REVIEW

Titanium reagents for the alkylidenation of carboxylic acid and carbonic acid derivatives

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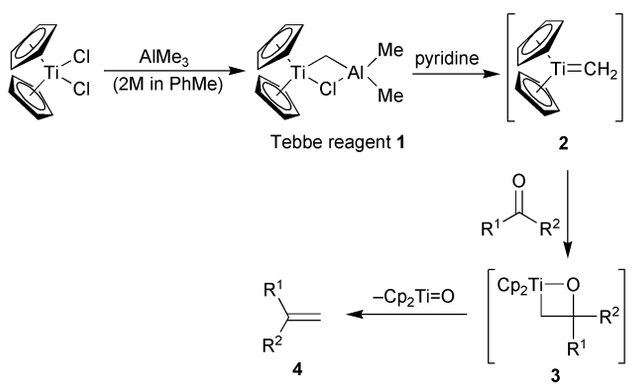
1 Introduction

The use of titanium-based reagents to alkylidenate carbonyl groups was last comprehensively reviewed in 1993 by Pine.[1] The methylenation of aldehydes and ketones by these non-basic, reactive reagents offers some advantages over other methylenation methods (*e.g.* the Wittig reaction), particularly in base-sensitive substrates or when the carbonyl group is sterically hindered. However, it is their ability to alkylidenate carboxylic acid and carbonic acid derivatives that makes these reagents most distinctive, and it is this aspect of their reactivity that is reviewed here. The review covers the literature comprehensively from the beginning of 1993, and we include only selected examples and references to seminal papers from the period covered by Pine's review. First we will discuss the range of titanium reagents that alkylidenate carboxylic acid and carbonic acid derivatives, the methods by which they are prepared, their chemoselectivity and functional group tolerance, and where relevant, their stereoselectivity. Only examples of each type of reactivity (preferably drawn from the review period) are presented and/or cited, and we do not list every occurrence of a particular reaction or tolerance of a particular functional group. Chemoselectivity will be discussed in terms of what functional groups are tolerated in carboxylic acid and carbonic acid derivatives that have been alkylidenated, and what functional groups are tolerated in the titanium reagents themselves. The second section of the review will discuss the synthetic strategies that have been facilitated by alkylidenation of carboxylic acid and carbonic acid derivatives.

2 Titanium alkylidenes (Schrock carbenes) and 1,1-bimetallics

2.1 Tebbe reagent

The Tebbe reagent **1** is a titanium–aluminium metallacycle prepared from titanocene dichloride and trimethylaluminium in toluene (Scheme 1).[2,3] The reagent is commercially available as a



Scheme 1

solution in toluene. Although it reacts rapidly with ketones and amides with second order kinetics, it reacts only sluggishly with esters.[4] However, when the Tebbe reagent is treated with a Lewis base such as pyridine or THF, a highly reactive titanocene methylidene **2** is generated. This methylenates a range of carboxylic and carbonic acid derivatives, presumably *via* oxatitanacyclobutane **3**,[5] to give alkenes **4** in a matter of minutes at room temperature and below. The reaction's driving force is probably the formation of the strong titanium oxygen double bond making it irreversible,[6,7] and this has prevented the development of a version that is catalytic in titanium. Titanocene methylidene **2** is a typical Schrock carbene being an electron-deficient (16e) complex of an early transition metal in a high formal oxidation state [titanium(IV)].[8] Such Schrock carbenes are nucleophilic at the carbene carbon atom and electrophilic at titanium, and their reactivity towards carbonyl groups is dominated by their high energy HOMOs. Thus, titanium alkylidenes would be expected to react with the most electrophilic carbonyl groups most readily, and this is the case for the Petasis and Takeda reagents discussed below. The fact that the Tebbe reagent reacts more rapidly with amides[4] than esters in the absence of an added Lewis base would at first sight seem aberrant. However, amides are better Lewis bases than esters and so generate the reactive titanium methylidene **2** more effectively. Schrock carbenes also catalyse alkene metathesis, and we consider that any titanium reagent that both alkylidenates carbonyl groups and induces alkene metathesis has a titanium alkylidene as its

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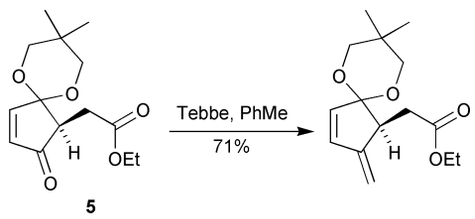
active species. Indeed this property is exhibited by the Tebbe reagent in Lewis basic solvents (see Grubbs' reagents below and the section on ring-closing metathesis),[9] but metathesis is generally slower than methylenation of carbonyl groups.

Tebbe methylenation of aldehydes and ketones in the presence of esters or amides is straightforward. Examples include methylenation of ketone **5** (Scheme 2) in high yield in toluene[10] and selective methylenation of aldehyde **6** can be achieved in Lewis basic THF (Scheme 3).[11]



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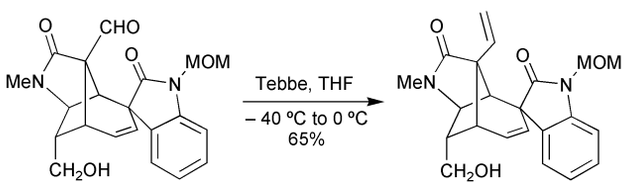
Scheme 2



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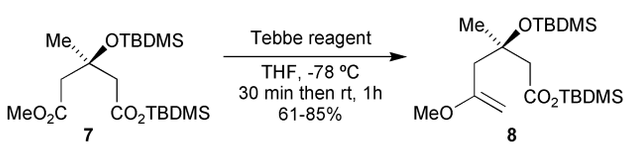
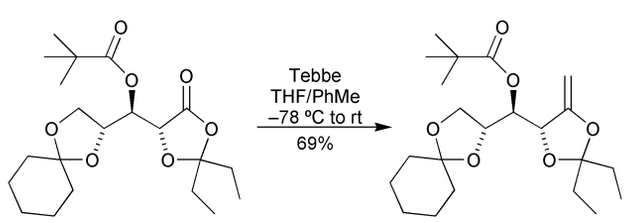
Scheme 3

Esters including lactones are methylenated by the Tebbe reagent to give enol ethers and there are a large number of recent examples of this reaction. Pine *et al.* have provided the definitive procedure for the preparation of the Tebbe reagent and its use in methylenation of esters and lactones.[3] Regioselective Tebbe methylenation of methyl ester **7** proceeds without affecting the bulky silyl ester group to give enol ether **8** (Scheme 4).[12] Similarly, lactone **9** is methylenated to give *exo*-methylene compound without affecting the pivaloate group (Scheme 5).[13]



7 **8**

Scheme 4



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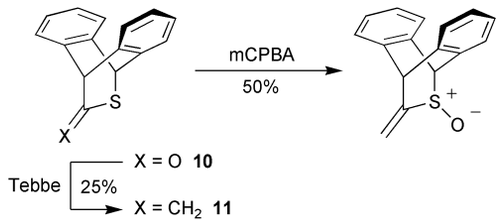
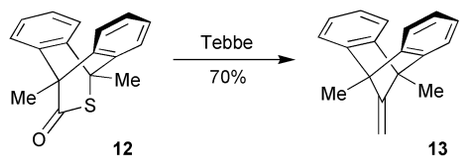
Scheme 5

Selective methylenation of an s-*cis*-constrained α,β-unsaturated lactone in the presence of an α,β-unsaturated methyl ester is an important step in Ley's approach to azadirachtin (see Section 3.2).[14]

Methylenation of thioesters to give vinyl sulfides is much rarer. The only recent example is the conversion of thiolactone **10** into the corresponding vinyl sulfide **11** in low yield (Scheme 6).[15] However, under the same conditions, thiolactone **12** gives methanoanthracene derivative **13** (Scheme 7). Methylenation of



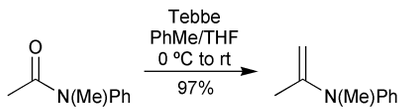
Scheme 6



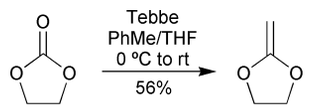
12 **13**

Scheme 7

tertiary amides (including *N*-acyl heterocycles[16]) gives enamines in high yield (Scheme 8[4]). Carbonates give ketene acetals (Scheme 9).[9]

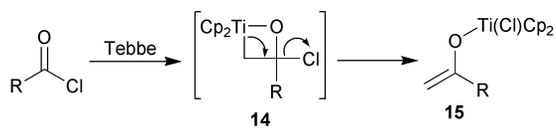


Scheme 8



Scheme 9

Carbonyl groups with very good leaving groups are not methylenated by the Tebbe reagent, but undergo other reactions. The Tebbe reagent **1**, in the presence of a Lewis base,[9] reacts with acid chlorides to give titanium enolates **15**, presumably *via* oxatitanacyclobutane **14** (Scheme 10).[17,18] Anhydrides

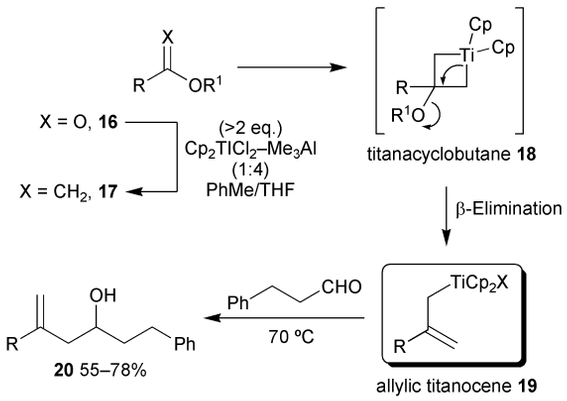


14 **15**

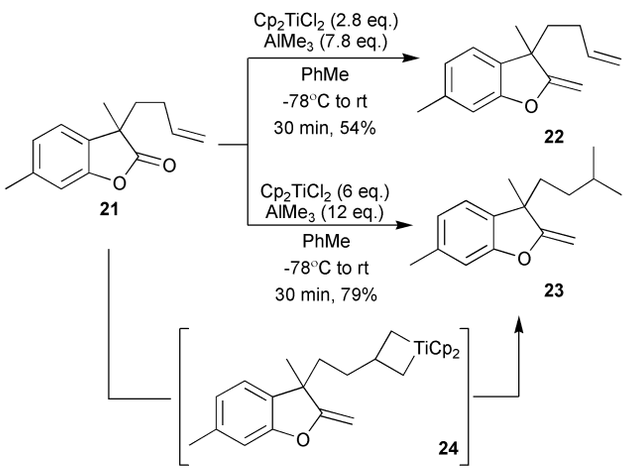
Scheme 10

and imides react with the Tebbe reagent in a similar way to acid chlorides,[19] in contrast to the Petasis reagent described below. A mechanistically related reaction is the formation of allylic titanocenes **19** when esters **16** are treated with >2 eq. of a 1 : 4 mixture of titanocene dichloride and trimethylaluminium (Scheme 11).[20] The mechanism presumably involves methylenation of the esters **16** to give enol ethers **17**, followed by conversion to titanacyclobutane **18** and elimination of alkoxide. Trapping the allylic titanocenes **19** with excess aldehyde gives homoallylic alcohols **20**. Allylic titanocenes can also be made from vinyl halides in a similar way.[20,21]

Tebbe methylenation of esters has been accomplished in the presence of many functional groups. Alkenes including dienes[22] and terminal alkenes react with the Tebbe reagent more slowly than esters and other carbonyl groups.[23] Thus, lactone **21** gives enol ether **22** in moderate yield (Scheme 12).[24] However, when the same lactone **21** is exposed to a vast excess of Tebbe reagent, it is both methylenated and methylated to give enol ether **23**, presumably *via* titanacyclobutane **24**.[24] There is one report of methylenation of α,β-unsaturated esters giving higher yields than with the Petasis reagent discussed below.[25] Vinyl and aryl halides including vinyl fluorides,[26] vinyl chlorides,[26] aryl bromides,[27] and aryl iodides,[28] are tolerated by the reagent. Ethers



Scheme 11



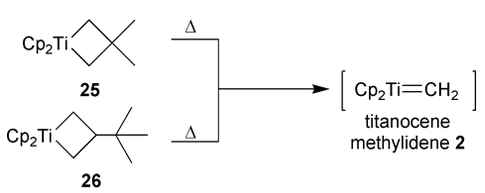
Scheme 12

including benzyl,[29] and trityl ethers[30] are stable to the reaction conditions. Silyl ethers including TMS,[30] TBDMS,[12] and di-*tert*-butylsilylene,[31] are tolerated. Acetals including benzylidene acetal,[31] MOM,[32] and acetonides[32] are unaffected by the Tebbe reagent. Selenoglycosides[33] and thioglycosides[34] are also tolerated. Unprotected indoles may be present in the substrate without affecting methylenation.[28] Carbamates including NHBoc,[31] and sulfonamides[35] are unaffected. Hydroxy groups should be protected as these protonate the reagent, but protection can sometimes be avoided if an excess of the reagent is used.

The key advantage of the Tebbe reagent over other titanium reagents used in alkylidenations is that the reactive titanium methylidene **2** is generated and reacted at low temperature. Its disadvantages are its high sensitivity to both moisture and air, its Lewis acidic character, and the fact that it is limited to methylenation. Using triethylaluminium instead of trimethylaluminium does not allow ethylidenation but leads to other products.[36]

2.2 Grubbs reagents

Titanacycles **25** and **26** may be prepared by the reaction of the Tebbe reagent **1** with a terminal alkene in the presence of a Lewis base.[1,9] When these complexes are heated titanocene methylidene **2** is regenerated and will methylenate carboxylic and carbonic esters (Scheme 13). Intramolecular versions of this

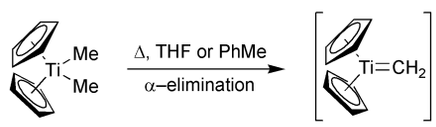


Scheme 13

reaction are known,[37,38] and a mechanistically related reaction of Takai reagents has been reported recently (See Section 2.5).[39,40] Although Grubbs reagents have not been used to alkylidenate carboxylic acid and carbonic acid derivatives during the review period, related combinations of carbonyl methylenation followed by ring-closing metathesis have been used extensively in the synthesis of cyclic enol ethers (see Section 3.9).

2.3 Petasis reagents

Dimethyltitanocene is easily prepared from methyllithium[41] or more preferably methylmagnesium chloride[42] and titanocene dichloride. It is non-pyrophoric and is relatively stable to both air and water. Petasis and co-workers showed that when this compound is heated to 60–75 °C either in THF or toluene in the presence of a carbonyl compound, methylenation of the carbonyl compound occurs.[41,43] Hughes *et al.* have provided strong evidence that the reaction proceeds by rate-determining generation of titanocene methylidene **2** by α-elimination, followed by rapid reaction with the

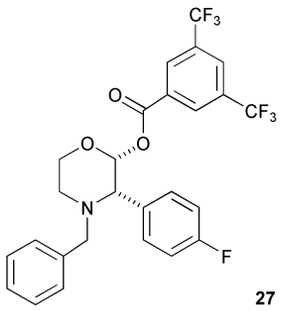


Scheme 14

carbonyl compound (Scheme 14).[44] Reactions are zero order in ester and first order in dimethyltitanocene, with ethyl acetate and methyl benzoate reacting at essentially the same rate; furthermore, reactions between esters and $Cp_2Ti(CD_3)_2$ produce substantial kinetic isotope effects of 9–10. In the absence of traces of acid, the regiochemistry of the newly formed alkene is controlled and no scrambling of isotopic labels from ester substrates is observed. Some isomerization is observed if acid-washed glassware is used or reactions are spiked with acid, presumably by protonation of the enol ether followed by deprotonation of the resulting oxonium ion. These findings combined with the ability of dimethyltitanocene to catalyse alkene metathesis reactions essentially prove reaction occurs *via* a Schrock carbene. They also underline the need to avoid acid-washed glassware if good regioselectivity is to be obtained. Hughes and co-workers have recently provided the definitive procedure for the preparation of dimethyltitanocene and illustrated its use in the methylenation of ester **27** (Scheme 15).[42,45]

As would be expected from a nucleophilic reagent, aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl groups such as esters, amides and carbamates. Examples include the final step in Hart's synthesis of 21-oxogelsemine **28** (Scheme 16),[46] and a key step in the Colson and Hegedus route to α-alkyl-α-amino acid **29** (Scheme 17).[47]

Dimethyltitanocene will methylenate esters, including silyl ester **30** (Scheme 18).[43] It will also methylenate lactones, including spirobislactone **31** (Scheme 19) and lactone **32** (Scheme 20).[43] By careful choice of conditions, it is possible to methylenate the less sterically hindered of two esters using the Petasis reagent. Thus, dimethyltitanocene can selectively methylenate the anomeric acetoxy group of glucoside **33** without affecting the pivaloate groups (Scheme 21).[48,49] Similarly, formate ester **34** can be selectively methylenated leaving the sterically hindered ethyl ester unchanged (Scheme 22).[50] Generally formate esters give poor yields in Petasis methylenations. The best alternative approaches are transvinylation using mercury(II) catalysis[51–53] and a two-step approach *via* thermal elimination of a sulfoxide. Both approaches were



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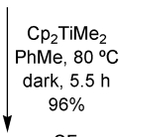
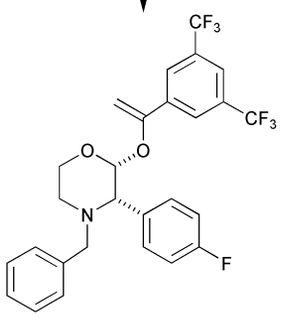
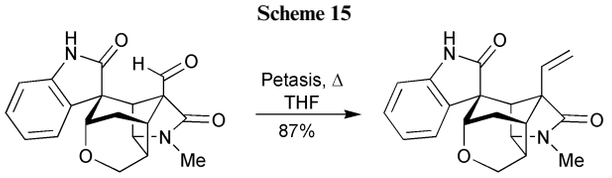




Scheme 15



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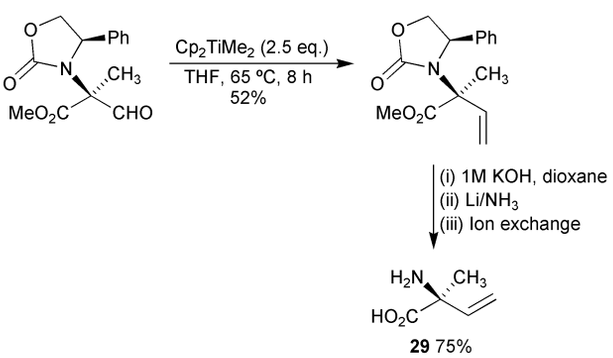
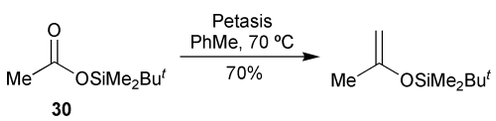
Scheme 16



29 75%

Scheme 17



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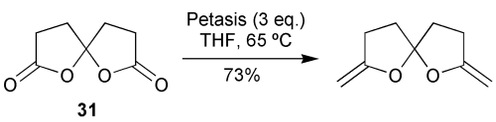
Scheme 18



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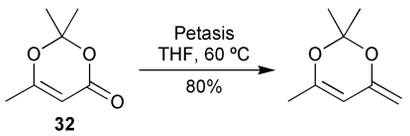
Scheme 19

successful in making *O*-substituted hydroxylamine **35** (Scheme 23), whereas Petasis methylenation of an *O*-formyl derivative failed.[54]



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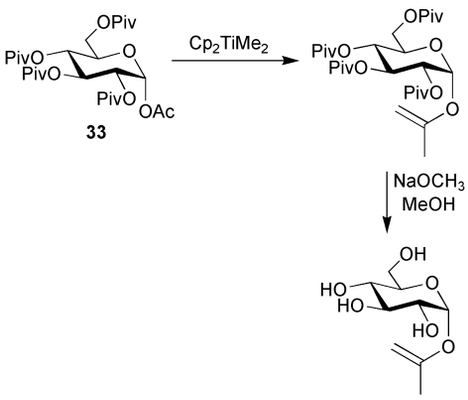
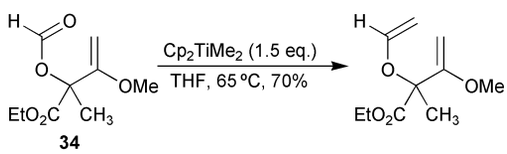
Scheme 20



Scheme 21



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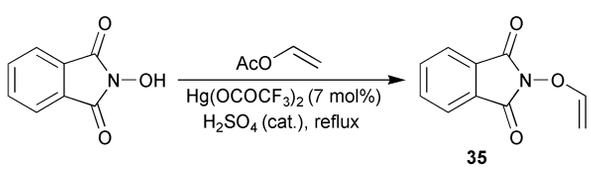
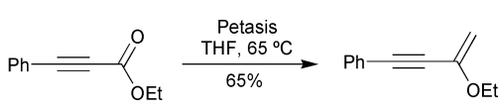
Scheme 22



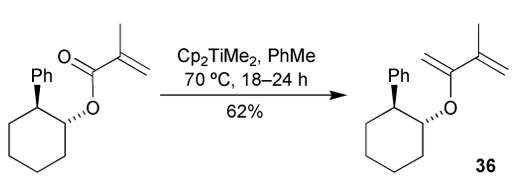
35

Scheme 23

Petasis methylenation of alk-2-ynoate esters (Scheme 24) and α,β-unsaturated esters is successful.[43] The latter reaction allows the preparation of 3-alkoxydiene **36** (Scheme 25), which is potentially useful as a substrate for Diels–Alder reactions.[55]



Scheme 24



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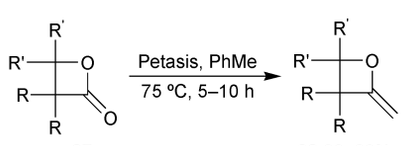
Scheme 25

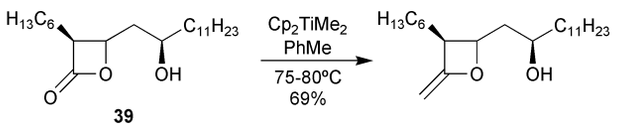
Petasis methylenation of β-lactones **37**, which are highly strained, proceeds in 20–86% yield with excellent chemoselectivity (Scheme 26).[56,57] Tebbe methylenation is unsuccessful



37 **38** 20–86%

Scheme 26

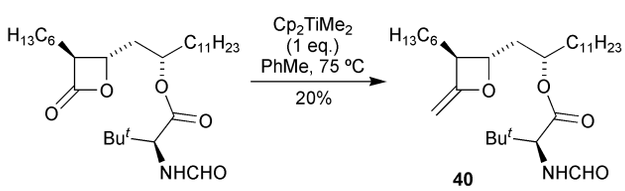
for the same transformation, perhaps due to the greater Lewis acidity of the Tebbe reagent. Petasis methylenation in toluene is higher yielding than that in THF, but more critical to the isolation of 2-methyleneoxetanes **38** is the use of silica deactivated with triethylamine (0.5–1% in eluting solvent) in chromatography rather than Florisil, neutral or basic alumina. Distillation also destroys the product. Carbamates, esters, alkenes and silyl ethers are all tolerated, and even methylenation of a β-lactone in the presence of a ketone is possible (though the mass balance is poor). Methylenation of lactone **39** was unproblematic (Scheme 27). However, an unprotected hydroxy



39

Scheme 27

group β to the carbonyl group prevents reaction. The 2-methyleneoxetane analogue **40** of the anti-obesity drug, orlistat, could be prepared by methylenation in spite of the formamide group, albeit in low yield (Scheme 28).[58] Orlistat and

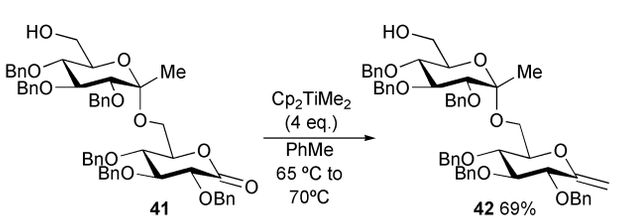


40

Scheme 28

compound **40** inhibit porcine pancreatic lipase to a similar degree.

