# Recent synthetic applications of the dealkoxycarbonylation reaction. Part 1. Dealkoxycarbonylations of malonate esters

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**Abstract**
The purpose of this review is to update (publications from 1981 to mid 2006) the synthetic applications of dealkoxycarbonylations of malonate esters, β-keto esters (and related esters with α-substituted electron-withdrawing functionalities) induced by heating with water or with water in the presence of salts (such as NaCN, NaCl or LiCl) in dipolar aprotic solvents. The presentation will be divided in two parts. In Part 1, discussion will focus on the dealkoxycarbonylations of malonate esters. Part 2 (to follow as a separate paper) will deal with the dealkoxycarbonylations of β-keto esters and α-cyano esters (and related analogues).

**Keywords:** Dealkoxycarbonylations, Krapcho, decarbalkoxylations, malonate esters

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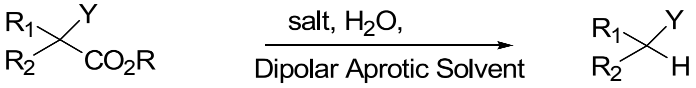
## Contents

## 1. Introduction

Activated esters, which include such substrates as malonates, β-ketoesters and α-cyanoesters, are of considerable importance in organic synthesis. We have reported in a number a publications that these substrates (and other activated analogues) undergo dealkoxycarbonylations on being heated in dipolar aprotic solvents (such as DMSO or DMF) in the presence of water, or in some substrates with water in the presence of added salts (such as NaCN, NaCl or LiCl) to yield the corresponding esters, ketones and nitriles. This procedure is facile, avoids harsh acidic and alkaline conditions and tolerates many protecting groups. In addition, this methodology is much more convenient than the classical procedures for accomplishing these transformations.



Y = COOR, COR, CN, $NO_2$, $SO_2R$

This overall process is a formal loss of $CO_2R$ and protonation of the intermediate carbanion ( a dealkoxycarbonylation or a decarbalkoxylation).

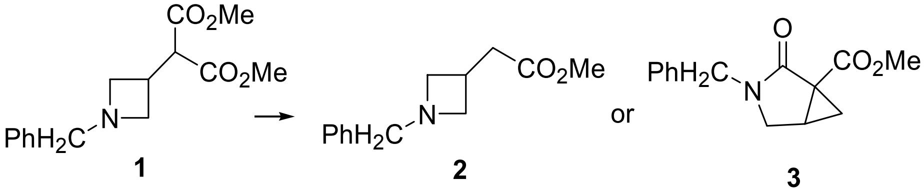
Two previous reviews of the synthetic applications of this methodology and mechanistic considerations were published in 1982.[1,2] Subsequently, this procedure has been referred to as the Krapcho reaction or the Krapcho dealkoxycarbonylation.[3-8]

A recent check of the Science Citation Index Expanded (1982 to mid 2006) indicated about 1100 citations to the papers published by the Krapcho group dealing with the dealkoxycarbonylation procedure. The goal of the present review is to update the literature on the more recent strategies of this methodology in synthesis. Because of the large numbers of published papers, the author is going to be somewhat selective in the illustrative synthetic examples chosen from the literature.

## 2. Mechanistic Considerations

Mechanistically, the dealkoxycarbonylation constitutes an ester hydrolysis followed by decarboxylation and subsequent protonation of a carbanion species or a concerted dealkylative decarboxylation followed by protonation of the incipient carbanion. The mechanism is clearly dependent on whether the substrate is heated in the dipolar aprotic solvent with water or water in the presence of salts. Some mechanism details have been discussed in the prior review.[1] The overall mechanistic pathway is dependent on the substrate structure and the reaction conditions.[3-9]

The cleavages of the aziridinyl malonate **1** have been studied using NaCN or NaCl in aqueous DMSO. In the case of NaCN in DMSO and water ( 110°C, 6 h), the product was **2** (49%). In the use of DMSO, NaCl and water (150°C, 2 h), the product was **3** (31%). A mechanistic rationalization possibly involving N-participation is proposed.[10]



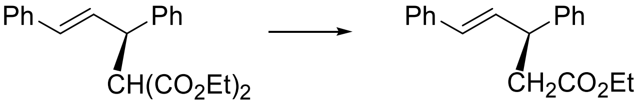
## 3. Esters

### 3.1. From mono substituted malonate esters

### 3.1.1. Water alone

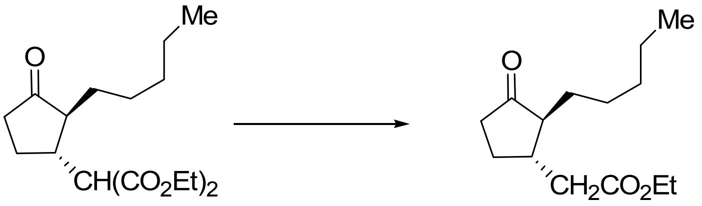
As noted in our previous review,[1] the dealkoxycarbonylations of a number of mono substituted malonates can be accomplished by heating in a dipolar aprotic solvent such as DMF or DMSO with added water to yield the corresponding mono esters. Additional examples of this methodology continue to be reported.

The diester **4**-(R) on heating in DMSO and water (170°C, 13 h) yielded the monoester **5**-(S) (80%).[11]



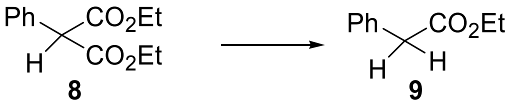
**4**-(R) **5**-(S)

The keto diester (+)-**6** on being heated in wet DMSO (190°C, 5 h) underwent decarbomethoxylation to afford the keto ester (+)-**7** (60%). In a similar manner the (-) diester enantiomer could be converted into the (-) ester.[12]



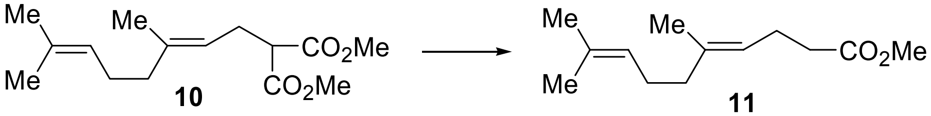
(+)-**6** (+)-**7**

The dealkoxycarbonylations of malonic esters have been performed using microwave irradiation under solvent free solid-liquid phase transfer conditions. For example treatment of **8** with LiBr and water, LiBr, water and a PTC agent such as Aliquat 336, or $NBu_4Br$ and water under microwave conditions (10 min at 30 W) led to the deethoxycarbonylated product **9** in 70%, 85% and 96% yields, respectively.[13a,b]

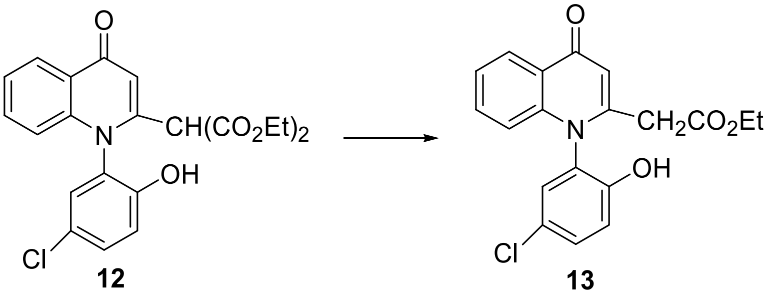


**8** **9**

The dealkoxycarbonylations of several mono-substituted malonates have been shown to proceed in wet DMF under microwave conditions. For example, the conversion of diester **10** to ester **11** (84%) was accomplished at 160°C for 20 min.[14]



The deethoxycarbonylation of **12** in HMPA and water (120°C, 2.5 h) afforded **13** (94%).[15]

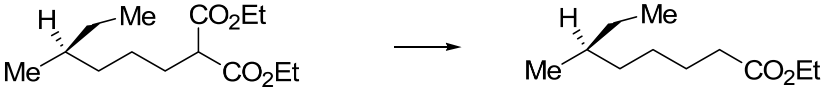


**12** **13**

### 3.1.2. Water – salts

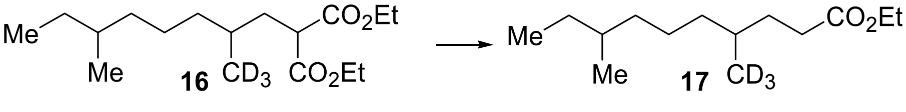
The dealkoxycarbonylations of a wide variety of substituted malonate esters have been reported using DMSO or DMF, water and salts such as NaCl, LiCl and NaCN. Numerous protective groups in the substrate are tolerated under the reaction conditions. The reactions are roughly classified according to the structure of the substituents.

**3.1.2.1. From alkyl, alkenyl, alkynyl and allenic malonate esters.** The diester 14-(S) on treatment with DMSO, NaCl and water (155°C, 48 h) led to ester **15-**(S) (89%), along with a small amount (6%) of the corresponding acid.[16]



**14-(S)** **15-(S)**

To ascertain the isotope effect on pheromonal activity, the aggregation pheromone of the red flour beetle, deuterated analogues of 4,8-dimethyldecanal were synthesized. Treatment of **16** with DMSO, LiCl and water (reflux, 48 h) led to the deuterated analogue **17** (53%) which was subsequently transformed into 4-trideuteriomethyl-8-methyldecanal .[17]

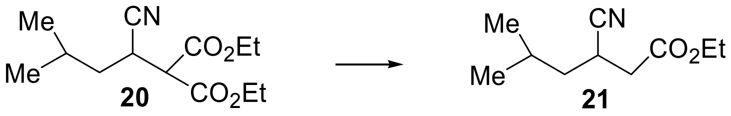


The deethoxycarbonylations of carbon-14 labelled malonate esters **18a** and **18b** can be readily accomplished on treatment with LiBr, Aliquat 336 and water under microwave irradiation (200°C, 10 min) to afford **19a** and **19b**, respectively. The synthesis of **19a** (60%) and **19b** (57%) could also be accomplished in a one-pot route based on a solvent –free alkylation of the carbon-14 labeled diethyl malonate followed by a microwave activated deethoxycarbonylation in the presence of LiBr, Aliquat 336 and water.[18]

$$\underset{\mathbf{18}}{R^{14}CH(CO_2Et)_2} \longrightarrow \underset{\mathbf{19}}{R^{14}CH_2CO_2Et}$$

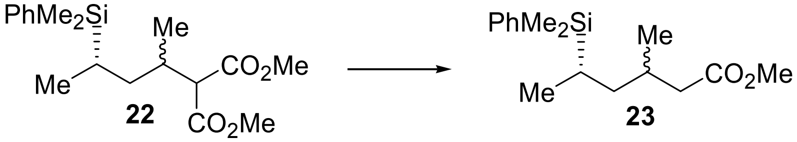
a, $R = C_{10}H_{21}$ b, $R = C_{18}H_{37}$

Treatment of racemic **20** (51.3 kg) with DMSO, NaCl and water (137-148°C, 8.5 h) led to the β-cyano ester **21** (86%). This substrate was evaluated as an intermediate in the synthesis of the anticonvulsant (S)-3(aminomethyl)-5-methylhexanoic acid.[19]



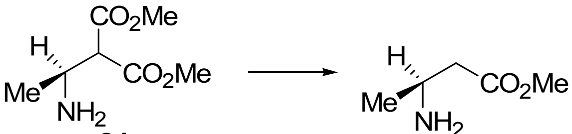
**20** **21**

A number of C-silylated malonate esters have been demethoxycarbonylated using DMSO, NaCl and water ( reflux, 24 h). A typical example is the conversion of a mixture of **22** [β-Me (85%) and α-Me (15%)] into **23** [β-Me(85%) and α-Me (15%)] in an overall 81% yield.[20]



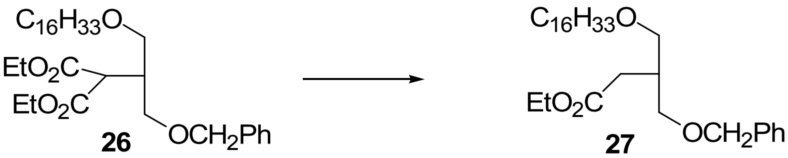
**22** **23**

The demethoxycarbonylation of **24·HCl** with DMSO, NaCl and water (reflux, 2 h) led to (S)-3-aminobutyrate (**25)** [86%> 95% ee], which was readily converted into the simple chiral β-lactam (95% ee).[21]



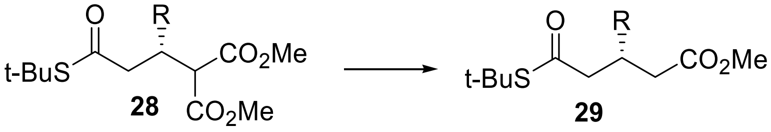
**24** **25**

Racemic **26** was converted into racemic **27** on treatment with tetrabutyl ammonium acetate in dry DMSO (100°C, heat). This procedure gave better yields than heating in DMSO with NaCl and water.[22]



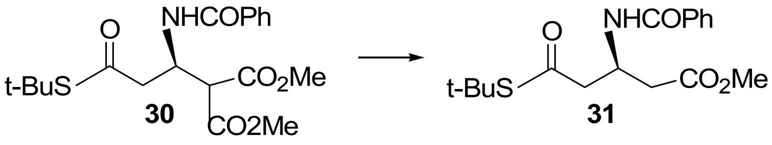
**26** **27**

The Michael adducts **28** upon heating in DMSO, NaCl and water (130°C, 24 h) led to the (3S)-substituted *tert*-butyl butanethioates **29**, chiral differentiated glutarate esters.[23]

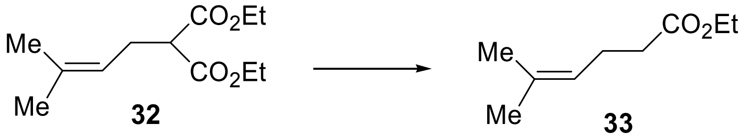


R = Ph, Cyclohexyl, i-Pr, Me (67-86%)

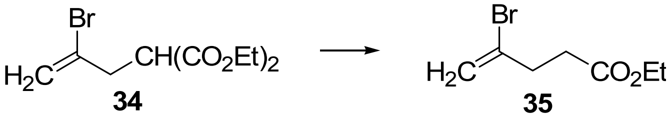
Treatment of **30** (40%ee) with DMSO and water (150°C, 20 h) led to the thio ester **31** (65%, 64%ee). This could be converted into chiral (R)-methyl 3-(benzoylamino)butanoate.[24]



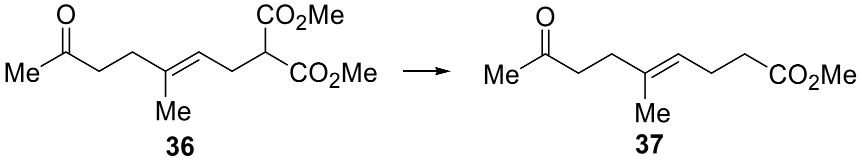
Treatment of **32** with DMSO, LiCl and water (reflux, 5 h) yielded **33** (95%).[25]



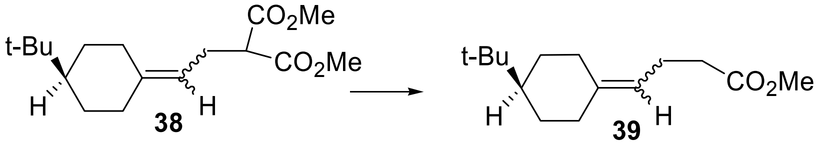
The bromo allyl diester **34** on heating in DMSO, NaCl and water (reflux, 8 h) led to the bromo monoester **35** (67%).[26]



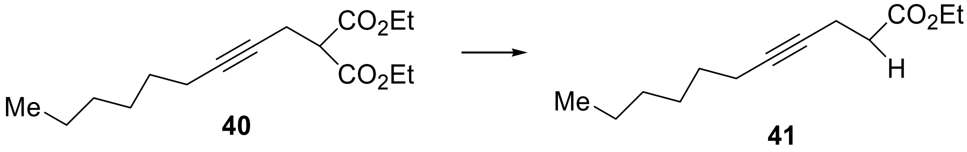
The decarbomethoxylation of **36** with DMSO, LiCl and water (130-160°C, 6 h) led to the keto ester **37** (65%).[27]



