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Tandem transformations initiated and determined by the Michael reaction

E V Gorobets, M S Miftakhov, F A Valeev

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Abstract. Data on tandem transformations initiated by the Michael reaction published over the last five years are analysed, systematised and generalised. The bibliography includes 86 references.

I. Introduction

Syntheses of polyfunctional organic compounds with complex structures from simpler compounds by tandem one-pot transformations were described in a series of reviews (see, for example, Refs 1 – 6). Tandem transformations are multistep transformations in which each subsequent step is strictly determined by the preceding one and occurs under the same reaction conditions. The advantage of these transformations is the formation of several bonds and complication of the structure of the compound in one step, which is generally accompanied by the high stereoselectivity of the reaction. Minimisation of waste products, a decrease in the amount of required solvents, reagents and adsorbents, reduction in the energy and a decrease in the number of laboratory operations provide the economic and ecological feasibility of this type of processes.

According to the mechanism of the first step, tandem conversions are divided into cationic, anionic, radical, pericyclic, photochemical and transition-metal-induced processes. The terms 'tandem', 'cascade' and 'domino' reactions are used as synonyms.

Most tandem transformations proceed through the formation of an anionic intermediate. This first step governs the subsequent transformations. Most often, deprotonation of the CH group of the substrate occurs giving rise to a carbanion followed by its reaction with an electrophile to form a new anionic intermediate. This anion can attack another electrophilic centre, *etc*. The sequence is completed with trapping of an electrophile (for example, H^+) or elimination of the leaving group X^-.

In many cases, anionic transformations are either initiated or governed by the Michael reaction. In the present review, most attention is given to this type of transformation studied in recent years.†

II. A tandem Michael reaction

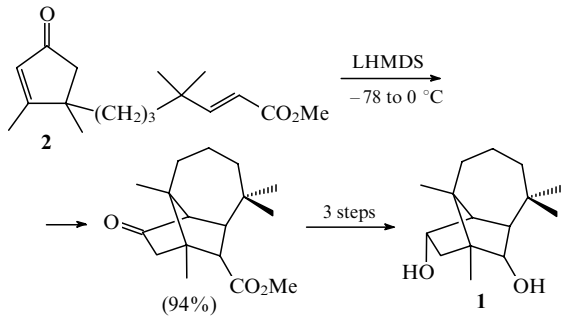
One of the approaches which is most popular for the formation of C – C bonds is based on the Michael reaction involving compounds containing an activated methylene group and α,β-unsaturated esters or ketones. A combination of two consecutive Michael addition reactions has considerable promise for the efficient construction of cyclic and polycyclic compounds because the second addition reaction often results in ring closure. This type of transformation is named the Michael Ring Closure (MIRC) or the Michael-Michael Ring Closure (MIMIRC).[2] Of all tandem transformations, a combination of two Michael reactions has been described in most detail. The examples considered below clearly demonstrate the importance of this approach in synthetic organic chemistry.

In studies of intramolecular double Michael addition reactions, a series of polycyclic structures were prepared [7] which served as the basis for the total synthesis of some natural compounds. The total synthesis of a sesquiterpenoid fungicide (±)-culmorin (**1**) was developed. [8] The tricyclo[6.3.0.0^{3,9}]undecan-10-one skeleton of **1** was constructed in one step by intramolecular cyclisation of 4-substituted cyclopent-2-enone **2** according to a scheme of double conjugate addition.

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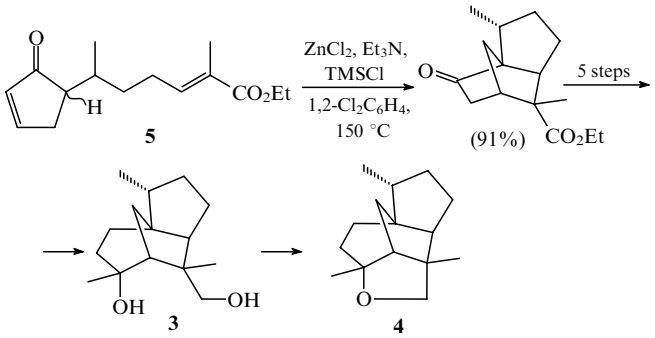
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† The data on tandem transformations published earlier have been surveyed in a monograph [1] and reviews.[2 – 6]



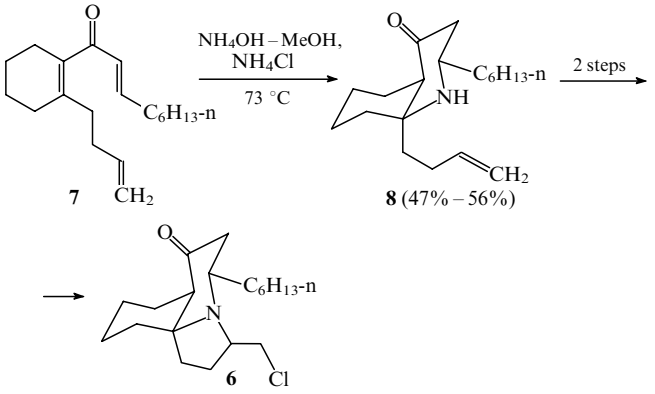
LHMDS is lithium hexamethyldisilazide.

The same strategy was used for the preparation of sesquiterpenoids (±)-8,14-cedranediol (**3**) and (±)-8,14-cedrane oxide (**4**) based on 5-substituted cyclopent-2-enone **5**.[9,10]

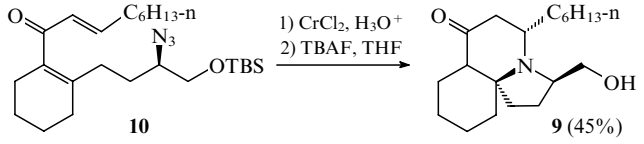


TMSCl is trimethylsilyl chloride.

The total synthesis of alkaloid cylindricine A (**6**) of animal origin, which was first isolated from ascidia in 1993, was performed.[11] The Michael addition of ammonia to the conjugated diene system of the ketone **7** afforded the key synthon, *viz*., perhydroquinolinone **8**. Its subsequent reaction with *N*-chlorosuccinimide and radical cyclisation gave rise to a 55 : 45 mixture of cylindricine A (**6**) and its epimer, which could be readily separated.



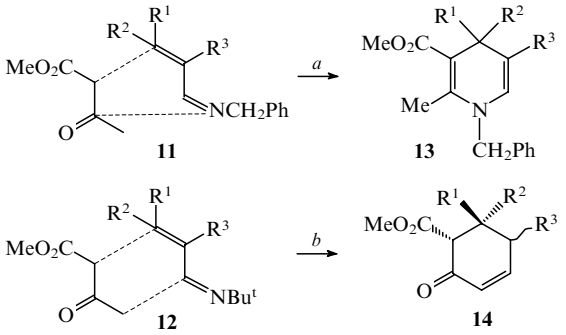
The total synthesis of alkaloid cylindricine C (**9**) related to compound **6** was performed in two steps [12] starting from the azide **10**. Selective reduction of the azide in the presence of the diene system was carried out with the use of $CrCl_2$. The resulting amine entered into the highly convergent and efficient double Michael addition reaction.



TBS is the *tert*-butyldimethylsilyl group,
TBAF is tetrabutylammonium fluoride.

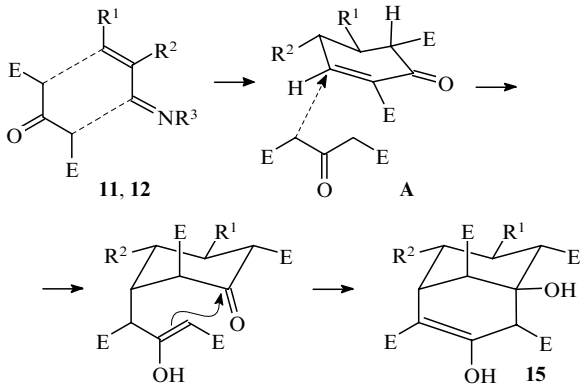
The synthetic potential of enimines in a two-step process involving the Michael addition followed by cyclisation has been examined.[13] Readily accessible 1-aza-1,3-butadienes (enimines) **11** and **12** reacted with methyl acetoacetate and acetylacetone in the presence of catalytic amounts of LiI to form unsymmetrically substituted 1,4-dihydropyridines **13** or cyclohexenone derivatives **14**.

The reaction pathway depends on the structure of the enimine used. The reaction of methyl acetoacetate with *N*-benzylenimines of type **11** gives rise to 1,4-dihydropyridine derivative **13**. If the benzyl group in the acceptor is replaced by the *tert*-butyl group (compound **12**), the reaction follows another pathway to form the cyclohexenone derivative **14**. In these reactions, either two (path *a*) or three (path *b*) carbon atoms of the 1,3-dicarbonyl compound are involved in the formation of the six-membered ring.



R^1 = Alk, Ar; R^2, R^3 = H, Alk.

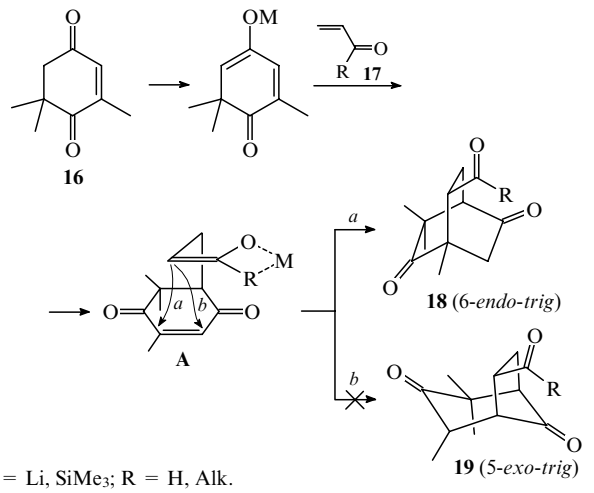
This divergence was not observed in the reactions of enimines **11** and **12** with dimethyl 3-oxoglutarate. Both enimines formed derivatives of bicyclo[3.3.1]nonan-3-one **15**.



E = CO_2Me; R^1, R^2 = H, Alk, Ar; R^3 = CH_2Ph (**11**), Bu^t (**12**).

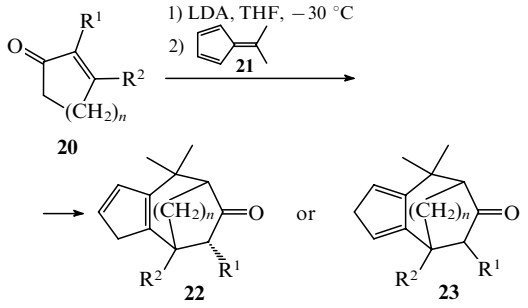
This result indicates that two molecules of the oxo diester are involved in the reaction. When the diester and enimine were taken in a ratio of 2 : 1, the product **15** was obtained in higher yield. The possible mechanism of transformation involves the formation of the intermediate **A**, which enters into the second Michael reaction followed by cyclisation.

The double Michael addition makes it possible to construct the bicyclo[2.2.2]octane skeleton of many natural compounds based on oxophorone (**16**) and its derivatives.[14] The reactions of oxophorone enolates with α,β-unsaturated carbonyl compounds **17** gave rise to the intermediate **A**, which underwent 6-*endo*-*trig* cyclisation following the path *a* to form the only product **18**. The isomer **19**, which could be formed in the case of the path *b*, was not detected.



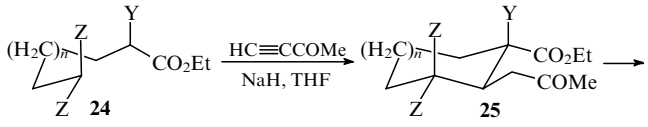
M = Li, $SiMe_3$; R = H, Alk.

The double conjugate addition of enones **20** to fulvene (**21**) offers a convenient approach to tricyclo[5.3.0.$n^{2,5}$]alkane systems.[15] The dienolate anion generated from enone enters into the Michael reaction with fulvene to give an anionic intermediate. The latter undergoes cyclisation as a result of the intramolecular Michael reaction giving rise to tricyclic ketone **22** or **23** with high stereoselectivity. The reaction is particularly efficient with the use of cyclopentenone as the Michael acceptor. In the latter case, tricycloalkanes are obtained in 75%–96% yields.

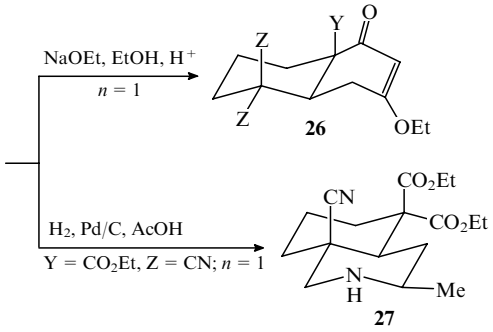


R^1, R^2 = H, Alk; n = 1–3; LDA is lithium diisopropylamide.

The new method for the construction of polyfunctional cyclic compounds containing several substituents developed by Grossman *et al.*[16–19] is based on the use of the double Michael reaction of carboxylates **24** with but-3-yn-2-one.

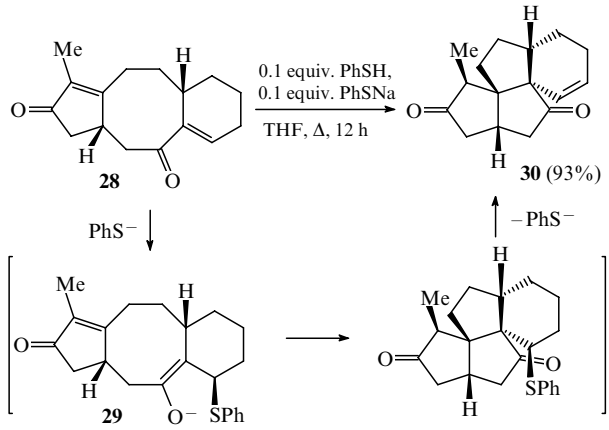


Y, Z = CN, CO_2Et; n = 0, 1.

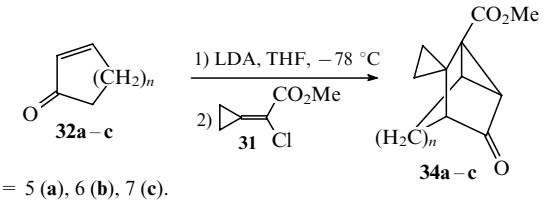


Cyclic products **25** are convenient starting compounds for the synthesis of biologically active polycyclic compounds. In particular, the Dieckmann reaction and intramolecular reductive amination of these compounds afforded *trans*-decalin **26** and *trans*-perhydroisoquinoline **27**, respectively. Three new C–C or C–N bonds, the ring system of bicyclo[4.4.0]decane and up to four new stereocentres can be constructed starting from two readily accessible acyclic compounds.

