

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

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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

Contents

1. Introduction
2. Ketones
 - 2.1. From monosubstituted β -keto esters
 - 2.1.1. Water alone
 - 2.1.2. Water-salts
 - 2.1.2.1. From alkyl, aryl, heterocyclic and heteroaryl substituted open chain substrates
 - 2.1.2.2. From fluoro substituted substrates
 - 2.1.2.3. From carbocyclic β -keto esters
 - 2.1.2.4. From heterocyclic β -keto esters
 - 2.1.2.5. From an α,α -dicarbethoxy ketone
 - 2.2. Disubstituted β -keto esters
 - 2.2.1. Water alone
 - 2.2.2. Water-salts
 - 2.2.2.1. Open chain substituents
 - 2.2.2.2. From carbocyclic β -keto esters
 - 2.2.2.2.3. Water-salts
 - 2.3. Heterocyclic substrates

- 2.3.1. From β -carbomethoxy substituted lactones
- 2.4. 1,3-Diones
 - 2.4.1. From substituted 2-carbalkoxy-1,3-diones
- 2.5. 1,4-Diones
 - 2.5.1. From α -carbalkoxy-1,4-diones
- 2.6. 1,5-Dione
 - 2.6.1. From α -carbomethoxy substituted substrate
- 2.7. β -Keto ester and malonate ester polyfunctional substrates
- 2.8. Aldehyde
 - 2.8.1. From α -methoxycarbonyl aldehyde
- 2.9. Nitriles
 - 2.9.1. From α -cyano esters
 - 2.9.2. From mono substituted substrates
 - 2.9.3. From disubstituted substrates
- 2.10. Sulfones
 - 2.10.1. From α -sulfonyl esters
- 2.11. Sulfoximines
 - 2.11.1. From α -carbomethoxy sulphoximines
- 2.12. Chiral phosphine oxides
 - 2.12.1. From P-chiral phosphinyl acetates
- 2.13. Ketophosphonates
 - 2.13.1. From 2-acylphosphonoacetates
- 2.14. Nitro analogues
 - 2.14.1. From α -nitro esters
- 2.15. 2-Cyclohexenone derivatives
 - 2.15.1. From 4-Carbalkoxy-2-cyclohexenones
- 2.16. Heterocyclic vinylogous deethoxycarbonylation
- 2.17. Tetra-demethoxycarbonylation
- 3. Conclusions
- 4. References

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

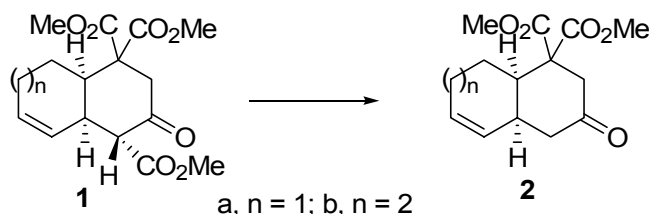
2. Ketones

2.1. From monosubstituted β -keto esters

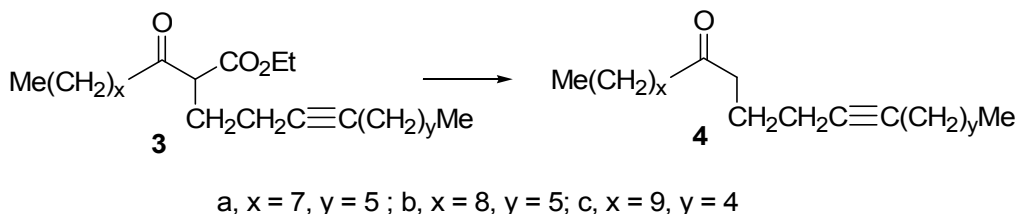
2.1.1. Water alone

As noted in our previous review,¹ 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.

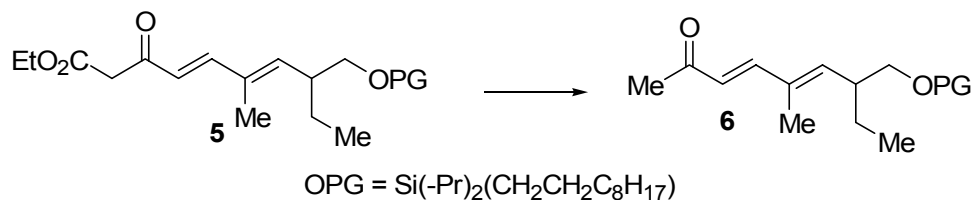
Treatment of *cis*-**1a** ($n = 1$) with DMSO and water (150°C , 15 h) led to *cis*-**2a** (68%, $n = 1$), the product from the decarbomethoxylation of the β -keto ester moiety. Analogue *cis*-**1b** ($n = 2$) in DMSO and water (140°C , 2 h) afforded *cis*-**2b** (80%).²



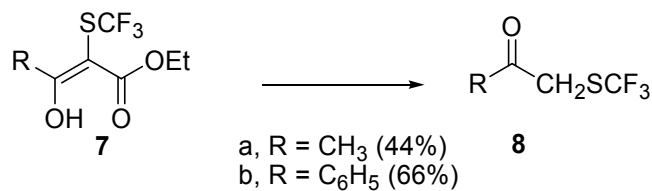
In routes to several sex pheromones of the peach fruit moth and the Douglas fir tussock moth, decarbomethoxylations of several long chain β -keto esters were investigated. Treatment of **3a,b,c** with DMSO and water (150°C , 3.5 h) led to the products **4a,b,c** in yields of 80%.³



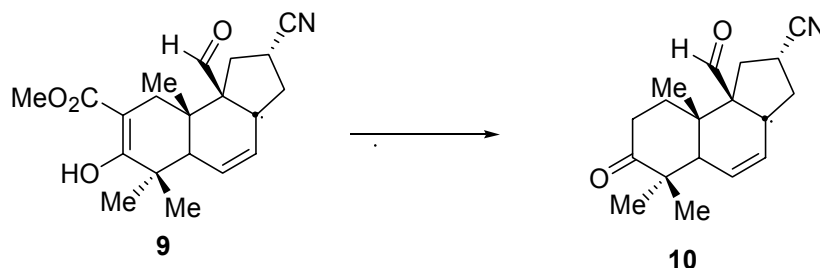
Brief microwave irradiation of mono-alkylated β -ketoesters at 160 - 200°C in wet DMF induced smooth and selective decarboalkoxylation. For example, treatment of **5** with DMSO and water (160°C , 3 min) under microwave irradiation led to **6** (89%).⁴



The deethoxycarbonylation of **7a,b** in wet DMSO (reflux, 4 h) afforded **8a** (44%) or **8b** (66%), respectively.⁵

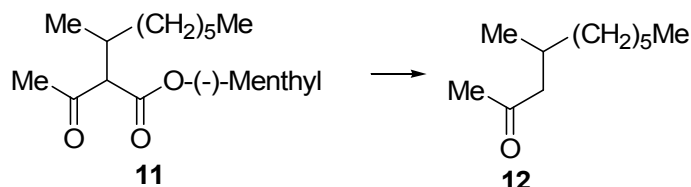


The demethoxycarbonylation of enantiomer **9** in DMSO and water (155°C, 2.5 h) led to the enantiomeric tricycle **10** (92%).⁶

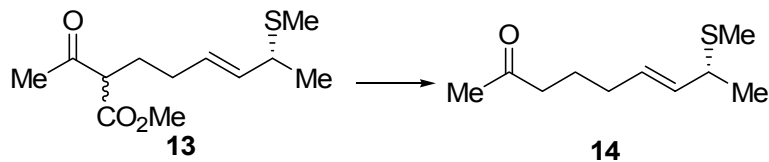


2.1.2. Water-salts

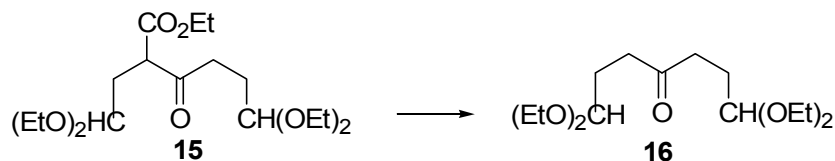
2.1.2.1. From alkyl, aryl, heterocyclic and heteroaryl substituted open chain substrates. A number of optically active acetoacetates were alkylated on a solid support (Al₂O₃, *t*-BuOH) with alkyl bromides and the products subjected to dealkoxycarbonylations using LiCl in DMSO. For example, derivative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



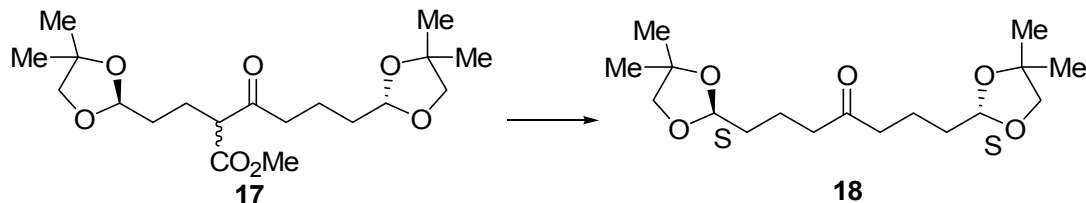
Keto ester **13** on treatment with DMSO, NaCl and water (70°C, 12 h) led to (+)-**14** in good yield. This intermediate was easily converted into the alkaloid (+)-pinidine.⁸



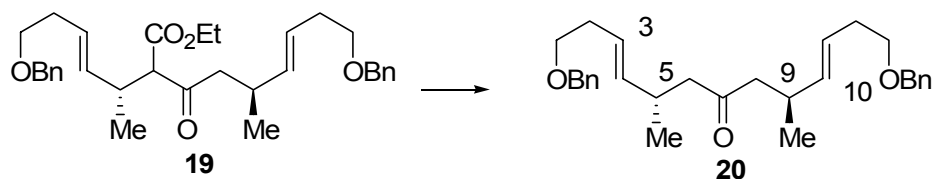
The β -keto ester **15** on heating in DMF, NaCl and water (reflux, 72 h) led to **16** (88%), which was converted into a octahydropyridopyrrolizine-2-(1H)-one.⁹



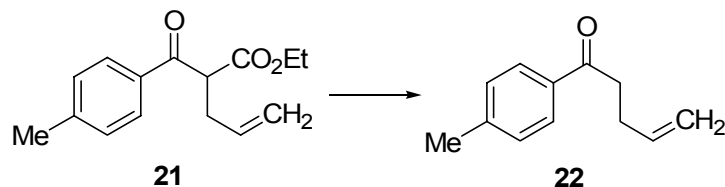
The decarbomethoxylation of **17** using DMSO, LiCl and water (reflux, 10 min) led to the C-2 symmetrical ketone **18** (94%). This intermediate could be readily transformed into the corresponding enantiomeric spiroketal on treatment with aqueous acetic acid.¹⁰



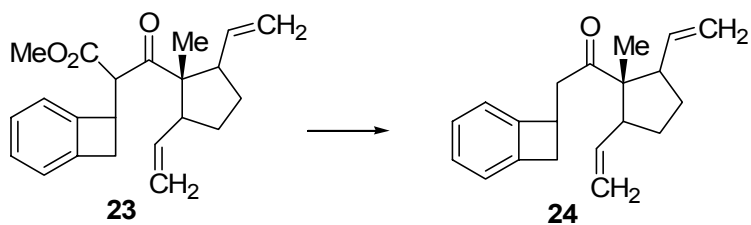
The decarbomethoxylation of **19** with DMSO, LiCl, and water (190°C, 40 min) provided the C₂-symmetric ketone **20** (3*E*,5*S*,9*S*,10*E*) (96%). This ketone on asymmetric syn- dihydroxylation and acid catalysis led to a mixture of dioxaspiro[5,5]undecane and dioaxospiro[4,5]decane.¹¹



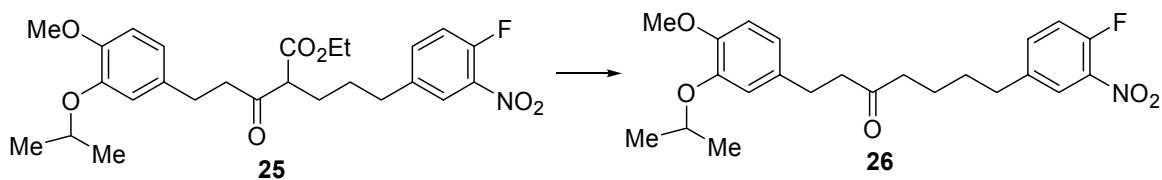
A number of ω-alkenyl ketones have been prepared by deethoxycarbonylation of the appropriate β-keto esters. For example, treatment of **21** with DMF and LiBr (195-200°C, 3 d) led to **22** (67%).¹²



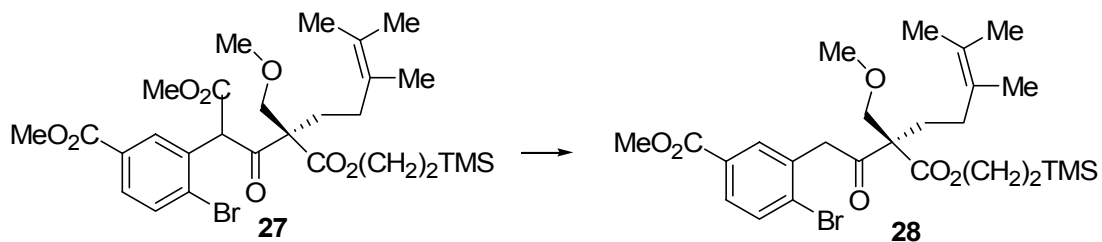
Treatment of **23** (isomeric mixture) with DMSO, NaCN (90°C, 22 h) led to **24** (70%) as an isomeric mixture. This intermediate was used in the synthesis of estrone derivatives.¹³



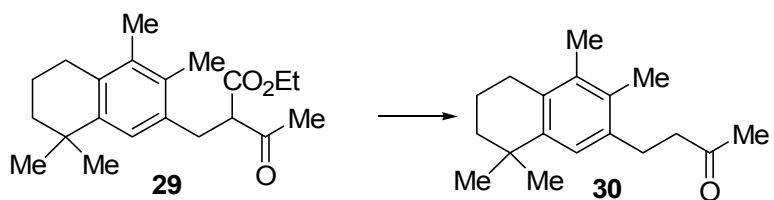
The deethoxycarbonylation of **25** was accomplished using DMSO, LiCl and water (160°C, 24 h) to yield **26** (83%). This was converted into an acrogenin-type diaryl heptanoid holding an endocyclic biaryl ether bond.¹⁴



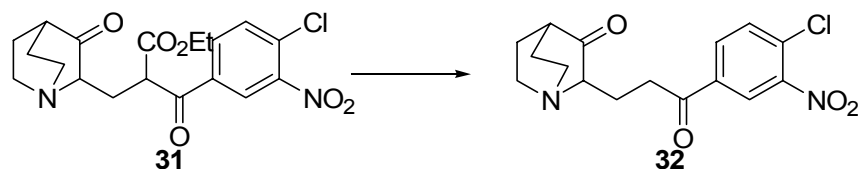
The chemoselective demethoxycarbonylation of the β -keto ester **27** was accomplished by treatment with DMSO, NaCl and water (125°C, 24 h) to afford optically active **28** (78%), which in a subsequent series of steps could be converted into (-)-virantmycin.¹⁵



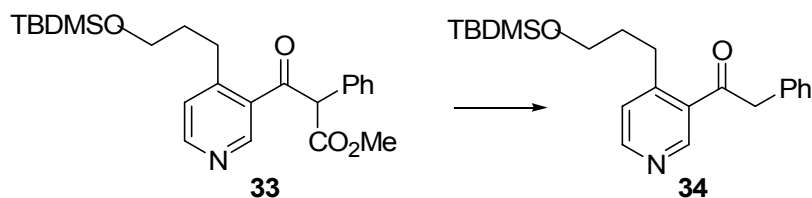
In a pathway to racemic chrysollic acid, the deethoxycarbonylation of **29** with DMSO, NaCN and water (140-150°C, 10 h) led to intermediate **30** (60%).¹⁶



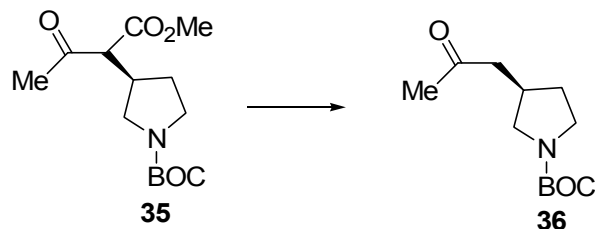
Treatment of **31** with DMSO, NaCl and water (135°C, 8 h) led to **32** (82%), isolated as the HCl salt.¹⁷



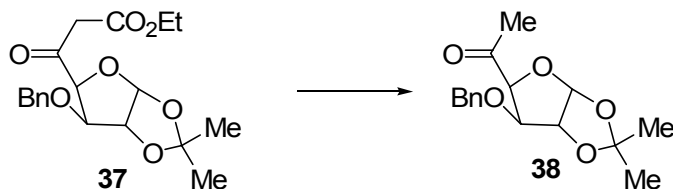
Treatment of keto ester **33** with DMSO, NaCl and water (150°C, 2 h) led to ketone **34**(70%).¹⁸



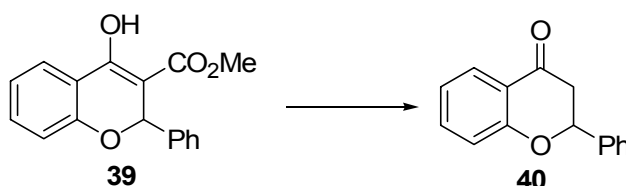
The enantiomeric β -keto ester **35** on treatment with DMF, NaCl and water (reflux, 9 h) led to the de-*t*-butoxycarbonylated pyrrolidine **36**-(3*R*) (92%). The stability of the BOC group under the reaction conditions is of particular note.¹⁹



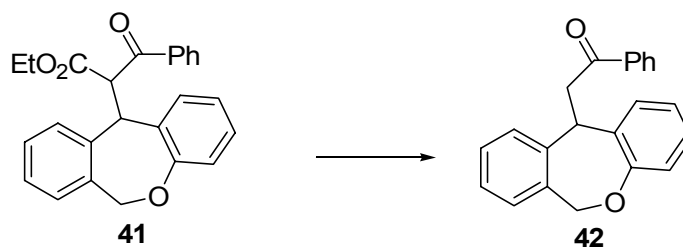
Treatment of β -keto ester **37** with DMSO, NaCl and water (135°C, 2 h) led to **38** (80%). This intermediate was converted into 1,6-dideoxynojirimycin (a polyhydroxy piperidine) in a series of subsequent steps.²⁰



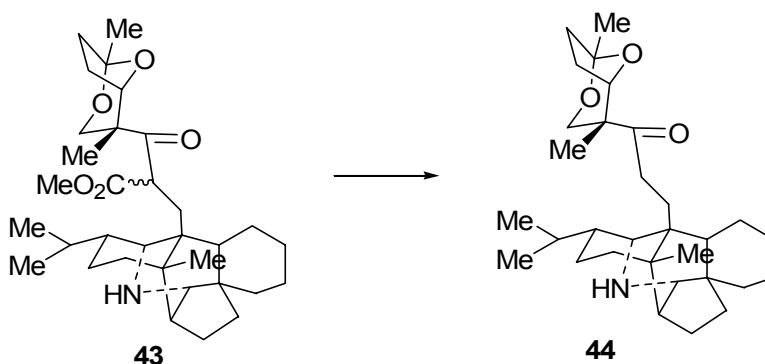
A mixture of enol **39** and the corresponding β -keto ester in DMSO, NaCl and water (150-160°C, 5 h) afforded the flavanoid **40** (89%).²¹



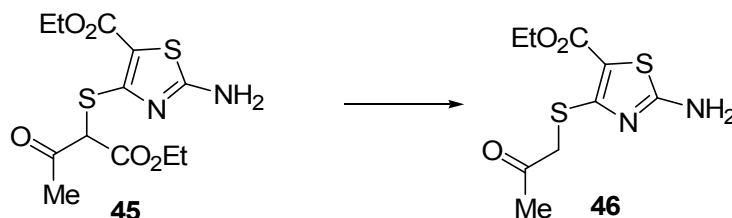
The deethoxycarbonylation of **41** was accomplished by heating in DMSO, NaCl and water (150-160°C, 8 h) to afford **42** (42%).²²



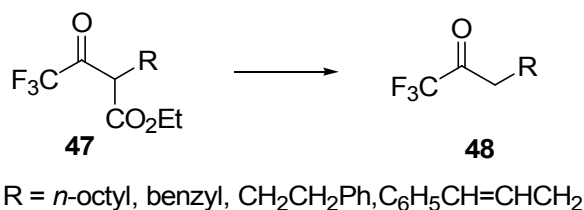
The synthesis of (-)-secodaphniphylline (**44**) (44%, 99.6% ee) has been accomplished by heating β -keto ester **43** with NaCN in DMSO containing a few drops of water (150°C, 2 h).²³



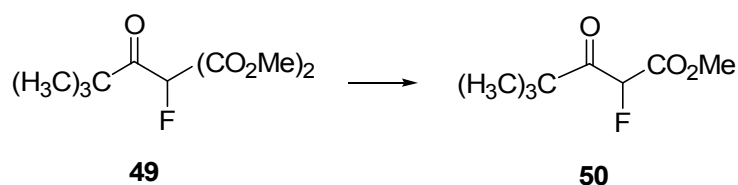
Treatment of **45** (and the enol tautomer) with DMSO, NaCl and water (150°C, 5 h) led to the ethyl thiazole-5-carboxylate **46** (47%).²⁴



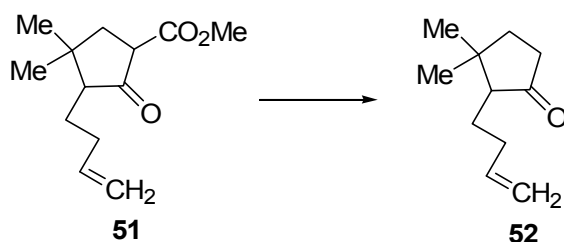
2.1.2.2. From fluoro substituted substrates. In a general method for the preparation of trifluoromethyl ketones, derivatives **47** on treatment with DMF, LiCl and water (reflux, 2 h) led to the ketones **48** (38-90%).^{25a,b}



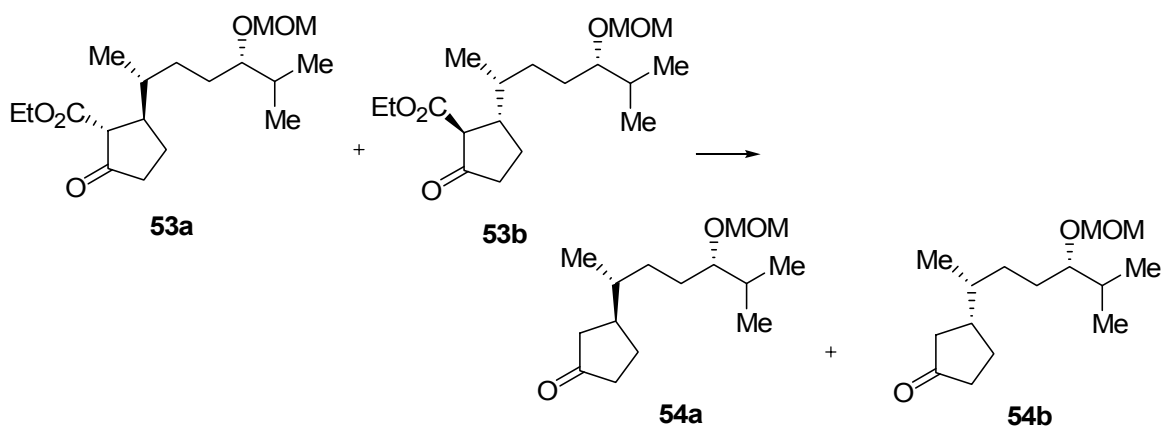
Treatment of **49** with DMSO, NaCl and water (150-160°C, 15 min) led to the loss of a methoxycarbonyl group to afford the fluoro keto ester **50** (32%).²⁶