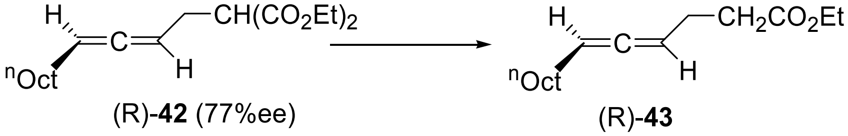
The demethoxycarbonylation of optically active **38** with NaCN and LiI in DMF (128°C, 16 h) led to optically active **39** (64%).[28a,b]



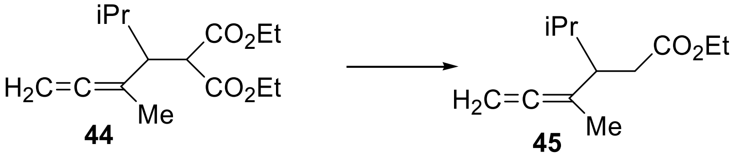
The deethoxycarbonylation of **40** with DMSO, NaCl and water (170-180°C, 8 h) led to **41** (60%), which was used in the synthesis of the sex pheromone of the rice green caterpillar.[29]



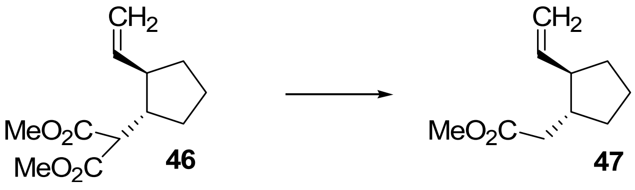
Treatment of (R)-**42** with a mixture of LiI and NaCN in DMF (120°C, 6 h) or NaCl and water in DMSO (130°C, 8 h) led to demethoxycarbonylation with partial racemization of the allenic axial chirality to afford (R)-**43** (82%, 54%ee) or (R)-**43** (35%, 69%ee), respectively.[30]



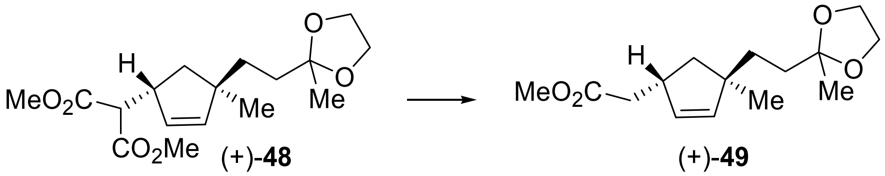
The deethoxycarbonylation of **44** with DMSO and NaCN (160°C, 4 h) afforded **45** (40%).[31]



**3.1.2.2. From 2-cycloalkyl and 2-cycloalkenyl malonic esters.** The racemic starting material **46** on treatment with DMSO, NaCl, water (160°C, 36 h) yielded **47** (40%).[32]

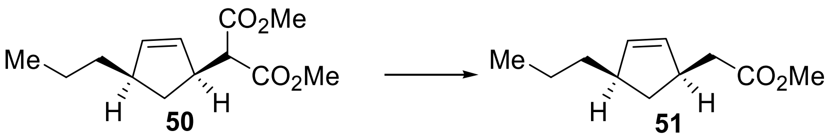


Treatment of (+) **48** with DMSO, NaCl and water (reflux, 1 h) led to (+)-**49** (92%) which was then transformed into the unnatural enantiomer (+)-$\Delta^{9(12)}$-capnellene.[33]



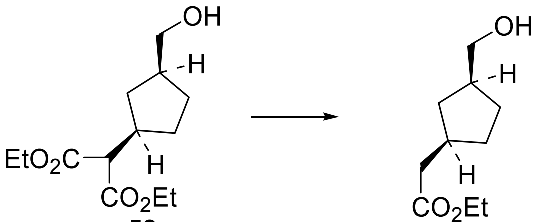
(+)-**48** (+)-**49**

The demethoxycarbonylation of (-)-(1S,4S) **50** with DMSO, LiCl and water (150°C, 4 h) led to **51**(1R,4R). The enantiomer (1R,4R) also led to the corresponding (1S,4S) enantiomer. These esters were used in a synthesis of compounds to assess the bioactive conformations and chiral recognition of a moth sex pheromone.[34]



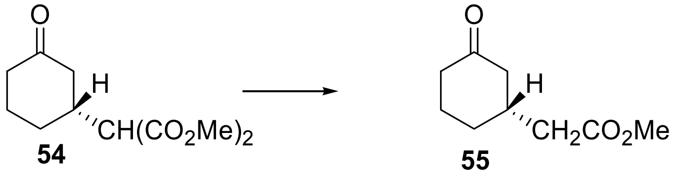
**50** **51**

Treatment of racemic **52** with DMSO, LiCl and water (178°C, 4.3 h) led to racemic **53** (69%).[35]



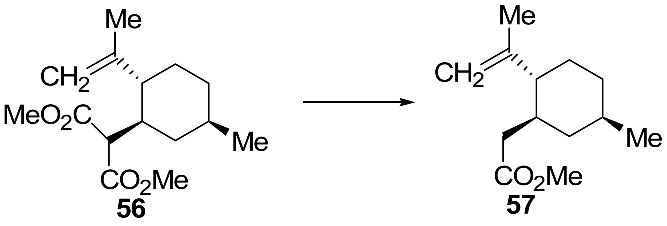
**52** **53**

The decarbomethoxylation of (R)-diester **54** using $LiI \cdot 3H_2O$ in DMSO (25 min, 180°C) led to (R)-**55** (52%). This intermediate was subsequently converted into (1R,4S,6S)-6-hydroxybicyclo[2.2.2]octan-one.[36]

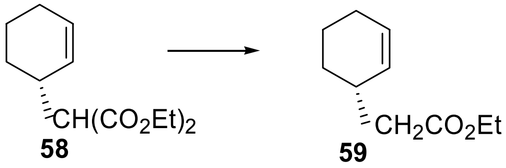


**54** **55**

Treatment of enantiomer **56** with DMSO, NaCl and water (150°C, 4 h) led to the decarbomethoxylated enantiomer **57** (92%). This intemediate was converted into the chiral cadinane-sesquiterpene veticadinol.[37]

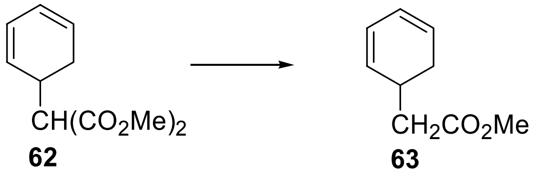


The demethoxycarbonylation of R-(+)-**58** in DMSO, NaCl and water (160°C, 24 h) led to S-(+)-**59** (74%).[38a] Racemic **58** on treatment with DMSO, LiCl and water (170°C, 24h) gave racemic **59** (61%).[38b] Similar conditions using DMSO, LiCl, and water had been previously reported (190°C, 6 h) for the conversion to the racemic mono ester **59** (84%).[38c] Also racemic **58** with DMSO, NaCl and water (170°C, 10 h) led to **59** (88%) which was converted into a substituted alanine analogue.[38d]

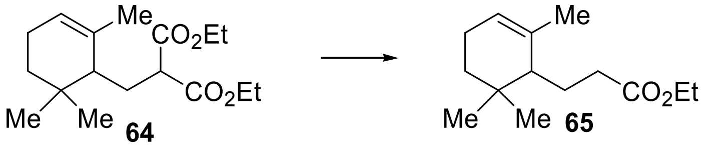


The demethoxycarbonylation of (S)-**60** in DMSO, NaCN and water (60°C, 48 h) afforded (R)-**61 (**80%).[39]

Treatment of **62** with DMSO, NaCN and water ( 110°C, 24 h) led to racemic **63** (62%).[40]

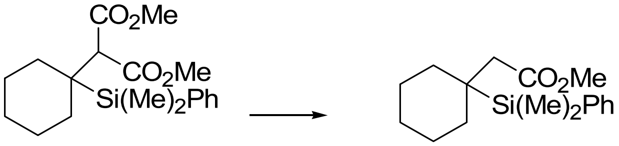


The deethoxycarbonylation of diester **64** with DMSO, NaCl and water (reflux, 22 h) led to racemic **65** (81%).[41]



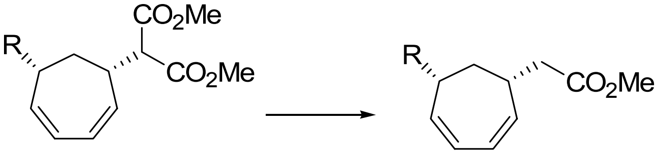
**64** **65**

The demethoxycarbonylation of **66** in DMSO, LiCl and water (reflux, 45 min) led to **67** (90%), an intermediate useful in studies to evaluate the application of silicon-containing compounds in synthesis.[42]



**66** **67**

Treatment of **68a** or **68b** with DMSO, NaCN and water (70°C, 36 h) led to **69a** (70%) or **69b** (60%), respectively. The lower temperature was necessary to avoid extensive rearrangements of the double bonds.[43]



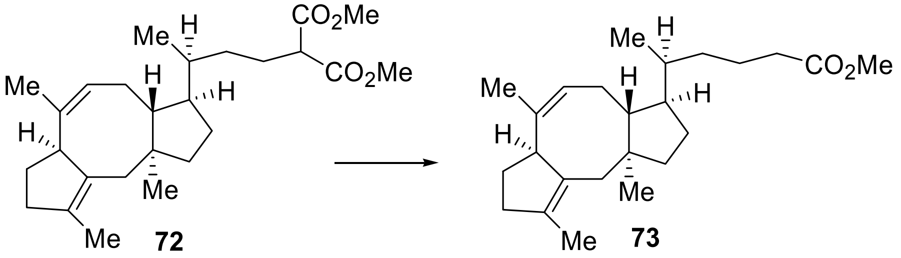
**68** **69**

a, R = H; b, R = Me

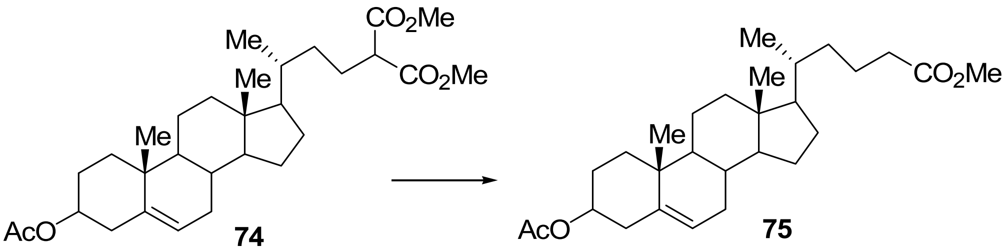
A mixture of the enantiomer **70** in DMSO, LiCl and water (160°C, 3 h) led to enantiomer **71** (87%).[44]

**70** **71**

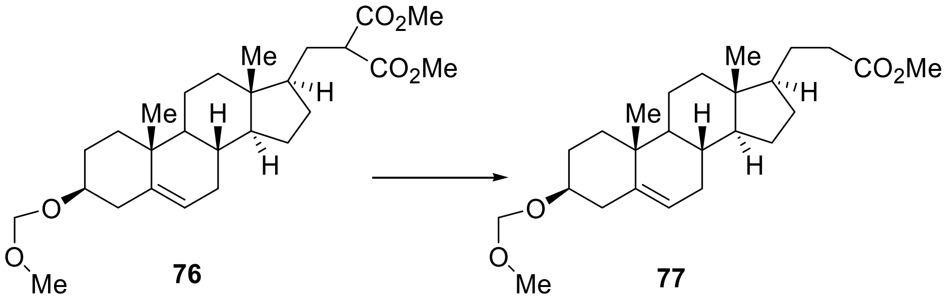
The demethoxycarbonylation of optically active **72** using NaCN in DMSO (no experimental details) led to **73** which was used in a total synthesis of optically active sesquiterpenes albolic acid and ceroplastol II, which have been found in the wax secretions of a scale insect.[45]



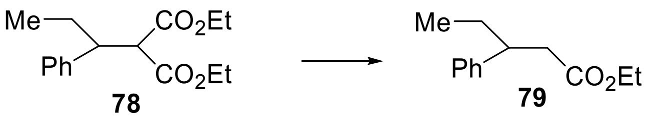
In a multi-gram scale up, treatment of **74** with DMSO, NaCl and water (170-180°C, 2.5 h) led to **75** (80%).[46]



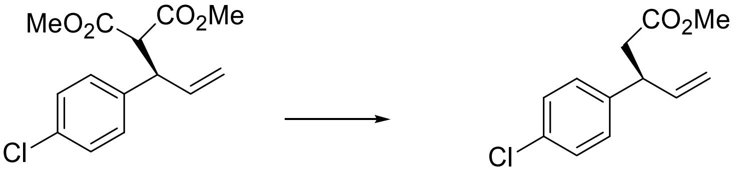
Treatment of enantiomer **76** with DMSO and NaCN ( heat , 6 h) led to enantiomer **77** (57%).[47]



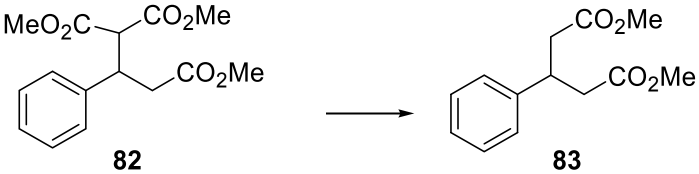
**3.1.2.3. From aryl substituted malonate esters.** The enantioselective conjugate addition of diethyl zinc with chiral phosphorus ligands to alkylidene malonates led to 3-ethyl substituted malonate esters. For example, the deethoxycarbonylation of **78** with DMSO, LiCl and water (160°C, 15 h) led to (R)-**79** (quantitative, 64% ee).[48]



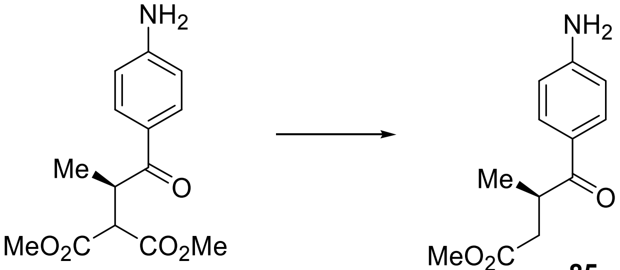
The decarbomethoxylation of (R)-**80** with DMSO, NaCl and $H_2O$ ( 200°C, 20 min) in a microwave cavity led to (S)-**81** (80%).[49]


(R)-**80** (S)-**81**

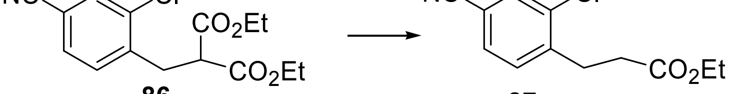
The demethoxycarbonylation of **82** ( no conditions listed) led to **83**. Other substituted analogues were also reported.[50]


**82** **83**

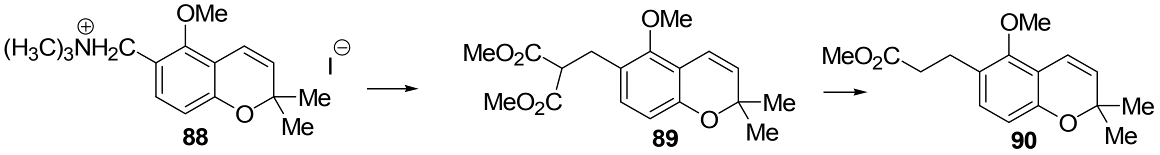
The demethoxycarbonylation of **84** (86%ee) was accomplished by using DMSO, NaCl and an aqueous phosphate buffer (170°C, 2.75 h) to afford **85** (38%, with no significant loss of enantiomeric purity), which was used as an intermediate for the preparation of cardiotonic agents.[51]


