crude 117 (obtained as two regioisomers via a ring expansion of a prostaglandin intermediate with ethyl diazoacetate) with DMSO, NaCl and water (150\textdegree C, 2 h) led to optially active 118 (52%).

\[
\begin{align*}
\text{EtO}_2\text{C} & \text{OAc} \\
\text{Me} & \text{CO}_2\text{Me} \\
\text{Me} & \text{CO}_2\text{Me}
\end{align*}
\]

117 118

In the total synthesis of tetracyclic Lycopodium alkaloids, the intermediate 120 was prepared by treatment of 119 with NaCl in DMF (no conditions or yield).

\[
\begin{align*}
\text{O} & \text{S} \\
\text{S} & \text{O} \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et}
\end{align*}
\]

119 120

Treatment of \(\beta\)-keto ester 121 with DMSO, NaCl and water (160\textdegree C, 6 h) led to 122 (85%) which was used in a synthesis of racemic isoclovene, a tricyclic ketonic sesquiterpene.

\[
\begin{align*}
\text{Me} & \text{CO}_2\text{Et} \\
\text{EtO}_2\text{C} & \text{O}
\end{align*}
\]

121 122
Treatment of a number of bicyclic β-keto esters with DMSO, NaCl and water led to the corresponding deethoxycarbonylated products. As an illustration, 123 on treatment with DMSO, NaCl and water (reflux, 2 h) led to chiral 124 (1S, 6S, 7S, 9R, 10R) (86%), used in a route leading to an enantiospecific synthesis of clavukerin A, a trinorguaiane sesquiterpene.63

\[
\begin{align*}
\text{TBDMSO} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{Me} & \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{TBDMSO}
\end{align*}
\]

123 → 124

Treatment of 125 with DMSO, NaCl and water (140°C, 0.5 h) led to 126 (82%).64

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{Me} & \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{Me}
\end{align*}
\]

125 → 126

Treatment of 127 with DMSO, LiCl and water (175°C, 3 h) led to racemic 128 (86%) which in a subsequent series of steps was converted into the furano sesquiterpene dihydropallescensin.65

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{Me} & \quad \text{O} \\
\text{CO}_2\text{Me} & \quad \text{Me}
\end{align*}
\]

127 → 128

The deethoxycarbonylation of 129 with DMSO, NaCl and water (160°C, 3 h) led to 130 (quantitatively). This key intermediate, in a series of steps, was converted into the sesquiterpene, racemic isoclovene.66a,b

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{Me} & \quad \text{O} \\
\text{CO}_2\text{Et} & \quad \text{Me}
\end{align*}
\]

129 → 130
The deethoxycarbonylation of 131 with DMSO, NaCl and water (150-160°C, 6 h) led to the hexacyclic dione 132 (56%).

\[ \text{131} \rightarrow \text{132} \]

The deethoxycarbonylation of 133 with DMSO, NaCl and water (150°C, 4 h) led to 134 (91%).

\[ \text{133} \rightarrow \text{134} \]

The deethoxycarbonylations of a mixture of chiral 135a and 135b with DMSO and water (165°C, 4 h) led to (R)-(−)-muscone (136, 59%).

\[ \text{135a} + \text{135b} \rightarrow \text{136} \]

In synthetic routes to m-pyrrolophanes, the β-keto ester 137 on treatment with DMSO, NaCl and water (180-190°C, 1.5 h) led to ketopyrrole 138 (91%).

\[ \text{137} \rightarrow \text{138} \]

2.1.2.4. From heterocyclic β-keto esters. Treatment of macrocycle 139 with DMSO, LiCl and water (reflux, 1 h) led to 140 (78%), which was used in a synthesis of glucosporone, an autoinhibitor of spore germination.
The lactone 141 on treatment in DMF with LiBr (reflux, 8 h) led to racemic 142 (90%) used in a synthesis of the male sex pheromones of Caribbean and Mexican fruit flies.⁷²

Treatment of lactone 143 with DMSO, NaCl and water (110°C) led to 144 (83%), which in a subsequent series of steps could be converted into racemic Corey’s lactone.⁷³

Treatment of (R)-145 with refluxing aqueous DMF for 12 h led to lactone (R)-146 (99% ee) in good yield.⁷⁴

Treatment of 147 with DMSO, LiCl and water (100°C, 24 h) led to racemic 148 (85%) which was used in the synthesis of the partial ring skeleton of the ginkolides.⁷⁵
Treatment of 149 with DMSO, NaCl and water (180°C, 50 min) afforded 150 (95%) which were used in a synthesis of guaianolides and related derivatives.76

\[ \text{149} \xrightarrow{\text{DMSO, NaCl, water}} \text{150} \]

Lactam 151 on treatment with DMF, NaCl and water (heat, 12 h) led to 152 (40%) and ring opened product 153 (29%).77

\[ \text{151} \xrightarrow{\text{DMF, NaCl, water}} \text{152, 153} \]

The dealkoxycarbonylation of 154 (where R* is a chiral appendage) with DMSO, NaCl and water at reflux led to (S)-155 (84%).78

\[ \text{154} \xrightarrow{\text{DMSO, NaCl, water}} \text{155} \]

The deethoxycarbonylation of the β-keto ester 156 in DMSO, NaCl and water (130-135°C, 20 h) led to a crude product which on chromatography gave enantiomer 157 (36%).79

\[ \text{156} \xrightarrow{\text{DMSO, NaCl, water}} \text{157} \]

The optically active ester lactams 158a and 158b on treatment with DMSO, NaCl and water (150°C, 28 h) led to 159a and 159b in good yields. In 158c, a similar procedure led to the desired product 159c along with some mono-desilylated product in a 1:4.3 ratio.80
Treatment of a number of 4-ethoxycarbonyl-N-substituted pyrrolidin-3-ones with DMSO, NaCl and water led to the corresponding decarboxylation products. For example, treatment of 160a or 160b with DMSO, NaCl and water (130°C) led to 161a (81%) or 161b (83%), respectively.81

A key 4-substituted 2-pyrrolidone intermediate 163 (97%, which after crystallization led to an optically pure sample (71%), was prepared by decarbomethoxylation of 162 (88% ee) on treatment with DMSO, NaCl and water (160°C, 2 h). This intermediate was converted into a phosphodiesterase type IV inhibitor (R)-(−)-rolipram.82

Treatment of the enol ester 164 with DMSO, NaCl and water (155-160°C, 3 h) led to the 3-oxo-2-piperidine-propionic acid 165 (78%). The intramolecular acylation of this analogue into the corresponding enol lactone was accomplished.83
Enantiomer 166 with DMSO, NaCl and water (160-170°C, 1 h) led to enantiomer 167 (63%), an intermediate used in the study of the synthesis of (+)-sesbanimide. In this case, perhaps the addition of salt might not be necessary.