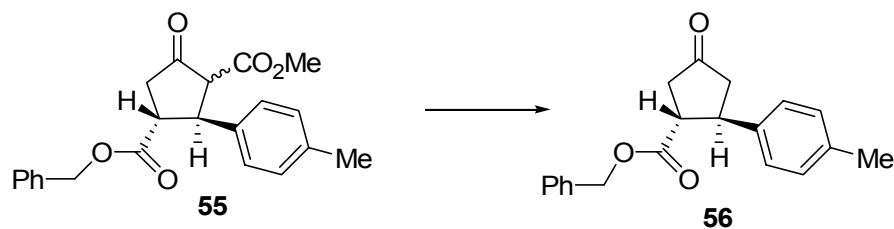
2.1.2.3. From carbocyclic β -keto esters. The β -keto ester **51** on treatment in DMF with LiI (reflux, 2 h) led to **52** (76%), an intermediate used in an attempted approach to the sesquiterpene quadrone.²⁷



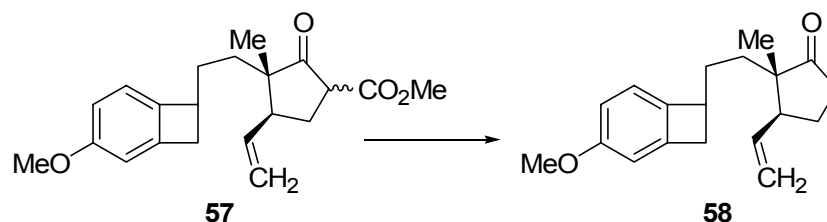
A mixture of **53a** and **53b** was treated with DMSO, LiCl and water (120-130°C, 3 h) to afford a mixture of optically active **54a** and **54b** (64%, ratio 2.45:1).²⁸



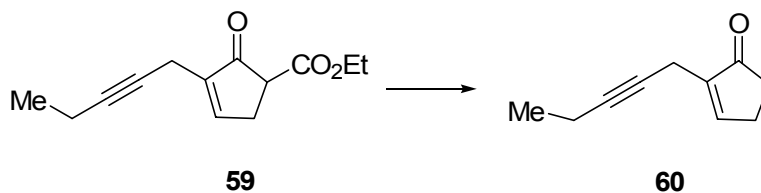
Treatment of chiral **55** with DMSO and NaI (100°C, 3 h) led to the (-)-**56** (3*S*, 4*S*) (89%). This intermediate was subsequently converted into cuparene, laurene, (-)- α - and (+)- β -cuparenones.²⁹



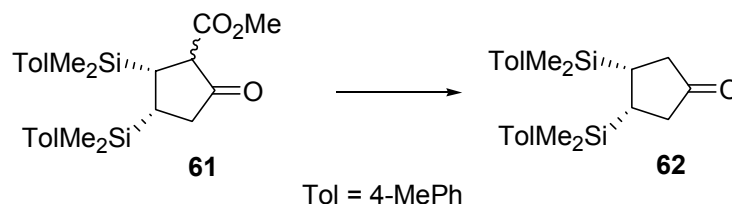
The synthesis of (+)-**58** (69%) was accomplished by heating **57** in DMSO, NaCl and water (165°C, 45 min). This intermediate was converted into (+)-estrone methyl ether.³⁰



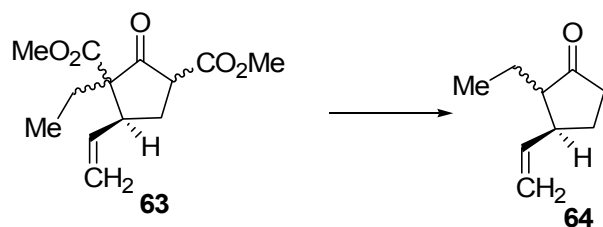
Upon heating β -keto ester **59** in DMSO, LiCl and water (190°C, 2 h), the α,β -unsaturated ketone **60** (73%) was obtained. This intermediate was subsequently transformed into *cis*-jasnone.³¹



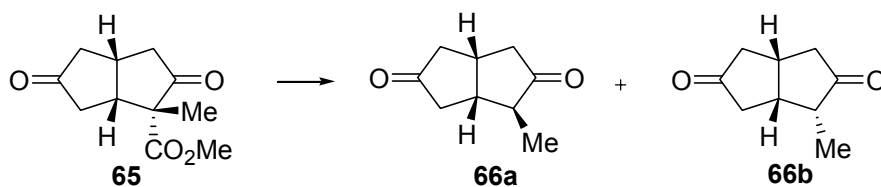
The bis-silylated keto ester **61** on treatment with DMSO, NaCl and water (130-150°C, 3 h) led to the decarbomethoxylated product **62** (86%).³²



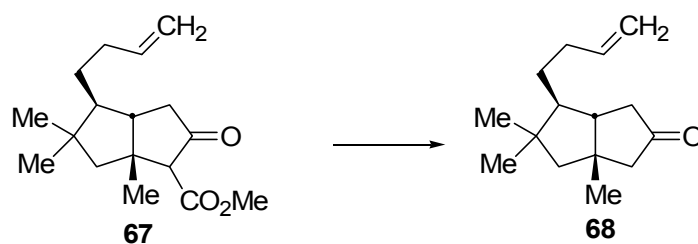
Treatment of *rac*-**63** with DMSO, LiCl and water (reflux, 5 h) led to *rac*-**64** (40%) which was used in a synthesis of (-)-norgestrel.³³



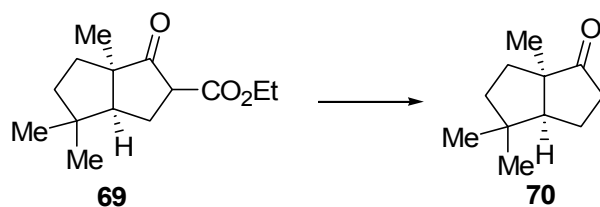
Treatment of **65** with DMSO, NaCl and water (reflux, 5 h) led to a mixture of **66a**:**66b** (69%).³⁴



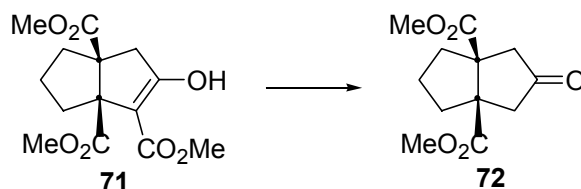
Treatment of **67** with DMSO, LiCl and water (145°C, quickly to room temperature) led to racemic **68** (96%) which was used in a synthesis of racemic silphinene.³⁵



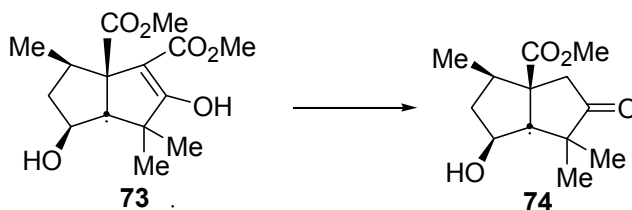
Treatment of **69** with DMSO, NaCl and water (150°C, 6 h) afforded (-)-**70** (86%) which in a series of steps could be converted into (+)-capnellene.³⁶



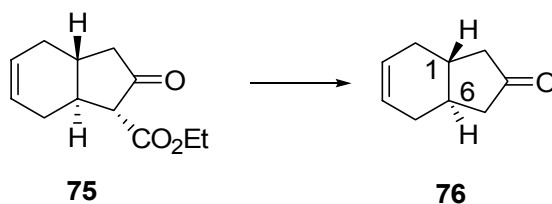
Treatment of enolic triester **71** with DMSO, NaCl and water (140°C, 2 h) led to keto diester **72** (92%). This was used as an intermediate in the synthesis of tricyclo octane structure.³⁷



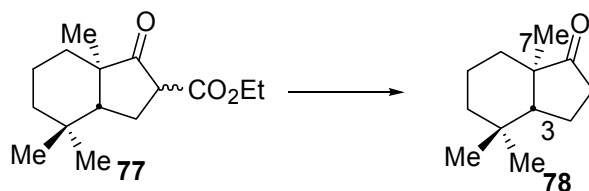
The demethoxycarbonylation of **73** was accomplished by heating in DMSO, NaCl and water (85°C, 19 h) to afford racemic **74** (62%). This was subsequently converted into the cedrenoid sesquiterpenes racemic α -biotol and β -biotol.^{37a} Other similar conversions have also been reported.^{38b,c}



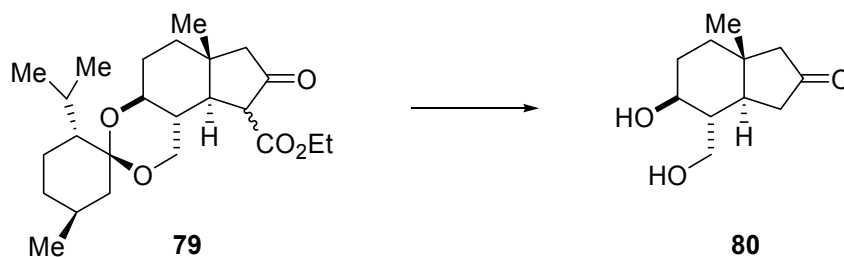
Enantiomerically pure **75** on treatment with DMSO and water (155°C, 2.5 h) led to the deethoxycarbonylated ketone **76** (1*R*,6*R*) (92%). Attempts to convert this ketone into (+)-papuamine, a pentacyclic alkaloid isolated from a sponge, were not successful.³⁹



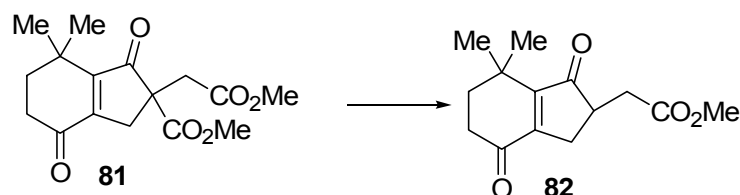
Treatment of **77** with DMSO, LiCl and water (120-140°C, 2 h) led to (3*aR*,7*aR*)-**78** (91%). This ketone was subsequently converted into (+)-grindelic acid in a 10-step sequence.⁴⁰



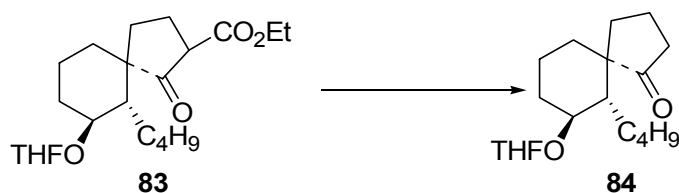
The dealkoxycarbonylation of **79** using DMSO, LiCl and water (reflux, 30 min) led to the removal of the protective group with formation of the keto diol **80** (78%).⁴¹



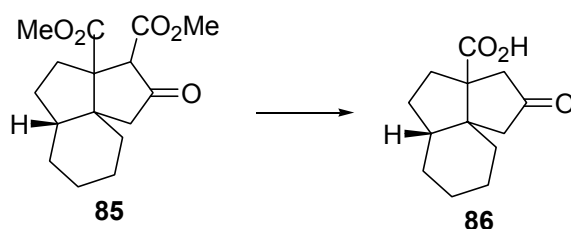
Treatment of **81** with N-methylpyrrolidone, LiCl and water (120-125°C, 6 h) led to **82** (70%), used in a synthesis of racemic strigol, a seed germination stimulant.⁴²



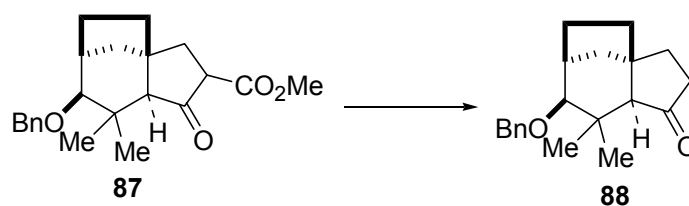
Treatment of **83** (THF = 2-tetrahydrofuran) with DMSO-LiCl, sodium bicarbonate and water (150°C, 3 h) led to racemic product **84** (92%), which was converted into a intermediate for the synthesis of racemic perhydrohistrionicotoxin.⁴³



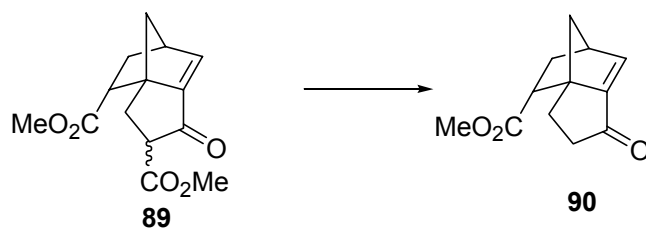
The demethoxycarbonylation of **85** (and the enol tautomer) with DMSO, LiCl and water (165-170°C, 8 h) led to **86** (67%) in which the tertiary ester was also hydrolyzed to the carboxylic acid.⁴⁴



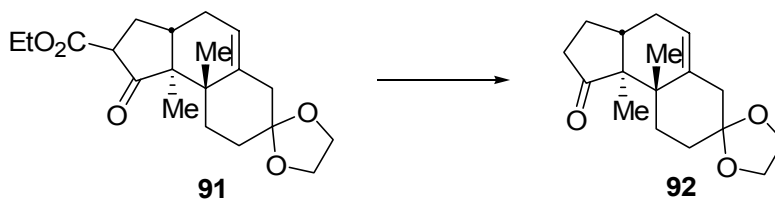
The demethoxycarbonylation of β -keto ester **87** with DMSO, NaCl and water (150°C, 8 h) led to **88** (88%) which was used in a synthetic pathway to several natural tricyclic sesquiterpenes.⁴⁵



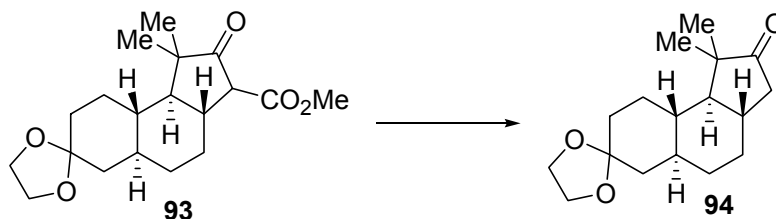
The β -keto ester **89** and DMSO, NaCl and water (110°C, 16 h) yielded **90** (72%), which could be converted into other functionalized tricyclicoundecanes.⁴⁶



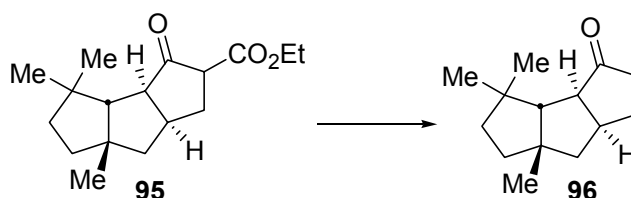
The deethoxycarbonylation of **91** with DMSO, NaCl (70°C, 3 h) led to (-)-**92** (73%, for 2 steps with prior CrO₃ oxidation of alcohol to the ketone), a common intermediate utilized in the synthesis of the indole diterpenes (+)-paspalicine and (+)-paspalinine.⁴⁷



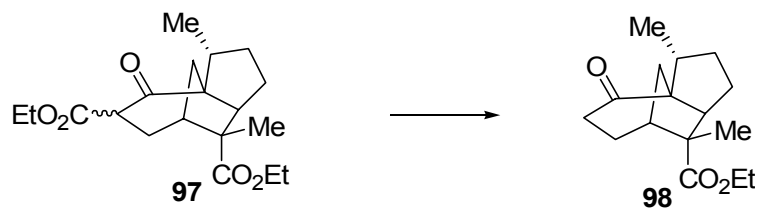
Treatment of racemic **93** with DMSO, LiCl and water (170°, 1.25 h) led to racemic **94** (92%).⁴⁸



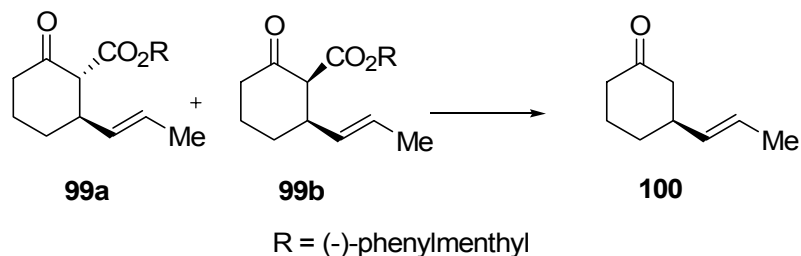
Treatment of **95** with DMSO, NaCl and water (150°C) led to **96**, used in a synthesis of a racemic capnellene.⁴⁹



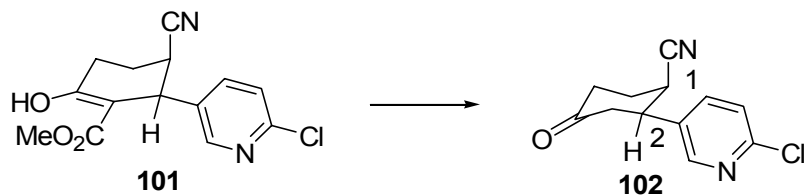
The deethoxycarbonylation of **97** with DMSO, MgCl₂ hexahydrate (140°C, 28 h) led to racemic **98** (74%) with the α -trisubstituted ester intact. Ester **98** was utilized in a synthesis of the sesquiterpenes cedranediol and cedranoxide.⁵⁰



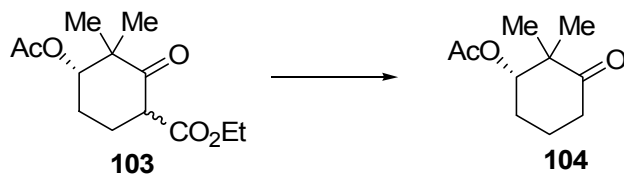
A 12:1 mixture of **99a** and **99b** on treatment with DMSO, NaCl and water (reflux, 24 h) led to **100** (*S*) (83%ee) (59%).⁵¹



Treatment of **101** with DMSO and water (130°C, 24 h) led to the demethoxycarbonylation product **102** (2*S*, 1*R*) (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 nonopioid analgesic.⁵²



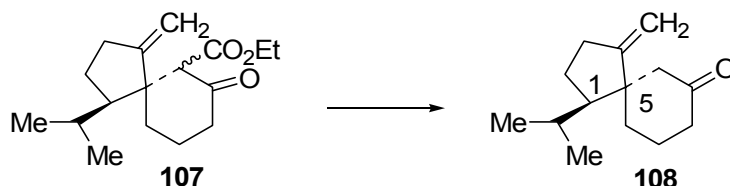
Treatment of optically active **103** with DMSO, NaCl and water (180-185°C, 3.5 h) led to (*3S*)-**104** (79%).⁵³



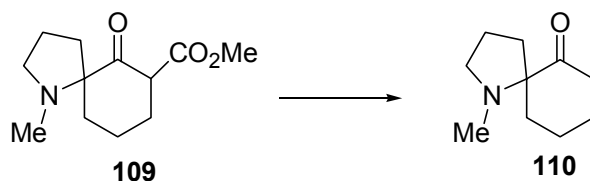
The β -keto ester **105** underwent decarbomethoxylation when treated with DMSO, NaCl and water (150°C, 4.5 h) to yield racemic β -vetivone **106** and racemic epi β -vetivone (1.7:1 ratio) (77%), which could be separated by column chromatography.⁵⁴



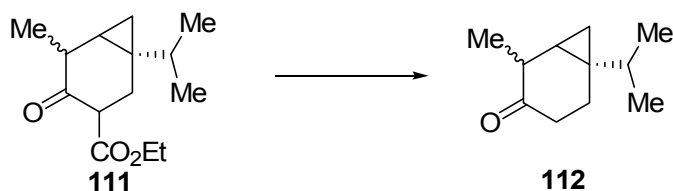
The spiro β -keto ester **107** on treatment with DMSO, NaCl and water (130°C, 2 h) led to the (1*R*,5*R*) spiro[4,5]decan-7-one (**108**, 70%).⁵⁵



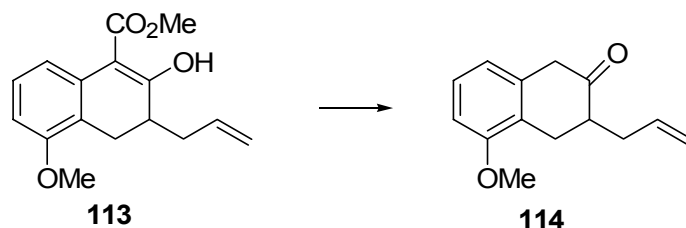
Treatment of **109** with DMSO and water (115-120°C, 3 h) gave **110** (73%).⁵⁶



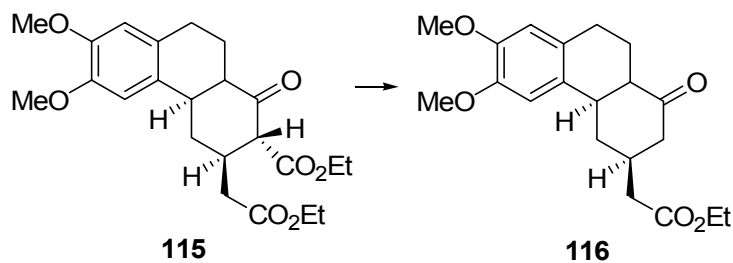
Treatment of **111** (and the enolic tautomer) with DMSO, NaCl and water (140°C, 4 h) led to homothujone **112** (as a mixture of α - and β -diastereoisomers in a 10:1 ratio).⁵⁷



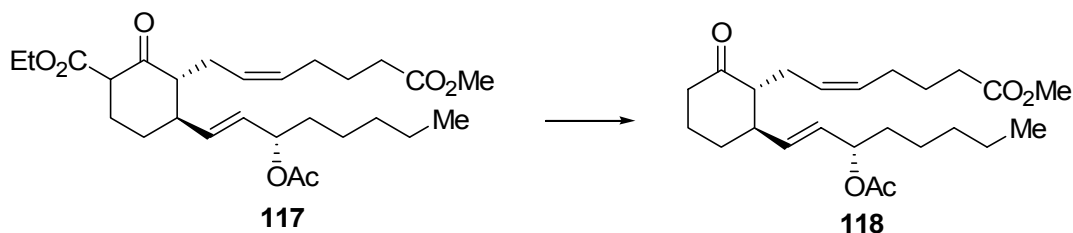
Treatment of enol **113** with DMSO, LiCl and water (150°C, 4 h) led to **114** in a quantitative yield, which was utilized in a synthesis of a benzindene prostacyclin analogue.⁵⁸



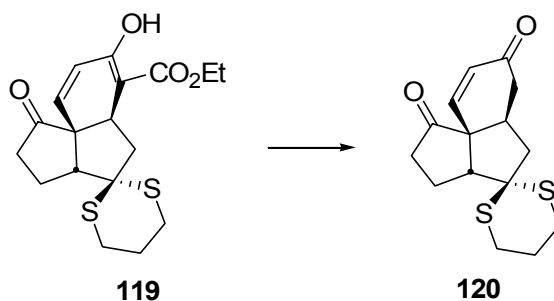
Treatment of **115** with DMSO, NaCl and water (heat) led to **116** (47%).⁵⁹



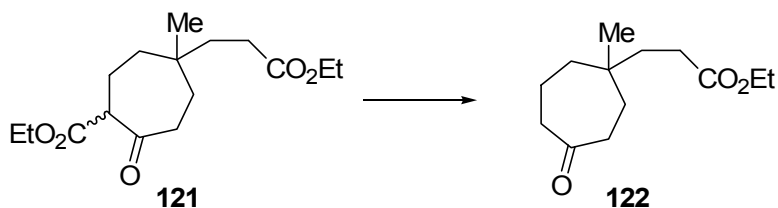
In a study dealing with thromboxane A₂ analogues, it was reported that treatment of crude **117** (obtained as two regioisomers via a ring expansion of a prostaglandin intermediate with ethyl diazoacetate) with DMSO, NaCl and water (150°C, 2 h) led to optically active **118** (52%).⁶⁰



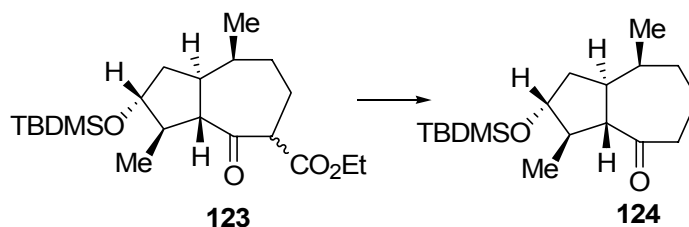
In the total synthesis of tetracyclic Lycopodium alkaloids, the intermediate **120** was prepared by treatment of **119** with NaCl in DMF (no conditions or yield).⁶¹