**84** **85**

Treatment of **86** with DMSO, NaCl and water (135-170°C, 3 h) led to **87** (84%). This was converted into a hapten for the radioimmunoassay of bupropion (a non tricyclc antidepressant).[52]

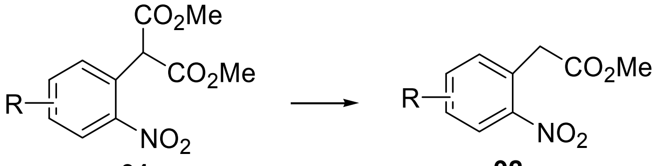

**86** **87**

The quaternary salt **88** and diethyl malonate (DMF, $K_2CO_3$, 156°, 39 h) led to **90** (70-75%). Shorter reaction times led to **89** , which on demethoxycarbonylation in the presence of KI led to **90**. This compound has been isolated from the roots of an endemic Guyana tree.[53]



**88** **89** **90**

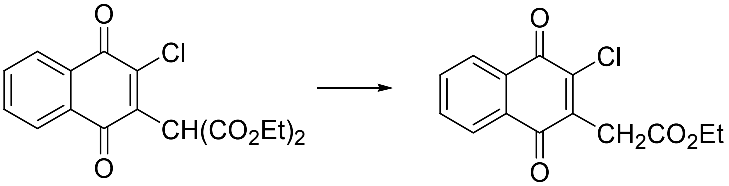
The demethoxycarbonylations of **91a-f** on treatment with DMSO, LiCl and $H_2O$ (100°C, 3 h) led to the respective esters **92a-f** (56-86%). [54]



**91** **92**

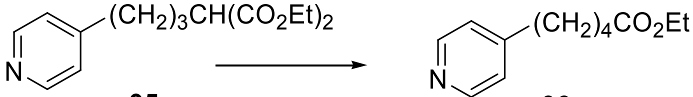
a, R = 5-Cl; b, R = 4-Cl; c, R = OMe;
d, R = 4-Br; e, R = 4-F; f, R = 6-Cl

The deethoxycarbonylation of **93** with DMSO, NaCl and water (110°C, 3 h) led to the quinone **94** (83%). [55]



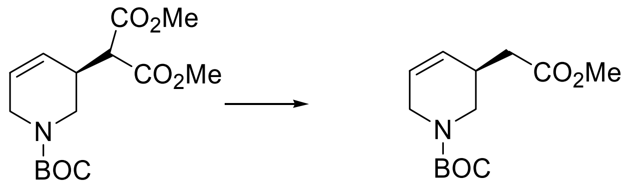
**93** **94**

**3.1.2.4. From 2-heterocyclic substituted malonic esters.** The deethoxycarbonylation of **95** using DMSO, NaCl and water led **96** (96%).[56]



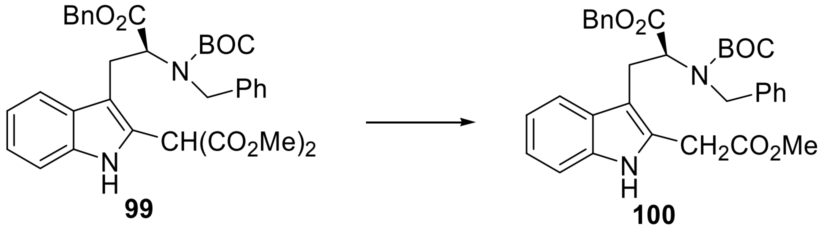
**95** **96**

Diester (-)-**97** (98%ee) on treatment with DMSO, NaCl and water(120°C, 16 h) led to (-)-(R)-**98** (58%).[57]

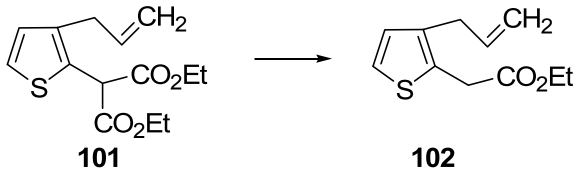


**97** **98**

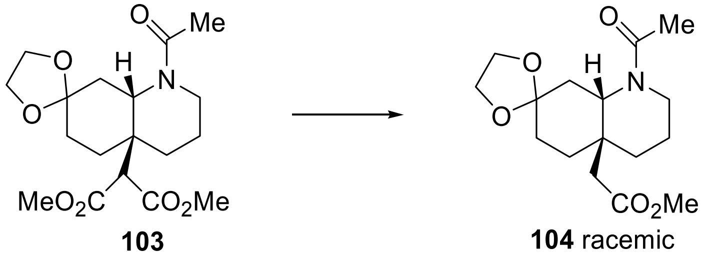
Upon treating the substituted indole **99** with DMF, LiCl, $Et_3N.HCl$ (130°C, 4 h), the demethoxycarbonylated indole **100** was obtained (85%). The N-BOC and benzyl ester functionalities were not affected. This intermediate was subsequentially converted to a tetracyclic ABCE Strychnos alkaloid precursor in an enantioselective manner. [58]



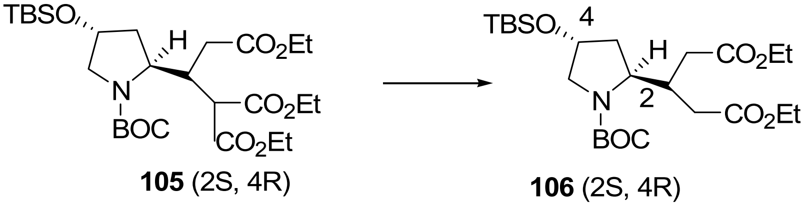
The synthesis of a 2-allyl substituted thiophene **102** (80%) was accomplished by treatment of the diester **101** with DMSO, NaCl and water (150-155°C, 8 h). [59]



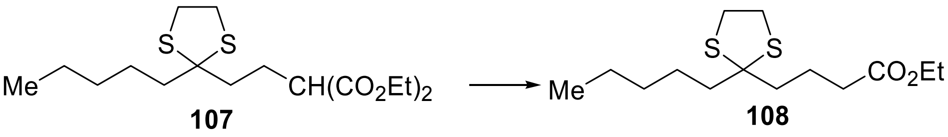
The decarbomethoxylation of racemic **103** with DMSO, NaCN and water (118°C, 3 h) led to monoester **104** (79%). [60]



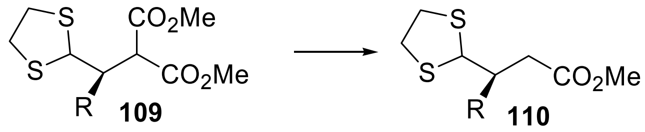
The decarboethoxylation of the pyrrolidine **105** (2S, 4R) with DMSO, NaCl and water (160°C, 1 h) led to **106** (2S, 4R) [88% for 2 steps which involve a prior Michael addition] in which the protective silyl and BOC groups remained intact. This intermediate was converted into the desired lactam in two steps.[61a,b]



The dithioketal **107** on treatment with DMSO, NaCl and water (155-160°C, 4 h) led to corresponding ester **108** with the dithio ketal functionality intact. This intermediate, in a series of subsequent steps, was converted into the δ-dioxo analogues.[62]

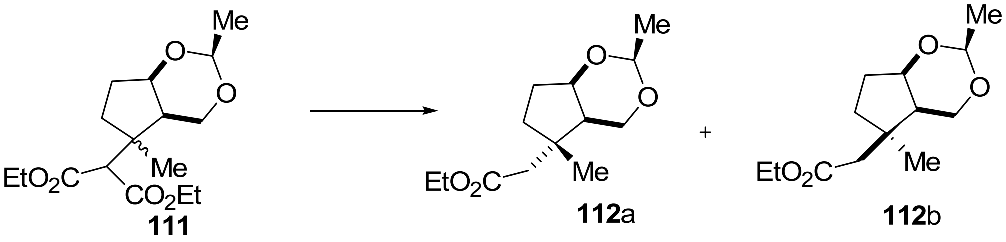


The demethoxycarbonylations of optically pure diesters **109a,b,c** in DMSO, NaCl and water (150°C, 2-3 h) afforded the respective asymmetric succinic semialdehyde derivatives **110a,b,c** (63-81%).[63]

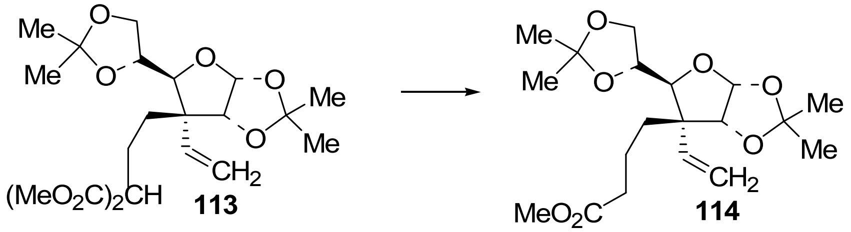


a, R = $(CH_2)_2Ph$: b, R = p-$NO_2C_6H_4$,; c, R = biphenyl

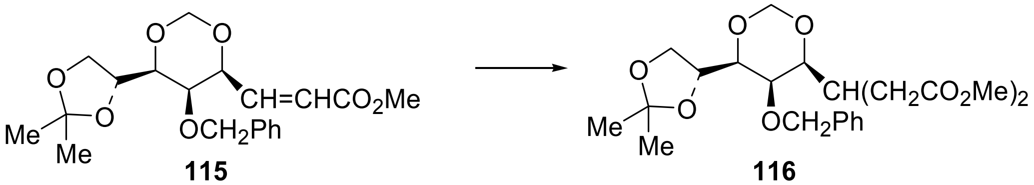
Treatment of diastereoisomers **111** with DMSO, LiCl and water (190°C, 5 h) led to **112**a and **112**b (65%, ratio 2.2:1) which were separated by chromatography. Compound **112**a, in a series of steps, was converted into dolabellane skeleton.[64]



The demethoxycarbonylation of diester **113** with DMSO, NaCl and water (160°C, 24 h) led to enantiomer **114** (75%). In a subsequent series of steps this intermediate was converted into the insect sex attractants (-)-anastrephin and (-)-epianastrephin.[65]

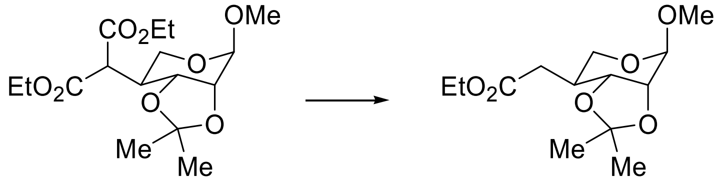


The Michael addition of the anion to **115** followed by demethoxycarbonylation using DMSO, NaCl and water (no conditions reported) led to enantiomeric **116** (55% for the two steps). This intermediate was used in an enantiospecific synthesis of sesbanimide.[66]



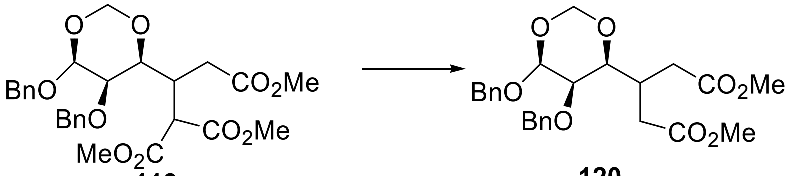
**115** **116**

The deethoxycarbonylation of **117** using DMSO, LiCl and water (reflux, 2 h) afforded **118** (quantitatively).[67]



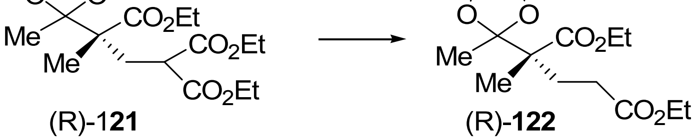
**117** **118**

The demethoxycarbonylation of **119** using DMSO, NaCl and water (160°, 1 h) led to optically active **120** (89%) which was used in a synthesis of (+)-sebanimide and (-)-sebanamide, antitumor alkaloids from the seeds of a leguminous plant.[68]



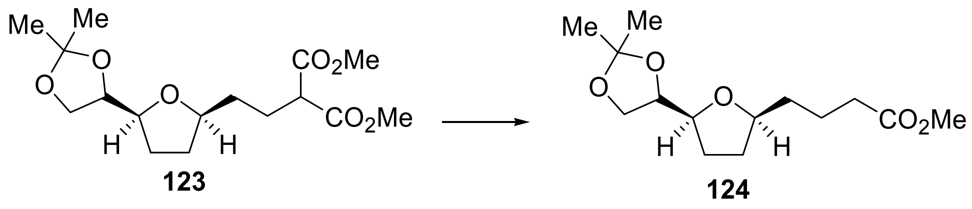
**119** **120**

The ketal (R)-**121** on treatment with DMSO, NaCN and water (160°C, 6 h) led to (R)-**122** (72%).[69]

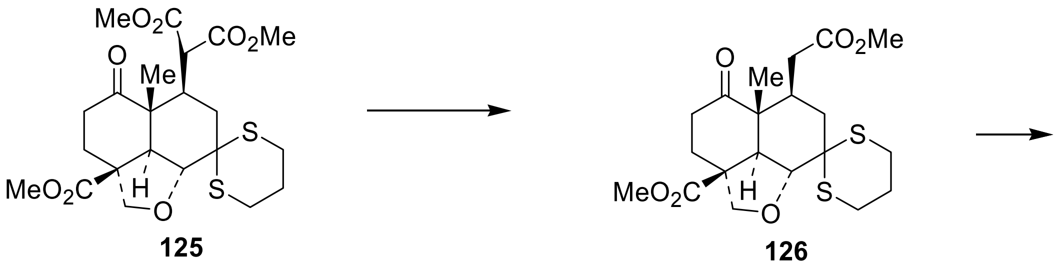


(R)-1**21** (R)-**122**

The decarbomethoxylation of **123** using DMSO, NaCN and water (115°C, 2 h) led to racemic mono ester **124** (90%), which was then converted into a dihydrofuran analogue of leukotriene $A_4$.[70]

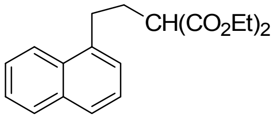
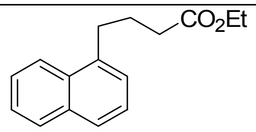
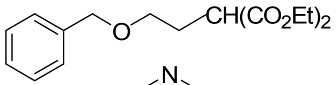
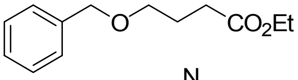
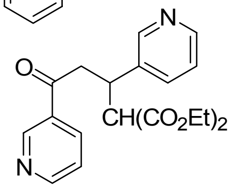
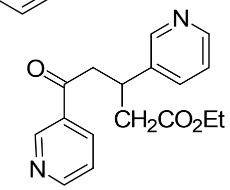
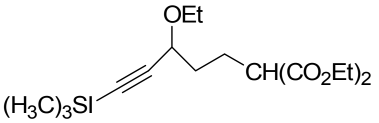
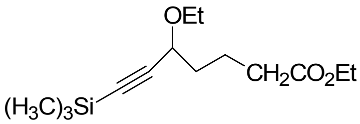
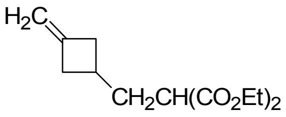
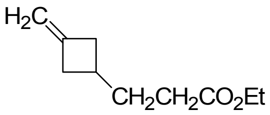
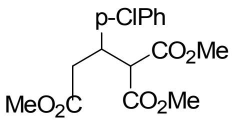
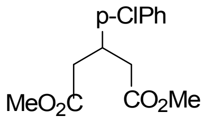


Treatment of **125** with DMSO, NaCl and water (160°C, 4 h) led to racemic **126** (91%).[71]



Some additional illustrative examples are tabulated in Table 1.