The deallyloxy carbonylation of substrate 168 with DMF, MgCl₂ hexahydrate and water (reflux, 20 h) yielded 169 (91%).

The decarbomethoxylation of 170 in DMSO, NaCl and water (155°C, 10 h) led to 171 (99%) which was converted into racemic pyrrolizidine alkaloid isoretronecanol.

The decarbomethoxylation of a mixture of the enol esters 172 and 173 in DMSO, NaCl and water (130°C, 4 min) led to the indolizinone 174 (92%). Intermediate 174 was subsequently transformed in a series of steps into natural (+)-lentiginosine.
Treatment of 175 with DMSO, NaCl and water (155-160°C, 3 h) gave 176 (74%).

Treatment of (R)-177 with DMSO, NaCl and water (140°C, 3 h) led to (R)-178 (60%). However, the ee of (R)-178 was only 0.5% which appeared to indicate that racemization had occurred in the demethoxycarbonylation step.

The decarbomethoxylation of (-)-179 (and the enol form) with DMF, NaCl and water (130°C, 6 h) led to (-)-180 (73%, >95%ee). A similar procedure on the enantiomer led to (+)-180. These intermediates could then be converted into several indole alkaloids such as (-)-ajmaline.

The demethoxycarbonylation of derivative 181 proved to be quite difficult. The best result was obtained by treatment of 181 with dry DMSO and LiI dihydrate (132°C, 36 h) to afford 182 (56%). The use of DMSO, NaCl and water at 180°C did not lead to demethoxycarbonylation.
Treatment of ester 183 with DMSO, LiCl and water (160°C, 3.5 h) led to 184 (99% ee). This intermediate was converted into (+)-geissoschizine.92

The decarbomethoxylation of of 185 with DMSO, LiCl and water (150°C, 25 min) led to 186 (98% ee), a known degradation product of vindoline.93

Keto ester 187 on treatment with DMSO, LiCl and water (reflux, 2.5 h) led to 188 (78%). A subsequent series of steps led to the racemic sesquiterpene davanone.94

In approaches to the cladiellin skeleton, the intermediate 189 on treatment with LiCl, DMSO (130°C, 3 h) and water led to enantiomer 190 (86%).95
The preparation of enantiomer 192 (41%) was performed by heating 191 in dry DMF and LiI dihydrate (130°C, 2.5 h).96

The demethoxycarbonylation of 193 (and the tautomeric enolic ester) was easily accomplished in DMSO and water (150°C, 1 h) to yield the thienoazepine dione 194 (82%).97 A related pyrimidine analogue underwent deethoxycarbonylation in DMSO and anhydrous NaCl.98

Additional examples are tabulated in Table 1.
Table 1. Dealkoxycarbonylations of monosubstituted β-keto esters

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>DMSO, NaCl, H$_2$O 150°C</td>
<td><img src="image2" alt="Image" /></td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O 130°C, 2 h</td>
<td><img src="image4" alt="Image" /></td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td>DMF, LiI reflux, 12 h</td>
<td><img src="image6" alt="Image" /></td>
<td>81</td>
<td>101</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O reflux, 10 h</td>
<td><img src="image8" alt="Image" /></td>
<td>40</td>
<td>102</td>
</tr>
<tr>
<td><img src="image9" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O reflux, 24 h</td>
<td><img src="image10" alt="Image" /></td>
<td>88</td>
<td>103</td>
</tr>
<tr>
<td><img src="image11" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O reflux, 10 h</td>
<td><img src="image12" alt="Image" /></td>
<td>74</td>
<td>104</td>
</tr>
<tr>
<td><img src="image13" alt="Image" /></td>
<td>DMSO, NaCl, H$_2$O 130°C, 3 h</td>
<td><img src="image14" alt="Image" /></td>
<td>quant</td>
<td>105</td>
</tr>
<tr>
<td><img src="image15" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O 160°C, 4 h</td>
<td><img src="image16" alt="Image" /></td>
<td>73</td>
<td>106</td>
</tr>
<tr>
<td><img src="image17" alt="Image" /></td>
<td>DMSO, LiCl, H$_2$O reflux, 3.5 h</td>
<td><img src="image18" alt="Image" /></td>
<td>76</td>
<td>107</td>
</tr>
<tr>
<td><img src="image19" alt="Image" /></td>
<td>DMSO, NaCl, H$_2$O 100°C, 5.5 h</td>
<td><img src="image20" alt="Image" /></td>
<td>83</td>
<td>108</td>
</tr>
</tbody>
</table>
2.1.2.5. From an $\alpha,\alpha$-diethoxycarbonyl ketone. Treatment of 195 with DMSO, NaCl and water (160-170°C, 6 h) afforded 196 (90%) the bis-deethoxycarbonylation product 196 (90%).

\[
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{MeO}_2\text{C}
\]

2.2. Disubstituted $\beta$-keto esters

2.2.1. Water alone

The de-t-butoxycarbonylation of the bis-(thiomethyl) substrate 197 with DMSO and water (160°C, 4 h) led to 1,1-bis-(methylthio)-2-propanone 198 (85%).

\[
\text{Me} \quad \text{OC(CH}_3\text{)}_3 \quad \text{H}_3\text{CS} \quad \text{SCH}_3 \quad \text{O} \quad \text{Me} \quad \text{H}_3\text{CS} \quad \text{SCH}_3
\]

2.2.2. Water-salts

2.2.2.1. Open chain substitutents. The racemic $\beta$-keto ester 199 on heating in DMSO with LiCl and water (170°C, 1.5 h) led to a key intermediate 200 (89%), which was converted in 2 steps to racemic stigmalone.

\[
\text{Me} \quad \text{Me} \quad \text{CH}_2 \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CH}_2
\]

A number of 3-acyloxymethyl ketones were synthesized by the chemoselective dealkoxyxycarbonylation of the tert-butoxycarbonyl group using DMSO, LiCl and water (160°C, 5 h). A typical illustrative example is the conversion of 201 to 202 (64%). In this case the presence of the salt might not be necessary.
The preparation of a number of 1-alkyl-1,3-dimethoxyacetones has been accomplished by treatment of the appropriate β-keto ester with DMSO, LiCl and water (120-140°C, 10 h). For example, under these reaction conditions the demethoxycarbonylation of 203 led to 204 (72%).113

2.2.2. From carbocyclic β-keto esters
2.2.2.3. Water-salts. Treatment of 205 with DMSO, NaCN and water (140°C, 1 h) led to 206 (53%).114

Upon treatment of 207 with DMSO and NaCN (135-140°C, 2 h) the de-ethoxycarbonylation and displacement of the bromide occurred to afforded nitrile 208 (75%).115