Tandem reactions giving rise to angular polyquinanes were reported.[20] The derivative of squaric acids, *viz.*, *cis*-13-methyltricyclo[10.3.0.$0^{4,9}$]pentadeca-4(5),12(13)-diene-3,14-dione (**28**), was involved in intramolecular cyclisation initiated by PhS^-. Enolate **29** formed in the first intermolecular Michael reaction underwent intramolecular transannular cyclisation in the second step to give the angular polyquinane **30**.

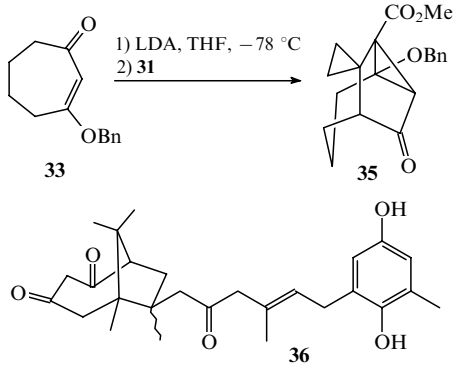


The Michael reactions of methyl (chloro)cyclopropylideneacetate (**31**) with cyclic dienolates formed from enones **32** and **33** were studied.[21] These reactions gave rise to tricyclic adducts **34** and **35**, respectively. It was proposed that the compound **35** can be used as an intermediate in the synthesis of sea diterpenoids, *viz.*, mediterraneols A and B (**36**).

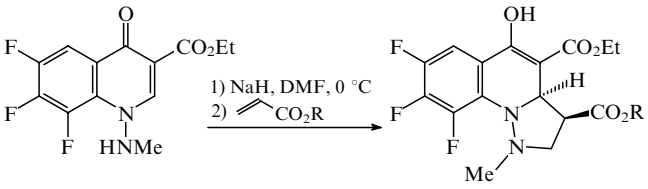


n = 5 (**a**), 6 (**b**), 7 (**c**).

Compound **34**	Yield (%)
a	40
b	34
c	78

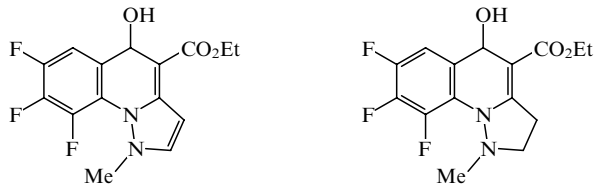


The methodology of tandem 1,4-inter- and intramolecular addition reactions has been used for the preparation of pyrazolo[1,5-*a*]quinoline ring systems **38** and **39** inhibiting DNA synthesis in bacteria starting from the quinolone **37**.[22] The key tricyclic synthons **40a**,**b** were synthesised by the reactions of the quinolone **37** with different acrylates.



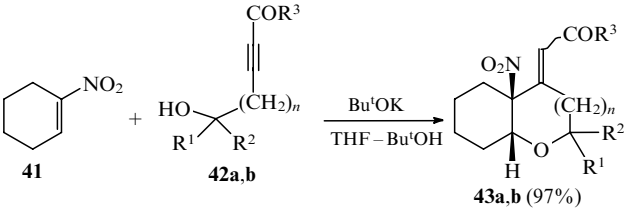
37 **40a,b** (88% – 97%)

R = Me (**a**), Bu^t (**b**).



38 **39**

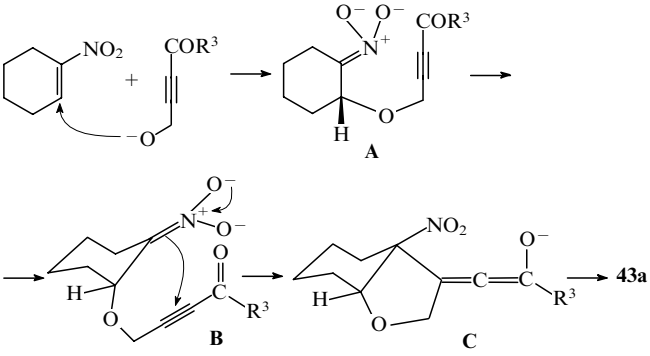
The double Michael reactions of 1-nitrocyclohexene (**41**) with ynols **42a**,**b** afforded nitrooctahydrobenzofurans (**43a**) and -pyrans (**43b**), respectively.[23] The possible reaction mechanism involves the addition of the alcohols **42a**,**b** at the double bond of the cycloalkene **41** and intramolecular cyclisation of the resulting anion **A** *via* the transition state **B** to give the anionic intermediate **C** containing *cis*-fused rings. Subsequent protonation of the anion **C** affords a mixture of the *E*- and *Z*-isomers **43a**,**b**.



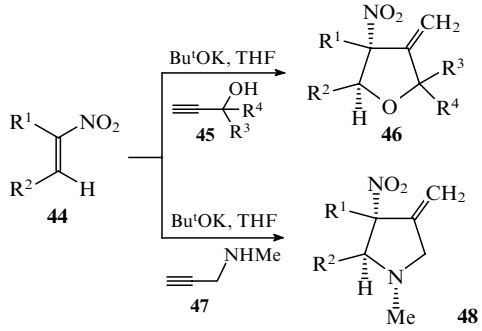
41 **42a**,**b** **43a**,**b** (97%)

E : *Z* = 55 : 45

n = 0 (**a**), 1 (**b**); R^1, R^2 = H, Alk; R^3 = OAlk, NMe$_2$.



The use of terminal alkynes enables one to change the order in which the reagents enter into the reaction. In this case also, the reaction results in a five-membered heterocyclic compound.[24] Thus the reaction of acyclic nitroalkene **44** with the ynol **45**

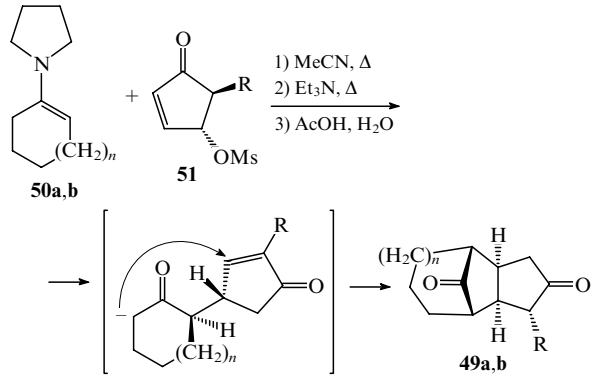


44 **45** **46** **47** **48**

R^1 = Alk; R^2 = Alk, Ar; R^3, R^4 = H, Alk.

afforded tetrahydrofuran derivative **46**. The aza-Michael addition of *N*-methylprop-2-ynylamine (**47**) to nitroalkenes **44** proceeded regio- and stereoselectively to form 3-methylenepyrrolidines **48**.

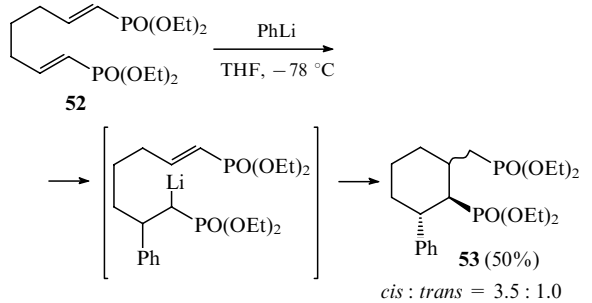
A new procedure for the stereoselective preparation of tricyclo[5.3.1.0^{2,6}]undecane-4,11-diones (**49a**) and tricyclo-[5.4.1.0^{2,6}]dodecane-4,12-diones (**49b**) is based on the inter- and intramolecular Michael reactions of 1-pyrrolidinocyclohexene (**50a**) and -cycloheptene (**50b**), respectively, with the mesylate **51**.[25]



50a,**b** **51** **49a**,**b**

R = Alk, Ar; *n* = 1 (**a**), 2 (**b**); Ms is mesyl.

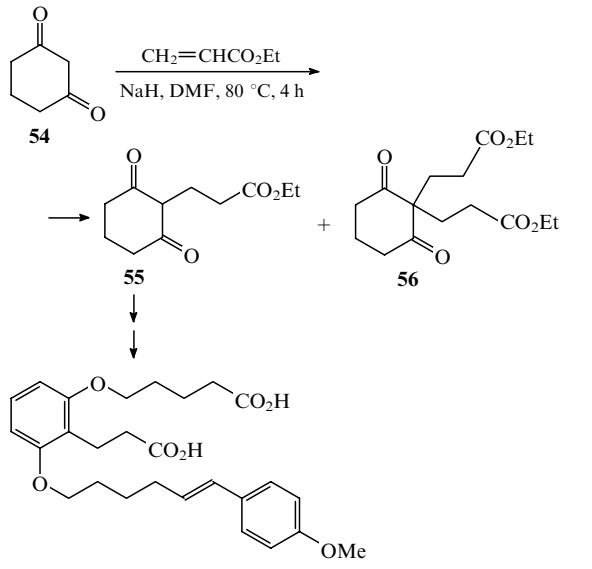
Organolithium compounds initiate Michael cyclisation of α,β,ψ,ω-unsaturated bisphosphonates **52**.[26] Thus the addition of PhLi to a solution of tetraester **52** afforded cyclic bisphosphonate **53**, which is a product of the tandem Michael reaction.



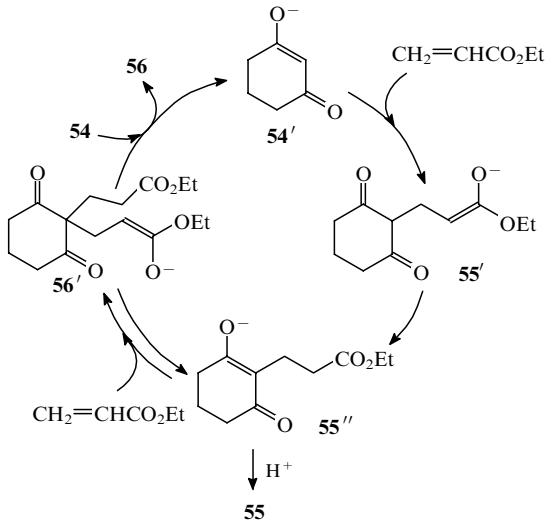
52 **53** (50%)

cis : *trans* = 3.5 : 1.0

The reaction of cyclohexane-1,3-dione (**54**) with ethyl acrylate proceeded as an intermolecular double Michael addition.[27]

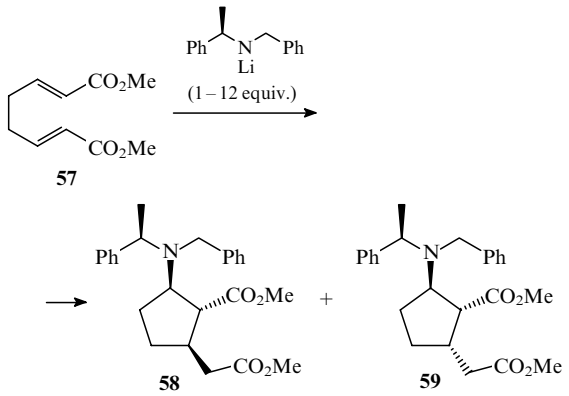


54 **55** **56**

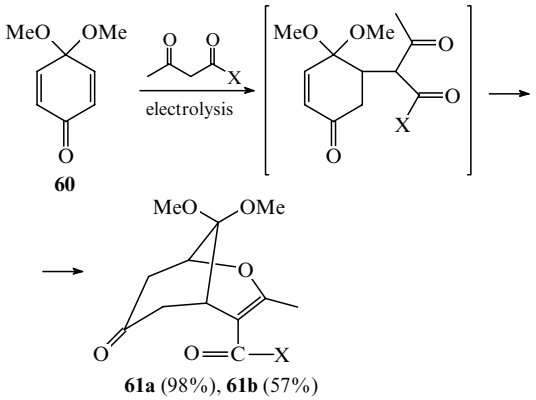


In the presence of catalytic amounts of a base, the reaction gave rise to a mixture of two products, *viz*., **55** and **56**, in a ratio of 3 : 1. The reaction in the presence of an equimolar amount of a base afforded only the monoaddition product **55**. The observed difference can be explained as follows. An appropriate amount of the enolate anion **54′** is generated under the action of catalytic amounts of a base. The Michael reaction of this anion with ethyl acrylate yields the anion **55′** whose intramolecular isomerisation gives rise to the anion **55″**. The latter either undergoes protonation to form the product **55** or enters into the second Michael reaction. The enolate anion **56′** abstracts the labile proton from the diketone **54** yielding the anion **54′** and the diester **56**. As a result, a mixture of the products **55** and **56** is obtained. In the presence of one equivalent of a base, the enolate anion **54′** is formed in quantitative yield. The Michael reaction affords the anion **55′**, which undergoes intramolecular deprotonation – protonation to give the anion **55″** and then exclusively the monoaddition product **55**.

Esters of α,β,α′,β′-dienedioic acids can serve as potential substrates for anionotropic tandem transformations. The intermediate enolate which is generated in the first step of intermolecular conjugate addition of the nucleophile attacks the second α,β-unsaturated ester group according to an intramolecular mechanism. The use of a chiral nucleophile in these tandem conversions allows the preparation of optically active adducts. Thus the reaction of homochiral lithium [(1*R*)-methylbenzyl]benzylamide with dimethyl octa-2,6-dienedioate (**57**) gave rise to chiral cyclopentane derivative **58**, the configurations of the C(1) and C(2) atoms being completely controlled and the configuration of the C(5) atom being controlled to a large degree [the content of the C(5)-epimer **59** was < 5%].[28]

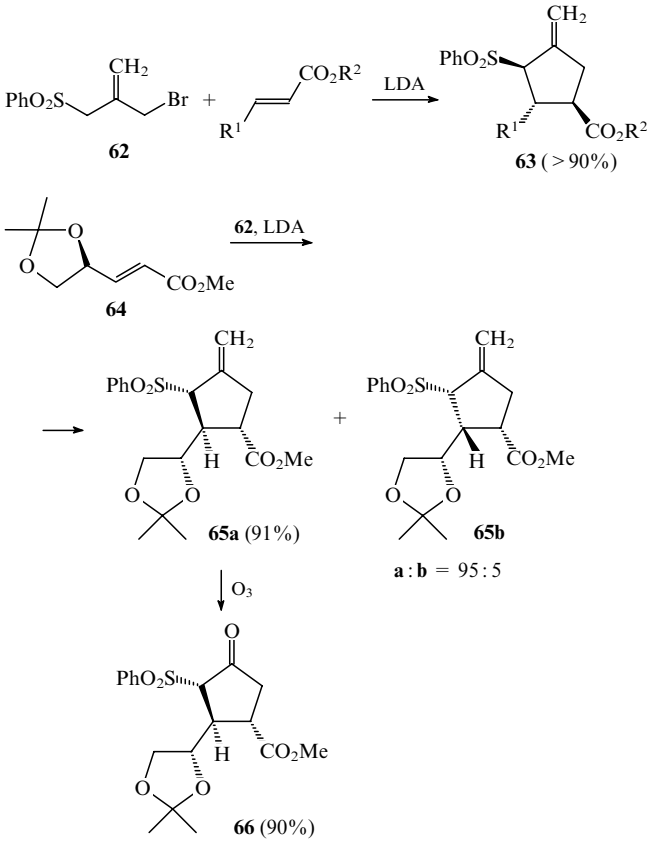


The reaction of 4,4-dimethoxycyclohexa-2,5-dienone (**60**) with ethyl acetoacetate and acetylacetone proceeded as a tandem Michael reaction.[29] Compounds **61a**,**b** were formed as a result of successive Michael C- and O-addition.