**Table 1.** Dealkoxycarbonylations of monosubstituted malonate esters

| Starting material | Conditions | Product | Yield(%) | Ref |
|---|---|---|---|---|
|  | DMSO, $H_2O$<br>200°C, 5 h |  | 75 | 72 |
|  | DMSO, LiCl,$H_2O$<br>140°-170°C, 5 h |  | 95 | 73 |
|  | DMSO,NaCl, $H_2O$<br>160°, 6 h |  | 80 | 74 |
|  | DMSO, LiCl, $H_2O$<br>150°C, 15 h |  | 55 | 75 |
|  | DMSO, NaCl, $H_2O$<br>140°C |  | 65 | 76 |
|  | DMSO, NaCl, $H_2O$<br>160°C, |  | 79 | 77 |

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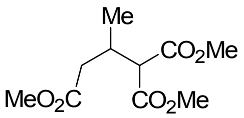
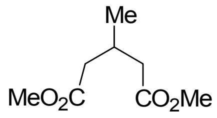
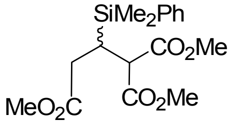
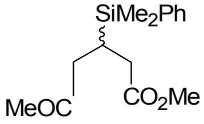
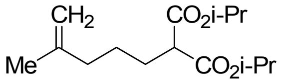
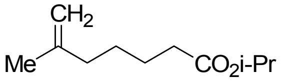
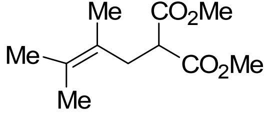
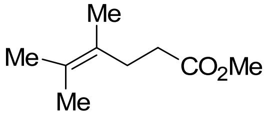
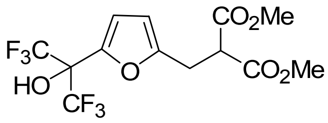
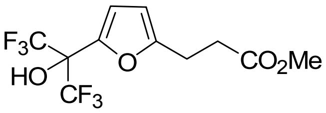
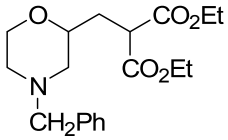
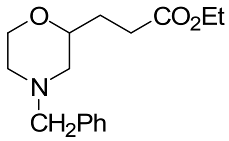
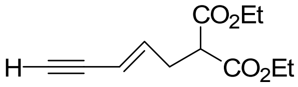
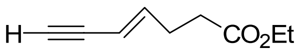
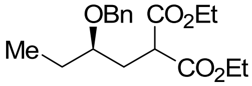
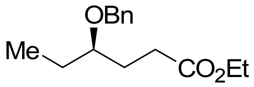
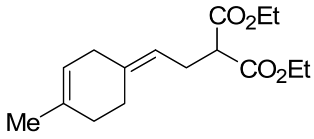
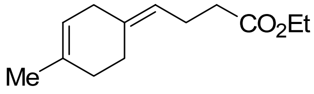
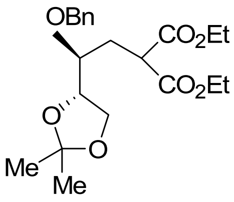
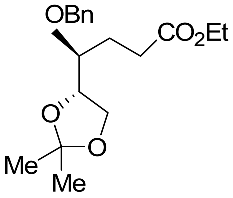
|---|---|---|---|---|
|  | DMSO, NaCl, $H_2O$<br>reflux, 4 h |  | 93 | 78 |
|  | DMSO,NaCl, $H_2O$<br>160$^{o}$C, 2,5 h |  | 97 | 79 |
|  | DMSO, LiCl, $H_2O$<br>150-180$^{o}$, 10 h |  | 60 | 80 |
|  | DMSO, NaCl, $H_2O$<br>!70$^{o}$C, 4.5 h |  | 80 | 81 |
|  | DMF, LiCl, $H_2O$<br>160-165$^{o}$C, 4 h |  | 48 | 82 |
|  | DMF, NaCl, $H_2O$<br>reflux, 23 h |  | 98 | 83 |
|  | DMSO, NaCN<br>120$^{o}$C, 3 h |  | quant | 84 |
|  | DMSO, LiCl, $H_2O$<br>140$^{o}$C, 4 h |  | 74 | 85 |
|  | DMSO, NaCl, $H_2O$<br>160-165$^{o}$C, 8 h |  | 84 | 86 |
|  | DMSO, NaCl, $H_2O$<br>180$^{o}$C |  | 87 | 87 |

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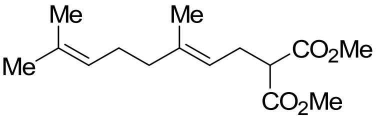
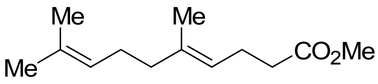
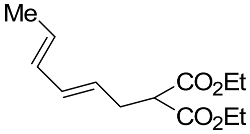
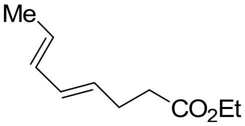
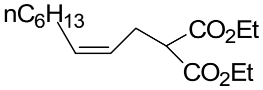
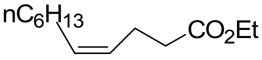
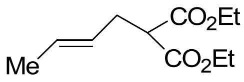
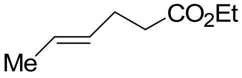
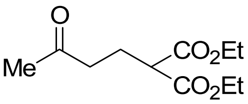
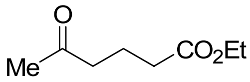
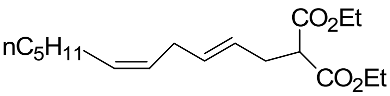
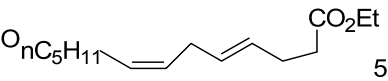
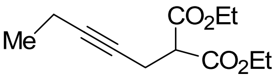
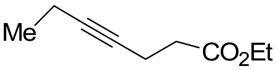
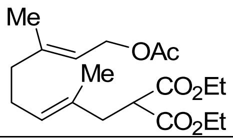
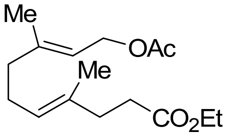
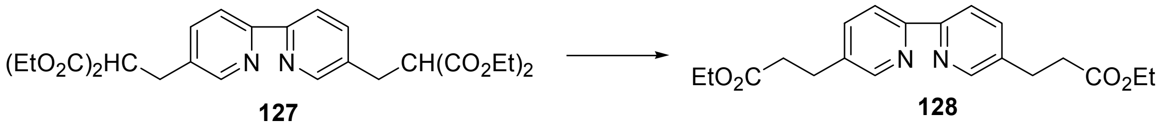
|---|---|---|---|---|
|  | DMSO, NaCl, $H_2O$<br>reflux, 3 h | 4S, 5S<br> | 72 | 88 |
|  | DMSO, NaCN<br>$120^{o}$C, 3 h |  | 75 | 89 |
|  | DMSO, NaCl, $H_2O$<br>140-$145^{o}$C, 8 h |  | 78 | 90 |
|  | DMSO, NaCl, $H_2O$<br>$180^{o}$C |  | 90 | 91 |
|  | DMSO, NaCl, $H_2O$<br>$145^{o}$C, 8 h |  | 80 | 92 |
|  | DMSO, NaCl, $H_2O$<br>$180^{o}$, 8 h |  | 58 | 93 |
|  | DMSO, NaCl, $H_2O$<br>$180^{o}$, 8 h |  | 65 | 94 |
|  | DMSO, NaCl,<br>water<br>160, 7 h |  | 68 | 95 |

## 4. Diesters

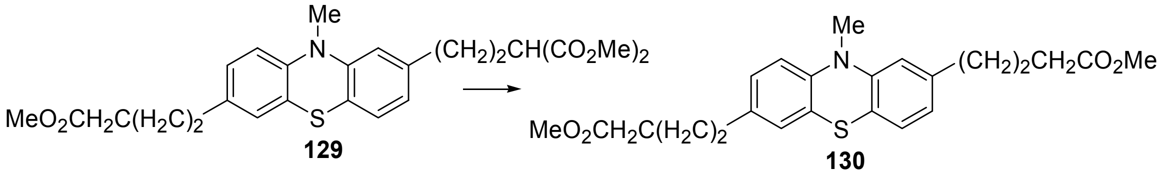
### 4.1. From substrates with two malonate ester functionalities

The substituted 2,2-bipyridine **127** underwent bis-deethoxycarbonylation on heating in DMSO, NaCl and water (reflux, 2.5 h, exclusion of light) to afford the bis-carboethoxyl ethyl substituted 2,2-bipyridine **128** (84%).[96]



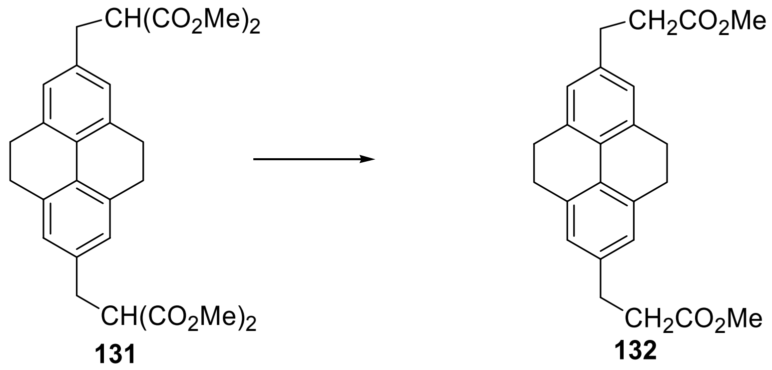
**127** **128**

The bis-demethoxycarbonylation of the substituted N-methylphenothiazine **129** on treatment with DMI (1,3-dimethylimidazolidin-2-one), tetramethyl ammonium acetate and water (140°C, 10 h) led to **130** (80%). These molecules were utilized in a synthesis of phenothiazine-bipyridinium cyclophanes.[97]



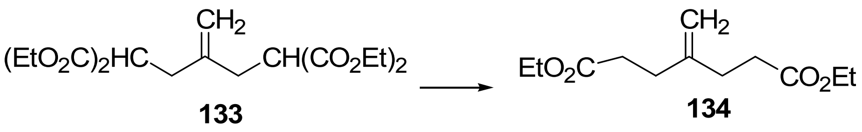
**129** **130**

In routes to pyrenophanes, the bis-demethoxylcarbonylation of **131** was accomplished on heating in DMSO, NaCl and water (160-170°C, 3 h) to yield **132** (59%).[98]



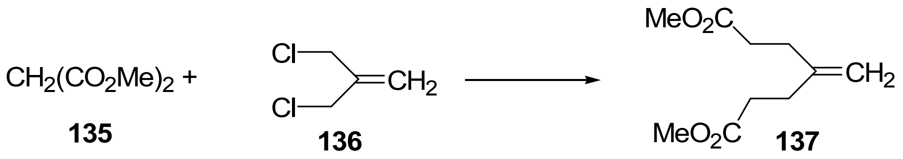
**131** **132**

Treatment of tetra ester **133** with DMSO, LiCl and water (no conditions given) led to diester **134** (35%) which was used in a synthesis of [3.3.1]propellane-2,8-dione.[99]



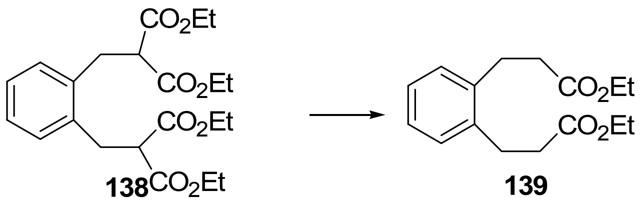
**133** **134**

Treatment of a mixture of KOH, dimethyl malonate (**135**) and chloromethallyl chloride (**136**) in DMF (150°C, 0.5 h) led to dimethyl 4-methylenepimelate (**137**, 88%), the process involving a bis-demethoxycarbonylation.[100]



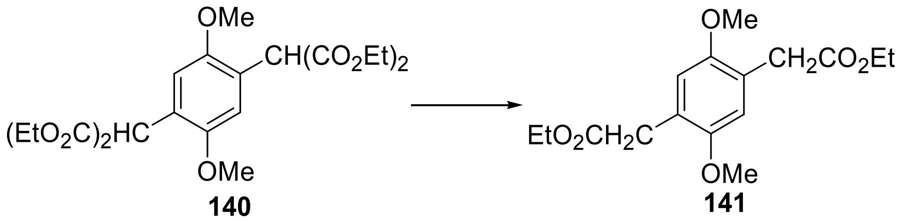
**135** **136** **137**

The conversion of the tetra ester **138** to the diester **139** (91%) can be accomplished by treatment with DMSO, LiCl and water (reflux, 4 h).[101]



**138** **139**

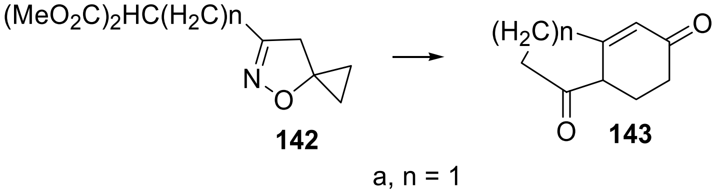
The bis-deethoxycarbonylation of **140** with DMSO, NaCl, water ( reflux, 4 h) led to the diester **141** (79%).[102]



**140** **141**

## 5. Demethoxycarbonylation - rearrangement

Treatment of **142a** (n = 1) with DMF, NaCl and water (reflux, 6 h) led to the rearranged product 1,2,5,6-tetrahydroindolizine-3,7-dione (**143a**, n = 1, 33%). Under similar conditions **142b** (n = 2) led to 3,4,6,7,8,9-hexahydro-2H-quinolizine-2,6-dione (**143b**, n = 2, 44%).[103a] Additional examples and mechanistic considerations are reported in several later publications.[103b,c]



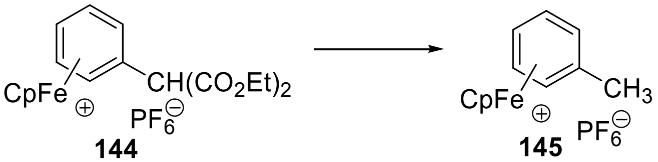
**142** **143**

a, n = 1
b, n = 2

## 6. Aryl methyl susbstituted benzenes

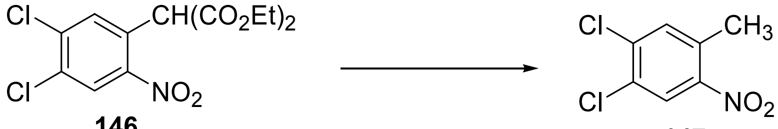
### 6.1. From bis-dealkoxycarbonylations

Treatment of **144** with DMSO, water and NaCl (160°C, 5 h) led to a double dealkoxycarbonylation to afford **145**.[104]



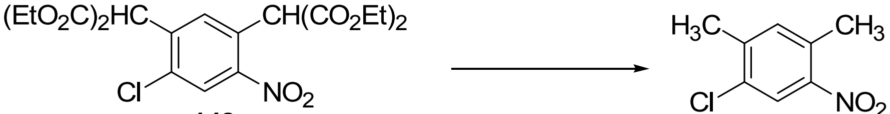
**144** **145**

A number of aryl esters, readily available by $S_NAr$ substitution of 2-fluoro- or -2-chloro nitrobenzene by the anion of diethyl malonate, undergo bis-deethoxycarbonylations to afford 2-methyl nitro benzenes. Treatment of **146** in DMSO, NaCl, water (160-170°C, 12 h) afforded **147** (35%) with a higher yield of **147** (77%) reported when using $MgCl_2.6H_2O$.[105a]



**146** **147**

The analogue **148** undergoes a tetra–deethoxycarbonylation to afford **149 (**60%) on treatment with $MgCl_2{\cdot}H_2O$ in DMA (reflux, 7 h).[105a,b]



**148** **149**

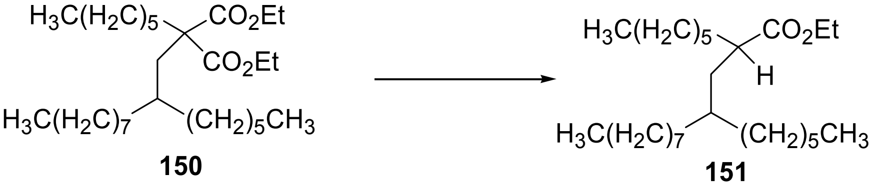
## 7. Esters

### 7.1. From disubstituted malonate esters

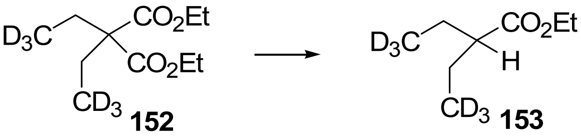
The dealkoxycarbonylations are arranged on the basis of the two types of substituents attached to the malonate ester moiety.