Treatment of enantiomer 209 with DMF and LiI (reflux, 2 h) led to enantiomer 210 (76%), which was used in a synthesis of a triquinane portion of retigeranic acid.116

Treatment of 211 with DMSO, NaCl, water (155-160°C, 5 h) led to 212 (53%), along with some ring-opened product. This intermediate was to be used in a synthetic approach to 11-deoxyprostaglandins.117
In studies dealing with the synthesis of protaglandins, the treatment of 213 with HMPA and NaCN (75-80°C, 1.5 h) led to racemic 214.\textsuperscript{118}

The β-keto ester 215 on treatment with DMF and LiI (reflux, 8 h) led to 216 (85%), a prostaglandin synthon.\textsuperscript{119}

The synthesis of racemic jasmonate 218 (78%) was accomplished by heating β-keto ester 217 in DMSO, NaCl and water (180°C, 4 h, sealed tube).\textsuperscript{120}

Racemic 219 on treatment with DMSO, NaCl and water (170°C, 18 h) led to methyl dihydrojasmonate 220 (83%). Under these conditions the demethoxycarbonylation of only the β-keto ester moiety occurred.\textsuperscript{121}
Treatment of 221 with HMPA and NaCN (75°C, 5 h) led to chiral (2R,3R,1R)-222 (72%).

Treatment of (+)-223 with DMSO, NaCN and water (140°C, 36 h) led to ketone (S)-224 (89%) with a trans: cis ratio of 9:1. The mixture of ketones was converted into the sesquiterpenic alcohol (+)-conocephalenol in several subsequent steps.

```
\begin{align*}
\text{O} & \text{CO}_2\text{Me} \\
\text{Me} & \text{MeO}_2\text{C} \\
\text{Me} & \text{Me} \\
\text{CH}_2 & \text{Me} \\
\end{align*}
```

The decarbomethoxylation of 225 in DMSO and NaCN (160°C, 2 h) yielded 226 (92%) used in a synthesis of chiral phenylalanine analogues isolated from Praxelis clematidea.

```
\begin{align*}
\text{O} & \text{CO}_2\text{Me} \\
\text{Me} & \text{MeO}_2\text{C} \\
\text{Me} & \text{Me} \\
\text{OAc} & \text{OAc} \\
\end{align*}
```

On treatment of (-)-227 (a vinylogous β-keto ester) with DMF and LiI trihydrate (reflux, 1 h) the demethoxylated products (+)-228a and (-)-228b (90%, 5:4 ratio) were isolated and could be separated by chromatography. Compound 228a was subsequently converted into the chiral sequiterpene alcohol (-)-silphiperfol-5-en-3-ol.

```
\begin{align*}
\text{Me}_3 & \text{MeO}_2\text{C} \\
\text{Me} & \text{Me} \\
\text{H} & \text{H} \\
\end{align*}
```

In the preparation of 16-(bromoalkyl)-estradiols, the intermediate 230 (71%, as a 16α,16β mixture 15:85) was obtained by treatment of 229 with DMF, LiCl and water (reflux). Other side chains at C-16 were also prepared by this route.
Treatment of 231a or 231b with DMSO, LiCl and water (180°C, 1.5 h) led to 232a (64%) or 232 (78%), respectively.\(^{127}\)

\[
\begin{align*}
\text{231} & \quad \text{232} \\
\text{a, R = C}_5\text{H}_{11}, \ n = 1; \ R = \text{C}_6\text{H}_{11}, \ n = 2
\end{align*}
\]

The decarbomethoxylation of 233 with DMSO, NaCl and water (160°C) led to a mixture of cis- and trans isomers 234 which could be separated by chromatography. These isomers were used in the synthesis of the sesquiterpene racemic vetiselinene.\(^{128}\)

The Krapcho dealkoxycarbonylations of substituted cyclic β-keto esters using LiBr, Bu\(_4\)NBr and water under microwave irradiation have been reported. For example, under these conditions the conversion of 235 to 236 (87%) was accomplished in 20 min at 186°C.\(^{129a,b,c}\)

\[
\begin{align*}
\text{235} & \quad \text{236}
\end{align*}
\]

The β-keto ester 237 on treatment with DMPU (dimethylpyrimidinone) and LiCl (130°C, 48 h) gave cyclohexenone 238 (45%).\(^{130}\)

\[
\begin{align*}
\text{237} & \quad \text{238}
\end{align*}
\]

Treatment of 239 with HMPA and LiCl (130°C) led to the demethoxycarbonylated product 240 (72%) which was converted into (+)-dysideapalaunic acid, a sesquiterpene aldose reductase inhibitor.\(^{131}\)
Treatment of 241 with LiCl in HMPA (130°C) afforded 242 (92%) which was used in the synthesis of (+)-perrottetianal A, sacculatane diterpene.132

The crystalline and oily stereoisomers 243 were treated with HMPA and LiCl (120-140°C, 8 h) to afford the dione 244 (84%), which was subsequently converted into (+)-pisiferol, an abietane-type diterpene alcohol.133

The demethoxycarbonylation of 245 with HMPA and LiCl (anhydrous conditions, 100°C, 20 h) led to an epimeric mixture of tricyclic ketones 246 (82%) which were subsequently converted into racemic sterpurene, a sesquiterpene hydrocarbon metabolite of Chondrostereum purpureum.134
Treatment of 247a (1-β-H) or 247b (1-α-H) with DMSO, NaCl and water at reflux led to 248a or 248b (90%), which were used in the synthesis of a defense substance of a termite soldier.\textsuperscript{135}

Treatment of 249 with DMSO, NaCl and water (150°C, 6 h) led to the decarbomethoxylation to afford racemic 250 (36%), an intermediate in approaches to a group of sesquiterpenes called tremulanes.\textsuperscript{136}

The decarbomethoxylation of 251 in aqueous DMSO (no conditions) led to ketone 252 (99%).\textsuperscript{137}
2.3. Heterocyclic substrates
2.3.1. From \(\beta\)-carbethoxy substituted lactones

The demethoxycarbonylation of the methoxycarbonyl substituted furanone 253 to \(\gamma\)-lactone 254 (72%) was accomplished on treatment with DMSO, NaCl and water (160\(^\circ\)C, 12 h).\(^{138}\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CH}_2 \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

Decarbomethoxylation of \(\gamma\)-lactone 255 with DMSO, NaCl and water (110\(^\circ\)C, 12 h) yielded chiral (4S) 2-butyrolactone 256 (84%) which in a series of subsequent transformations was transformed into the pentacyclic alkaloids (-)-eburnamonine and (+)-\textit{epi}-eburnamonine.\(^{139a,b}\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Et} \quad \text{(CH}_2\text{)}_3\text{OTBDPS} \\
\text{O} & \quad \text{O} \quad \text{Et} \quad \text{(CH}_2\text{)}_3\text{OTBDPS} \\
\text{4} & \quad \text{4}
\end{align*}
\]

