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Titanium carbenoid reagents for converting carbonyl groups into alkenes

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Contents

1. Introduction

Titanium-based carbenoids are commonly used to convert carbonyl groups into alkenes. They fall into two main categories: those in which the active species is a titanium alkylidene complex **1** or **2**, and those which are considered to be 1,1-bimetallics **3** (Fig. 1). The titanium alkylidene complexes **1** and **2** are typical Schrock carbenes, being electron-deficient complexes of an early transition metal in a high oxidation state, and as such they are nucleophilic in character (interacting primarily through their HOMO).[1,2] They are also capable

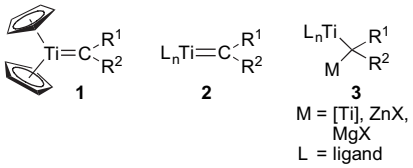

Figure 1.

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of inducing alkene metathesis, although the alkylidene complexes of the middle transition metals, molybdenum and ruthenium, are more effective metathesis catalysts.[3] The 1,1-bimetallics **3** have similar reactivity towards carbonyl compounds, but do not induce alkene metathesis.

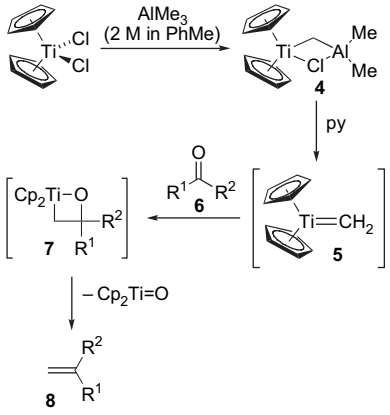
Titanium-based alkylidenating reagents have been employed to prepare synthetic intermediates that cannot be accessed effectively using other more traditional alkenation methods, e.g., Wittig and Horner–Wadsworth–Emmons alkenation,[4,5] Julia and modified Julia alkenation,[6] or Peterson alkenation.[7] When these other alkenation methods fail, it is often due to steric interactions between substrate and reagent, or the basicity of the reagent used. Titanium alkylidenating reagents have the unique advantage of being non-basic. Consequently, they neither epimerize sensitive chiral centres α to carbonyl groups nor facilitate destructive retro-Michael pathways. They are also relatively small in size, and are able to react with more sterically hindered carbonyl groups. However, their most notable property is that their substrate range is wider: carbonyl compounds such as esters, thioesters, amides, carbonates and ureas are all substrates for alkylidenation.

We have previously comprehensively reviewed the use of titanium reagents to alkylidenate carboxylic acid and carbonic acid derivatives (1993–end of July 2002).[8] We now discuss how such reagents have been further developed and employed to enable synthetic strategies in the last three years (2002–2005 inclusive). Unlike the previous article, where alkylidenations of aldehydes and ketones were omitted, all examples of carbonyl alkylidenations are included here. The only exceptions are McMurry couplings, which are not discussed, even though titanium carbenoids are believed to be intermediates in some cases.[9] Since we have already discussed the carbenoid reagents in detail in the previous review, we provide here only a short introduction to each type of reagent, concentrating on what is new, before turning our attention to the synthetic strategies that they enable.

2. Reagents

2.1. Tebbe reagent

In 1978, Tebbe and co-workers showed that the titanium–aluminium complex **4** (now termed the Tebbe reagent) would methylenate carbonyl compounds when activated with a suitable Lewis base (e.g., pyridine or THF, Scheme 1).[10] Pine and co-workers have provided a definitive procedure for the generation of this reagent (from Cp_2TiCl_2 with $AlMe_3$ in toluene) for immediate use in methylenation of carbonyl compounds.[11] However, occasionally, a purified, standardised toluene solution of the Tebbe reagent prepared by Paquette's earlier procedure[12] gives higher yields.[13] The reagent is now commercially available as a solution in toluene. The reactive species believed to be responsible for alkenation is titanocene methylidene **5** (a Schrock carbene), which is generated by the Lewis-base promoted elimination of $AlClMe_2$ (Scheme 1) from bimetallic **4**. Titanocene methylidene **5**, which is nucleophilic at carbon and electrophilic at titanium, reacts with carbonyl compounds **6** to form oxatitanacyclobutanes **7**, which decompose with elimination of $Cp_2Ti{=}O$ to give alkenes **8**. A major driving force for this transformation is most likely the formation of a strong Ti–O double bond, which renders the reaction irreversible. The Tebbe reagent methylenates a broad range of carbonyl compounds including aldehydes, ketones, esters, thioesters, amides and carbonates. However, carbonyl compounds with good leaving groups, such as acid chlorides and anhydrides, are not good substrates for the Tebbe reagent as they undergo other reactions. The range of substrates is summarised in Table 1, and a large number of examples demonstrating the substrate range for this reagent can be found in our previous review.[8]



Scheme 1.

Table 1. Methylenation of carbonyl compounds using Tebbe reagent

Carbonyl groups successfully methylenated
(i) Aldehydes and ketones into alkenes[10,20]
(ii) Carboxylic acid derivatives into 1-heteroalkenes:

X=OR (including α,β-unsaturated esters,[21] and unstrained lactones),[11] NR (including *N*-acyl heterocycles[22]),[20] SR (only one example and in low yield)[23]
(iii) Carbonates into ketene acetals[16]

Carbonyl groups where reaction gives undesired products
Acid chlorides (give titanium enolates),[24,25] anhydrides and imides react similarly[26]
β-Lactones[27,28]

Functional groups shown to be tolerated in ester substrates
Acetals including benzylidene acetal,[29] MOM[30] and acetonides[30]
Alkenes including dienes and terminal alkenes[31–33]
Aromatics including unprotected indoles[34]
Carbamates including NHBoc[29]
Ethers including benzyl[35] and trityl ethers[36]
Haloalkenes and aryl halides including vinyl fluorides,[37] vinyl chlorides,[37] aryl bromides[38] and aryl iodides[34]
Selenoglycosides[39] and thioglycosides[40]
Silyl ethers including TMS,[36] TBDMS[41] and di-*tert*-butylsilylene[29]
Sulfonamides[42]

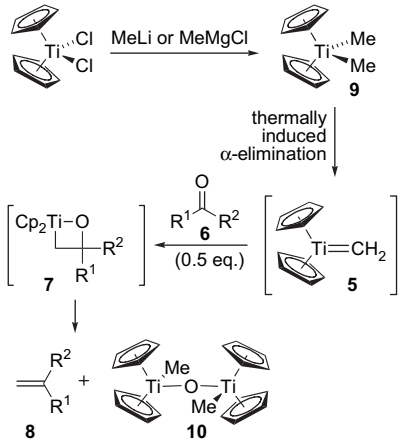
The reactivity profile of the Tebbe reagent (when activated by Lewis base) is as expected for a Schrock carbene, i.e., more electrophilic carbonyl groups react faster. Indeed, there are many examples where the less electrophilic of two carbonyl groups is left untouched when 1 equiv of the reagent is used. Selective methylenation of the less sterically hindered of two carbonyl groups is also possible (e.g., a less sterically hindered ester in the presence of a *tert*-butyl ester[14])

and this can in rare cases override the electronic preference (e.g., a carbonate has been selectively methylenated in the presence of an enol acetate).[15] The Tebbe reagent can also catalyse alkene metathesis and Grubbs and co-workers showed that titanacyclobutanes formed from the Tebbe reagent could be used as Lewis-acid free alkylidenating agents.[16] Although this property has been exploited,[17–19] metathesis does not generally compete with methylenation of carbonyl groups. Functional groups that have been tolerated during the methylenation of esters are shown in Table 1.

The main advantages of the Tebbe reagent are that it methylenates a range of carbonyl compounds, and that the reactive titanocene methylidene **5** is generated and reacted at low temperature. Unfortunately, the Tebbe reagent is limited to methylenation. Furthermore, the bimetallic **4** and the by-products formed by its decomposition are Lewis acidic, and the Tebbe reagent is air and moisture sensitive.

2.2. Petasis reagents

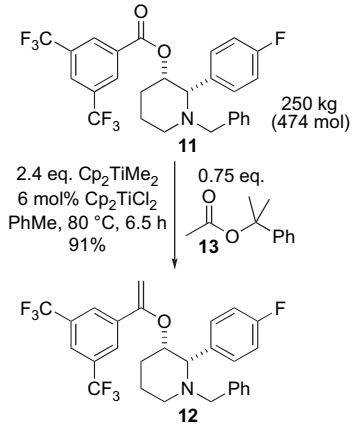
Petasis and Bzowej developed dimethyltitanocene (DMT) **9** as an alternative to the Tebbe reagent (Scheme 2).[43] The reagent is easily prepared by reacting MeLi[43] or preferably MeMgCl[44] with Cp_2TiCl_2; definitive procedures for the preparation, storage and use of DMT **9** on a small[44] and a multikilogram scale[45] have been provided by Payack's team at Merck Research Laboratories. Unlike the Tebbe reagent, DMT **9** is relatively stable to moisture and air. For prolonged storage, DMT **9** should be stored refrigerated as a solution (10 wt % in toluene or THF) as it is unstable in the solid state and decomposes exothermically. The reactive titanocene methylidene **5** is generated from DMT **9** in the presence of the carbonyl compound **6** by heating in toluene or THF, and reacts immediately via oxatitanacyclobutane **7** to give the alkene **8** and titanocene oxide (Scheme 2). Payack recommends quenching the methylenation reaction with a mixture of aqueous sodium bicarbonate and methanol and stirring for 14 h at 40 °C to convert titanium residues into insoluble material that can be removed by filtration.[44] Ethanol can be used instead of methanol with stirring for 6 h at 60 °C.[45] The mechanism of methylenation has been elucidated by Hughes et al.,[46] who have shown that the titanocene methylidene **5** is produced by a heat-induced α-elimination, which is rate determining for the alkylidenation reaction as a whole. Recently, Meurer et al. have confirmed the second and third steps of the mechanism by spectroscopically characterising the oxatitanacyclobutane intermediate **7** and observing its dissociation into $Cp_2Ti{=}OH^+$ and $R^1R^2CCH_2H^+$ using atmospheric pressure chemical ionisation mass spectrometry (APCI-MS) and tandem mass spectrometry (APCI-MS/MS).[47]



Scheme 2.

On a large scale, it is best to use 2 equiv of DMT as the titanocene oxide reacts with DMT **9** to give an oxo-bridged titanocene dimer **10**.[45] Clean formation of this dimeric by-product improves yields by aiding purification and its formation can be encouraged by the addition of a few mole per cent of Cp_2TiCl_2 to the DMT solution to give $Cp_2TiMeCl$ by ligand exchange.[45] At the end of the reaction, the titanium-containing dimer **10** is easily precipitated using heptane. Importantly for industrial-scale synthesis, the recovered dimer **10** can easily be converted into Cp_2TiCl_2 by HCl in THF or toluene, allowing recycling of the titanocene.[45]

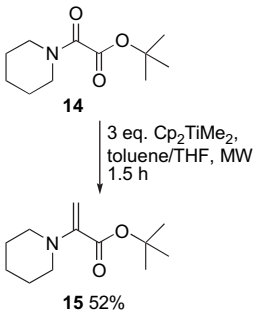
The titanium methylidene **5** is extremely reactive, and if there is no carbonyl compound present, will decompose by other mechanisms. This can sometimes be detrimental as the product alkene may react when the carbonyl substrate is exhausted. When carrying out the methylenation of ester **11** to give enol ether **12** on an industrial scale, Payack's team overcame this problem by spiking the reaction with a sacrificial ester **13** (Scheme 3). Bulky tertiary alkyl ester **13** is more reactive than the enol ether **12**, but less reactive than the starting ester **11**.[45] Addition of 0.75 equiv of the ester **13** prevented decomposition of the product enol ether **12** for as long as 24 h of additional heating following completion of the reaction (6.5 h). A similar strategy was employed by Smith and co-workers in their second-generation synthesis of phorboxazole A, when they used ethyl pivalate as a sacrificial ester and a fairly concentrated solution (0.7 M) of DMT in THF to ensure methylenation of a lactone in the presence of an *exo*-methylene substituent on a tetrahydropyran unit.[48]



Scheme 3.

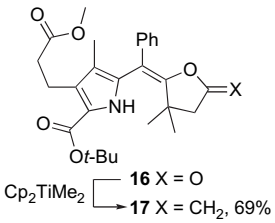
Microwave-assisted generation of the titanocene methylidene is a useful innovation as it is quick, clean and requires fewer equivalents of reagent.[49,50] It has been employed by Gallagher and co-workers for conversion of oxalate derivatives into pyruvate-based enol ethers and enamines.[50] The chemistry exploits the unreactivity of *tert*-butyl esters to

allow selective methylenation of primary alkyl esters and even tertiary amides, e.g., amide **14** was converted into enamine **15** in respectable yield (Scheme 4). This latter reaction is exceptional as titanocene methylidene is a nucleophilic reagent and without a strong steric bias, the most electrophilic carbonyl group reacts first, e.g., aldehydes and ketones react faster than esters,[51] amides[52] and carbamates.[51]



Scheme 4.

Interestingly, under normal thermal conditions, selective methylenation of the enol-lactone in compound **16** was possible, giving enol ether **17** with very little double methylenation product (Scheme 5),[53] and there is an example of selective methylenation of a six-membered lactone in the presence of an acetate group.[54]



Scheme 5.

Petasis methylenation is now very popular for a number of reasons. DMT **9** is easy to prepare, and is relatively air and moisture stable. It will methylenate a wide range of carbonyl groups effectively including carboxylic acid and carbonic acid derivatives that cannot be methylenated by other reagents (see Table 2). The reactions tend to be very clean and the work-ups simple with titanium-containing impurities being removed by precipitation and filtration. The reaction conditions are non-basic and unlike the Tebbe reagent, no Lewis acid is involved. Thus, epimerization of chiral centres is avoided and a range of functional groups are tolerated (Table 2).

Functionalised Petasis reagents can be prepared (Fig. 2), but these reagents are only useful for alkylidenation of carbonyl groups if they cannot undergo a fast β-elimination process, otherwise this occurs in preference to the α-elimination required to generate the titanium alkylidene complex. Bis-(benzylic)titanocenes **18**,[71] bis(trimethylsilylmethyl)titanocene **19** (and related complexes **20** and **21**, which is a Grubbs-type reagent[16])[72–74] and bis(cyclopropyl)titanocene **22**[75] are all converted into Schrock carbenes upon heating (Fig. 2), and can effectively alkylidenate carbonyl

Table 2. Methylenation of carbonyl compounds using Cp_2TiMe_2 (Petasis methylenation)

Carbonyl groups successfully methylenated
(i) Aldehydes into alkenes[43]
(ii) Ketones into alkenes[43]
(iii) Carboxylic acid derivatives into 1-heteroalkenes:

X=OR (including α,β-unsaturated esters,[55] alk-2-ynoates,[56] formate esters,[57] lactones[56] and strained lactones[28,27,58])[56]
X=$OSiR_3$[56]
X=O_2CR (single or double methylenation)[56,59]
X=NR (including strained lactams[60,61])[56]
X=N(R)COR (single or double methylenation)[56]
X=$N(R)CO_2R$[62] (including lactam[60] and strained lactam derivatives[63])
X=$NRSO_2Me$ (R is alkyl, but not aryl)[62]
X=SR[56]
X=SCOR (single or double methylenation)[59]
X=SeR,[56] SiR_3[56]
(iv) Carbonates into ketene acetals[56]

Carbonyl groups where reaction gives undesired products
Acid chlorides, *N*-sulfonylacetanilides[62]

Functional groups shown to be tolerated in ester substrates
Aromatic groups and alkenes (including terminal alkenes)[43,56,64]
Alkynes (susceptible to [2+2] additions, but some tolerated)[49,56]
Alkyl and aryl halides including alkyl bromides[65] and aryl fluorides[44]
Ethers including benzyl[66] and *p*-methoxybenzyl ethers[64]
Silyl ethers including TMS,[67] TBDMS,[68] TBDPS[64] and TIPS[67]
Amines including benzylamines[69] and oxazoles[64]
Acetals including MOM[70]
Bulky esters, e.g., *tert*-butyl esters[50]

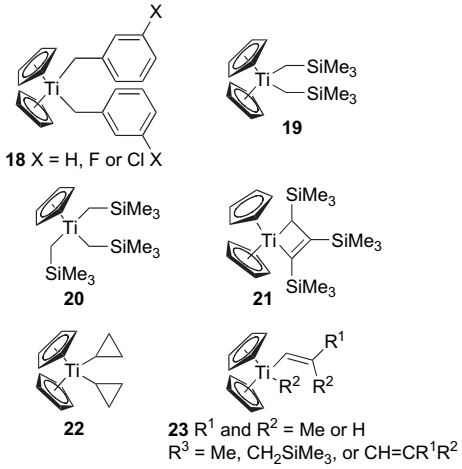
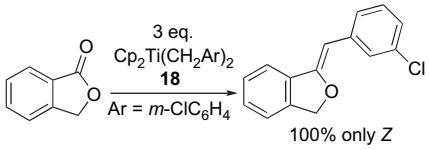
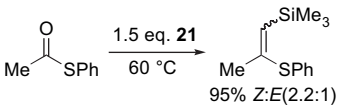


Figure 2.

compounds (e.g., Schemes 6 and 7). Similarly, bis(vinylic)-titanocenes **23**[76] can convert aldehydes and ketones into allenes. Functional groups in benzylidene reagents **18** are limited to groups that are tolerated in the organomagnesium or organolithium compounds used to prepare them. Although potentially useful, complexes **18**–**23** have not been much exploited during the current review period.