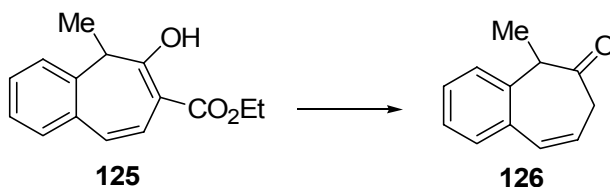
Treatment of β -keto ester **121** with DMSO, NaCl and water (160°C, 6 h) led to **122** (85%) which was used in a synthesis of racemic isoclovene, a tricyclic ketonic sesquiterpene.⁶²



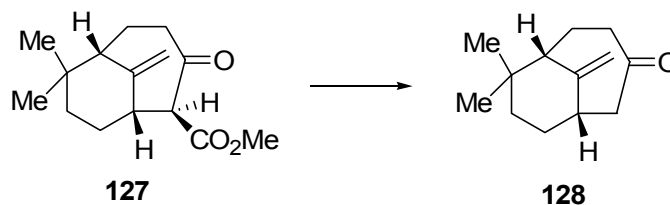
Treatment of a number of bicyclic β -keto esters with DMSO, NaCl and water led to the corresponding deethoxycarbonylated products. As an illustration, **123** on treatment with DMSO, NaCl and water (reflux, 2 h) led to chiral **124** (1*S*, 6*S*, 7*S*, 9*R*, 10*R*) (86%), used in a route leading to an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



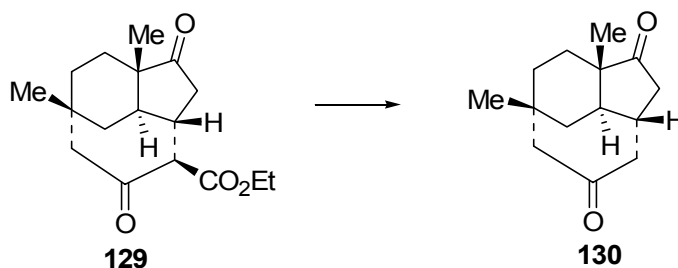
Treatment of **125** with DMSO, NaCl and water (140°C, 0.5 h) led to **126** (82%).⁶⁴



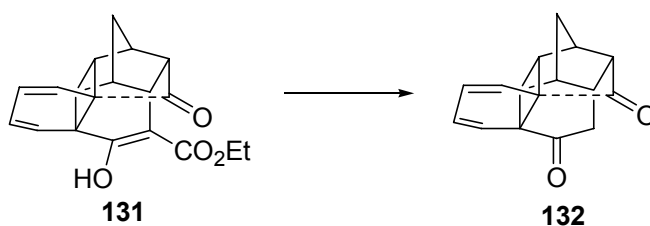
Treatment of **127** with DMSO, LiCl and water (175°C, 3 h) led to racemic **128** (86%) which in a subsequent series of steps was converted into the furano sesquiterpene dihydropallescensin.⁶⁵



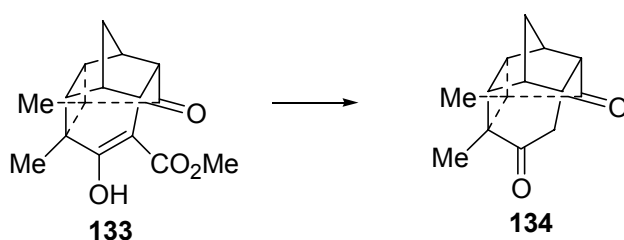
The deethoxycarbonylation of **129** with DMSO, NaCl and water (160°C, 3 h) led to **130** (quantitatively). This key intermediate, in a series of steps, was converted into the sesquiterpene, racemic isoclovene.^{66a,b}



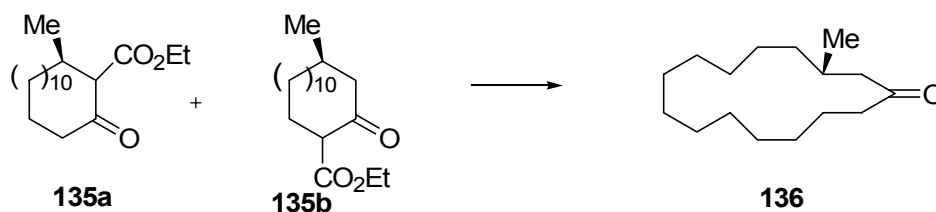
The deethoxycarbonylation of **131** with DMSO, NaCl and water (150-160°C, 6 h) led to the hexacyclic dione **132** (56%).⁶⁷



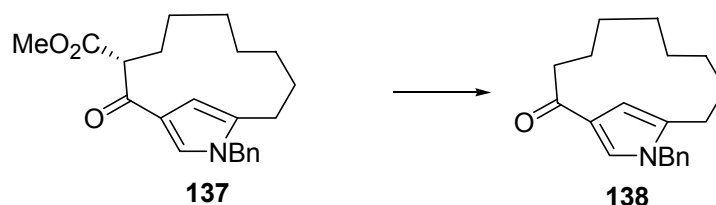
The deethoxycarbonylation of **133** with DMSO, NaCl and water (150°C, 4 h) led to **134** (91%).⁶⁸



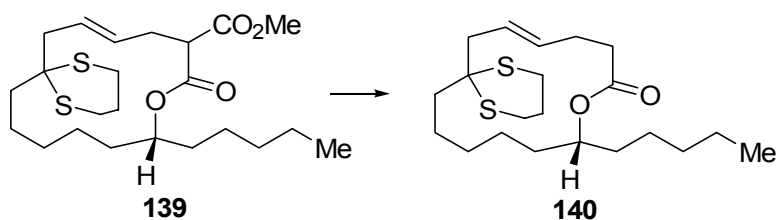
The deethoxycarbonylations of a mixture of chiral **135a** and **135b** with DMSO and water (165°C, 4 h) led to (*R*)-(-)-muscone (**136**, 59%).⁶⁹



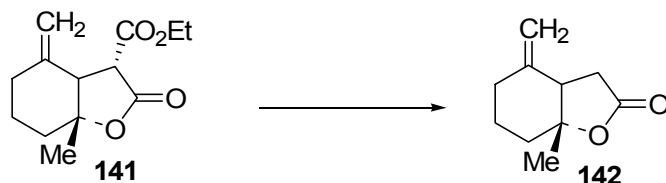
In synthetic routes to *m*-pyrrolophanes, the β -keto ester **137** on treatment with DMSO, NaCl and water (180-190°C, 1.5 h) led to ketopyrrole **138** (91%).⁷⁰



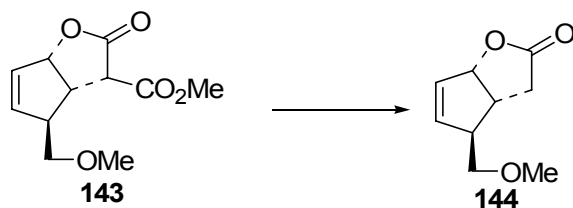
2.1.2.4. From heterocyclic β -keto esters. Treatment of macrocycle **139** with DMSO, LiCl and water (reflux, 1 h) led to **140** (78%), which was used in a synthesis of glucosporone, an autoinhibitor of spore germination.⁷¹



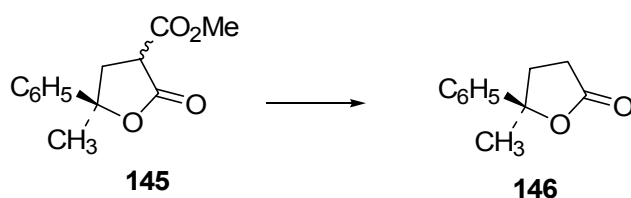
The lactone **141** on treatment in DMF with LiBr (reflux, 8 h) led to racemic **142** (90%) used in a synthesis of the male sex pheromones of Caribbean and Mexican fruit flies.⁷²



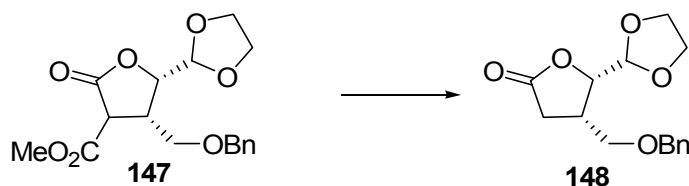
Treatment of lactone **143** with DMSO, NaCl and water (110°C) led to **144** (83%), which in a subsequent series of steps could be converted into racemic Corey's lactone.⁷³



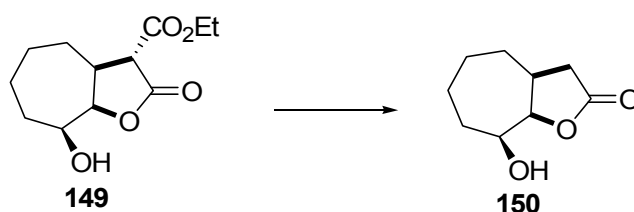
Treatment of (*R*)-**145** with refluxing aqueous DMF for 12 h led to lactone (*R*)-**146** (99%ee) in good yield.⁷⁴



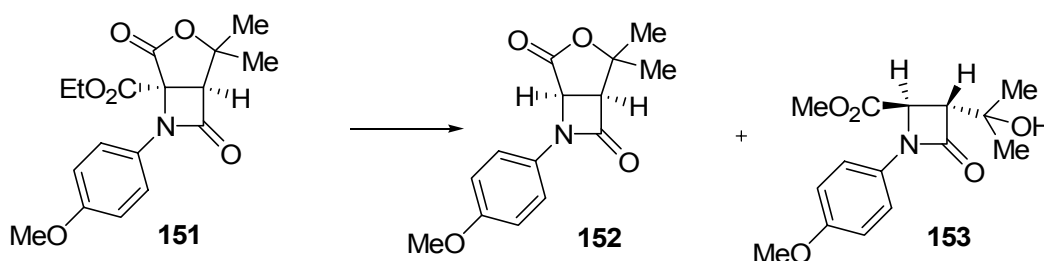
Treatment of **147** with DMSO, LiCl and water (100°C, 24 h) led to racemic **148** (85%) which was used in the synthesis of the partial ring skeleton of the ginkgolides.⁷⁵



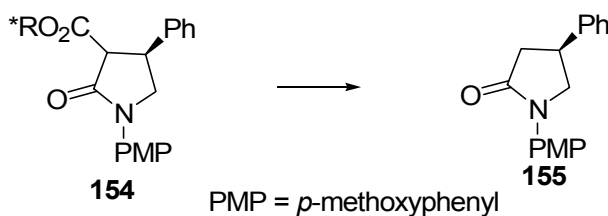
Treatment of **149** with DMSO, NaCl and water (180°C, 50 min) afforded **150** (95%) which were used in a synthesis of guaianolides and related derivatives.⁷⁶



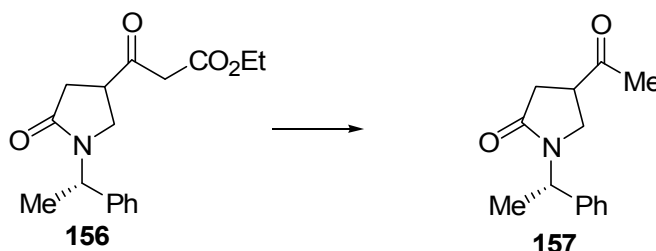
Lactam **151** on treatment with DMF, NaCl and water (heat, 12 h) led to **152** (40%) and ring opened product **153** (29%).⁷⁷



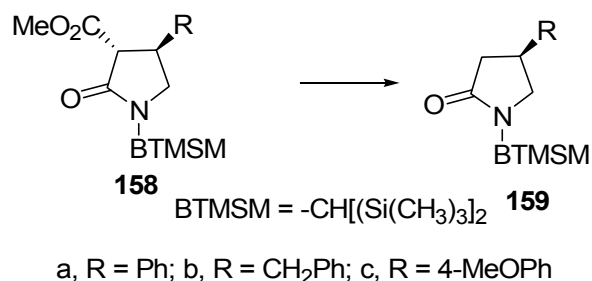
The dealkoxycarbonylation of **154** (where R* is a chiral appendage) with DMSO, NaCl and water at reflux led to (*S*)-**155** (84%).⁷⁸



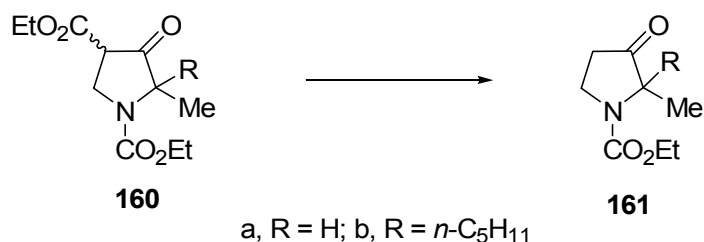
The deethoxycarbonylation of the β -keto ester **156** in DMSO, NaCl and water (130-135°C, 20 h) led to a crude product which on chromatography gave enantiomer **157** (36%).⁷⁹



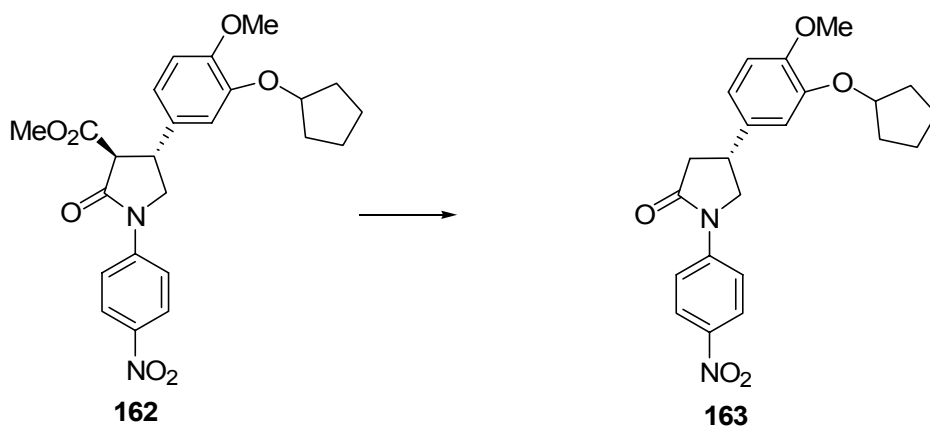
The optically active ester lactams **158a** and **158b** on treatment with DMSO, NaCl and water (150°C, 28 h) led to **159a** and **159b** in good yields. In **158c**, a similar procedure led to the desired product **159c** along with some mono-desilylated product in a 1:4.3 ratio.⁸⁰



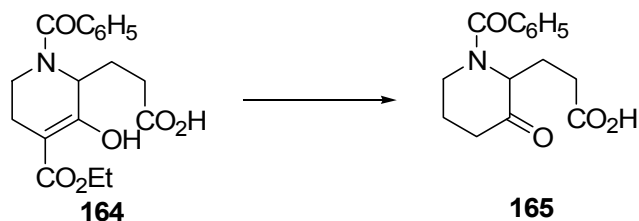
Treatment of a number of 4-ethoxycarbonyl-N-substituted pyrrolidin-3-ones with DMSO, NaCl and water led to the corresponding decarbomethoxylation products. For example treatment of **160a** or **160b** with DMSO, NaCl and water (130°C) led to **161a** (81%) or **161b** (83%), respectively.⁸¹



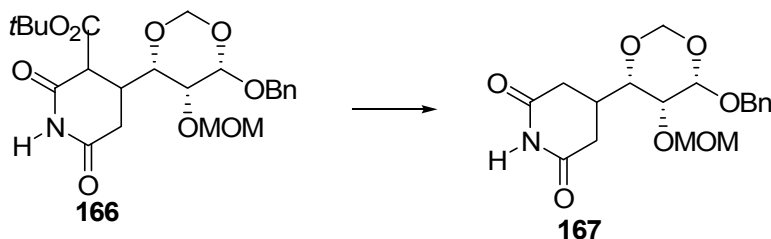
A key 4-substituted 2-pyrrolidone intermediate **163** (97%, which after crystallization led to an optically pure sample (71%)), was prepared by decarbomethoxylation of **162** (88%*ee*) on treatment with DMSO, NaCl and water (160°C, 2 h). This intermediate was converted into a phosphodiesterase type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



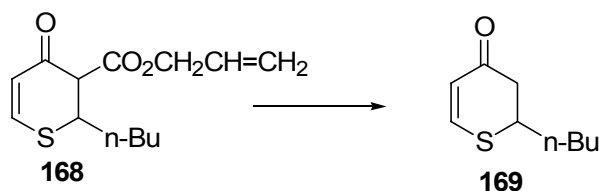
Treatment of the enol ester **164** with DMSO, NaCl and water (155-160°C, 3 h) led to the 3-oxo-2-piperidine-propionic acid **165** (78%). The intramolecular acylation of this analogue into the corresponding enol lactone was accomplished.⁸³



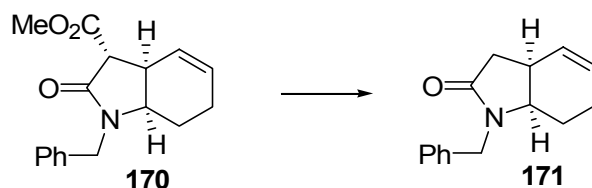
Enantiomer **166** with DMSO, NaCl and water (160-170°C, 1 h) led to enantiomer **167** (63%), an intermediate used in the study of the synthesis of (+)-sesbanimide.⁸⁴ In this case, perhaps the addition of salt might not be necessary.



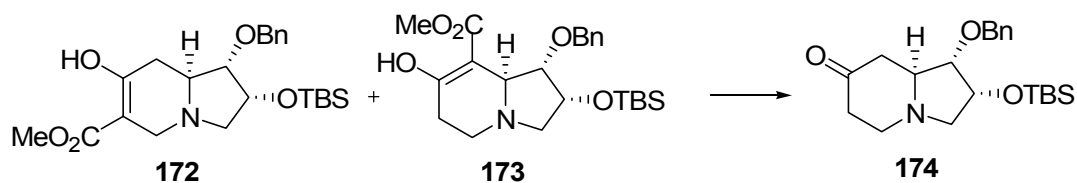
The deallyloxycarbonylation of substrate **168** with DMF, MgCl₂ hexahydrate and water (reflux, 20 h) yielded **169** (91%).⁸⁵



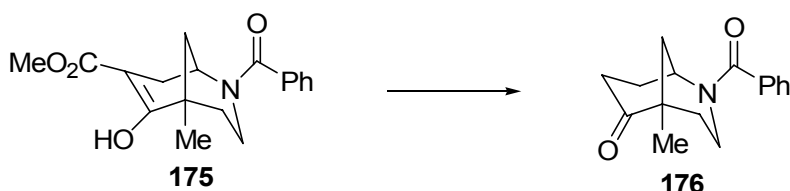
The decarbomethoxylation of **170** in DMSO, NaCl and water (155°C, 10 h) led to **171** (99%) which was converted into racemic pyrrolizidine alkaloid isoretronecanol.⁸⁶



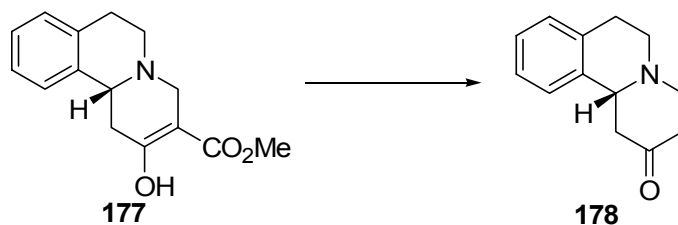
The decarbomethoxylation of a mixture of the enol esters **172** and **173** in DMSO, NaCl and water (130°C, 4 min) led to the indolizone **174** (92%). Intermediate **174** was subsequently transformed in a series of steps into natural (+)-lentiginosine.⁸⁷



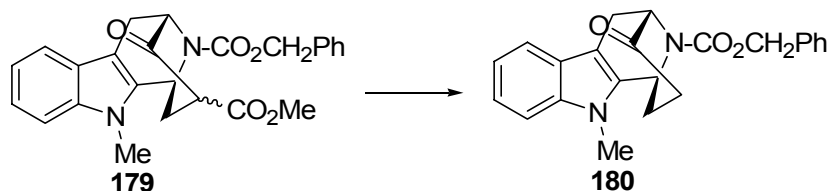
Treatment of **175** with DMSO, NaCl and water (155-160°C, 3 h) gave **176** (74%).⁸⁸



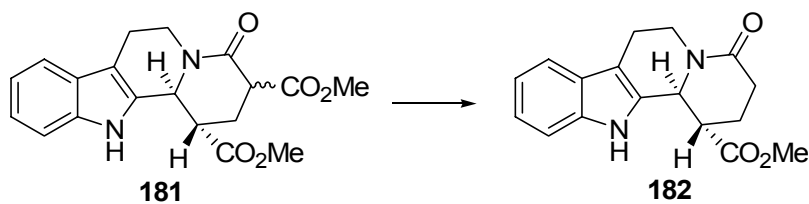
Treatment of (*R*)-**177** with DMSO, NaCl and water (140°C, 3 h) led to (*R*)-**178** (60%). However, the ee of (*R*)-**178** was only 0.5% which appeared to indicate that racemization had occurred in the demethoxycarbonylation step.⁸⁹



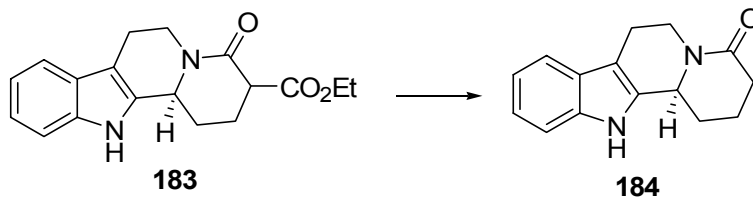
The decarbomethoxylation of (-)-**179** (and the enol form) with DMF, NaCl and water (130°C, 6 h) led to (-)-**180** (73%, >95% ee). A similar procedure on the enantiomer led to (+)-**180**. These intermediates could then be converted into several indole alkaloids such as (-)-ajmaline.⁹⁰



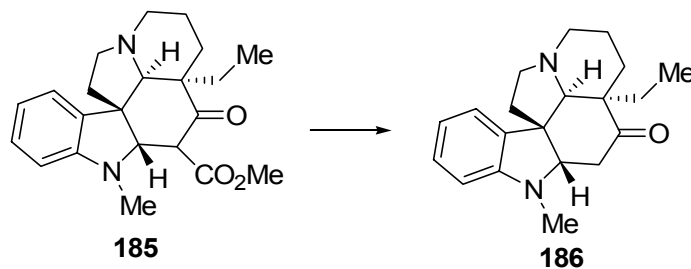
The demethoxycarbonylation of derivative **181** proved to be quite difficult. The best result was obtained by treatment of **181** with dry DMSO and LiI dihydrate (132°C, 36 h) to afford **182** (56%). The use of DMSO, NaCl and water at 180°C did not lead to demethoxycarbonylation.⁹¹



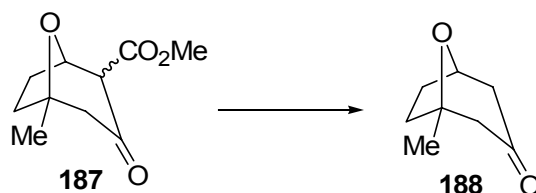
Treatment of ester **183** with DMSO, LiCl and water (160°C, 3.5 h) led to **184** (99%ee). This intermediate was converted into (+)-geissoschizine.⁹²



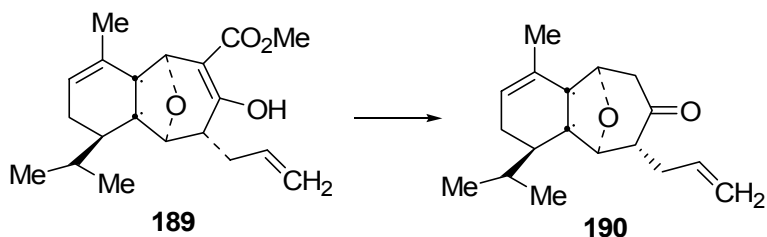
The decarbomethoxylation of of **185** with DMSO, LiCl and water (150°C, 25 min) led to **186** (98% ee), a known degradation product of vindoline.⁹³