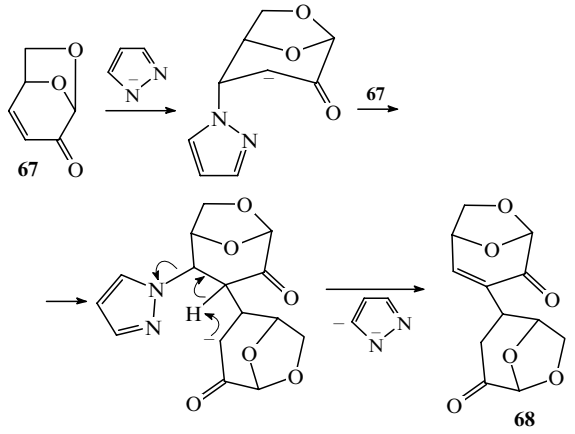
X = OEt (**a**), Me (**b**).

The bifunctional reagent, *viz*., 2-bromomethyl-3-phenylsulfonylprop-1-ene (**62**), reacts with different electrophilic alkenes to give [3 + 2]-cycloadducts.[30] The use of acyclic (*E*)-enoates in these reactions allows the preparation of stereohomogeneous *trans*, *trans*-trisubstituted methylenecyclopentanones **63** in high yields (90%). The tandem reactions of bromosulfone **62** with α,β-unsaturated esters containing the O atom at the γ position, in particular, with (4*S*)-enoate **64**, also proceeded with good facial selectivity. Subsequent ozonolysis of the alkene **65a** gave rise to enantiomerically pure cyclopentanone **66**.

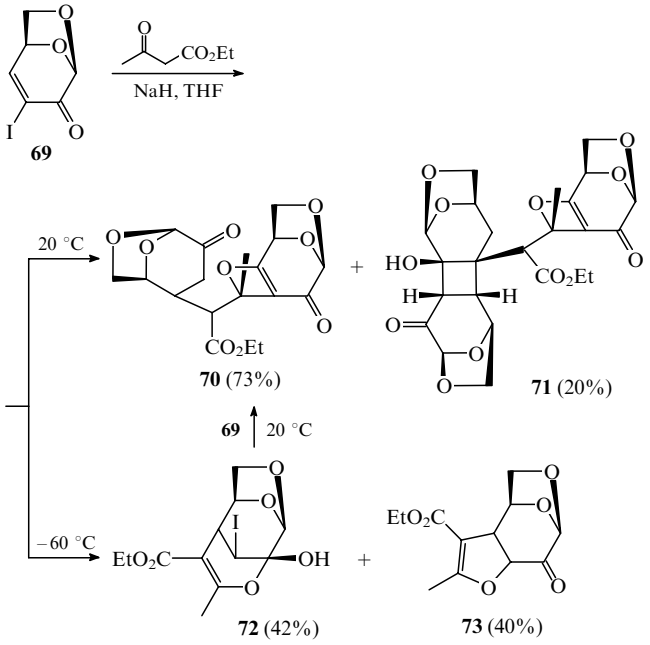


Abundant data on tandem reactions of 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-3-en-2-one, the so-called levoglucosenone (**67**), are now available in the literature (see, for example, Refs 31 – 33). Interesting conversions take place upon treatment of levoglucosenone with pyrazole under conditions of electrolysis. The first stage involves the cathode-initiated addition of pyrazole followed by the selective addition of yet another molecule **67** to the adduct to form the dimer **68** in quantitative yield.[34] Previously, the dimer **68** was obtained in low yield (8%)

along with trimers[33] by heating levoglucosenone in aqueous Et_3N.

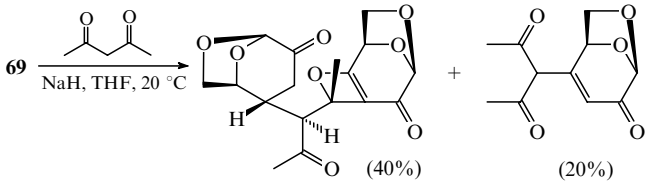


The introduction of the halogen atom at position 3 of levoglucosenone extends the possibilities of its tandem transformations. The effects of the temperature and the reagent ratio on the structure of the product were examined using the reaction of sodium ethyl acetoacetate with 3-iodolevoglucosenone (**69**) as an example.[35]

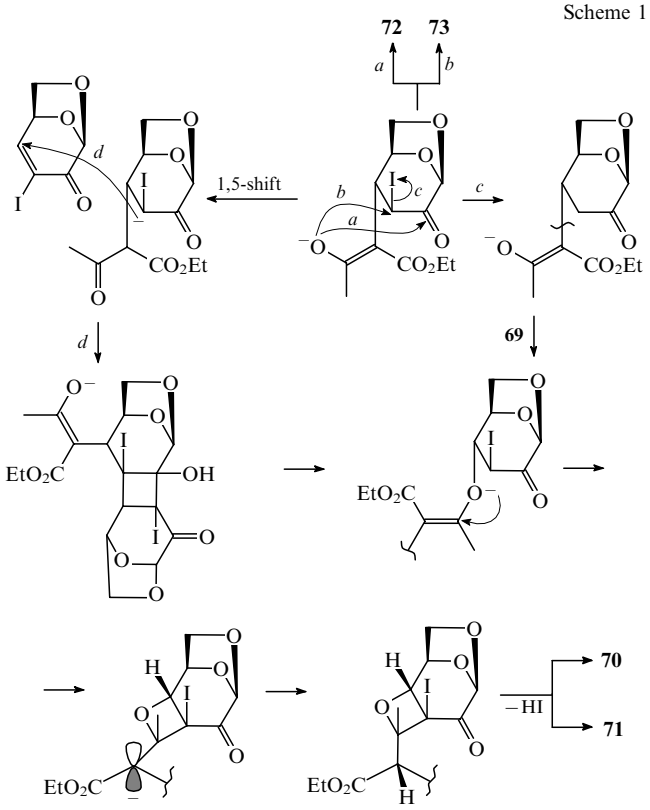


The reactions with an excess of the ketone **69** (2 equiv.) at room temperature afforded two products, *viz*., stable oxetene derivative **70** and polycyclic compound **71**[36] containing the cyclobutane fragment. The reaction of equimolar amounts of the reagents at −60 °C gave rise to 1 : 1 adducts **72** and **73**. It should be noted that the reaction of the compound **72** with 3-iodolevoglucosenone in the presence of NaH yielded the adduct **70**.[36] The assumed mechanism of conversions is shown in Scheme 1.

The reaction of yet another representative of CH-acids, *viz*., acetylacetone, with 3-iodolevoglucosenone (**69**) proceeded analogously.



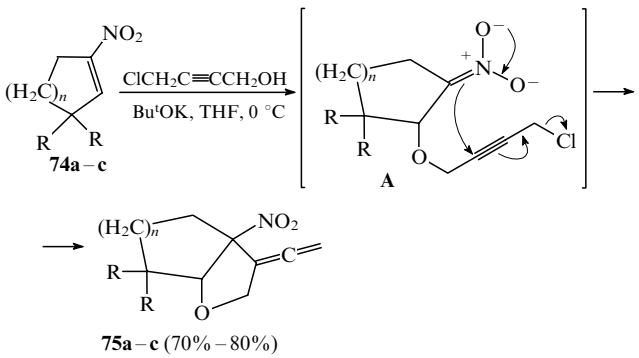
Scheme 1



III. Tandem 'Michael reaction – nucleophilic substitution' sequence

As mentioned above, the addition of a nucleophile to an acceptor gives rise to an anionic intermediate, which can act as a new nucleophile. If the molecule of the latter contains a good leaving group X, the subsequent intramolecular nucleophilic substitution can occur.

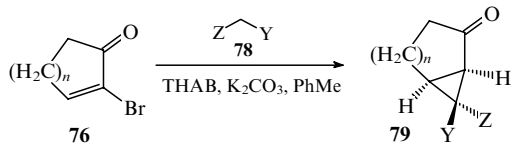
The procedure 'tandem oxa-Michael addition – intramolecular S_N2'-substitution' was used[37] for the efficient and stereocontrolled synthesis of poorly studied allenetetrahydrofurans. Nitrocycloalkenes **74a – c** react smoothly with 4-chlorobut-2-yn-1-ol to give bicyclic adducts **75a – c**. The reaction mechanism is analogous to that of the well-studied reactions of nitroalkenes with O-nucleophiles. Initially, the oxa-Michael addition affords the nitronate **A**, which undergoes cyclisation of the S_N2' type to form the allene derivative **75**.



R = H, *n* = 1 (**a**); R = H, *n* = 2 (**b**); R – R = OCH_2O, *n* = 2 (**c**).

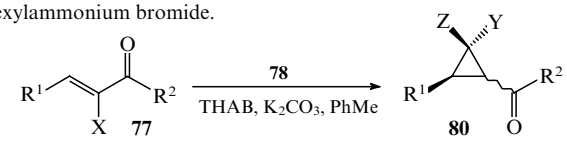
A procedure for cyclopropanation of cyclic and acyclic enones is based on the 'intermolecular Michael reaction – intramolecular alkylation' sequence.[38] Thus the reactions of readily accessible

α-haloenones **76** and **77** with mild C-nucleophiles **78** gave rise to cyclopropane derivatives **79** and **80**, respectively.



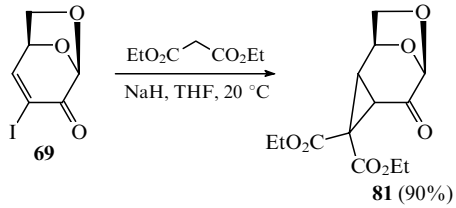
76 **79**

n = 1, 2; Y = CO_2Alk, CN, H; Z = CO_2Alk, NO_2; THAB is tetrahexylammonium bromide.

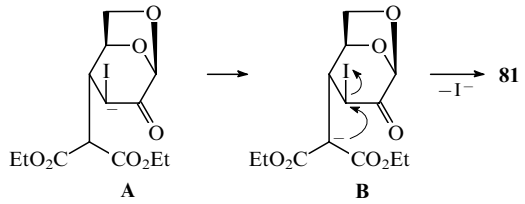


X = Cl, Br; R^1, R^2 = Alk, Ar.

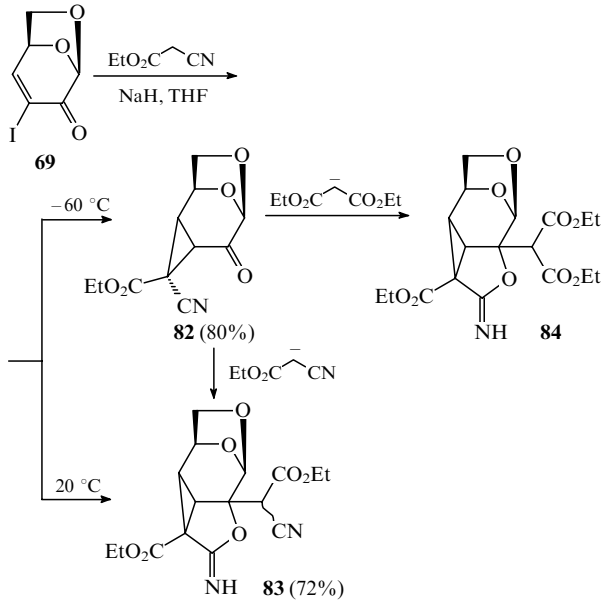
Cyclopropane derivative **81** was synthesised by the reaction of the malonate anion with 3-iodolevoglucosenone (**69**) as an electrophilic component.[39]



Apparently, a 1,3-shift of electron density occurs in the intermediate carbanion **A** resulting in generation of the more stable carbanion **B**, which eliminates the iodide ion to give the product **81** containing the cyclopropane ring.

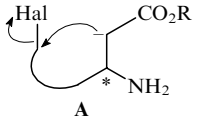


Analogously, 3-iodolevoglucosenone (**69**) reacted with sodium ethyl cyanoacetate at −60 °C to give the corresponding cyclopropane **82**.[35] However, the reaction of the ketone **69** with ethyl cyanoacetate at 20 °C afforded imidate **83**, which is the product of the cascade reaction of the cyclopropane **82** with a second cyanoacetate anion. This fact was confirmed by the reaction of the individual cyclopropane **82** with sodium ethyl cyanoacetate or the malonate anion at 20 °C giving rise to tetracyclic compounds **83** and **84**, respectively.

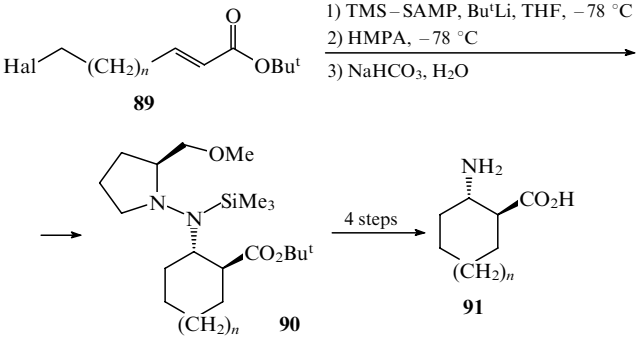


The classical tandem reaction of polyfunctional substrates, *viz*., of electrophile **85** and nucleophile **86**, (Scheme 2) has been described.[40] It appeared that the result of transformations is governed by the order in which the reagents are added. The addition of dimethyl 3-oxoglutarate (**86**) to a suspension of the dibromide **85** (*i.e*., in the presence of an excess of **85**) and Na_2CO_3 in dry THF afforded substituted benzo[*g*]isochromene **87**. On the contrary, the addition of the dibromide **85** to a suspension of the diester **86** (*i.e*., in the presence of an excess of **86**) and Na_2CO_3 in THF gave rise to a derivative of cyclopenta[1,3]cyclopropa[1,2-*b*]-naphthalene **88**. The observed selectivity can be explained as follows. Alkylation of the β-oxo ester **86** with the highly reactive benzyl-type bromide **85** leads to the intermediate **A**. The latter can react in two different ways. In the presence of an excess of the bromide **85**, the intermediate **A** is subjected to O-alkylation to form the intermediate **B**, which undergoes the intramolecular Michael cyclisation with elimination of HBr to give benzoisochromene **C**. Isomerisation of the double bond in the latter affords the final product **87**. If the reagents are added in the reverse order, the intramolecular Michael reaction takes place and the intermediate **A** is converted into the spiro compound **D**. The latter undergoes smooth cyclisation to form cyclopropane **E** and subsequent alkylation at the activated CH group with the second molecule of the dibromide **85** affords the product **88**.