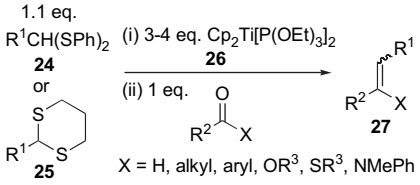
Scheme 6.



Scheme 7.

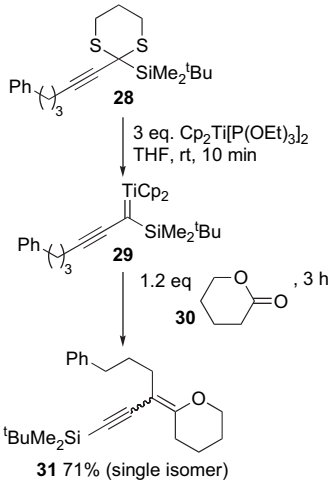
2.3. Takeda alkylidenation

A major breakthrough in the use of titanium alkylidene reagents came when Takeda and co-workers discovered that the easily accessible thioacetals **24** and **25** can be reduced by a low-valent titanium reagent **26** to give Schrock carbenes that will alkylidenate aldehydes,[77] ketones,[77] esters,[77] lactones,[77] thioesters[78] and *N*-methylanilides[79] (Scheme 8).



Scheme 8.

The method has the advantage of tolerating hydrogens on the carbon atom β to the titanium atom in the Schrock carbene. As with Takai reagents (see below), control of the alkene geometry is governed by steric factors so that the *Z*-isomers of enol ethers **27** (X=OR) and vinyl sulfides **27** (X=SR) are produced with moderate to excellent selectivity (62:38 to completely *Z*), depending mainly on the bulk of R^1 and R^2. Lactones are good substrates (Scheme 9).[77] Benzamides produce enamines **27** (X=NMePh) as single geometrical isomers, reportedly the *Z*-isomer.[79] The few drawbacks of the method are that methylenation is ineffective, and stereoselectivity in alkylidenation of aldehydes and ketones is poor. The diphenyldithioacetals **24** are more easily reduced than the dithianes **25** and so a wider spectrum of alkylidenating reagents can be prepared from the former. However, 2-vinyl- and 2-aryl-1,3-dithianes are more easily prepared than the corresponding diphenyldithioacetals and are effective substrates because of their allylic and benzylic nature, respectively. 2-Silyl-2-alkynyl-1,3-dithianes undergo an allylic rearrangement when



Scheme 9.

treated with the low-valent titanium complex **26** and react with esters to give tetrasubstituted alkenes as single geometrical isomers (although which geometry is favoured is not clear), e.g., the Schrock carbene **29** generated from dithiane **28** reacted with lactone **30** to give the enol ether **31** as a single isomer (geometry not known).[80,81] Ketones undergo the same reaction with slightly lower stereoselectivity.

A distinct advantage of the Takeda procedure is that functionality can be introduced by the titanium alkylidene complex and effective alkylidenating reagents have been generated from a range of functionalized thioacetals **32**–**39** (Fig. 3). Thus, thioacetals **32** give allylsilanes,[82] triphenyltrithioorthoformate **33** introduces a vinyl sulfide functionality,[83] and dithiorthoformates **34** give enol ethers.[83,84] Hartley and co-workers have used functionalized benzylic and homobenzylic thioacetals **35**–**38** in the solid-phase synthesis of bicyclic aromatic heterocycles (see Section 3.12),[85–89] and simple benzylic thioacetals **39** were used by Knaus' group in the synthesis of alkenes.[90] Aryl bromides react with the low-valent titanium used to generate the titanium alkylidene complex,[86] and although aryl chlorides are sometimes tolerated,[90] they can suffer dehalogenation by the low-valent titanium complex **26**.[86] Interestingly, the α-alkoxymethylidene titanocenes derived from thioacetals **34** can contain terminal alkene units. This is in contrast to other thioacetals containing terminal alkenes, which cyclise smoothly when subjected to the low-valent titanium complex **26**.[91,92] Thus, alkene **40** gives cyclopentene **41** in high yield (Scheme 10),[91] but alkene **42** does not cyclise and can be used to make 1,2-dialkoxyalkene **43** in high yield (Scheme 11).[84]

In the case of alkylidenation of anilides, if a small quantity of water is added after alkylidenation is complete and the mixture stirred for 30 min before alkaline aqueous work-up, the enamine is reduced in situ to the tertiary amine (e.g., Scheme 12).[93] The intramolecular version of this reaction allows

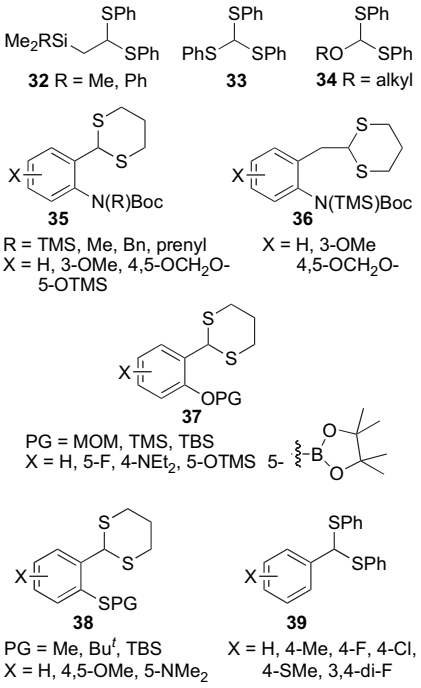
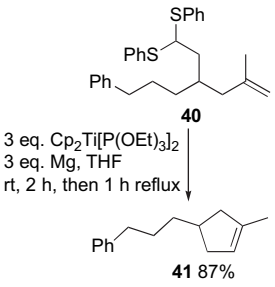
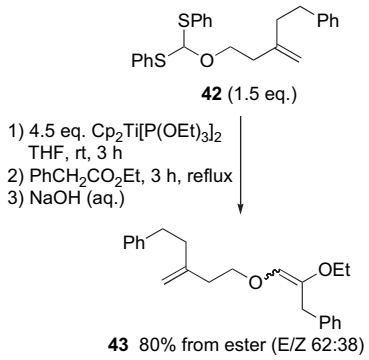


Figure 3.

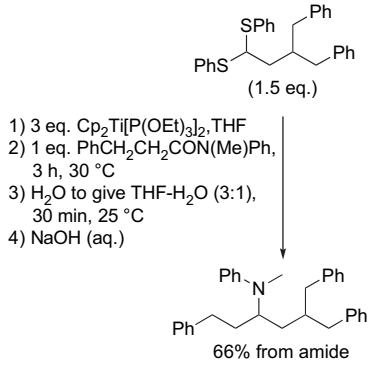


Scheme 10.

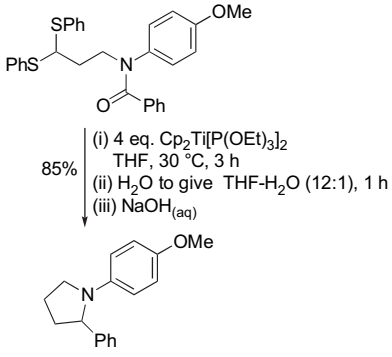


Scheme 11.

access to cyclopentylamines[93] and pyrrolidines (e.g., Scheme 13).[79] The successful intramolecular alkylidenation of carboxylic acid derivatives is one of the distinct advantages of the Takeda reaction, and as discussed in our earlier review,[8] cyclic enol ethers[94] and 2,3-dihydrothiophenes[95] have been prepared in this way.

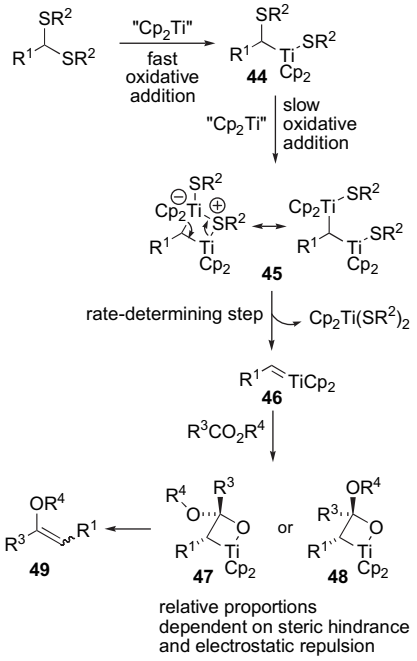


Scheme 12.



Scheme 13.

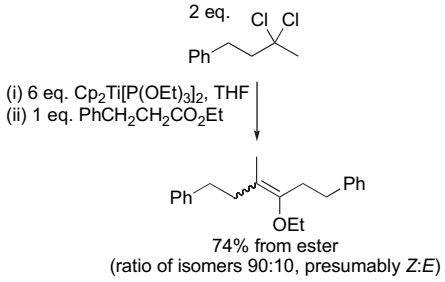
A plausible mechanism for the Takeda alkylidenation of esters is shown in Scheme 14. The first oxidative addition to give titanocene complex **44** is essentially instantaneous, while the second oxidative addition to give bimetallic **45** is slower and may fail with dithianes and sterically hindered substrates. By analogy with the Petasis reagent, the rate-determining step is likely to be the generation of the titanium(IV) alkylidene complex **46**, which then reacts with the ester to give oxatitanacyclobutanes **47** or **48**, the relative proportion of which is determined by steric and electrostatic factors and which collapse stereospecifically to give the *Z*- and *E*-enol ethers **49**, respectively.



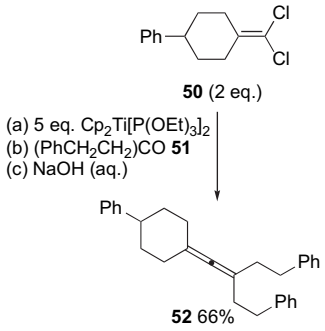
Scheme 14.

Although diphenyldithioacetals derived from acetone[77] and cyclobutanone[96] can be used to make tetrasubstituted alkenes and hetero-substituted alkenes, the thioacetals of other ketones suffer from elimination to give vinyl sulfides. This is because the elimination competes with the slower second oxidative addition. The problem can be overcome by replacing thioacetals with 1,1-dichloroalkanes (e.g., Scheme 15), which are easily accessible from ketones (with the exception of aryl ketones).[97,98] In the same way, carbon tetrachloride gives 1,1-dichloroalkenes.[99] Chloroform gives predominantly chloroalkenes, but the control of the double-bond geometry is poor and 1,1-dichloroalkenes are also produced under these conditions.

Titanium vinylidene complexes can also be generated from 1,1-dichloroalkenes and used to form allenes from ketones in good yield.[100] Thus, the titanium alkylidene complex generated from dichloroalkene **50** converts ketone **51** into allene **52** in good yield (Scheme 16). The same type of titanium vinylidene intermediates are generated by the thermolysis of the divinylic titanocenes **23** that have been used by Petasis and Hu to make allenes (Fig. 2).[76]



Scheme 15.

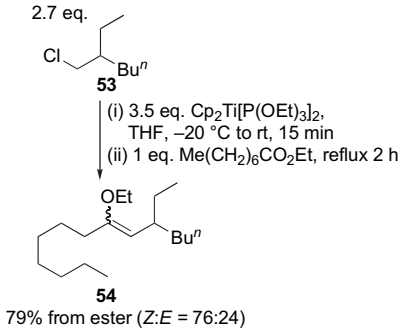


Scheme 16.

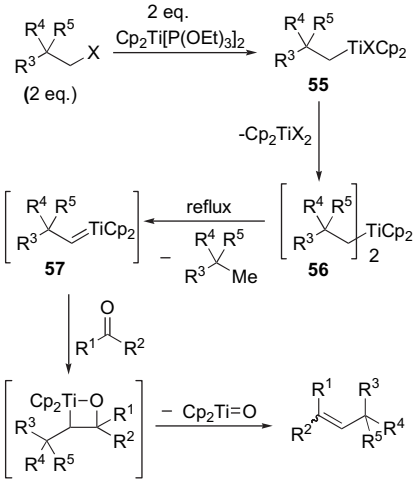
Recently, Takeda and co-workers have shown that the 1,1-dihaloalkane may be replaced by bulky primary alkyl halides that have a branch β to the halogen atom. Thus, alkyl chloride **53** gave enol ether **54** in good yield (Scheme 17).[101] The reaction mechanism presumably involves a Schlenk equilibrium between the initially formed alkyltitanocene **55** and dialkyltitanocene **56** (Scheme 18). The latter may then undergo α-elimination to give a titanium alkylidene complex **57**, which will react with the carbonyl compound as usual. It is significant that α-elimination seems to be faster than β-elimination when R^5=H and R^4 and R^5 are alkyl groups bigger than methyl. The reaction also works well for alkoxymethyl chlorides (e.g., Scheme 19).[102]

2.4. 1,1-Bimetallic reagents for the methylenation and heteromethylenation of ketones

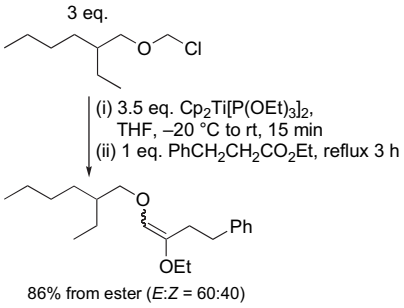
Titanium carbenoids have been generated from dihalomethanes under a variety of conditions and used to methylenate aldehydes and ketones (Scheme 20 and Table 1). The active reagents are presumably 1,1-bimetallics **58**, since alkene metathesis has never been observed with such reagents. Reagents with bidentate diamine ligands are exceptions to



Scheme 17.

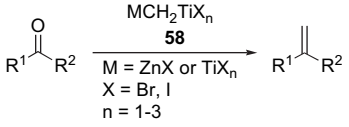


Scheme 18.



Scheme 19.