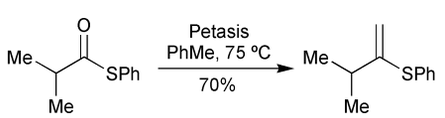
Petasis methylenation of unstrained esters has also been accomplished in the presence of many functional groups. Alkenes including terminal alkenes are tolerated.[59] Alkyl and aryl halides including alkyl bromides,[60] and aryl fluorides are unaffected.[42] Ethers including benzyl[61] and *p*-methoxybenzyl[59] ethers are stable to the reaction conditions. Silyl ethers including TMS,[62] TBDMS,[63] TBDPS,[59] and TIPS[62] are tolerated. Acetals including MOM[64] are unaffected by the Petasis reagent. Amines including benzylamines[65] and oxazoles[59] may be present in the substrate without preventing methylenation. Hydroxy groups are best protected, but Petasis methylenation is possible in the presence of free hydroxys provided an excess of the reagent is used. Thus, lactone **41** is converted into enol ether **42** in good yield (Scheme 29).[66]



41 **42** 69%

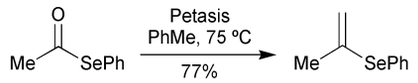
Scheme 29

Thioesters, selenoesters, and acylsilanes are also substrates for Petasis methylenation (Schemes 30–32).[43] Methylenation of

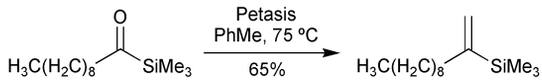


Scheme 30

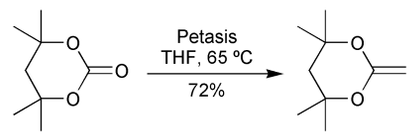
carbonates is also effective (Scheme 33)[43] and methylenation of six and seven-membered carbonates has been achieved in the presence of benzyl[67] and TBDPS ethers,[68] terminal alkenes,[68]



Scheme 31



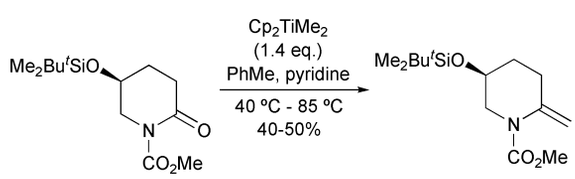
Scheme 32



Scheme 33

and a secondary alkyl chloride.[68] Indeed, some selectivity is observed for methylenation of these cyclic carbonates over reaction with the medium-ring lactones produced by tandem methylenation–Claisen rearrangement (see Section 3.8.1 below).[68]

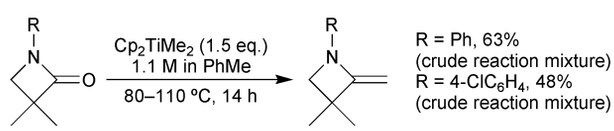
As would be expected from the nucleophilic nature of the titanocene methylidene **2** intermediate, Petasis methylenation of amides proceeds more slowly than the methylenation of other carbonyl groups (with the exception of carbamates).[43] Furthermore, the resulting enamines are often difficult to purify. These problems were overcome by Herdeis and Heller in their route to pipecolic acid derivatives, by carrying out Petasis methylenation of *N*-methoxycarbonyl-protected lactam **43** to give carbamate **44** (Scheme 34).[69] This involves selective reaction



43 **44**

Scheme 34

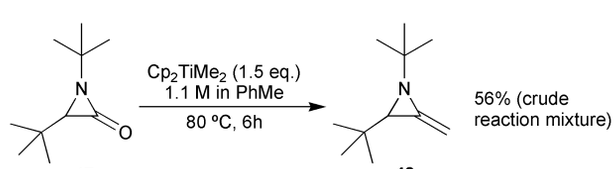
with the amide-like carbonyl group, and the methoxycarbonyl group not only protects but also activates the lactam towards methylenation. In contrast, no *N*-benzylenamine is isolated when *N*-benzyl-lactam is subjected to Petasis methylenation. In a footnote in the same paper, it is stated that methylenation of β-lactams is possible, but no details are given.[69] In a later paper, Tehrani and De Kimpe reported that methylenation of β-lactams **45** gives 2-methyleneacetidines **46** (Scheme 35), and



45 **46**

Scheme 35

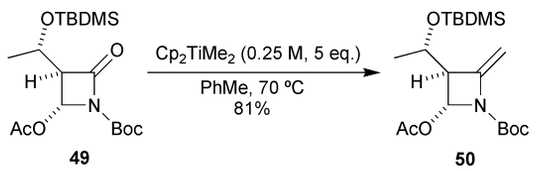
methylenation of α-lactam **47** gives 2-methyleneaziridine **48** (Scheme 36), but stated that these strained enamines are difficult to purify.[70] On the other hand, Martínez and Howell used an



47 **48**

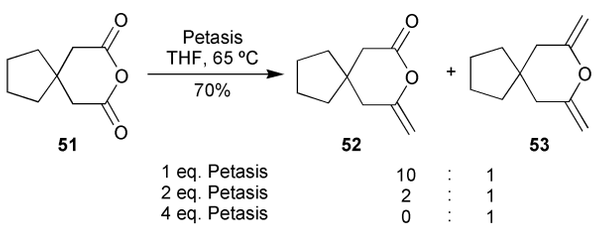
Scheme 36

excess of dimethyltitanocene to synthesise 2-methyleneacetidines in good isolated yields, and with excellent chemoselectivity when the reactions were quenched as soon as the β-lactams were consumed.[71] Their most impressive result is the methylenation of the strained β-lactam **49** to give 2-methyleneacetidine **50**, without affecting the acetate ester or the Boc group (Scheme 37).

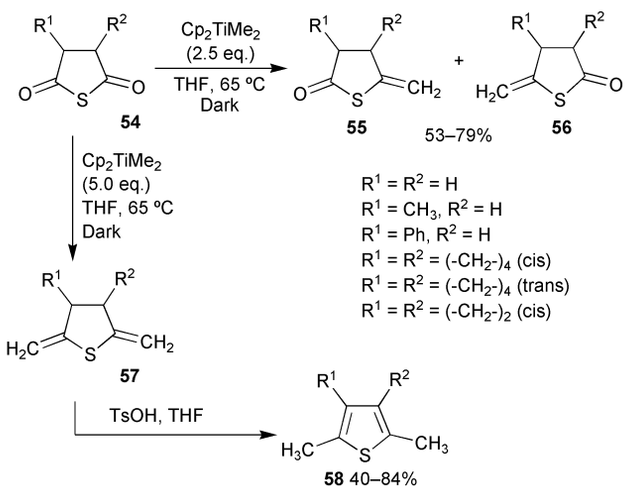


Scheme 37

Petasis methylenation of acid anhydrides is successful.[43,72] Selective mono- or bismethylenation of anhydride **51** is possible to give either enol ether **52** or enol ether **53**, respectively (Scheme 38).[43] Cyclic thioanhydrides **54** similarly give monomethylenated products **55** and **56** or bismethylenated products **57** selectively (Scheme 39).[72] However, monomethylenated

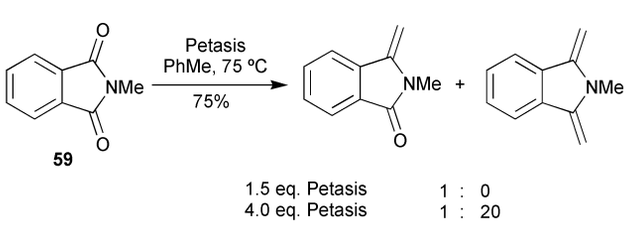


Scheme 38



Scheme 39

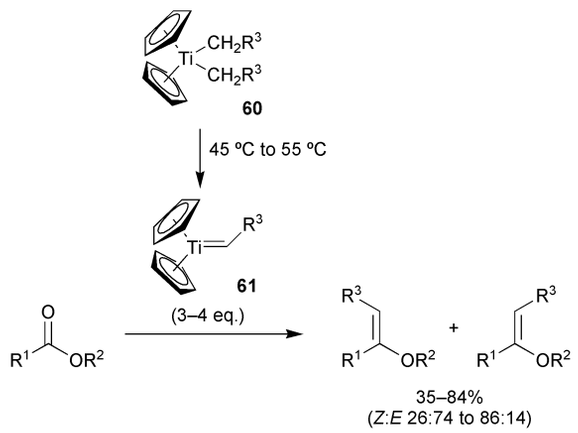
compounds **52**, **55** and **56** are never the exclusive products. When bis(vinyl)sulfide **57** is treated with acid, thiophene **58** is formed. Selective mono- and bis-methylenation of an imide **59** has also been demonstrated (Scheme 40).[43] It should be noted that the more Lewis acidic Tebbe reagent leads to conversion of



Scheme 40

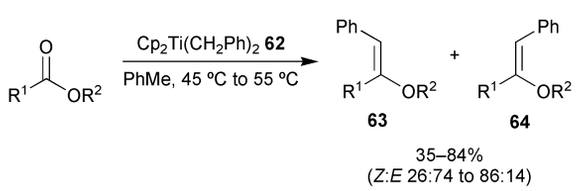
acid anhydrides and imides to titanium enolates (see Scheme 10 for a related reaction).[19]

A further advantage of Petasis' method of generating titanocene methylidene **2**, is that a range of dialkyltitanocenes **60** can be used to alkylidenate carbonyl compounds in the same way (Scheme 41). Presumably, titanium alkylidenes **61** are

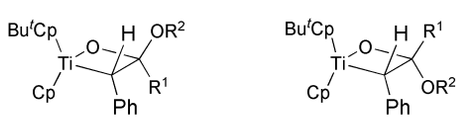


Scheme 41

generated by α-elimination and are the active alkylidenating species. However, since β-elimination is generally faster than α-elimination, any dialkyltitanocenes **60** with hydrogen atoms (β to the titanium atom) that will readily undergo β-elimination are likely to fail to act as alkylidenating agents.[73] Dibenzyltitanocene **62** is easily prepared from benzylmagnesium chloride and titanocene dichloride, and when it is heated with esters, *E* and *Z* enol ethers **63** and **64** are produced.[74] Unless R^1 is small (R^1 = H or Me), the products are formed with good *Z*-selectivity (Scheme 42). The *Z*-selectivity can be explained by the relative steric interactions in the formation of oxatitanacyclobutane intermediates **65** and **66** (Scheme 43).[75] Large R^1

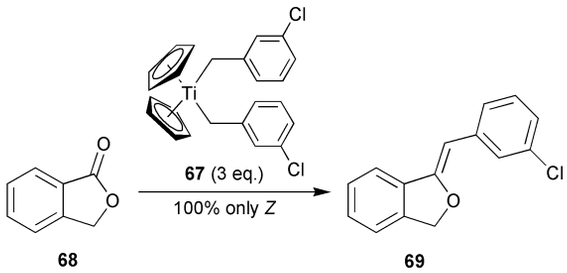


Scheme 42

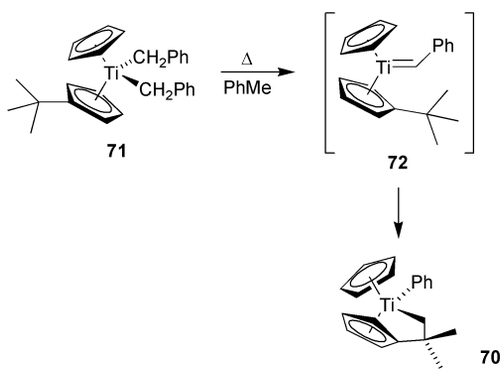


Scheme 43

will disfavour formation of intermediate **65**, while large R^2 will disfavour formation of intermediate **66**. In this model, *Z*-enol ethers **64** are favoured because the oxygen atom acts as a spacer, so that the reaction is less sensitive to the bulk of R^2 and formation of intermediate **65** is preferred. Reaction with amides (including DMF) gives enamines in modest yield (45–48%) and good *E*-selectivity (*E*:*Z* = 71 : 29 to >99 : 1) and the stereoselectivity can be explained using similar steric arguments to those presented for *Z*-selectivity in enol ether formation. Bis(3-fluorobenzyl)titanocene and bis(3-chlorobenzyl)titanocene **67** also benzylidenate carbonyl compounds and more readily and with greater selectivity than the parent complex **62**. Thus, lactone **68** is converted into enol ether **69** in quantitative yield with total *Z*-selectivity (Scheme 44).[74] Isolation of compound **70** upon thermolysis of benzylidenation agent **71** is consistent with the intermediacy of benzylidene complex **72** (Scheme



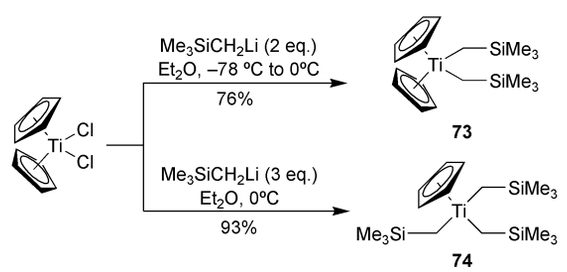
Scheme 44



Scheme 45

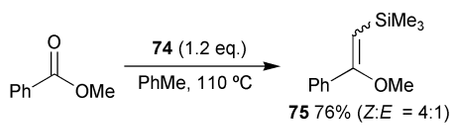
45).[75] Reagent **71** benzylidenates methyl benzoate with slightly higher *Z*-selectivity than using dibenzyltitanocene **62** [dr (*E* : *Z*) = 90 : 10 rather than 86 : 14].

Bis(trimethylsilylmethyl)titanocene **73** and tris(trimethylsilylmethyl)titanocene **74** can be prepared from titanocene dichloride using appropriate amounts of trimethylsilylmethyllithium (Scheme 46),[76] but complex **73** is better made by consecutive



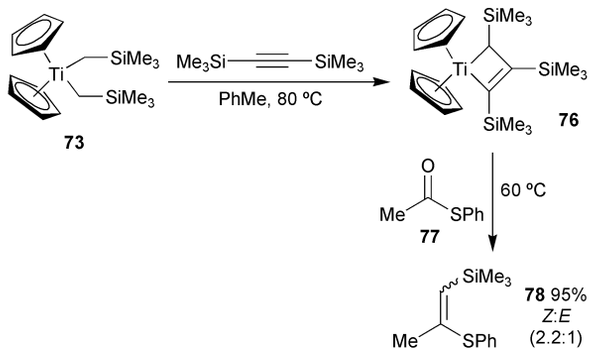
Scheme 46

addition of trimethylsilylmethylmagnesium bromide and trimethylsilylmethyllithium.[77] Both will alkylidenate esters, but complex **73** requires a higher temperature (110 °C in ethylene glycol diethyl ether) and gives lower yields.[76] Complex **74** converts methyl benzoate into vinylsilane **75** in good yield (Scheme 47). The *Z*-selectivity is slightly lower than observed in the



Scheme 47

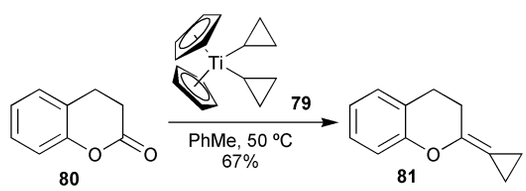
corresponding benzylidenation discussed above. Unsurprisingly, acid chlorides give α-trimethylsilylketones with either complex **73** or **74**. Esters, thioesters and amides derived from trifluoroacetate have been alkylidenated with complex **74**, though the thioester gave a very poor yield and no stereoselectivity.[78] However, a better trimethylsilylmethylenating agent is titanacyclobutene **76**, formed in near quantitative yield by thermolysis of complex **73** in the presence of bis(trimethylsilyl)ethyne (Scheme 48).[77] Esters are alkylidenated in high yield



Scheme 48

using 1.5 eq. of complex **76** at only 25–60 °C, and thioester **77** is converted into vinyl sulfides **78** in excellent yield. However, *Z* : *E* stereoselectivities were always ≤2.2 : 1.

Bis(cyclopropyl)titanocene **79** is easily prepared from titanocene dichloride and cyclopropyllithium, cleanly generated from cyclopropyl bromide and lithium metal.[79] Although it is thermally unstable at room temperature, turning brown within a few hours, bis(cyclopropyl)titanocene can be stored at −20 °C for several months without any significant decomposition. Esters, including formate esters and lactones, are cyclopropylidenated by heating with 2.5 eq. of this reagent. Thus, lactone **80** gives enol ether **81** in good yield (Scheme 49).



Scheme 49

Bis(vinylic)titanocenes **82** (Fig. 1) react with ketones to form allenes, but vinylidenation was unsuccessful with esters and lactones.[80]

82 R^1 & R^2 = H or Me

Fig. 1

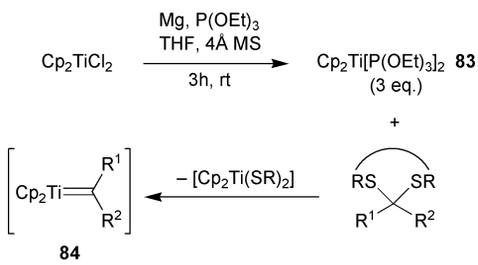
Petasis summarised his work with titanocene reagents in 1996.[81] The advantages of Petasis methylenation of carbonyl groups are the stability to air and moisture of dimethyltitanocene, the absence of Lewis acid from these reactions and the ease of purification following reaction (titanium-containing impurities can often be precipitated and removed by simple filtration). The disadvantages are the high temperature (≥65 °C) needed to induce α-elimination and that several equivalents of the reagent are often necessary for complete reaction. Petasis methylenation is now widely used in synthesis. However, other Petasis alkylidenations have not been used, though they have similar advantages and disadvantages to Petasis methylenation. The use of organometallics in the preparation of dialkyltitanocenes limits functionality in such complexes, and the greater range of alkylidenating reagents that can be generated under Takeda and Takai conditions (see below) may account for this lack of popularity.

2.4 Takeda reagents

Takeda *et al*. demonstrated that thioacetals can be reduced by low valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ **83** to give

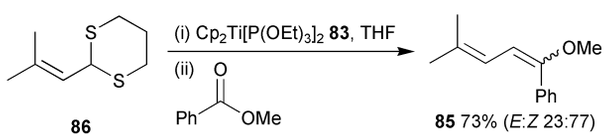
titanium reagents that will alkylidenate esters[82] and thioesters.[83] The active species are almost certainly titanium alkylidenes as they catalyse alkene metathesis,[84–87] add to alkynes[88] and nitriles,[89] and can cyclopropanate alkenes.[90] Takeda and Fujiwara have discussed their work on desulfurisation of thioacetals and its applications in 1999.[91]

Titanium complex **83** is generated by reduction of titanocene dichloride with magnesium in the presence of 2 eq. of triethylphosphite in dry THF (Scheme 50).[82] 4 Å Molecular sieves are



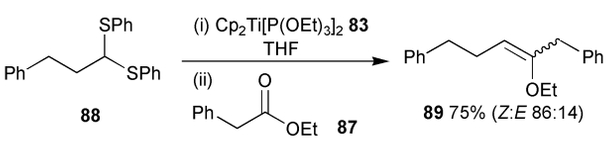
Scheme 50

essential for rapid reduction (3 h). 3 equivalents of the low valent titanium reagent are then added to thioacetals to generate the titanium alkylidenes **84**. Either 1,3-dithianes or diphenyldithioacetals may be used,[82] though the latter are more reactive.[91] Methylenation is ineffective under Takeda conditions, but allylic, benzylic or alkyl thioacetals are suitable substrates for generating alkylidenating reagents. Thus, methyl benzoate is converted into dienes **85** using 1.1 eq. of titanium alkylidene derived from dithiane **86** (Scheme 51), and ethyl ester



Scheme 51

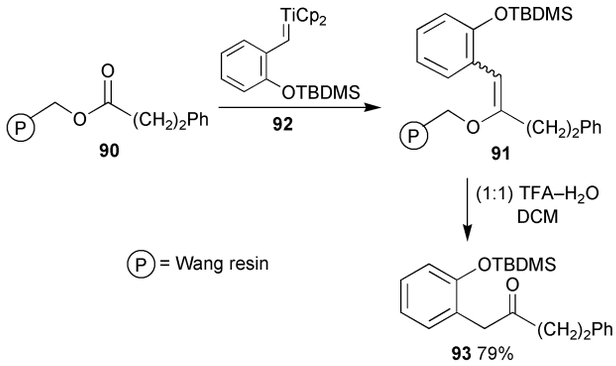
87 reacts with titanium alkylidene derived from diphenyldithioacetal **88** to give enol ether **89** with good *Z*-selectivity (Scheme 52). Stereoselectivity in Takeda benzylidenations



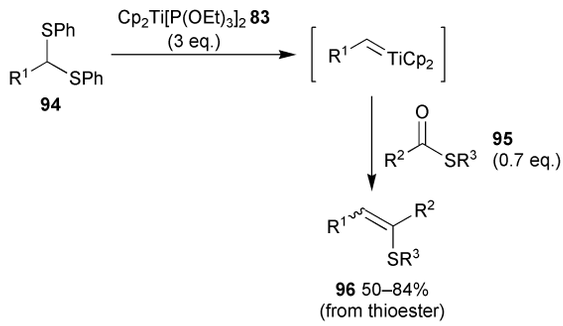
Scheme 52

appears to be slightly higher than in Petasis benzylidenations. We have shown that functional groups are tolerated on the aromatic ring of titanium benzylidenes generated under Takeda conditions, even *ortho* to the carbene itself. Such functionality includes *N*-silyl and *N*-alkyl carbamates, methyl and TBDMS ethers and cyclic acetals.[92,93] Thus, resin-bound ester **90** is converted into resin-bound enol ether **91** with titanium benzylidene **92** and treatment with acid gives ketone **93** in high yield and purity (Scheme 53).[93] The use of solid phase makes the otherwise difficult separation of enol ether products from triethylphosphite and other compounds, a simple matter of washing the resin with solvent (see Section 4 below for further discussion of alkylidenations on solid phase).

When thioacetals **94** are reacted with 3 eq. of low valent titanium complex **83** and then with 0.66 eq. of thioesters **95** in refluxing THF vinyl sulfides **96** are produced (Scheme 54). When R^1, R^2 and R^3 are alkyl the *Z*-stereoselectivity is 64–78% and there is no significant effect or correlation with the steric bulk of the substituents. Phenyl thioesters and *S*-alkyl thiobenzoates give higher selectivity, while reactions of titanium benzylidenes are essentially unselective.

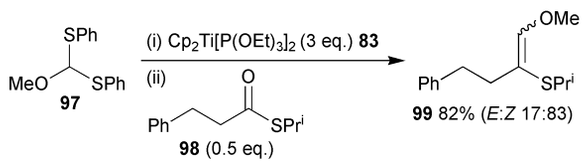


Scheme 53



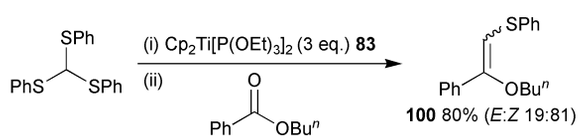
Scheme 54

The titanium alkylidene generated from methoxybis(phenylthio)methane **97** converts esters and thioester into β-(alkoxy)vinyl ethers and β-(alkylthio)vinyl ether, respectively.[94] Thus, thioester **98** gives vinyl sulfides **99** in good yield and good stereoselectivity (Scheme 55). The only ester to give



Scheme 55

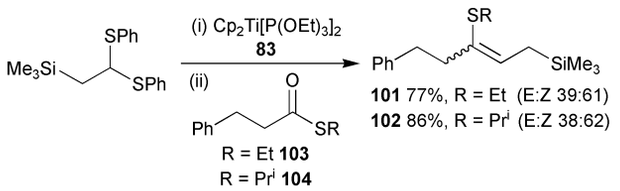
high stereoselectivity was butyl benzoate, which gave a single isomer, but the geometry was not determined. In a similar way, triphenyl trithio-orthoformate converts esters and thioesters into β-(alkoxy)vinyl sulfides and β-(alkylthio)vinyl sulfides, respectively, with modest *E*-selectivity, except for the alkylidenation of butyl benzoate which gives enol ether **100** with good *Z*-stereoselectivity (Scheme 56).