The demethoxycarbonylation of 257 in DMSO (or DMF), NaCl and water (150\(^\circ\)C, 3-5 h) yielded the lactone 258 (75%).\(^{140}\)

\[
\begin{align*}
\text{H} & \quad \text{CO}_2\text{Me} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

The silylated butenyl lactone 260 (77%) was obtained by treatment of 259 with DMSO and LiCl (reflux, 3 h). Further elaborations of the lactone and terminal silyl group were performed.\(^{141}\)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{SiEt}_3 \\
\text{259} & \quad \text{260}
\end{align*}
\]

The deethoxycarbonylation of the fluorinated lactone 262 with DMSO, NaCl and water (reflux, 2.5 h) led to a diastereoisomeric mixture of lactones 263 (73%) which in a few steps could be converted in 5-amino-2-fluorolevulinic acid.\(^{142}\)
Of particular interest is the conversion of 264 to the naturally occurring racemic spirolactone andirolactone (265). Treatment of 264 with DMSO, NaCl and water (160⁰, 2 h) afforded 265 (90%).

The lactone 266 on heating in DMSO, LiCl and water (125⁰C, 12 h) led to (S)-sotolon (267) (80%, 92%ee), a volatile compound isolated from raw cane sugar.

Treatment of lactone 268 with DMSO and water (110-120⁰C, 1 h) led to 269 (99%), which was used in the synthesis of potential phenolic antioxidants.

The synthesis of (3S, 4S) 271 (60%, 99.9%ee) was accomplished by treatment of 270 with DMSO, LiCl and water (reflux, 3.5 h). This intermediate was used in a synthesis of the sex pheromones of pine sawflies.
The bicyclic lactone 272 on treatment with DMSO, LiCl and water (195°C, 3 h) led to the bicyclic lactone 273 (64%).

The α-carbomethoxy-α-hydroxy-γ-lactone 274 on treatment with DMF, NaCl and water (150°C, 3 h) led to 275a and 275b (84%, 68:32 ratio) which could be separated by chromatography.

The demethoxycarbonylation of 276 (a 3:1 mixture of diastereoisomers) with DMF and LiI (reflux) led to 277 (86%) which in a subsequent series of reactions was used in an enantioselective total synthesis of (+)-methyl pederate.

The lactone 278 with DMSO, NaCl and water (150-160°C, 2 h) led to 279 (75%). In a similar manner the β-methyl analogue was converted into the corresponding deethoxycarbonylated product. Other substituted analogues were also deethoxy-carbonylated. These derivatives were used in a synthesis of perhydrofuro[2,3-b]furan ring systems.
Treatment of lactone 280 with HMPA, NaCl and water (190°C, 2.5 h) gave 281 (65%).\textsuperscript{151}

\[
\begin{align*}
\text{280} & \quad \rightarrow \quad \text{281}
\end{align*}
\]

Treatment of 11-carbomethoxy-18-norestrane 282 with DMSO and NaCN (100°C, 19 h) led to racemic 283 (no yield given).\textsuperscript{152}

\[
\begin{align*}
\text{282} & \quad \rightarrow \quad \text{283}
\end{align*}
\]

The decarbomethoxylation of 284 on treatment with DMSO, and NaCN (90°C, 24 h) led to isomeric mixtures of 285a and 285b (78%), which were used in a steroid analogue synthesis.\textsuperscript{153} A similar strategy was used for the incorporation of fluoro substituent\textsuperscript{153} and a 3-hydroxy steroidal group.\textsuperscript{154}

\[
\begin{align*}
\text{284} & \quad \rightarrow \quad \text{285a} + \text{285b}
\end{align*}
\]

Treatment of 286a and 286b (diastereoisomeric mixture) with DMSO and NaCN (90°C, 24 h) led to an inseparable mixture of 4-azabenzocyclobutane diastereoisomers 287a and 287b (91%) which were subsequently converted into the aza steroidal analogues.\textsuperscript{155}
In the preparation of dihydroisoquinolines, the intermediate 289 was prepared by treatment of 288 (44%) with DMSO, NaCl and water (145-150°C, 6 h).\textsuperscript{156}

The ester 290 on treatment with DMF, LiCl and water (92°C, 16 h) led to compound 291 (78%) as an epimeric mixture which could not be separated.\textsuperscript{157}

The thieno[2,3-d]pyrimidin-4-one (292) on treatment with DMSO, LiCl (150°C) led to the pyrimidinone 293 (no experimental conditions).\textsuperscript{158}
The use of MgCl₂ hexahydrate (in place of NaCl) in DMSO (130-140°C, 2.5 h) for the demethocycarbonylation of 294 led to deoxybrevianamide 295 (59%) along with the corresponding epimer (38%).

The dealkoxycarbonylations of β-keto esters using halides of group IIa metals have been studied. For example, treatment of 296 with MgCl₂ hexahydrate or CaCl₂ dihydrate in DMSO (in the presence of PhSH, at 150-160°C) led to 297 (50-60%).

The deethoxycarbonylation of substituted derivatives such as 298 have been accomplished using MgCl₂ hexahydrate in DMSO (or HMPA) in the presence of PhSH (150-155°C, 2 h) to yield 299 (73%). These derivatives were used in a synthesis of erythrina and related alkaloids.

The decarbomethoxylation of 300 with DMSO, NaCl and water (135-140°C, 5-8 h) led to the ketones 301 (49-90%). Intermediate 301c was converted into racemic α-lipoic acid.

a, R = n-butyl; b, R = benzyl; c, R = (CH₂)₄CO₂Me; d, R = allyl; e, R = Et
Treatment of \(302\) with HMPA and LiCl (65-75°C, 20 h) led to \(303\) (65%), which was used in a synthesis of 2-alkyl-3-cyclopentenones.\(^{163}\)

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\begin{array}{c}
\text{Me} \\
\end{array} & \quad \rightarrow \\
\text{O} & \quad \begin{array}{c}
\text{H} \\
\text{Me} \\
\end{array}
\end{align*}
\]

\(302\) \(\rightarrow\) \(303\)

In a study of routes to thia thromboxane analogues, the dealkoxycarbonylations of a number of 3-methoxy carbonyl-3-substituted thiin-4-ones were evaluated. Treatment of \(304\) with DMF, anhydrous MgCl\(_2\) and a phosphate buffer (160°C, 21 h) led to enone \(305\) (69%) as an inseparable mixture of the 2,3-\textit{trans} and 2,3-\textit{cis} isomers along with 16% of the corresponding desilylated products, namely the 2,3-\textit{trans} and 2,3-\textit{cis} alcohols.\(^{164}\)