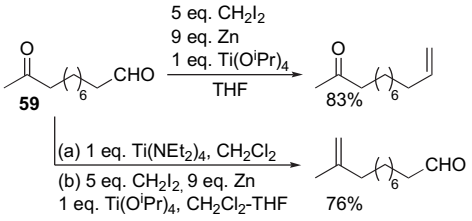
this rule and are discussed separately in Section 2.5. In 1978, Takai et al. first showed that a reagent generated by the addition of $TiCl_4$ to a suspension of dibromomethane and zinc in dichloromethane at room temperature methylenates ketones (Scheme 20, Table 3, entry 1).[103,104] Lombardo later reported a procedure for the preparation of the same reagent in THF at 5 °C over 3 days (Table 3, entry 2).[105] Reaction times for methylenation in THF–DCM were shortened to 1.5 h at room temperature using this preformed reagent. Pinacol coupling competes with methylenation of aldehydes and aromatic ketones when dibromomethane is used according to Takai's original procedure, presumably due to the presence of titanium(III) in the mixture.[106,107] This is not a problem when diiodomethane is the substrate[106] and methylenation of aldehydes is successful, as the formation of the methylenating agent is faster and is probably complete prior to the addition of the carbonyl substrate. Furthermore, shorter reaction times are required for the methylenation of ketones (Table 3, entry 3). The reagent is not very selective for the methylenation of aldehydes in the presence of ketones. However, replacing $TiCl_4$ with $Ti(O^iPr)_4$ gives a less reactive reagent that methylenates the aldehyde group of 10-oxoundecanal **59** selectively, while using the more reactive reagent, but pre-complexing the aldehyde group with $Ti(NEt)_4$, allows the selective methylenation of the ketone group (Scheme 21).[107]



Scheme 20.

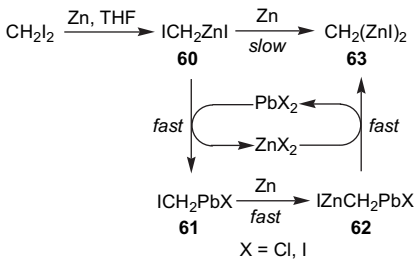
Table 3. Comparison of different 1,1-bimetallic reagents **58** for the methylenation of ketones

Entry	Reagent preparation	Ketone	Alkene yield (%)	Ref.
1	(a) 9 equiv Zn, 3 equiv CH_2Br_2, THF (b) 2.2 equiv $TiCl_4$, THF–DCM, rt, 15 min (c) 1 equiv ketone, rt, 12 h	4-Dodecanone	89	103
2	(a) 4.4 equiv Zn, 1.44 equiv CH_2Br_2, THF (b) 1.03 equiv $TiCl_4$, −40 °C then 5 °C, 3 d (c) 1 equiv ketone, THF–DCM, rt, 1.5 h	Isomenthone	89	105
3	(a) 9 equiv Zn, 5 equiv CH_2I_2, THF, rt, 30 min (b) 2 equiv $TiCl_4$, THF–DCM, 0 °C then rt, 30 min (c) 1 equiv ketone, rt, 20 min	4-Dodecanone	86	106
4	2 equiv $CH_2(ZnI)_2$, 1 equiv $TiCl_4$, 1 equiv ketone, THF, rt—exact conditions unclear	2-Dodecanone	78	108
5	(a) 0.75 equiv Nysted reagent **64** (see Scheme 23), 1 equiv $TiCl_4$, THF, 0 °C (b) 1 equiv ketone, rt	2-Dodecanone	91	109
6	(a) 0.75 equiv Nysted reagent **64**, 0.1 equiv $BF_3{\cdot}OEt_2$, THF, 0 °C, 5 min (b) 1 equiv $TiCl_3$ (c) 1 equiv ketone, rt	2-Dodecanone	78	109
7	(a) 1 equiv Nysted reagent **64**, $BF_3{\cdot}OEt_2$, THF, 0 °C, 5 min (b) 2 equiv $TiCl_2$ (c) 1 equiv ketone, rt	2-Dodecanone	96	109
8	(a) 1 equiv $TiCl_2$, THF, rt, 10 min (b) 1 equiv $CH_2(ZnI)_2$, rt, 2 h (c) 1 equiv ketone, 0 °C then rt, 1 h	2-Dodecanone	83	108



Scheme 21.

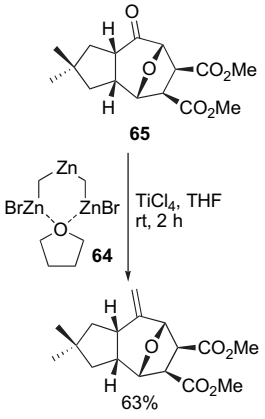
Takai et al. showed that the presence of a small amount of lead in the zinc was essential for the efficient formation of the methylenating reagents from dihalomethanes and that it was best to add a trace of lead(II) chloride at the beginning of the procedure.[110] They demonstrated that geminal dizinc **63** was formed from diiodomethane and zinc in THF in the presence of lead salts, but not in their absence, and suggested that the lead catalysed the conversion of zinc carbenoid **60** into the dizinc **63** through a fast reduction of the organolead intermediate **61** to give bimetallic **62** and lead–zinc exchange to give bis(iodozincio)methane **63** (Scheme 22). The active methylenating species **58** is then formed by transmetalation with titanium. Fewer equivalents of methylenating agent



Scheme 22.

are required when the Takai reagent is prepared from $TiCl_4$ and bis(iodozincio)methane **63**, preformed in THF with lead(II) catalysis under sonication (Table 3, entry 4).[111,108] Small-angle neutron scattering and anomalous X-ray scattering on the THF solution of bis(iodozincio)methane **63** indicate that the reagent is homogeneous and monomeric when prepared in this way.[112]

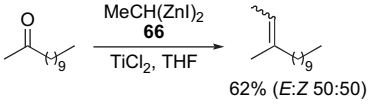
In 1995, Tochtermann and co-workers reported that commercially available Nysted reagent **64** could replace the dihalomethane and zinc (and lead chloride) mix in Takai methylenation of ketone **65** (Scheme 23),[113] and this modification was thoroughly explored by Matsubara et al. a few years later.[109] The Nysted reagent **64** has two methylene dianion equivalents and so only 0.75 equiv of the reagent was necessary for good yields of alkene (Table 3, entry 5).



Scheme 23.

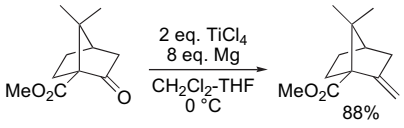
Matsubara and co-workers also showed that reagents prepared by combining the Nysted reagent **64** or preformed

bis(iodozincio)methane **63** with $TiCl_3$ or $TiCl_2$ can methylenate ketones (Table 3, entries 6–8).[109,108] Although the reagent formed from the Nysted reagent **64** and $TiCl_2$ appears to be marginally more effective than other Takai reagents when used in the presence of 10 mol % BF_3, it requires the rather arduous preparation of the titanium(II) salt and has not found use in synthesis. 1,1-Bis(iodozincio)ethane **66** can be generated from 1,1-diiodoethane in up to 50% yield at 25 °C (formation of 2,3-diiodobutane dominates at lower temperature) and will ethylidenate aldehydes and ketones in the presence of $TiCl_2$, but yields are modest and there is little or no control of the alkene geometry (e.g., Scheme 24). In a similar way, *E*-vinylsilanes can be prepared from 1,1-dibromomethylsilane, but higher stereocontrol is obtained for the silylmethylenation of aldehydes using a related chromium(II)-mediated process.[114]

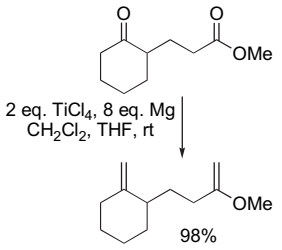


Scheme 24.

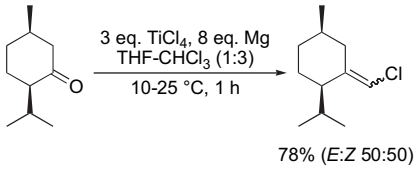
Recently, Yan and co-workers found that dichloromethane acted as a methylene donor when an aldehyde or ketone was treated with 2 equiv of $TiCl_4$ and 8 equiv of magnesium in a dichloromethane–THF (3:1–6:1) mixture at 0 °C.[115] Reduction of the carbonyl compound was a minor side product in some cases, but even an aromatic aldehyde could be methylenated in good yield. A Lewis base is necessary for the reaction to occur and THF was better than a range of other coordinating solvents tested. Ketones could be methylenated in the presence of acetals, sulfones, amides, carboxylic acids and esters (e.g., Scheme 25). At room temperature, both ketones and esters react (e.g., Scheme 26), and even isopropyl benzoate can be methylenated in good yield.[116] Methylenation of lactones benefits from the use of toluene as a co-solvent, as this lowers the tendency to isomerise to give endocyclic alkenes. Chloromethylenation of aldehydes and ketones is possible when chloroform is used as the substrate.[117] Sterically hindered ketones and ketones with epimerizable centres are chloromethylenated smoothly (e.g.,



Scheme 25.



Scheme 26.



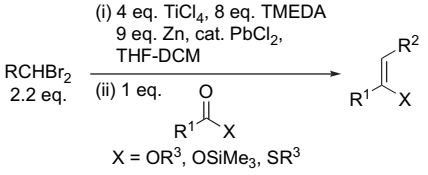
Scheme 27.

Scheme 27), but stereocontrol is generally poor, so that, for aldehydes, the related chromium chemistry is superior for halomethylenation.[118]

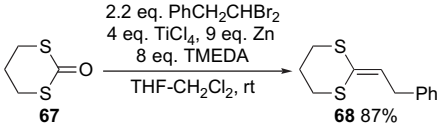
All the reagents discussed above will selectively methylenate ketones in the presence of carboxylic acid and carbonic acid derivatives. Indeed, only Yan's magnesium-derived reagent will react with these higher-oxidation-state carbonyl compounds (see below). None of the reagents have been reported to carry out alkene metathesis and so they should all be considered to be 1,1-bimetallics, rather than titanium methylidenes.

2.5. Takai alkylidenation of carboxylic acid and carbonic acid derivatives

Takai and co-workers have shown that a range of carbonyl compounds are converted into *Z*-hetero-substituted alkenes (*E* in the case of enamines) by a reagent that is prepared by the addition of 4 equiv of titanium(IV) chloride (neat or in dichloromethane) to THF, followed by 8 equiv of TMEDA, then 9 equiv of zinc containing a trace of lead [usually added as lead(II) chloride[110]], and finally, 2.2 equiv of 1,1-dibromoalkane.[119,120] Thus, esters are converted into enol ethers (with lactones, some ring opening is observed),[119,120] silyl esters into silyl enol ethers[121] and thioesters into vinyl sulfides[122] with good *Z*-selectivity (Scheme 28). The stereoselectivity is governed by steric interactions and is generally >89:11 (*Z*:*E*) when enol ethers are prepared and esters with a branch α to the carbonyl group ensure near-total *Z*-selectivity. Tertiary amides give *E*-enamines,[122] but fast isomerisation leads to a mixture of regioisomers with straight-chain amides. 1,3-Dithian-2-ones are also alkylidenated, e.g., diathianone **67** gave ketene dithioacetal **68** in excellent yield (Scheme 29).[122] Alkylidenation is generally superior to methylenation (although this is widely used) and hydrogen atoms may be attached to the β-carbon atom, which makes



Scheme 28.

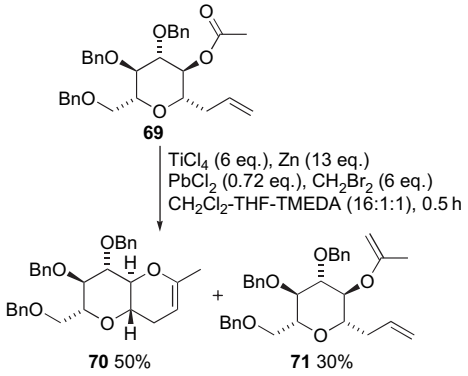


Scheme 29.

this method complementary to the Petasis and Tebbe reagents. Matsubara and co-workers advocate the use of a variation of the Takai method for methylenating esters, where titanium(II) chloride is used instead of titanium(IV) chloride and preformed $CH_2(ZnI)_2$ replaces the dibromomethane–zinc mix,[123] while Yan and co-workers have reported an alternative reagent for methylenating esters generated from dichloromethane with magnesium and titanium(IV) chloride (see above),[116] but neither has been exploited in the review period. A definitive procedure for Takai alkylidenation of esters has been published,[120] and since there are now good methods for accessing 1,1-dibromoalkanes,[97,98,124] it is surprising that, although methylenation under these conditions is widely used, alkylidenation is not.

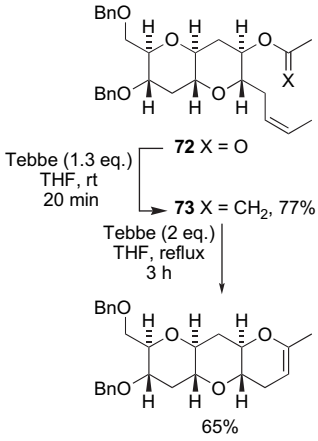
Many functional groups are tolerated when esters are methylenated/alkylidenated under Takai conditions including the following: ethers, including benzyl[125] and *p*-methoxybenzyl ethers;[126] alkenes, including terminal alkenes;[127] acetals, including glycosides[125] and dimethyl acetals;[128] silyl ethers, including TMS,[129] TES[129] and TBDMS ethers;[130] and aryl and vinyl halides, including vinyl iodides,[131] and aryl bromides.[132] In theory the alkylidene unit may also contain functional groups, but this has only been demonstrated for THP acetals,[133] and for trimethylsilylmethylenation of esters using (dibromomethyl)trimethylsilane as the substrate.[134]

The mechanism of the Takai alkylidenation is still not known, and evidence about the nature of the organotitanium reagent involved was discussed in detail in our previous review. The results from the Rainier group indicate that the methylenating reagent does not catalyse ring-closing metathesis (RCM), but can be used to generate an alkylidenating agent from allyl groups by a metathesis process.[135,136] Thus, C-glucoside **69** reacts with a reagent generated under modified Takai conditions [more lead(II) chloride, higher dilution] to give cyclic enol ether **70** and acyclic enol ether **71** (Scheme 30), but the acyclic enol ether **71** is not converted into the cyclic enol ether **70** when re-subjected to the reaction conditions. Since the Takai methylenating reagent (with TMEDA) is capable of alkene metathesis with the allyl group, it is probably a titanium methylidene rather than a 1,1-bimetallic. Interestingly, the reactivity is quite different from that of the titanocene methylidene **5** generated from the Tebbe or Petasis reagent **4** or **9**, which reacts preferentially with esters, but can then catalyse RCM of the resulting enol ethers, e.g., Nicoloau and co-workers showed that ester **72** was methylenated



Scheme 30.

with the Tebbe reagent **4** at room temperature to give the enol ether **73** and could then be cyclised with the same reagent at higher temperature (Scheme 31).[19] This tandem methylenation–RCM can be done as a one-pot procedure.



Scheme 31.

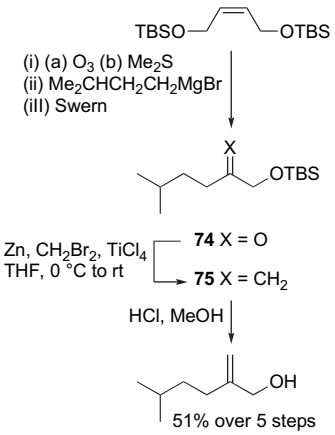
3. Synthetic strategies

Alkylidenation of aldehydes, ketones, carboxylic acid derivatives and carbonic acid derivatives using titanium reagents followed by manipulation of the resulting alkenes has been key to many synthetic strategies. In the sections that follow, these synthetic strategies are categorised in terms of the first transformation applied to the alkenes following their introduction by the titanium reagents. However, we will begin with the most common application of the titanium chemistry: simple methylenation or alkylidenation of aldehydes or ketones to give an alkene that is present in the target structures.