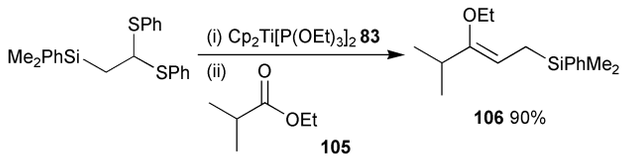
Scheme 56

Allylsilanes can be prepared by Takeda alkylidenation of esters or thioesters using β-silylthioacetals as substrates.[95] Vinyl sulfides **101** and **102** are formed with moderate *Z*-selectivity, seemingly unaffected by the bulk of the *S*-alkyl group of thioesters **103** and **104** (Scheme 57). A branch α to the ester carbonyl group leads to very high stereoselectivity so that ester **105** gives only one allylsilane, which we presume to be the *Z*-isomer **106** (Scheme 58).

Intramolecular alkylidenations are also possible. Treatment of *S*-[3,3-bis(phenylthio)propyl]thioalkanoates with 4 eq. of low-valent titanium complex **83** in THF produced 5-substituted

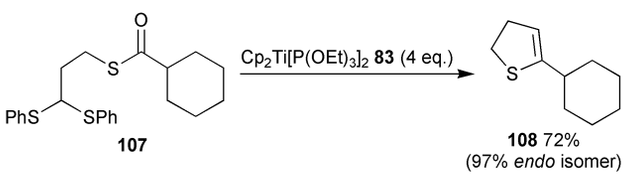


Scheme 57



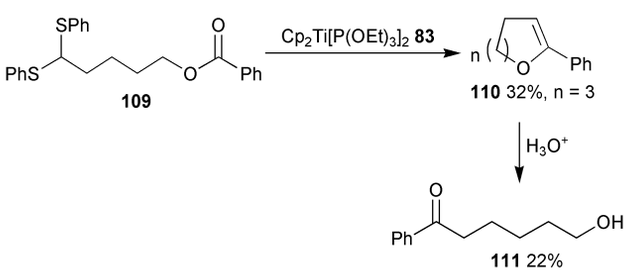
Scheme 58

2,3-dihydrothiophenes.[96] Yields were best when there was a branch α to the carbonyl group as in thioester **107** (Scheme 59).



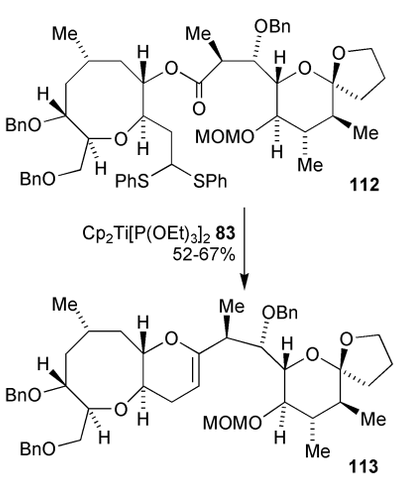
Scheme 59

The product vinyl sulfide **108** isomerises in light towards an equilibrium mixture with the corresponding exocyclic alkene. Titanium alkylidenes generated from ω,ω-bis(phenylthio)alkyl esters **109** oligomerise as well as cyclise and the best yield of a cyclic enol ether **110** was only 32% (Scheme 60).[97] However, the



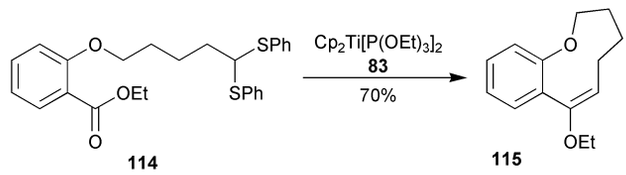
Scheme 60

reaction provides a useful route to ω-hydroxy ketones **111**. Surprisingly, intramolecular reaction of a titanium alkylidene generated from thioacetal **112** under Takeda's conditions gave cyclic enol ether **113** in high yield (Scheme 61).[98] Intramolecular alkylidenation is much more reliable if the oxygen atom of the



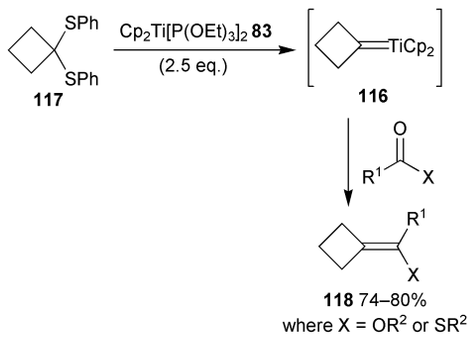
Scheme 61

enol ether is exocyclic and 5-, 6-, 7- and 9-membered rings have been made in this way. Thus, thioacetal **114** gave cyclic *E*-enol ether **115** in 70% yield (Scheme 62).[99]



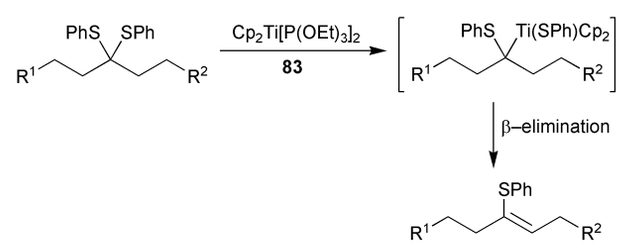
Scheme 62

Titanium cyclobutylidene complex **116**, generated from 1,1-bis(phenylthio)cyclobutane **117**, alkylidenates esters and thioesters to give alkylidene cyclobutanes **118** in good yield (Scheme 63).[100] However, generation of titanium alkylidenes

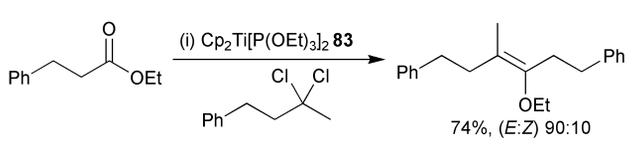


Scheme 63

from thioketals is generally problematic leading to the formation of vinyl sulfides, presumably by the mechanism shown (Scheme 64). On the other hand, more reactive *gem* dichlorides allow a practical method for the conversion of esters and lactones into trisubstituted enol ethers (*e.g.* Scheme 65).[101] The



Scheme 64



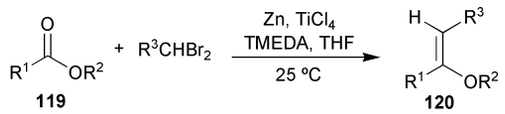
Scheme 65

reaction is effective even if none of the substituents is cyclic and *E* : *Z* ratios range from 60 : 40 to 90 : 10. Takeda's group have recently reported an easy approach to the synthesis of *gem* dichlorides,[102] but unfortunately it cannot be used to make benzylic dichlorides and there remains no reported method for the production of titanium benzylidenes with an alpha substituent.

The key advantages of Takeda alkylidenation are the range of alkylidenating agents that can be produced, the mildness of the conditions, and the ease of synthesis of thioacetal substrates. Tolerance of functionality within the carboxylic and carbonic acid derivatives has not been fully investigated, but a range of functionality is tolerated in the alkylidene reagents themselves. Disadvantages include the use of excess titanocene (at least 3 eq.) and triethylphosphite (at least 6 eq.).

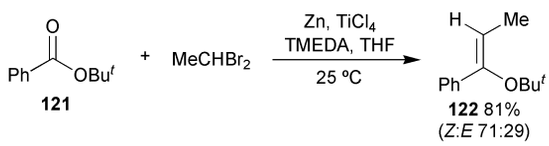
2.5 Takai reagents

In 1987 Takai and co-workers reported a simple, general and stereoselective method for the alkylidenation of esters **119** to give *Z*-enol ethers **120**, using a reagent prepared from 1,1-dibromoalkane, zinc, titanium(IV) chloride and *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) in THF (Scheme 66).[103] An

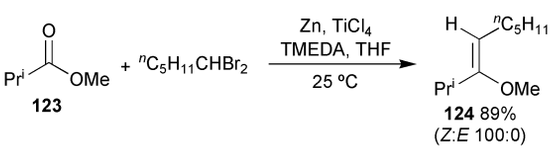


Scheme 66

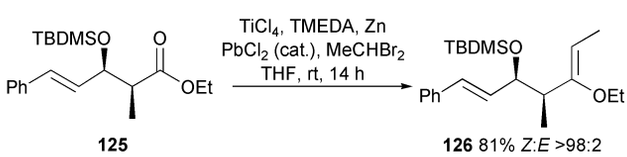
α,β-unsaturated ester (R^1 = MeCH=CH, R^2 = Et) is alkylidenated (R^3 = cyclohexyl) in 90% yield. Alkylidenation is also successful with diiodoalkanes, but the yields are lower. All reactions are *Z*-selective and stereoselectivities are generally over 89%. The reaction is not very sensitive to the bulk of R^3, but bulky R^2 reduces the stereoselectivity and a branch in R^1 α to the carbonyl group ensures total *Z*-selectivity. Thus *tert*-butyl ester **121** still gives modest selectivity for *Z*-enol ether **122** (Scheme 67), but *iso*-butyrate **123** gives solely *Z*-enol ether **124** (Scheme 68). Similarly, we found that ester **125** is ethylidenated to give enol ether **126** with >98% *Z*-selectivity (Scheme 69).[104]



Scheme 67

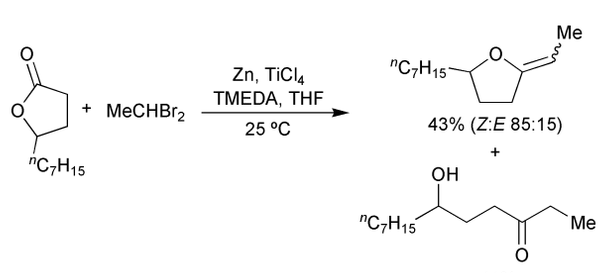


Scheme 68



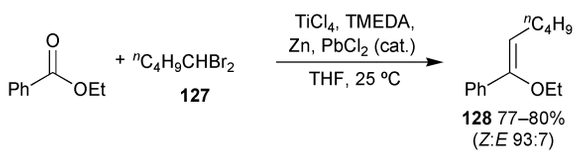
Scheme 69

Takai and co-workers found that methylenation gave very poor yields.[103] Some other researchers have found the same, but reports of successful Takai methylenations in good yield are widespread. What is clear is that Takai alkylidenation is more reliable and generally higher yielding than the corresponding methylenation. Pivaloate esters[105] and formate esters are poor substrates for Takai alkylidenation,[106] and lactones produce mixtures of enol ethers and ketones (Scheme 70).



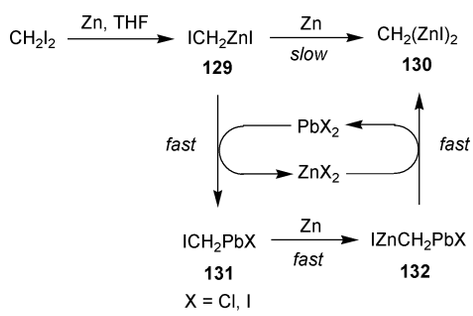
Scheme 70

Takai reagents are prepared by addition of 4 eq. titanium(IV) chloride in dichloromethane to THF, followed by 8 eq. TMEDA, which turns the suspension from yellow to orange–brown. Addition of 9 eq. of zinc then leads to a dark greenish blue suspension. After addition of 1 equivalent of the ester and 2.2 equivalents of a dibromoalkane the mixture turns dark brown or black and the reaction is quenched with aqueous potassium carbonate to give the enol ether. The presence of trace amounts of lead(II) is reported to be vital to the success of the reaction.[107,108] This is often present in commercially available zinc, but the quantity varies and it is best to add a small quantity of lead(II) chloride to ensure the success of the reaction. Yields are best using the DCM–THF mixed solvent system,[109] but reactions in THF alone are successful.[110,111] Although the commercially available DCM solution of titanium(IV) chloride can be used, ourselves[110] and others[111] have found that it is best to freshly prepare solutions from high quality titanium(IV) chloride. Takai *et al.* have published a definitive procedure for the preparation of their reagent from 1,1-dibromide **127** and its use in converting ethyl benzoate into the corresponding enol ether **128** (Scheme 71).[108]



Scheme 71

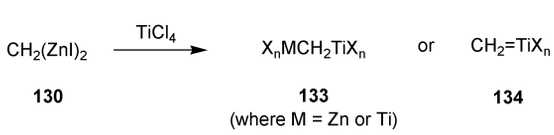
The reaction mechanism is not yet clear. In the absence of lead, diiodomethane is rapidly converted into zinc carbenoid **129**, but is converted only very slowly into geminal dizinc **130** (Scheme 72). Lead(II) chloride accelerates the formation of



Scheme 72

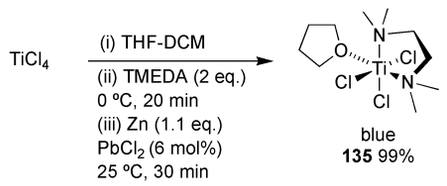
geminal dizinc **130** from diiodomethane and dibromomethane,[107] and so would seem to catalyse the conversion of zinc carbenoid **129** into geminal dizinc **130**. Takai proposed that transmetalation from zinc to lead gives rise to carbenoid **131**, which is reduced by zinc to give lead zinc compound **132**. He suggested that lead carbenoid **131** is more easily reduced than the corresponding zinc carbenoid **129** as the Pb–C bond has greater covalent character. Transmetalation from lead to zinc then gives geminal dizinc **130**.

In the same paper,[107] Takai proposed that in the presence of titanium(IV) salts, geminal dizinc **130** transmetalates to give a titanium-containing geminal dimetallic **133** or a titanium methylidene **134**, which is the active methylenating agent (Scheme 73). However, titanium complexes must be involved in the reduction of the dibromoalkanes used in Takai



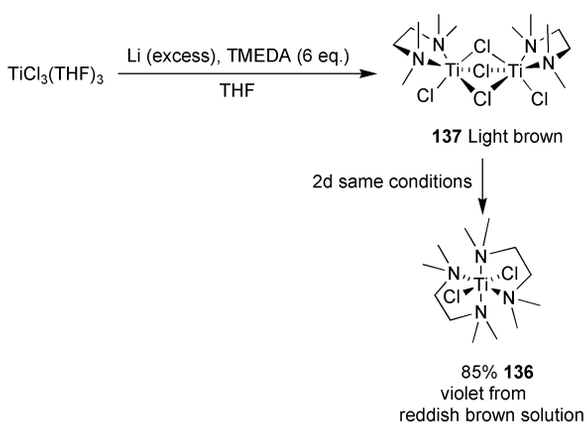
Scheme 73

alkylidenation of esters, as the rate of conversion of dibromomethane into a geminal dizinc in the absence of titanium salts is too slow to account for the alkylidenation reaction times. Furthermore, low valent titanium complexes are generated prior to the addition of dibromoalkanes. The identity of these low valent titanium complexes and the role of lead(II) salts in reactions involving titanium has not yet been established. Blue titanium(III) complex **135** can be obtained from titanium(IV) chloride in DCM–THF by treating it with 2 eq. TMEDA, and only 1.1 equivalents of zinc (half the stoichiometry used in the generation of the alkylidenating agent) and 6 mol% lead(II) chloride (Scheme 74).[112] In this case, it was suggested that



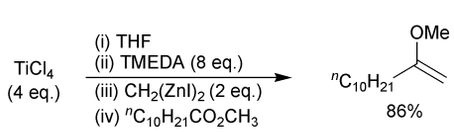
Scheme 74

lead(II) chloride has a quite different role from that described above, and it accelerates the formation of complex **135**. When $TiCl_3(THF)_3$ is reduced in THF with excess lithium in the presence of 6 eq. TMEDA, violet titanium(II) complex **136** is formed slowly (2 d) *via* the brown mixed valence titanium(II)–titanium(III) species **137** (Scheme 75).[113] Complex **136** dissolves



Scheme 75

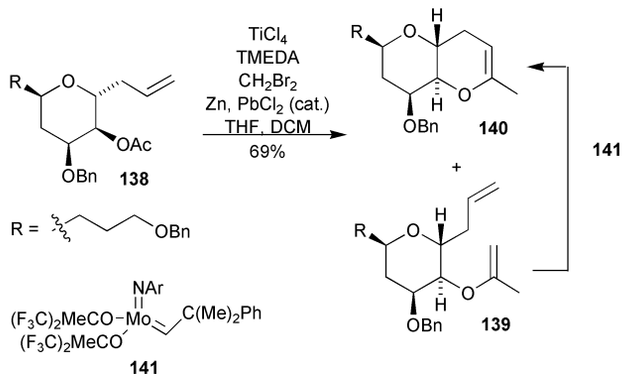
in THF to give a golden yellow solution. A mixture of titanium species **135** and **137** would account for the greenish blue colour formed under Takai conditions in THF. We propose that oxidative addition of titanium(II) is involved in the formation of at least one of the carbon–metal bonds to give a titanium(IV)-containing geminal dimetallic or titanium(IV) alkylidene. Matsubara and co-workers have shown that a titanium(II) species can carry out methylenation of esters (Scheme 76)[114]



Scheme 76

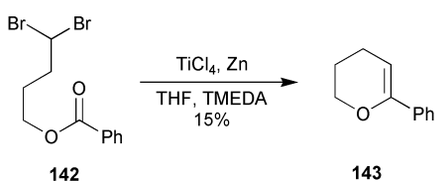
but the reagent is a different colour (reddish brown) and methylenates esters more effectively than the Takai reagent. Furthermore, it is unlikely that a titanium(II) reagent would be compatible with the reducible functional groups that the Takai reagent has been shown to tolerate *e.g.* vinyl iodides,[115,116] and aryl bromides.[105]

Until recently, there was no example of Takai reagents giving the products of alkene metathesis. However, Rainier *et al.* have reported that exposure of ester **138** to modified Takai conditions gives a mixture of enol ethers **139** and **140** in 69% yield (Scheme 77).[39] When the mixture of enol ethers **139** and **140** is



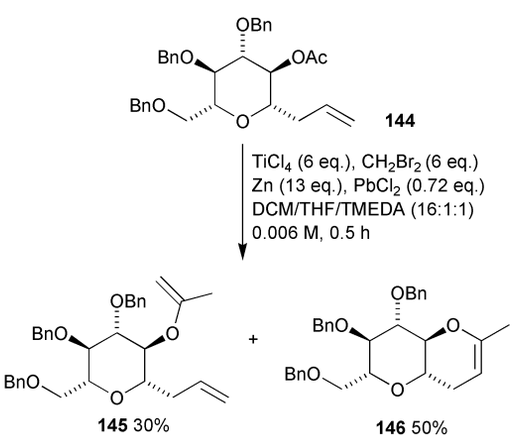
Scheme 77

exposed to the Schrock molybdenum catalyst **141**, all of the acyclic enol ether **139** is converted into the cyclic enol ether **140** and the latter is isolated in 93% yield. Since an acyclic enol ether similar to compound **139** failed to cyclise under Takai conditions, the researchers proposed that a titanium alkylidene is generated from the allylic group of ester **138** and that this then alkylidenates the carbonyl group intramolecularly. A related method of generating titanium alkylidenes using the Tebbe reagent has been reported (see Grubbs reagents),[37] but an early attempt to cyclise 1,1-dibromide **142** under Takai conditions gave very poor yields of cyclic enol ether **143** (Scheme 78).[111]



Scheme 78

Later Rainier and co-workers found that cyclisation is encouraged by using more lead(II) chloride and high dilution in predominantly dichloromethane.[40] In this way, *C*-glucoside **144** gives a mixture of acyclic and cyclic enol ethers **145** and **146** (Scheme 79). Again acyclic enol ether **145** is not converted into

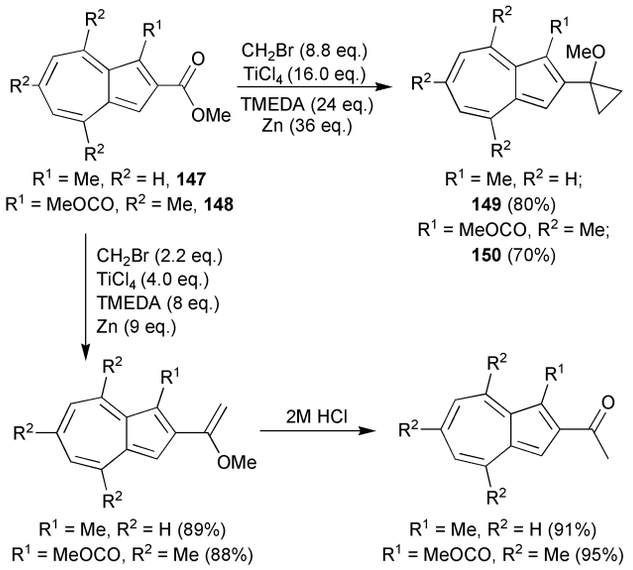


Scheme 79

the cyclic enol ether **146** when resubjected to the reaction conditions. The metathesis reaction is substrate dependant as the homoallylic analogue of *C*-allyl glucoside **144** gives no RCM products.

Aromatic esters can be cyclopropanated with an excess of Takai reagent. Methylenation of methyl azulene carboxylates **147** and **148** proceeds smoothly under standard Takai

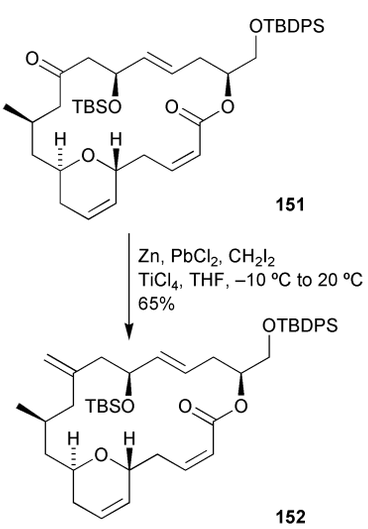
conditions, but when an excess of the reagent is used, cyclopropyl ethers **149** and **150** are produced in good yield (Scheme 80).[117] Methyl benzoate undergoes the same reaction, albeit in



Scheme 80

modest yield, but methyl phenylacetate does not. Enol ethers are not cyclopropanated under these conditions. This indicates that a titanium-containing intermediate derived from the ester reacts with excess reagent.

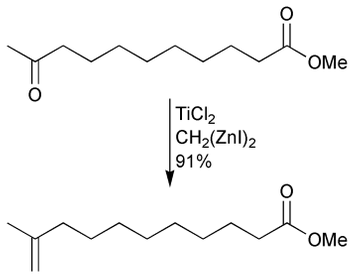
Takai reagents are nucleophilic in character and esters cannot be made to react in the presence of aldehydes and ketones. The only mention of alkylidenation of a ketone is in a footnote of Takai's original paper.[103] Selective methylenation of ketones and aldehydes in the presence of carboxylic acid or carbonic acid derivatives is possible using similar reagents[118–121] in the absence of TMEDA. One recent example is the methylenation of ketone **151** to give alkene **152** in Paterson's synthesis of the macrocyclic core of laulimalide (Scheme 81).[122] Similarly



Scheme 81

the analogous titanium(II) reagent prepared using bis(iodozincio)methane and titanium(II) chloride selectively methylenates ketones without affecting esters (Scheme 82).[123]

Takai alkylidenation (including methylenation) of esters tolerates many functional groups in the ester substrates: ethers, including benzyl[124] and *p*-methoxybenzyl ethers;[125] alkenes, including terminal alkenes;[126] acetals including glycosides,[124] and dimethyl acetals;[127] silyl ethers including TMS,[110] TES[110] and TBDMS ethers;[104] aryl and vinyl halides, including vinyl

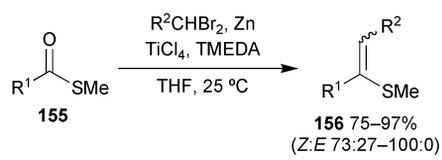


Scheme 82

iodides,[115] and aryl bromides.[105] Tolerance of functional groups in the titanium reagents themselves has not been properly investigated, but THP acetals are known to be tolerated.[111] Trimethylsilylmethylenation of esters has been achieved using (dibromomethyl)trimethylsilane as the 1,1-dibromide under Takai conditions.[109] The reactions are slower than other alkylidenations, and 3.3 eq. rather than 2.2 eq. of dibromide is needed to obtain good yields in 3–5 h. Enol ethers are formed with >86% *Z*-stereoselectivity and a branch α to the carbonyl group again ensures almost complete *Z*-selectivity. Thus ester **153** gives essentially only *Z*-enol ether **154** (Scheme 83).