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\begin{array}{c}
\text{Me} \\
\end{array} & \quad \rightarrow \\
\text{O} & \quad \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Me} \\
\end{array}
\end{align*}
\]

\(304\) \(\rightarrow\) \(305\)

Treatment of \(306\) with DMF and LiBr (137°C, 5 h) in the presence of \(p\)-amino thiophenol (a trap for MeBr formed during the reaction) gave the demethoxycarbonylated product \(307\) (96%) with less than 3% of the corresponding \textit{trans}-isomer. Initial attempts to use only DMF and LiI led to \(307\) along with 30% of the corresponding N-methyl analogues. Intermediate \(307\) was utilized in the preparation of analogues related to diltiazem used in the treatment of hypertension.\(^{165}\)

\[
\begin{align*}
\text{O} & \quad \text{Me} \\
\begin{array}{c}
\text{OMe} \\
\end{array} & \quad \rightarrow \\
\text{O} & \quad \begin{array}{c}
\text{Me} \\
\text{OMe} \\
\end{array}
\end{align*}
\]

\(306\) \(\rightarrow\) \(307\)

Upon heating \(308\) in dry HMPA and LiCl (120°C, 10 min) the demethoxycarbonylation led to the intramolecular cyclization product \(309\) (61%).\(^{166}\)
Table 2 lists some additional examples.

**Table 2.** Dealkoxycarbonylations of disubstituted β-keto esters

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 308" /></td>
<td>DMF, LiCl, H₂O reflux, 18 h</td>
<td><img src="image" alt="Structure 309" /></td>
<td>80</td>
<td>167</td>
</tr>
<tr>
<td><img src="image" alt="Structure 308" /></td>
<td>DMSO, LiCl, H₂O 149°C, 20 h</td>
<td><img src="image" alt="Structure 309" /></td>
<td>54</td>
<td>168</td>
</tr>
<tr>
<td><img src="image" alt="Structure 308" /></td>
<td>DMF, LiCl, H₂O reflux, 1 h</td>
<td><img src="image" alt="Structure 309" /></td>
<td>64</td>
<td>169</td>
</tr>
<tr>
<td><img src="image" alt="Structure 308" /></td>
<td>DMF, LiCl, H₂O HOAc, reflux, 5h</td>
<td><img src="image" alt="Structure 309" /></td>
<td>84 exo:endo 55:45</td>
<td>170</td>
</tr>
</tbody>
</table>

2.4. 1,3-Diones

2.4.1. From substituted 2-carbalkoxy-1,3-diones

A wide variety of β-diketones (for identification of potential secretions from the paracloacal glands of alligator and caimans) have been prepared by treatment of substituted 2-carbalkoxy-1,3-diones with NaCl and water at reflux (12 h). The following reaction sequence for the preparation of 5-ethylnonane-2,4-dione (311) from the corresponding β-2-carethoxy-1,3-dione is illustrative 310 (62%).

![Chemical Structures 310 and 311](image)
The synthesis of a wide variety of β-diketones found in sunflower pollen has been accomplished. For example, the conversion of 312 with DMSO, NaCl and water (reflux, 8 h) led to 313 (40-60%).\textsuperscript{172}

\[
\begin{array}{c}
\text{C}_9\text{H}_{19}\text{C}_17\text{H}_{35}\text{C}_2\text{Et} \\
\rightarrow \\
\text{C}_9\text{H}_{19}\text{C}_17\text{H}_{35}
\end{array}
\]

Treatment of enol 314 with DMSO, NaCl and water (reflux, 18 h) led to ketone 315 (62%).\textsuperscript{173}

\[
\begin{array}{c}
\text{Me}\text{Me}\text{CO}_2\text{Me} \\
\text{Me}\text{Me}\text{CO}_2\text{Me} \\
\rightarrow \\
\text{Me}\text{Me}
\end{array}
\]

The facile demethoxycarbonylations of 316\textit{a} (n,m = 6) and 316\textit{b} (n = 6, m = 20) were accomplished by heating in DMSO and water to yield the corresponding long-chain 1,3-diones 317\textit{a} (82%) and 317\textit{b} (98%).\textsuperscript{174}

\[
\begin{array}{c}
\text{CH}_3\text{(CH}_2\text{)}_n\text{CO}_2\text{Me} \\
\text{CH}_3\text{(CH}_2\text{)}_n\text{CO}_2\text{Me} \\
\rightarrow \\
\text{CH}_3\text{(CH}_2\text{)}_n\text{CO}_2\text{Me}
\end{array}
\]

Treatment of 318 with DMSO, NaCl, water (reflux, 8 h) led to the 1,3-dione 319 in good yield.\textsuperscript{175}

\[
\begin{array}{c}
\text{Me}\text{(CH}_2\text{)}_3\text{CO}_2\text{Et} \\
\rightarrow \\
\text{Me}\text{(CH}_2\text{)}_3\text{CO}_2\text{Me}
\end{array}
\]

Treatment of the enolic tautomer 320 with DMSO, NaCl and H\textsubscript{2}O (160-170°C, 4 h) led to the enolic form of the 1,3-dione 321 (54%).\textsuperscript{176}
Treatment of 322 with DMSO, NaCl and water (reflux, 1 h) led to 323.\(^{177}\)

The ester 324 in acetonitrile and water was refluxed for 2.5 h to yield 325 (95\%).\(^{178}\)

2.5. 1,4-Diones
2.5.1. From \(\alpha\)-carbalkoxy-1,4-diones
The demethoxy carbonylation of 326 with DMSO, NaCl and water (160-170\(^\circ\)C, 6 h) led to 1,4-dione 327 (40\%).\(^{179}\)

Treatment of the \(\beta\)-keto ester 328 with DMSO, NaCl and water (110\(^\circ\)C, 2.5 h) led to 1,1,1-trifluoro-2,5-hexanedione 329 (73\%).\(^{180}\)
The deethoxycarbonylations of β-keto esters 330a-c in DMSO, NaCl and water (180°C, 20 h) led to good yields of the corresponding 1,4-diones 331a-c (48-75%).

2.6. 1,5-Dione

2.6.1. From α-carbomethoxy substituted substrate

The decarbomethoxylation of β-keto ester 332 was accomplished using DMPU and LiCl (120°C, 7 h) to afford (R)-333 (72%). It was noted that the use of HMPA or DMSO as solvents did not give satisfactory yields. The RCM macrocyclization of this keto diene led to the 15-membered carbocyclic substrate which was converted into (R)-(+)—muscopyridine.

2.7. β-Keto ester and malonate ester polyfunctional substrates

Treatment of 334 with DMSO, NaCl and water (173°C, 45 min) led to 335 (65%), resulting from the decarbomethoxylation of the malonate ester group and the β-keto ester group.