3.1. Preparation of alkenes in target structures

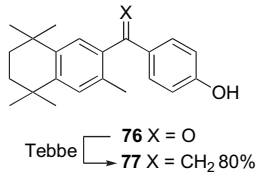
Titanium carbenoid reagents may simply be used as an alternative to other methylenating or alkylidenation reagents, as in Lee and co-workers' use of Takai methylenation to convert ketone **74** into alkene **75** in an early part of their total synthesis of lasonolide A (Scheme 32).[137] However, titanium reagents have two key advantages in the methylenation of ketones and aldehydes: they are small and so can effectively methylenate very sterically hindered carbonyl groups, and they are non-basic, so they do not epimerize chiral centres α to carbonyl groups and do not induce eliminations via a retro-Michael reaction (with the occasional exception[138]). We will consider these advantages in turn, beginning with the methylenation of sterically hindered substrates, then considering carbonyls with α-chiral centres, then compounds which may be susceptible to fragmentation by a retro-Michael reaction, and finally, structures in which both fragmentation and epimerization of α-chiral centres could be a problem. For convenience, we group together the large number of examples from the total synthesis of macrocyclic natural products.

Winum et al. used the Tebbe reagent **4** to methylenate the sterically hindered benzophenone **76** to give alkene **77** in their programme to synthesise novel Tergretin® analogues

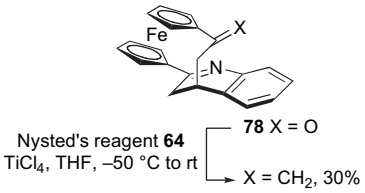


Scheme 32.

(Scheme 33).[139] Presumably, an extra equivalent of the reagent was used to accommodate the reaction with the phenol. Hindered ketone **78** was successfully methylenated using the Nysted reagent **64** under Tochtermann–Matsubara conditions in Tarraga et al.'s synthesis of ferrocene-derived ligands for metal(II) ions (Scheme 34).[140]

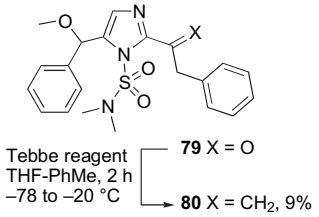


Scheme 33.



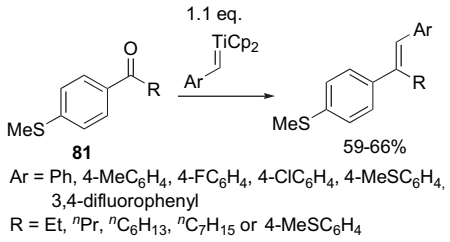
Scheme 34.

Tebbe methylenation was the only method that allowed conversion of ketone **79** into alkene **80** (Scheme 35), both Wittig and Petasis reagents having failed, but the yield was very poor.[141] Consequently, Diederich and co-workers used a different approach to complete the synthesis of their metalloprotease inhibitors.



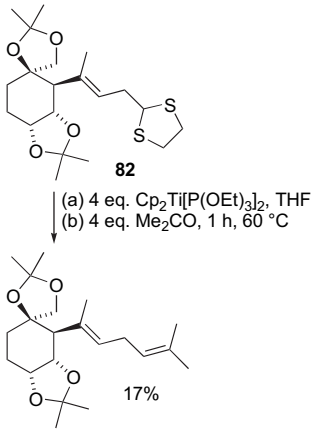
Scheme 35.

In order to access new COX-2 inhibitors, Knaus and co-workers prepared 1-alkyl-1,2-diarylalkenes[142] and 1,1,2-triarylalkenes[90] from ketones **81** using titanium benzylidene complexes (Scheme 36), which were generated from thioacetals **39** using Takeda's method (see Fig. 3 and Scheme 8 in Section 2.3). Benzylidenation placed the two aryl groups of the 1-alkyl-1,2-diarylalkenes trans to each other with >90% selectivity.



Scheme 36.

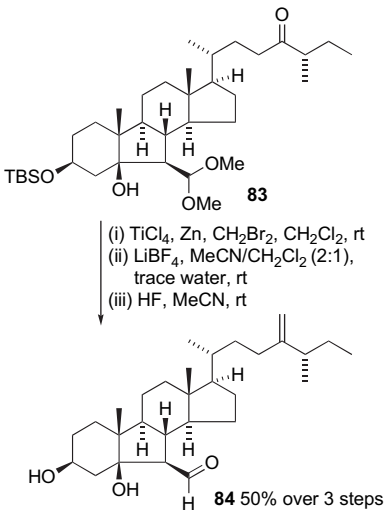
Takeda reaction with 1,3-dithiolane **82** met with less success, and Langlois and co-workers[143] completed their formal synthesis of (−)-fumagillol using Kocienski–Julia chemistry (Scheme 37). Possibly, a diphenyldithioacetal would have given better yields.



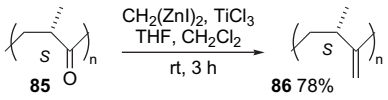
Scheme 37.

When a basic reagent, such as a Wittig reagent, is used to methylenate ketones or aldehydes that have adjacent chiral centres, epimerization often occurs via an enolate intermediate. The non-basic titanium reagents, on the other hand, generally furnish *exo*-methylene groups without epimerization of neighbouring centres. Thus, in their synthesis of orostanal **84**, Liu and Zhou used Lombardo's method to methylenate ketone **83**.[144,145] The free hydroxyl group did not need to be protected, as an excess of the titanium reagent was used. Methylenation and double deprotection proceeded in good yield to complete the synthesis of orostanal, in good yield for the three steps (Scheme 38).

Methylenation of optically active γ-polyketones **85** with the dizinc-titanium reagent, $CH_2(ZnI)_2$–$TiCl_3$, afforded methylenated polymers **86** in high isolated yield with no significant epimerization (Scheme 39).[146] The Tebbe reagent, which could also carry out the methylenation, gave a lower yield and sometimes a second treatment was required to complete the reaction. This is perhaps due to the greater steric bulk of the Tebbe reagent or it may be that the titanium(IV) methylidene is intrinsically less nucleophilic than the titanium(III) carbenoid.

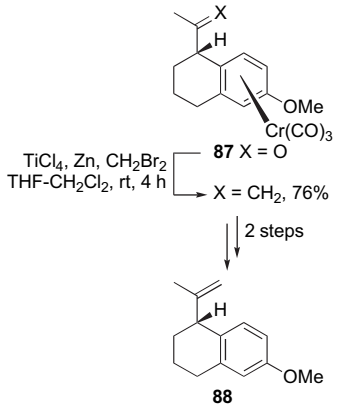


Scheme 38.



Scheme 39.

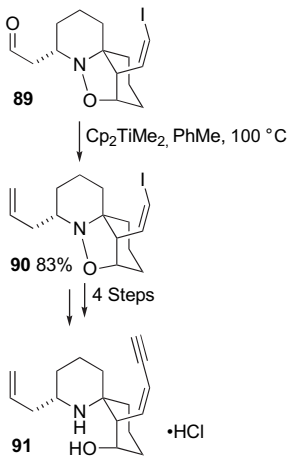
When Schmalz and co-workers synthesised norcalamene **88**[147] (Scheme 40), they methylenated acyl compound **87** under Lombardo conditions to avoid epimerization at the benzylic position. It is interesting that the chromium carbonyl complex remained unaffected by the methylenation reaction conditions.



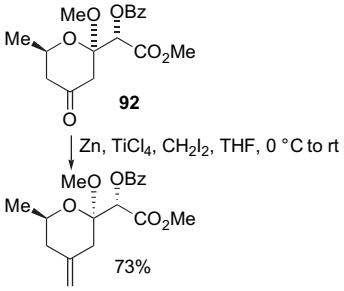
Scheme 40.

Titanium carbenoids are also useful when fragmentation or epimerization by *retro*-Michael reaction could be a problem. Holmes and co-workers used a Petasis reagent when methylenating the β-amino aldehyde **89** as part of their synthesis of a histrionicotoxin analogue **91**.[148] Retro-Michael reaction was avoided and terminal alkene **90** obtained in excellent yield (Scheme 41).

As part of a synthesis of analogues of the potential antitumour agent, mycalamide A, Nakata and co-workers methylenated ketone **92** under non-basic conditions, so avoiding elimination to give the corresponding α,β-unsaturated ketone (Scheme 42).[149]



Scheme 41.

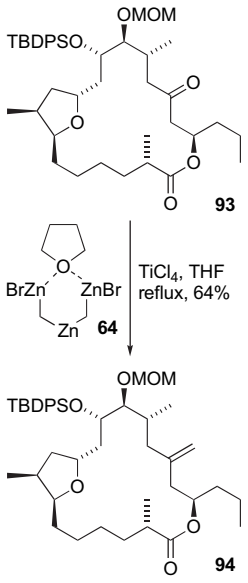


Scheme 42.

Titanium reagents have been used extensively for the introduction of *exo*-methylene groups during total syntheses of marine macrolides. These natural products have a highly oxygenated and stereochemically rich macrocycle, varying in size from 12 to 29 atoms, and have attracted significant interest because of their cytotoxicity against various human cancer cell lines. The titanium reagents are chosen, as they are very chemoselective and do not induce epimerization or retro-Michael reactions.

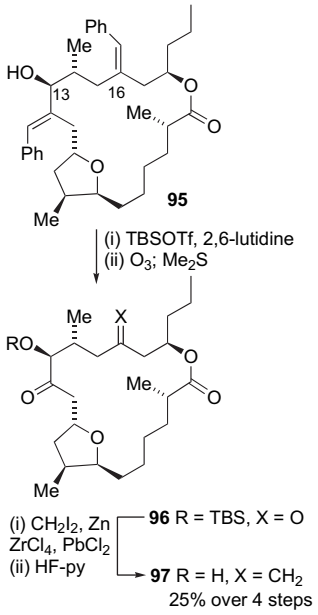
A macrocyclic lactone **94** bearing an *exo*-methylene group was an important intermediate in Fürstner and co-workers' total synthesis of amphidinolides T1 and T4 and formal synthesis of amphidinolide T5 (Scheme 43).[150,151] The key to its preparation was methylenation of ketone **93**, but a Wittig reagent induced ring opening by a retro-Michael reaction and a modified Peterson reagent failed to yield any of the desired alkene **94**. Semi-empirical calculations showed the structure of the ketone **93** to be very compact with both π-faces of the ketone shielded from attack. Standard Takai methylenation [CH_2Br_2 in the presence of $TiCl_4$ or $Ti(O^iPr)_4$ and Zn] provided alkene **94**, but in variable yields. However, using Nysted's reagent **64** with $TiCl_4$ gave the desired *exo*-methylene **94** in a consistent 64% yield (Scheme 43). A similar procedure was used in the preparation of amphidinolide T3.

After investigating several end-game strategies for their synthesis of amphidinolide T1, Jamison and co-workers found that protection of the C-13 hydroxyl of macrocycle **95** and global ozonolysis gave diketone **96** (Scheme 44).[152] Selective methylenation of the less sterically hindered C-16 ketone, without inducing a *retro*-Michael reaction, was then



Scheme 43.

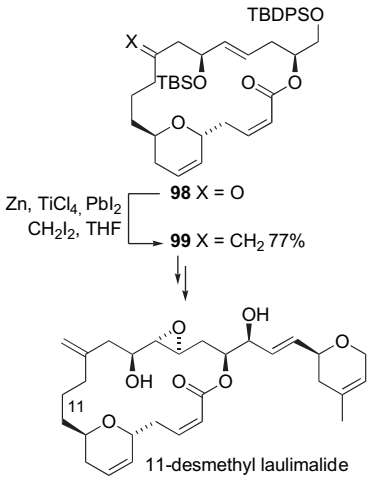
achieved using a modification of Takai's method, but replacing $TiCl_4$ with $ZrCl_4$. Finally, HF–pyridine removal of the TBS protecting group afforded the target compound **97**, in moderate yield over the final four steps.



Scheme 44.

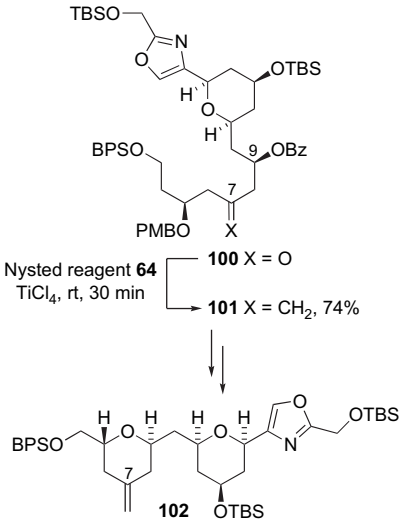
In their synthesis of laulimalide analogues, Paterson and co-workers used Takai methylenation of ketone **98** to give the *exo*-methylene compound **99** in good yield (Scheme 45).[153]

In their synthesis of the C-3 to C-19 fragment **102** of phorboxazole B, Zhang and Zhou carried out the methylenation of a mixture of ketone **100** and its C-9 epimer (89:11) with the Nysted reagent in the presence of $TiCl_4$ to give alkene **101** in good yield after separation from its C-9 epimer (Scheme 46),[154] avoiding elimination to give an α,β-unsaturated ketone. Smith and co-workers[48] and Burke and co-workers[155]

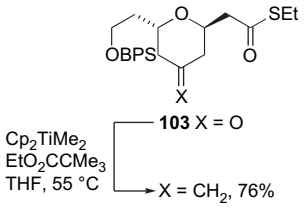


Scheme 45.

prepared similar fragments of phorboxazole A and phorboxazole B, respectively, using the Petasis reagent to install the C-7 methylene unit from a preformed tetrahydropyranone. In Smith and co-worker's route, the thioester in ketone **103** was left unaffected by the transformation and a small quantity of ethyl pivalate was used to prevent side products, as illustrated in Scheme 47 (see discussion of Petasis reagent in Section 2.2).



Scheme 46.



Scheme 47.

Two Cambridge groups have used Petasis methylenation in different fragments of spongistatin 1 **104** (Fig. 4). Paterson's team used methylenation for temporary protection of a ketone, required for later introduction of the vinyl chloride

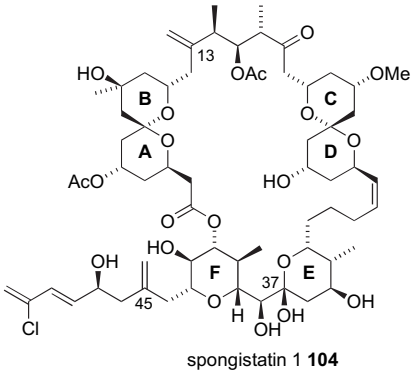
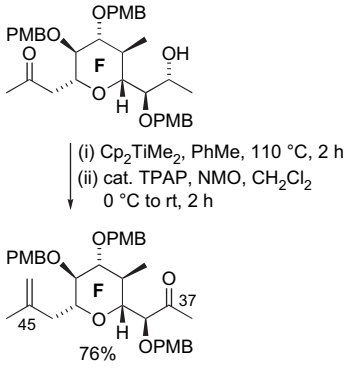
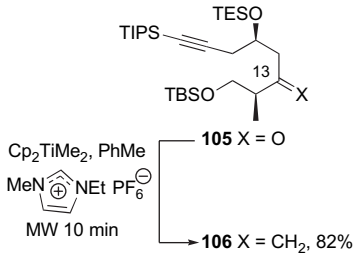


Figure 4.

side chain, so that the E-ring could be constructed from the ketone at C-37 (Scheme 48),[156] while in their synthesis of the C-1 to C-28 portion of spongistatin 1 **104** (Fig. 4),[49] Ley and co-workers used a Petasis reagent to methylenate ketone **105** in excellent yield, avoiding both epimerization of the α-chiral centre and retro-Michael reaction (71%; PhMe, 110 °C, 3 h). Interestingly, the reaction proceeded in only 10 min under microwave heating in toluene with a small amount of ionic liquid and gave an improved yield of alkene **106** (Scheme 49). Protection of the terminal alkyne with a TIPS group was essential to the success of this transformation. Presumably, the large silyl group prevents the reactive titanocene methylidene from undergoing a [2+2] cycloaddition with the alkyne.