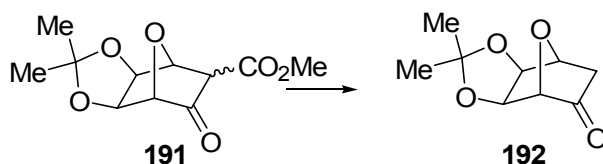
Keto ester **187** on treatment with DMSO, LiCl and water (reflux, 2.5 h) led to **188** (78%). A subsequent series of steps led to the racemic sesquiterpene davanone.⁹⁴



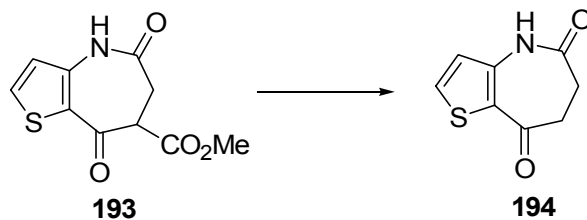
In approaches to the cladiellin skeleton, the intermediate **189** on treatment with LiCl, DMSO (130°C, 3 h) and water led to enantiomer **190** (86%).⁹⁵



The preparation of enantiomer **192** (41%) was performed by heating **191** in dry DMF and LiI dihydrate (130°C, 2.5 h).⁹⁶

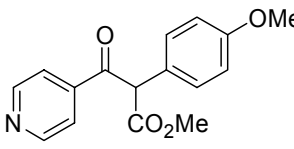
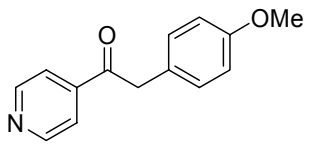
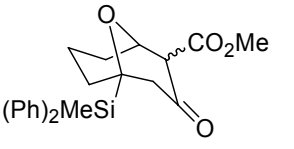
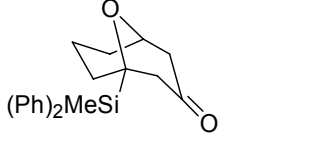
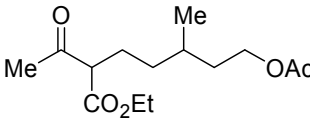
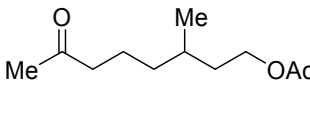
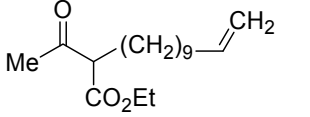
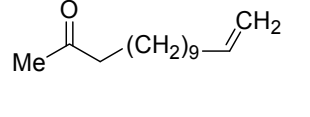
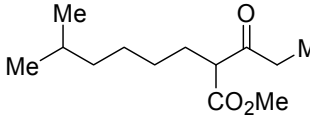
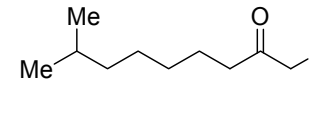
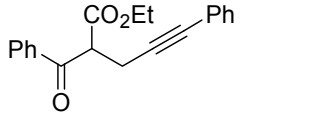
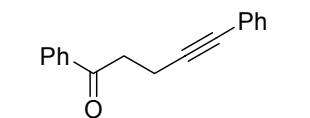
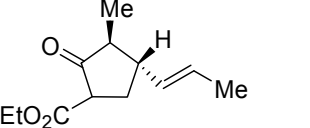
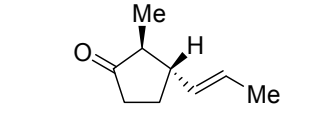
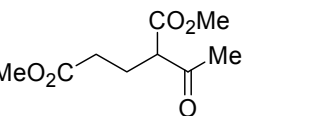
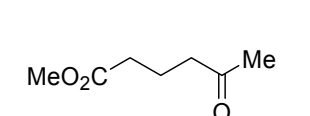
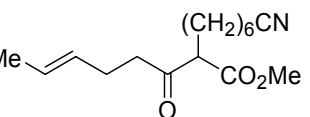
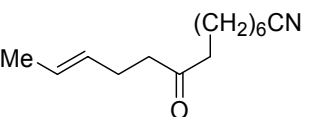
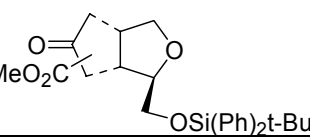
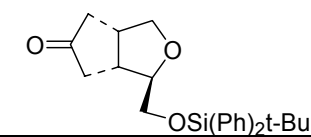


The demethoxycarbonylation of **193** (and the tautomeric enolic ester) was easily accomplished in DMSO and water (150°C, 1 h) to yield the thienoazepine dione **194** (82%).⁹⁷ A related pyrimidine analogue underwent demethoxycarbonylation in DMSO and anhydrous NaCl.⁹⁸

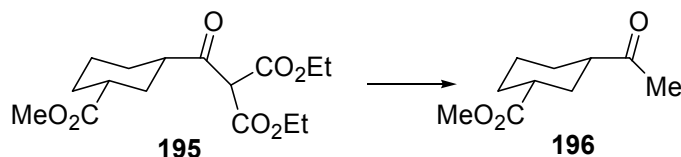


Additional examples are tabulated in Table 1.

Table 1. Dealkoxycarbonylations of monosubstituted β -keto esters

Starting Material	Conditions	Product	Yield (%)	Reference
	DMSO, NaCl, H ₂ O 150°C		47	99
	DMSO, LiCl, H ₂ O 130°C, 2 h		91	100
	DMF, LiI reflux, 12 h		81	101
	DMSO, LiCl, H ₂ O reflux, 10 h		40	102
	DMSO, LiCl, H ₂ O reflux, 24 h		88	103
	DMSO, LiCl, H ₂ O reflux, 10 h		74	104
	DMSO, NaCl, H ₂ O 130°C, 3 h		quant	105
	DMSO, LiCl, H ₂ O 160°C, 4 h		73	106
	DMSO, LiCl, H ₂ O reflux, 3.5 h		76	107
	DMSO, NaCl, H ₂ O 100°C, 5.5 h		83	108

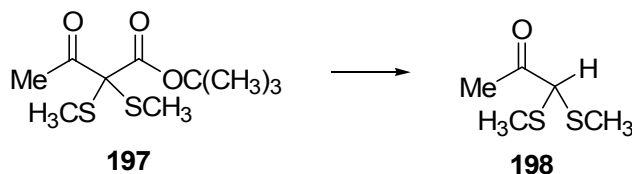
2.1.2.5. From an α,α -diethoxycarbonyl ketone. Treatment of **195** with DMSO, NaCl and water (160-170°C, 6 h) afforded **196** (90%) the bis-deethoxycarbonylation product **196** (90%).¹⁰⁹



2.2. Disubstituted β -keto esters

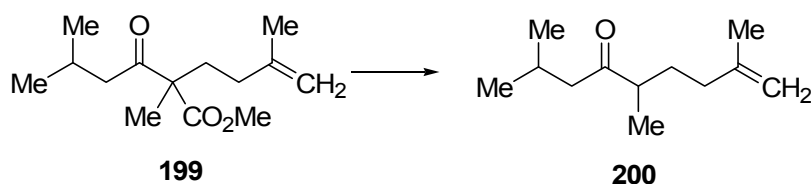
2.2.1. Water alone

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%).¹¹⁰

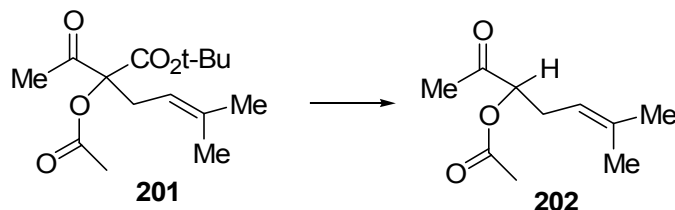


2.2.2. Water-salts

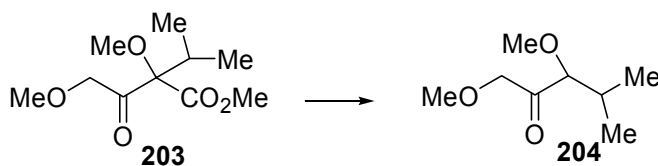
2.2.2.1. Open chain substituents. The racemic β -keto ester **199** on heating in DMSO with LiCl and water (170°C, 1.5 h) led to a key intermediate **200** (89%), which was converted in 2 steps to racemic stigmalone.¹¹¹



A number of 3-acyloxymethyl ketones were synthesized by the chemoselective dealkoxycarbonylation 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%).¹¹² In this case the presence of the salt might not be necessary.

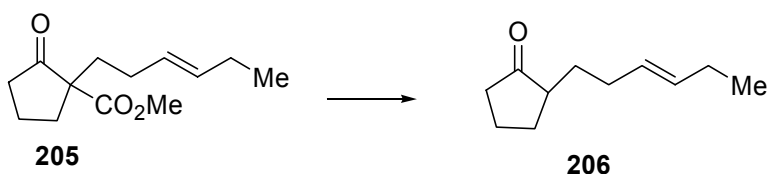


The preparation of a number of 1-alkyl-1,3-dimethoxyacetones has been accomplished by treatment of the appropriate β -keto ester with DMSO, LiCl and water (120-140°C, 10 h). For example, under these reaction conditions the demethoxycarbonylation of **203** led to **204** (72%).¹¹³

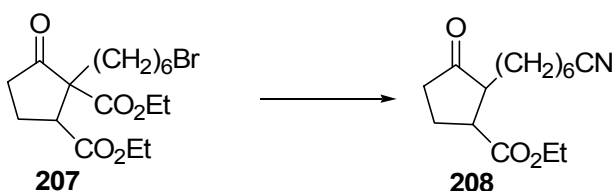


2.2.2.2. From carbocyclic β -keto esters

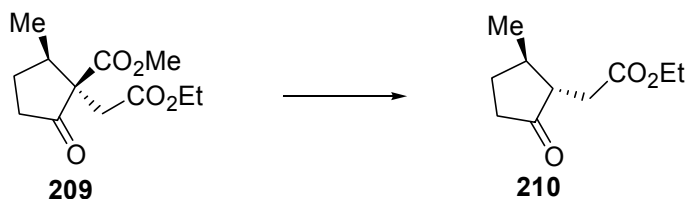
2.2.2.3. Water-salts. Treatment of **205** with DMSO, NaCN and water (140°C, 1 h) led to **206** (53%).¹¹⁴



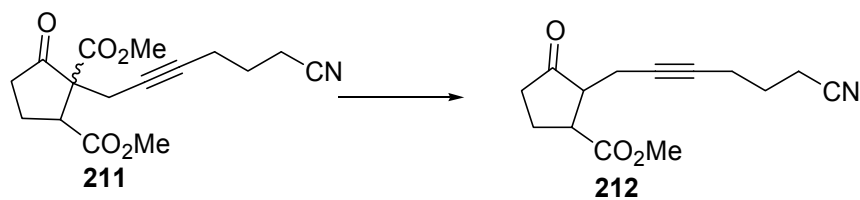
Upon treatment of **207** with DMSO and NaCN (135-140°C, 2 h) the de-ethoxycarbonylation and displacement of the bromide occurred to afford nitrile **208** (75%).¹¹⁵



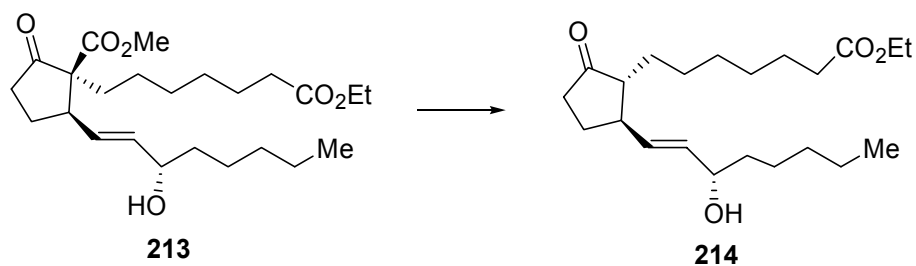
Treatment of enantiomer **209** with DMF and LiI (reflux, 2 h) led to enantiomer **210** (76%), which was used in a synthesis of a triquinane portion of retigeranic acid.¹¹⁶



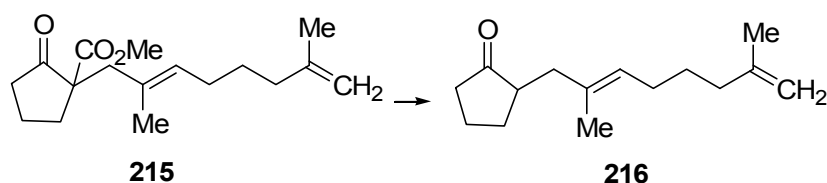
Treatment of **211** with DMSO, NaCl, water (155-160°C, 5 h) led to **212** (53%), along with some ring-opened product. This intermediate was to be used in a synthetic approach to 11-deoxyprostaglandins.¹¹⁷



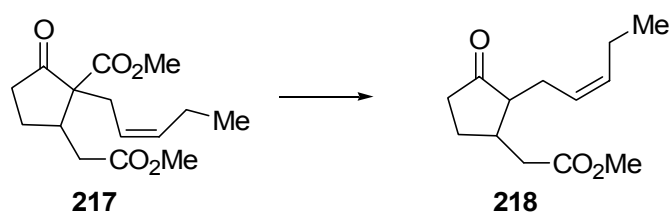
In studies dealing with the synthesis of prostaglandins, the treatment of **213** with HMPA and NaCN (75-80°C, 1.5 h) led to racemic **214**.¹¹⁸



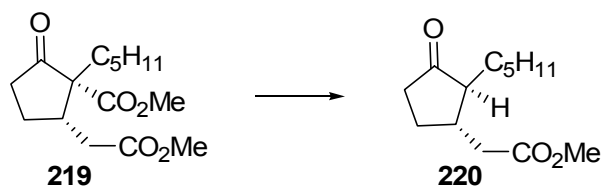
The β -keto ester **215** on treatment with DMF and LiI (reflux, 8 h) led to **216** (85%), a prostaglandin synthon.¹¹⁹



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).¹²⁰

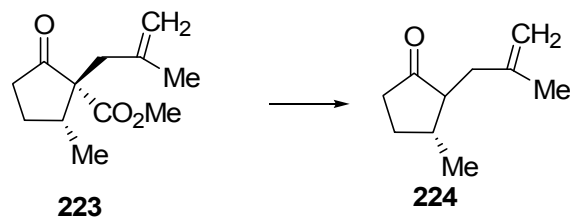


Racemic **219** on treatment with DMSO, NaCl and water (170°C, 18 h) led to methyl dihydrojasmonate **220** (83%). Under these conditions the demethoxycarbonylation of only the β -keto ester moiety occurred.¹²¹

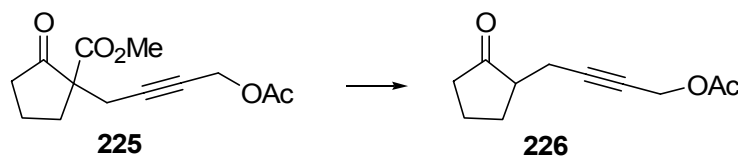


Treatment of **221** with HMPA and NaCN (75°C, 5 h) led to chiral (2*R*,3*R*,1*R*)-**222** (72%).¹²²

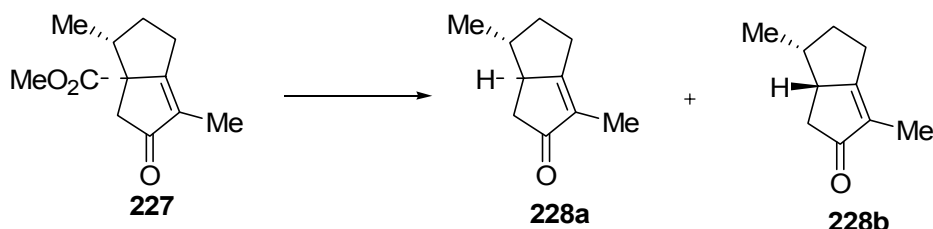
Treatment of (+)-**223** with DMSO, NaCN and water (140°C, 36 h) led to ketone (*S*)-**224** (89%) with a *trans*:*cis* ratio of 9:1. The mixture of ketones was converted into the sesquiterpenic alcohol (+)-conocephalenol in several subsequent steps.¹²³



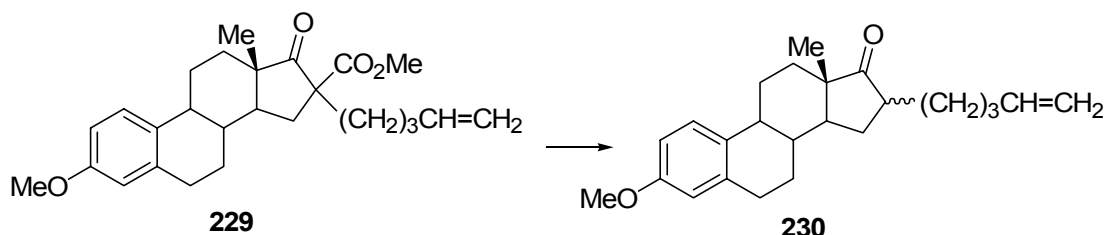
The decarbomethoxylation of **225** in DMSO and NaCN (160°C, 2 h) yielded **226** (92%) used in a synthesis of chiral phenylalanine analogues isolated from *Praxelis clematidea*.¹²⁴



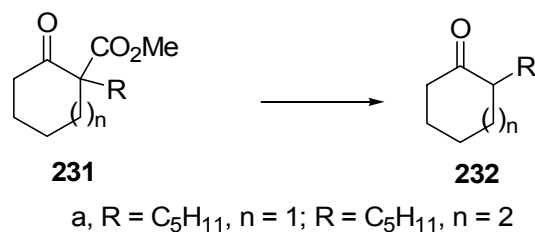
On treatment of (-)-**227** (a vinylogous β -keto ester) with DMF and LiI trihydrate (reflux, 1 h) the demethoxylated products (+)-**228a** and (-)-**228b** (90%, 5:4 ratio) were isolated and could be separated by chromatography. Compound **228a** was subsequently converted into the chiral sesquiterpene alcohol (-)-silphiperfol-5-en-3-ol.¹²⁵



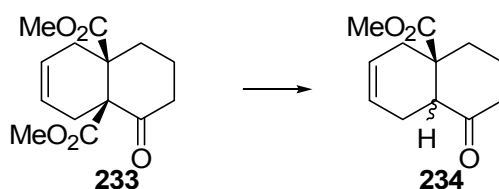
In the preparation of 16-(bromoalkyl)-estradiols, the intermediate **230** (71%, as a 16 α ,16 β mixture 15:85) was obtained by treatment of **229** with DMF, LiCl and water (reflux). Other side chains at C-16 were also prepared by this route.¹²⁶



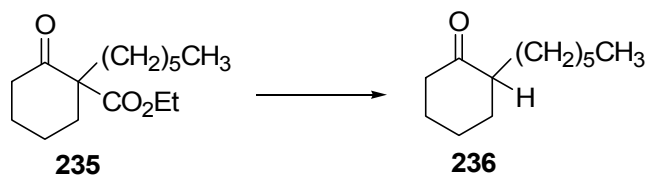
Treatment of **231a** or **231b** with DMSO, LiCl and water (180°C, 1.5 h) led to **232a** (64%) or **232** (78%), respectively.¹²⁷



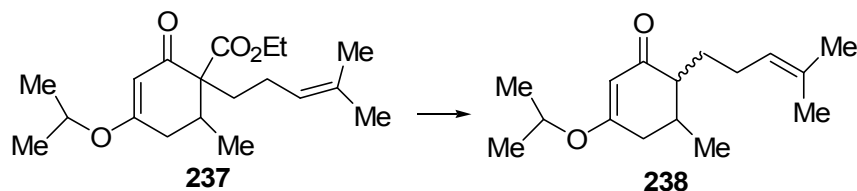
The decarbomethoxylation of **233** with DMSO, NaCl and water (160°C) led to a mixture of cis- and trans isomers **234** which could be separated by chromatography. These isomers were used in the synthesis of the sesquiterpene racemic vetiselinene.¹²⁸



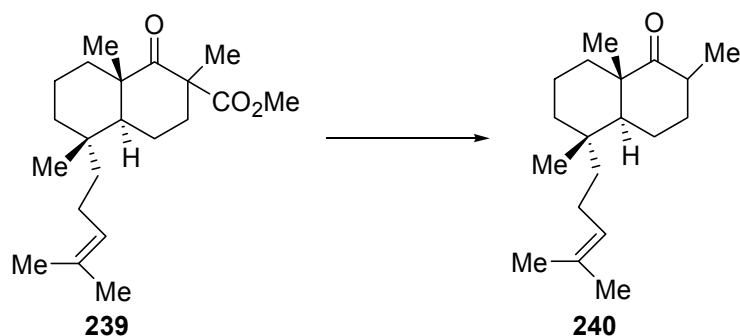
The Krapcho dealkoxycarbonylations of substituted cyclic β-keto esters using LiBr, Bu₄NBr and water under microwave irradiation have been reported. For example, under these conditions the conversion of **235** to **236** (87%) was accomplished in 20 min at 186°C.^{129a,b,c}



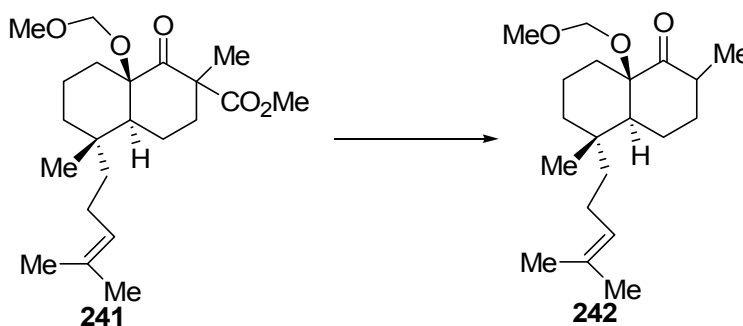
The β-keto ester **237** on treatment with DMPU (dimethylpyrimidinone) and LiCl (130°C, 48 h) gave cyclohexenone **238** (45%).¹³⁰



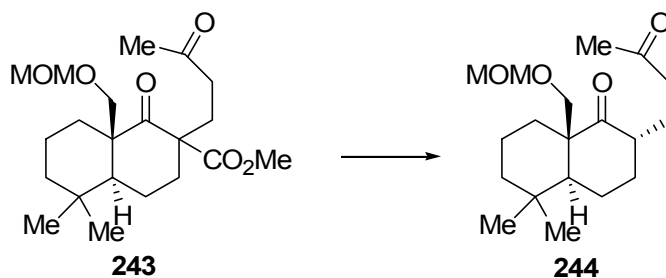
Treatment of **239** with HMPA and LiCl (130°C) led to the demethoxycarbonylated product **240** (72%) which was converted into (+)-dysideapalaunic acid, a sesquiterpene aldose reductase inhibitor.¹³¹



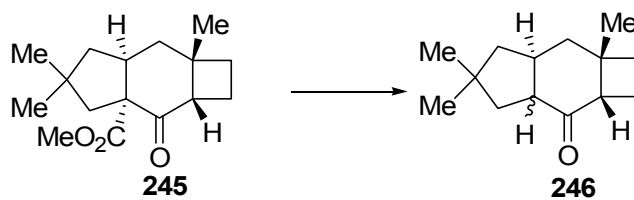
Treatment of **241** with LiCl in HMPA (130°C) afforded **242** (92%) which was used in at synthesis of (+)-perrottetianal A, sacculatane diterpene.¹³²



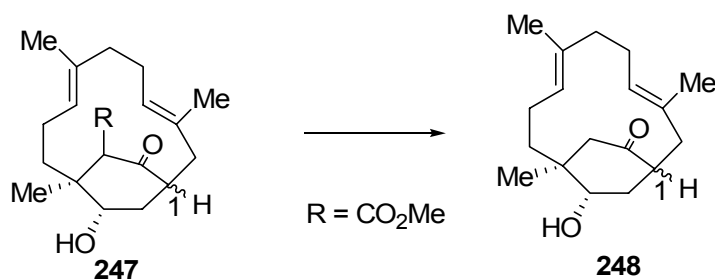
The crystalline and oily stereoisomers **243** were treated with HMPA and LiCl (120-140°C, 8 h) to afford the dione **244** (84%), which was subsequently converted into (+)-pisiferol, an abietane-type diterpene alcohol.¹³³