Compound 336 in DMF, LiCl and water (reflux, 18 h) led to 337a (36%) and 337b (25%).

Treatment of 338 with DMSO, NaCl and water (155-160°C) led to 339 (61%).
Upon heating 340 in DMSO, NaCl and water (150-160°C, 2 h) 341 was formed (83%), the product of a deethoxycarbonylation of the β-keto ester functionality. If diester 341 is heated with DMSO, LiCl and water with a small amount of pyridine (150-160°C, 14 h), 342 (72%) was obtained. Heating diester 340 with DMSO, LiCl and water (150-160°C, 14 h) and a small amount of pyridine afforded 342 (70%).186

2.8. Aldehyde
2.8.1. From α-methoxycarbonyl aldehyde
Treatment of 343 with DMF and LiI hydrate (reflux, 1 h) led to racemic 344 (89%).187

2.9. Nitriles
The dealkoxycarbonylation of an α-cyano ester is a useful preparative route leading to nitriles.

2.9.1. From α-cyano esters

2.9.2. From mono substituted substrates
The conjugate addition product obtained by addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one using a chiral(salen)Al complex led to 345 which on treatment with DMSO and water (130°C) led to 346 (85% for two steps in 93% ee).188
The chemoselective deethoxycarbonylation of α-cyano ester 347 was accomplished by treatment with DMSO, water and LiCl (140°C, 4 h) to yield 348 (75%).\textsuperscript{189}

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{CN} \\
\text{CO}_2\text{Et} \\
347 \quad \rightarrow \\
\text{EtO}_2\text{C} \quad \text{CN} \\
\text{CO}_2\text{Et} \\
348
\end{array}
\]

The deethoxycarbonylation of α-cyano ester 349 was accomplished by treatment with DMSO, water and NaCl (reflux, 20 h) to afford 350 (48%).\textsuperscript{190}

\[
\begin{array}{c}
\text{Ph} \quad \text{CN} \\
\text{O} \\
\text{CO}_2\text{Et} \\
349 \quad \rightarrow \\
\text{Ph} \quad \text{CN} \\
\text{O} \\
350
\end{array}
\]

Treatment of 351 with DMSO, LiCl (130°C, 5 h) led to 352 (75%).\textsuperscript{191}

\[
\begin{array}{c}
\text{OMe} \quad \text{CN} \\
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{CO}_2\text{Et} \\
351 \quad \rightarrow \\
\text{OMe} \quad \text{CN} \\
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{CO}_2\text{Et} \\
352
\end{array}
\]

Treatment of the diester 353 with DMSO, NaCl and water (140°C, 2.5 h) led to the deethoxycarbonylation of the ester group attached to the carbon holding the cyanide group to afford 354 (77%). The ester was subsequently converted into the corresponding pyrrolidone.\textsuperscript{192}

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{CN} \\
\text{CO}_2\text{Et} \\
353 \quad \rightarrow \\
\text{Ph} \quad \text{CO}_2\text{Et} \\
\text{CN}
\end{array}
\]

Treatment of 355 with DMSO, NaCl and H\textsubscript{2}O (160°C, 4 h) led to nitrile 356 (65%).\textsuperscript{193}

\[
\begin{array}{c}
\text{H}_2\text{C} \quad \text{CN} \\
\text{CO}_2\text{Et} \\
355 \quad \rightarrow \\
\text{H}_2\text{C} \quad \text{CN}
\end{array}
\]

Treatment of cyano ester 357 with DMSO, NaCl and H\textsubscript{2}O (160°C, 3 h) led to 358 (82%).\textsuperscript{194}
The decarbomethoxylations of 359a (64%ee) and 359b (96%ee) with DMSO, water and NaCl (reflux, 4 h) led to the enantioselective synthesis of 360a (74%) and 360b (80%), respectively.195

Homo- and copolymers of CNEVE 361 were deethoxycarbonylated by heating in DMSO in the presence of NaCl to yield poly(vinyl ethers) with 2-cyanoproxy side chains 362.196

Treatment of α-cyano ester 363 (89%ee) with DMSO, water and NaCl (130°C, 24 h) led to chemoselective removal of the carbomethoxyl group α to the cyano group to afford 364 (89%ee) without loss of stereochemistry.197

Analogue (2S, 4R)-365 on heating with DMSO, NaCN and water (140°C, 1 h) led to 366 (67%).198
The deethoxycarbonylation of nitrile ester 367 was accomplished using DMSO, LiCl and water (150°C, 1 h) to yield nitrile 368 (84%).

Treatment of the oxindole 369 with DMSO, NaCN and water (160°C, 2 h) led to 370 (80%) with decarbomethoxylation of the ester functionality and the N-CO₂Me group. This intermediate was converted into racemic physostigmine in a subsequent series of steps.

The lactonization of 371 to yield racemic 372 (70%, cis-trans fused ratio 4:1) was accomplished by heating in DMSO and water and additional NaCN (100°C, 0.5 h). In this case, lactonization is faster than the expected Krapcho demethoxycarbonylation.

The N-benzyl protected analogue 373 on treatment in DMF, LiCl and water (no experimental conditions) led to 374. This compound could readily be converted into the hexahydroazocino[4,5-b] indole on catalytic hydrogenation.
The α-cyano acid 375 on treatment with DMF and NaCl in water (125°C, 2.5 h) led to the decarboxylated product 376 (91%).

Treatment of the substituted cholesterol 377 with DMSO, LiCl and water (140°C, 20 h) led to the 7β-(2-cyanoethyl) analogue 378 (84%), the product of a de-t-butoxycarbonylation.

The deethoxycarbonylation of 379 with DMSO, NaCl and water (160°C, 2 h) led to nitrile 380 (91%).

In the preparation of 13C-labelled substrates, treatment of the phthalimido analogue 381 with DMSO, NaCl and water (no conditions or yield) led to 382.
In a route to the antibiotic anticapsin, the intermediate 384 (73%) was prepared by deethoxycarbonylation of racemic 383 with DMSO, LiCl, water (reflux, 6 h).\textsuperscript{207}

\[
\text{EtO}_2\text{C} - \text{CN} \xrightarrow{\text{OAc}} \text{CN} \]

Treatment of 385 with DMSO, NaCl and water (165°C) led to cyano ester 386 and cyanolactone 387 (72-78%, 1:1 ratio) with the removal of the t-butoxy group as well as deprotection of the MOM ether. This intermediate was converted into the AB ring system of sesbanamide.\textsuperscript{208}

\[
\text{CN} \quad \text{cyno ester} \quad \text{cyanolactone} \]

\textbf{2.9.3. From disubstituted substrates}

The pentafluoro \(\alpha\)-cyano ester 388 on treatment with DMSO and water (160°C, 120 h, or for shorter times in aqueous DMSO containing NaCl) led to nitrile 389 (78%).\textsuperscript{209}