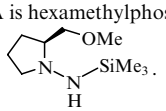
A new strategy for the synthesis of carbocyclic β-amino acids was reported.[41] The conjugate addition of the chiral analogue of ammonia, *viz*., (*S*)-(−)-1-(trimethylsilylamino)-2-(methoxymethyl)pyrrolidine (TMS–SAMP), to ω-halogen-substituted enoates **89** gave rise to intermediate ester **A**,



which underwent intramolecular cyclisation to give compound **90** with high stereoselectivity. Subsequent removal of the protective trimethylsilyl group, reduction of the N–N bond and hydrolysis of the ester group afforded carbocyclic β-amino acid **91**.

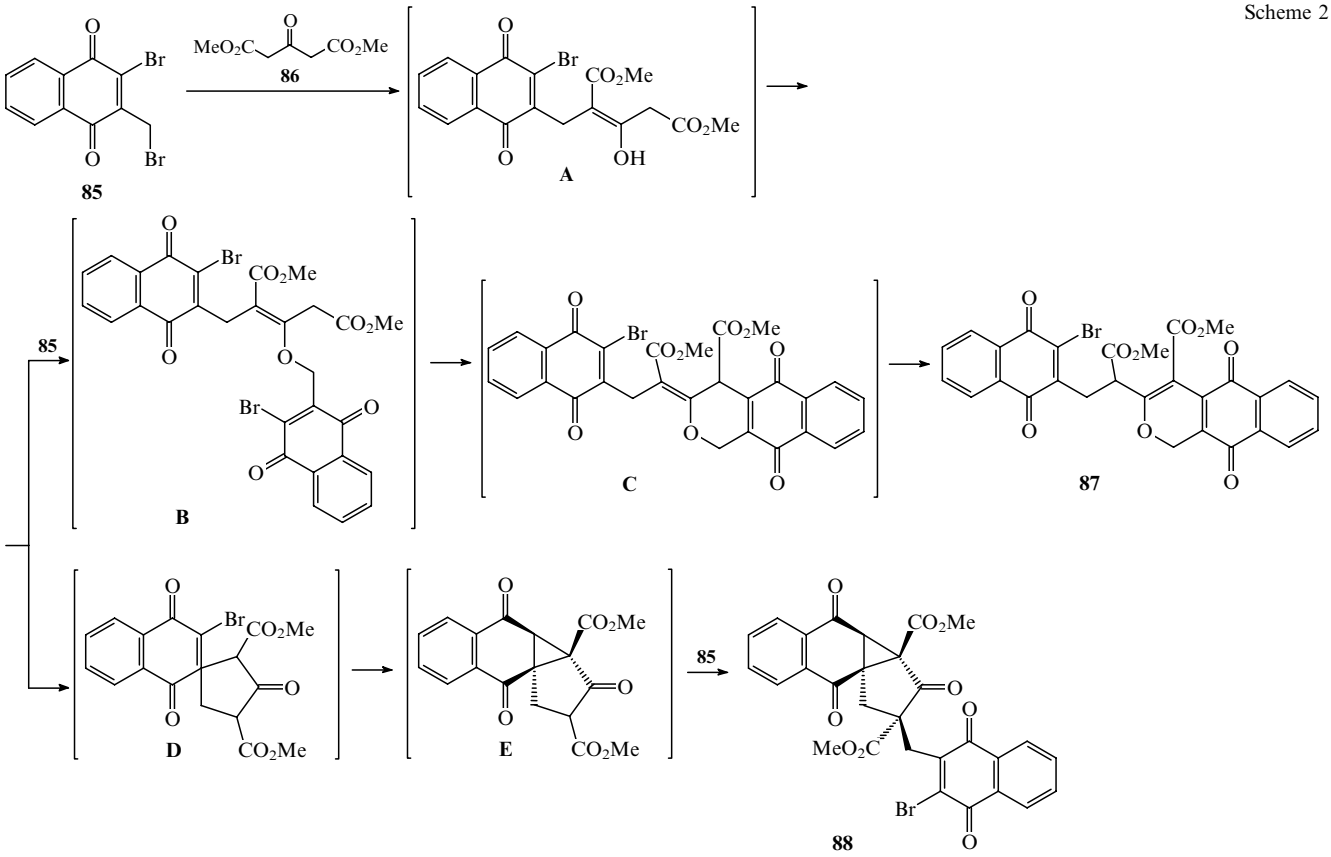


n = 0–4; HMPA is hexamethylphosphoramide;

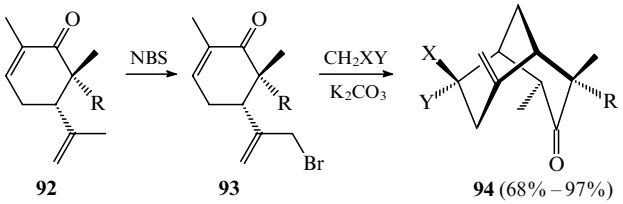
TMS–SAMP = 

A procedure for the synthesis of chiral bicyclo[3.3.1]nonanes from homologues of carvone (**92**) has been developed.[42] The reactions of allylic bromides **93** with different CH-acids occur as

Scheme 2



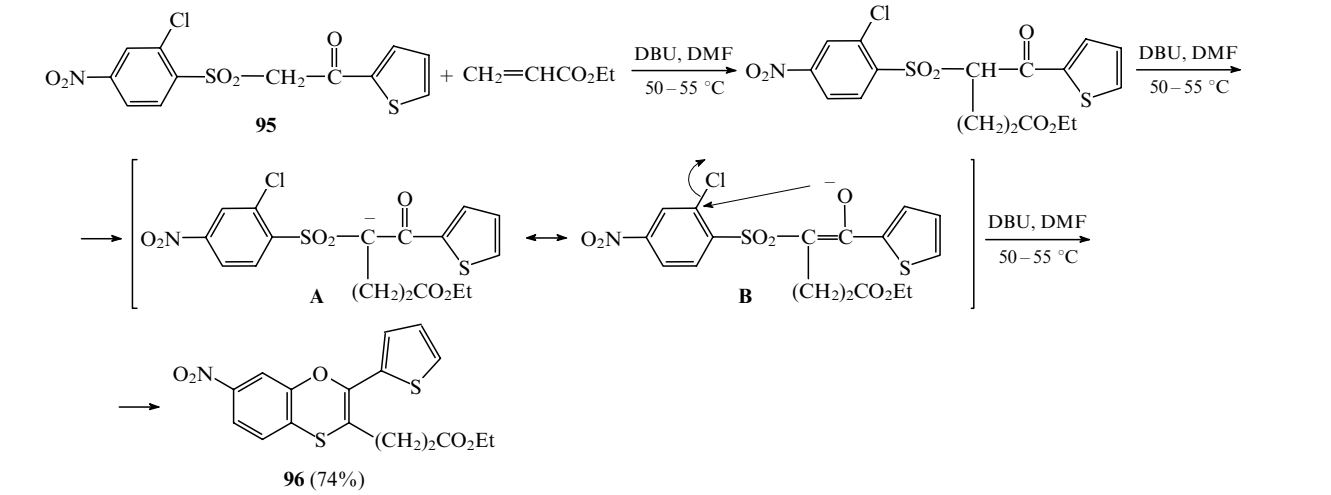
the tandem 'intermolecular alkylation – intramolecular Michael reaction' sequence giving rise to bicyclic compounds **94**.



R = H, Me; X, Y = CO_2Alk; NBS is *N*-bromosuccinimide.

The reaction of 2-(2-chloro-4-nitrophenylsulfonyl)acetylthiophene (**95**) with ethyl acrylate proceeds in a 'Michael reaction – nucleophilic substitution' sequence.[43] The possible mechanism involves generation of the anions **A** and **B** under basic conditions. The oxygen atom of the anion **B** bearing a negative charge can readily attack the C(2) atom of the benzene ring resulting in intramolecular nucleophilic substitution to form cyclic product **96** (Scheme 3).

Scheme 3

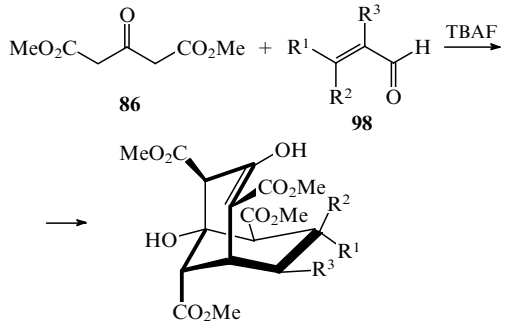


DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

IV. Tandem 'Michael reaction – aldol reaction' sequence

The basic medium required for the Michael reaction favours a subsequent aldol reaction. This type of transformation has been described in the literature in detail.

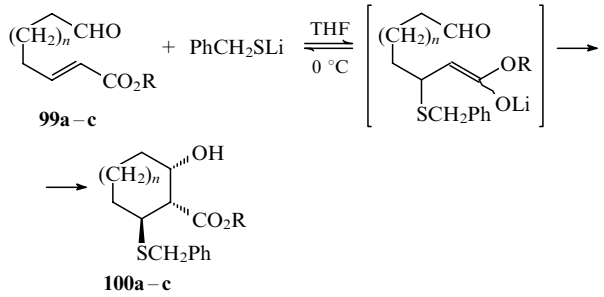
The short stereospecific synthesis of bicyclo[3.3.1]nonane derivatives (**97**) from acyclic diester **86** and enal **98** was performed by Michael addition followed by intramolecular aldolysation with the use of the reagent ratio **86** : **98** = 2 : 1.[44]



97 (53% – 99%)

R^1, R^2, R^3 = H, Alk, Ar.

An efficient procedure was developed for the construction of five – seven-membered carbocycles by the tandem 'Michael reaction – aldol cyclisation' sequence based on ω-oxo-α,β-unsaturated esters **99**.[45] Treatment of the latter with lithium α-toluenethiolates afforded cyclisation products **100** with a good stereoselectivity and in high yields.

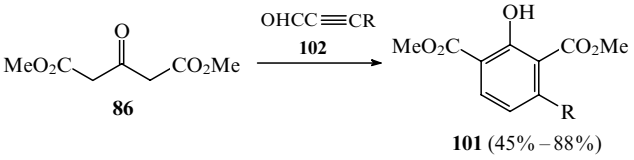


99a – c

100a – c

Compounds **99** and **100**	R	*n*	Yield of **100** (%)
a	Et	0	96
b	Me	1	95
c	Et	2	33

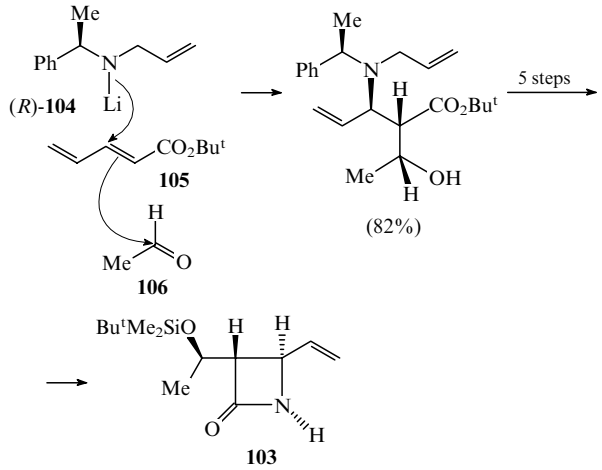
An efficient one-pot procedure was proposed for the construction of trisubstituted phenols **101** starting from prop-2-ynals **102** and the diester **86**.[46] This tandem process involves the Michael addition followed by aldol cyclisation of the intermediate enolate anion. The phenols **101** were obtained in high yields. Only the reaction with the use of propynal (R = H) as an acceptor gave the product in low yield (11%), which is attributable to side anionic polymerisation of propynal.



101 (45% – 88%)

R = H, Alk.

The tandem 'conjugate addition – aldol condensation' sequence has been used in the synthesis of the β-lactam fragment of thienamycin (**103**).[47] The highly stereoselective conjugate addition of lithium (*R*)-(α-methylbenzyl)allylamide (**104**) to an unsaturated ester, *viz*., to (*E*)-*tert*-butylpenta-2,4-dienoate (**105**), followed by aldol condensation with acetaldehyde (**106**) led to assembly of all three stereocentres of azetidinone **103** with the required absolute stereochemistry.