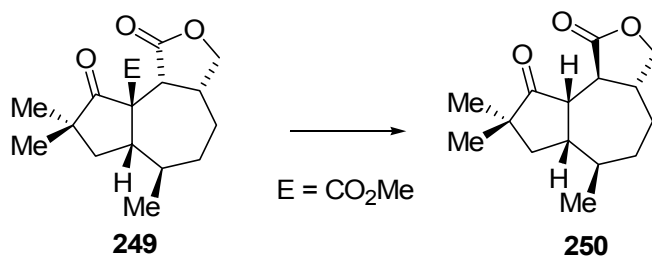
The demethoxycarbonylation of **245** with HMPA and LiCl (anhydrous conditions, 100°C, 20 h) led to a epimeric mixture of tricyclic ketones **246** (82%) which were subsequently converted into racemic sterpurene, a sesquiterpene hydrocarbon metabolite of *Chondrostereum purpureum*.¹³⁴



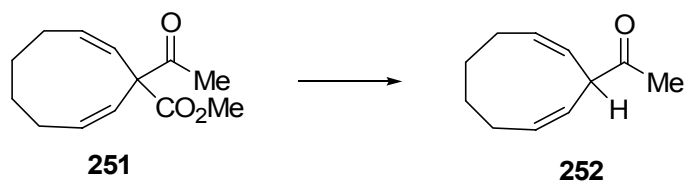
Treatment of **247a** (1- β -H) or **247b** (1- α -H) with DMSO, NaCl and water at reflux led to **248a** or **248b** (90%), which were used in the synthesis of a defense substance of a termite soldier.¹³⁵



Treatment of **249** with DMSO, NaCl and water (150°C, 6 h) led to the decarbo-methoxylation to afford racemic **250** (36%), an intermediate in approaches to a group of sesquiterpenes called tremulanes.¹³⁶



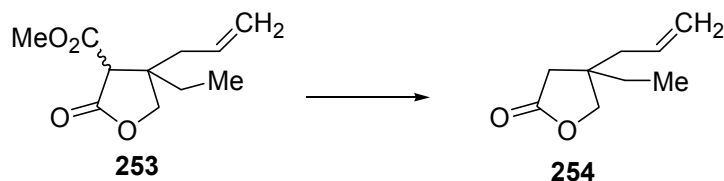
The decarbomethoxylation of **251** in aqueous DMSO (no conditions) led to ketone **252** (99%).¹³⁷



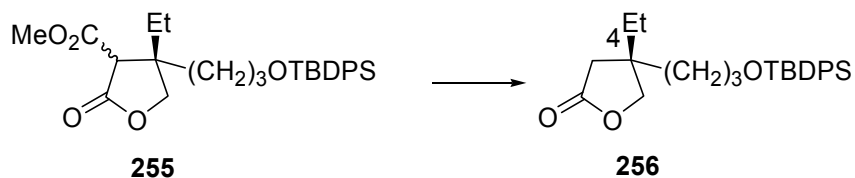
2.3. Heterocyclic substrates

2.3.1. From β -carbethoxy substituted lactones

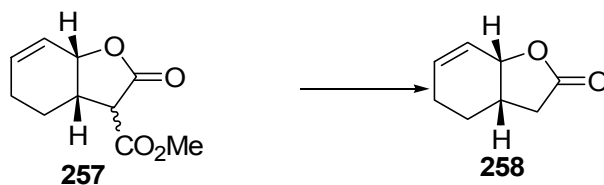
The demethoxycarbonylation of the methoxycarbonyl substituted furanone **253** to γ -lactone **254** (72%) was accomplished on treatment with DMSO, NaCl and water (160°C, 12 h).¹³⁸



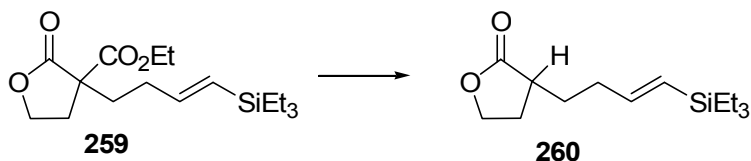
Decarbomethoxylation of γ -lactone **255** with DMSO, NaCl and water (110°C, 12 h) yielded chiral (4S) 2-butyrolactone **256** (84%) which in a series of subsequent transformations was transformed into the pentacyclic alkaloids (-)-eburnamonine and (+)-*epi*-eburnamonine.^{139a,b}



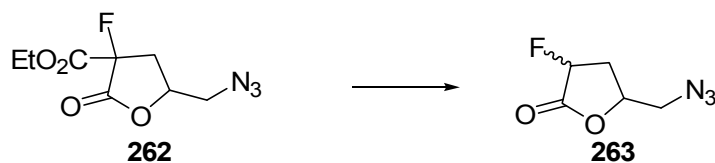
The demethoxycarbonylation of **257** in DMSO (or DMF), NaCl and water (150°C, 3-5 h) yielded the lactone **258** (75%).¹⁴⁰



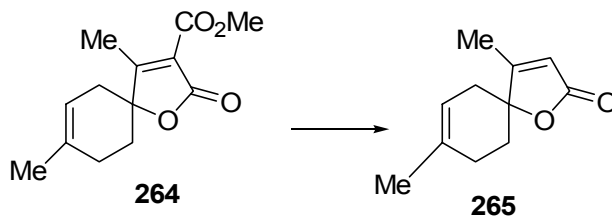
The silylated butenyl lactone **260** (77%) was obtained by treatment of **259** with DMSO and LiCl (reflux, 3 h). Further elaborations of the lactone and terminal silyl group were performed.¹⁴¹



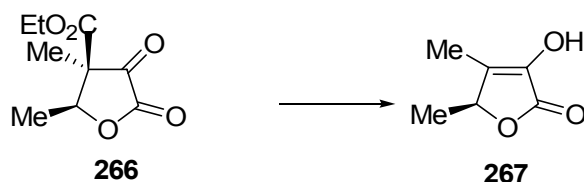
The deethoxycarbonylation of the fluorinated lactone **262** with DMSO, NaCl and water (reflux, 2.5 h) led to a diastereoisomeric mixture of lactones **263** (73%) which in a few steps could be converted in 5-amino-2-fluorolevulinic acid.¹⁴²



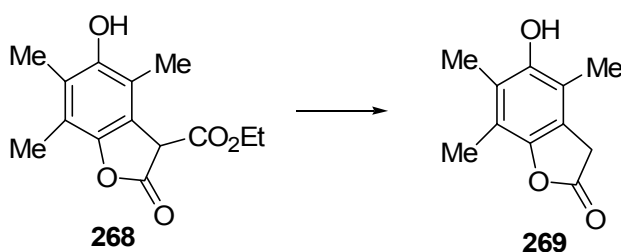
Of particular interest is the conversion of **264** to the naturally occurring racemic spiro lactone andirolactone (**265**). Treatment of **264** with DMSO, NaCl and water (160°, 2 h) afforded **265** (90%).¹⁴³



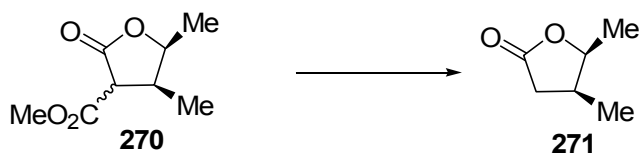
The lactone **266** on heating in DMSO, LiCl and water (125°C, 12 h) led to (*S*)-sotolon (**267**) (80%, 92%ee), a volatile compound isolated from raw cane sugar.¹⁴⁴



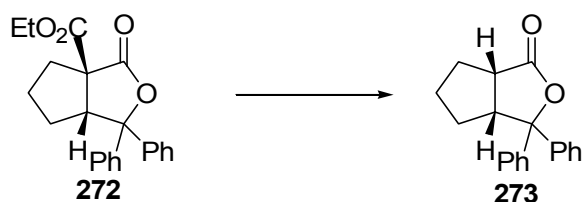
Treatment of lactone **268** with DMSO and water (110-120°C, 1 h) led to **269** (99%), which was used in the synthesis of potential phenolic antioxidants.¹⁴⁵



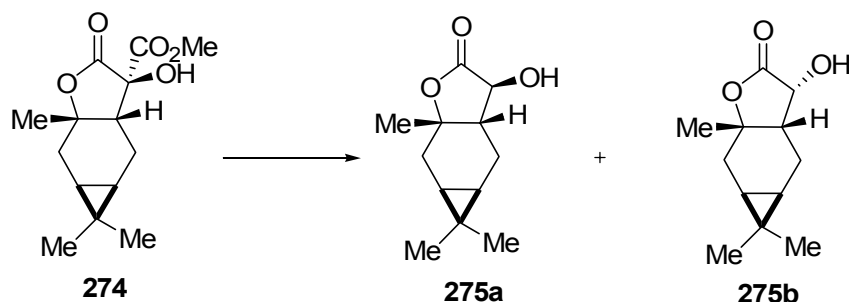
The synthesis of (*3S*, *4S*) **271** (60%, 99.9%ee) was accomplished by treatment of **270** with DMSO, LiCl and water (reflux, 3.5 h). This intermediate was used in a synthesis of the sex pheromones of pine sawflies.¹⁴⁶



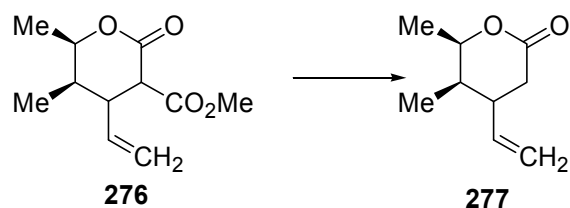
The bicyclic lactone **272** on treatment with DMSO, LiCl and water (195°C, 3 h) led to the bicyclic lactone **273** (64%).¹⁴⁷



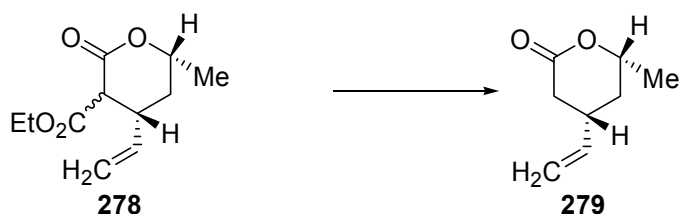
The α -carbomethoxy- α -hydroxy- γ -lactone **274** on treatment with DMF, NaCl and water (150°C, 3 h) led to **275a** and **275b** (84%, 68:32 ratio) which could be separated by chromatography.¹⁴⁸



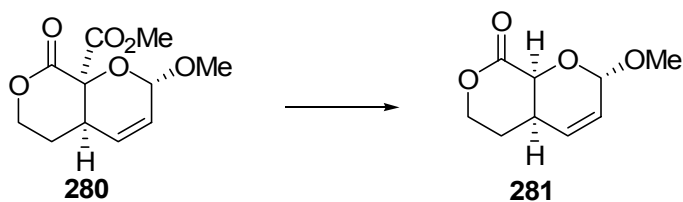
The demethoxycarbonylation of **276** (a 3:1 mixture of diastereoisomers) with DMF and LiI (reflux) led to **277** (86%) which in a subsequent series of reactions was used in an enantioselective total synthesis of (+)-methyl pederate.¹⁴⁹



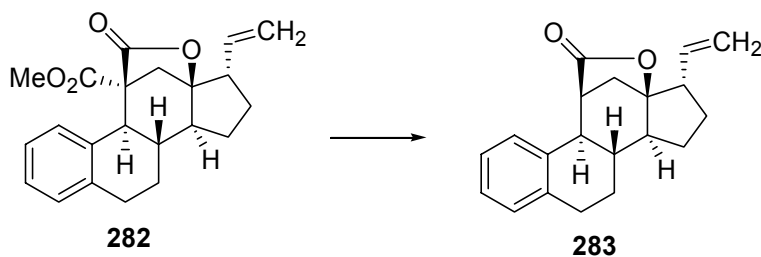
The lactone **278** with DMSO, NaCl and water (150-160°C, 2 h) led to **279** (75%). In a similar manner the β -methyl analogue was converted into the corresponding deethoxycarbonylated product. Other substituted analogues were also deethoxy-carbonylated. These derivatives were used in a synthesis of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



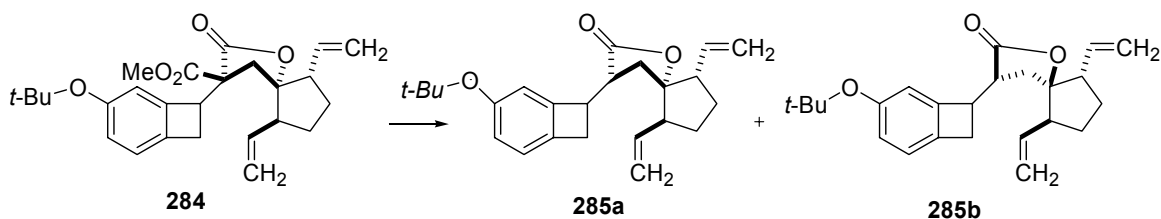
Treatment of lactone **280** with HMPA, NaCl and water (190°C, 2.5 h) gave **281** (65%).¹⁵¹



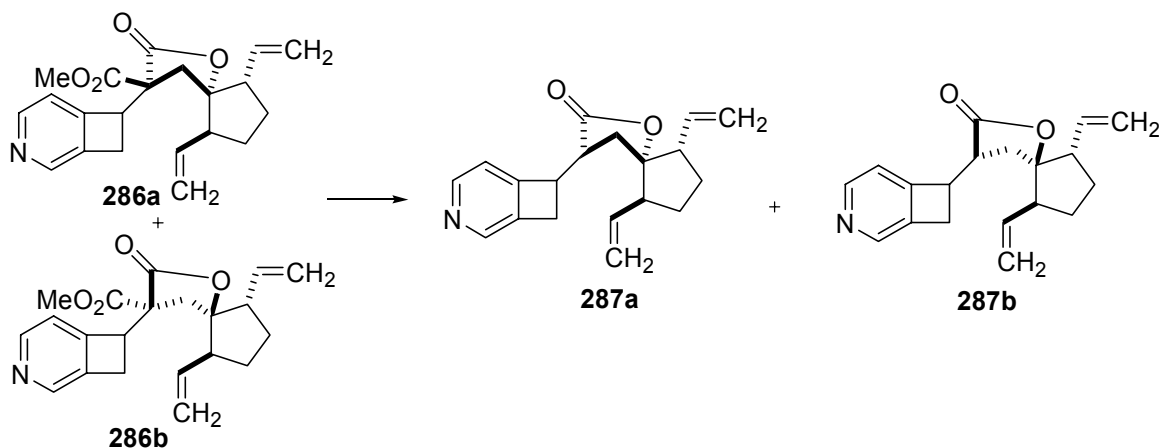
Treatment of 11-carbomethoxy-18-norestrane **282** with DMSO and NaCN (100°C, 19 h) led to racemic **283** (no yield given).¹⁵²



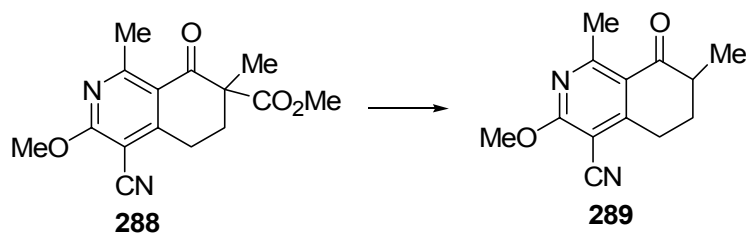
The decarbomethoxylation of **284** on treatment with DMSO, and NaCN (90°C, 24 h) led to isomeric mixtures of **285a** and **285b** (78%), which were used in a steroid analogue synthesis.¹⁵³ A similar strategy was used for the incorporation of fluoro substituent¹⁵³ and a 3-hydroxy steroidal group.¹⁵⁴



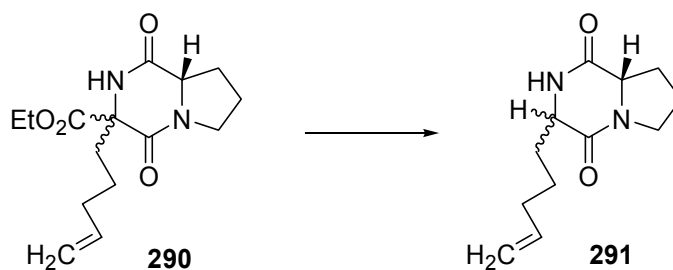
Treatment of **286a** and **286b** (diastereoisomeric mixture) with DMSO and NaCN (90°C, 24 h) led to an inseparable mixture of 4-azabenzocyclobutane diastereoisomers **287a** and **287b** (91%) which were subsequently converted into the aza steroidal analogues.¹⁵⁵



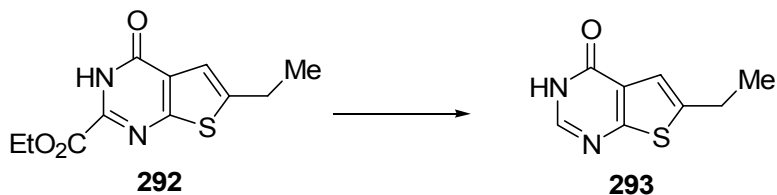
In the preparation of dihydroisoquinolines, the intermediate **289** was prepared by treatment of **288** (44%) with DMSO, NaCl and water (145-150°C, 6 h).¹⁵⁶



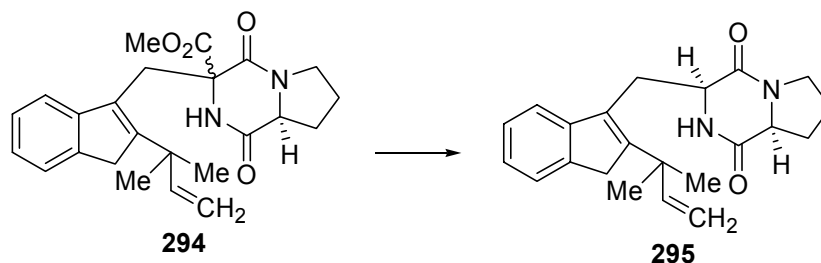
The ester **290** on treatment with DMF, LiCl and water (92°C, 16 h) led to compound **291** (78%) as an epimeric mixture which could not be separated.¹⁵⁷



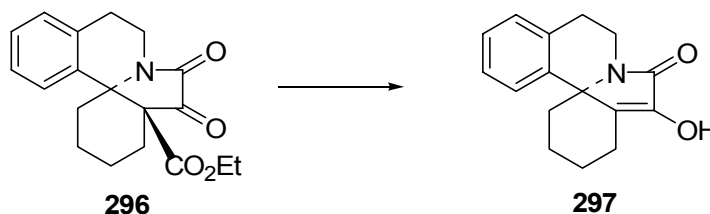
The thieno[2,3-d]pyrimidin-4-one (**292**) on treatment with DMSO, LiCl (150°C) led to the pyrimidinone **293** (no experimental conditions).¹⁵⁸



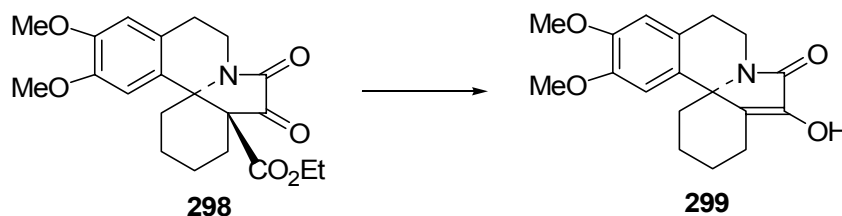
The use of MgCl_2 hexahydrate (in place of NaCl) in DMSO ($130\text{-}140^\circ\text{C}$, 2.5 h) for the demethoxycarbonylation of **294** led to deoxybrevianamide **295** (59%) along with the corresponding epimer (38%).¹⁵⁹



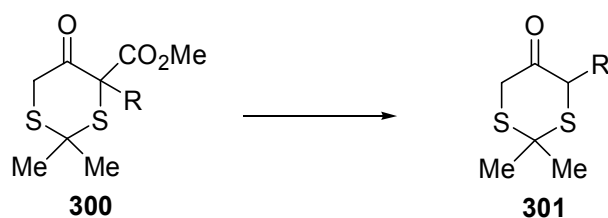
The dealkoxycarbonylations of β -keto esters using halides of group IIa metals have been studied. For example, treatment of **296** with MgCl_2 hexahydrate or CaCl_2 dihydrate in DMSO (in the presence of PhSH , at $150\text{-}160^\circ\text{C}$) led to **297** (50-60%).¹⁶⁰



The deethoxycarbonylation of substituted derivatives such as **298** have been accomplished using MgCl_2 hexahydrate in DMSO (or HMPA) in the presence of PhSH ($150\text{-}155^\circ\text{C}$, 2 h) to yield **299** (73%). These derivatives were used in a synthesis of erythrina and related alkaloids.¹⁶¹

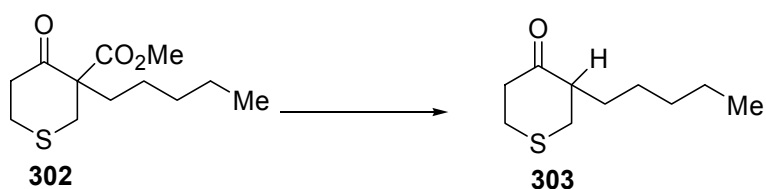


The decarbomethoxylation of **300** with DMSO, NaCl and water ($135\text{-}140^\circ\text{C}$, 5-8 h) led to the ketones **301** (49-90%). Intermediate **301c** was converted into racemic α -lipoic acid.¹⁶²

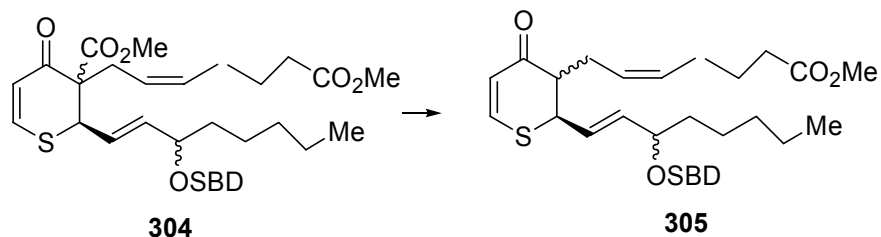


a, R = *n*-butyl; b, R = benzyl; c, R = $(\text{CH}_2)_4\text{CO}_2\text{Me}$; d, R = allyl; e, R = Et

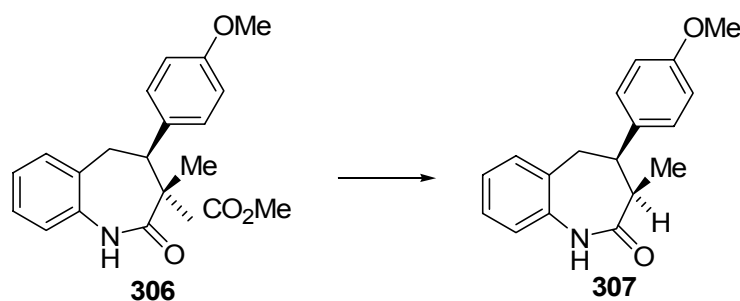
Treatment of **302** with HMPA and LiCl (65-75°C, 20 h) led to **303** (65%), which was used in a synthesis of 2-alkyl-3-cyclopentenones.¹⁶³



In a study of routes to thiathromboxane analogues, the dealkoxycarbonylations of a number of 3-methoxycarbonyl-3-substituted thiin-4-ones were evaluated. Treatment of **304** with DMF, anhydrous MgCl₂ and a phosphate buffer (160°C, 21 h) led to enone **305** (69%) as an inseparable mixture of the 2,3-*trans* and 2,3-*cis* isomers along with 16% of the corresponding desilylated products, namely the 2,3-*trans* and 2,3-*cis* alcohols.¹⁶⁴



Treatment of **306** with DMF and LiBr (137°C, 5 h) in the presence of *p*-aminothiophenol (a trap for MeBr formed during the reaction) gave the demethoxycarbonylated product **307** (96%) with less than 3% of the corresponding *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



Upon heating **308** in dry HMPA and LiCl (120°C, 10 min) the demethoxycarbonylation led to the intramolecular cyclization product **309** (61%).¹⁶⁶

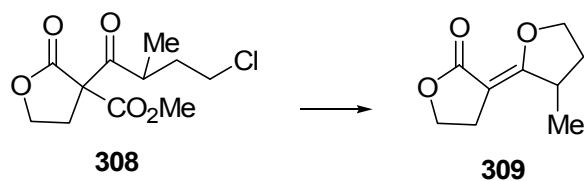


Table 2 lists some additional examples.