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CN} \quad \text{CO}_2\text{Et} \xrightarrow{\text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F}} \text{Me} \quad \text{Me} \quad \text{CN} \quad \text{388} \quad \text{389} \]

Treatment of the cyano acid 390 with DMSO, LiCl and water (in the presence of NaHCO\textsubscript{3}) at 165°C for 4.5 h led to the decarboxylation to give the cyclopropane nitriles 391 and 392 as a 55:45 mixture (60%). These derivatives were used in the synthesis of the acid component of insecticidal pyrethoids.\textsuperscript{210}

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{H} \quad \text{CN} \xrightarrow{\text{H} \quad \text{H} \quad \text{Ph} \quad \text{Ph}} \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CN} \quad \text{390} \quad \text{391} \quad \text{392} \]
The demethoxycarbonylation of 393 with DMSO, LiCl (7 equivalents) and water (7 equivalents) in the presence of NaHCO₃ (2 equivalents) (165°C, 0.5 h) led to a 5:1 mixture of cis- and trans stereoisomers 394 and 395. The product isomer ratio was dependent on the molar equivalents of the reagents.²¹¹

\[
\text{Me}\text{MeCO}_2\text{Me} \quad \text{Me}\text{MeCO}_2\text{Me}
\]
\[
\text{H} \quad \text{H}
\]

The decarbomethoxylation of the cyano cyclobutane 396 with DMSO, NaCl and water (150°C, 4 h) led to a mixture of cis- and trans-isomers 397 (77%).²¹²

\[
\text{MeO}_2\text{C} \quad \text{CN}
\]
\[
\text{CN} \quad \text{CO}_2\text{Me}
\]

In the enantioselective synthesis of 11-keto steroids, treatment of a mixture of isomers 398 with DMF and LiI (140°C, 40 h) led to the demethoxycarbonylation product 399 (no yield recorded).²¹³

\[
\text{NC} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\]
\[
\text{MeO}_2\text{C} \quad \text{H}_2\text{C} \quad \text{O} \quad \text{O}
\]

The transannular Diels-Alder reaction and demethoxycarbonylation of macrocycle 400 yielded 401 as a diastereoisomeric mixture (89%) was accomplished by treatment with NaCN and DMSO (160°C, 8 h) followed by an aqueous workup.²¹⁴ Treatment of 402 with NaCN and DMSO (160°C, 8 h) followed by water gave 403 (97%).²¹⁴
The deethoxycarbonylation and aromatization of dihydrocarbazole 404 with DMSO, LiCl and water (100°C, 26 h) led to 405 (45%).

Treatment of α-cyano ester 406 with DMF, NaCN (160°C, 4 h) led to an epimeric racemic mixture of 407 and 408 (63%) in a 2:1 ratio.

The deethoxycarbonylation of 409 with HMPA, LiCl (160°C, 3 h) yielded 410 (85%).

Treatment of 411 with DMF and CaCl₂ dihydrate (160°C, 2.5 h) led to mixture of exo/endo (1:1) epimers 412 (79%) which were used in a route leading to an azadicarbaprostaglandin.
The deethoxycarbonylation of 413 (or the corresponding methyl ester) with DMSO, LiCl and H₂O (173°C, 4 h) led to 414 (78%).

\[
\begin{align*}
\text{413} & \quad \text{Ph} \quad \text{NC} \quad \text{CO}_2\text{Et} \\
\text{414} & \quad \text{Ph} \quad \text{CN} \quad \text{Ph}
\end{align*}
\]

The demethoxycarbonylation of methyl ester 415 (or the corresponding ethyl ester) with DMSO, LiCl and NaHCO₃ (165°C, 3 h) led to 1:1 mixture of the E- and Z-stereoisomeric nitriles 416 (75%), along with benzaldehyde (18%).

\[
\begin{align*}
\text{415} & \quad \text{Ph} \quad \text{H} \quad \text{CN} \quad \text{CO}_2\text{Me} \\
\text{416} & \quad \text{Ph} \quad \text{H} \quad \text{CN} \quad \text{H}
\end{align*}
\]

2.10. Sulfones
2.10.1. From α-sulfonyl esters
Treatment of sulfone 417 with DMSO, NaCl and water (reflux, 8h) led to the decarbomethoxylated product 418 (63%).

\[
\begin{align*}
\text{417} & \quad \text{CHSO}_2\text{Ph} \quad \text{MeO}_2\text{C} \\
\text{418} & \quad \text{CH}_2\text{SO}_2\text{Ph}
\end{align*}
\]

The 1,6-α-tolylsulfonyl ester 419 on treatment with DMSO and NaCl (170°C, 18 h) led to decarbomethoxylation product 420 (99%).

\[
\begin{align*}
\text{419} & \quad \text{Me} \quad \text{SO}_2\text{CO}_2\text{Me} \\
\text{420} & \quad \text{Me} \quad \text{SO}_2\text{H}
\end{align*}
\]
The α-carbomethoxy sulfone 421 on heating in DMSO, NaCl and water (160°C, 6 h) led to sulfone 422 (86%).

Without providing any experimental details, the demethoxycarbonylation of 423 was reported to afford a good yield of non-racemic 424, an intermediate to be used in the synthesis of additional chiral analogues.

2.11. Sulfoximines
2.11.1. From α-carbomethoxy sulfoximines
The demethoxycarbonylations of both enantiomers of 425 using DMSO and NaCN (120°C) led to the corresponding sulfoximine enantiomers 426.

The diastereoisomeric chiral mixture of 427 on treatment with DMSO, NaCN (80°C, 48 h) led to optically active 428 (80%) as a diastereoisomeric mixture.
2.12. Chiral phosphine oxides

2.12.1. From P-chiral phosphinyl acetates

One illustrative example of the preparation of chiral phosphine oxides involves the treatment of (+)-(R) \(429\) with DMSO, LiCl which led to (-)-(S) \(430\) (34% yield)\(^{226a,b}\).

\[
\begin{align*}
&\begin{array}{c}
\text{Ph} \\
\text{Et}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CO}_2\text{Me}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Et}
\end{array} \\
\text{P} \\
429 \\
\Rightarrow \\
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{CH}_3
\end{array}
\begin{array}{c}
\text{P} \\
\text{O}
\end{array}
\begin{array}{c}
\text{CH}_2\text{CO}_2\text{Me}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Et}
\end{array} \\
430
\end{align*}
\]

Treatment of \(\alpha\)-substituted (-)-(SP)-ethyl((menthoxycarbonyl)methyl)phenylphosphine oxides \(431\) with LiCl in aqueous DMSO (reflux, 8-18 h) led to the corresponding (-)-R\(_p\)-alkylethylphosphineoxides \(432\) in 54-70% yields in 100% enantiomeric purity\(^{227}\).