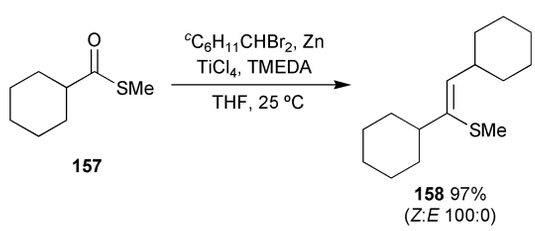
Takai alkylidenation of thioesters **155** gives *Z*-vinyl sulfides **156** (Scheme 84).[128] Unfortunately, α,β-unsaturated thioesters

Scheme 83



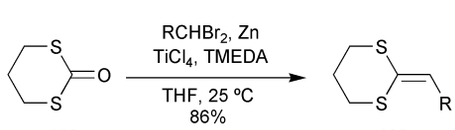
Scheme 84

do not give vinyl sulfides. The *Z*-selectivity is lower than for alkylidenation of esters, but total *Z*-selectivity is obtained when both R^1 and R^2 are branched (Scheme 85). Trimethylsilyl-



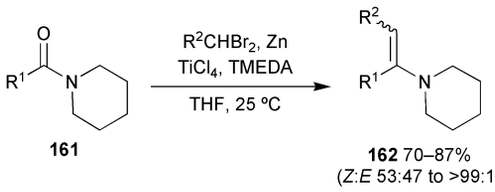
Scheme 85

methylenation of thioesters is also less *Z*-selective than the corresponding reaction with esters.[109] However, thioester **157**, which has a branch α to the carbonyl group, gives β-(methylthio)vinylsilane **158** in good yield and with good stereoselectivity. 1,3-Dithian-2-ones **159** are converted into ketene dithioacetals **160** in good yield (Scheme 86).[128] Tertiary amides



Scheme 86

161 give enamines **162** in good yield, and with >96% *E*-selectivity when R^1 = Ph or primary alkyl (Scheme 87). How-



Scheme 87

ever, when R^1 = cyclohexyl, there is almost no stereoselectivity. A mixture of regioisomers is obtained from straight chain amides **161** (R^1 = primary alkyl) presumably due to isomerisation of the initially formed enamine *via* an iminium ion intermediate (Scheme 87).

The advantage of Takai alkylidenation is that it is a mild one-pot procedure that allows the alkylidenation of a range of carboxylic acid and carbonic acid derivatives with good stereoselectivity. Its main disadvantage is that it requires a source of 1,1-dibromoalkanes. However, there are now a number of methods for the preparation of 1,1-dibromoalkanes,[102,129,130] including an easy two step synthesis from ketones or aldehydes.[102]

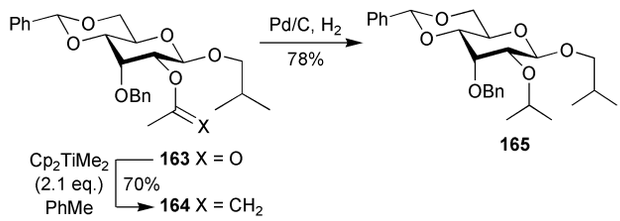
3 Synthetic strategies – reactions following alkylidenation

Alkylidenation of carboxylic and carbonic acid derivatives, particularly methylenation of esters and lactones, followed by manipulation of the resulting enol ethers or ketene acetals has been the key feature of a range of synthetic strategies. In the following subsections we classify synthetic strategies in terms of the first transformation applied to the enol ether and discuss them in detail, but first we will summarise the most common applications of this chemistry. Methylenation of esters and lactones has been widely used in combination with ring-closing metathesis and/or hydroboration for the construction of the tetrahydrofuran and tetrahydropyran rings of marine polyether toxins (Sections 3.2 and 3.9). Related approaches have commonly been applied to the synthesis of *C*-glycosides, and medium-ring and macrocyclic ethers (Sections 3.1, 3.2 and 3.9). Methylenation of lactones and cyclic carbonates followed by Claisen rearrangement has also been a favourite method for the construction of medium-ring ketones and lactones (Section 3.8). Methylenation of 1,3-dioxan-4-ones, followed by Lewis acid-induced rearrangement has been exploited for the synthesis of macrolides (3.4). The enol ether products of methylenation have often been used to make acetal tethers to control glycosylation reactions and cycloadditions (Section 3.3). Finally, the useful chameleon catch strategy in solid-phase synthesis relies on transformation of acid-stable esters into acid-sensitive enol ethers and this will be discussed in Section 4.0.

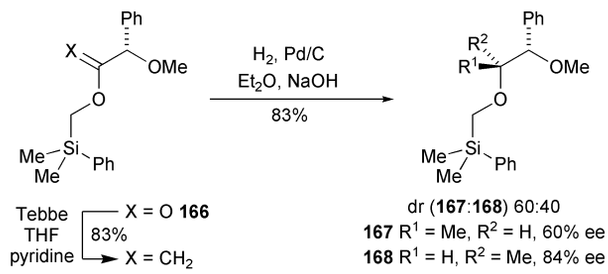
3.1 Hydrogenation

Isopropyl ethers cannot be prepared in good yield by alkylation of secondary alkoxides with isopropyl halides due to competition with E2 elimination. However, acetylation of secondary alcohols followed by methylenation (the Petasis reagent giving better yields than the Tebbe reagent) and hydrogenation gives isopropyl ethers in high yield.[131] Thus, acetate **163** gives enol ether **164**, which could be hydrogenated without affecting either the benzyl or benzylidene protecting group to give ether **165** (Scheme 88). Glucose derivative **165** has been used in the preparation of peptidomimetics.[132]

In Bienz's synthesis of a chiral auxiliary attached to silicon, enantiopure ester **166** is methylenated and then hydrogenated to give enantiomerically enriched silanes **167** and **168**, but with poor diastereoselectivity (Scheme 89).[133] The enantiomeric



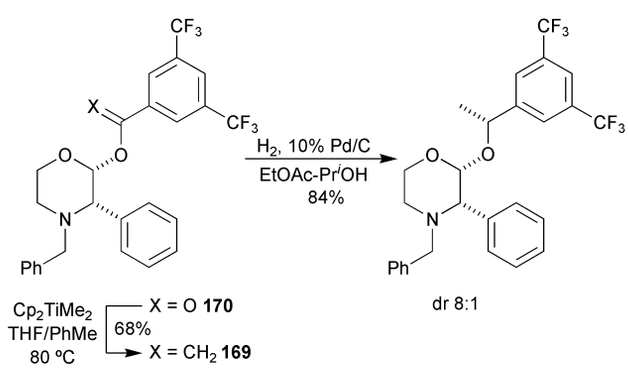
Scheme 88



Scheme 89

purities of diastereomers **167** and **168** were deduced from the enantiomeric purities of derivatives later in the sequence. It is not clear where in the sequence enantiomeric purity is reduced and how the difference in enantiomeric purities of diastereomeric derivatives arises.

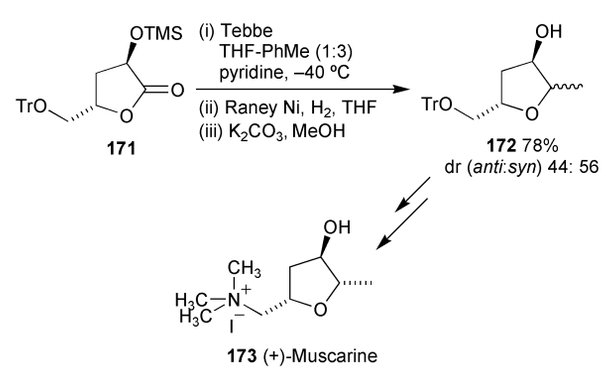
A Merck team preparing potent selective hNK-1 receptor antagonists obtained better diastereoselectivity in the hydrogenation of enol ether **169**.[65] Presumably the rigidity of the morpholine ring allows effective shielding of the *Re*-face of the enol ether by the phenyl group (Scheme 90). Enol ether **169** is



Scheme 90

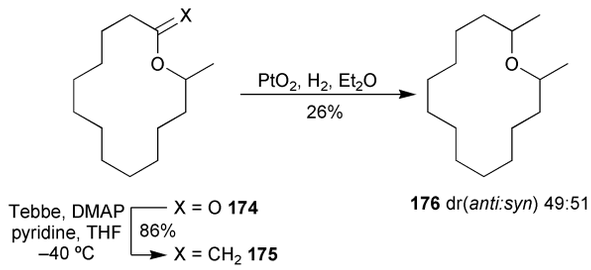
prepared by Petasis methylenation of ester **170** as Tebbe methylenation gives only 15% yield of enol ether **169**.

Methylenation of lactones followed by hydrogenation of the resulting enol ethers has been used to make cyclic ethers. Thus, methylenation, hydrogenation and desilylation of lactone **171**, gives a mixture of tetrahydrofurans **172** with poor diastereoselectivity (Scheme 91).[30] The 2,3-*anti*-isomer can be converted



Scheme 91

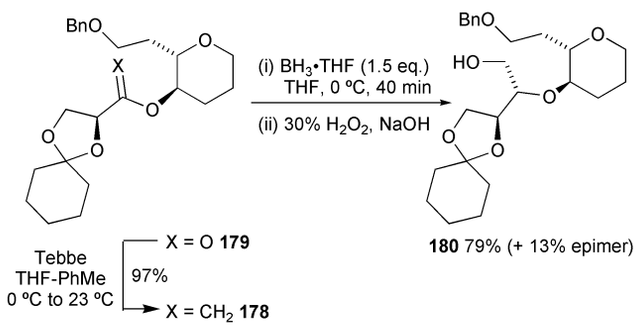
into (+)-muscarine **173** in 6 steps. Similarly, lactone **174**, synthesised from a cyclic ketone by Baeyer–Villiger oxidation, is methylenated and the resulting enol ether **175** hydrogenated to give a mixture of macrocyclic ethers **176** with no stereoselectivity (Scheme 92).[134]



Scheme 92

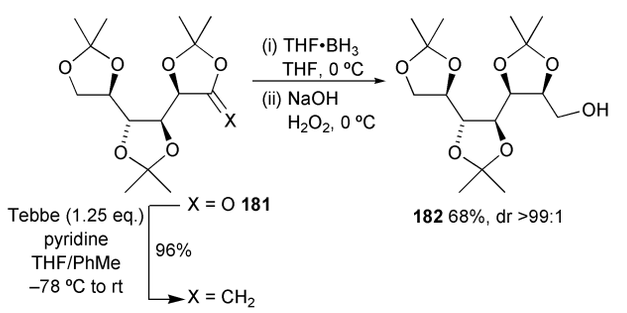
3.2 Hydroboration and hydrosilylation

Hydroboration of acyclic enol ethers can be diastereoselective when there are matched neighbouring chiral centres. Thus, hydroboration of enol ether **178**, produced by Tebbe methylenation of ester **179**, gives predominantly alcohol **180** as part of an approach to the A ring of polycyclic ether, Ciguatoxin (Scheme 93).[29]



Scheme 93

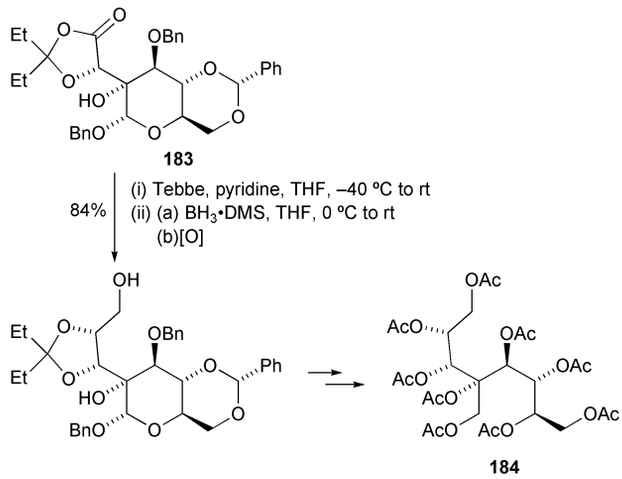
A related diastereoselective chain extension procedure developed by Sinaÿ and co-workers involves Tebbe methylenation of 1,3-dioxolan-4-ones followed by diastereoselective hydroboration–oxidation.[13] Thus, lactone **181** is converted into alcohol **182** with the hydroxymethyl group introduced *syn* to the neighbouring alkyl chain (Scheme 94). Interestingly, a bulky



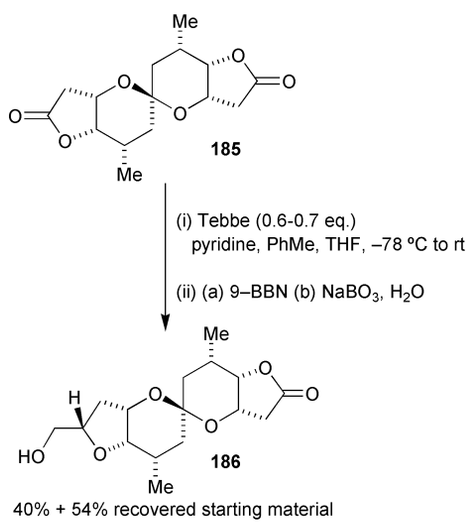
Scheme 94

borane is not needed to obtain total stereoselectivity. This procedure has been used by the same group to convert lactone **183** into a peracetylated stereoisomer of calditol **184**, a constituent of the membrane of thermoacidophilic archaebacteria (Scheme 95).[135]

Desymmetrization of C_2-symmetric bis(lactone) **185** by monomethylenation–hydroboration–oxidation is a key step in Burke's approach to marine polycyclic toxin, halichondrin B (Scheme 96).[136] Bis(lactone) **185** is treated with 0.6–0.7 eq. of Tebbe reagent, followed by hydroboration–oxidation to give



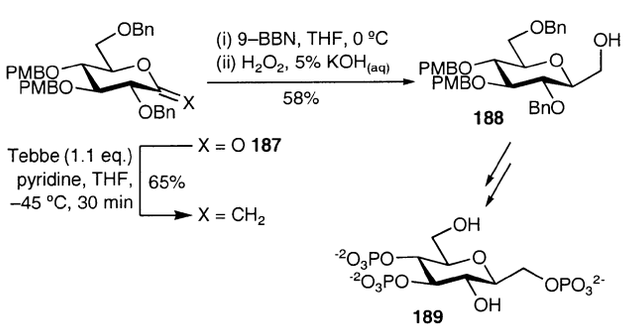
Scheme 95



Scheme 96

alcohol **186** together with unreacted bis(lactone) **185**. This time a bulky borane, 9-BBN, is used to ensure stereoselectivity.

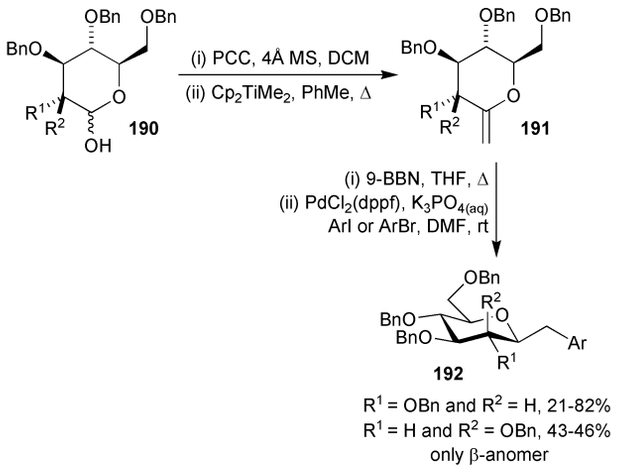
Following the procedure developed by Rajanbabu and Reddy,[137] Potter and co-workers carried out Tebbe methylenation of sugar lactone **187** followed by stereoselective hydroboration with a bulky hydroborating agent, 9-BBN, and oxidation to give exclusively β-*C*-glucosides **188** (Scheme 97).[138]



Scheme 97

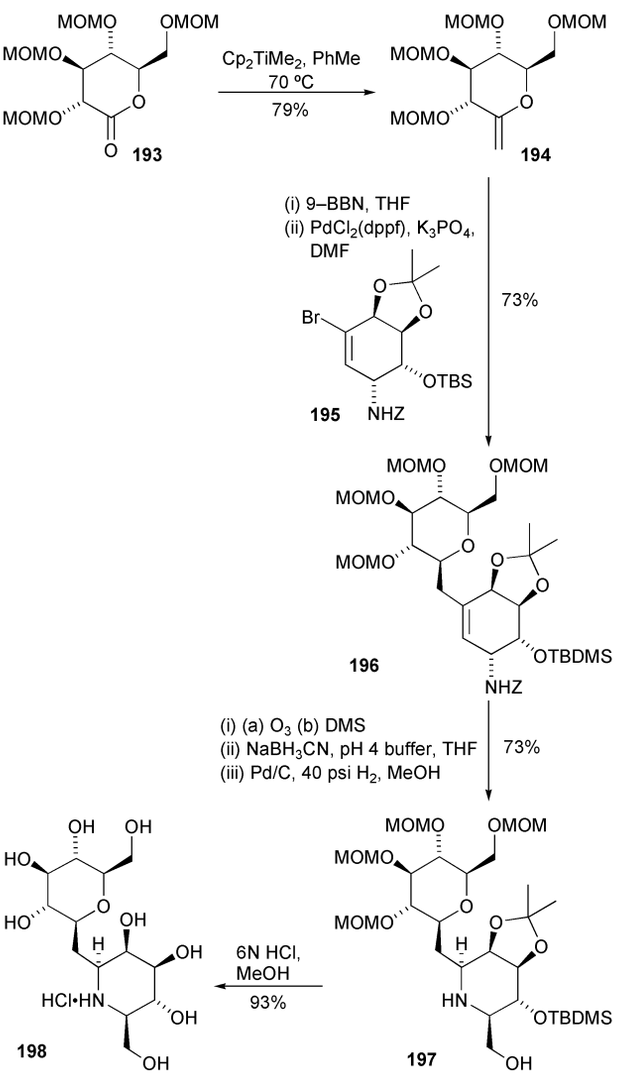
A 1 : 2 mixture of α- and β-anomers is obtained with borane–THF. *C*-Glucoside **188** is easily converted into a β-glucopyranosylmethanol analogue **189** of inositol trisphosphate.

Johnson and Johns[139] adapted Rajanbabu and Reddy's methylenation–stereoselective hydroboration of sugar lactones by replacing oxidation of the borane products with a Suzuki cross-coupling reaction (Scheme 98). Like Csuk and Glänzer,[140]



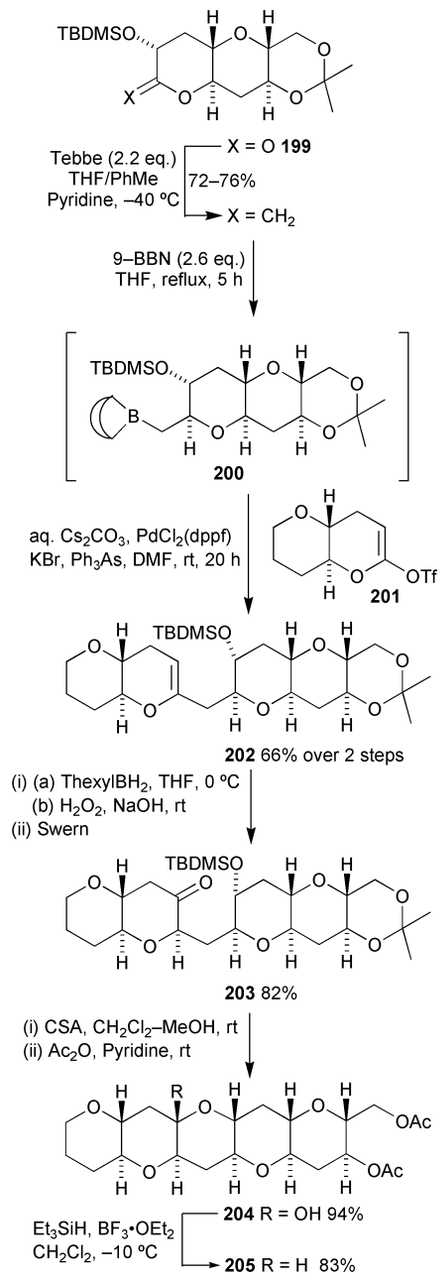
Scheme 98

they used Petasis methylenation rather than Tebbe methylenation of sugar lactones. Thus, glucose and mannose derivatives **190** give enol ethers **191** that undergo mild hydroboration–Suzuki cross-coupling to give only the β-anomers of arylmethylglycosides **192**. Similarly, in the synthesis of amylglycosidase inhibitor **198**,[64] exocyclic enol ether **194** is prepared by Petasis methylenation of lactone **193** and is then subjected to hydroboration and Suzuki cross-coupling with vinyl bromide **195** (Scheme 99). Conversion of the resulting carbocycle **196** into piperidine **197** and global deprotection gives the target



Scheme 99

aza-*C*-disaccharide **198**. A very similar approach was adopted by Sasaki *et al.* to make polycyclic ethers (Scheme 100).[32] Tebbe

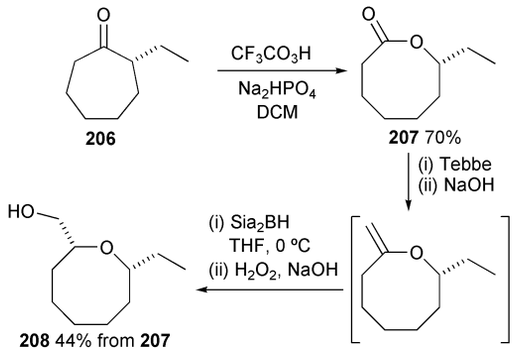


Scheme 100

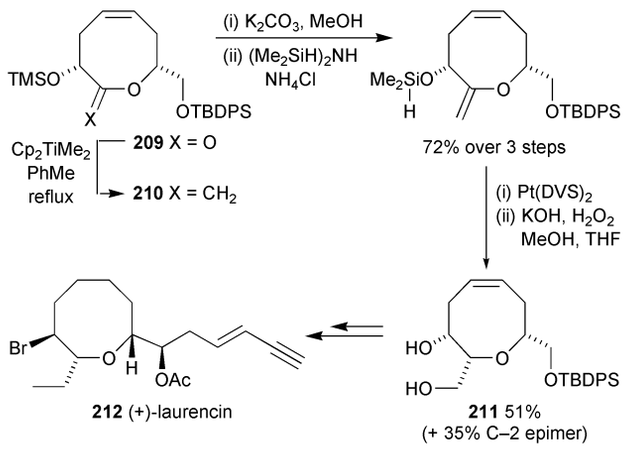
methylenation of lactone **199**, followed by hydroboration generates a substrate **200** for Suzuki cross-coupling with triflate† **201** to give enol ether **202**. The linking ring is formed by cyclising ketone **203** and reducing the resultant hemiacetal **204** to give pentacycle **205**.

The Holmes group used Baeyer–Villiger oxidation of cyclic ketone **206**, followed by Tebbe methylenation of the resulting lactone **207**, hydroboration with diisoamylborane and oxidation to give medium-ring ether **208** as the only alcohol product (Scheme 101).[62] In their synthesis of (+)-laurencin **212**, they found Petasis methylenation more convenient than using the Tebbe reagent to methylenate lactone **209**, and hydroxylation of enol ether **210** to give alcohol **211** was achieved by hydrosilylation using bis(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)-platinum(0) [Pt(DVS)$_2$] as catalyst followed by Tamao oxidation (Scheme 102).[62]

† The IUPAC name for triflate is trifluoromethanesulfonate.