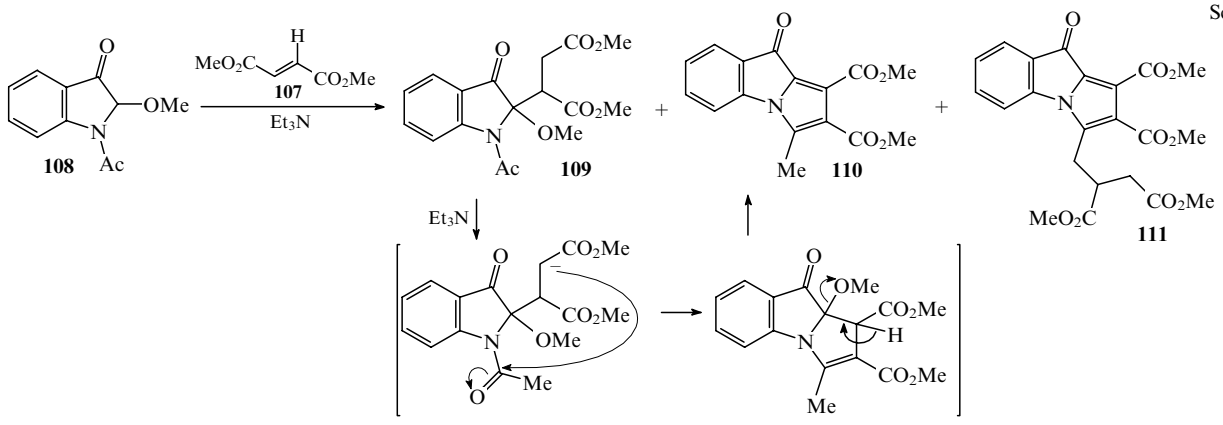


103

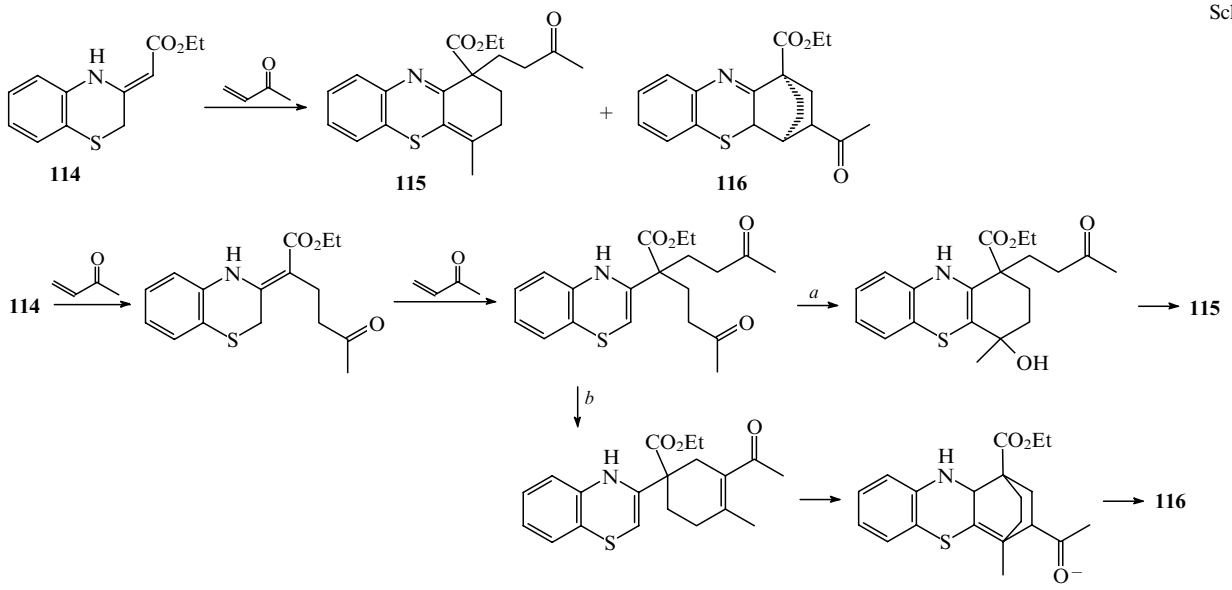
The tandem 'Michael addition – aldol reaction' and 'Michael addition – aldol reaction – Michael reaction' sequences have been described.[48] Dimethyl fumarate **107** reacted with heterocyclic ketone **108** in the presence of Et_3N to give the expected Michael adduct **109** (the yield was 38%) along with pyrrolo[1,2-*a*]indoles **110** (16%) and **111** (3%) (Scheme 4). Heating of the individual compound **109** with Et_3N afforded the product **110** the formation of which is attributable to spontaneous intramolecular cyclisation of the diester **109** followed by elimination of MeOH. The Michael addition of the pyrrole **110** to the dimethyl fumarate **107** afforded the tetraester **111**.

The 'Michael reaction – intramolecular aldol cyclisation' sequence was used for the synthesis of cycloalkenols **112** from oxo aldehydes **113** under the action of piperidine.[49] The resulting

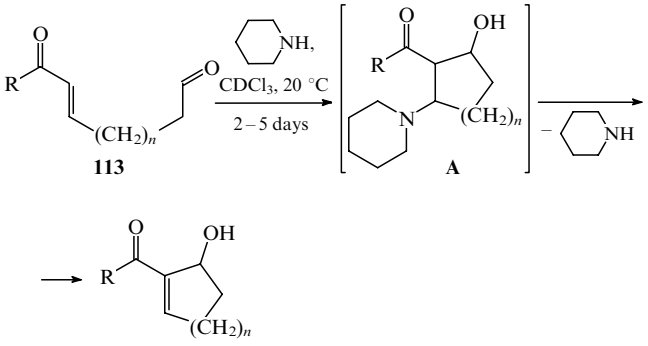
Scheme 4



Scheme 5



cyclic intermediate **A** (for R = Ph, this intermediate is stable for several days) eliminated piperidine (slowly for R = Ph) to give the enol **112**.

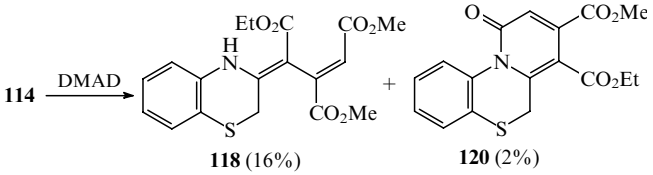


112 (20%–25%)

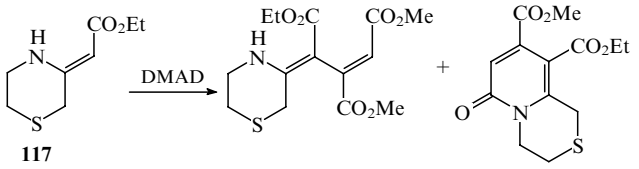
R = Alk, Ph; n = 1, 2.

The reaction of enamine **114** with methyl vinyl ketone at room temperature afforded only the product **115** in 95% yield (Scheme 5).[50] Refluxing of the reactants gave rise to the tetracycle **116** (the yield was 72%) along with the compound **115** (10%). Apparently, this is attributable to the initial addition of one molecule of methyl vinyl ketone at the α-carbon atom of the enamine followed by isomerisation of the double bond of the adduct and addition of the second molecule of methyl vinyl ketone. The process is completed with intramolecular aldol condensation (path *a*) giving rise to the tricycle **115**. Upon heating, aldol condensation (path *b*) occurs faster than the reaction following the path *a* and product **116** is formed.

The reactions of heterocyclic enamines **114** and **117** with dimethyl acetylenedicarboxylate (DMAD) afforded a mixture of the corresponding Michael addition (**118** and **119**) and cyclisation products (**120** and **121**). The individual compounds **118** and **119** were quantitatively converted upon heating into the cyclic ketones **120** and **121**, respectively.

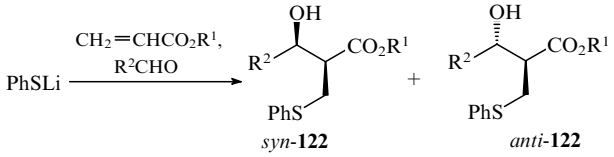


118 (16%) **120** (2%)



119 (62%) **121** (16%)

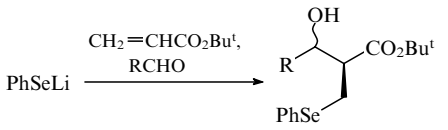
The adduct **122** was obtained in good yield and high *syn*-selectivity by the reaction of a mixture of lithium thiophenoxide, an α,β-unsaturated ester and an aldehyde.[51] The reaction began with the nucleophilic attack of the thiolate at the β-carbon atom of the acceptor giving rise to intermediate enolate which entered into the aldol reaction with the aldehyde to form the polyfunctionalised adduct **122** as a mixture of the *syn*- and *anti*-isomers. An analogous mixture of isomers was obtained in the reaction with the use of lithium selenolate generated *in situ* under the action of methyllithium on diphenyl selenide.



syn-**122** *anti*-**122**

syn : *anti* = 9 : 1

R^1, R^2 = H, Alk.

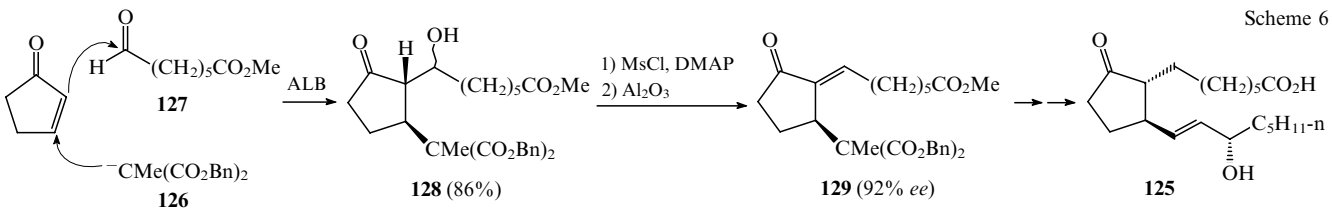


syn : *anti* = 8.5 : 1.0

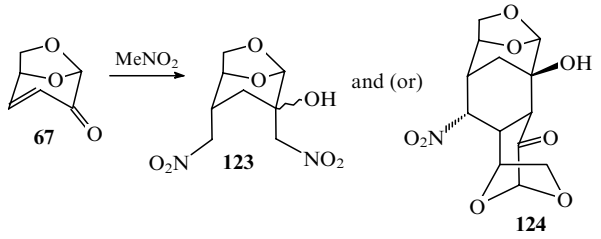
R = H, Alk.

Previously, it had been demonstrated that the reaction of levoglucosenone (**67**) with an excess of nitromethane afforded the addition product **123** (the yield was 89%). The reaction in the presence of an excess of levoglucosenone gave rise to the adduct **124** (95%).[31] The reaction with the use of an equimolar mixture of the reagents gave both products **123** and **124** in 18% and 61% yields, respectively.[32] The electrochemical method proved to be more selective.[34] Electrolysis of an equimolar mixture of nitromethane and levoglucosenone afforded exclusively the ketone **124** (the yield was 92%).

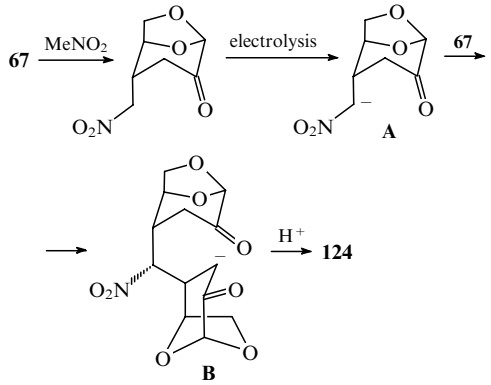
Scheme 6



MsCl is mesyl chloride; DMAP is dimethylaminopyridine.



The assumed mechanism of formation of the adduct **124** involves the Michael addition of the anion **A**, which is generated by the addition of the nitromethane molecule to the ketone **67**, to the second levoglucosenone molecules followed by intramolecular aldol condensation of the intermediate diketone **B**.

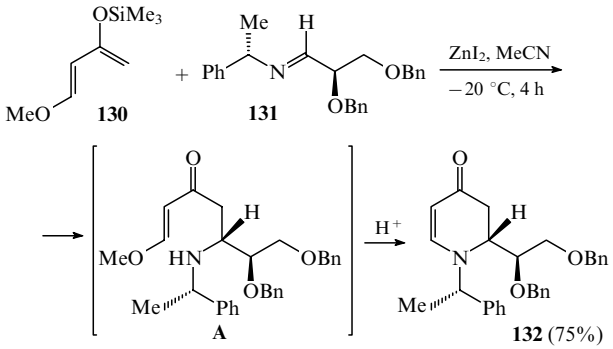


The 'Michael reaction – aldol reaction' sequence was used as the key stage in the synthesis of the prostaglandin 11-deoxy-$PGF_{1\alpha}$ (**125**).[52] The reaction of cyclopent-2-enone with dibenzyl methylmalonate (**126**) and the aldehyde **127** in the presence of aluminium lithium bis[(*S*)-1,1′-bi-2-naphthoxide] (ALB) as a catalyst produced the expected three-component coupling product **128** as a mixture of two diastereomers in a ratio varying from 6 : 1 to 17 : 1. The use of this catalyst not only initiates tandem conversions, but also provides high stereoselectivity of addition. Mesylation of the adduct **128** followed by elimination of MsOH afforded optically pure compound **129**, which can be converted into the target product **125** (Scheme 6).

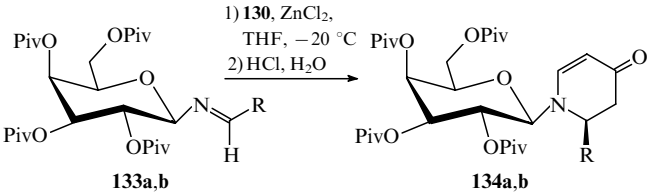
V. Tandem Mannich and Michael reactions

It is known that Mannich bases are very convenient intermediates in a number of syntheses. These bases can readily be converted into vinyl ketones and used in the Michael reaction as electrophiles. Due to their proneness to polymerisation, acceptors are generated from Mannich bases *in situ*. Since decomposition of Mannich bases produces secondary amines, which can catalyse the Michael reaction, an additional amount of base need not be added.

The Mannich and Michael reactions of imines with the Danishefsky diene proceed in tandem.[53] Electron-excessive 1-methoxy-3-trimethylsilyloxybutadiene (**130**) reacted with the imine **131** in the presence of a Lewis acid to give the addition product **A**. Acid treatment of the latter led to rapid intramolecular Michael addition and elimination of MeOH to form cyclic enaminone **132**.

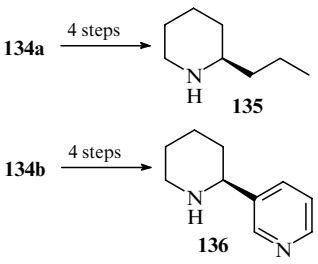


The tandem Mannich and Michael reactions were used for the enantioselective synthesis of chiral piperidine derivatives.[54] Aldimines derived from tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**133a**,**b**) and the diene **130** gave 2-substituted dehydropiperidine derivatives **134a**,**b**, respectively. The latter were transformed into alkaloids coniine (**135**) and anabasine (**136**).

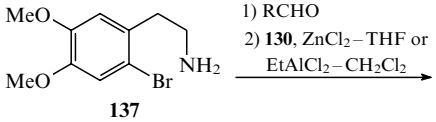


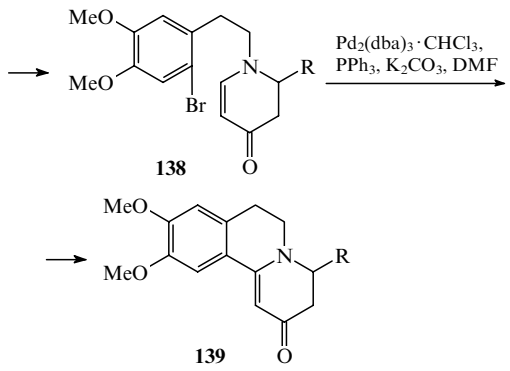
Piv = $C(O)CMe_3$.

Compounds **133** and **134**	R	Yield of **134** (%)
a	Pr^n	96
b	3-Pyridyl	90



An efficient and short procedure was developed for the synthesis of tetra- and hexahydrobenzoquinolizinones, which are precursors of psychoactive alkaloids of the berberine series.[55] The Mannich and Michael reactions of 2-bromohomoveratrylamine (**137**) and silyloxydiene **130** gave rise to *N*-substituted enaminone **138**, which underwent Heck cyclisation to form the heterocycle **139**.

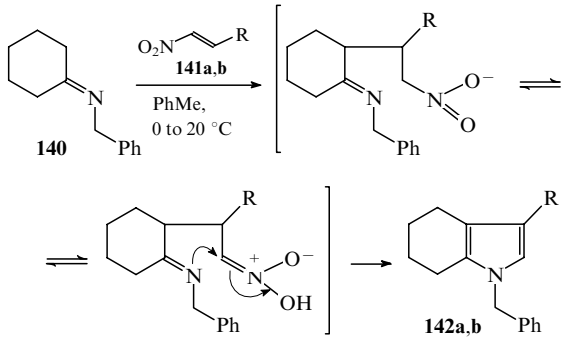




R = H, Alk or Ar; dba is dibenzylideneacetone.