#### 7.1.2. Bis-alkyl

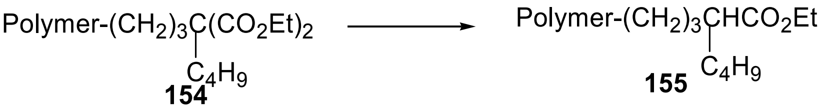
The deethoxycarbonylation of diester **150** with DMSO, LiCl and water (reflux, 4 h) led to **151** (73%), a derivative for use in a study of hydrocarbon type dielectric fluids.[106]


**150** **151**

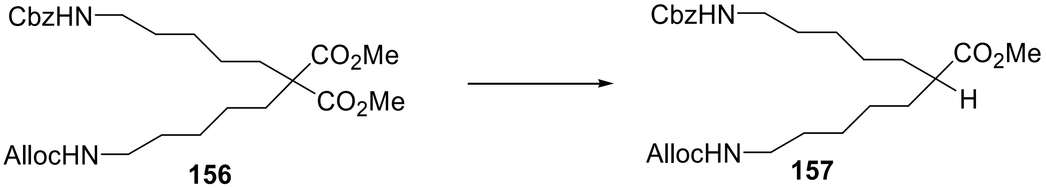
The synthesis of the deuterated ester **153** (90-95%) was accomplished by heating **152** in DMSO, LiCl and water (reflux, 12 h).[107]


**152** **153**

The quantitative deethoxycarbonylation of C,C-disubstituted malonates such as **154** supported on polystyrene can be accomplished by heating the polymer with NaI and anhydrous DMSO at 100°C to afford **155**. Calcium chloride in DMSO or NaI in nitromethane were also found to be useful for the deethoxycarbonylations.[108]

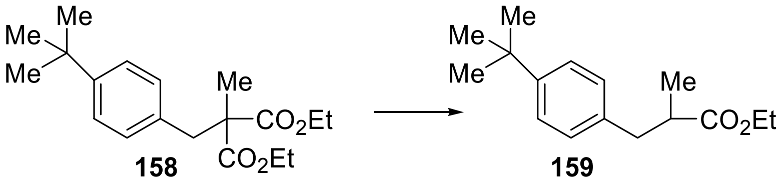

$$\text{Polymer-}(CH_2)_3\underset{C_4H_9}{C}(CO_2Et)_2 \longrightarrow \text{Polymer-}(CH_2)_3\underset{C_4H_9}{C}HCO_2Et$$
**154** **155**

Compound **156,** on solution in DMSO, LiCl and water (160°C, 4 h), led to the decarbomethoxylated product (S)-**157** (66%) with retention of the Cbz and Alloc amino protecting groups.[109]

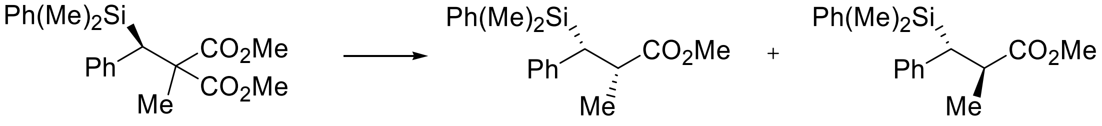

**156** **157**

### 7.1.3. Alkyl - benzylic

The diester **158** on heating with DMSO, NaCN (160-170°C, 4.5 h) afforded **159** (85%).[110]


**158** **159**

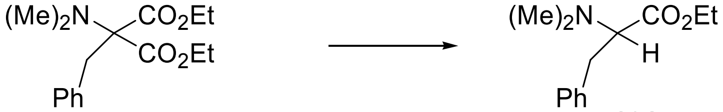
The β-silylated malonate ester **160** on treatment with DMSO, LiCl and water (reflux, 25 min) led to **161** and **162** (68%) as a 70:30 mixture.[111]



**160** 28 **161** **162**

### 7.1.4. Dimethylamino-benzyl

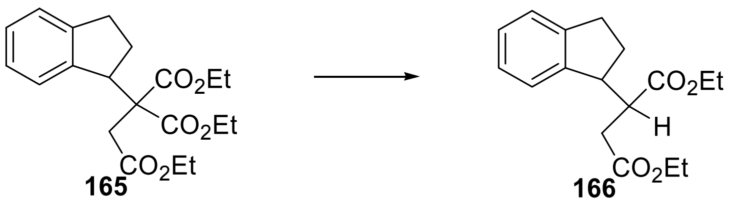
Without the benefit of any reactions conditions, it was noted that treatment of **163** with DMSO and NaCN cleanly afforded **164**.[112]



**163** **164**

### 7.1.5. Indanyl-carboethoxymethylene

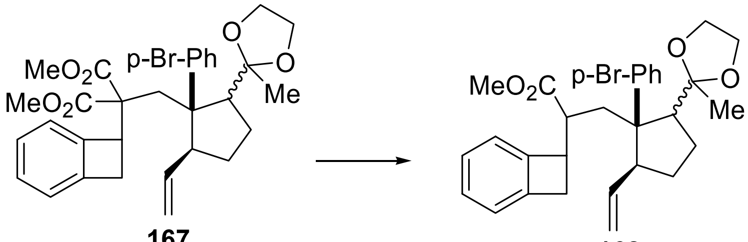
The triester **165** on heating in DMSO, NaCl and water (178-183°C, 6 h) led to **166** (85%).[113]



**165** **166**

### 7.1.6. Benzocyclobutane substituted cyclopentane

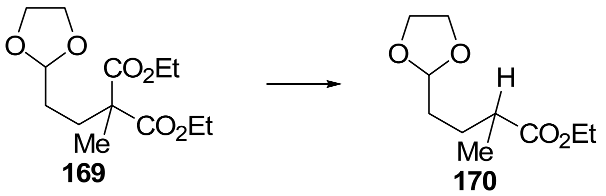
Treatment of diester **167** in DMSO, NaCN and water (90°C, 19 h) led to mono ester **168** (78%) as an inseparable mixture of isomers.[114a] Several other related analogues were also dealkoxycarbonylated under similar conditions.[114b,c]



**167** **168**

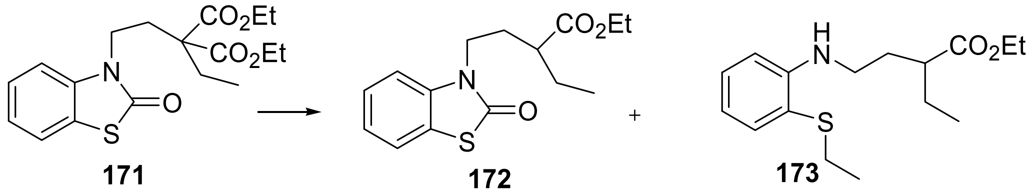
### 7.1.7. Alkyl-heterocyclic

The deethoxycarbonylation of **169** with DMSO, LiCl and water (reflux, 3 h) yielded **170** (83%) which was used in a synthesis of an indoloquinolizidine.[115]



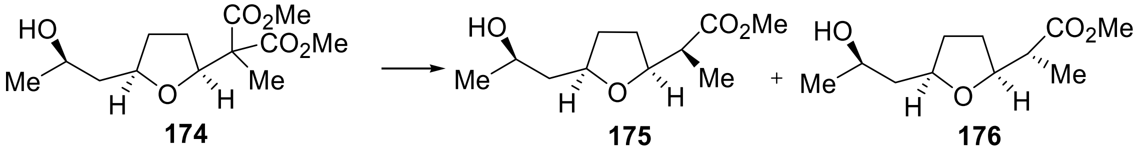
**169** **170**

During the decarbomethoxylation of the benzothiazolone **171** in DMSO, KCN and water (reflux, 12 h), the expected product **172** (75%) along with the ring-opened 2-alkylsulfanyl aniline **173** (25%) were isolated.[116]



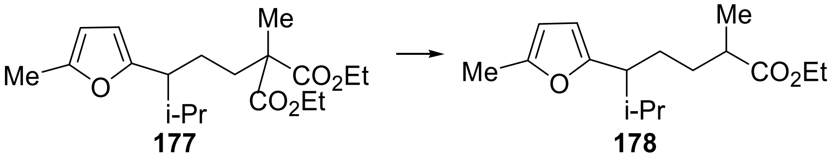
**171** **172** **173**

Methyl nonactate (+)-**175** and 2-epi-methyl nonactate (-)-**176** (overall yield 78% in a 1:1 ratio and separated by chromatography) were prepared by heating diester **174** in DMSO with NaCl and water (reflux, 3 h).[117]



**174** **175** **176**

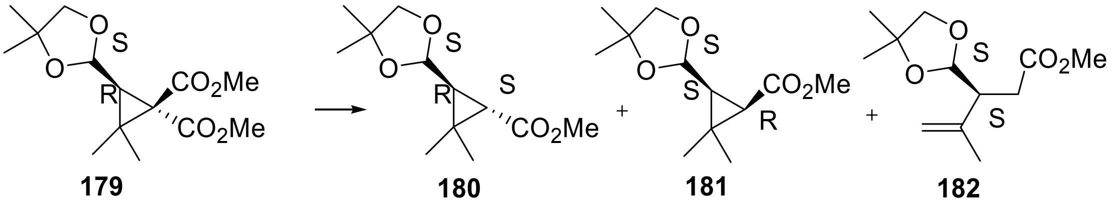
The deethoxycarbonylation of **177** was accomplished using DMSO, LiCl and water (180°C, 4 h) to afford **178** (81%).[118]



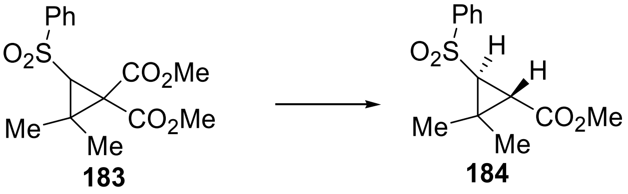
**177** **178**

### 7.1.8. Cycloalkyl-1,1-dicarboxylic esters

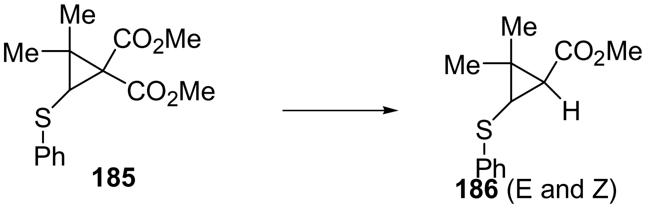
The demethoxycarbonylation of the cyclopropane-1,1-dicarboxylic acid methyl ester (**179**) has been studied under several different conditions. With DMSO, NaCl and water (160°C, 6 h) the three products **180, 181** and **182** were obtained in 73% yield with the trans/cis/ ring opening ratio of 27/21/52. With NaCN in aqueous DMF (120°C, 48 h) total yield was 88% with the ratios of 50/34/16. In the use of tetramethyl ammonium acetate in HMPA (95°C, 4 h, 90% yield) with the ratio being 70/30/0 with no ring opened product.[119]



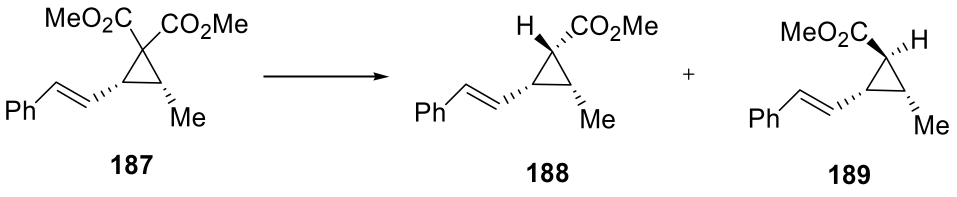
The dealkoxylcarbonylations of several sulfur- and alkoxy substituted cyclopropane derivatives have been evaluated. The demethoxycarbonylation of alkylthio or aryl thio analogues led to esters as an isomeric mixture with the trans isomers in a large excess, where as in the sulfonyl analogues the dealkoxycarbonylations were diasteroselective and led exclusively to the trans-derivatives. For example, the sulfonyl analogue **183** on treatment with DMSO, NaCl and water (reflux, 4 h) led to trans-**184**.[120a,b,c]



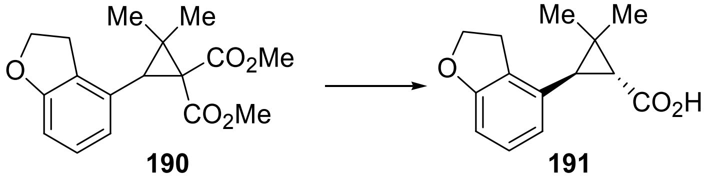
Treatment of **185** with DMSO, NaCl and water (reflux) led to **186** (80%, isomeric mixture).[121]



In a synthesis leading to 1,2,3-trisubstituted cyclopropanes, the demethoxycarbonylations of several isomeric cyclopropanes have been evaluated. Treatment of **187** with DMSO, LiCl and water (195°C, 2 h) led to **188** (2R,3S,E) and **189** (96%) in a 1:1 product ratio which could be separated by chromatography.[122]

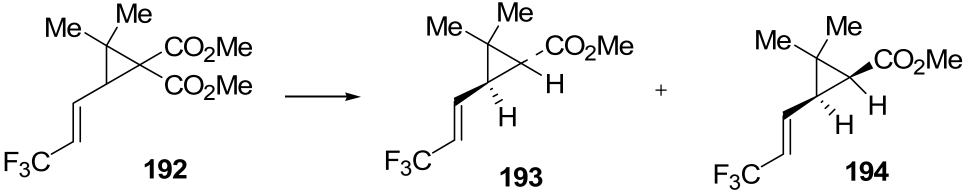


The diester **190** on treatment with DMSO and NaCN (150°C, 23 h) led to racemic **191** (15%, 9:1 trans:cis) which could be crystallized to obtain pure trans product. This was resolved to give enantiomerically pure **191** (1R,3R). This was converted into a cyclopropyl guanidine for evalution of of its activity against the sodium hydrogen exchanger isoform-I.[123]



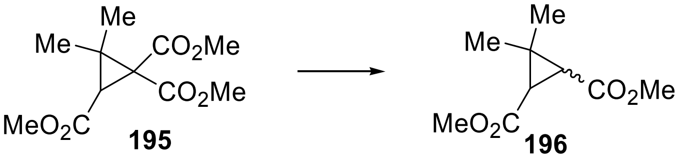
**190** **191**

Treatment of **192** with DMSO and NaCN (160°C, 1.5 h) led to the demethoxycarbonylated products **193** and **194** (47%, 1:1 ratio).[124]



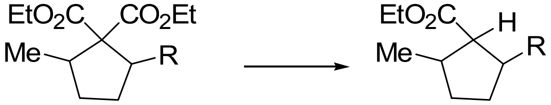
**192** **193** **194**

Treatment of **195** in DMF, NaCl and water led to methyl caronate **196** (high yield) which could be converted into chrysanthemates.[125]



**195** **196**

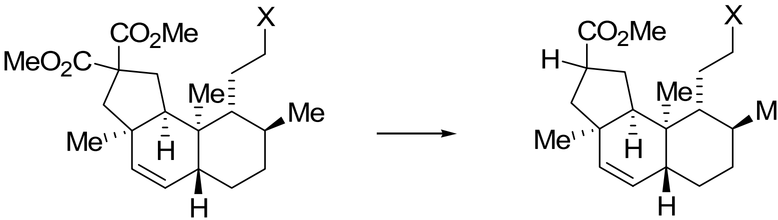
Treatment of **197a** or **197b** with DMSO, LiCl and water (190°C, overnight) afforded mono ester **198a** (80%) or **198b** (78%), respectively.[126]