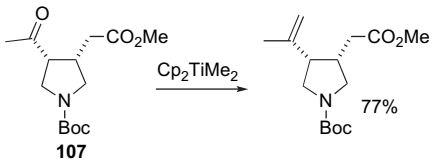


Scheme 48.

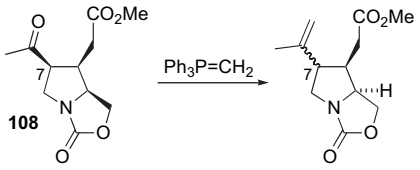


Scheme 49.

In Parsons' model study towards kainic acid, methylenation of ketone **107** was achieved using a Petasis reagent avoiding epimerization of the neighbouring stereocentre and a far less likely retro-Michael fragmentation (Scheme 50).[157] Unfortunately, submission of oxazolidinone **108** to the same reaction conditions gave only starting material. The use of a Takai reagent was also attempted without success. However, it should be noted that the more basic Wittig reagent did indeed result in epimerization at C-7 as feared (Scheme 51).



Scheme 50.

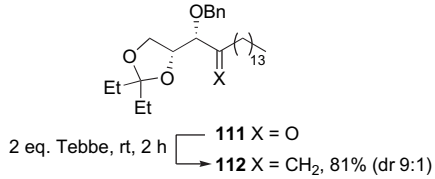


Scheme 51.

Bonjoch and co-workers chose a Takai reagent to perform the non-basic methylenation of ketone **109** in an unsuccessful approach to nakamurol A (Scheme 52).[158] The choice of reagent avoids base-induced elimination of phenylsulfinate or epimerization, and the phenyl sulfone functional group was unaffected by the Takai methylenation conditions. However, lithiation–alkylation of sulfone **110** failed and an alternative route was implemented to complete the total synthesis.

Scheme 52.

Methylenation was the key step in Bittman and co-workers' synthesis of a methylene ceramide analogue.[159] Wittig methylenation of ketone **111** was low yielding under a variety of conditions (perhaps due to retro-Michael reaction), but gave only the desired diastereomer **112** (Scheme 53). Surprisingly, the Tebbe reagent gave a mixture of epimers at C-3. However, epimerization could be minimised and the yield maximised by slow addition of the ketone to an excess of the Tebbe reagent at rt.

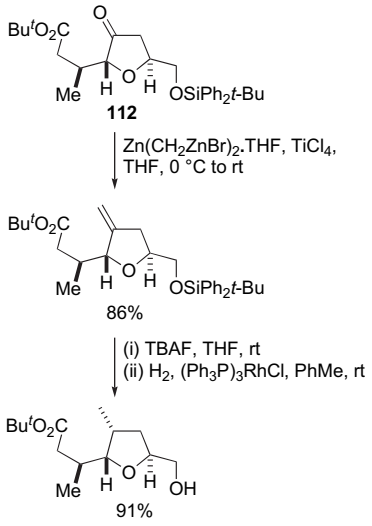


Scheme 53.

3.2. Hydrogenation

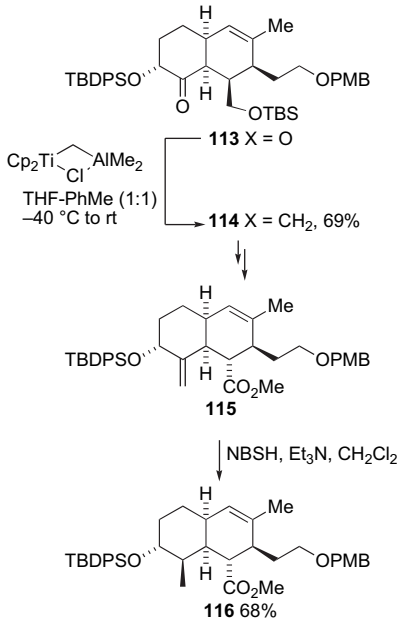
Methylenation of cyclic ketones followed by hydrogenation of the resulting *exo*-methylene is a good method of introducing a pendant methyl group in a stereocontrolled way. Thus,

having constructed the key 3(2*H*)-furanone precursor **112** to the A-ring of the gambieric acid polyether natural products, Clark and co-workers introduced a methyl group stereoselectively using the Tochtermann–Matsubara modification of Takai methylenation (in which the Nysted reagent is used), followed by hydrogenation (Scheme 54).[160]



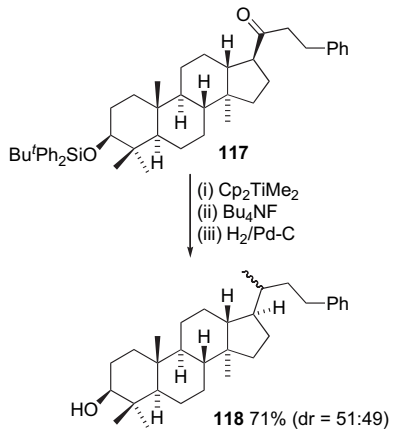
Scheme 54.

Dineen and Roush used an intramolecular Diels–Alder reaction to prepare ketone **113**. Methylenation without epimerization of neighbouring centres gave alkene **114**, and after conversion into ester **115**, selective hydrogenation of the *exo*-methylene with diimide [generated in situ from *o*-nitrobenzenesulfonylhydrazide (NBSH)] completed the octahydronaphthalene core **116** of integramycin, an HIV-1 integrase inhibitor (Scheme 55).[161]



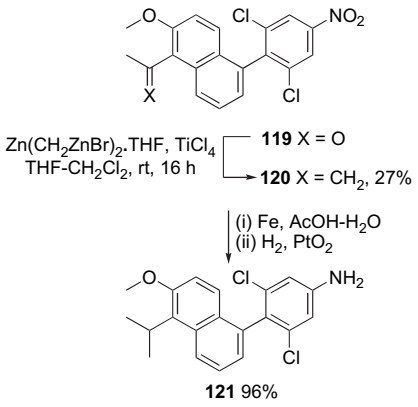
Scheme 55.

In contrast to reduction of the *exo*-methylene groups above, there was very little stereoselectivity in the hydrogenation of the acyclic alkene derived from ketone **117** (Scheme 56).[162] Fortunately, the C-18 stereochemistry had no effect on the anti-inflammatory properties of triterpenoids **118**.



Scheme 56.

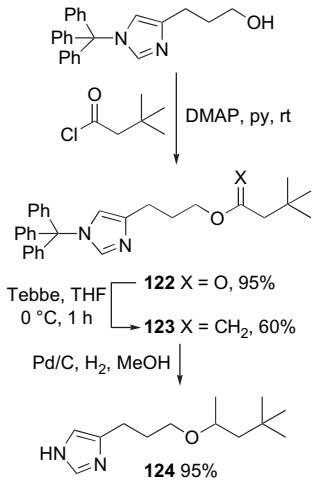
A Friedel–Crafts acylation, alkylidenation and hydrogenation sequence is an alternative to Friedel–Crafts alkylation with a secondary alkyl halide. Such a sequence was employed by Hangeland et al. to introduce the isopropyl group of amine **121** (Scheme 57).[163] Thus, the Friedel–Crafts acylation product **119** was methylenated to give alkene **120** in low yield using the Nysted reagent, and reduction of the nitro group followed by hydrogenation of the alkene then gave amine **121**.



Scheme 57.

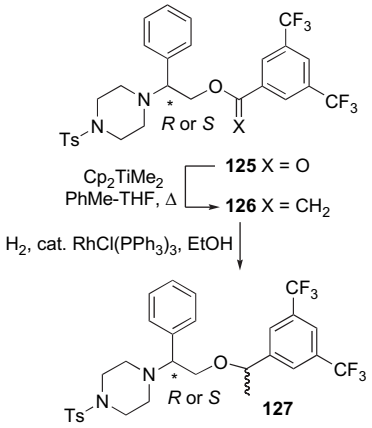
α-Branched ethers cannot be prepared in good yield by alkylation of alkoxides with secondary halides, due to rapid decomposition via the E2 elimination pathway. However, acylation of alcohols followed by methylenation and hydrogenation gives α-branched ethers in high yield. Thus, Stark and co-workers prepared ester **122** and subjected it to the Tebbe methylenation conditions to afford enol ether **123**.[164] Hydrogenation of the alkene and removal of the trityl group were then accomplished together to give the α-branched ether **124**, which was tested for activity as a histamine H_3 receptor agonist/antagonist (Scheme 58).

Similarly, Genicot et al. used this method to prepare α-branched ethers **127** as part of a programme to develop NK_1 antagonists (Scheme 59).[165] Enantiopure esters **125**



Scheme 58.

were methylenated with a Petasis reagent. Hydrogenation of the resulting alkene **126** using homogeneous catalysis gave the α-branched ethers as mixtures of separable isomers **127** (yields were not given).

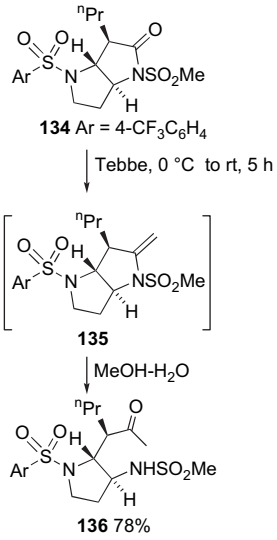


Scheme 59.

3.3. Hydrolysis or reaction of enol ethers with alcohols

Methylenation of esters followed by acid-catalysed hydrolysis of the enol ether constitutes a one-carbon chain extension. Thus, Aubé and co-workers made lactone **129** from acid **128** in two steps and treated it with a Petasis reagent to provide the enol ether **130**.[166,167] The enol ether **130** was then hydrolysed on silica gel to the hemiacetal **131** and oxidised to aldehyde **132**. This aldehyde is a precursor to indolizidine **133**, which is related to a dendrobatid alkaloid (Scheme 60).

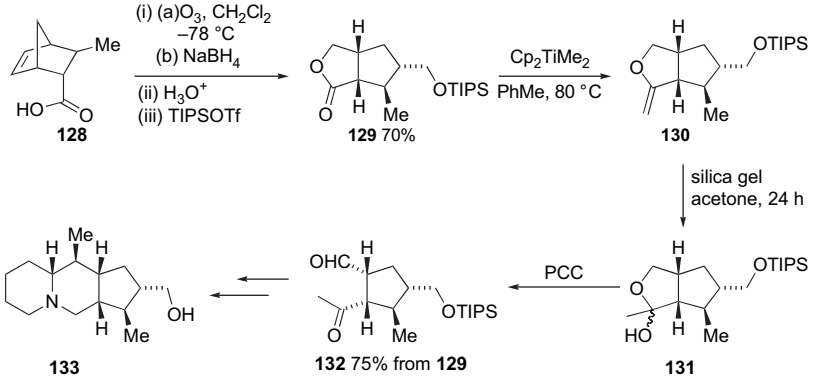
Similar access to a methyl ketone was employed by Macdonald and co-workers in their syntheses of scaffolds derived from pyrrolidine *trans*-lactams.[168] A one-pot, methylenation–hydrolysis reaction of the *trans*-lactam **134** with the Tebbe reagent proceeded via enamine **135** to give the methyl ketone **136** (Scheme 61).



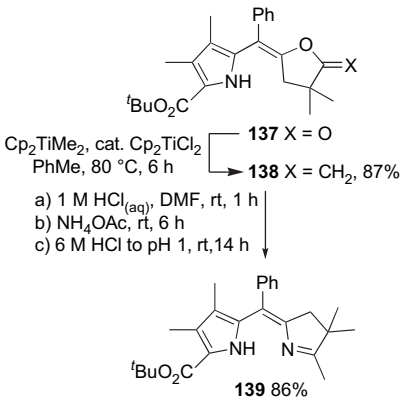
Scheme 61.

Jacobi and co-workers found that Payack's improved procedure[44,45] for Petasis methylenation converted lactone **137** into enol ether **138** in high yield, without affecting the *tert*-butyl ester, and one-pot hydrolysis–amination–cyclisation then gave dihydrodipyrrin **139**,[53] which is a building block for the synthesis of hydroporphyrins (Scheme 62).

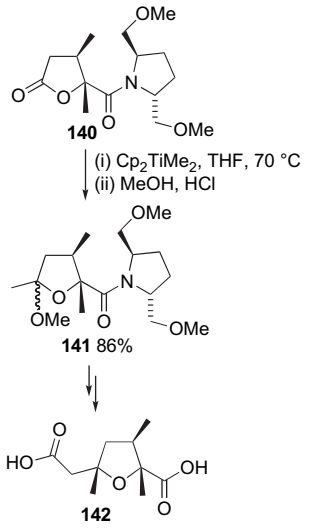
Alcoholysis has also been employed. In Donohoe et al.'s preparation of (+)-nemorensic acid **142**,[169] lactone **140** was treated with a Petasis reagent to produce an enol ether, which was immediately reacted with acidic methanol to afford acetal **141** as a 1:1 mixture of two diastereoisomers in excellent yield (Scheme 63).



Scheme 60.

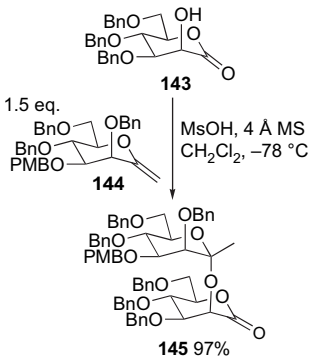


Scheme 62.



Scheme 63.

Ikegami and co-workers have extended their method of forming ketal analogues of oligosaccharides by synthesising a mannose-derived pentasaccharide by sequential additions of *exo*-methylene sugars prepared from lactones using Petasis methylenation,[170] e.g., lactone **143** reacted under acidic conditions with *exo*-methylene sugar **144** to give an excellent yield of disaccharide **145** (Scheme 64).[171]



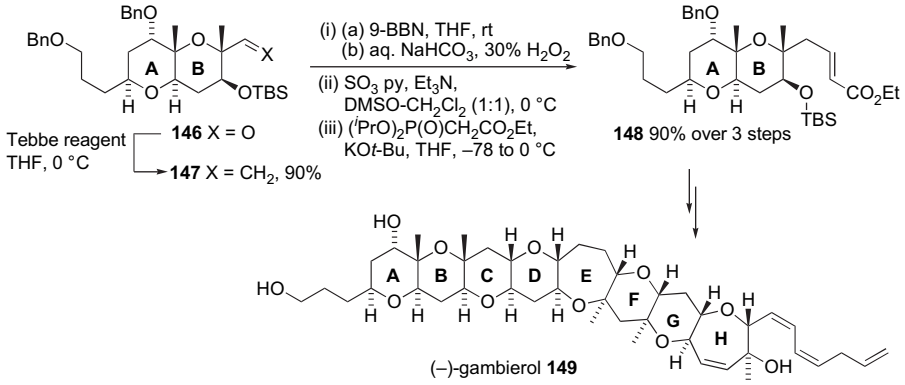
Scheme 64.

3.4. Hydroboration

The combination of carbonyl methylenation and hydroboration is particularly effective, as hydroboration of alkenes, particularly *exo*-methylenes and enol ethers, is highly regioselective and oxidative work-up produces alcohols. The hydroboration reaction is also stereoselective when a chiral centre in the alkene can influence the approach of the borane, or if a chiral borane is used. Titanium methylenating reagents are particularly attractive for this reaction sequence, as not only are they small and non-basic, but they can also convert acyclic esters and lactones into enol ethers, giving rise to synthetic strategies not available through other methylenating reagents. We will begin by discussing traditional methylenation–hydroboration of ketones and aldehydes, before turning our attention to the distinctive methylenation–hydroboration of acyclic esters and lactones.