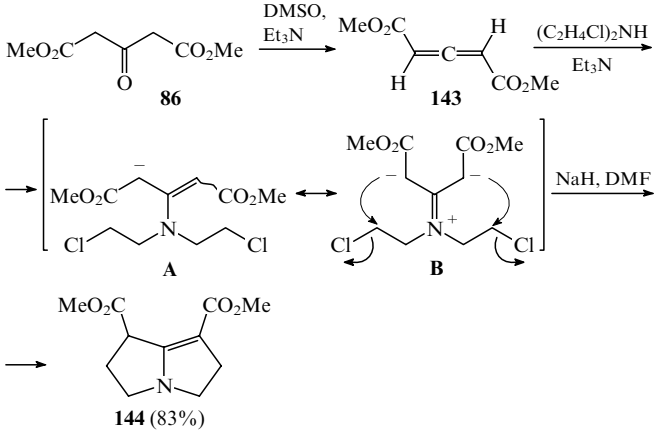
VI. Tandem Michael reaction and heterocyclisation

The Michael addition of cyclohexaneimines (which react as enamines) to β-substituted nitroalkenes is accompanied by cyclisation and elimination of the nitro group to form substituted tetrahydroindoles.[56] The imine **140** reacted with *trans*-β-nitro alkenes **141a**,**b** to give the expected tetrahydroindoles **142a**,**b**, respectively.

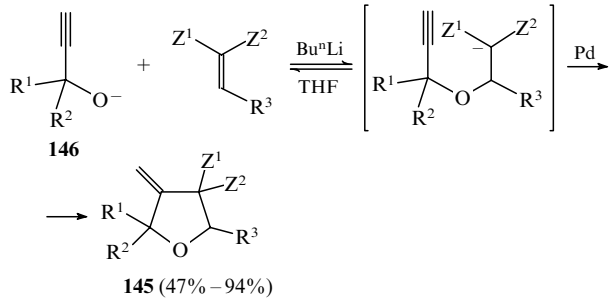


Compounds **141** and **142**	R	Yield of **142** (%)
a	Ph	70
b	Et	76

Allene-1,3-dicarboxylate (**143**) acts as an extremely reactive acceptor in the Michael reaction. This compound reacts with secondary amines to give the ion **A** as a result of conjugate addition. The ion **A** can also exist as the dianion **B**. The latter contains a good leaving group and undergoes smooth cyclisation. The final product, *viz*., azabicycle **144**, represents a skeleton of pyrrolizidine alkaloids.[57]

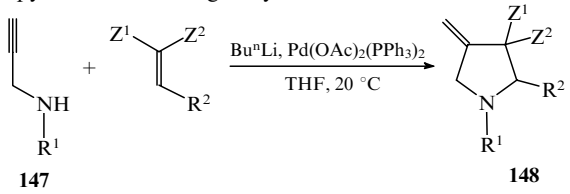


The procedure for the synthesis of various different functionalised 3-methylidenetetrahydrofurans **145**[58] is based on the conjugate addition of anions of propargylic alcohols **146** to alkylidene- or arylmethylidenemalonate initiated by catalytic amounts of a base and subsequent *in situ* Pd-catalysed *exo-dig* cyclisation.



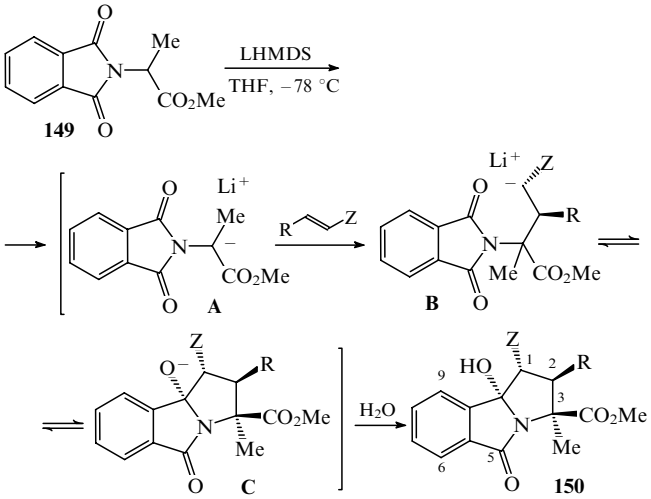
R^1, R^2 = H, Alk, Ar; R^3 = Alk, Ar; Z^1, Z^2 = CO_2Et, CN.

This approach was used in the synthesis of 3-methylidenepyrrolidines **148**.[59] *N*-Substituted propargylamine **147** is used as the nucleophilic substrate, which reacts with different acceptors to give pyrrolidines **148** in good yields.



R^1, R^2 = Alk, Ar; Z^1, Z^2 = CO_2Et, CN.

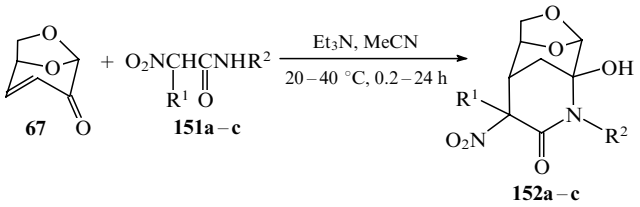
The tandem 'Michael addition – intramolecular condensation' sequence was used in the synthesis of functionalised pyrroloisoindoles.[60] Treatment of methyl ester of *N*-phthaloylalanine (**149**) with lithium hexamethyldisilazide afforded carbanion **A**, which reacted with α,β-unsaturated compounds to give intermediates **B** and **C** and then pyrrolo[2,1-*a*]isoindol-5-ones (**150**) according to a standard scheme.



R = H, CO_2Et; Z = CO_2Et, CN.

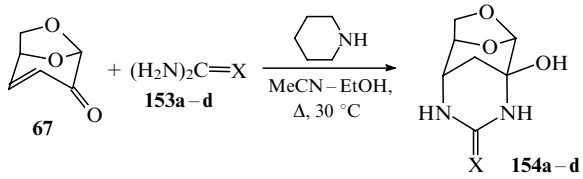
The reactions of levoglucosenone (**67**) with binucleophiles proceed with the participation of the C=C and C=O bonds and can be used for the synthesis of fused heterocyclic systems containing the carbohydrate fragment. Thus the addition of nitroacetamide (**151a**) to levoglucosenone was accompanied by cyclisation to yield exclusively the stereoisomer **152a**.[34] The reactions of *N*-hexylnitroacetamide (**151b**) and α-nitropropion-

amide (**151c**) with levoglucosenone produced compounds **152b**,**c**, respectively.[61]



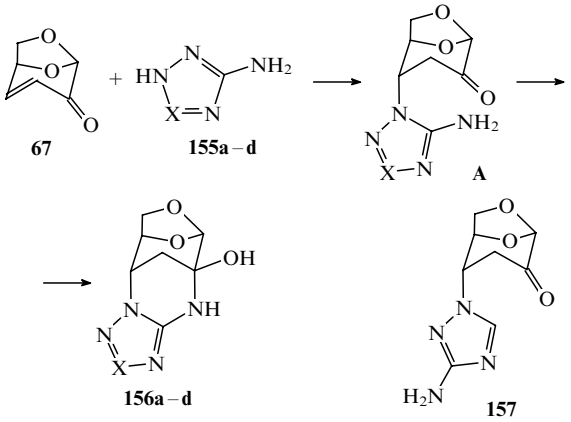
Compounds **151** and **152**	R^1	R^2	Yield of **152** (%)
a	H	H	62
b	H	$(CH_2)_5Me$	49
c	Me	H	69

The reactions of levoglucosenone with urea (**153a**), thiourea (**153b**), *N*-cyanoguanidine (**153c**) and *N*-nitroguanidine (**153d**) in the presence of bases were accompanied by pyrimidine-ring closure to form compounds **154a**–**d**, respectively.[62] In spite of drastic reaction conditions, water was not eliminated from the molecule **154**, as in the above-considered reaction, which is in agreement with the Bredt rule.



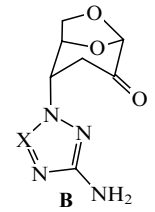
Compounds **153** and **154**	X	Yield of **154** (%)
a	O	58
b	S	53
c	NCN	31
d	NNO_2	48

The reactions of levoglucosenone with α-aminoazoles **155a**–**d** gave rise to azolo[1,5-*a*]pyrimidine systems **156a**–**d**, respectively.[63] In the reaction with the triazole **155b**, the Michael adduct **157** was also formed.

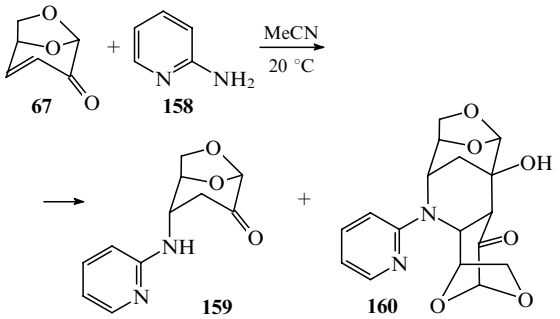


Compounds **155** and **156**	X	Yield of **156** (%)
a	N	75
b	CH	39
c	CNO_2	76
d	CCF_3	62

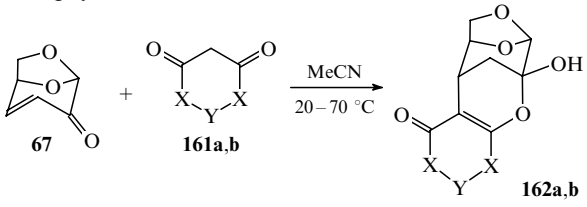
Apparently, deprotonation of the NH group of the heterocycle under the action of the base results in the anion, which attacks the double bond of levoglucosenone. If the C=C bond is subjected to the attack of the nitrogen atom adjacent to the amino group, the reaction is not terminated at the stage of formation of the intermediate **A** and the latter undergoes cyclisation to give compound **156**. On the contrary, if the C=C bond is subjected to attack by the nitrogen atom remote from the amino group (the intermediate **B**), cyclisation does not take place because it should lead to the closure of the seven-membered ring, which is much less probable than the closure of the six-membered ring.



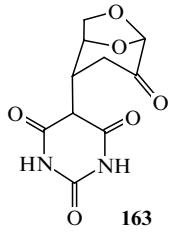
The reaction of levoglucosenone with 2-aminopyridine (**158**) was examined.[63] If the reagents were taken in an equimolar ratio, the reaction gave rise to a mixture of the addition product **159** and polycyclic compound **160**. The reaction with a twofold molar excess of levoglucosenone afforded virtually exclusively the product **160**. The compound **160** is structurally very similar to the 2 : 1 adduct of levoglucosenone with nitromethane, and, consequently, the probable mechanism of its formation involves the addition of two levoglucosenone molecules at the nucleophilic centre followed by intramolecular aldol condensation.



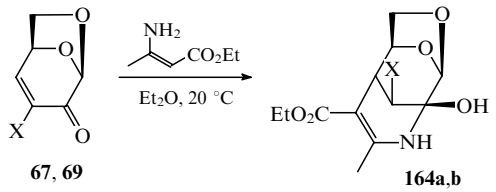
The reaction of levoglucosenone with dimedone (**161a**) yielded only the product **162a**. The reaction of levoglucosenone with barbituric acid (**161b**) produced the tetraketone **163** along with the heterocyclisation product **162b**. The formation of pyrans of the type **162** in the reactions of dimedone or barbituric acid with compound **67** may result from the enhanced reactivity of the carbonyl group of levoglucosenone as well as from steric factors favouring cyclisation.



X = CH_2, Y = CMe_2 (**a**); X = NH, Y = CO (**b**).



Six-membered hemiaminals **164a**,**b** smoothly formed in the reactions of the enamine derived from ethyl acetoacetate with levoglucosenone (**67**)[63] and 3-iodolevoglucosenone (**69**), respectively.[36]

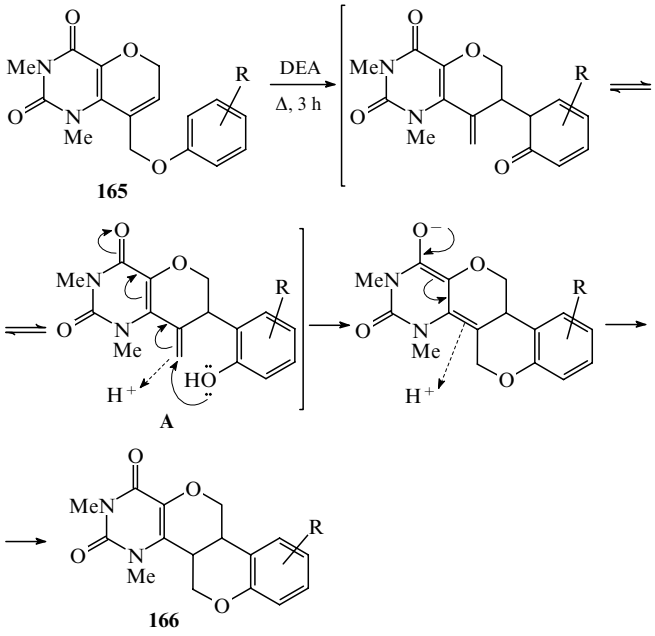


67, **69** **164a**,**b**

X = H (**67**, **164a**), I (**69**, **164b**).

VII. Tandem 'anionotropic rearrangement – Michael reaction' sequence

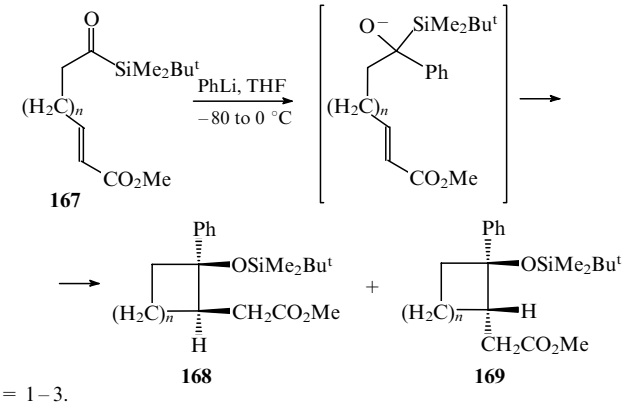
Heating of diketones **165** with *N*,*N*-diethylaniline (DEA) to 200 °C afforded pyranopyrans **166**.[64] Apparently, the compound **165** undergoes a sigmatropic rearrangement upon heating to give intermediate **A**, which can undergo intramolecular Michael cyclisation giving rise to the final product **166** due to the suitable arrangement of the phenolic OH group.



165 **A** **166**

R = H, Alk, Cl, NO_2.