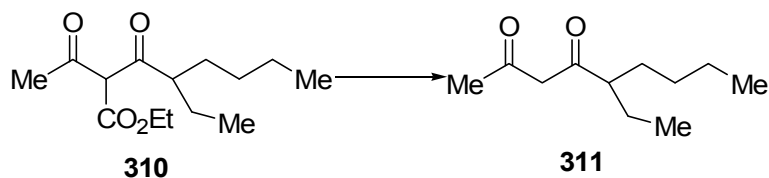
Table 2. Dealkoxycarbonylations of disubstituted β -keto esters

Starting Material	Conditions	Product	Yield (%)	Reference
	DMF, LiCl, H ₂ O reflux, 18 h		80	167
	DMSO, LiCl, H ₂ O 149°C, 20 h		54	168
	DMF, LiCl, H ₂ O reflux, 1h		64	169
	DMF, LiCl, H ₂ O HOAc, reflux, 5h		84 exo:endo 55:45	170

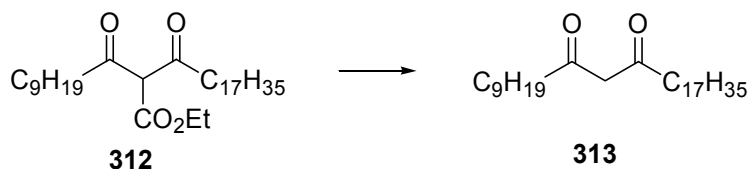
2.4. 1,3-Diones

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

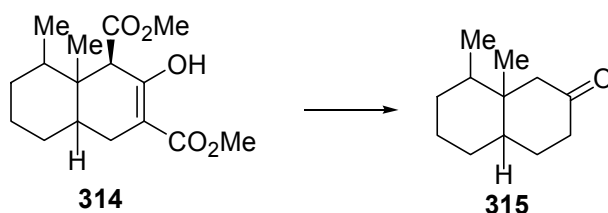
A wide variety of β -diketones (for identification of potential secretions from the paracloacal glands of alligator and caimans) have been prepared by treatment of substituted 2-carbalkoxy-1,3-diones with NaCl and water at reflux (12 h). The following reaction sequence for the preparation of 5-ethylnonane-2,4-dione (**311**) from the corresponding β -2-carbalkoxy-1,3-dione is illustrative **310** (62%).¹⁷¹



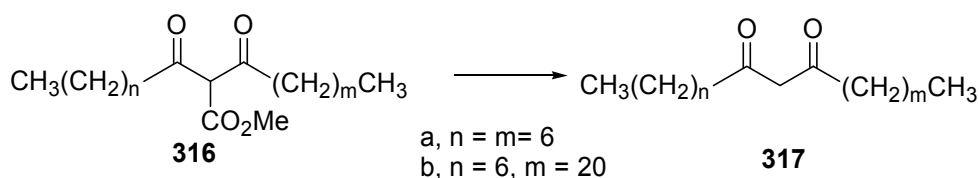
The synthesis of a wide variety of β -diketones found in sunflower pollen has been accomplished. For example, the conversion of **312** with DMSO, NaCl and water (reflux, 8 h) led to **313** (40-60%).¹⁷²



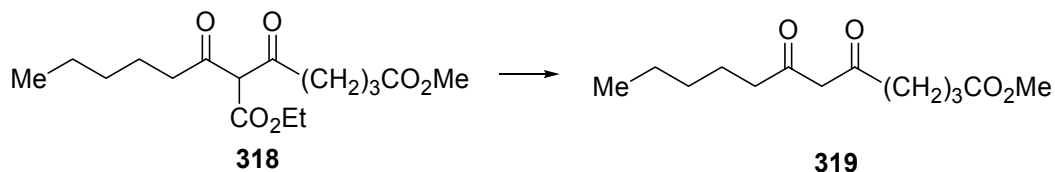
Treatment of enol **314** with DMSO, NaCl and water (reflux, 18 h) led to ketone **315** (62%).¹⁷³



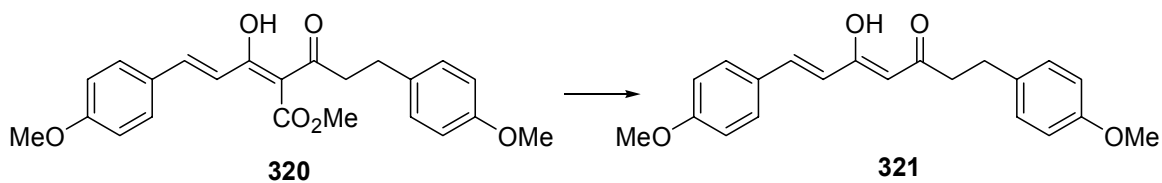
The facile demethoxycarbonylations of **316a** ($n, m = 6$) and **316b** ($n = 6, m = 20$) were accomplished by heating in DMSO and water to yield the corresponding long-chain 1,3-diones **317a** (82%) and **317b** (98%).¹⁷⁴



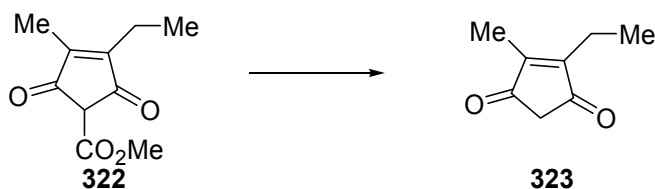
Treatment of **318** with DMSO, NaCl, water (reflux, 8 h) led to the 1,3-dione **319** in good yield.¹⁷⁵



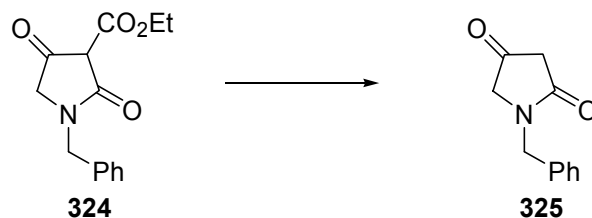
Treatment of the enolic tautomer **320** with DMSO, NaCl and H₂O (160-170°C, 4 h) led to the enolic form of the 1,3-dione **321** (54%).¹⁷⁶



Treatment of **322** with DMSO, NaCl and water (reflux, 1 h) led to **323**.¹⁷⁷



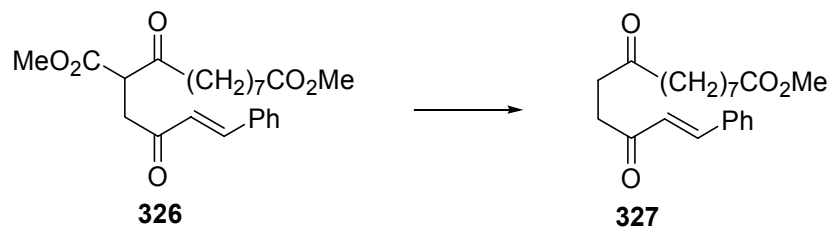
The ester **324** in acetonitrile and water was refluxed for 2.5 h to yield **325** (95%).¹⁷⁸



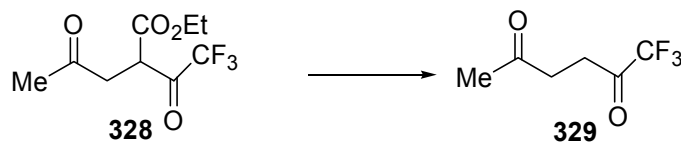
2.5. 1,4-Diones

2.5.1. From α -carbalkoxy-1,4-diones

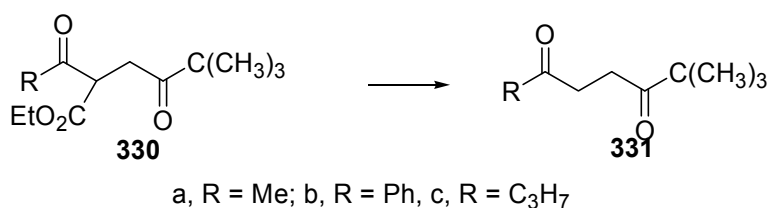
The demethoxycarbonylation of **326** with DMSO, NaCl and water (160-170°C, 6 h) led to 1,4-dione **327** (40%).¹⁷⁹



Treatment of the β -keto ester **328** with DMSO, NaCl and water (110°C, 2.5 h) led to 1,1,1-trifluoro-2,5-hexanedione **329** (73%).¹⁸⁰



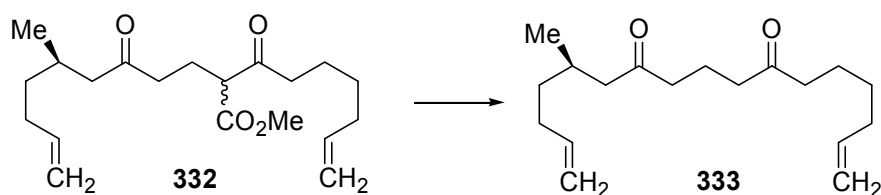
The deethoxycarbonylations of β -keto esters **330a-c** in DMSO, NaCl and water (180°C, 20 h) led to good yields of the corresponding 1,4-diones **331a-c** (48-75%).¹⁸¹



2.6. 1,5-Dione

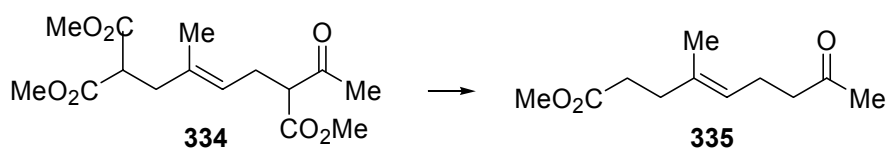
2.6.1. From α -carbomethoxy substituted substrate

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*)-(+)-muscovyridine.¹⁸²

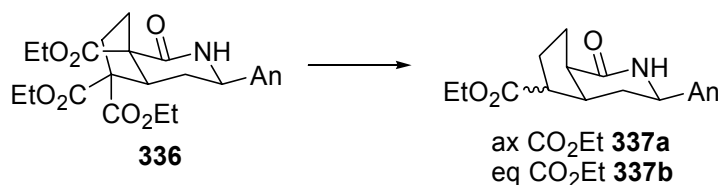


2.7. β -Keto ester and malonate ester polyfunctional substrates

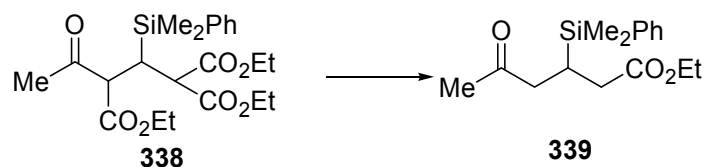
Treatment of **334** with DMSO, NaCl and water (173°C, 45 min) led to **335** (65%), resulting from the decarbomethoxylation of the malonate ester group and the β -keto ester group.¹⁸³



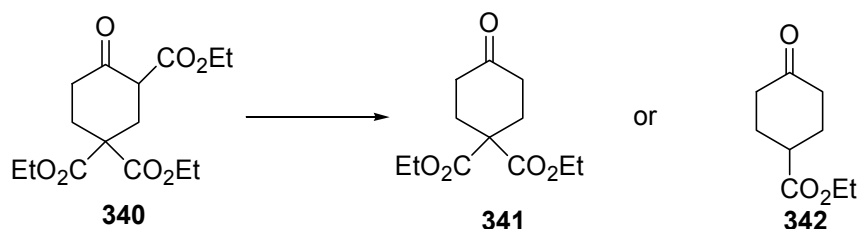
Compound **336** in DMF, LiCl and water (reflux, 18 h) led to **337a** (36%) and **337b** (25%).¹⁸⁴



Treatment of **338** with DMSO, NaCl and water (155-160°C) led to **339** (61%).¹⁸⁵



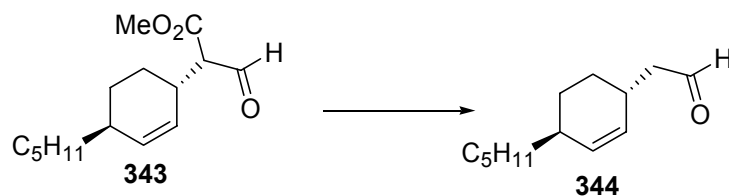
Upon heating **340** in DMSO, NaCl and water (150-160°C, 2 h) **341** was formed (83%), the product of a deethoxycarbonylation of the β -keto ester functionality. If diester **341** is heated with DMSO, LiCl and water with a small amount of pyridine (150-160°C, 14 h), **342** (72%) was obtained. Heating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



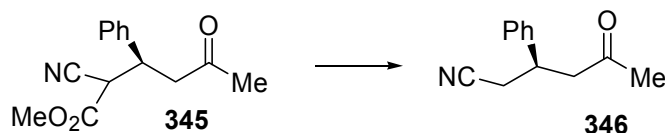
2.9. Nitriles

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

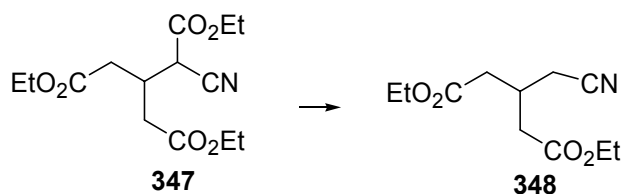
2.9.1. From α -cyano esters

2.9.2. From mono substituted substrates

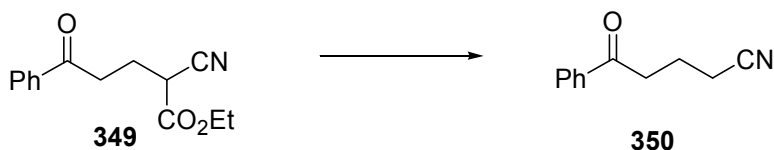
The conjugate addition product obtained by addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one using a chiral(salen)Al complex led to **345** which on treatment with DMSO and water (130°C) led to **346** (85% for two steps in 93% ee).¹⁸⁸



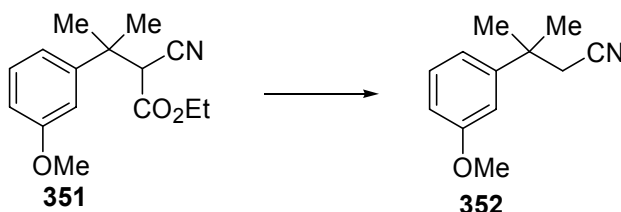
The chemoselective deethoxycarbonylation of α -cyano ester **347** was accomplished by treatment with DMSO, water and LiCl (140°C, 4 h) to yield **348** (75%).¹⁸⁹



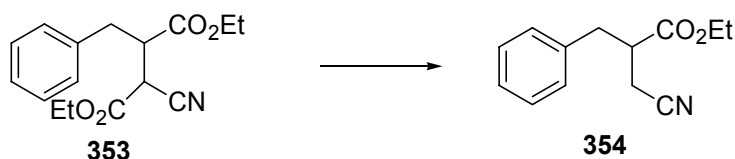
The deethoxycarbonylation of α -cyano ester **349** was accomplished by treatment with DMSO, water and NaCl (reflux, 20 h) to afford **350** (48%).¹⁹⁰



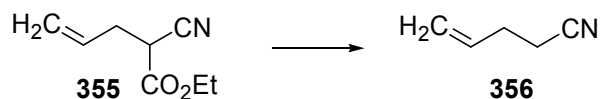
Treatment of **351** with DMSO, LiCl (130°C, 5 h) led to **352** (75%).¹⁹¹



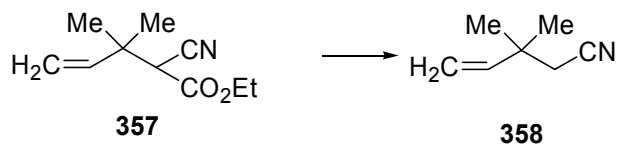
Treatment of the diester **353** with DMSO, NaCl and water (140°C, 2.5 h) led to the deethoxycarbonylation of the ester group attached to the carbon holding the cyanide group to afford **354** (77%). The ester was subsequently converted into the corresponding pyrrolidone.¹⁹²



Treatment of **355** with DMSO, NaCl and water (160°C, 4 h) led to nitrile **356** (65%).¹⁹³



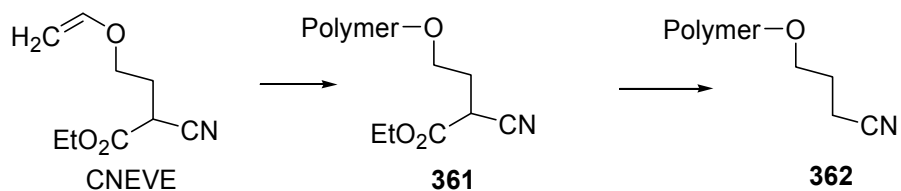
Treatment of cyano ester **357** with DMSO, NaCl and H₂O (160°C, 3 h) led to **358** (82%).¹⁹⁴



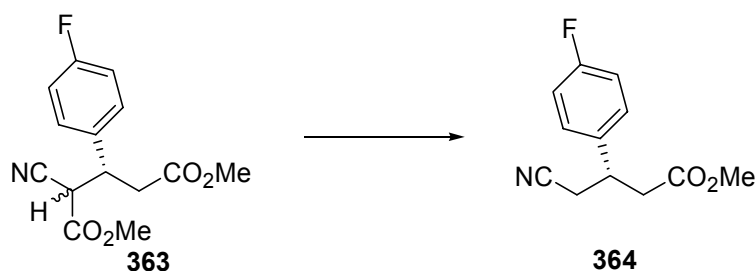
The decarbomethoxylations of **359a** (64%ee) and **359b** (96%ee) with DMSO, water and NaCl (reflux, 4 h) led to the enantioselective synthesis of **360a** (74%) and **360b** (80%), respectively.¹⁹⁵



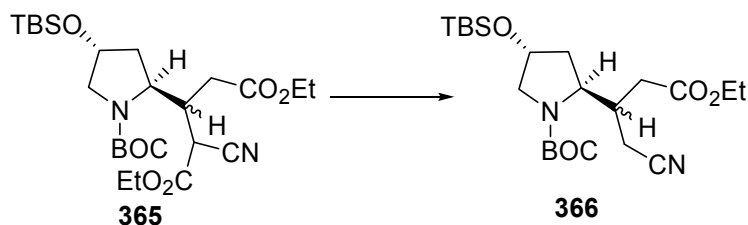
Homo- and copolymers of CNEVE **361** were deethoxycarbonylated by heating in DMSO in the presence of NaCl to yield poly(vinyl ethers) with 2-cyanopropoxy side chains **362**.¹⁹⁶



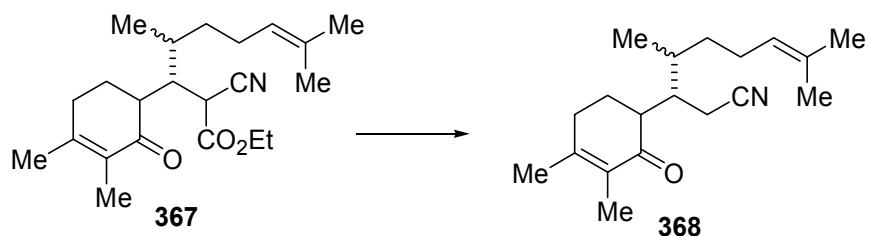
Treatment of α -cyano ester **363** (89%ee) with DMSO, water and NaCl (130°C, 24 h) led to chemoselective removal of the carbomethoxyl group α to the cyano group to afford **364** (89%ee) without loss of stereochemistry.¹⁹⁷



Analogue (2*S*, 4*R*)-**365** on heating with DMSO, NaCN and water (140°C, 1 h) led to **366** (67%).¹⁹⁸



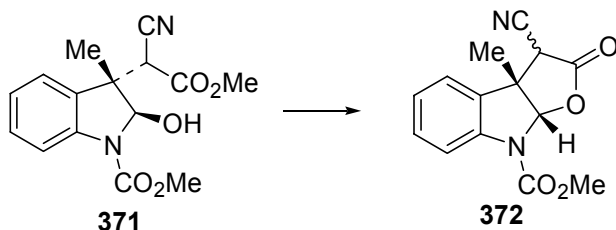
The deethoxycarbonylation of nitrile ester **367** was accomplished using DMSO, LiCl and water (150°C, 1 h) to yield nitrile **368** (84%).¹⁹⁹



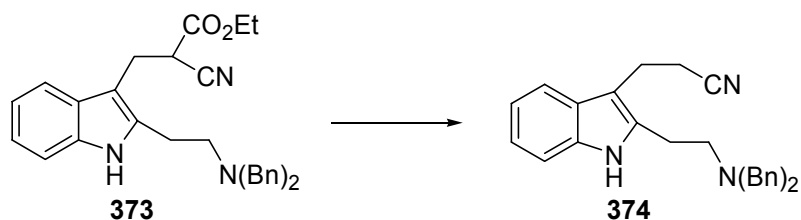
Treatment of the oxindole **369** with DMSO, NaCN and water (160°C, 2 h) led to **370** (80%) with decarbomethoxylation of the ester functionality and the N-CO₂Me group. This intermediate was converted into racemic physostigmine in a subsequent series of steps.²⁰⁰



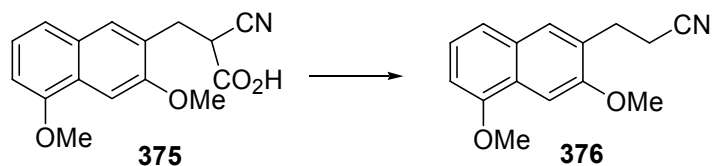
The lactonization of **371** to yield racemic **372** (70%, *cis-trans* fused ratio 4:1) was accomplished by heating in DMSO and water and additional NaCN (100°C, 0.5 h).²⁰¹ In this case, lactonization is faster than the expected Krapcho demethoxycarbonylation..