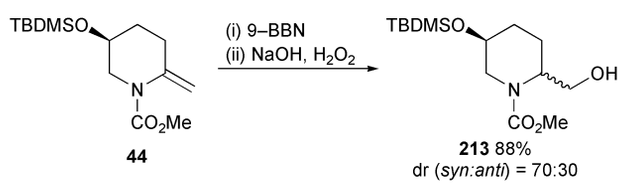


Scheme 101



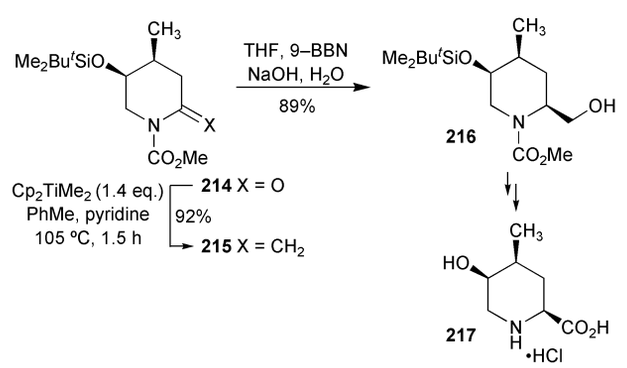
Scheme 102

As described above (Section 2.3), in 1993 Herdeis and Heller showed that Petasis methylenation of *N*-methoxycarbonyl-protected lactam **43** gives carbamate **44** (Scheme 34).[69] Hydroboration–oxidation of carbamate **44** then gives a mixture of piperidines **213** (Scheme 103). The same researchers later



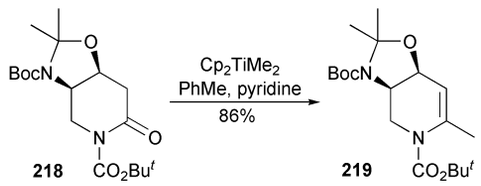
Scheme 103

showed that Petasis methylenation of *N*-methoxycarbonyl lactam **214** followed by hydroboration–oxidation of enamine **215** gives exclusively the all *syn* piperidine **216**, which can be used to make novel pipecolic acid **217** (Scheme 104).[141] In a similar system, Langlois found that Petasis methylenation of lactam **218** gives exclusively the endocyclic enamine **219**



Scheme 104

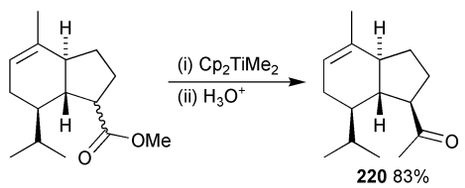
presumably due to facile isomerization of the exocyclic double bond (Scheme 105).[142]



Scheme 105

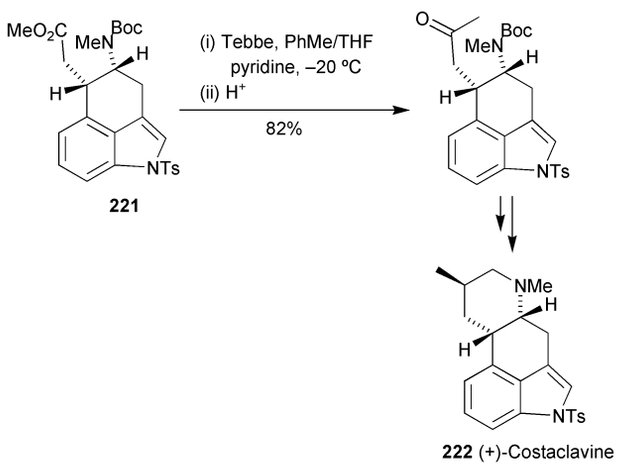
3.3 Hydrolysis or reaction of enol ethers with alcohols

Taber and co-workers used Petasis methylenation followed by acid hydrolysis as a one-carbon homologation to complete their total synthesis of racemic α-oplopenone **220** (Scheme 106).[143] A



Scheme 106

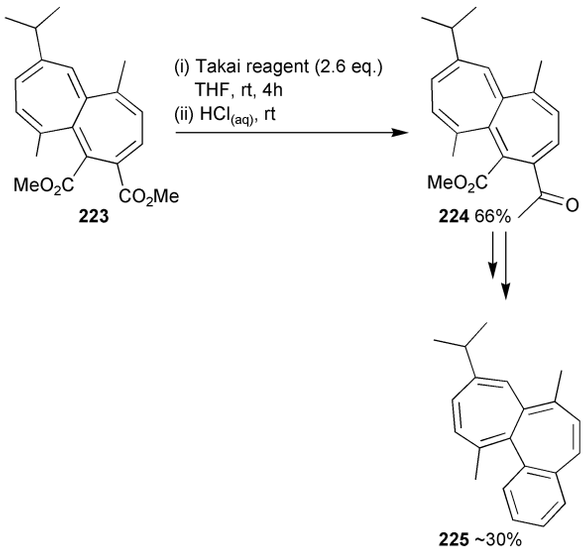
similar chain extension was achieved using Tebbe methylenation of ester **221** followed by acid hydrolysis in a synthesis of the fungal alkaloid costaclavine **222** (Scheme 107).[35] Selective



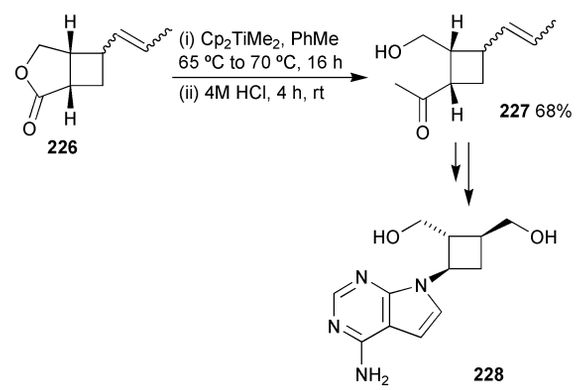
Scheme 107

Takai methylenation of the less sterically hindered methyl ester of diester **223**, followed by hydrolysis to give ketone **224** was a key step in the construction of heptazulene **225** (Scheme 108).[144]

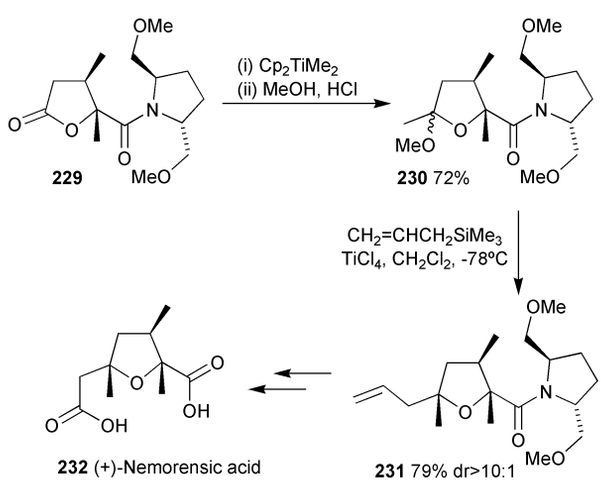
A similar procedure was employed by Ghosh and co-workers to open strained bicyclic lactones **226**, prepared from the products of intramolecular [2+2] cycloaddition, to give ketones **227** as part of a synthesis of the antiviral cyclobut-A **228** (Scheme 109).[145] On the other hand, in Donohoe's synthesis of (+)-nemorensic acid **232**[146] methylenation of γ-lactone **229** and methoxylation gave cyclic acetals **230**, which were then reacted with allyltrimethylsilane under Lewis acidic conditions to give ether **231** (Scheme 110). Similarly, in Kitahara's synthesis of FR901464 **236**, lactone **233** was methylenated and the resulting enol ether **234** reacted with acidic methanol to give predominantly acetal **235** (Scheme 111).[147] Reaction of enol ethers with alcohols other than methanol is also possible. Ikegami showed that *exo*-methylenesugars, prepared by Petasis methylenation, can be coupled with the primary or secondary hydroxy groups of sugar lactones under acidic conditions to give sugars as large as tetrasaccharides **237**, but yields were not reported (Scheme 112).[66]



Scheme 108

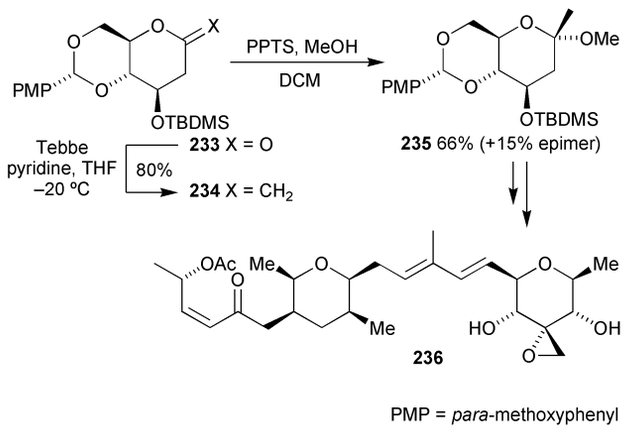


Scheme 109

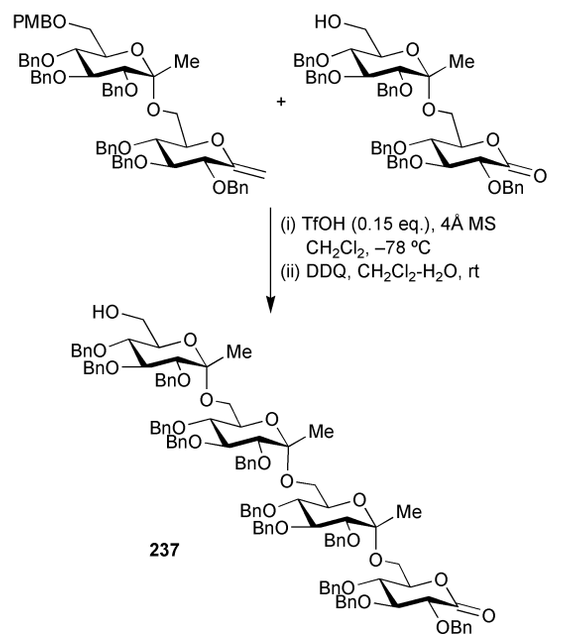


Scheme 110

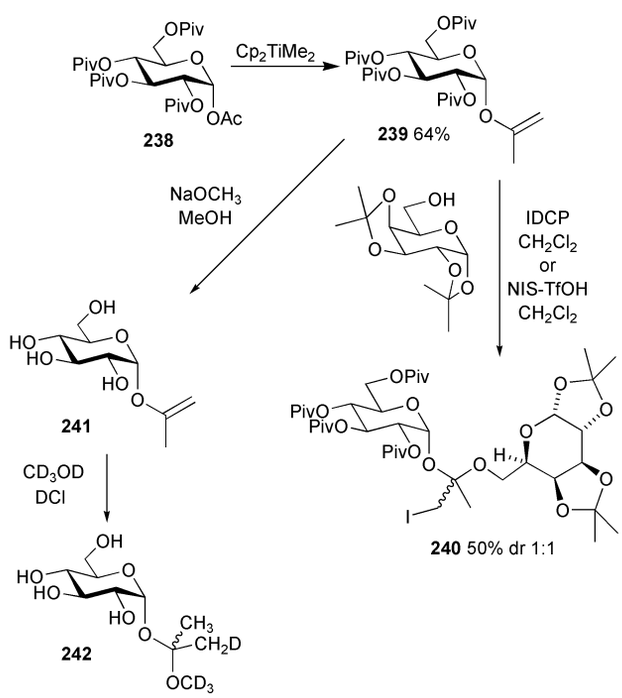
While attempting to carry out transglycosylation reactions, Chenault showed that enol ether **239**, prepared using Petasis methylenation of ester **238**, can be smoothly converted into iodide **240** (Scheme 113).[49] Hydrolysis of the pivaloate esters of glycoside **239** was also carried out to give *O*-isopropenyl α-glucopyranoside **241**, whose reactions with acidic methanol and aqueous acid were then studied.[48] Hydrolysis occurs exclusively by rate-determining *C*-protonation and vinyl ether (not glycosidic) C–O bond cleavage. α-Glucopyranoside **241** hydrolyses 4.5 times faster than the corresponding β-glucopyranoside at pH 3.0. α-Glucopyranoside **241** reacts with acidic deuteromethanol to give mixed acetal **242** and this proceeds 2.6



Scheme 111



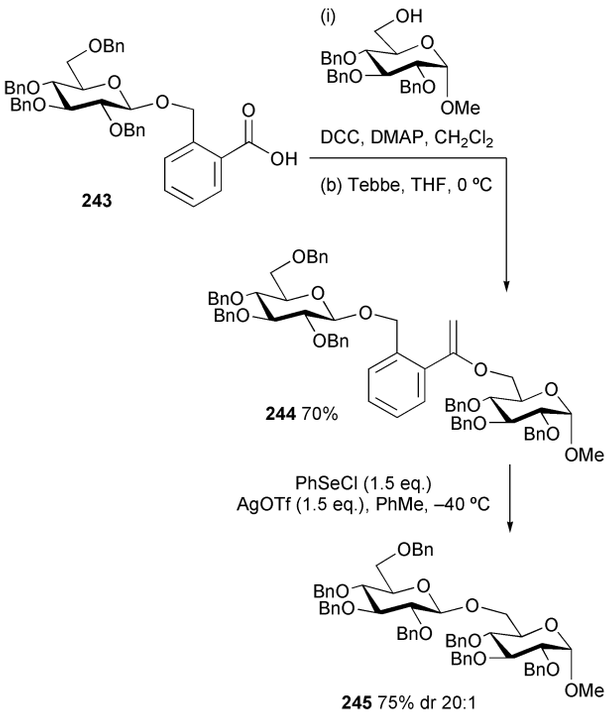
Scheme 112



Scheme 113

times faster than the same reaction with the corresponding β-glucopyranoside.

Schmidt and co-workers modified the known pent-4-enyloxy leaving group so as to link the glycosyl donors and acceptors (Scheme 114).[148] Esterification of carboxylic acid **243** followed



243

244 70%

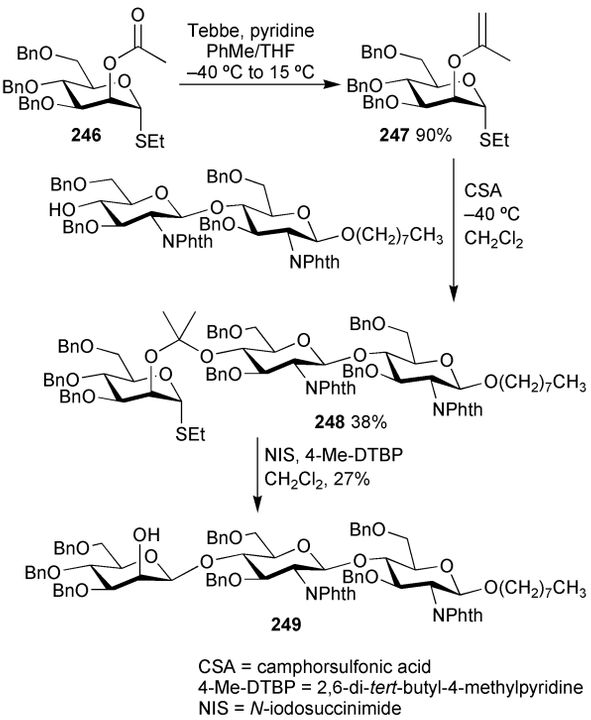
245 75% dr 20:1

Scheme 114

by Tebbe alkylidenation gave glucopyranosyl precursor **244**. Electrophilic activation of the enol ether led to the formation of β-anomer **245** with high diastereoselectivity. The glycosylation proceeds by an intermolecular reaction mechanism.

In contrast, Barresi and Hindsgaul have developed a stereoselective route to β-mannopyranosides that involves intramolecular aglycon delivery. In one example, thioglycoside **246** was converted into enol ether **247** using the Tebbe reagent and then acetonide **248** was formed under acidic conditions (Scheme 115).[149–151] Treatment of acetonide **248** with *N*-iodosuccinimide (NIS) gave only β-glycoside **249**, albeit in modest yields. The intramolecular nature of glycoside delivery was proven using cross-over experiments. Barresi and Hindsgaul noted that NIS would also induce acetonide formation, but only when the nucleophilic alcohol was primary. However, no example was given. It was left to Fairbanks and co-workers to modify the Barresi and Hindsgaul mixed acetal procedure[149–151] so that NIS is used for both the tethering and the glycosylation steps.[34] Thus, enol ether **250**, was converted into β-mannoside **251** in high yield and with excellent diastereoselectivity (Scheme 116). Tethering was also employed by Sinaÿ and co-workers to make α-*C*-disaccharide **256** (Scheme 117).[33] α-Phenylselenomannoside **252** was methylenated with the Tebbe reagent to give enol ether **253**, which was then coupled with primary alcohol **254** to give acetal **255**. 9-*endo*-*trig* Radical cyclisation, followed by untethering and acetylation gave α-*C*-disaccharide **256** in modest yield. The corresponding β-*C*-mannoside was also formed in the cyclisation reaction, but the dr(α–β) was 10 : 1.

Such tethering procedures are not restricted to sugar chemistry. Craig and co-workers have investigated the intramolecular Diels–Alder reactions of dienes linked to dienophiles by acetal tethers, introduced using Tebbe methylenation.[22] In one example, Tebbe methylenation of ester **257** followed by palladium-catalysed addition of allylic alcohol **258** to the resulting enol ether **259** gave acetal-tethered triene **260** (Scheme



246

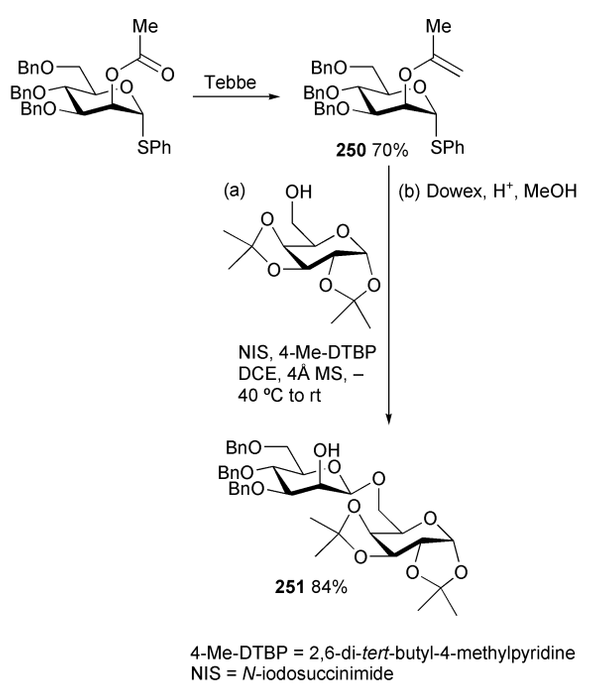
247 90%

248 38%

249

CSA = camphorsulfonic acid
4-Me-DTBP = 2,6-di-*tert*-butyl-4-methylpyridine
NIS = *N*-iodosuccinimide

Scheme 115



250 70%

251 84%

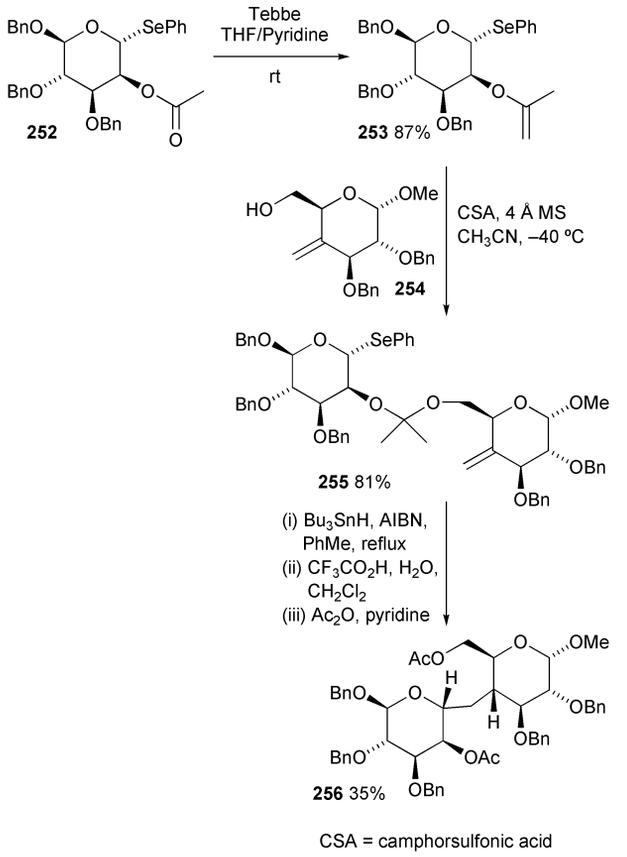
4-Me-DTBP = 2,6-di-*tert*-butyl-4-methylpyridine
NIS = *N*-iodosuccinimide

Scheme 116

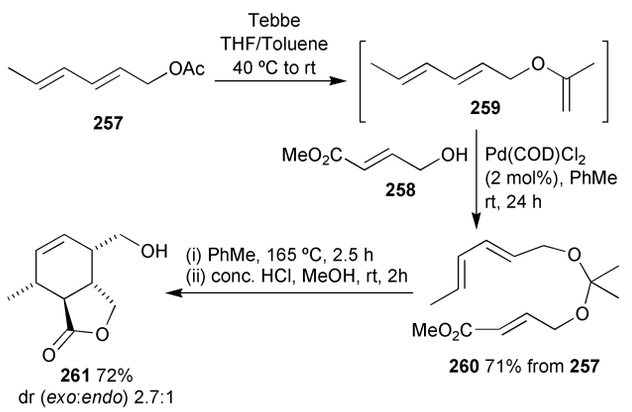
118). This underwent thermal intramolecular Diels–Alder reaction to give predominantly the ester-*exo* product **261**.

3.4 Acid-induced rearrangements including Petasis–Ferrier rearrangement

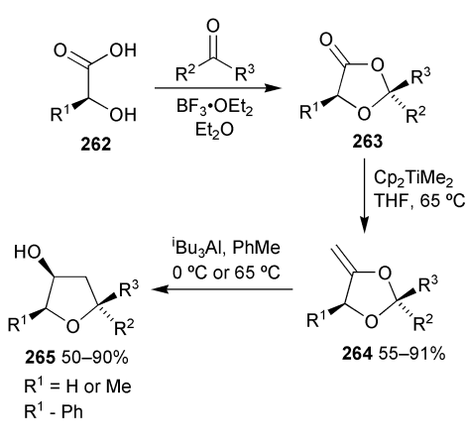
Petasis and Lu have developed a three step stereocontrolled route to tetrahydrofurans.[152] α-Hydroxycarboxylic acids **262** are condensed with an aldehyde to give 1,3-dioxolanones **263**, which are then methylenated with dimethyltitanocene (Scheme 119). The resulting enol ethers **264** undergo Ferrier rearrangement[153] using trialkylaluminium reagents, but not other Lewis acids, to give predominantly 2,3-*syn*, 3,5-*syn* tetrahydrofurans **265**. Disubstituted enol ether **266**, prepared using dibenzyltitanocene (no yield given), also undergoes rearrangement and stereoselective reduction in high yield (Scheme 120). 1,3-



Scheme 117

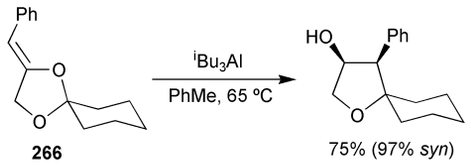


Scheme 118



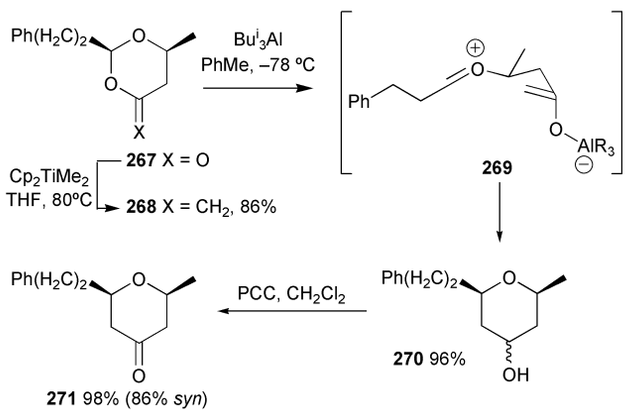
Scheme 119

Dioxan-4-ones can be converted stereoselectively into tetrahydropyrans using the same method.[154] Thus, 1,3-dioxan-4-one **267** was methylenated to give enol ether **268**, which then



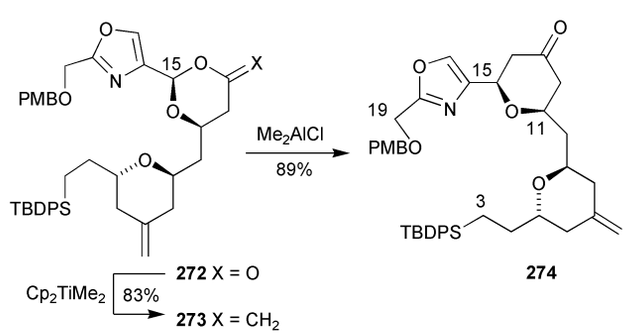
Scheme 120

underwent stereocontrolled aluminium-mediated rearrangement, presumably *via* intermediate **269**, and *in situ* reduction to give tetrahydropyran **270** (Scheme 121). Oxidation then gave predominantly *syn* ketone **271**.