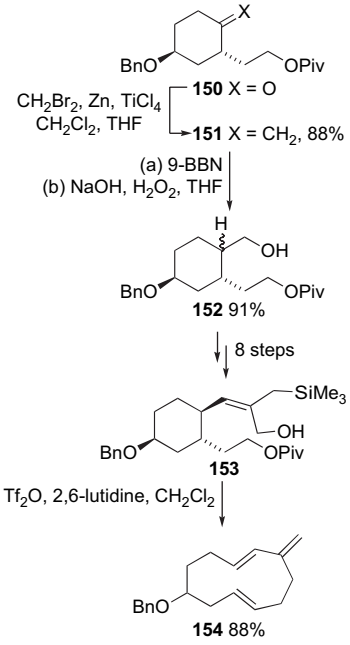
While synthesising the C-ring in their total synthesis of (−)-gambierol **149** (Scheme 65),[172,173] Sasaki and co-workers treated sterically hindered aldehyde **146** with the Tebbe reagent to afford alkene **147**, as conventional Wittig methylenation resulted in a poor yield. Hydroboration of alkene **147** with 9-BBN followed by oxidation and Horner–Wadsworth–Emmons reaction gave α,β-unsaturated ester **148** in excellent yield over three steps from alkene **147**.

During a study on the synthesis of 11-membered carbocycles by a homo-Cope-type ring-expansion route, Suzuki and Kuroda used a sequence of methylenation and hydroboration to



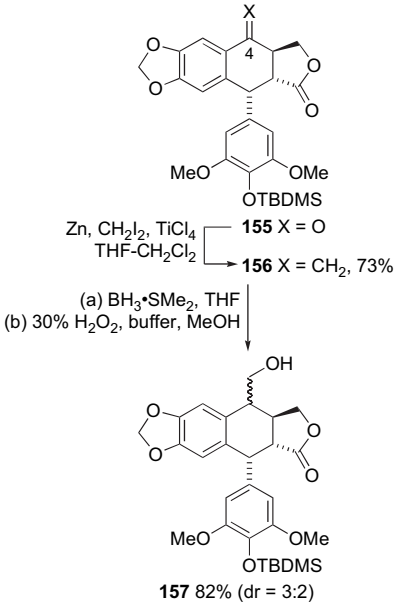
Scheme 65.

give the *trans*-substituted cyclohexane **153** necessary for obtaining the *E*,*E*-cyclotriene **154** stereospecifically (Scheme 66).[174] Methylenation of cyclohexanone **150** using Lombardo's procedure gave alkene **151** in excellent yield avoiding the epimerization observed when a Wittig reagent was used. Hydroboration of the alkene gave a mixture of diastereomeric alcohols **152** regioselectively, which were carried on together and separated at a later stage in the synthesis.



Scheme 66.

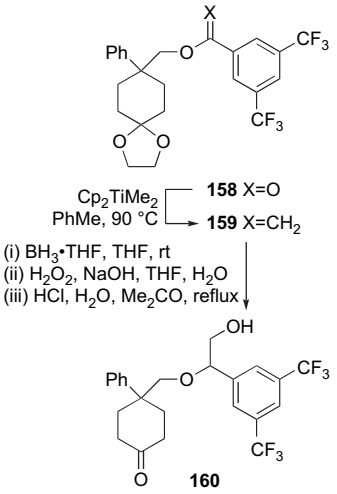
Monneret and co-workers used hydroboration–oxidation as a key step in their synthesis of podophyllotoxin.[175] Attempts to methylenate the ketone **155** with a Wittig reagent led to epimerization α to the ketone. On the other hand, Takai methylenation gave the intended *trans*-fused lactone product **156** without loss of stereochemistry (Scheme 67). Subjecting



Scheme 67.

the alkene **156** to hydroboration with BH_3–SMe_2 followed by oxidative work-up gave a 3:2 mixture of alcohol products **157**, which were difficult to separate.

As part of a project to synthesise NK_1 receptor antagonists, Elliot and co-workers methylenated ester **158** with a Petasis reagent to give enol ether **159**, which was subjected to hydroboration and oxidative work-up conditions to give alcohol **160** (Scheme 68).[176] No yields were given.



Scheme 68.

In their synthesis of the AB-ring segment of ciguatoxin **161** (Fig. 5), Fujiwara and co-workers began construction of the A-ring with a methylenation–hydroboration of a glucose-derived lactone precursor **162** to the B-ring.[177] The lactone **162** was then methylenated with the Tebbe reagent to give the vinyl ether **163** in quantitative yield. Hydroboration with 9-BBN followed by oxidation then produced alcohol **164** as a single diastereomer. A further six steps proceeded smoothly to give lactone **165**. The pendant arm was then introduced by Tebbe methylenation of lactone **165** to give vinyl ether **166** in good yield, provided there was careful temperature control (−40 °C) to avoid cyclopropanation of the endocyclic double bond. As before, the enol ether **166** was subjected to hydroboration with 9-BBN followed by oxidation to afford alcohol **167** in 59% yield together with its epimer **168** in 5% yield (Scheme 69).

Inoue and co-workers were also interested in ciguatoxin **161** as a target (Fig. 5)[178–181] and applied an intramolecular Takeda reaction to ester **169** to close the J-ring of the right-hand fragment (Scheme 70).[182] The resulting cyclic enol ether **170** was subjected to hydroboration conditions and upon oxidative work-up a 3:1 mixture of alcohols **171** and **172** was isolated, with the undesired isomer in the majority, necessitating a later oxidation–epimerisation sequence.

Burke and co-workers recognised that two portions of the antimitotic polyether macrolide, halichondrin B **173** (Fig. 6), have local C_2-symmetry and applied desymmetrisation strategies to the both C-37 to C-54 [183] and the C1 to C-14 portions.[184,185]

In the synthesis of the KLMN unit, a C_2-symmetric spirolactone **174** corresponding to the LM-ring system was

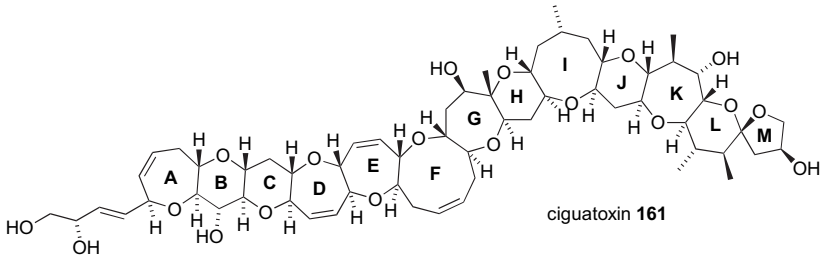
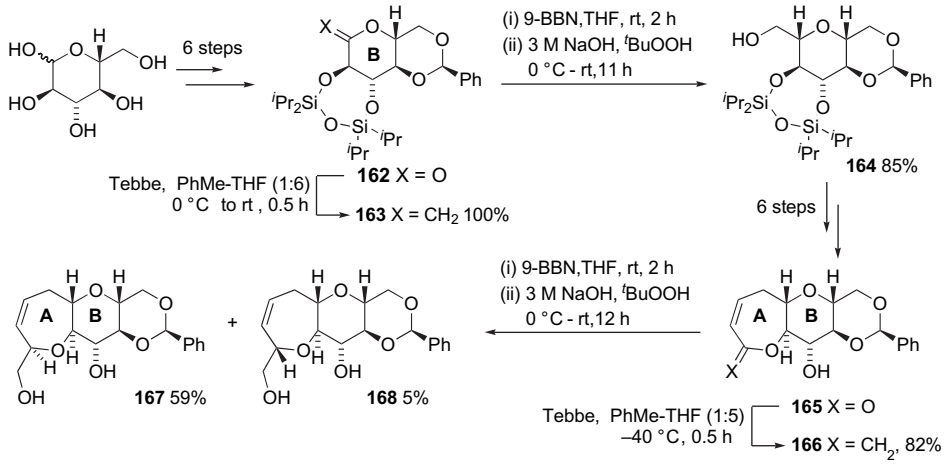
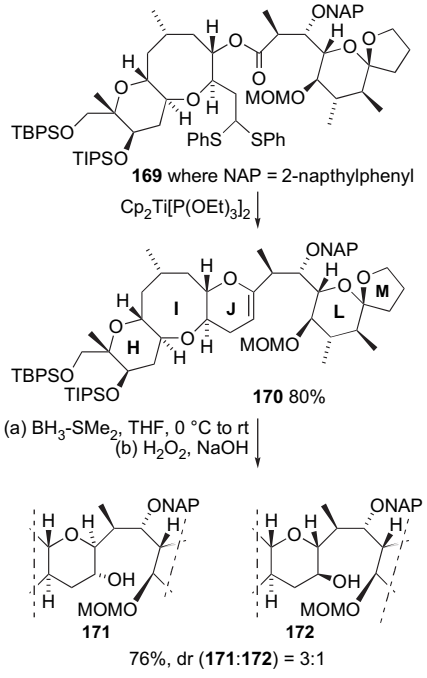


Figure 5.



Scheme 69.



Scheme 70.

monomethylenated using the Tebbe reagent.[183] All attempts to isolate the resulting enol ether **175** failed because it readily isomerised to the *endo*-enol ether, and so a one-pot procedure was devised where the dilactone was reacted with 0.6–0.7 equiv of Tebbe reagent, and the product was then immediately subjected to the hydroboration conditions with

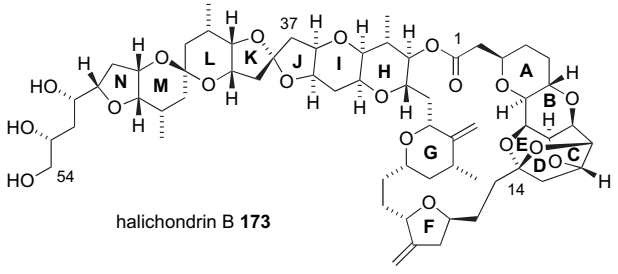
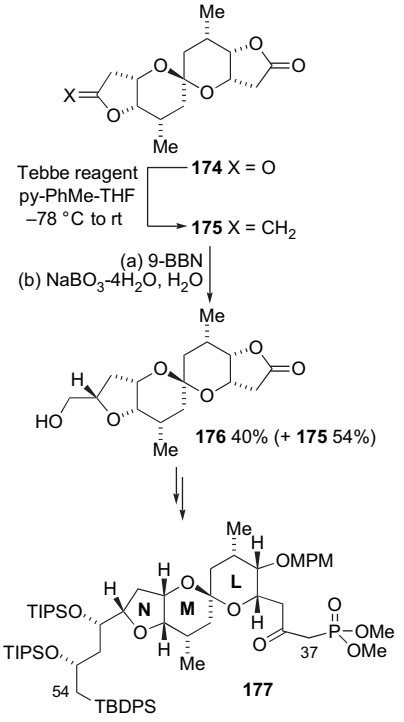


Figure 6.

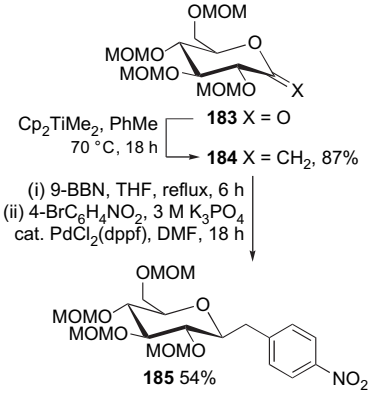
oxidative work-up. The alcohol **176** was isolated in 40% yield along with 54% recovered starting material and then elaborated to the LMN-ring portion **177** (Scheme 71). The sodium perborate oxidation was superior to NaOH–H_2O_2, because, under these conditions, saponification of the dilactone proved to be a problem, resulting in lower yields.

The synthesis of the ABCD-ring portion started from desymmetrisation of (+)-conduritol to give the lactone **178** (Scheme 72).[184,185] In a similar fashion to the desymmetrisation reaction in the LMN-ring portion, the lactone **178** was treated with a Petasis reagent to give the enol ether **179**, which, unlike the case discussed above, was isolated after column chromatography. Hydroboration then gave alcohol **180** in good yield (along with a small amount of the C-12 epimer). The hydroxy group was later converted into the aldehyde group in tricycle **181** that allowed attachment of the F-ring by Wittig reaction and elaboration of the resulting enol ether generated the D- and E-rings so completing the ABCDE-ring portion **182**.



Scheme 71.

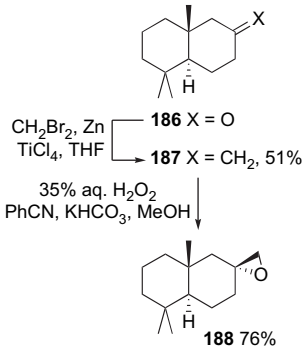
Oxidation is not the only strategic option following hydroboration. When synthesising *N*-(4-hydroxyphenyl)retinamide analogues, Curley and co-workers employed a methylenation–hydroboration–Suzuki coupling protocol.[186] A sugar-derived lactone **183** was methylenated with the Petasis reagent in excellent yield to give enol ether **184**. This was reacted with 9-BBN and the resulting alkylborane was coupled with 4-bromonitrobenzoic acid to give the 2-aryl-*C*-glycoside **185** (Scheme 73).



Scheme 73.

We will first consider epoxidation of alkenes produced using titanium carbenoids.

Winter used Takai methylenation to convert ketone **186** into alkene **187**, which was then transformed into epoxide **188** that was needed for the construction of a structure–odour relationship for compounds related to Ambrox® (Scheme 74).[187]

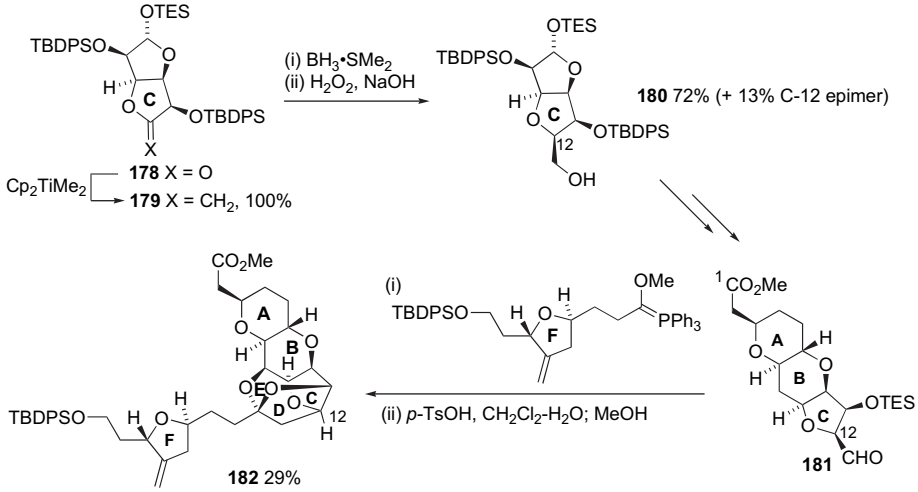


Scheme 74.

3.5. Epoxidation and dihydroxylation

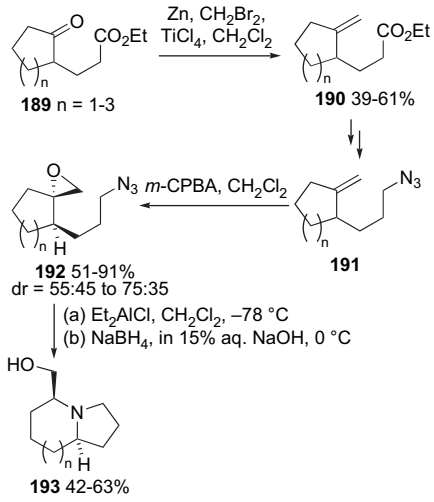
Epoxidation and dihydroxylation of alkenes are both excellent reactions that can provide highly functionalized synthetic intermediates in preparation for further elaboration.