**197** **198**

a, R = H; b, R = Me

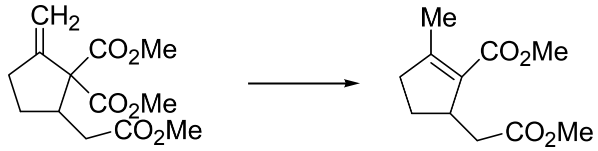
In a route to the total synthesis of kempane diterpenes, the intermediate racemic diesters **199a** and **199b** underwent demethoxycarbonylation on treatment with DMF, NaCN, and water (120°C, 5 h) to afford the mono esters **200a** (85%) and **200b** (81%), respectively.[127]



**199** **200**

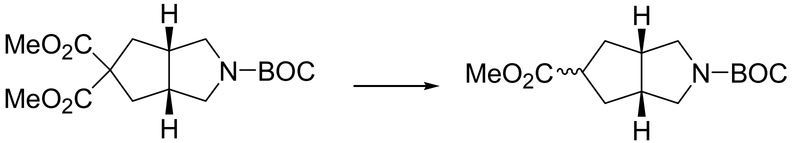
a, X = CH=CH$_2$; b, X = CH$_2$OH

The demethoxycarbonylation of racemate **201** using DMSO, LiCl and water (130°C) led to the product **202**, with rearrangement of the double bond (90%).[128]



**201** **202**

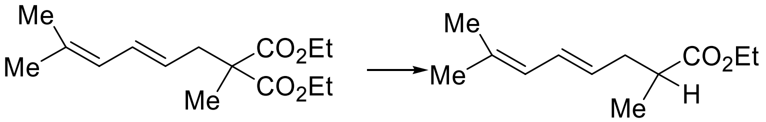
Treatment of **203** with DMSO and NaCN (160°C) led to **204** (63%) which was converted into azanoradamantyl amine in a subsequent series of steps.[129]



**203** **204**

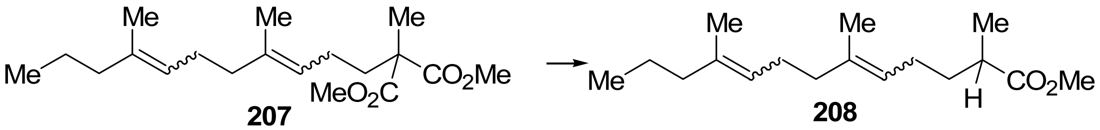
### 7.1.9. Alkyl–alkenyl

The diester **205** on treatment with DMSO, NaCN and water (170°C, 5 h) led to **206** (82%), an intermediate used in the synthesis of furanoid terpenes.[130]



**205** **206**

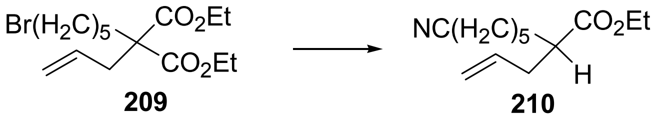
Treatment of **207** with DMSO, NaCl and water (190°C, 12 h) led to **208** (85%). This intemediate was converted into methyl 2,6,10-trimethyltridecanoate, a male-produced pheromone of several stink bugs.[131]



**207** **208**

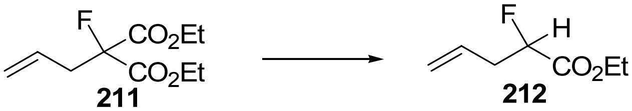
### 7.1.10. Alkenyl-bromoalkyl

Treatment of diester **209** with NaCN in DMSO and water led to decarboethoxylation and displacement of the terminal Br to afford cyano ester **210** (60%).[132]



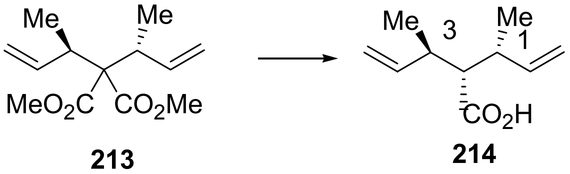
### 7.1.11. Alkenyl-fluoro

The deethoxycarbonylation of the α-fluoro diester **211** to the α-fluoro ester **212** (78%) can be accomplished by heating in DMSO, NaCl, and water (reflux, 4 h).[133]

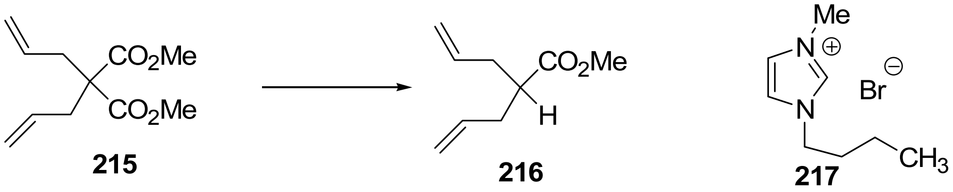


### 7.1.12. Alkenyl-alkenyl

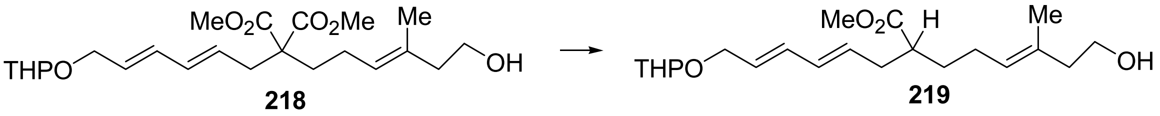
Upon heating diester **213** in anhydrous DMSO and KCN (140°C, 43 h) , the pseudo-$C_2$-symmetrical carboxylic acid **214** (3R,1R) (93%) was obtained. These analogues could be desymmetrized and utilized in a target-directed synthesis.[134]



The decarbalkoxylations of several disubstituted malonates were shown to proceed in good yields when heated with LiCl and water in [bmim]Br to afford the corresponding esters. This ionic liquid functions as an alternative to the use of dipolar aprotic solvents such as DMSO or DMF. Upon heating diester **215** with LiCl and water in the presence of [bmim]br (**217**) (160°C, 14 h) the mono ester **216** (99%) was obtained.[135]

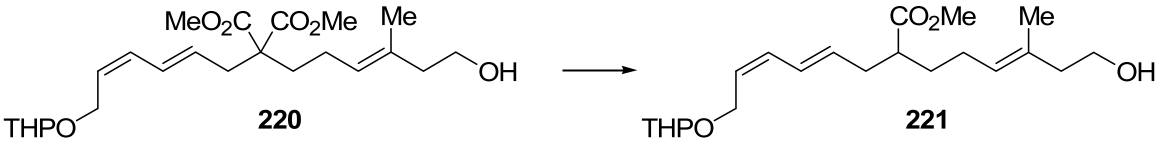


Treatment of **218** with DMSO, NaCN and water (95°C, 48 h) afforded **219** (72%).[136]



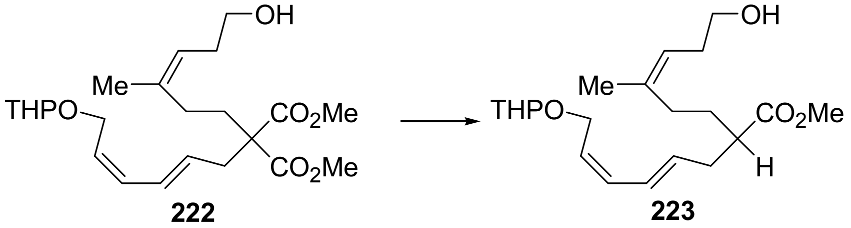
**218** **219**

Treatment of **220** with DMSO, NaCN and water (95°C, 25 h), with the addition of more NaCN, with stirring for 25 h at 95°C led to the decarbomethoxylated product **221** (88%).[137]



**220** **221**

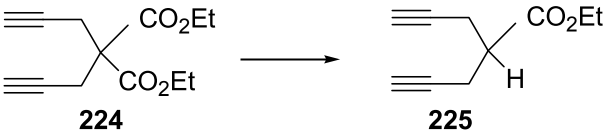
The demethoxycarbonylations of several disubstituted malonate esters with unsaturated side chains have been reported. A typical example is the conversion of **222** on treatment with DMSO, NaCN and water (95°C, 3 h) to yield **223** (81%).[138]



**222** **223**

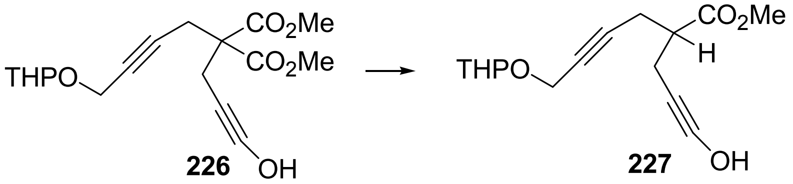
## 7.1.13. Alkynyl – alkynyl

Treatment of the bis-propargyl substituted diester **224** with DMSO, LiCl and water (reflux, 2 h) led to the deethoxycarbonylated product **225** (82%).[139]



**224** **225**

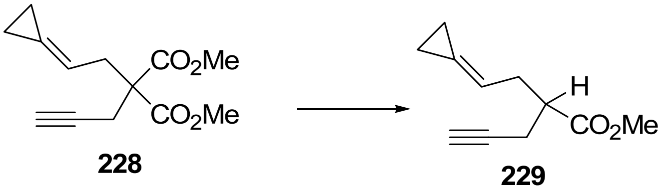
The demethoxycarbonylation of **226** with DMSO, NaCN (100°C) led to **227** (58%).[140]



**226** **227**

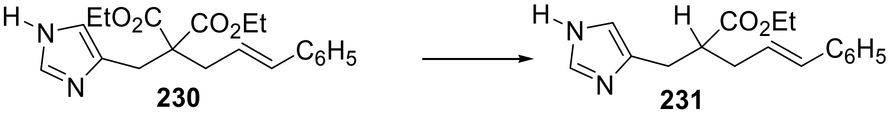
## 7.1.14. Alkenyl-alkynyl

Treatment of malonate ester **228** in DMSO and NaCN (120°C, 4 h) led to the demethoxylcarbonylated product **229** (62%).[141]



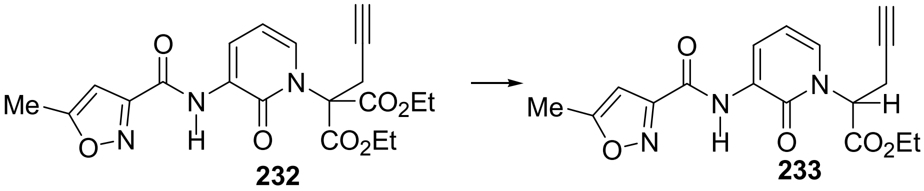
### 7.1.15. Alkenyl-heterocyclic

The substituted imidazole **230** on treatment with DMSO, NaCN and water (120°C, 48 h) led to the deethoxycarbonylation product **231** (45%). Further elaboration of this product led to histamine analogues as potential cardiovascular selective $H_2$ agonists.[142]



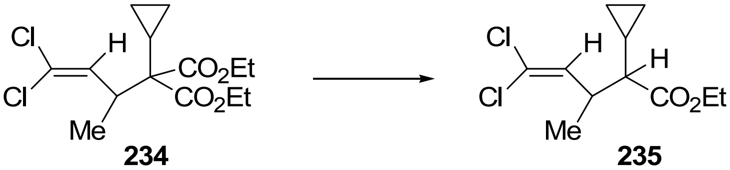
### 7.1.16. Ethynyl-heterocyclic

The malonate ester **232** (**140 g**) underwent a deethoxycarbonylation when heated in DMA or DMPU) with a large excess of LiBr (85°C, 16 h) to afford the (pyridonyl-1)propargyl acetic ester **233** (87%, 99.5% HPLC purity). This was a key intermediate for the synthesis of a selective inhibitor of a human rhinovirus.[143]



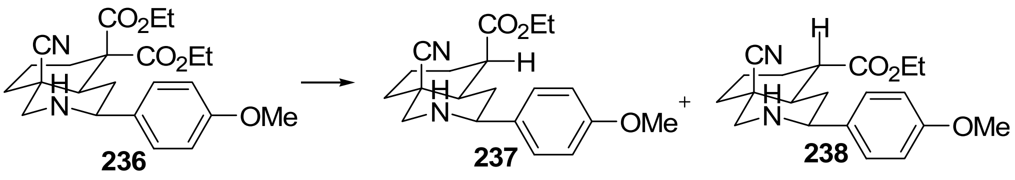
### 7.1.17. Cyclopropyl-dichloroalkenyl

A number of halo substituted 4-alkenoic esters have been prepared via the dealkoxycarbonylation procedure. For example, treatment of malonate ester **234** with DMSO, NaBr and water (190°C, 8 h) led to monoester **235** (80%).[144]



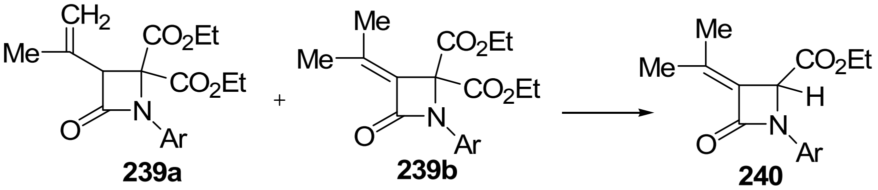
### 7.1.18. Carbocyclic-1,1-dicarboxylic acid diesters

Treatment of **236** with DMF, LiCl and water (reflux, 48 h) led to **237** (41%) and **238** (29%).[145]



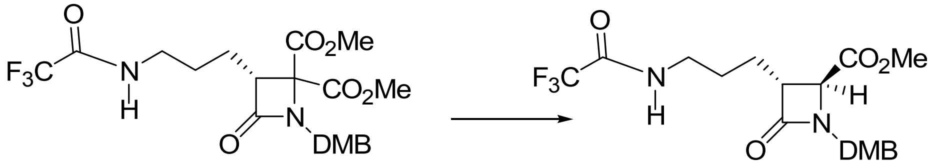
### 7.1.19. Heterocyclic-1,1-dicarboxylic acid dialkyl diesters

The deethoxycarbonylations of bis-carbethoxy -β-lactams under microwave irradiation have been studied. As an illustrative example, **239a** and **239b** using LiCl in DMF under microwave irradiation led to product **240** (50%).[146a,b,c]



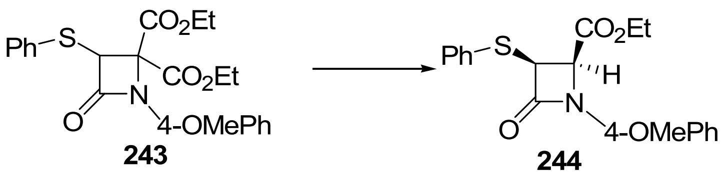
Ar = p=Anisyl

The deethoxycarbonylation of **241** using DMF, LiCl, and water (130°C, 3 h) led to azetidinone **242** (93%, trans:cis 36.3:1), which was subsequently converted into a tryptase inhibitor BMS-262084 (99%ee) for potential treatment of asthma. A study was also perfomed on the use of other N-protecting groups and the effect of water on the diasteroselectivity of the reaction.[147]

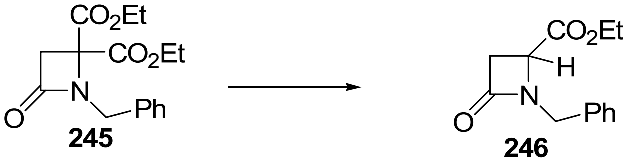


**241** DMB = 2,4-dimethoxybenzyl **242**

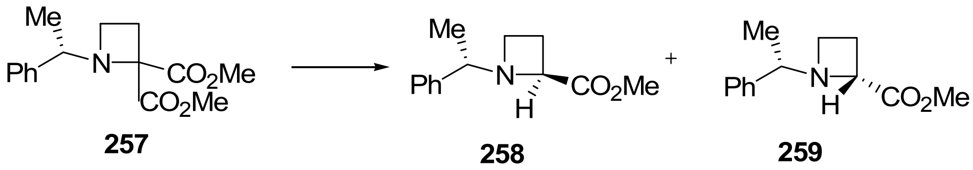
Treatment of azetidin-2-one **243** with DMSO, NaCl and water (reflux, 4 h) afforded predominantly cis-3-phenylthio-4-ethoxycarbonylazetidin-2-one (**244**) along with small amounts of the trans isomer, cis:trans ratio (12:1).[148]