The tandem 'Brook rearrangement – intramolecular Michael reaction' sequence is suitable for the construction of functionalised carbocycles.[65] Acylsilanes containing the double bond at a suitable position (separated by 2, 3 or 4 carbon atoms) serve as substrates for cyclisation. The addition of phenyllithium to a solution of the acylsilane **167** brings about the Brook rearrangement and the intramolecular Michael reaction, which proceed smoothly to form diastereomeric cycloalkanes **168** and **169** in a total yield of 70% – 82%.



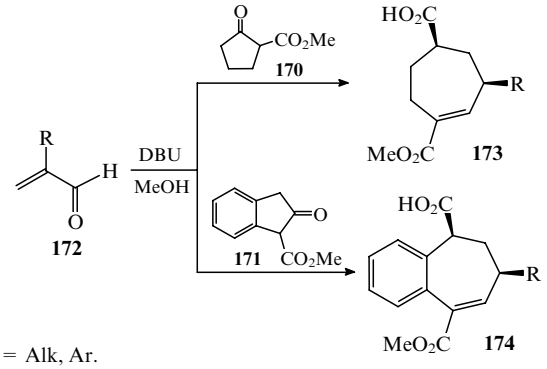
167 **168** **169**

n = 1 – 3.

VIII. Tandem Michael and Dieckmann reactions

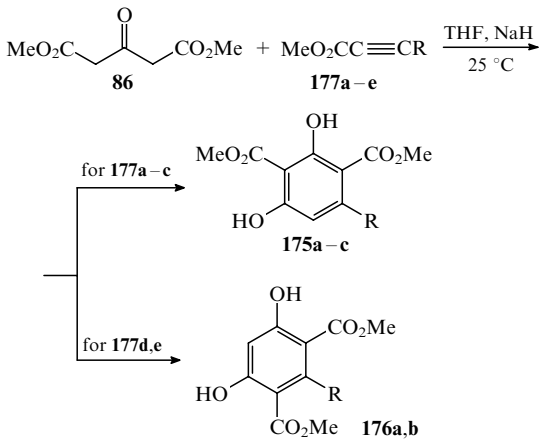
The cascade processes involving more than three different reactions remain poorly studied. Of these processes, the 'Michael reaction – aldol condensation – retro-Dieckmann reaction' sequences, which are also called MARD cascades, have received the most study.

Previously, it has been demonstrated[66] that the reactions of α-oxocyclopentanecarboxylates with acroleins under mild conditions were accompanied by two-carbon-atom ring expansion. The five-step domino reactions of simple cyclic β-oxo esters **170** and **171** with 2-substituted acroleins **172** were used for the synthesis of valuable highly substituted cycloheptenones **173** and **174**, respectively, containing two stereocentres, the double bond and two chemically different carbonyl groups.[67] The transformation cascade involves the Michael addition, intramolecular aldol condensation and retro-Dieckmann reaction followed by dehydration and chemoselective saponification of one ester group. The configurations of the asymmetric centres are determined by the stereodifferentiating stage of the aldol cyclisation.



R = Alk, Ar.

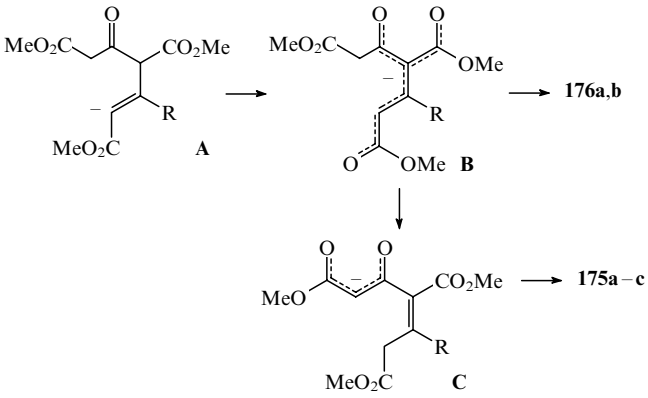
The synthesis of non-symmetrical and symmetrical resorcinols **175** and **176** from aliphatic compounds by the tandem 'Michael reaction – Dieckmann cyclisation' sequence was investigated.[68] The reactions of dimethyl 3-oxoglutarate (**86**) with alkyl alkynoates **177a** – **c** at 25 °C produced non-symmetrical resorcinols **175a** – **c**, respectively. The reactions with the use of methyl alkynoates **177d**,**e** at low temperatures afforded symmetrical resorcinols **176a**,**b**, respectively. Apparently, conjugate addition of the enolate **86** to methyl alkynoates **177a** – **e** affords vinyl



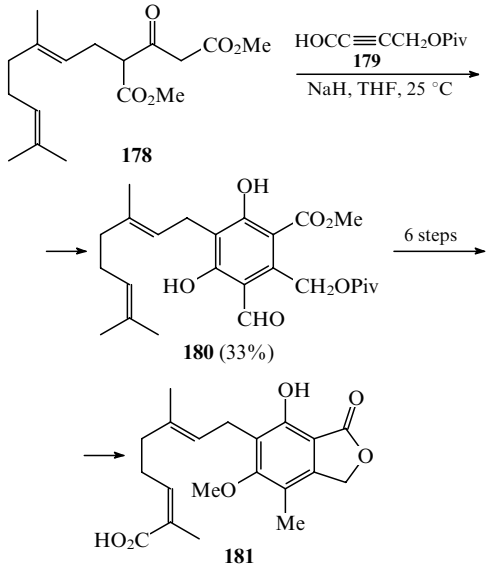
86 **177a** – **e** **175a** – **c** **176a**,**b**

Compound **177**	R	Product	Yield (%)
a	Me	**175a**	59
b	Ph	**175b**	84
c	CH_2OBz	**175c**	67
d	H	**176a**	18
e	CO_2Me	**176b**	34

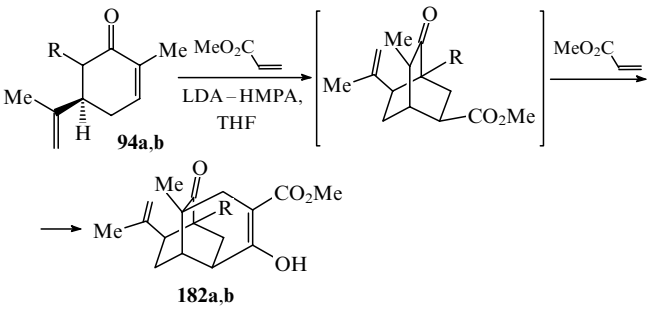
carbanion **A**. The latter is rapidly protonated with the most acidic methylene proton to give carbanion **B**, which is a precursor of symmetrical products **176a**,**b**. Contrary to the expected stability, the anion **B** underwent isomerisation (at 25 °C) to form enolate **C**, which is a precursor of the non-symmetrical products **175a**–**c**. It is believed that the delocalised anion **B** is more rapidly generated from the vinyl carbanion **A** and is stable only at low temperatures (up to 0 °C). On the contrary, this anion undergoes isomerisation to give the more stable enolate at room temperature. Consequently, the enolate **A** undergoes cyclisation to form symmetrical resorcinols **176a**,**b** when low temperature is required for prevention of polymerisation.



The tandem 'Michael addition–intramolecular Dieckmann cyclisation' sequence was used as the key stage in the total synthesis of mycophenolic acid exhibiting fungicidal, antibacterial, antiviral and immunosuppressive properties.[69] The reaction of dimethyl 2-geranyl-3-oxoglutarate (**178**) with 4-pivaloyloxybut-2-ynal (**179**) gave rise to the totally substituted resorcinol **180** with the required arrangement of all substituents. The resulting adduct was converted into the target mycophenolic acid (**181**) in six steps.



The use of readily accessible optically pure α,β-unsaturated ketones, such as carvone (**94a**) or methylcarvone (**94b**), in the tandem sequence of three Michael reactions and Dieckmann cyclisation allows the preparation of optically pure tricyclo[5.3.1.$0^{3,8}$]undecanes **182a**,**b**,[70] which are structural cores of seychellane.

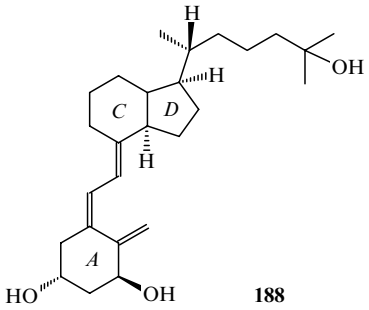


Compounds **94** and **182**	R	Yield of **182** (%)
a	H	40
b	Me	44

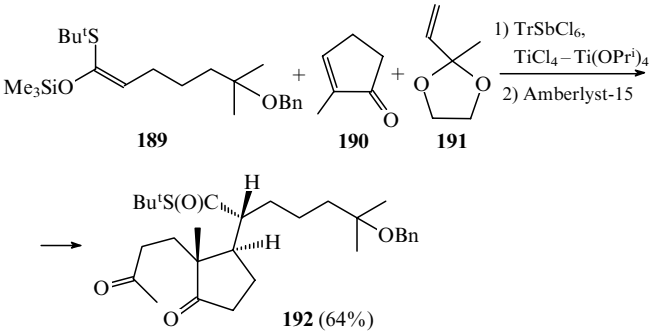
IX. Tandem Mukaiyama and Michael reactions

The tandem 'Mukaiyama reaction–Michael reaction–aldol cyclisation' sequence was used as the key stage in the synthesis of biologically active compound **183**.[71] Under conditions of the Mukaiyama reaction, enol silyl ether **184** and spiro compound **185** gave enolate **A** whose conjugate addition to the chalcone **186** afforded enolate **B**. Intramolecular aldol condensation of the latter gave rise to compound **187** from which the target product **183** was obtained (Scheme 7).

The tandem Michael and Mukaiyama reactions were used in the total synthesis of vitamin D_3 (**188**).[72]

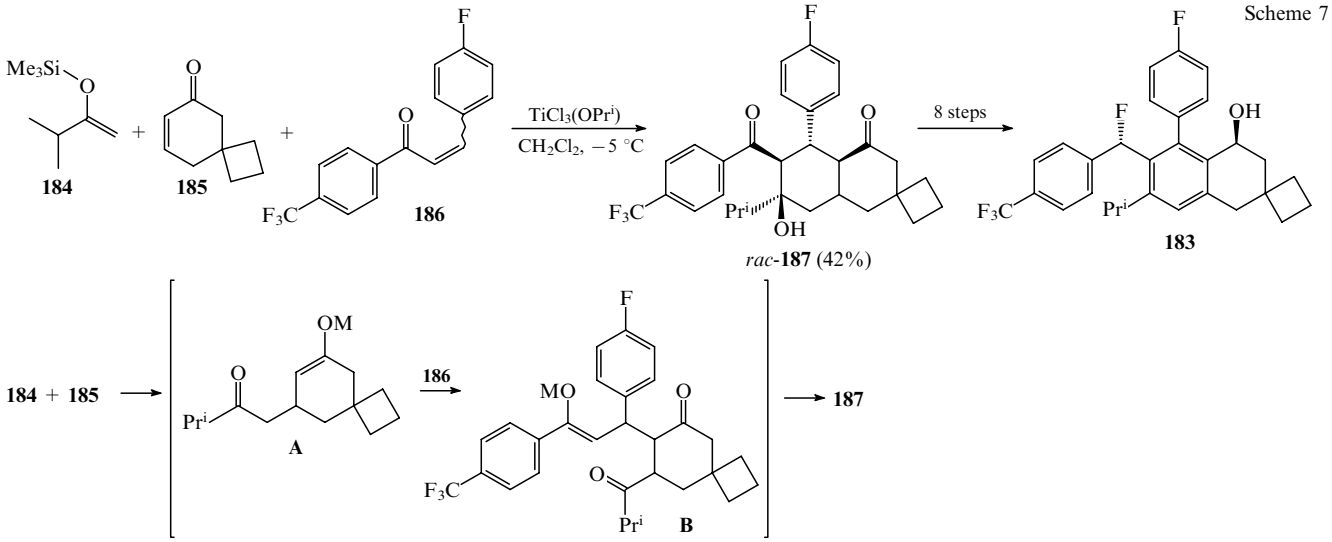


The reaction of ketene hemithioacetal **189** with 2-methylcyclopent-2-enone (**190**) catalysed by a Lewis acid afforded enol silyl ether. The latter entered into the second conjugate addition reaction with methyl vinyl ketone acetal **191** as a reactive intermediate. The key precursor of blocks of the *C*/*D* type (**192**) was prepared in one step starting from three components.



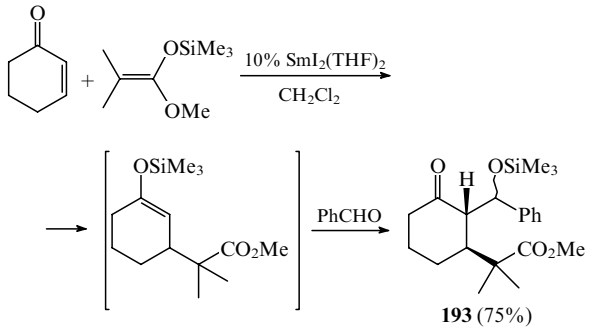
The tandem 'Mukaiyama–Michael reaction–Mukaiyama reaction–aldol reaction' sequence was used for the introduction of two chains at the α and β positions of cyclic α,β-unsaturated ketones.[73] The low temperature at which this reaction was performed (−60 °C) hindered the formation of by-products of the crotonic type and enabled the achievement of high dia-

Scheme 7



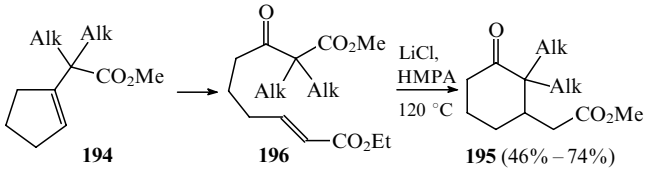
M is a group stabilising enolate.

stereoselectivity (*cis* : *trans* = 98 : 2) and good yields of the adduct **193**. This reaction is the first example of the lanthanide-catalysed tandem formation of C—C intermolecular bonds.

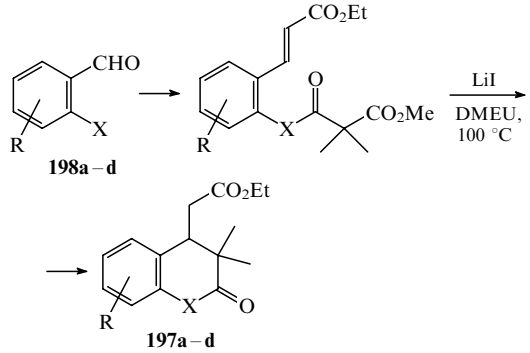


X. Miscellaneous tandem transformations involving Michael reactions

Recently, a large number of new tandem reactions have been developed. Thus a three-step ring expansion was used for the conversion of methyl dialkylcyclopent-1-en-1-ylacetate **194** into methyl cyclohexylacetate **195**.[74] The process involved ozonolytic cleavage of the double bond in **194**, the Wittig olefination of the product and the tandem sequence of dealkoxycarbonylation of the oxo ester **196** and the Michael addition. Intramolecular cyclisation gave rise to the ester **195**.