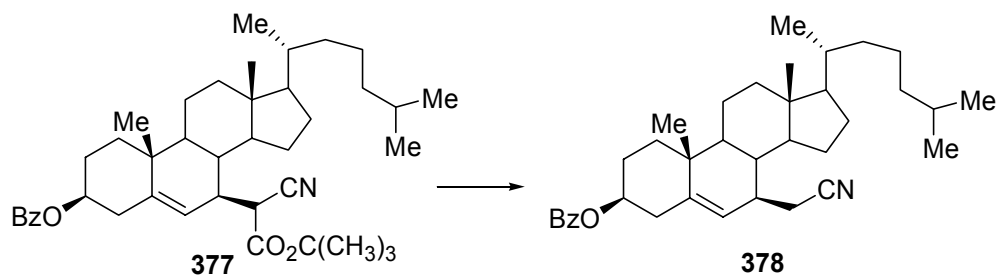
The N-benzyl protected analogue **373** on treatment in DMF, LiCl and water (no experimental conditions) led to **374**. This compound could readily be converted into the hexahydroazocino[4,5-b] indole on catalytic hydrogenation.²⁰²



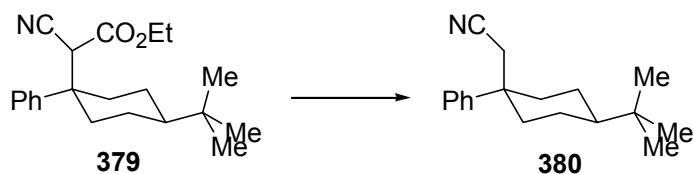
The α -cyano acid **375** on treatment with DMF and NaCl in water (125°C, 2.5 h) led to the decarboxylated product **376** (91%).²⁰³



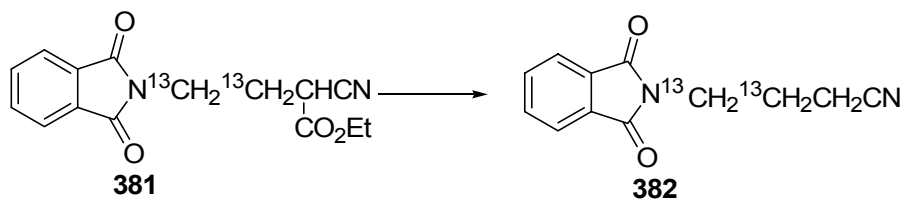
Treatment of the substituted cholesterol **377** with DMSO, LiCl and water (140°C, 20 h) led to the 7 β -(2-cyanoethyl) analogue **378** (84%), the product of a de-*t*-butoxycarbonylation.²⁰⁴



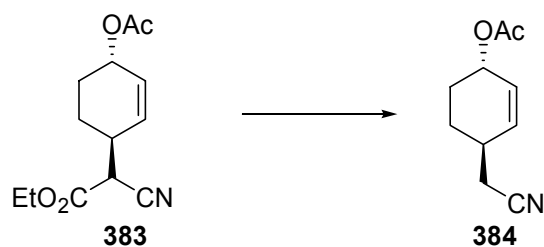
The deethoxycarbonylation of **379** with DMSO, NaCl and water (160°C, 2 h) led to nitrile **380** (91%).²⁰⁵



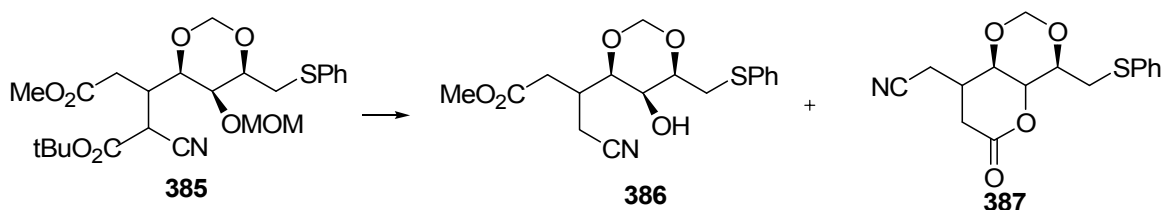
In the preparation of ¹³C-labelled substrates, treatment of the phthalimido analogue **381** with DMSO, NaCl and water (no conditions or yield) led to **382**.²⁰⁶



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).²⁰⁷

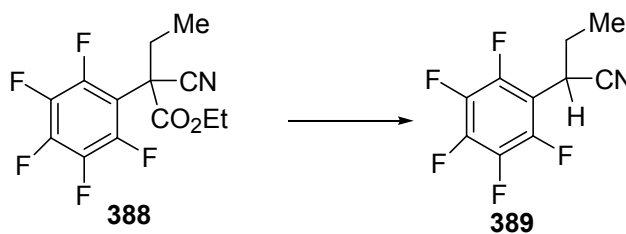


Treatment of **385** with DMSO, NaCl and water (165°C) led to cyano ester **386** and cyanolactone **387** (72- 78%, 1:1 ratio) with the removal of the *t*-butoxy group as well as deprotection of the MOM ether. This intermediate was converted into the AB ring system of sesbanamide.²⁰⁸

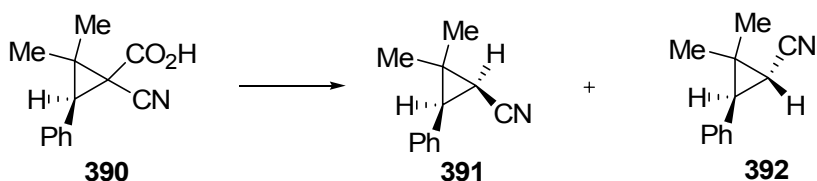


2.9.3. From disubstituted substrates

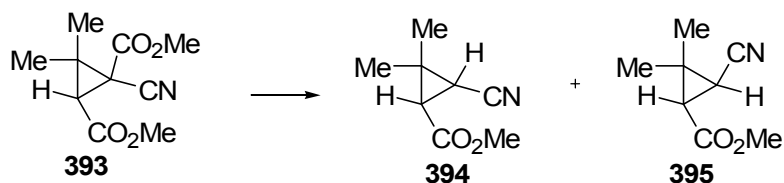
The pentafluoro α -cyano ester **388** on treatment with DMSO and water (160°C, 120 h, or for shorter times in aqueous DMSO containing NaCl) led to nitrile **389** (78%).²⁰⁹



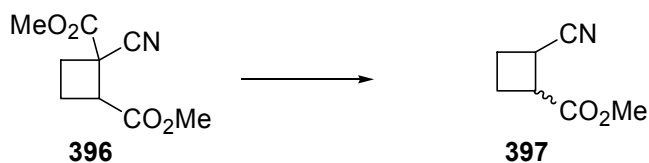
Treatment of the cyano acid **390** with DMSO, LiCl and water (in the presence of NaHCO₃) at 165°C for 4.5 h led to the decarboxylation to give the cyclopropane nitriles **391** and **392** as a 55:45 mixture (60%). These derivatives were used in the synthesis of the acid component of insecticidal pyrethroids.²¹⁰



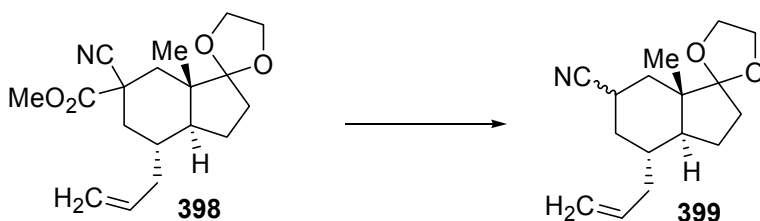
The demethoxycarbonylation of **393** with DMSO, LiCl (7 equivalents) and water (7 equivalents) in the presence of NaHCO₃ (2 equivalents) (165°C, 0.5 h) led to a 5:1 mixture of *cis*- and *trans* stereoisomers **394** and **395**. The product isomer ratio was dependent on the molar equivalents of the reagents.²¹¹



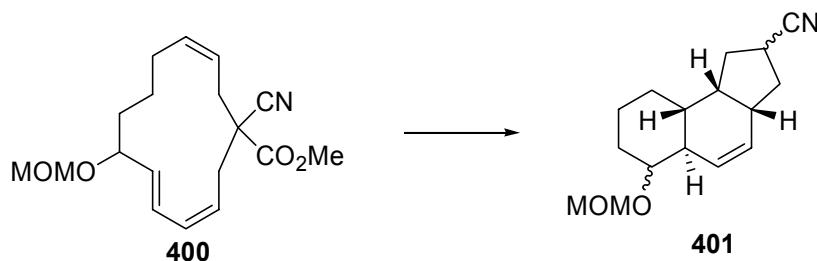
The decarbomethoxylation of the cyano cyclobutane **396** with DMSO, NaCl and water (150°C, 4 h) led to a mixture of *cis*- and *trans*-isomers **397** (77%).²¹²

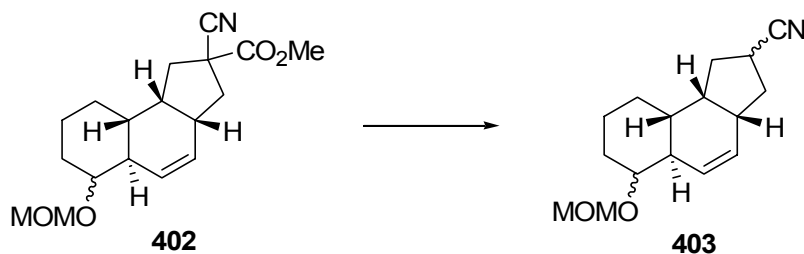


In the enantioselective synthesis of 11-keto steroids, treatment of a mixture of isomers **398** with DMF and LiI (140°C, 40 h) led to the demethoxycarbonylation product **399** (no yield recorded).²¹³

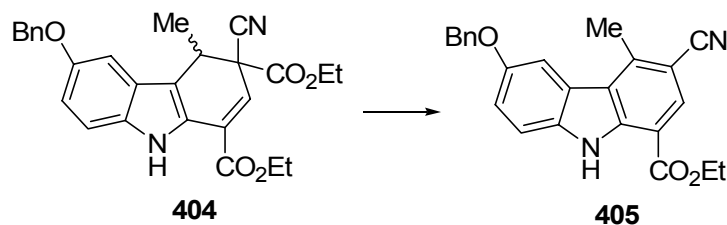


The transannular Diels-Alder reaction and demethoxycarbonylation of macrocycle **400** yielded **401** as a diastereoisomeric mixture (89%) was accomplished by treatment with NaCN and DMSO (160°C, 8 h) followed by an aqueous workup.²¹⁴ Treatment of **402** with NaCN and DMSO (160°C, 8 h) followed by water gave **403** (97%).²¹⁴

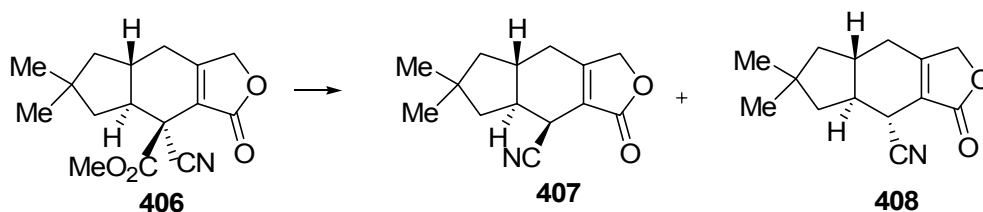




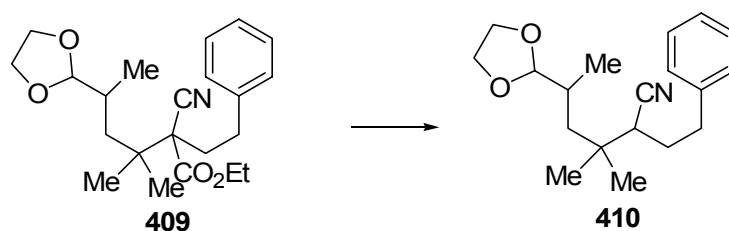
The deethoxycarbonylation and aromatization of dihydrocarbazole **404** with DMSO, LiCl and water (100°C, 26 h) led to **405** (45%).²¹⁵



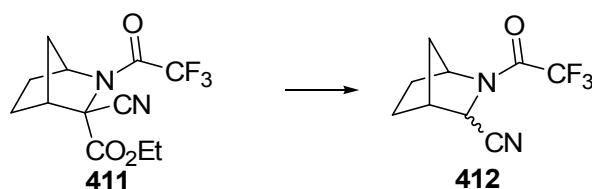
Treatment of α -cyano ester **406** with DMF, NaCN (160°C, 4 h) led to an epimeric racemic mixture of **407** and **408** (63%) in a 2:1 ratio.²¹⁶



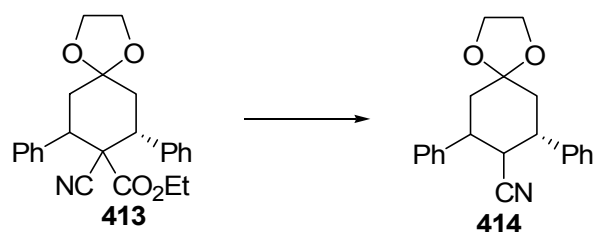
The deethoxycarbonylation of **409** with HMPA, LiCl (160°C, 3 h) yielded **410** (85%).²¹⁷



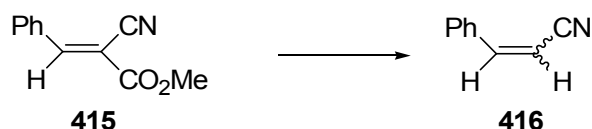
Treatment of **411** with DMF and CaCl₂ dihydrate (160°C, 2.5 h) led to mixture of exo/endo (1:1) epimers **412** (79%) which were used in a route leading to an azadicarbaprostaglandin.²¹⁸



The deethoxycarbonylation of **413** (or the corresponding methyl ester) with DMSO, LiCl and H₂O (173°C, 4 h) led to **414** (78%).²¹⁹



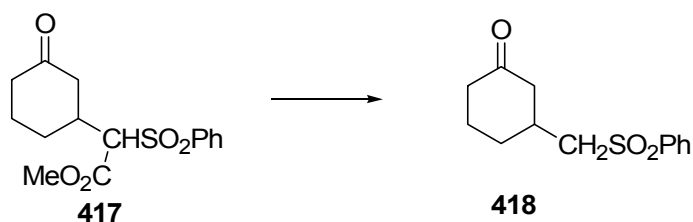
The demethoxycarbonylation of methyl ester **415** (or the corresponding ethyl ester) with DMSO, LiCl and NaHCO₃ (165°C, 3 h) led to 1:1 mixture of the *E*- and *Z*-stereoisomeric nitriles **416** (75%), along with benzaldehyde (18%).²²⁰



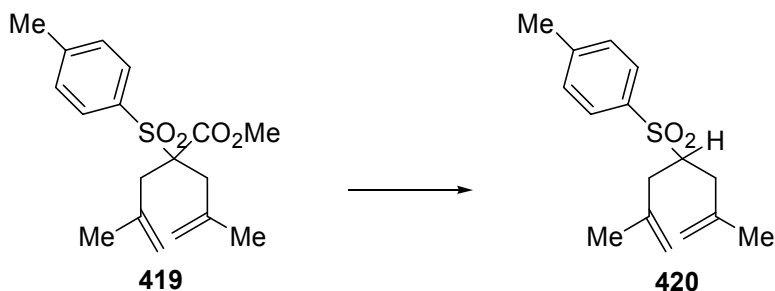
2.10. Sulfones

2.10.1. From α -sulfonyl esters

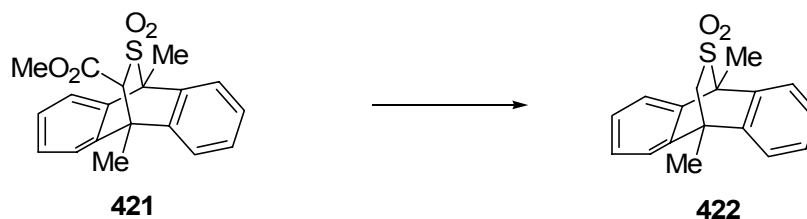
Treatment of sulfone **417** with DMSO, NaCl and water (reflux, 8h) led to the decarbomethoxylated product **418** (63%).²²¹



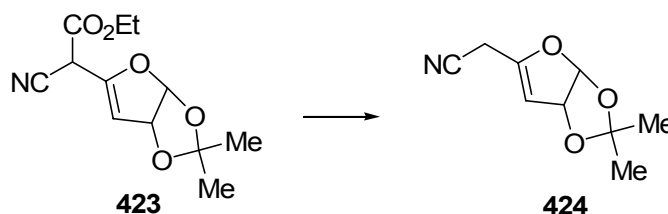
The 1,6- α -tolylsulfonyl ester **419** on treatment with DMSO and NaCl (170°C, 18 h) led to decarbomethoxylation product **420** (99%).²²²



The α -carbomethoxy sulfone **421** on heating in DMSO, NaCl and water (160°C, 6 h) led to sulfone **422** (86%).²²³



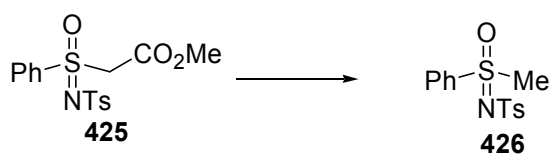
Without providing any experimental details, the demethoxycarbonylation of **423** was reported to afford a good yield of non-racemic **424**, an intermediate to be used in the synthesis of additional chiral analogues.²²⁴



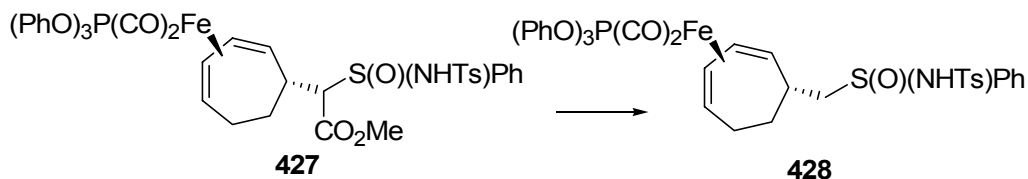
2.11. Sulfoximines

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**.²²⁵



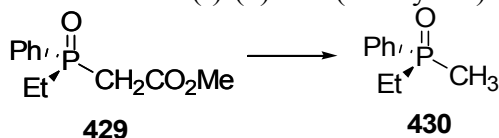
The diastereoisomeric chiral mixture of **427** on treatment with DMSO, NaCN (80°C, 48 h) led to optically active **428** (80%) as a diastereoisomeric mixture.²²⁵



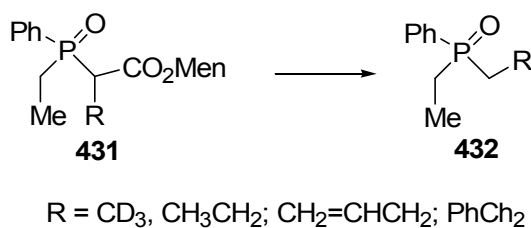
2.12. Chiral phosphine oxides

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}



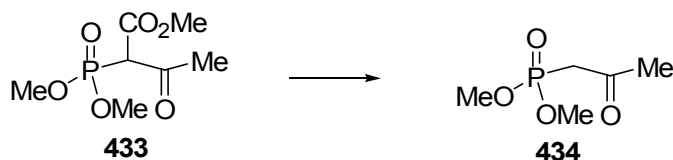
Treatment of α -substituted (-)-(*S_P*)-ethyl((menthoxy-carbonyl)methyl)phenylphosphine oxides **431** with LiCl in aqueous DMSO (reflux, 8-18 h) led to the corresponding (-)-*R_P*-alkylethylphosphineoxides **432** in 54-70% yields in 100% enantiomeric purity.²²⁷



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°C, 2-3 h) to afford β -ketophosphonates such as **434** (70%). A number of other substrates were also evaluated.²²⁸

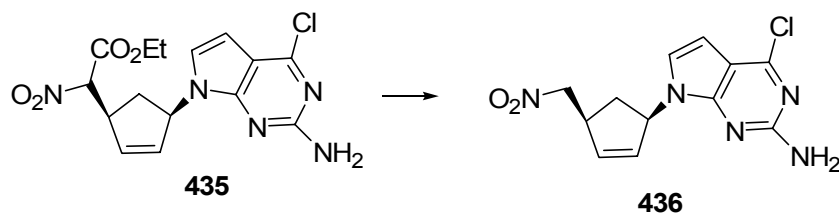


2.14. Nitro analogues

2.14.1. From α -nitro esters

Only one example of a dealkoxycarbonylation of an α -nitro ester could be found.

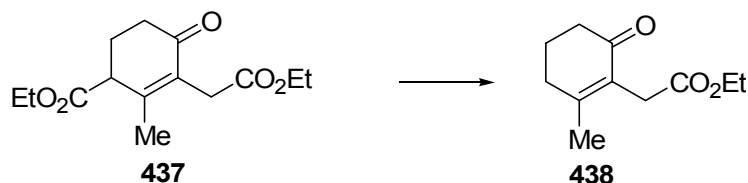
Treatment of α -nitro ester **435** with DMSO, NaCl and water (150°C, 4 h) led to deethoxycarbonylation to afford nitro derivative **436** (66%).²²⁹



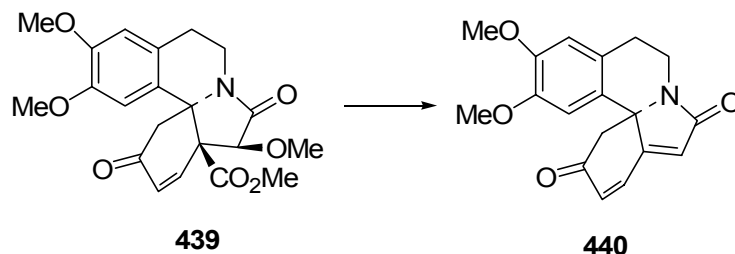
2.15. 2-Cyclohexenone derivatives

2.15.1. From 4-carbalkoxy-2-cyclohexanones

The chemoselective deethoxycarbonylation of the keto diester **437** on treatment with DMSO, LiCl and water (180-190°C, 5 h) led to **438** (70%).²³⁰

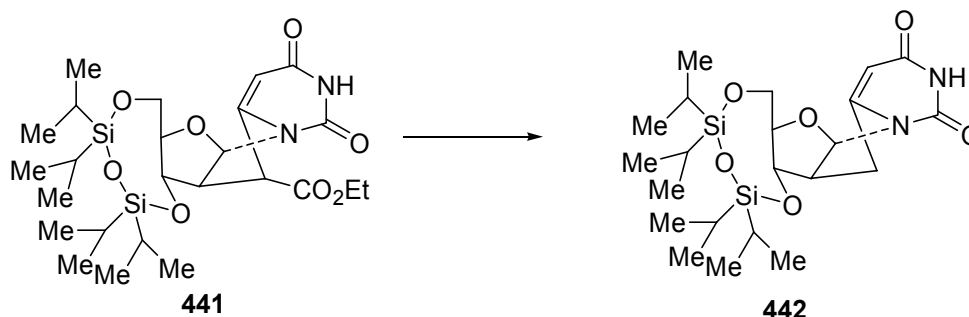


Upon heating **439** in DMSO, NaCl and water (140°C, 10 h, sealed tube), **440** (19%) was obtained, the product of a demethoxycarbonylation and a demethoxylation. This yield (40%) was improved with the use of MgCl₂. The mesylate (OMs instead of OMe in **439**, α-position to the ester group) under the MgCl₂-DMSO conditions led to **440** (89%). This intermediate was used in a synthesis of *Erythrina* and related alkaloids.²³¹



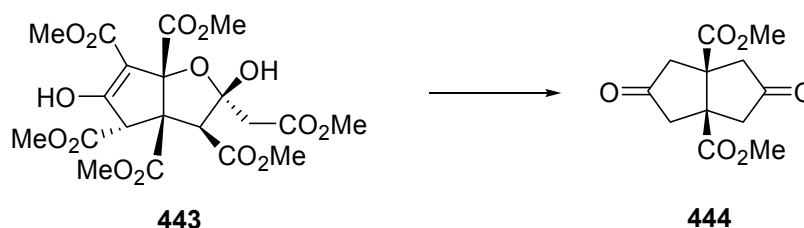
2.16. Heterocyclic vinylogous deethoxycarbonylation

The deethoxycarbonylation of the heterocyclic substrate **441** to afford **442** (32%) was accomplished by treatment with DMSO, NaCl and water (145°C, 6 h).²³²



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



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

1. Krapcho, A. P. *Synthesis* **1982**, 893.
2. Backvall, J.-E.; Vagberg, J.-O.; Granberg, K. L. *Tetrahedron Lett.* **1989**, *30*, 617.
3. Ito, S.; Saito, N.; Hatekeda, K.; Goto, T.; Ikushima, Y.; Asano, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2015.
4. Curran, D. P.; Zhang, Q. *Adv. Synth. Catal.* **2003**, *345*, 329.
5. Kolasa, A. *J. Fluorine Chem.* **1987**, *36*, 29.
6. Toro, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526.
7. Bram, G.; Cabaret, D.; Welvert, Z.; Geraghty, N. W. A.; Garvey, J. *Tetrahedron Lett.* **1988**, *29*, 4615.
8. Dolle, R. E.; Osifo, K. I. Li, C.-S. *Tetrahedron Lett.* **1991**, *32*, 5029.
9. Langlois, M.; Yang, D.; Soulier, J.-L.; Florac, C. *Synth. Commun.* **1992**, *22*, 3115.
10. Lastdrager, B.; Timmer, M. S. M.; van der Marel, G. A.; Overkleeft, H. S. *Tetrahedron Lett.* **2005**, *46*, 6195.
11. Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011.
12. Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736.
13. Pellissier, H.; Santelli, M. *Tetrahedron* **1996**, *52*, 9093.
14. Gonzalez, G. I.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 914.
15. Back, T. G.; Wulff, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6493.
16. Murali, D.; Rao, G. S. Krishna, *Indian J. Chem.* **1987**, *26B*, 158.
17. Morgan, T. K., Jr.; Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 2259.