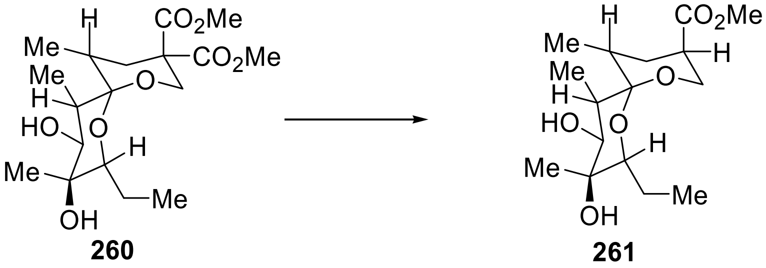
The deethoxycarbonyations of several N-aryl- and N-aralkyl-4-oxo-azetidine-2,2-dicarboxylates were performed using DMSO, NaCl and water (170-180°C, 5 h ). For example, treatment of **245** led to **246** (94%).[149] Other related dealkoxycarbonylations have been reported.[150a,b,c]



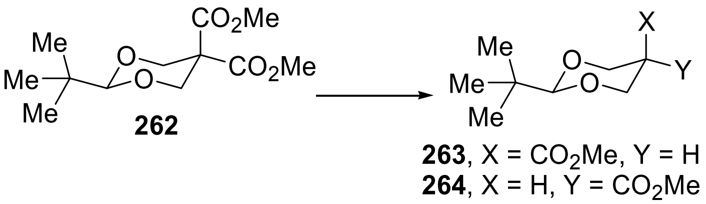
The deethoxycarbonylation of diethyl ester **257** using DMSO and LiCl under anhydrous conditions in the presence of molecular sieves and 2,6-di-tert-butyl-4-methylphenol (140° C, 2 h) led to (2S,1'S)-**258** and (2R,1'S)-**259** (78%) (diastereoisomeric ratio 2.7:1) which could be separated by column chromatography. These isomers were utilized in a synthesis of (S)-azetidine-2-carboxylic acid.[151]



The demethoxycarbonylation of **260** with DMSO, LiCl and water (165-170°C, 70 min) led predominantly to **261** (83%).[152]

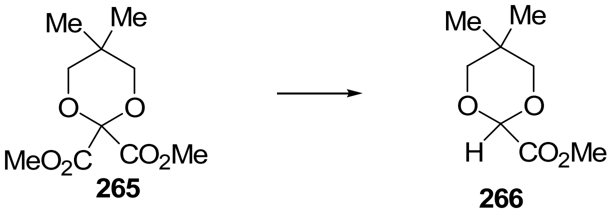


Treatment of **262** with DMSO, LiCl and water (140-145°C, 4 h) afforded a mixture of **263** and **264** (80%, ratio cis:trans 89:11), which could be separated.[153]

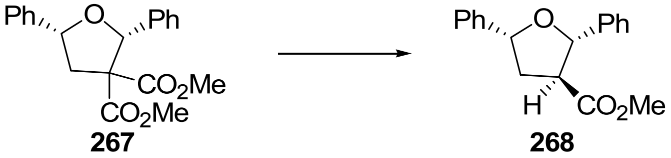


**263**, X = $CO_2Me$, Y = H
**264**, X = H, Y = $CO_2Me$

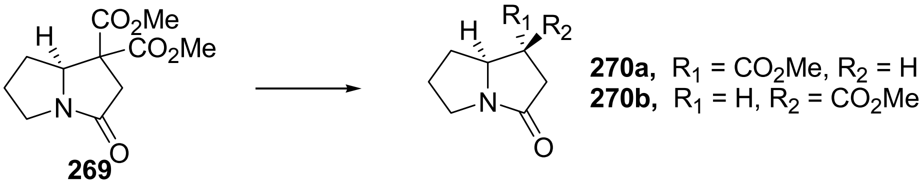
The diester **265** in DMSO, NaCl and water (reflux, 24 h) led to the demethoxycarbonylation product **266** (69%) with the ketal group intact.[154a,b]


**265** **266**

Upon treatment of the diester rac-**267** with DMSO, NaCN and water (110°C, 20 h) a diastereoisomeric mixture of rac-**268** (6.7:1) was obtained. These diastereoisomers could be separated by chromatography to afford rac-**268** as the major product. Chiral diester **267** (97% ee) led to enantiomer **268**.[155]

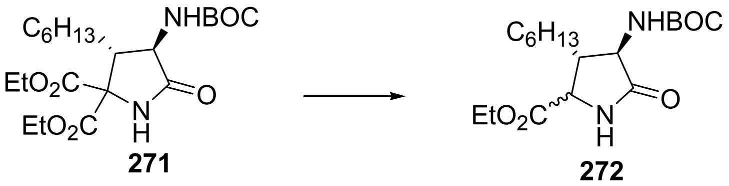

**267** **268**

The demethoxycarbonylation of **269** with DMSO, LiCl and water (reflux until no further gas evolution) led to **270a:270b** (85%) in a 4:1 ratio which could be separated by chromatography.[156]

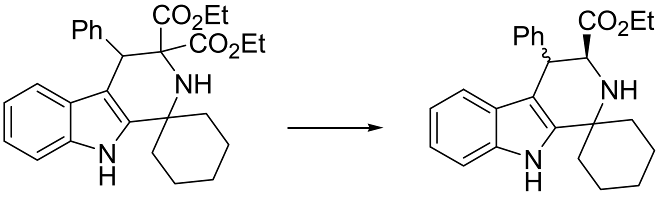

**269**

**270a,** $R_1 = CO_2Me$, $R_2 = H$
**270b,** $R_1 = H$, $R_2 = CO_2Me$

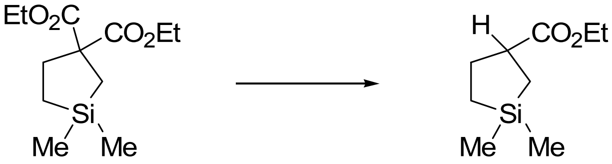
The pyrrolidinone **271** on treatment with DMSO, NaCl and water led to **272**. However it was found that treatment of **271** with LiBr in DMI (1,3-dimethyl-2-imidazolidinone) and water (155°C) led to **272** (64%) as an inseparable mixture of C-5 isomers ( ratio 1:1).[157]


**271** **272**

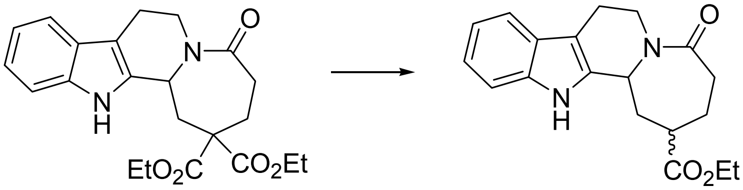
In routes leading to the preparation of tetrahydro-β-carboline analogues, the deethoxycarbonylation of **273** using DMSO, LiCl and water (180°C, 7 h) led to a diastereoisomeric mixture of **274** (98%) which could be separated by TLC.[158]


**273** **274**

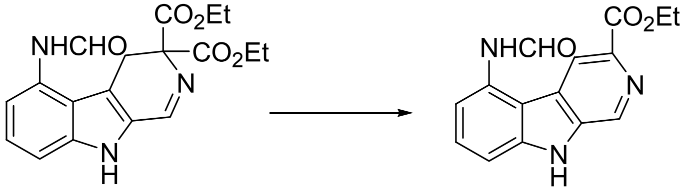
The deethoxycarbonylation of the silacyclopentane analogue **275** with DMSO, NaCl and water (no conditions reported ) led to monoester **276** (90%).[159]


**275** **276**

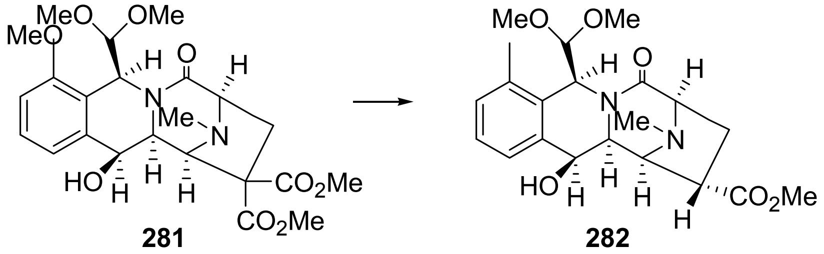
Treatment of **277** with DMSO, LiCl and water (170-180°C, 5 h) to **278** (96%) as a mixture mixture of diastereomeric esters used in a multi-step synthesis of vinblastine analogues.[160]


**277** **278**

The deethoxycarbonylations of several 3,4-dihydro-β-carbolines with DMSO, LiCl and water (170°C, 7-9 h) led to the 5,6 and 7-acylamino-β-carbolines. As an illustrative example, analogue **279** led to **280** (30%).[161]

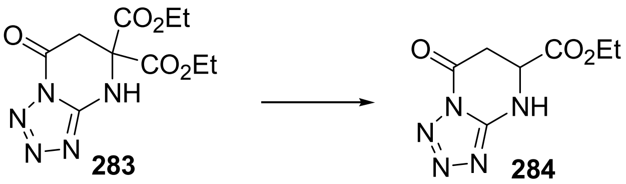

**279** **280**

Treatment of racemic **281** with DMSO, NaCl and water (140°C, 20 min) led to racemic **282** (75%) which was utilized in a synthesis of quinocarcinol. In the decarbomethoxylation process, about 10% of the endo-carbomethoxyl analogue was also obtained.[162]



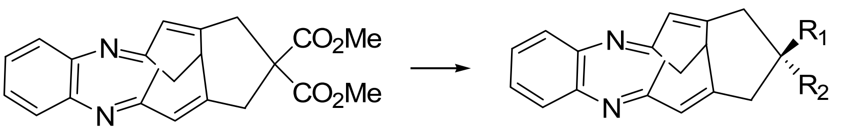
**281** **282**

Treatment of **283** with DMSO, NaCl and water (190°C, 25 min) led to the demethoxycarbonylated pyrimidine-5-carboxylate **284** (21%).[163]



**283** **284**

Diester **285** on treatment with DMF, LiCl and water (110°C, 10 h) led to **286a** and **286b** which were separated by preparative tlc. Several other related systems were also dealkoxycarbonylated.[164]

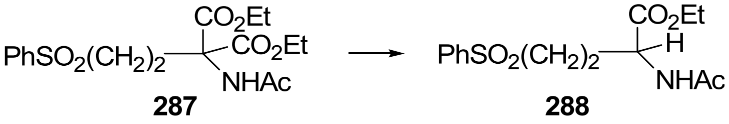


**285**

**286a**, $R_1 = CO_2Me$, $R_2 = H$ (24%)
**286b**, $R_1 = H$, $R_2 = CO_2Me$ (37%)

### 7.1.20. 2-Acylamino substituted analogues

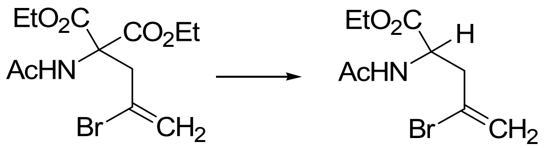
Treatment of **287** with DMSO and LiCl ( 120°C, 2 h) led to **288** (88%). On the other hand, the corresponding sulfoxide under similar conditions led to (Z)-ethyl-2-acetylamino-2-butenoate (38%).[165]



$PhSO_2(CH_2)_2C(CO_2Et)_2(NHAc) \longrightarrow PhSO_2(CH_2)_2CH(CO_2Et)(NHAc)$

**287** **288**

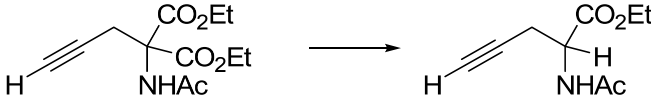
Treatment of the diester **289** with DMF, LiBr and water (reflux, 6 h) led to **290** (unspecified yield). It was also noted that the use of LiBr led to dramatic increases in the rate of reaction in comparison to other salts. This intermediate was utilized for the synthesis of several optically active unnatural amino acids.[166]



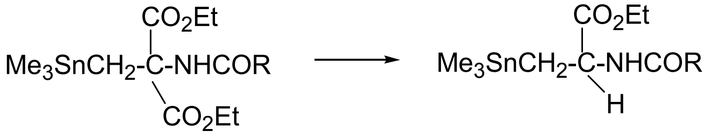
**289** **290**

In pathways leading to 3 -deoxy sphingolipids, the diester **291** on treatment with DMSO, NaCl and water (reflux, 18 h) led to intermediate **292** (82%).[167]

Treatment of **293** with DMF, NaCl and water (150°C, 4 h) led to **294** (58%).[168]

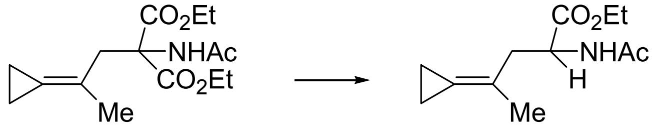


The decarboethoxylation of the stannyl substituted derivatives **295a** and **295b** on treatment with DMF, LiCl and water (reflux, 12 h) led to poor yields of **296a** (4.2%) and **296b** (5.8%), respectively.[169]



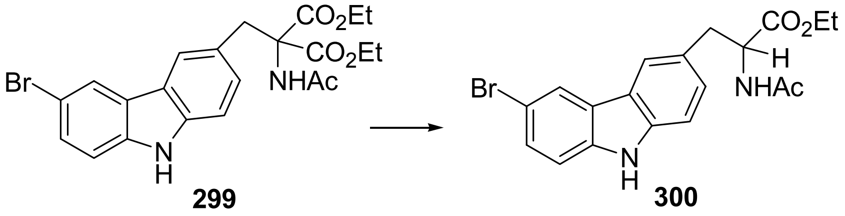
**295** a, R = Me b, R = H **296**

Treatment of **297** with DMSO, NaCl and water (165°C, 8 h) led to the deethoxycarbonylation product **298** (73%).[170]

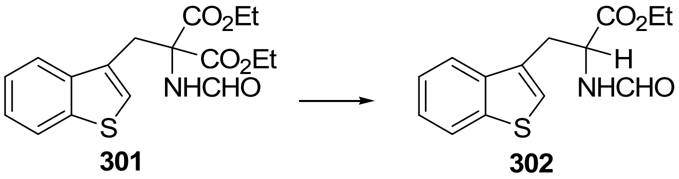


**297** **298**

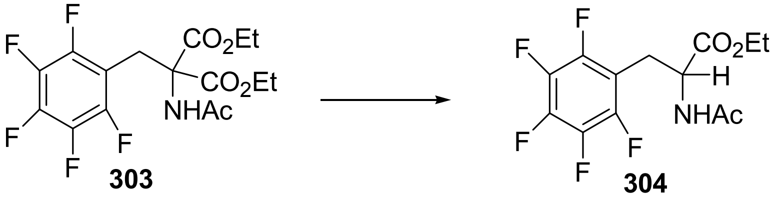
In synthetic pathways to carbazole-linked cyclic peptoids, treatment of **299** with DMSO, LiCl and water (reflux, 1.75 h) led to intermediate **300** (70%).[171a,b]



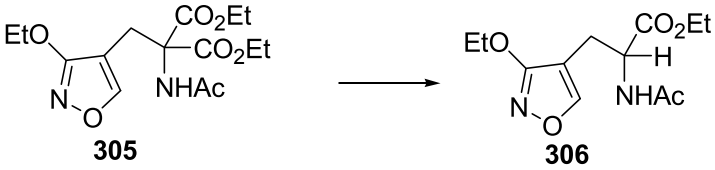
Treatment of **301** with DMSO, NaCl and water (200°C, 15 min) led to **302** ( 53%).[172]