An analogous sequence was used for the preparation of lactones and lactams.[75] Precursors of lactones **197a–c** were synthesised from the corresponding salicylaldehyde derivatives **198a–c** by introducing the acrylic-acid fragment using the Wittig olefination and esterification of the 2-OH group for the subsequent ring closure. The precursor of the lactam **197d** was synthesised analogously from 2-aminobenzaldehyde (**198d**).

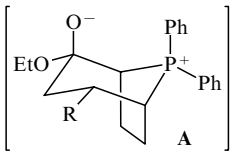


DMEU is 1,3-dimethyl-2-imidazolidinone.

Compounds **197** and **198**	R	X	Yield of **197** (%)
a	H	O	62
b	5-OMe	O	50
c	3,4-benzo	O	52
d	H	NH	76

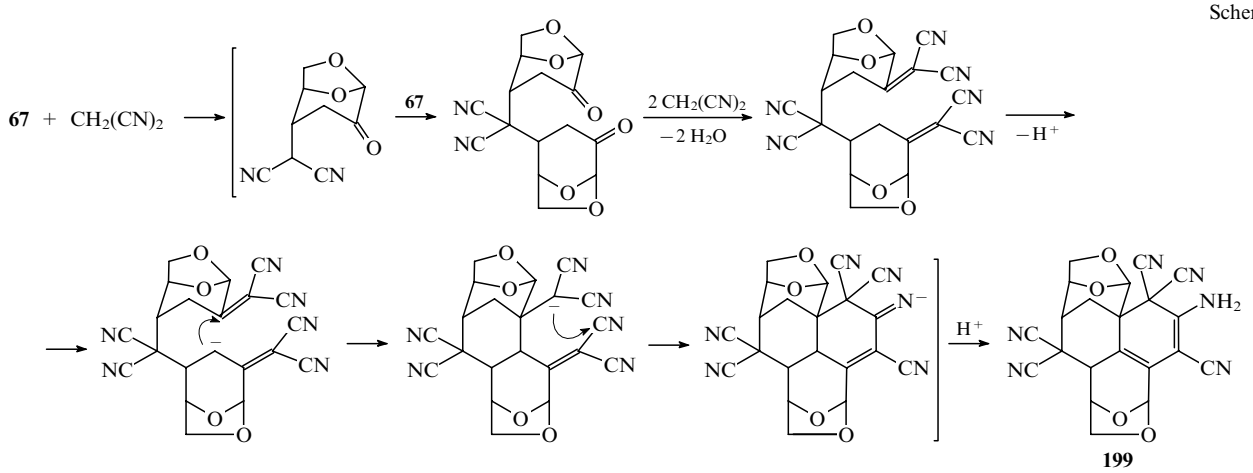
The reaction of levoglucosenone with malononitrile in the presence of piperidine afforded polycyclic compound **199** (Scheme 8).[76]

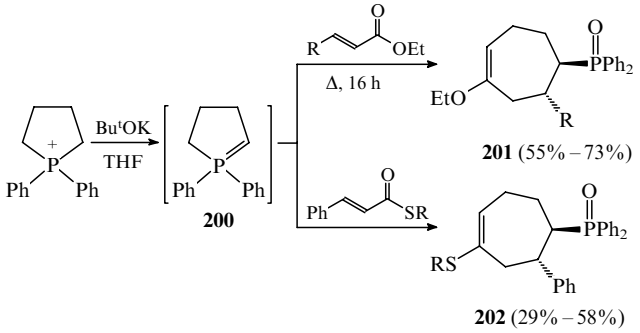
The tandem Michael and Wittig reactions involving five-membered phosphonium ylides **200** and α,β-unsaturated esters gave rise to seven-membered vinyl ethers **201**.[77] The process occurred *via* the structurally rigid phosphorus-containing bicyclic intermediate **A**



which provided high stereoselectivity of the formation of vinyl ethers. Analogous reactions were observed in the case of α,β-unsaturated thioesters [78] yielding cycloheptene derivatives **202**.

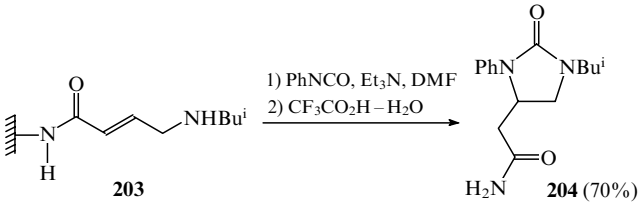
Scheme 8



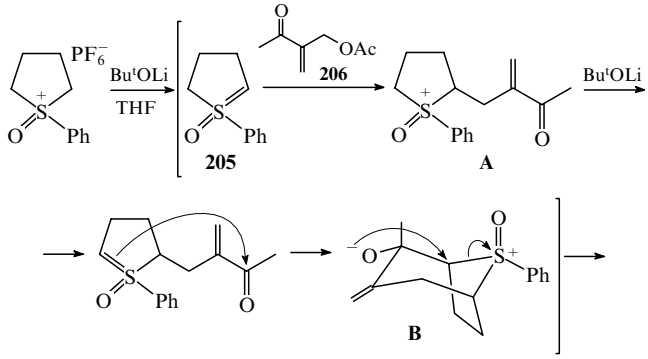


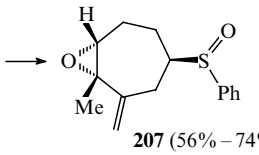
R = Alk, Ar.

A new procedure was developed for the solid-phase synthesis of imidazolidin-2-ones with the use of the tandem 'aminoacylation – Michael addition' sequence.[79] The reaction of the allylic amine **203** bound to an ion-exchange resin with phenyl isocyanate proceeded regioselectively to form imidazolidin-2-one **204**.

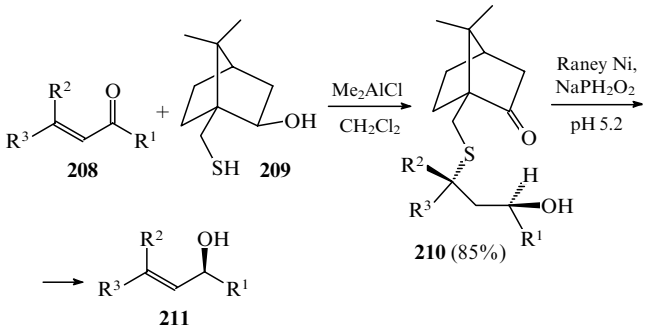


The tandem Michael and Corey – Chaykovsky reactions of five-membered oxosulfonium ylides **205** with β-acetoxy-α-methylidene ketones **206** produced cycloheptene oxide derivatives **207**.[80] Initially, the Michael addition of the ylide **205** to the enone **206** occurred. Then the acetoxy group was eliminated to form the cation **A** followed by generation of the ylide and the intramolecular Corey – Chaykovsky reaction, which proceeded *via* the stable intermediate **B**. The latter was converted into epoxide **207**.



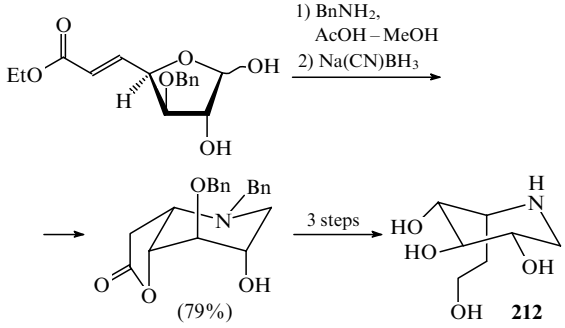


The tandem 'Michael addition – Meerwein – Ponndorf – Verley reduction' sequence was used for the asymmetric reduction of α,β-unsaturated ketones giving rise to secondary alcohols.[81] The reaction of the enone **208** with (−)-10-mercaptoisoborneol (**209**) in the presence of Me_2AlCl afforded the expected product **210**. In this tandem process, the chiral mercaptoalcohol reacted with enone to give an adduct, which was converted into the alcohol **210** as a result of intramolecular proton transfer. Reductive desulfurisation of the latter produced the optically active alcohol **211**.



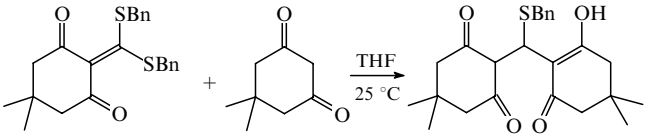
R^1, R^2, R^3 = H, Alk, Ar.

The three-step 'reductive amination – intramolecular Michael reaction – lactonisation' sequence was used for the construction of the ring skeleton of homoaza-sugars in the synthesis of higher homologues of 1-deoxy-L-*ido*-nojirimycin (**212**) exhibiting a broad spectrum of biological activities.[82] Apparently, reductive amination of the anomeric centre was succeeded by intramolecu-



lar ring closure at the activated double bond and lactonisation. Reduction of the ester group and deprotection gave rise to the target product **212**.

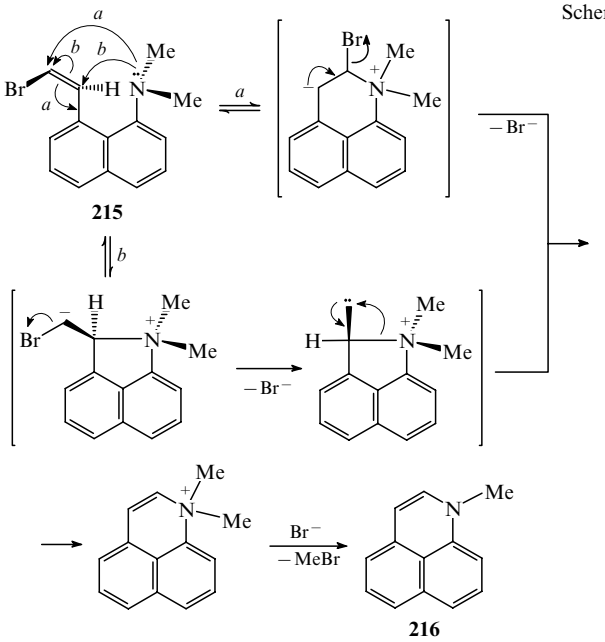
The tandem Michael addition and elimination were used as the key stages in the total synthesis of the S-containing yellow pigment of Australian sponges, *viz*., benzylthiocrellidone (**213**),[83] which was prepared by the reaction of ketene dithioacetal **214** with dimedone.



214 **213** (60%)

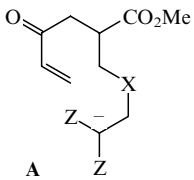
The transformation of *cis*-1-bromo-2-(1-naphthyl)ethylene containing the dimethylamino group at the *peri* position (**215**) into *N*-methylbenzo[*de*]quinoline **216** was studied.[84] The tandem addition–elimination reactions can follow two alternative pathways, *viz*., 6-*endo*-*trig* addition–elimination (path *a*) or tandem 5-*exo*-*trig* Michael addition followed by the carbene rearrangement (path *b*) (Scheme 9).

Scheme 9



A new approach to the synthesis of 9–15-membered cyclic compound was devised.[85] Very dilute solutions of substrates **217**–**219** were treated with cesium fluoride, which induced a sequence of ring opening and ring closure reactions to yield cyclopentadecanone, cyclotetradecanone and cyclononanone derivatives (**220**, **221** and **222**), respectively (Scheme 10).

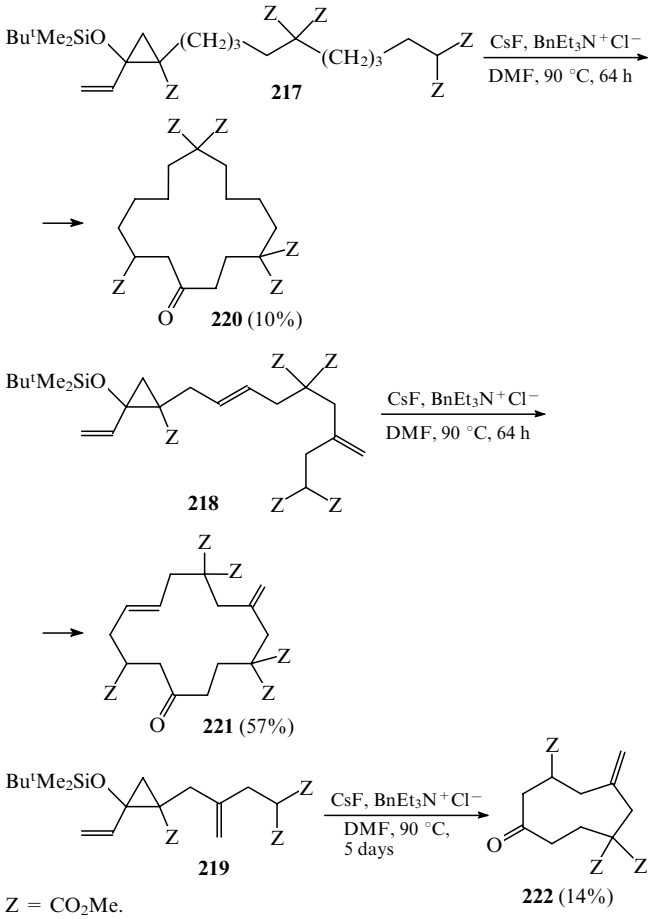
The efficiency of the intramolecular Michael addition, which is the crucial step and consists in the transformation of the carbanion **A** into the final product, depends essentially on the 'bridging' X group.



X = $(CH_2)_2$, CH=CH.

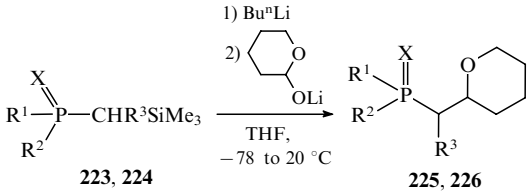
The tandem Peterson and Michael reactions have been described.[86] The reactions of α-silyl-α-formyl carbanions with carbonyl compounds containing a nucleophilic group gave rise to

Scheme 10



Z = CO_2Me.

cyclic compounds with a functionalised side chain. Tandem reactions of α-trimethylsilylalkylphosphine oxide (**223**) or α-trimethylsilylalkylphosphine sulfide (**224**) with n-butyllithium and then with lithium tetrahydropyran-2-olate gave rise to products **225** and **226**, respectively, in high yields.



223, **224** **225**, **226**

X = O (**223**, **225**), S (**224**, **226**); R^1, R^2, R^3 = H, Ar.

* * *

To summarise, tandem transformations, which represent an advantageous combination of the thermodynamic and kinetic parameters of a single process, play an important role in procedures for the preparation of complex organic compounds. There is no doubt that the development of one-pot tandem reactions based on compounds containing various functional groups resulting in substantial complication of the starting structures is an important problem of modern organic synthesis.

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