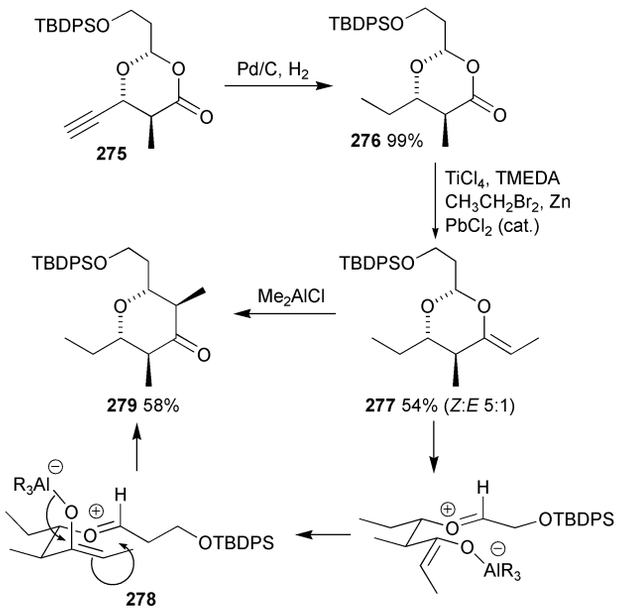
Scheme 121

The same Petasis modification[154] of the Ferrier rearrangement[153] was used by Smith and co-workers to construct the C(3–19) subunit of phorboxazole A (Scheme 122).[59,155] Petasis

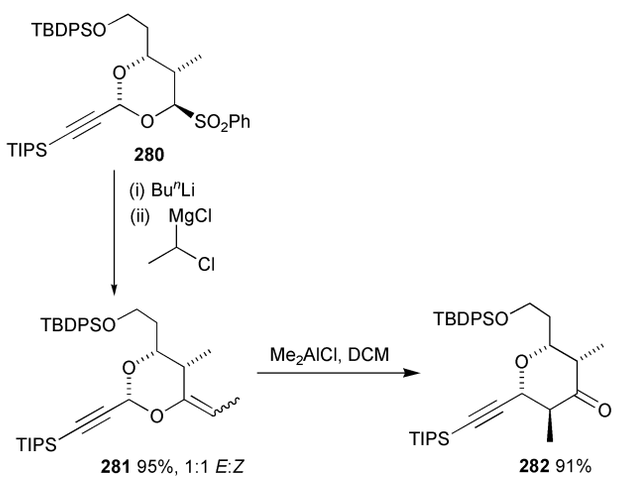


Scheme 122

methylenation of lactone **272** gave enol ether **273** which rearranged under Lewis acidic conditions to give ketone **274**. The use of Me_2AlCl instead of *i*-Bu_3Al was vital to inducing the rearrangement (possibly because bidentate coordination of aluminium between the oxazole nitrogen atom and the enol ether oxygen atom encourages rearrangement) and avoided the undesirable reduction of the ketone. A similar strategy was attempted for the synthesis of the C(22–26) central tetrahydropyran subunit.[155] Attempted Takai ethylidenation of lactone **275** led only to decomposition (Scheme 123). The same result was obtained with both Takai and Takeda ethylidenation when the terminal alkyne was protected with a TIPS group. The alkyne was responsible for the problem, as lactone **276** was smoothly ethylidenated under Takai conditions to give predominantly *Z*-enol ether **277**. The pure *Z*-enol ether underwent stereoselective Petasis–Ferrier rearrangement, presumably *via* intermediate **278**, to give the all equatorial tetrahydropyran **279**. Ultimately, the desired enol ethers **281** were prepared by α-alkylation of a sulfone **280** with an electrophilic Grignard reagent (Scheme 124). Interestingly, Petasis–Ferrier rearrangement of the mixture proceeded in a stereoconvergent way to give only tetrahydropyranone **282**. Petasis–Ferrier rearrange-



Scheme 123



Scheme 124

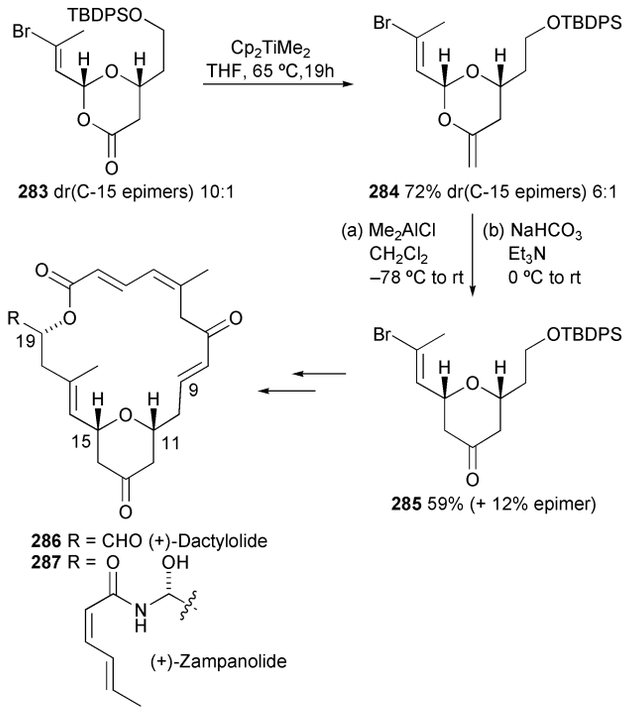
ment was also a key step[156] in Smith's total synthesis of both natural (+)-dictylolide **286** and unnatural (+)-zampanolide **287**.[157] Thus, Petasis methylenation of lactone **283** gave enol ether **284**, which was rearranged to give predominantly ketone **285** in good yield (Scheme 125).

Ley and co-workers showed that anomerically linked enol ethers can be converted selectively into either 2,6-*anti*- or 2,6-*syn*-pyranyl ketones. In one example, Tebbe methylenation of ester **288** gives enol ether **289**, and diastereoselective oxygen to carbon rearrangement then gives 2,6-*anti*-pyranyl ketone **290** under kinetic control. This can be equilibrated to give the more thermodynamically favourable 2,6-*syn*-pyranyl ketone **291** at room temperature (Scheme 126).[158]

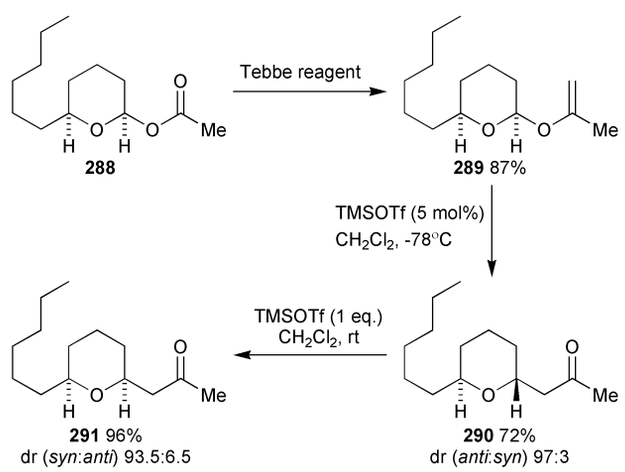
3.5 Miscellaneous reactions with electrophiles

The second step of Petasis–Ferrier rearrangement involves intramolecular reaction between an aluminium enolate and an activated carbonyl group. A similar reaction was employed in Steglich's enantioselective synthesis of (*R*)-atrochrysone **293**. Tebbe methylenation of enantiopure diester **7** was followed by intramolecular acylation of enol ether **8** induced by *N*-triflyl-4-(dimethylamino)pyridinium triflate (formed from triflic anhydride and DMAP) to give cyclohexenone **292** (Scheme 127, see also Scheme 4).[12]

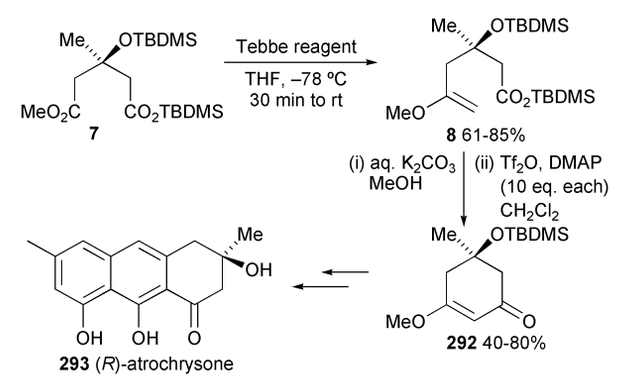
In van Boom's synthesis of potential fucosyltransferase inhibitor **297**, lactone **294** was methylenated and the resulting



Scheme 125



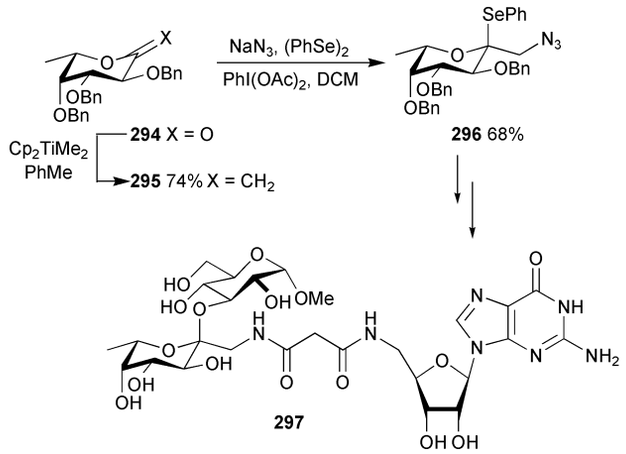
Scheme 126



Scheme 127

enol ether **295** was subjected to azido-phenylselenation to produce the fucosyl donor **296** (Scheme 128).[61] Fucosyltransferase is involved in the biosynthesis of sialyl Lewis X, which is implicated in inflammatory diseases.

Howell and co-workers have shown that methyleneoxetanes **38** (Scheme 26) react with dimethyldioxirane to give 1,5-dioxaspiro[3.2]hexanes.[57] These strained spirocycles react with a range of nucleophiles to give polyfunctionalised ketones or

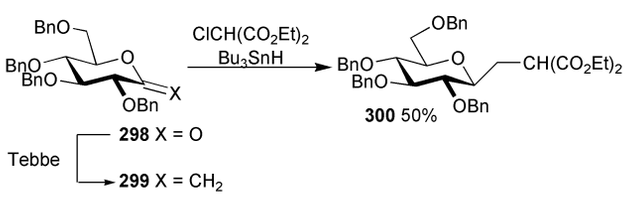


Scheme 128

2,2-disubstituted oxetanes, and have proved to be useful precursors to both aminodiol and aminotriol sphingoid bases.

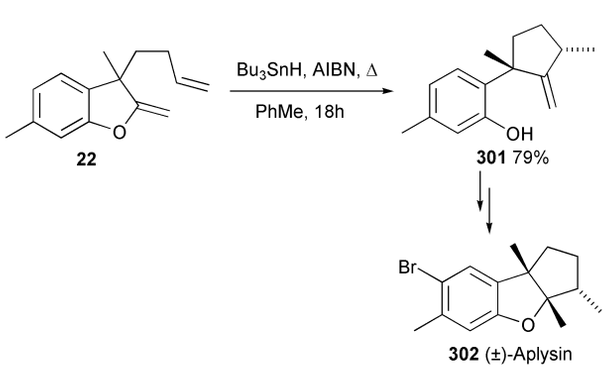
3.6 Radical reactions

Radicals add regioselectively to enol ethers to give carbon-centred radicals adjacent to the ether's oxygen atom. Such radicals are stabilised by overlap with one of the lone pairs on oxygen. Nicotra and co-workers used Tebbe methylenation of lactones **298** followed by reaction of the resulting *exo*-methylene compounds **299** with the malonyl radical to form *C*-glycosides **300** as the key steps in a route to *C*-glycoside analogues of glycosyl glycerols (Scheme 129).[159]



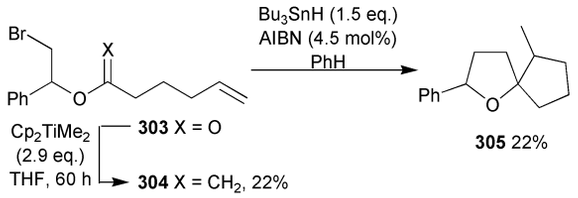
Scheme 129

A route to racemic aplysin **302** and related natural products involved 5-*exo* radical cyclisation of diene **22**, prepared by Tebbe methylenation of lactone **21** (see Scheme 12), followed by elimination to give alkene **301** in good yield (Scheme 130).[24]



Scheme 130

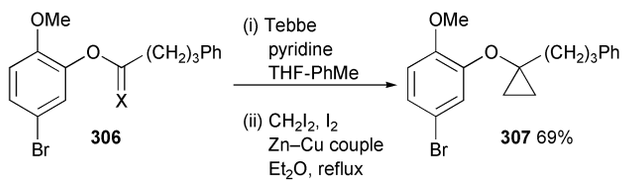
Crich and Yao demonstrated that a 2-(vinyloxy)alkyl radical will undergo 5-*endo-trig* cyclisation to give a stabilised carbon-centred radical adjacent to the ether's oxygen atom, opening can then give a 4-ketobutyl radical. In one example, where the intermediate cyclic radical is trapped intramolecularly, enol ether **304**, prepared by Petasis methylenation of ester **303**,[60] underwent tandem radical cyclisations to give a 50 : 50 mixture of spirocyclic ethers **305** with the product of simple reduction (Scheme 131).



Scheme 131

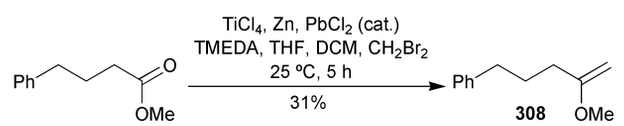
3.7 Cycloadditions

Cyclopropanyl ether **307** was synthesised by Duplantier *et al.* at Pfizer as a potential antiinflammatory (Scheme 132).[27] Tebbe



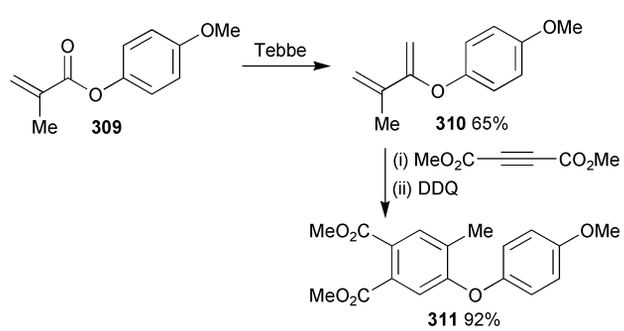
Scheme 132

methylenation of ester **306** followed by Simmons–Smith reaction gave the ether **307** in good yield. De Zwart attempted to induce intramolecular *meta* photocycloaddition reaction between the enol ether and phenyl ring of compound **308**, prepared by Takai methylenation, but the reaction gave a mixture of other products (Scheme 133).[160]



Scheme 133

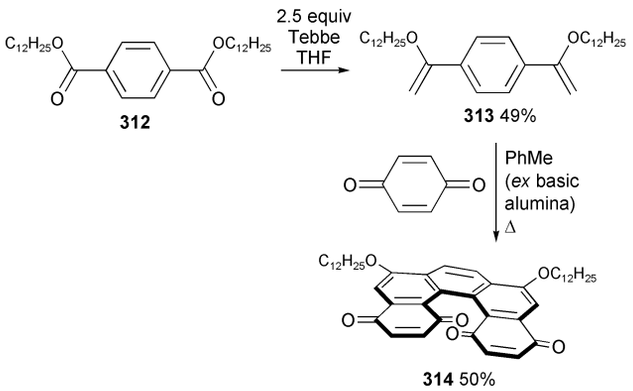
Olsen and co-workers have shown that diaryl ethers can be prepared by Diels–Alder reactions between aryloxy dienes and substituted alkynes.[25] The aryloxy dienes were prepared by Tebbe or Petasis methylenation of α,β-unsaturated esters with the former proving more successful. Thus, aryl ester **309** was methylenated to give diene **310** and Diels–Alder reaction with acetylenic ester and DDQ oxidation then gave phthalate **311** (Scheme 134). A similar approach was used by Katz *et al.* for the



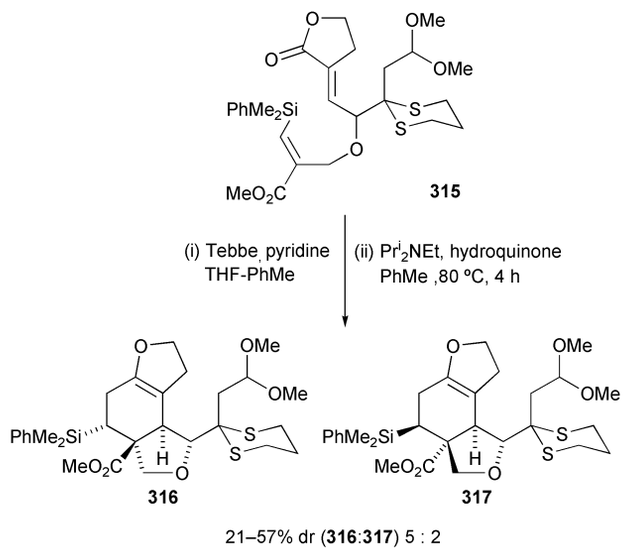
Scheme 134

synthesis of helicene **314**.[161] Tebbe methylenation of diester **312** gave enol ether **313**, which underwent Diels–Alder reaction with benzophenone and *in situ* oxidation to give the functionalised helical compound **314** (Scheme 135). In Ley's approach to azadirachtin, methylenation of s-*cis*-constrained lactone **315** followed by intramolecular Diels–Alder reaction gave some selectivity for (ester *endo*) adduct **316** over (ester *exo*) adduct **317** (Scheme 136).[14]

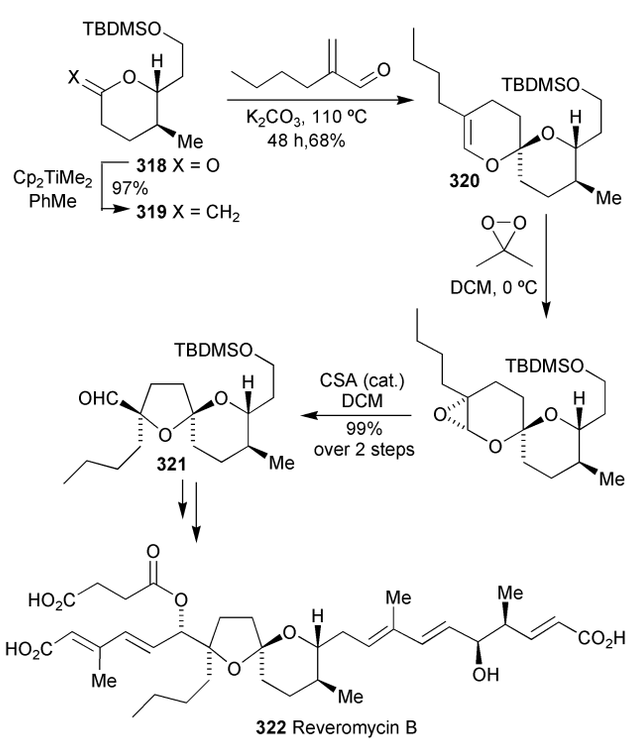
McRae and Rizzacasa showed that Petasis methylenation of lactone **318**, followed by inverse electron demand hetero-Diels–Alder reaction between the resulting *exo*-methylene compound



Scheme 135



Scheme 136



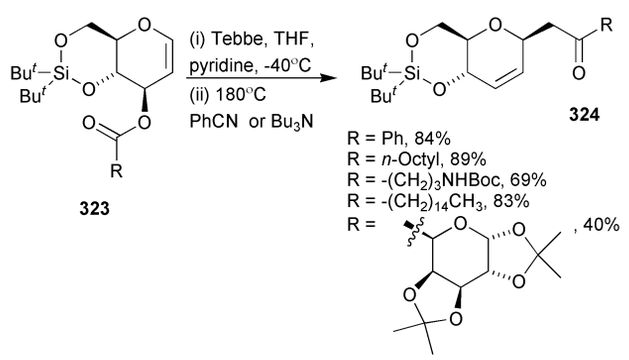
Scheme 137

319 and 2-butylacrolein gave spiroketal **320** (Scheme 137).[63] Epoxidation followed by acid-induced ring contraction gave the 5,6-spiroketal core **321** of reveromycin B **322**. This key intermediate was used in the total synthesis of reveromycin B **322**.[162]

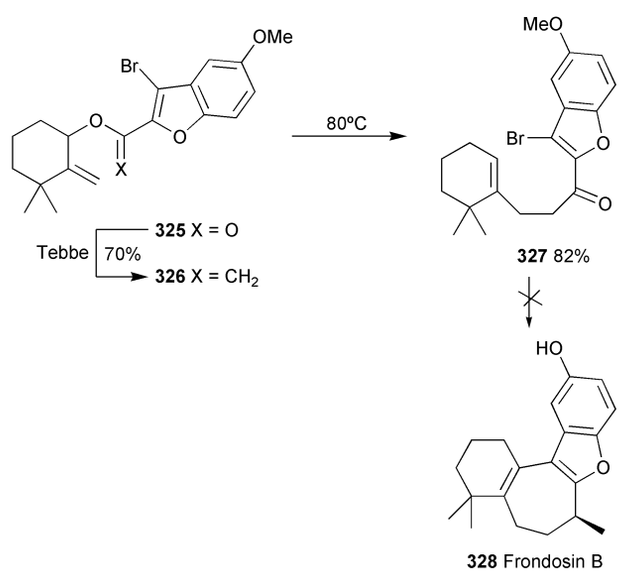
3.8 Sigmatropic rearrangement

3.8.1 Claisen rearrangement

Claisen rearrangements of enol ethers derived from both esters and lactones have been exploited in target-based synthesis. As part of Vedejs' approach to the cytochalasins, formate ester **34** was methylenated to give an enol ether, which underwent Claisen rearrangement upon heating (Scheme 22).[50] A general route to *C*-glycosides involves methylenation of glycals **323** followed by Claisen rearrangement to the *C*-glycosides **324** (Scheme 138).[31] In Danishefsky's first approach to frondosin B **328**, ester **325** was methylenated and the product **326** was rearranged to give ketone **327** (Scheme 139).[23] Unfortunately,



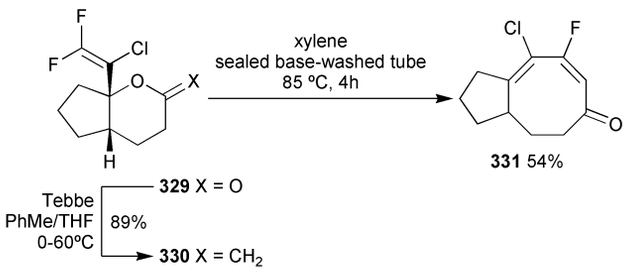
Scheme 138



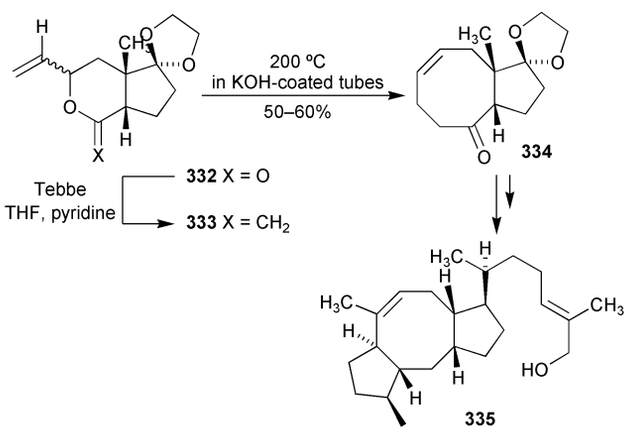
Scheme 139

Heck and Stille reactions failed to close the seven membered ring and synthesis of the target **328** was completed by an alternative route.