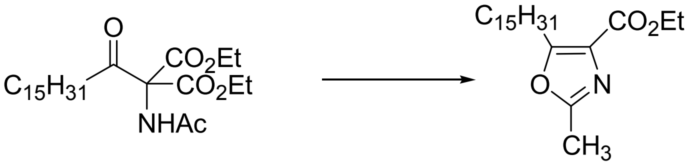
Treatment of the fluorinated analogue **303** with DMF, LiBr and water (reflux, 270 min) led to the deethoxycarbonylation product **304** (73%), which was converted into optically active p-azidotetrafluorophenylalanine and further evaluated as a potential photoaffinity reagent.[173]



Treatment of the substituted isoxazole **305** with DMSO, NaCl and water (160°C, 7 h) led to mono ester **306** (78%). Further elaboration by a α-chymotrypsin resolution led to the corresponding amino acid.[174]

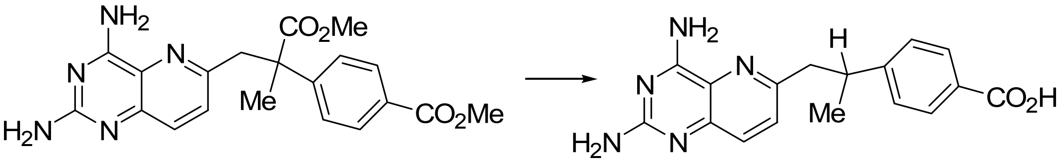


Treatment of **307** with LiCl or LiBr in DMSO and water (120°C, 2 h) led only to the deacylation products along with the acetamido substituted diethyl malonate. If **307** is heated with DMSO and water ( 2 eq) (reflux, 2 h) **308** (62%) was obtained and a mechanism has been proposed.[175]


**307** **308**

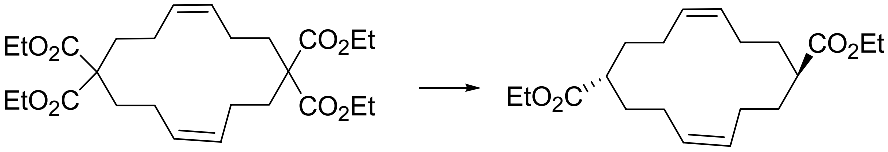
### 7.1.21. Aryl-heteroaryl

The extended malonate system on treatment with DMSO and 3 eq of NaCN (170-180°C, 1-2 h) led to decarbomethoxylation and ester cleavage of the p-$CO_2Me$ group to yield the 2,4-diamino-10-alkyl-8,10-dideazapteric acid.[176,177] For example, under these conditions, the methyl substituted derivative **309** led to **310** (96%).[176]


**309** **310**

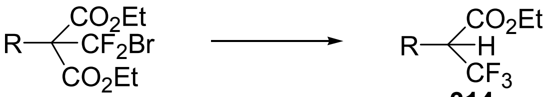
### 7.1.22. Bis-cyclic malonic ester

Treatment of the tetra ester **311** under Krapcho's conditions (not specified) led to cis,cis-3,8-cyclodecadiene-1,1,6,6-tetracarboxylate (**312**).[178]


**311** **312**

### 7.1.23. Substituted α-difluorobromomethyl malonate

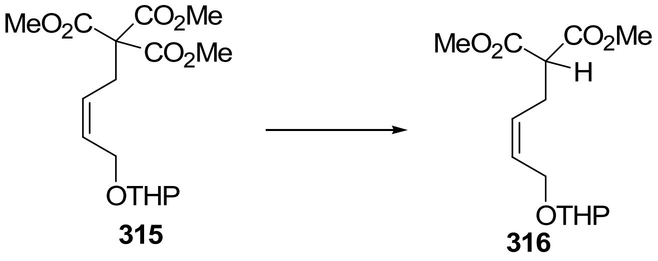
The conversion of malonic esters to esters holding an α-$CF_3$ group has been accomplished by a dealkoxycarbonylation-fluoridation route. Treatment of α-bromodifluoromethyl substituted malonates **313** with KF in dry DMSO (150°C) led to the α-$CF_3$ substituted esters **314**. Low boiling products were isolated by distillation from the reaction mixture and the higher boiling esters by dilution of the reaction mixture with water and extraction into ether.[179a,b]


**313** **314**

R = Me, Et, n-Pr, n-Bu (35-61%)

### 7.1.24. Trimethyl methanetricarboxylate

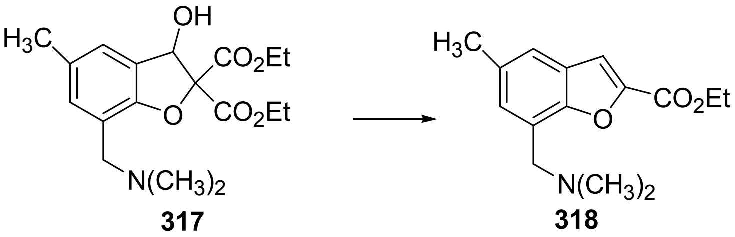
Treatment of **315** with DMSO and KCN (2 eq) (90°C, 0.5 h) led the mono-demethoxycarbonylation product **316** (63%). A similar procedure using the triethyl ester led to the diethyl ester.[180]



Some additional illustrative examples are tabulated in Table 2.

### 7.1.25. Dealkoxycarbonylation-eliminations

The demethoxycarbonylation of **317** on heating in DMSO (reflux, 2 h) led to the corresponding ethyl-2-benzofuran carboxylate **318** (75-80%), used in the preparation of analogues tested for histamine $H_2$ receptor antagonist activity.[200]



Treatment of **319** with DMSO, LiCl and water (165°C, 1 h) led to the benzofuran derivative **320** (86%).[201a] A related example with a different substitution pattern in the aromatic ring has also been reported.[201b]

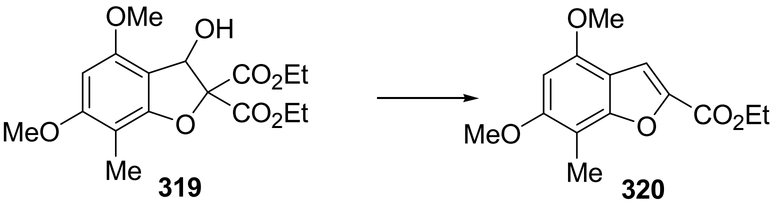
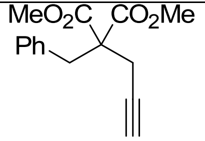
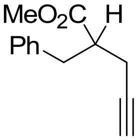
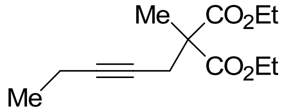
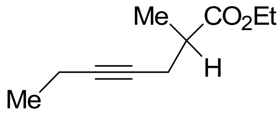
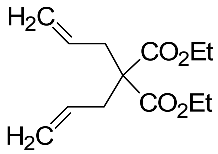
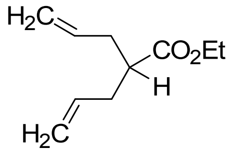
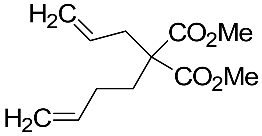
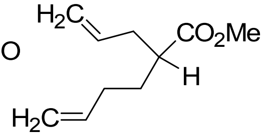
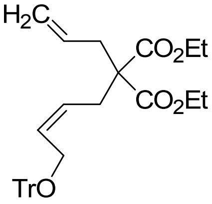
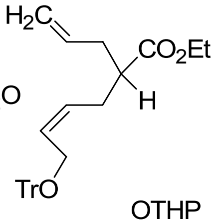
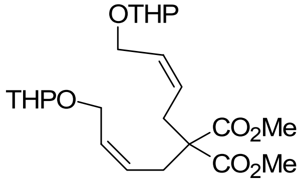
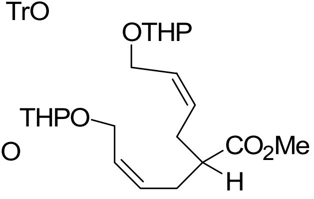
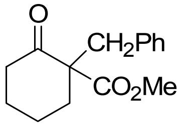
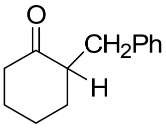
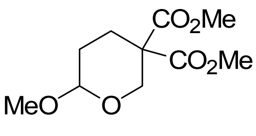
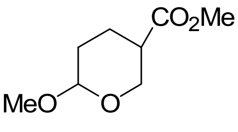
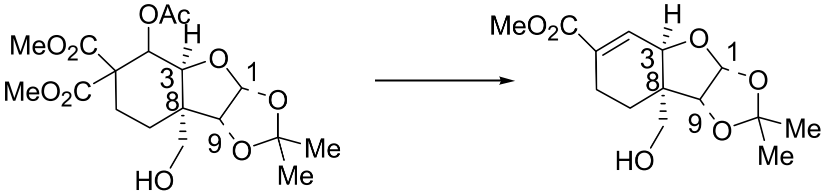


**Table 2.** Dealkoxycarbonylations of disubstituted malonate esters

| Starting material | Conditions | Product | Yield(%) | Ref |
|---|---|---|---|---|
|  | DMSO,NaCl, $H_2O$<br>150°C, 12 h |  | 82 | 191 |
|  | DMSO, LiCl, $H_2O$<br>reflux, 5 h |  | 75 | 192 |
|  | DMSO,LiCl, $H_2O$<br>reflux, 6 h |  | 86 | 193 |
|  | DMSO, NaCl, $H_2O$<br>180°C |  | 72 | 194 |
|  | DMSO, NaCl, $H_2O$<br>180°C, 12 h |  | 69 | 195 |
| | DMSO, NaCN, $H_2O$<br>150°C, 5 h | | 64 | 196 |
|  | DMSO, KOAc, $H_2O$<br>140°C, 5 h |  | 81 | 197 |
|  | DMF, LiCl<br>145-150°C, 7h |  | 90 | 198 |
|  | DMSO, NaCl, $H_2O$<br>150°C, 10 h | <br>cis:trans 56:44 | 81 | 199 |

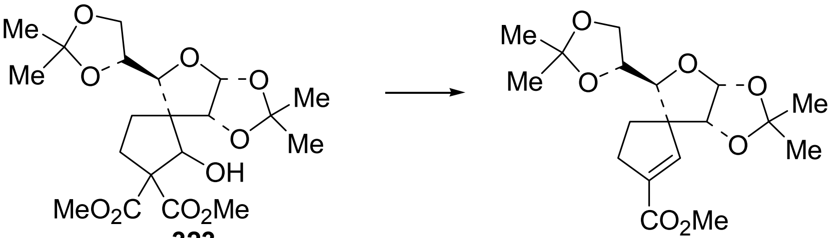
Treatment of a diastereoisomer mixture of (12R,12S) **321** with DMSO, NaCl and water (110-160°C,3 h) and 160°C (0.5 h) led to the β-elimination of the acetoxy group to afford **322**

(1R,3R,8R,9R) (47%), along with some recovered starting material, which could be recycled. This derivative was used in a synthetic study of routes to the trichothecene sesquiterpenes.[202]



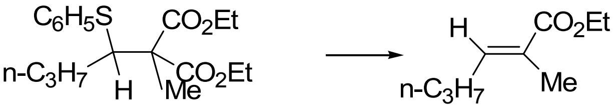
**321** **322**

The decarbomethoxylation of **323** using DMSO, NaCl and water ($160^{o}$C, 4 h) led to β-elimination of the OH group to form the enantiomerically pure α,β-unsaturated ester **324** (80%). This intermediate could not be converted into enantiomerically pure 2-oxospiroalkanes.[203]



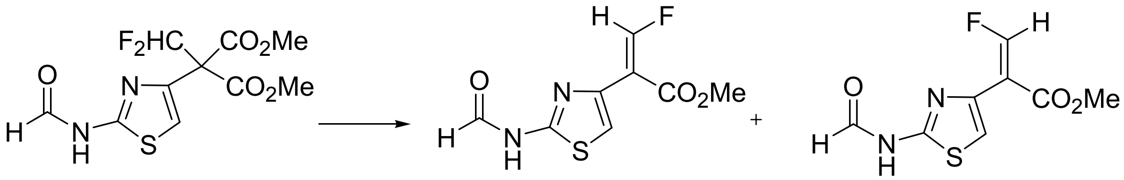
**323** **324**

A convenient synthesis of 2-alkenoic esters involved treatment of numerous β-substituted derivatives with solvents such as DMSO, DMF or HMPT and salts such as NaBr or LiCl ($130^{o}$C, 5 h). For example, treatment of **325** with HMPT, NaBr at $135$-$140^{o}$C for 5 h gave **326** (86%) with an E/Z ratio of 88:12.[204,205]



**325** **326**

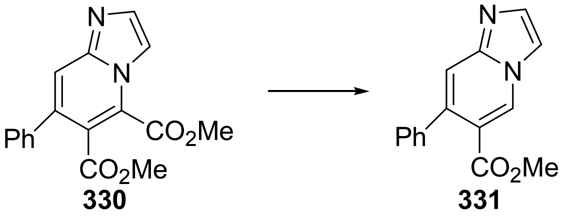
The demethoxycarbonylation of **327** using DMF and LiI ($160^{o}$C) led to **328-**(Z) (14%) and **329**-(E) (52%), respectively.[206]



**327** **328**-(Z) **329**-(E)

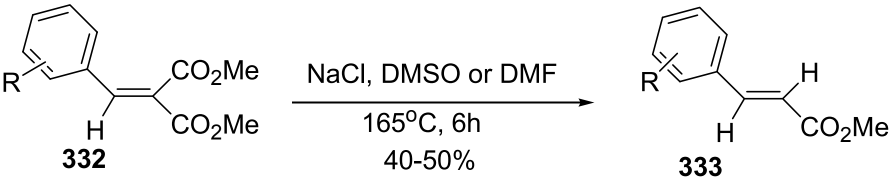
### 7.1.26. Substituted heterocyclic system

Treatment of the imidazo[1,2a]pyridine **330** with DMSO, NaCl and water (150°C, 5 h) led regioselectively to the 6-methoxycarbonyl derivative **331** (61%).[207]



### 7.1.27. Cinnamic esters: from arylmethylene-propanedioic acid dimethyl esters

The dealkoxycarbonylations of arylmethylene-propanedioic acid dimethyl esters (**332**) in DMSO-NaCl-$H_2O$ (and in DMF with other salts) have been studied. In general, the esters led predominantly to the trans-cinnamic esters (**333**).[208a,b]



R = H, o-Me, o-OMe, o-OCH$(CH_3)_2$, p-Me, p-OMe, p-$NO_2$

## 8. Conclusions

The dealkoxycarbonylation procedure is a useful synthetic method for the formal replacement of a $CO_2R$ moiety with a H atom and should continue to find numerous applications in synthetic strategies.

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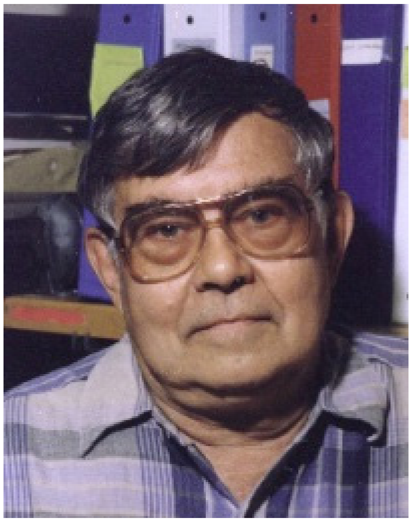

A. Paul Krapcho was born in Alden Station, PA on March 6, 1932. He did his undergraduate work at Penn State (B.S. in Chemistry, 1953) and graduate studies at Harvard University (Ph.D. 1957). He then spent the 2-year period of 1957-1959 teaching at Smith College and then held a post-doctoral position 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 α-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).