In order to access azido epoxides **192** as substrates for Lewis acid-induced rearrangement, Reddy and Baskaran selectively methylenated a range of ketoesters **189** using the Takai



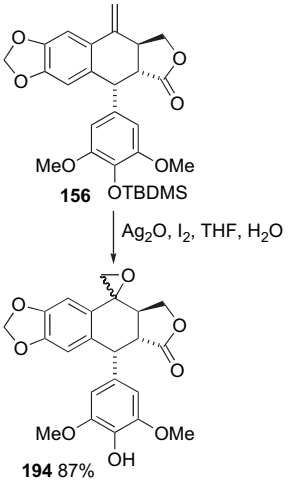
Scheme 72.

methylenation (Scheme 75).[188,189] The esters **190** were manipulated to give azides **191** and the alkenes were then converted into epoxides **192** and rearranged with Et_2AlCl to give hydroxymethyl azabicyclic compounds **193** as single diastereomers, regardless of the epoxide stereochemistry. The route was adapted to allow asymmetric synthesis of indolizidines through asymmetric dihydroxylation of the racemic alkene **191** (n=1) and separation of diastereomeric epoxides derived from the resulting diols.



Scheme 75.

In the synthesis of podophyllotoxin analogues, alkene **156** was produced as discussed above without epimerization of the trans ring junction (Scheme 67),[175] and epoxidation with iodine and silver(II) oxide gave oxirane **194** as a single diastereomer (the configuration of the C-4 centre was not established) (Scheme 76).



Scheme 76.

When Mori and Hayashi were synthesising the BCDE-ring portion of yessotoxin **195** (Fig. 7), they established the tertiary ether stereocentre at the EF-ring juncture by epoxidation of an *exo*-methylene unit introduced by Tebbe methylenation of ketone **196** (Scheme 77).[190] Epoxidation of the alkene **197** with the dioxirane derived from Oxone® and trifluoroacetone proceeded with good stereoselectivity (10:1)

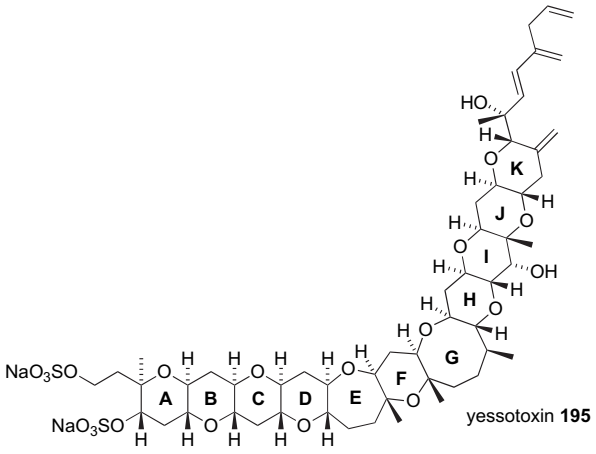
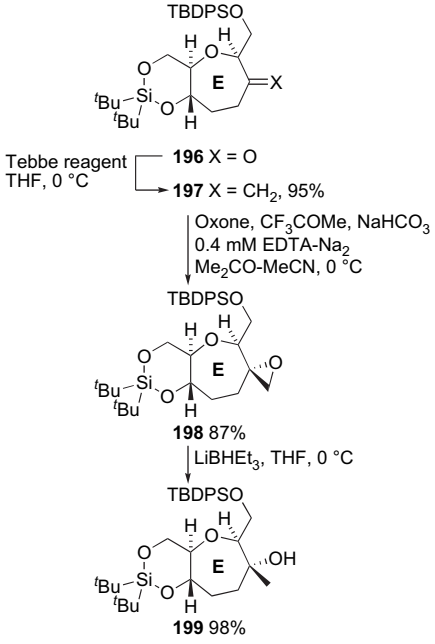


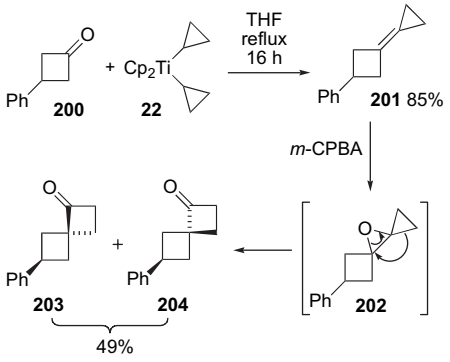
Figure 7.

and the desired alcohol **199** was isolated in excellent yield after reductive ring opening of the epoxide **198**.



Scheme 77.

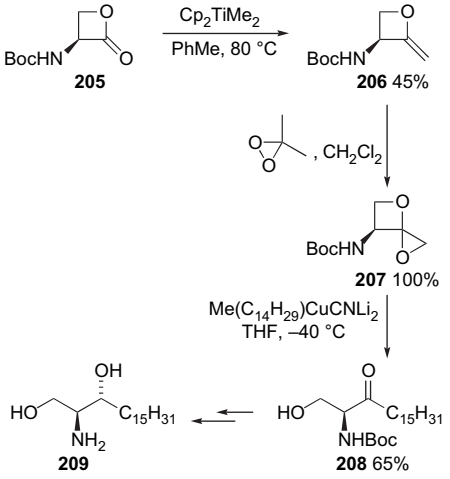
Sharon and Frimer synthesised photosensitive cyclopropylidenecyclobutenes **201** by cyclopropylidenation of cyclobutanone **200** using a Petasis reagent **22** (Scheme 78).[191]



Scheme 78.

Auto-epoxidation could be achieved under air oxidation or using *m*-CPBA to give the epoxide **202**, which rearranged to give a 1:1 mixture of *syn* and *anti* spiroketones **203** and **204**.

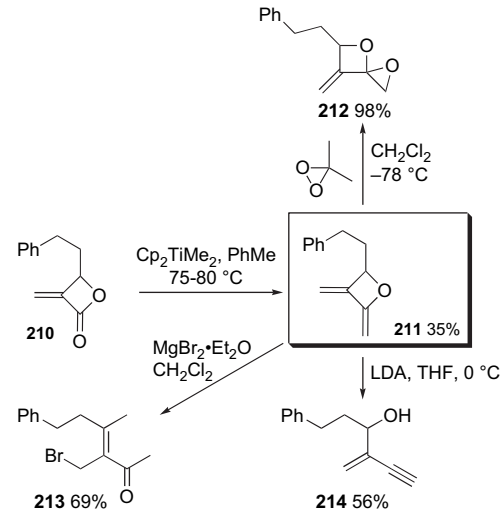
As discussed in our previous review, Howell and co-workers have thoroughly investigated Petasis methylenation of β-lactones to give 2-methylene oxetanes. The methylene oxetanes can be opened with nucleophiles to give ketones,[192] but, of more interest, is their epoxidation to give 1,5-dioxaspiro[3,2]-hexanes. These spirocycles react with basic or neutral nucleophiles to give ketones, while acidic nucleophiles or reactions in the presence of a Lewis acid give oxetanes.[193] The former reaction has been exploited to access sphingosines and phytosphingosines,[194] e.g., lactone **205** was converted into 1,5-dioxaspiro[3,2]hexane **206** and epoxidised to give spirocycle **207** in moderate overall yield (Scheme 79). Addition of a higher-order cuprate then gave ketone **208** that could be converted into D-*erythro*-dihydrosphingosine **209**. However, the low yields meant that Howell's group have developed an alternative route based on Taylor's Weinreb amide.[195]



Scheme 79.

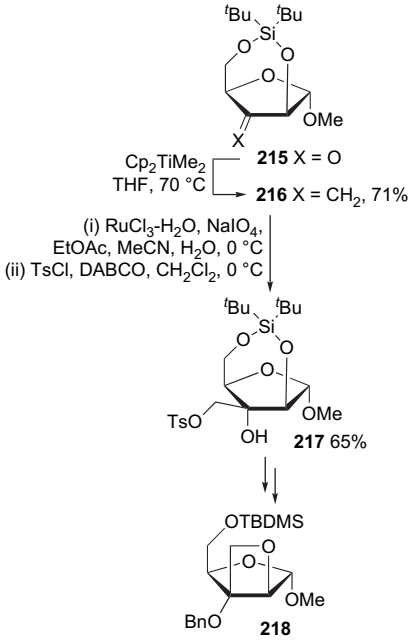
Even more challenging is methylenation of α-alkylidene-β-lactones (e.g., **210**) to give 3-alkylidene methylene oxetanes (e.g., **211**, Scheme 80).[196] By using a Petasis reagent, various 4-substituted-β-lactones were successfully methylenated in yields ranging from 28 to 75%. As the size of the C-4-substituent increases so does the isolated yield and this is probably a direct result of each enol ether's propensity to be decomposed by reacting with methylidene titanocene, as described by Payack et al.[45] One example of the 3-alkylidene methylene oxetanes **211** was successfully oxidised to give 1,5-dioxaspiro[3.2]hexane **212** as a mixture of diastereomers in excellent yield. The enol ether **211** could also be treated with $MgBr_2$–Et_2O to give allylic bromide **213** and deprotonated with LDA to give enynol **214**.

Methylenation–dihydroxylation has also been used as a strategy. When preparing oligofuranosides with conformationally restricted residues (e.g., **218**), Houseknecht and Lowery used the Petasis reagent to methylenate ketone **215** (Scheme 81).[197] Attempts to use a Wittig reagent for this purpose were unsuccessful due to the instability of the



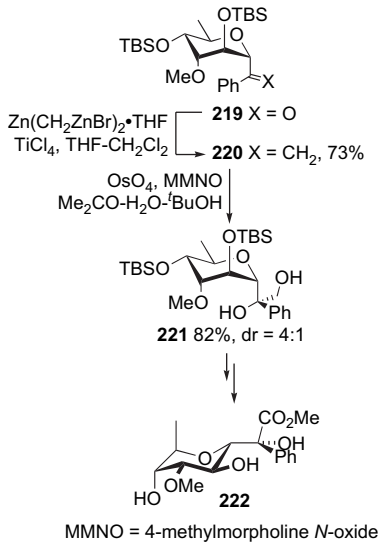
Scheme 80.

di-*tert*-butylsilyl group under the reaction conditions. The alkene **216** was dihydroxylated under ruthenium(III) chloride catalysis and converted into tosylate **217**. Further elaboration then gave oxetane **218**.



Scheme 81.

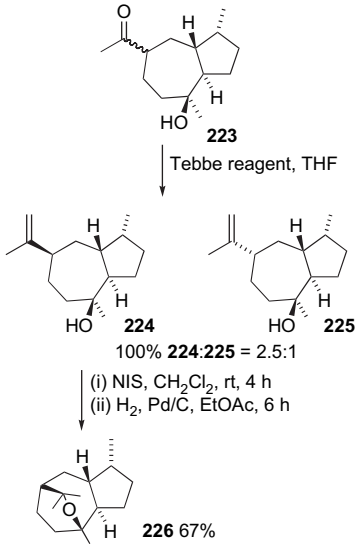
Pasetto and Franck have also provided an example of methylenation followed by dihydroxylation in their synthesis of an altrose-derived C-glucoside that models part of the potential anticancer compound, altromycin B.[198] Using the Nysted reagent under Matsubara conditions allowed ketone **219** to be converted into the corresponding alkene **220** without the epimerization of the neighbouring centre or the elimination of the OTBS group that occurred under Wittig conditions. Dihydroxylation then gave diol **221** as the major epimer and this was converted into the corresponding ester **222** in three more steps (Scheme 82).



Scheme 82.

3.6. Halogenation and selenation

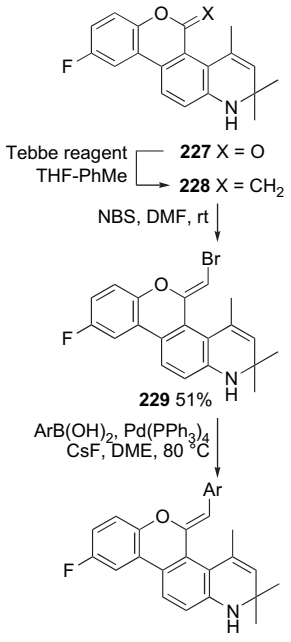
A halogen cation equivalent can regioselectively add to alkenes generated by methylenation of ketones or esters to produce a carbocation equivalent as a new reactive centre. This strategy was employed in Booker–Milburn's total synthesis of (±)-kessane **226**.[199] Tebbe methylenation of a 2:1 mixture of epimeric ketones **223** gave a partially separable 2.5:1 mixture of (±)-pogostol **224** and *epi*-pogostol **225**. Treatment of racemic (±)-pogostol **224** with *N*-iodosuccinimide (NIS) afforded a mixture of epimeric iodides, which were hydrogenated to give synthetic (±)-kessane **226** (Scheme 83).[199]



Scheme 83.

When alkylidenating, rather than methylenating, an ester under Takai or Takeda conditions, the major product is the *Z*-enol ether, with the composition of the mixture depending on the reagent type used and the size of the substituents on the substrate. However, *Z*-products can be obtained exclusively, in certain cases, by using a sequence of methylenation, then halogenation of the enol ether, and finally, cross coupling. Exposing the enol ether to a source of Br^+ or I^+ will favour rearrangement of the intermediate to put the large halogen atom on the side of oxygen, if there is a sufficient steric interaction to disfavour formation of the *E*-product.

Zhi and co-workers used this transformation to prepare synthetic intermediates to be used as substrates **228** in Suzuki cross-coupling reactions (Scheme 84).[200,201] Thus, Tebbe methylenation of lactone **227** gave enol ether **228**, which was brominated to give *Z*-bromoalkene **229**.



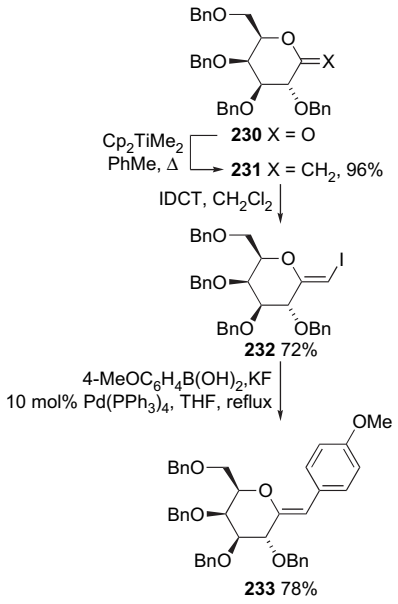
Scheme 84.

Gómez et al. used a similar strategy to make *exo*-glycal derivatives from sugar-derived lactones, e.g., Petasis methylenation of sugar-derived lactone **230** gave *exo*-glycal **231** that was then iodinated with iodonium dicollidinium triflate (IDCT) to generate an iodoalkene substrate **232** for the Suzuki coupling reaction to give *exo*-glycal **233** (Scheme 85).[202]

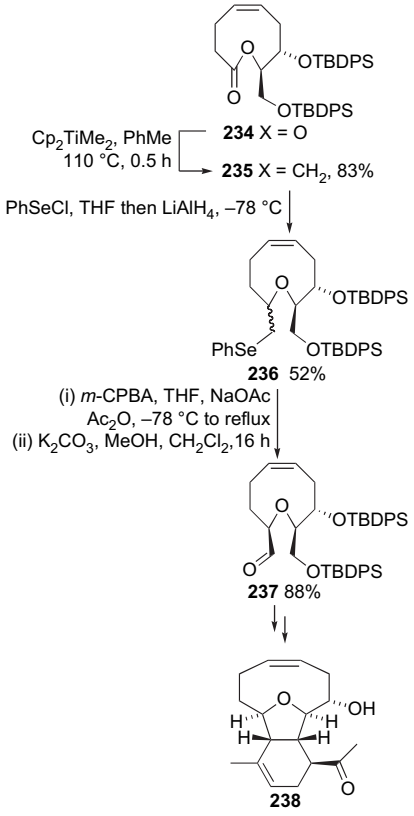
Selenation of the enol ether **235** derived from medium-ring lactone **234** allowed Burton and co-workers to access novel analogues (e.g., **238**) of the cytotoxic diterpenoid, eunicellin (Scheme 86).[203] Oxidation–Pummerer rearrangement of selenides **236** followed by methoxide cleavage gave the thermodynamically favoured 2,9-*syn* aldehyde **237**, which was a useful precursor to tricycle **238**.