A popular method for the construction of medium-ring ketones involves methylenation of lactones followed by ring expansion using the Claisen rearrangement. Thus, Tebbe methylenation of lactone **329** gives enol ether **330**, which undergoes Claisen rearrangement and elimination of hydrogen fluoride to give conjugated ketone **331** (Scheme 140).[26] The favourable rehybridisation of the sp^2 CF_2 centre to sp^3 probably accounts for rearrangement at an unusually low temperature. Paquette *et al.* employed the ring expansion methodology developed in their research group[163,164] to construct the B ring of (+)-ceroplastol **335** (Scheme 141).[165] Thus, Tebbe methylenation of lactone **332** gave enol ether **333**, which underwent

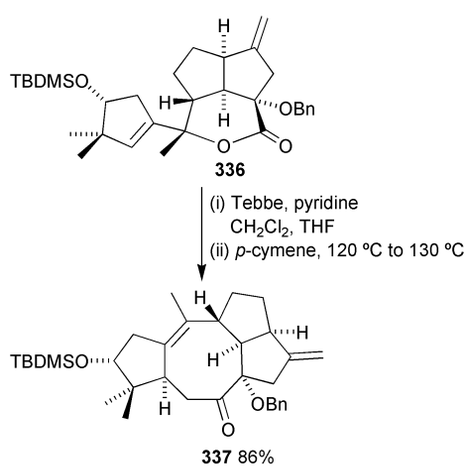


Scheme 140



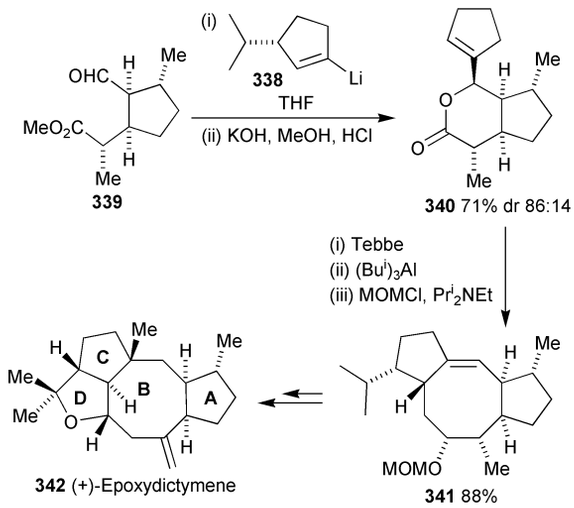
Scheme 141

Claisen rearrangement to give medium-ring ketone **334**. Organometallic impurities had to be removed before Claisen rearrangement as they led to isomerisation of the exocyclic double bond to give the corresponding endocyclic enol ether. Similarly, the key steps in Paquette's approach to the tetracyclic framework of kalmanol were Tebbe methylenation of lactone **336** followed by thermal Claisen rearrangement to give tetracycle **337** in 86% yield (Scheme 142).[166] The stereochemistry of



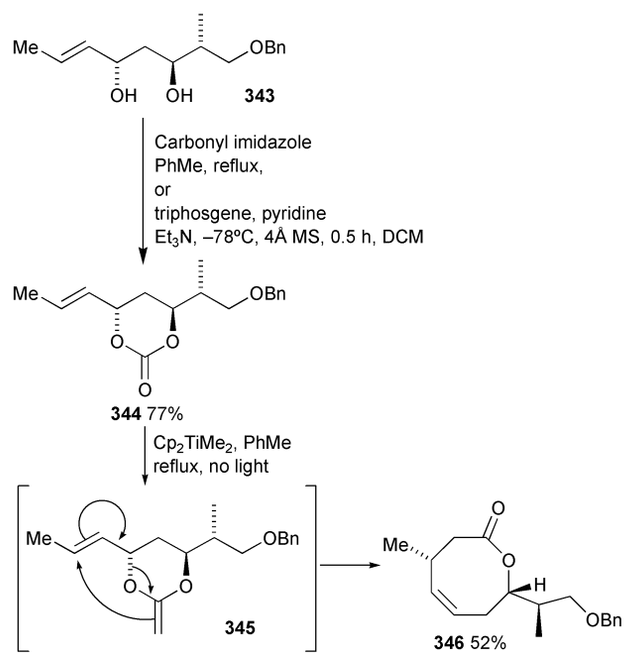
Scheme 142

the newly formed ring junction is a result of the thermodynamic preference for a *Z* double bond in the cyclooct-4-enone ring and the chair-like nature of the Claisen rearrangement's transition state. Later, Paquette *et al.* employed the same approach as an early step in their syntheses of (+)-epoxydictymene **342**.[167,168] In one of their two closely related routes to this compound, diastereoselective addition of vinyllithium **338** to aldehyde **339** followed by cyclisation gave lactone **340** with good diastereoselectivity (Scheme 143). Tebbe methylenation, Claisen rearrangement with concomitant reduction followed by protection then gave the tricyclic core **341** of (+)-epoxydictymene **342**.

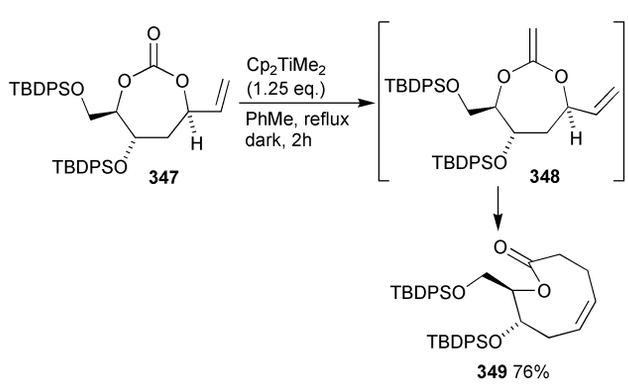


Scheme 143

Holmes and co-workers have used a tandem Petasis methylenation of cyclic carbonates and Claisen rearrangement to synthesise medium-sized lactones as single diastereomers.[67,68] In one example, diol **343** was converted into carbonate **344**. Petasis methylenation then gave 8-membered-ring lactone **346** presumably *via* ketene acetal **345** (Scheme 144).[67] In the same way 7-membered cyclic carbonate **347** gave 9-membered ring lactone **349**, *via* ketene acetal **348** (Scheme 145).[68] The researchers



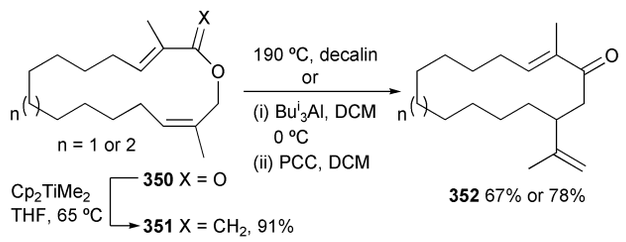
Scheme 144



Scheme 145

observed that when cyclic carbonate and lactone were present together addition of more Petasis reagent still gave predominantly lactone product, implying some selectivity for methylenation of carbonate in the presence of lactone.

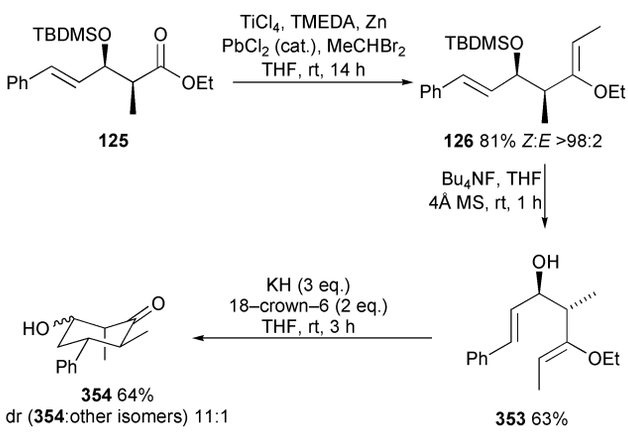
An alternative ring-contraction approach has been applied to the synthesis of macrocyclic ketones. This involves Petasis methylenation of macrocyclic lactones followed by a Claisen rearrangement to give a two-carbon atom ring contraction.[169] Yields are better for low temperature rearrangement–reduction induced by *i*-Bu_3Al followed by oxidation than for thermal rearrangement, as this avoids isomerization of the exocyclic enol ether to its endocyclic isomer. In one example, α,β-unsaturated ester **350** was methylenated to give enol ether **351**, which underwent Claisen rearrangement to give ketone **352** in 67% yield thermally, and in 78% yield by the two step procedure (Scheme 146).



Scheme 146

3.8.2 Cope rearrangement

We have developed a general method for the stereocontrolled synthesis of β-hydroxycyclohexanones from α,β-unsaturated aldehydes using four key reactions:[104,110,170] the aldol reaction, Takai alkylidenation, anionic oxy-Cope (AOC) rearrangement of acyclic enol ethers and intramolecular aldol reaction. In one example,[104] 2,3-*syn* protected aldol **125** was ethylidenated to give only the *Z*-enol ether **126** (Scheme 147, see also Scheme 69).



Scheme 147

Desilylation gave alcohol **353**. When alcohol **353** was deprotonated with potassium hydride–18-crown-6, it underwent AOC rearrangement. Acid quench then led to intramolecular aldol reaction to give predominantly the 2,5-*anti*, 5,6-*anti* cyclohexanones **354** in moderate yield.

3.9 Ring-closing metathesis (RCM) reactions

Over the last decade, ring-closing metathesis (RCM) of alkenes has become one of the most popular methods of forming hetero- and carbo-cycloalkenes, and a variety of transition metal complexes have been introduced to catalyse these reactions.[171–173] These include molybdenum complex **141** introduced by Schrock[174] and a range of ruthenium complexes **355**,[175] **356**[176] and **357**[177] developed by Grubbs (Fig. 2). In 1994 Grubbs and co-workers introduced a two step protocol for the synthesis of carbocyclic enol ethers and heterocycles from esters involving Tebbe methylenation or Takai alkylidenation followed by RCM mediated by the Schrock catalyst **141**.[178] Grubbs' own catalyst **355** failed to cyclise enol ethers.[178] In one example, the procedure was used in an efficient and convergent synthesis of antifungal phytoalexine **358** (Scheme 148). Coupling of acid chloride **359** and phenol

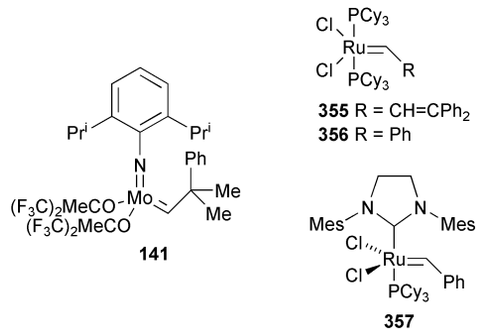
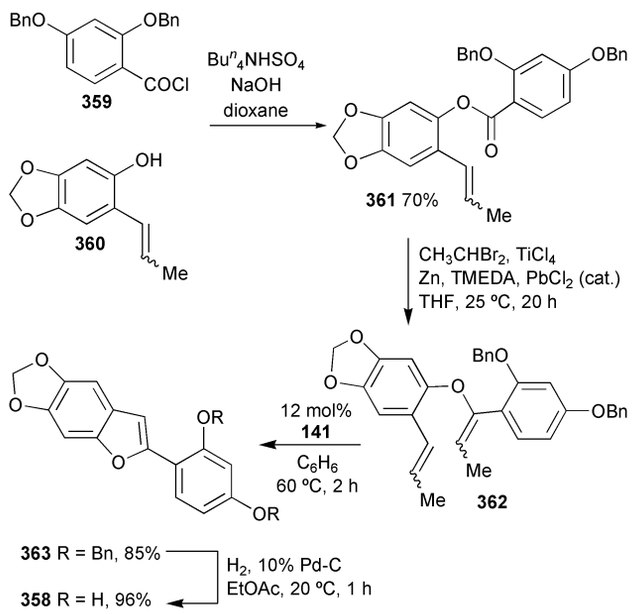
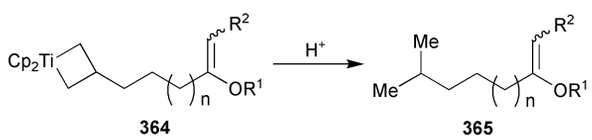


Fig. 2 Ring-closing metathesis catalysts



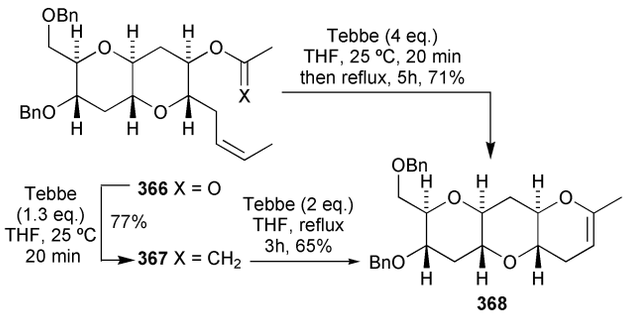
Scheme 148

360 gave ester **361**, which was smoothly ethylidenated under Takai conditions to give enol ethers **362**. RCM then gave benzofuran **363**, which was deprotected to give phytoalexine **358**. A temperature of 60 °C was used for the Tebbe methylenation of esters bearing a terminal alkene as titanacyclobutanes **364** were formed reversibly and these were stable at low temperature giving rise to methylated products **365** (Scheme 149). Later, Nicolaou took advantage of this side reaction



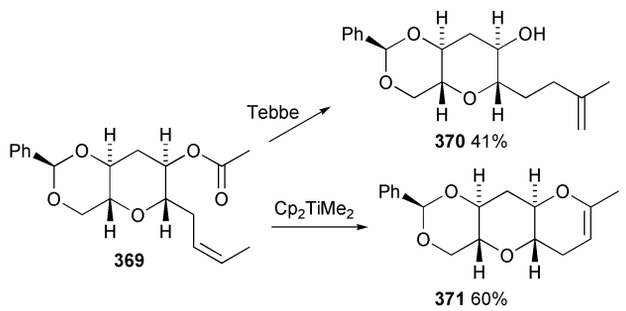
Scheme 149

and introduced a one-pot methylenation–RCM procedure that used Tebbe and Petasis reagents as both methylenating reagents and RCM catalysts.[179] Thus, Tebbe methylenation of ester **366** was carried out at room temperature and heating the resulting acyclic enol ether **367** with the same reagent gave cyclic enol ether **368** (Scheme 150). A combination of the two steps in a single pot procedure proved convenient. The Petasis methylenation is preferable in cases where the product enol ether is susceptible to hydrolysis and



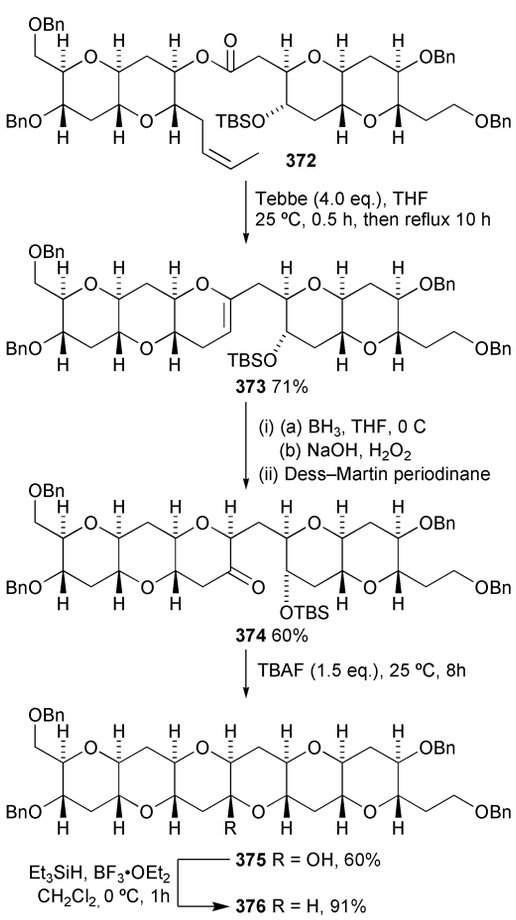
Scheme 150

methylenation to give an alkene. Thus, ester **369** gives only alkene **370** with the Tebbe reagent, but the desired cyclic ether **371** when heated with dimethyltitanocene (Scheme 151).



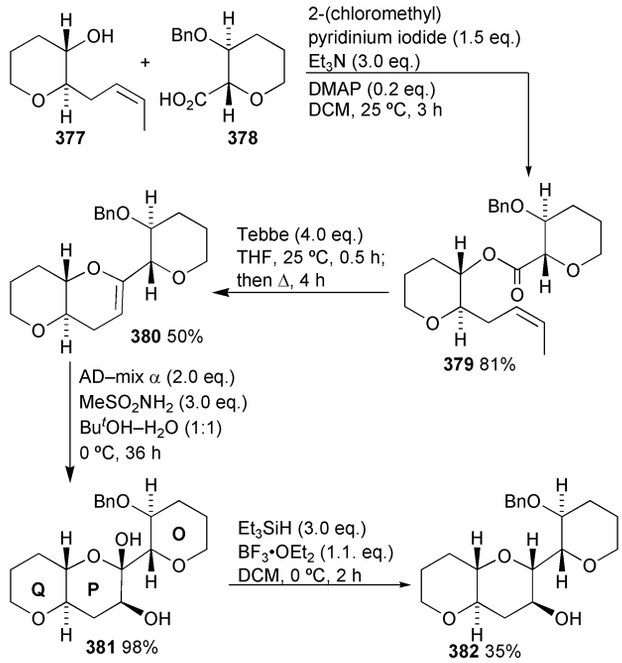
Scheme 151

Nicolaou's team showed that the product cyclic ethers could be further manipulated either by hydroboration–oxidation[179] or by Sharpless dihydroxylation[180] to allow the synthesis of marine polycyclic ether toxins. In one example,[179] ester **372** was converted into enol ether **373**, which was oxidised to ketone **374** (Scheme 152). Cyclisation and reduction then gave lactol **375**.



Scheme 152

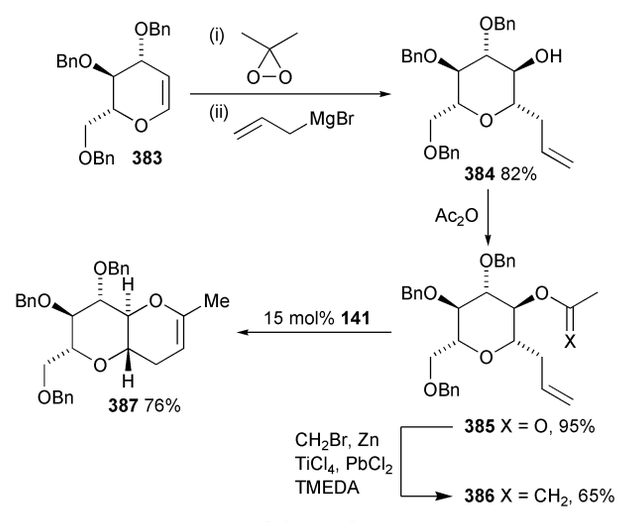
Finally, reduction produced pentacyclic ether **376**. In another example,[180] the OPQ ring system (minus one methyl group) of maitoxin was made by coupling alcohol **377** and acid **378** to give ester **379**, which was subjected to methylenation–RCM to give cyclic ether **380** (Scheme 153). Sharpless asymmetric



Scheme 153

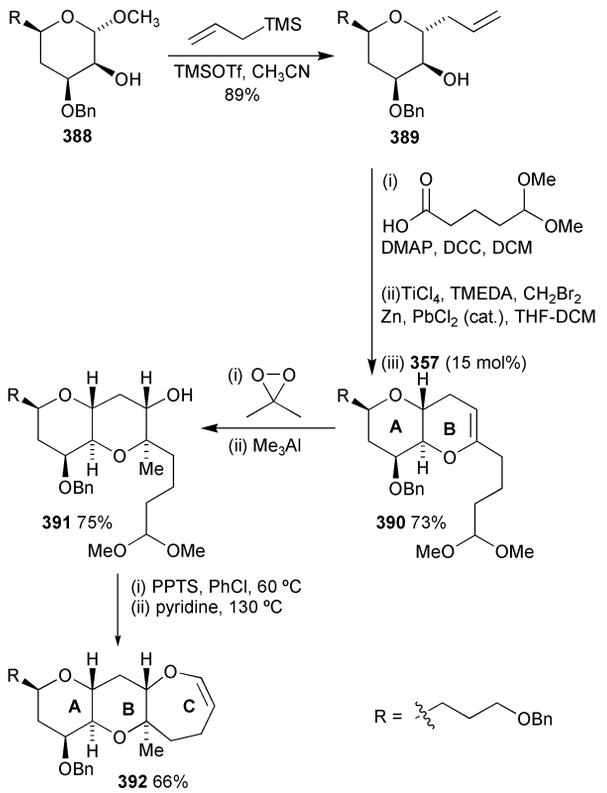
dihydroxylation gave diol **381**, which was reduced to complete model compound **382**.