18. Gibson, K. R.; Hitzel, L.; Mortishire-Smith, J.; Gerhard, U.; Jelley, R. A.; Reeve, A. J.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354.
19. Narukawa, Y.; Nishi, K.; Onoue, H. *Tetrahedron* **1997**, *53*, 539.
20. Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482.
21. Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1990**, *46*, 3029.
22. Oshima, E.; Kumazawa, T.; Obase, H. *Chem. Pharm. Bull.* **1993**, *41*, 36.
23. Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566.
24. Atkins, E. F.; Dabbs, S.; Guy, R. G.; Mahomed, A. A.; Mountford, P. *Tetrahedron* **1994**, *50*, 7253.
25. (a) Aubert, C.; Begue, J.-P.; Charpentier-Morize, M.; Nee, G.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 377. (b) Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.
26. Bogolyubskii, A. V.; Il'chenko, A. Ya.; Yagupol'skii, L. M. *J. Org. Chem. USSR (Engl. Transl)* **1987**, *23*, 2027.
27. Cooper, K.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1984**, 799.
28. Daniewski, A. R.; Warchol, T. *Polish J. Chem.* **1992**, *66*, 1985.
29. Okano, K.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 1379.
30. Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.
31. Islam, Md. S.; Kawanao, T.; Hatanaka, M.; Ueda, I. *Tetrahedron Lett.* **1996**, *37*, 5735.
32. Fleming, I.; Ghosh, S. K. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 2711.
33. Baier, H.; Durner, G.; Quinkert, G. *Helv. Chim. Acta* **1985**, *68*, 1054.
34. Knolker, H. J.; Winterfeld, E. *Liebigs Ann. Chem.* **1986**, 465.
35. Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435.
36. Sonawane, H. R.; Naik, V. G.; Bellur, N. S.; Shah, V. G.; Purohit, P. C.; Kumar, M. U.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron* **1991**, *47*, 8259.
37. Camps, P.; Figueredo, M. *Can. J. Chem.* **1984**, *62*, 1184.
38. (a) Yates, P.; Grewal, R. S.; Hayes, P. C.; Sawyer, J. F. *Can. J. Chem.* **1988**, *66*, 2805. (b) Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. (c) Yates, P.; Stevens, K. E. *Can. J. Chem.* **1982**, *60*, 825.
39. Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Org. Chem.* **1996**, *61*, 685.
40. Paquette, L. A.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 5352.
41. Taber, D. F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem.* **2002**, *67*, 4821.
42. Brooks, D. W.; Bevinakatti, H. S.; Kennedy, E.; Hatthaway, J. *J. Org. Chem.* **1985**, *50*, 628.
43. Ibuka, T.; Minakata, H.; Mitsui, Y.; Hayashi, K.; Taga, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1982**, *30*, 2840.
44. Maiti, B. C.; Lahiri, S. *Tetrahedron* **1998**, *54*, 9111.
45. Selvakumar, N.; Subba Rao, G. S. R. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3217.
46. Subba Rao, G. S. R.; Hariprakash, H. K.; Girija, A. T.; Bhaskar, K. V. *J. Indian Chem. Soc.* **1997**, *74*, 961.
47. Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438.

48. Suto, M. J.; Tramposch, K. M.; Wierzba, M.; Solo, A. J.; Duax, W. *J. Org. Chem.* **1987**, *52*, 2263.
49. Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855.
50. Ihara, M.; Makita, K.; Takasu, K. *J. Org. Chem.* **1999**, *64*, 1259
51. Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.
52. Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009.
53. Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. D.; Duax, W. L.; Djerassi, C. J. *J. Org. Chem.* **1983**, *48*, 4549.
54. Posner, G. H.; Shulman-Roskes, E. M. *Tetrahedron* **1992**, *48*, 4677.
55. Kido, F.; Akibo, T.; Kato, M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 229.
56. Duhamel, P.; Kotera, M. *J. Org. Chem.* **1982**, *47*, 1688.
57. Kutney, J. P.; Chen, Y.-H.; Rettig, S. J. *Can. J. Chem.* **1996**, *74*, 666.
58. Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.
59. Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. *Chem. Lett.* **1987**, 2417.
60. Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron* **1983**, *39*, 4269.
61. Paquette, L. A.; Friedrich, D.; Pinard, E.; Williams, J. P.; St. Laurent, D.; Roden, B. A. *J. Am. Chem. Soc.* **1993**, *115*, 4377.
62. Ahmad, Z.; Goswami, P.; Venkateswaran, R. V. *Tetrahedron* **1989**, *45*, 6833.
63. Honda, T.; Ishige, H.; Nagase, H. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3305.
64. Bradbury, R. H.; Gilchrist, T. L.; Rees, C. W. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3225.
65. White, J. D.; Somers, T. C.; Yager, K. M. *Tetrahedron Lett.* **1990**, *31*, 59.
66. (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Org. Chem.* **1985**, *50*, 23. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1983**, *24*, 5669.
67. Marchand, A. P.; Chong, H.-S.; Shukla, R.; Sharma, G. V. M.; Kumar, K. A.; Zope, U. R.; Bott, S. G. *Tetrahedron* **1996**, *52*, 13531.
68. Marchand, A. P.; Rajapaksa, D.; Reddy, S. P. Watson, W. H.; Nagl, A. *J. Org. Chem.* **1989**, *54*, 5086.
69. Terunuma, D.; Motegi, M.; Tsuda, M.; Sawada, T.; Nozawa, H.; Nohira, H. *J. Org. Chem.* **1987**, *52*, 1630.
70. Furstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281.
71. Schreiber, S. L.; Kelley, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210.
72. Streckowski, L.; Visnick, M.; Battiste, M. A. *J. Org. Chem.* **1986**, *51*, 4836.
73. Augustyns, B.; Maulide, N.; Marko, I. E. *Tetrahedron Lett.* **2005**, *46*, 3895
74. Eliel, E. L.; Bax, X.; Ohwa, M. *J. Chin. Chem. Soc.* **2000**, *47*, 63.
75. Villhauer, E. B.; Anderson, R. C. *J. Org. Chem.* **1987**, *52*, 1186.
76. Ando, M.; Kataoka, N.; Yasunami, M.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 1429.

77. Manhas, M. S.; Bhawal, B. M.; Shankar, B. B.; Bose, A. K. *J. Indian Chem. Soc.* **1985**, *62*, 891.
78. Wee, A. G. H.; Liu, B.; McLeod, D. D. *J. Org. Chem.* **1998**, *63*, 4218.
79. Schroeder, M. C.; Kiely, J. S.; Laborde, E.; Johnson, D. R.; Szotek, D. L.; Domagala, J. M.; Stickney, T. M.; Michel, A.; Kampf, J. W. *J. Heterocyclic Chem.* **1992**, *29*, 1481.
80. Wee, A. G. H.; Duncan, S. C.; Fan G.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 297.
81. Giles, M.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc. Chem. Commun.* **1990**, 1047.
82. Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775.
83. Bosch, J.; Bonjoch, J.; Serret, I. *J. Heterocyclic Chem.* **1982**, *19*, 489.
84. Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1994**, *59*, 3055.
85. Jeffery, S. M.; Sutherland, A. G.; Pyke, S. M.; Powell, A. K.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2317.
86. Lemaire, S.; Giambastiani, G.; Prestat, G.; Polli, G. *Eur. J. Org. Chem.* **2004**, 2840.
87. Rabczko, J.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433.
88. Bosch, J.; Bonjoch, J. *J. Org. Chem.* **1981**, *46*, 1538.
89. Takeuchi, Y.; Kamada, Y.; Nishimura, K.; Nishioka, H.; Nishikawa, M.; Hashigaki, K.; Yamato, M.; Harayama, T. *Chem. Pharm. Bull.* **1994**, *42*, 796.
90. Bailey, P. D.; McLay, N. R. *J. Chem. Soc. Perkin Trans. 1* **1993**, 441.
91. Stoit, A. R.; Pandit, U. K. *Tetrahedron* **1989**, *45*, 849.
92. Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300.
93. Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603.
94. Molander, G. A.; Haas, J. *Tetrahedron* **1999**, *55*, 617.
95. Molander, G. A.; Czako, B.; St. Jean, D. J. *J. Am. Chem. Soc.* **2006**, *71*, 1172.
96. Takahashi, T.; Kotsubo, H.; Koizumi, T. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1667.
97. Kunick, C. *Arch. Pharm. (Weinheim)* **1991**, *324*, 579.
98. Jeanneau-Nicolle, E.; Benoit-Guyod, M.; Leclerc, G. *Synth. Commun.* **1991**, *21*, 1443.
99. Collins, I.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 4069.
100. Molander, G. A.; Siedem, C. S. *J. Org. Chem.* **1995**, *60*, 130.
101. Ishmuratov, G. Yu.; Kakovleva, M. P.; Galyautinova, A. V.; Muslukhov, R. R.; Tolstikov, G. A. *Russ. Chem. Bull. Int. Edit.* **2003**, *52*, 74.
102. Artal, C.; Ros, M. B.; Serrano, J. L.; Pereda, N.; Etxebarria, J.; Folcia, C. L.; Ortega, J. *Macromolecules* **2001**, *34*, 4244.
103. Dickschat, J. S.; Wenzel, S. C.; Bode, H. B.; Muller, R.; Schulz, S. *ChemBioChem* **2004**, *5*, 778.
104. Tokuda, M.; Fujita, H.; Nitta, M.; Suginome, H. *Heterocycles* **1996**, *42*, 385.
105. Nishikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354.
106. Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368.
107. Holmes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc. Chem. Commun.* **1986**, 265.
108. Drew, M. G. B.; Mann, J.; Alison, T. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2279.

109. Yamazaki, T.; Matoba, K.; Itooka, T.; Chintani, M.; Momose, T.; Muraoka, O. *Chem. Pharm. Bull.* **1987**, *35*, 3453.
110. Solladie, G.; Boeffel, D.; Maignan, J. *Tetrahedron*, **1995**, *51*, 9559.
111. Domon, K.; Mori, K. *Eur. J. Org. Chem.* **1999**, 979.
112. Schied, G.; Kuit, W.; Ruijter, E.; Orru, R. V. A.; Henke, E.; Bornscheuer, U.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2004**, 1063.
113. Yu, Y.; Chen, G.-Q.; Zhu, J.; Zhang, X.-S.; Chen, S.-X.; Tang, H.-T.; Zhang, P. *J. Chem. Soc. Perkin Trans. I* **1990**, 2239.
114. Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043.
115. Dombrovskii, V. A.; Fonskii, D. Yu.; Filippova, T. M.; Mironov, V. A. *J. Org. Chem. USSR (Engl. Transl)* **1986**, *22*, 1471.
116. Hudlicky, T.; Short, R. P. *J. Org. Chem.* **1982**, *47*, 1522.
117. White, W. L.; Anzeveno, P. B.; Johnson, F. *J. Org. Chem.* **1982**, *47*, 2379.
118. Greene, A. E.; Teixeira, M. A.; Barreiro, E. Cruz, A.; Crabbe, P. *J. Org. Chem.* **1982**, *47*, 2553.
119. Tolstikov, G. A.; Miftakhov, M. S.; Valeev, F. A. *J. Org. Chem. USSR (Engl. Transl)* **1984**, *20*, 1522.
120. Lee, W. Y.; Jang, S. Y.; Kim, M.; Park, O. S. *Synth. Commun.* **1992**, *22*, 1283.
121. Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1982**, *12*, 501.
122. He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307.
123. Cossy, J.; Bouzbouz, S.; Hakiki, A. *Tetrahedron* **1999**, *55*, 11289.
124. Bohlmann, F.; Wegner, P.; Jakupovic, J.; King, R. M. *Tetrahedron* **1984**, *40*, 2537.
125. Weyerstahl, P.; Brendel, J.; *Liebigs Ann. Chem.* **1992**, 669.
126. (a) Tremblay, M. R.; Auger, S.; Poirier, D. *Bioorg. Med. Chem.* **1995**, *3*, 505. (b) Tremblay, M. R.; Auger, S.; Poirier, D. *Synth. Commun.* **1995**, *25*, 2483.
127. Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc. Perkin Trans. I* **1992**, 83.
128. Garratt, P. J.; Porter, J. R. *J. Org. Chem.* **1986**, *51*, 5450.
129. (a) Barnier, J. P.; Loupy, A.; Pigeon, P.; Ramdani, M.; Jacquault, P. *J. Chem. Soc. Perkin Trans. I*, **1993**, 397. (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Bouillet, F.; Jacquault, P.; Mahe, D. *Synthesis* **1998**, 1213. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
130. Spreitzer, H.; Piringer, I.; Pichler, A.; Holzer, W.; Schreder, P.; Widhalm, M. *Chirality* **1999**, *11*, 14.
131. Hagiwara, H.; Uda, H. *J. Chem. Soc. Chem. Commun.* **1988**, 815.
132. Higiwara, H.; Uda, H. *J. Chem. Soc. Chem. Commun.* **1987**, 1351.
133. Tamai, Y.; Hagiwara, H.; Uda, H. *J. Chem. Soc. Perkin Trans. I* **1986**, 1311.
134. Strunz, G. M.; Bethel, R.; Dumas, M. T.; Boyonoski, N. *Can. J. Chem.* **1997**, *75*, 742.
135. Kato, T.; Hirukawa, T.; Uyehara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1987**, *28*, 1439.
136. Tochtermann, W.; Panitzsch, T.; Habeck, T.; Wolff, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Tetrahedron* **1999**, *55*, 1027.
137. Furstner, A.; Radkowski, K. Peters, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2777.

138. Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **1997**, *62*, 3324.
139. (a) Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001**, *66*, 8935. (b) Wee, A. G. H.; Yu, Q. *Tetrahedron Lett.* **2000**, *41*, 587.
140. Lamarque, L.; Meou, A.; Brun, P. *Tetrahedron* **1998**, *54*, 6497.
141. Nylund, C. S.; Smith, D. T.; Klopp, J. M.; Weinreb, S. M. *Tetrahedron* **1995**, *51*, 9301.
142. Leeper, F. J.; Rock, M. *J. Fluorine Chem.* **1991**, *51*, 381.
143. Orduna, A.; Zepeda, L. G.; Tamariz, J. *Synthesis* **1993**, 375.
144. Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Servi, S. *Tetrahedron Lett.* **1992**, *33*, 5625.
145. Gilbert, J. C.; Pinto, M. *J. Org. Chem.* **1992**, *57*, 5271.
146. Hedenstrom, E.; Hogberg, H.-E.; Wassgren, A.-B.; Bergstrom, G.; Lofqvist, J.; Hanson, B.; Anderbrant, O. *Tetrahedron* **1992**, *48*, 3139.
147. Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333.
148. Lamarque, L.; Meou, A.; Brun, P. *Can. J. Chem.* **2000**, *78*, 128.
149. Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Heterocycles* **1998**, *47*, 675.
150. (a) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc. Chem. Commun.* **1990**, 418. (b) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 4887.
151. Abele, W.; Schmidt, R. R. *Tetrahedron Lett.* **1981**, *22*, 4807.
152. Michellys, P.-Y.; Pellissier, H.; Santelli, M. *Tetrahedron Lett.* **1993**, *34*, 1931.
153. Maurin, P.; Ibrahim-Ouli, M.; Santelli, M. *Eur. J. Org. Chem.* **2002**, 151.
154. Maurin, P.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 847.
155. Oumzil, K.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2005**, 1695.
156. Kasturi, T. R.; Jois, H. R. Y.; *Indian J. Chem.* **1990**, *29B*, 615.
157. Sanz-Cervera, J. F.; Williams, R. M.; Marco, J. A.; Lopez-Sanchez, J. M.; Gonzalez, F.; Martinez, M. E.; Sancenon, F. *Tetrahedron* **2000**, *56*, 6345.
158. Stewart A.O.; Bhatia, P. A.; McCarty, C. M.; Patel, M. V.; Staeger, M. A.; Arendsen, D. L.; Gunawardana, I. W.; Melcher, L. M.; Zhu, G.-D.; Boyd, S. A.; Fry, D. G.; Cool, B. L.; Kifle, L.; Lartey, K.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Wisdom, W.; Meyer, J.; Gallatin, W. M.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 988.
159. Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc. Perkin Trans. 1* **1981**, 950.
160. Tsuda, Y.; Sakai, Y. *Synthesis* **1981**, 119.
161. (a) Tsuda, Y.; Murata, M. *Tetrahedron Lett.* **1986**, *27*, 3385. (b) Tsuda, Y.; Sakai, Y.; Nakai, A.; Ohshima, T.; Hosoi, S.; Isobe, K.; Sano, T.; *Chem. Pharm. Bull. Jpn.* **1990**, *38*, 1462
162. Chavan, S. P.; Kale, R. R.; Pasupathy, K. *Synlett* **2005**, 1129.
163. Matsuyama, H.; Miyazawa, Y.; Takei, Y.; Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 1703.
164. Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1397.
165. Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergel, S. H.; Gougoutas, J. Z.; Malley, M. F. *J. Org. Chem.* **1990**, *55*, 5572.
166. Bohrer, G.; Bohrer, P. Knorr, *Chem. Ber.* **1990**, *123*, 2167.

167. Harmata, M.; Gamlath, C. B.; Barnes, C. L.; Jones, D. E. *J. Org. Chem.* **1995**, *69*, 5077.
168. Sworen, J. C.; Smith, J. A.; Berg, J. M.; Wagener, K. B. *J. Am. Chem. Soc.* **2004**, *126*, 11238.
169. Schafer, H.-J.; Baringhaus, K.-H. *Liebigs Ann. Chem.* **1990**, 351.
170. (a) Duval, O.; Rguigue, A.; Gomes, L. M. *Heterocycles* **1994**, *38*, 2709. (b) Duval, O.; Gomes, L. M. *Tetrahedron* **1989**, *45*, 4471.
171. Kruckert, K.; Flashbarth, B.; Schulz, S.; Hentschel, U.; Weldon, P. J. *J. Nat. Prod.* **2006**, *69*, 863.
172. Schulz, S.; Arsene, C.; Tauber, M.; McNeil, J. N. *Phytochemistry* **2000**, *54*, 325.
173. Irie, H.; Mizuno, Y.; Taga, T.; Osaki, K. K. *J. Chem. Soc. Perkin Trans. I* **1982**, 25.
174. Bianchi, G.; Grugni, M. *Gazz. Chim. Ital.* **1985**, *115*, 633.
175. Stritzke, K.; Schulz, S.; Nishida, R. *Eur. J. Org. Chem.* **2002**, 3884.
176. Venkateswarlu, S.; Ramachandra, M. S.; Rambabu, M.; Subbaraju, G. V. *J. Asian Nat. Prod. Rep.* **2000**, *2*, 111.
177. Jondiko, I. J. O.; Pattenden, G. *J. Chem. Soc. Perkin Trans. I* **1983**, 467.
178. Heinicke, G. W.; Morella, A. M.; Orban, J.; Prager, R. H.; Ward, A. D. *Aust. J. Chem.* **1985**, *38*, 1847.
179. Moorthy, B. K.; Miller, D. D. *Indian J. Chem.* **1990**, *29B*, 1084.
180. Smith, J. O.; Mandal, B. K.; Filler, R.; Beery, J. W. *J. Fluorine Chem.* **1997**, *81*, 123.
181. Smith, J. O.; Mandal, B. K.; *J. Heterocyclic Chem.* **1997**, *34*, 1441.
182. Hagiwara, H.; Katsumi, T.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Org. Chem.* **2000**, *65*, 7531.
183. Nystrom, J.-E.; Backvall, J.-E. *J. Org. Chem.* **1983**, *48*, 3947.
184. Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409.
185. Iyer, P.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 9437.
186. Sanchez, I. H.; Ortega, A.; Garcia, G.; Larraza, M. I.; Flores, H. J.; *Synth. Commun.* **1985**, *15*, 141.
187. Sucrow, W.; Radecker, G. *Chem. Ber.* **1988**, *121*, 219.
188. Taylor, M. S.; Zalatn, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313.
189. Amat, M.; Basas, O.; Canto, M.; Llor, N.; Santos, M. M. M.; Bosch, J. *Tetrahedron* **2005**, *61*, 7693.
190. Wessig, P.; Muhling, O. *Helv. Chim. Acta* **2003**, *86*, 865.
191. Bhattacharyya, S.; Mukherjee, D. *Synth. Commun.* **1981**, *11*, 993.
192. Horwell, D. C.; Howson, W.; Naylor, D.; Willems, H. M. G. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1445.
193. Abd El Samii, Zakaria K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc. Perkin Trans. I*, **1988**, 2523.
194. Cuvigny, T.; Julia, M.; Rolando, C. *J. Organometal. Chem.* **1985**, *285*, 395.
195. Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723.

196. Castelvetro, V.; Pittaluga, G. B.; Ciardelli, F. *Macromol. Chem. Phys.* **2001**, *202*, 2093.
197. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.
198. Ohtake, N.; Yamada, K.; Mano, E.; Okamoto, O. Ushijima, R.; Nakagawa, S. *J. Antibiotics* **1997**, *50*, 567.
199. Sutherland, A. J.; Sutherland, J. K.; Crowley, P. J. *J. Chem. Soc. Perkin Trans. 1* **1996**, 349.
200. Morales-Rios, M. S.; Bucio, M. A.; Garcia-Martinez, C.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 6087.
201. Suarez-Castillo, O. R.; Garcia-Velgara, M.; Morales-Rios, M. S.; Joseph-Nathan, P. *Can. J. Chem.* **1997**, *75*, 959.
202. Diker, K.; deMaindreville, M. D.; Levy, J. *Tetrahedron Lett.* **1995**, *36*, 3511.
203. Banziger, M.; Kusters, E.; La Vecchia, L.; Marterer, W.; Nozulak, J. *Org. Process Res. Dev.* **2003**, *7*, 904
204. Elkihel, L.; Bourass, J.; Dherbomez, M.; Letourneux, Y. *Synth. Commun.* **1997**, *27*, 1951.
205. Davis, A. P.; Egan, T. J.; Orchard, M. G.; Cunningham, D.; McArdle, P. *Tetrahedron* **1992**, *48*, 8725.
206. Robins, D. J. *J. Chem. Research (S)* **1983**, 326.
207. Souchet, M.; Baillarge, M.; Le Goffic, F. *Tetrahedron Lett.* **1988**, *29*, 191.
208. Rousch, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353.
209. Plevey, R. G.; Sampson, P. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2129.
210. Babler, J. H.; Spina, K. P. *Tetrahedron Lett.* **1985**, *26*, 1923.
211. Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 2743.
212. Earl, H. A.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1273.
213. Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087.
214. Chantigny, Y. A.; Dory, Y. L.; Toro, A.; Deslongchamps, P. *Can. J. Chem.* **2002**, *80*, 875.
215. Hogan, I.; Jenkins, P. D.; Sainsbury, M. *Tetrahedron* **1990**, *46*, 2943.
216. Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.
217. Nasipuri, D.; Banerjee, S. *J. Indian Chem. Soc.* **1984**, *61*, 1038.
218. Blondet, D.; Morin, C. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1085.
219. Rowland, A. T.; Gill, B. C. *J. Org. Chem.* **1988**, *53*, 434.
220. Babler, J. H.; Spina, K. P. *Tetrahedron Lett.* **1983**, *24*, 3835.
221. Tanikaga, R.; Obata, Y.; Kawamoto, K.-I. *Tetrahedron: Asymmetry* **1997**, *8*, 3101.
222. Craig, D.; Henry, G. D. *Tetrahedron Lett.* **2005**, *46*, 2559.
223. Bladon, C. M.; Ferguson, I. E. G.; Kirby, G. W.; Lohead, A. W.; McDougall, D. C. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1541.
224. Capobianco, M.; Mezzina, E.; Savoia, D.; Tagliavini, E.; Trombini, C. Umani-Ronchi, A. *Tetrahedron Lett.* **1986**, *27*, 1387.
225. Pearson, A. J.; Yoon, J. *J. Chem. Soc. Chem. Commun.* **1986**, 1467.
226. (a) Kielbasinski, P.; Zurawinski, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikolajczyk, M. *Tetrahedron Lett.* **1994**, *35*, 7081. (b) Kielbasinski, P.; Zurawinski, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikolajczyk *Polish J. Chem.* **1998**, *72*, 564.

227. Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522.
228. Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. *Synth. Commun.* **1996**, *26*, 2561.
229. Peel, M. R.; Sternbach, D. D.; Johnson, M. R. *J. Org. Chem.* **1991**, *56*, 4990.
230. Pal, S.; Satyanarayana, G.O.S.; Bhattacharjee, G. Ghatak, U. R. *Indian J. Chem.* **1996**, *35B*, 286.
231. Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479.
232. Sano, T.; Inoue, H.; Ueda, T. *Chem. Pharm. Bull.* **1985**, *33*, 3595.
233. Deslongchamps, G.; Mink, D.; Boyle, P. D.; Singh, N. *Can. J. Chem.* **1994**, *72*, 1162.

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