\[
\begin{align*}
&\begin{array}{c}
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{P} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{CO}_2\text{Men}
\end{array}
\begin{array}{c}
\text{Me}
\end{array} \\
431 \\
\Rightarrow \\
\begin{array}{c}
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{P} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{Me}
\end{array}
\begin{array}{c}
\text{R}
\end{array}
\begin{array}{c}
\text{Me}
\end{array} \\
432
\end{align*}
\]

\(R = \text{CD}_3, \text{CH}_3\text{CH}_2; \text{CH}_2=\text{CHCH}_2; \text{PhCH}_2\)

2.13. Ketophosphonates

2.13.1. From 2-acylphosphonoacetates

It has been reported that 2-acylphosphonoacetates such as \(433\) undergo deethoxy-carbonylations with water (oil bath, 120-140\(^\circ\)C, 2-3 h) to afford \(\beta\)-ketophosphonates such as \(434\) (70%). A number of other substrates were also evaluated\(^{228}\).

\[
\begin{align*}
&\begin{array}{c}
\text{MeO}
\end{array} \\
\begin{array}{c}
\text{P} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{MeO}
\end{array} \\
\begin{array}{c}
\text{CO}_2\text{Me}
\end{array} \\
\text{Me}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{P}
\end{array}
\begin{array}{c}
\text{MeO}
\end{array} \\
433 \\
\Rightarrow \\
\begin{array}{c}
\text{MeO}
\end{array} \\
\begin{array}{c}
\text{P} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{MeO}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{Me}
\end{array}
\begin{array}{c}
\text{O}
\end{array} \\
434
\end{align*}
\]

2.14. Nitro analogues

2.14.1. From \(\alpha\)-nitro esters

Only one example of a dealkoxycarbonylation of an \(\alpha\)-nitro ester could be found.

Treatment of \(\alpha\)-nitro ester \(435\) with DMSO, NaCl and water (150\(^\circ\)C, 4 h) led to deethoxycarbonylation to afford nitro derivative \(436\) (66%)\(^{229}\).

\[
\begin{align*}
&\begin{array}{c}
\text{O}_2\text{N}
\end{array} \\
\begin{array}{c}
\text{CO}_2\text{Et}
\end{array} \\
\begin{array}{c}
\text{Cl}
\end{array} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{NH}_2
\end{array} \\
435 \\
\Rightarrow \\
\begin{array}{c}
\text{O}_2\text{N}
\end{array} \\
\begin{array}{c}
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{NH}_2
\end{array} \\
436
\end{align*}
\]
2.15. 2-Cyclohexenone derivatives
2.15.1. From 4-carbalkoxy-2-cyclohexanones
The chemoselective deethoxycarbonylation of the keto diester \( \text{437} \) on treatment with DMSO, LiCl and water (180-190°C, 5 h) led to \( \text{438} \) (70%).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{O} \quad \text{EtO}_2\text{C} \\
\text{Me} & \quad \text{CO}_2\text{Et} \\
\text{437} & \quad \text{438}
\end{align*}
\]

Upon heating \( \text{439} \) in DMSO, NaCl and water (140°C, 10 h, sealed tube), \( \text{440} \) (19%) was obtained, the product of a demethoxycarbonylation and a demethoxylation. This yield (40%) was improved with the use of MgCl\(_2\). The mesylate (OMs instead of OMe in \( \text{439} \), \( \alpha \)-position to the ester group) under the MgCl\(_2\)-DMSO conditions led to \( \text{440} \) (89%). This intermediate was used in a synthesis of \( \text{Erythrina} \) and related alkaloids.

\[
\begin{align*}
\text{MeO} & \quad \text{N} \quad \text{O} \quad \text{Si} \quad \text{O} \\
\text{MeO} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{439} & \quad \text{440}
\end{align*}
\]

2.16. Heterocyclic vinylogous deethoxycarbonylation
The deethoxycarbonylation of the heterocyclic susbstrate \( \text{441} \) to afford \( \text{442} \) (32%) was accomplished by treatment with DMSO, NaCl and water (145°C, 6 h).

\[
\begin{align*}
\text{Me} & \quad \text{Si} \quad \text{O} \quad \text{O} \\
\text{Me} & \quad \text{Me} \quad \text{Si} \quad \text{O} \\
\text{441} & \quad \text{442}
\end{align*}
\]

2.17. Tetra-demethoxycarbonylation
Treatment of 443 with DMSO, NaCl and water (140°C, 4 h) led to 444 (quantitatively). A rational mechanism is proposed.233

\[
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{HO} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me}
\end{array} \quad \text{443}
\]
\[
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array} \quad \text{444}
\]

3. Conclusions

Dealkoxycarbonylations of a wide variety of substrates have been accomplished using NaCN, NaCl or LiCl and water in dipolar aprotic solvents such as DMSO and DMF. This procedure will continue to be useful in the dealkoxycarbonylations of activated ester functionalities.

4. References

A. Paul Krapcho was born in Alden Station, PA on March 6, 1932. He did his undergraduate work at Penn State (B.S. in Chemistry, 1953) and graduate studies at Harvard University (Ph.D. 1957). He then spent the 2-year period of 1957-1959 teaching at Smith College and then held a post-doctoral position at Penn State from 1959-1960 (with Phil Skell). In 1960 he joined the faculty at the University of Vermont, where he is currently an Emeritus Professor of Chemistry still active in research. He has directed the research of numerous undergraduate and graduate students in projects related to natural product synthesis, solvolytic studies of spiro analogues, reaction mechanism studies of metal-ammonia reductions, chemistry of carbenes (or carbenoids), reactions of $\alpha$-anions of acids and esters, and the preparation of anticancer heterocyclic analogues. Krapcho has been a Fulbright scholar at the University of Montpellier, France (1968-1969), a research scholar at Stanford University (1976-1977) and an invited lecturer at Addis Ababa University in Ethiopia (1981). He was a research scholar at Duke University (1983-1984), the University research scholar in Physical Sciences (1990), a visiting Professor at the University of Auckland Medical School in Auckland, New Zealand (Spring 1991) and, for a short period, at Humboldt University in Berlin, Germany (1998). He has been involved over the past 15 years in a collaborative anticancer drug development program initially with the Vermont Cancer Center, and then with Novuspharma SpA of Milan, Italy (recently merged with CTI) and the University of Padova, Padova, Italy. These projects deal with the synthesis of telomerase inhibitors. Recently (2005-present) he was awarded a Dreyfus Senior Scientist Mentor grant. Krapcho is a Scientific Editor for ARKIVOC (2000-present) and a Co-Editor-in-Chief of Mini-Reviews in Medicinal Chemistry (2001-present).