In 1998 Rainier and Allwein introduced an iterative approach to the synthesis of fused ethers (Scheme 154).[181] In one example,



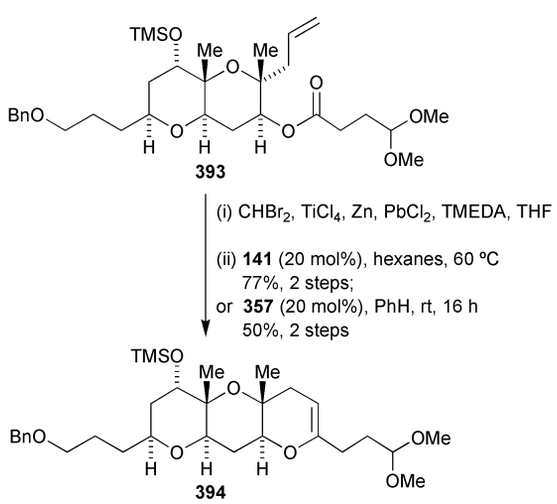
Scheme 154

epoxidation and allylation of glucal **383** gave alcohol **384**, which was then converted into ester **385**. Following Grubbs two-step protocol (Nicoloau's one pot method giving lower yields), methylenation of ester **385** using Takai's procedure to give enol ether **386** was followed by RCM with Schrock's catalyst **141** to give a new cyclic enol ether **387**, which was ready for a repeat of the procedure. The same researchers have applied their iterative procedure to the formal total synthesis of (±)-hemibrevetoxin B.[39,127] Allylation of acetal **388** gave alcohol **389**, which was esterified and subjected to methylenation followed by ring-closing metathesis to give enol ether **390** (Scheme 155). Both Schrock catalyst **141** and modified Grubbs catalyst



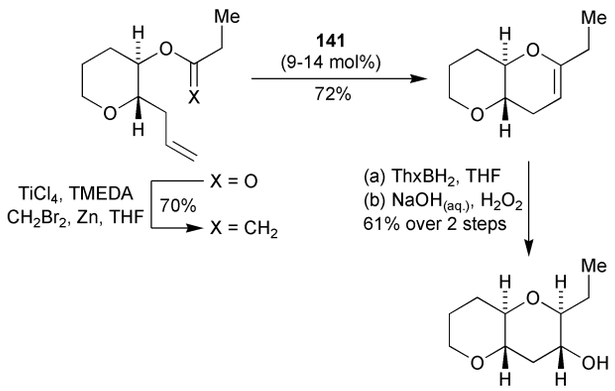
Scheme 155

357 effected the transformation, with the latter giving higher yields, but Grubbs catalyst **356** was unsuccessful. Epoxidation and methylation completed the B ring of (±)-hemibrevetoxin B. Methylenation of a formate ester would have been required to make the C-ring by Rainier's iterative procedure, but such reactions are low yielding, so an alternative approach was used to convert alcohol **391** into enol ether **392**. In their synthesis of the A–D ring system of gambierol,[125] Cox and Rainier found that although their standard procedure was effective in the construction of the A and B rings, preparing the substrate **393** for C-ring construction from the A,B-dihydropyran required a more convoluted Claisen rearrangement sequence. However, Takai methylenation and RCM of ester **393** gave dihydropyran **394**, with the Schrock catalyst **141** proving superior in this case (Scheme 156). Methylenation of formate esters was again avoided in the synthesis of the D-ring.



Scheme 156

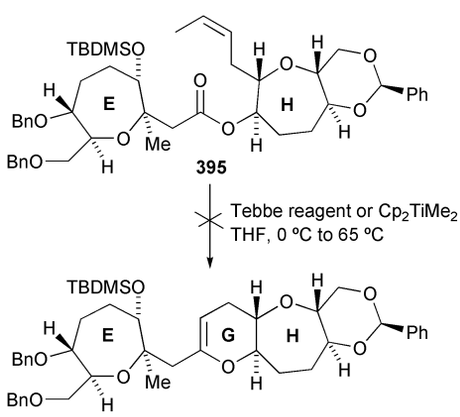
Clark has developed a general synthetic strategy for the construction of polycyclic ethers that involves sequential acylation, Takai methylenation, RCM catalysed by the Schrock catalyst **141** (Grubbs catalyst **356** was ineffective) and stereoselective hydroboration (Scheme 157).[182] The route, which is related to



Scheme 157

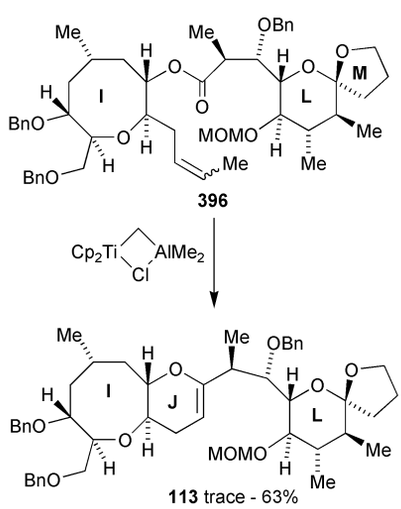
that of Nicolaou (Scheme 152), is effective for six- and seven-membered fused cyclic ethers but not for eight-membered rings. Interestingly, methylenation of formyl esters is avoided by using mercury(II) acetate-catalysed interconversion of enol ethers.[51]

Yamamoto and co-workers found Nicolaou cyclisation of ester **395** was ineffective and used a different approach to the synthesis of the EFGH ring framework of gambierol (Scheme 158).[183] The Grubbs two step procedure was not attempted.



Scheme 158

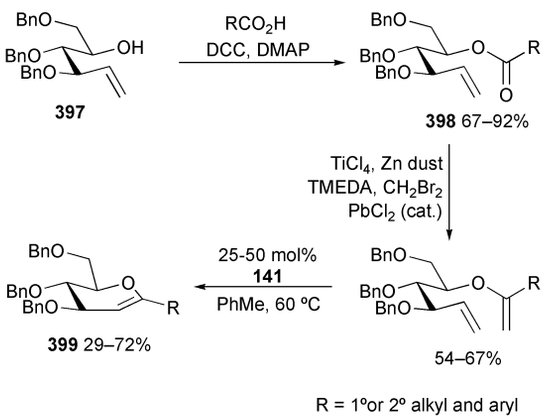
Similarly, Hirama and co-workers found that tandem methylenation–RCM can be difficult when the ester is sterically hindered and conversion of ester **396** into enol ether **113** proved capricious (Scheme 159).[98] However, the intramolecular Takeda



Scheme 159

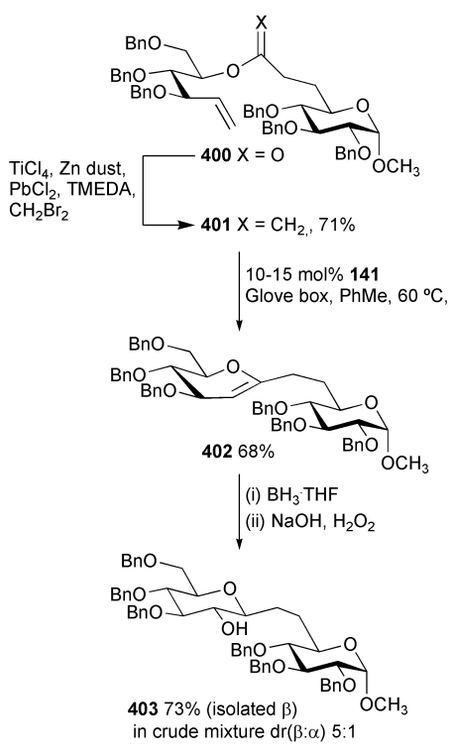
alkylidenation described in Section 2.3 above gave the same enol ether **113** (Scheme 61) in good yield and allowed the synthesis of the HIJKLM ring segment of ciguatoxin CTX3C.

Postema and co-workers introduced a flexible approach to C-1 glycals in which alcohol **397** is esterified to give esters **398** (Scheme 160).[105] Takai methylenation followed by RCM using



Scheme 160

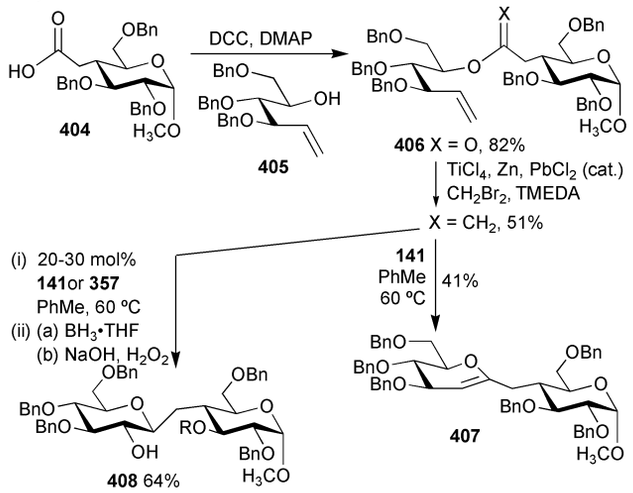
the Schrock catalyst **141** in a glove box then gives the glycals **399**. A range of C-1 alkyl and aryl glycals have been synthesised, but attempts to make C-1 vinyl and *tert*-butyl glycals were unsuccessful. A variety of *C*-1 disaccharide glycals have been made by Takai methylenation of esters of C-5- and C-6-monosaccharides, followed by RCM mediated by the Schrock catalyst **141**.[124,126] Grubbs catalyst **356** was less effective. In this way, ester **400** was methylenated to give enol ether **401**, cyclised to glycal **402** and then converted to the corresponding *C*-saccharide **403** in good yield (Scheme 161).[124]



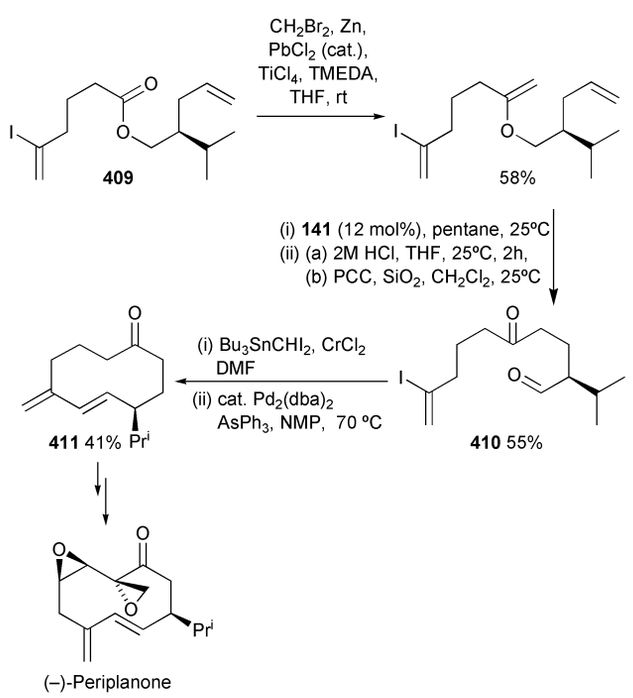
Scheme 161

β-*C*-Disaccharide **408** was synthesised by coupling carboxylic acid **404** with secondary alcohol **405** to give ester **406**, followed by Takai methylenation (with a large excess of reagent) and a one pot RCM–hydroboration–oxidation (Scheme 162).[184] 20–30 mol% of either Schrock catalyst **141** or modified Grubbs catalyst **357** was required for the RCM and it was best not to isolate the sensitive glycal intermediate **407**.

Hodgson and co-workers used Takai methylenation of ester **409**, followed by RCM, hydrolysis and oxidation to give aldehyde **410**, which was then converted into cyclic ketone **411**, thus completing a formal synthesis of (−)-periplanone B (Scheme 163).[115,116]

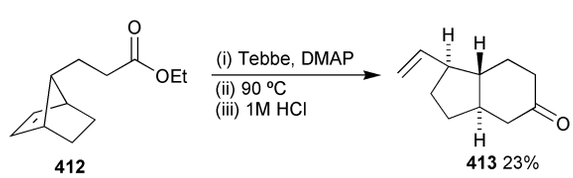


Scheme 162



Scheme 163

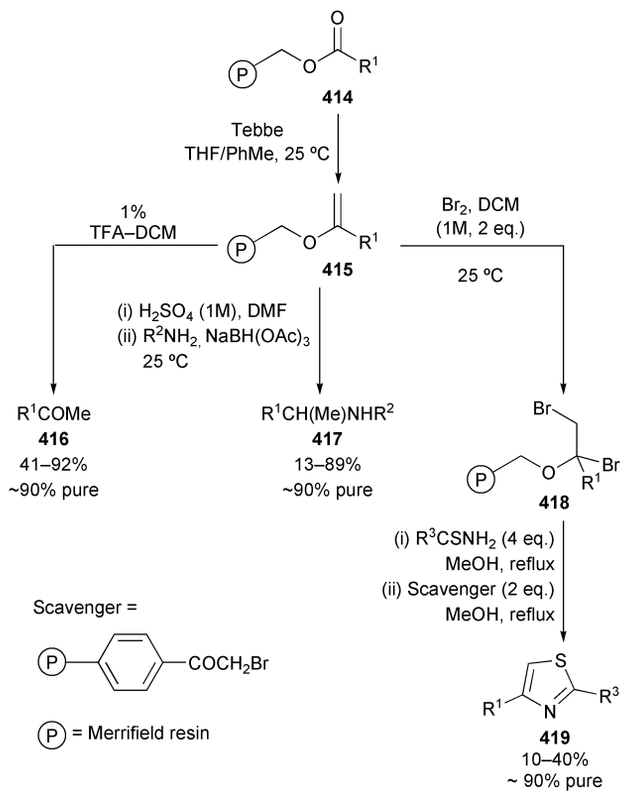
Ring-opening metathesis of strained alkenes can be induced by the Tebbe reagent. In work reminiscent of Grubbs' synthesis of (±)-$\Delta^{9(12)}$-capnellene,[38] Halterman and Ramsey showed that when ester **412** was methylenated at low temperature with the Tebbe reagent and then heated with the same reagent, ring-opening metathesis of the norbornene ring occurred followed by ring-closing metathesis to give a more stable fused bicycle **413** (Scheme 164).[185] Hydroindanone **413** was isolated in poor yield but only a single isomer was formed.



Scheme 164

4.0 Solid-phase reactions

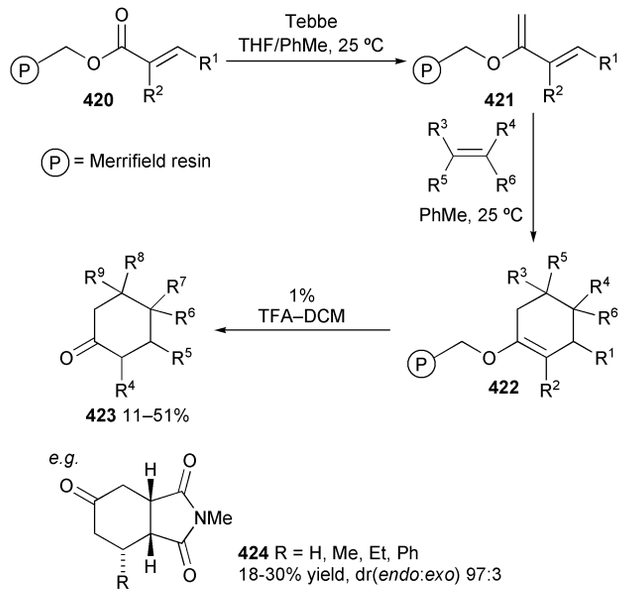
Titanium alkylidene reagents have been used to convert relatively acid stable Merrifield resin-bound esters into acid-sensitive resin-bound enol ethers. This switch in the nature of the linker ensures the purity of products released from resin under mild acid conditions as any unreacted ester remains attached to resin (a "chameleon catch" strategy). In 1998, Barrett, Commerçon, Smith and co-workers showed that Tebbe methylenation of Merrifield resin-bound esters **414** gives resin-bound enol ethers **415**, which can be cleaved with mild acid to give pure methyl ketones **416** in moderate to good yield (Scheme 165).[28] Tebbe



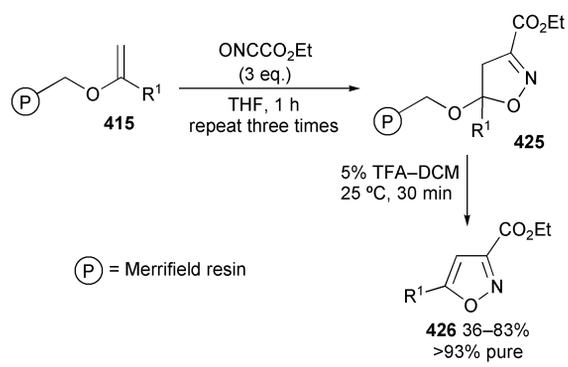
Scheme 165

methylenation is superior to Petasis methylenation in this system and Wang resin-bound esters may also be methylenated. The switch of the linker from acid-stable to acid-sensitive ensures the purity of the ketones **416**, as any unreacted ester **414** is unaffected by mild acid. Resin-bound enol ethers **415** can also be converted into amines **417**, or brominated to give resin-bound dibromides **418** and converted into thiazoles **419** using thioureas (excess thiourea is removed with a scavenger resin). When resin-bound α,β-unsaturated esters **420** are used, the resulting dienes **421** will undergo Diels–Alder reactions with *N*-methylmaleimide, 2-chloroacrylonitrile, methyl vinyl ketone, dimethyl fumarate or 2-ethylacrolein, and subsequent treatment of the cycloadducts **422** with acid leads to release of cyclic ketones **423** (Scheme 166). Generally, *N*-methylmaleimide adducts **424** are produced with high *endo*-selectivity. Resin-bound enol ethers **415** also undergo 1,3-dipolar cycloadditions with ethyl cyanoformate *N*-oxide to give supported isoxazoline derivatives **425** that can be cleaved from resin in the same way to give isoxazoles **426** (Scheme 167).[186] When the starting ester **414** bears an aryl iodide or aryl bromide, Suzuki cross-coupling is possible prior to the cycloaddition. The best example involved conversion of aryl bromide **427** into biaryl **428**, followed by cycloaddition and release from resin to give isoxazole **429** in good yield and about 90% purity (Scheme 168).[186]

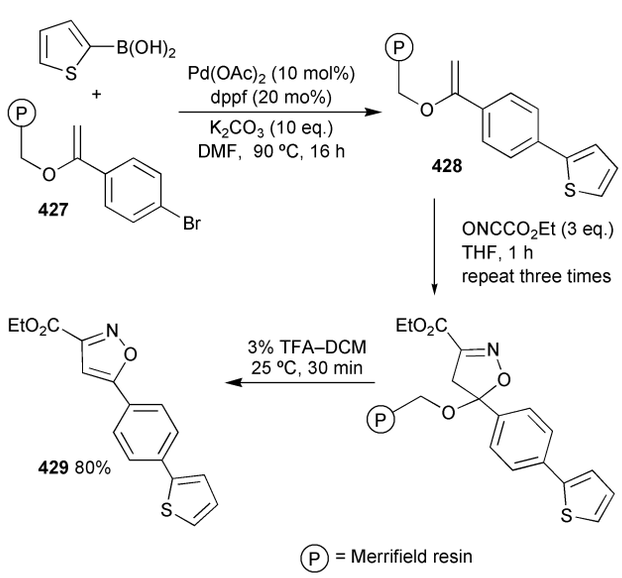
We have shown that Takeda alkylidenation can be carried out on solid phase.[92,93] This not only has the advantage that products of alkylidenation are easily purified, but also allows



Scheme 166

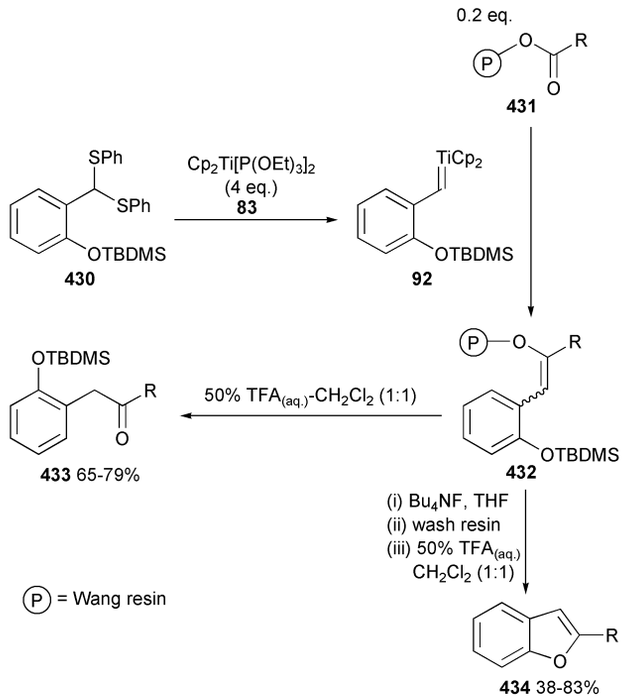


Scheme 167



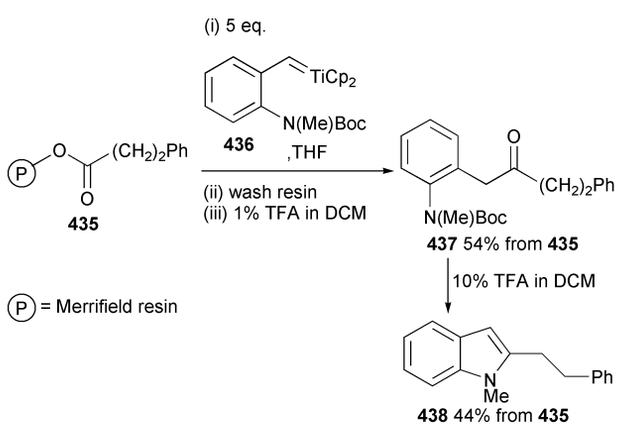
Scheme 168

the introduction of functionality in the alkylidenation step. Thus, thioacetal **430** was treated with low valent titanium complex **83** to generate a titanium reagent, presumably titanium benzylidene **92** that benzylidenated Wang resin-bound esters **431** to give enol ethers **432** (Scheme 169).[93] Treatment with acid, released ketones **433** in good yield and high purity, while deprotection of the phenolic hydroxy on resin and then treatment with acid gave benzofurans **434**. The strategy of introducing a



Scheme 169

masked nucleophile in the alkylidenation step[93,111] was extended to nitrogen nucleophiles.[92] Unfortunately, we were unable to generate an effective benzylidenating agent from a thioacetal bearing an unprotected primary amino group. However, Merrifield resin-bound ester **435** was successfully benzylidenated with a titanium benzylidine **436** bearing a tertiary carbamate group (Scheme 170).[92] Following resin washing,

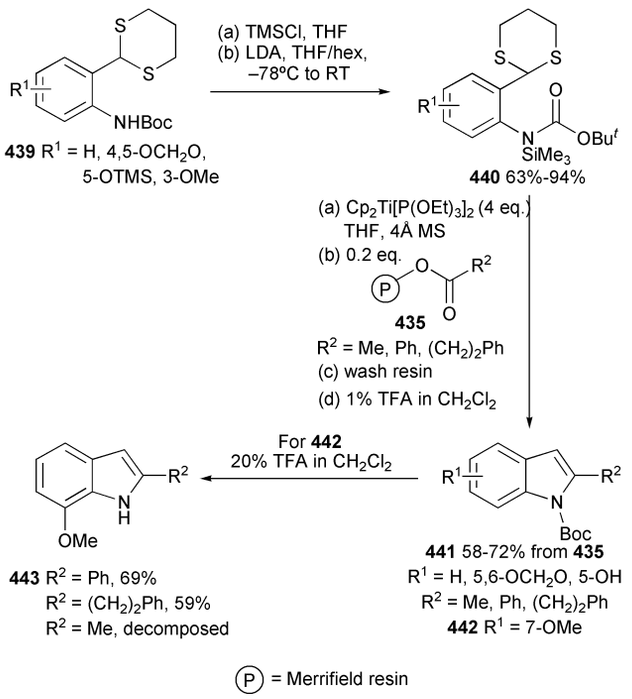


Scheme 170

treatment with mild acid released ketone **437** in high purity since the acid conditions were too mild to affect any unreacted ester **435**. Treatment with stronger acid then gave clean *N*-methylindole **438**. The discovery that a carbonyl group can be tolerated within a titanium alkylidene reagent was significant, and we adapted our route to synthesise *N*-Boc and *N*-H indoles, by silylating secondary carbamates **439** (Scheme 171). Titanium benzylidenes were generated from the silylated carbamates **440** and reacted with Merrifield resin-bound esters **435**. Resin washing and treatment with acid gave *N*-Boc indoles **441** in good yield (based on resin loading) and high purity. Partial deprotection of the 7-methoxyindoles **442** was observed, so these were treated with stronger acid to give N–H indoles **443**.

5 Summary

A wide range of carbonic and carboxylic acid derivatives can be alkylidenated with titanium reagents. However, no reagent



Scheme 171

exists for the conversion of acid halides into vinylic halides. The alkylidenating species in most of the titanium reagents are Schrock carbenes, but Takai alkylidenation may involve a 1,1-bimetallic. While methylenation of carboxylic esters and lactones has been widely applied in the synthesis of complex organic compounds, methylenation of other carboxylic acid and carbonic acid derivatives is under-explored. Furthermore, synthetic methods based on alkylidenation rather than simple methylenation of carboxylic acid derivatives are much less widespread, and more research in this area is needed.

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