3.7. Sigmatropic rearrangements including Claisen and Cope rearrangements

Methylenation of allylic esters followed by Claisen rearrangement is a popular strategy for transfer of stereochemical information from more synthetically accessible positions to less easily accessed sites and as a method of ring expansion. Spino and co-workers used this sequence to set up quaternary chiral centres employing a chiral auxiliary derived from menthone.[204] They illustrated their method in a synthesis of (+)-cuparenone **241**, where Petasis methylenation of ester **239**



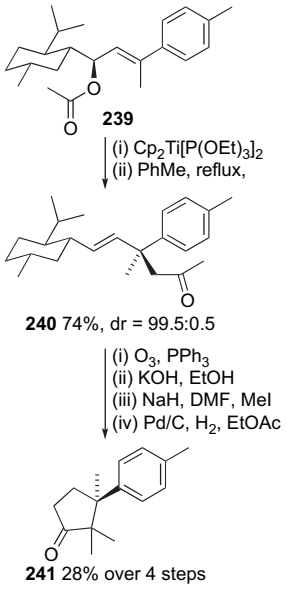
Scheme 85.



Scheme 86.

was followed by rearrangement to give ketone **240** with near-total stereocontrol (Scheme 87). The auxiliary was removed by ozonolysis, and cyclisation, methylation and hydrogenation then gave the target compound.

In their asymmetric synthesis of pectonotoxin 4, **242** (Fig. 8) and pectonotoxin 8,[205] Evans and co-workers used a methylenation/Claisen sequence to prepare the C20–C28 portion[206] (Scheme 88). The ester **244**, sensitive to epimerization under



Scheme 87.

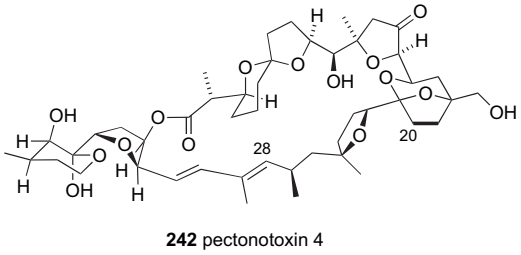
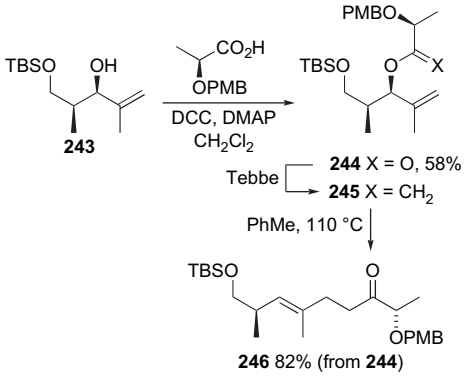


Figure 8.

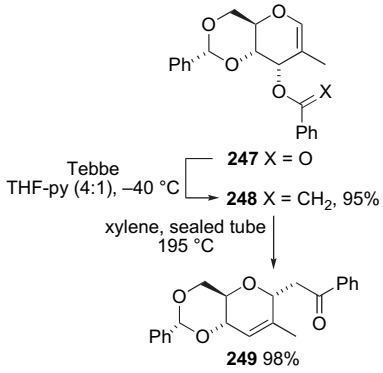
basic conditions, was formed using a mild procedure starting from the chiral allylic alcohol **243**, then methylenated using the Tebbe reagent to give the enol ether **245**. When heated, the allyl enol ether **245** underwent Claisen rearrangement to give the δ,γ-unsaturated ketone **246** as a single isomer in good yield over two steps.



Scheme 88.

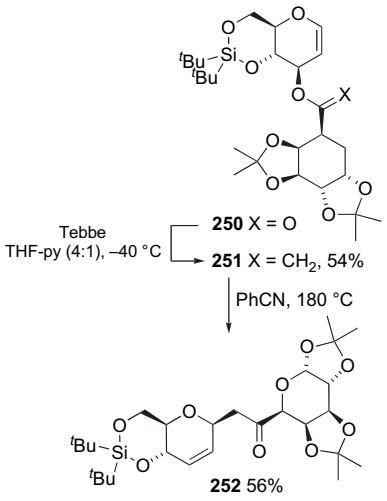
Fairbanks and co-workers have carried out an extensive investigation into tandem Tebbe methylenation and Claisen rearrangement to give C-glycosides from sugar derivatives.[14,207–209] In one example, starting from the allose derivative **247**, methylenation of the acetate group gave enol ether

248, which rearranged to give only the α-C-glycoside **249** in near-quantitative yield (Scheme 89).[207]



Scheme 89.

In contrast, starting from the glucose-derived glycal **250** and following the same sequence of Tebbe methylenation and rearrangement, the β-C-glycoside **252** was formed selectively via bis-enol ether **251**, although in lower yield and by using different conditions in the rearrangement (Scheme 90).[207]

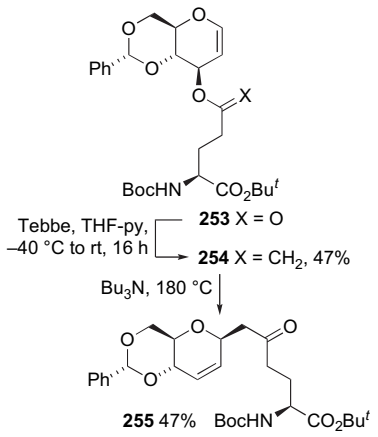


Scheme 90.

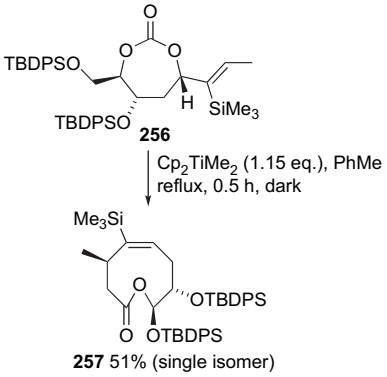
Significantly, Tebbe methylenation was possible in the presence of an α,β, or γ Boc-protected amine, and even protected amino acids could be tolerated.[209] Thus, the less sterically hindered ester in bis-ester **253** was selectively methylenated to give enol ether **254**, which rearranged to give the corresponding *C*-glycosyl amino acid derivative **255**, albeit in modest yield (Scheme 91).

A similar strategy is often used for ring expansion. Thus, Burton and co-workers employed a tandem Petasis methylenation and Claisen rearrangement to make 8- and 9-membered medium-ring lactones.[210] In one example, treating the seven-membered carbonate **256** with dimethyltitanocene and then heating the resulting mixture gave the nine-membered lactone **257** as a single isomer (Scheme 92).

Eight-membered lactones can also be formed by this method (Scheme 93). Thus, methylenation rearrangement of

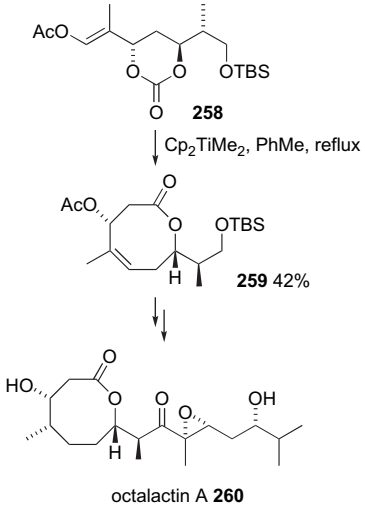


Scheme 91.



Scheme 92.

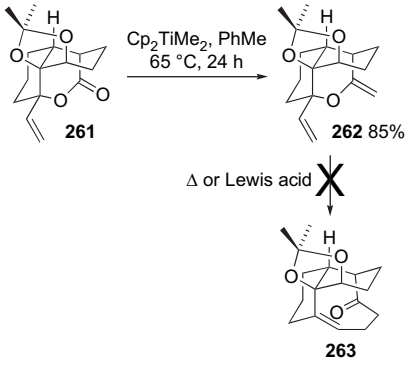
carbonate **258** gave the eight-membered lactone **259** in 42% yield, which was a key intermediate in Holmes and co-workers' total synthesis of octalactin A **260**.[15] The selectivity in this reaction sequence is interesting, as it is the first example of selective methylenation of a carbonate group in the presence of an ester.



Scheme 93.

Morency and Barriault had less success in constructing an eight-membered ring using a similar strategy in one of their

three approaches to the synthesis of vinigrol (Scheme 94). Petasis methylenation of lactone **261** gave enol ether **262**, but the ring expansion to ketone **263** failed under a wide variety of conditions.[211]



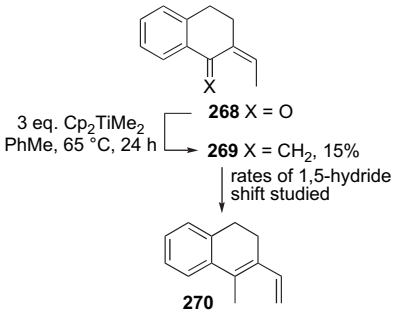
Scheme 94.

Hartley and co-workers used the anionic oxy-Cope (AOC) rearrangement to access alcohols bearing a vinyl sulfide group in a 1,5-relationship.[212] Vinyl sulfide substrates for the AOC rearrangement were prepared by stereoselective aldol reaction, thioesterification and unusual *Z*-selective alkylidenations of the resulting thioesters. In one example, 2,3-*anti* thioester **264** was ethylenated using Takai's procedure to give predominantly *Z*-vinyl sulfide **265** contaminated by the *E*-isomer. Deprotection gave alcohol **266**, which underwent AOC rearrangement in base to give a stable 5*E*-3,4-*syn* alcohol **267** as the major product following reduction (Scheme 95).

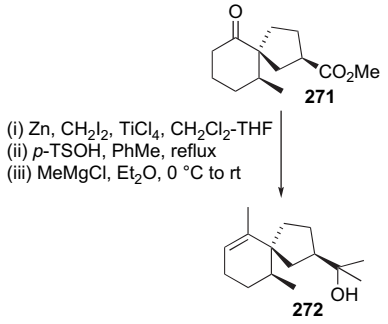
The 1,3(*Z*)-pentadiene **269**, which was used by Doering and co-workers to study the 1,5-hydrogen shift to give diene **270**, was prepared by Petasis methylenation of ketone **268**, as the standard Wittig protocols proved unsatisfactory, presumably due to the basicity of the Wittig reagents (Scheme 96).[213]

3.8. Brönsted and Lewis acid-promoted rearrangements

The simplest acid-induced rearrangement that has been used following methylenation with a titanium carbenoid is isomerisation of an *exo*-methylene to give an endocyclic alkene. Du and Lu[214] used Takai methylenation of sterically hindered ketone **271** to install an *exo*-methylene group without affecting the methyl ester, and isomerisation followed by di-alkylation then gave (−)-hinesol **272** (Scheme 97).

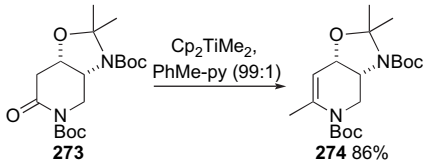


Scheme 96.

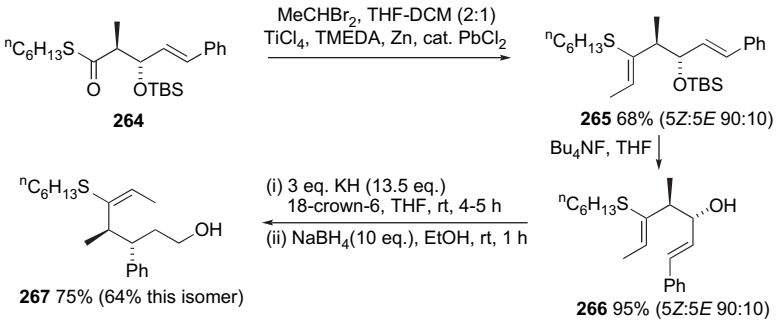


Scheme 97.

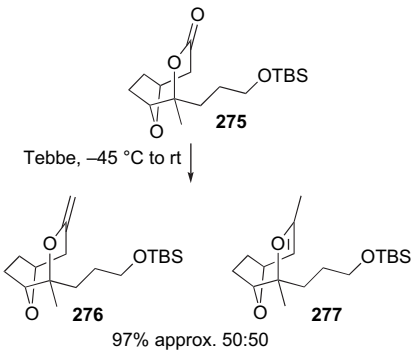
More often than not, this type of isomerisation is a frustration rather than the desired synthetic strategy. Indeed, a number of routes to natural products have stalled because of it. Langlois was intending to use an *exo*-enamine as an intermediate in the synthesis of pseudodistomin C, but found that methylenation of imide **273** gave only the internal enamine **274** resulting from isomerisation (Scheme 98).[215] Similarly, Jung and Pontillo could not find a way to avoid significant isomerisation of the *exo*-enol ether **276** to the *endo*-enol ether **277** when lactone **275** was methylenated, and this frustrated their initial approach to sclerophytin A (Scheme 99).[13]



Scheme 98.

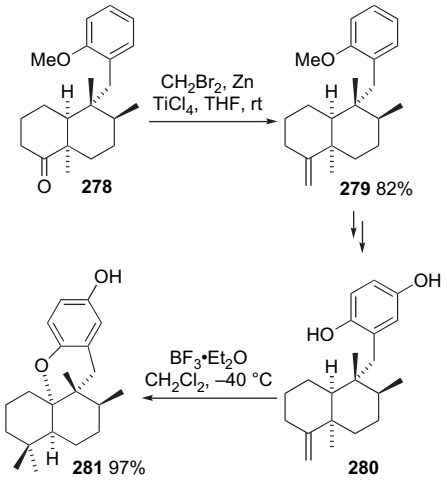


Scheme 95.



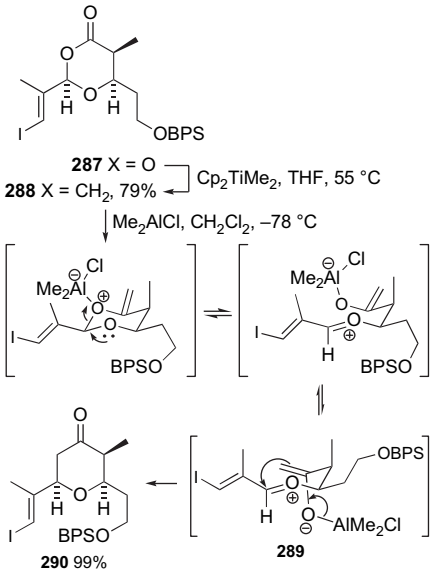
Scheme 99.

The marine natural product, (+)-aureol **281**, was synthesised by Katoh and co-workers[216,217] by exploiting the Lewis acid-initiated rearrangement of alkene **280**. The *exo*-methylene unit of this substrate had been introduced by Takai methylenation of the sterically hindered ketone **278** to give alkene **279** (Scheme 100).



Scheme 100.

Smith and co-workers have pioneered the use of the Petasis–Ferrier rearrangement in total synthesis: during the review period they have employed it to construct 2,6-*syn* tetrahydropyranyl units in their total syntheses of (+)-spongistatin 1 **104** (Fig. 4),[218] (+)-zampanolide **282**,[219] (+)-dactylolide **283**,[219] (−)-kendomycin **284**[220] and (+)-phorboxazole A **285**,[48] and in synthetic studies towards (+)-sorangicin A **286**.[221] The regions of the molecules **282**–**286** constructed using this procedure are indicated in Figure 9. The transformation involves Petasis methylenation of a 1,3-dioxan-4-one followed by Lewis acid-mediated rearrangement to give a tetrahydropyranone. The mechanism is shown for the highly diastereoselective transformation of ketene acetal **288** (formed from dioxanone **287**) into tetrahydropyranone **290**, which was a key step in the Smith and co-worker's second-generation synthesis of (+)-phorboxazole A **285** (Scheme 101).[48] The *syn* stereochemistry is determined by the



Scheme 101.

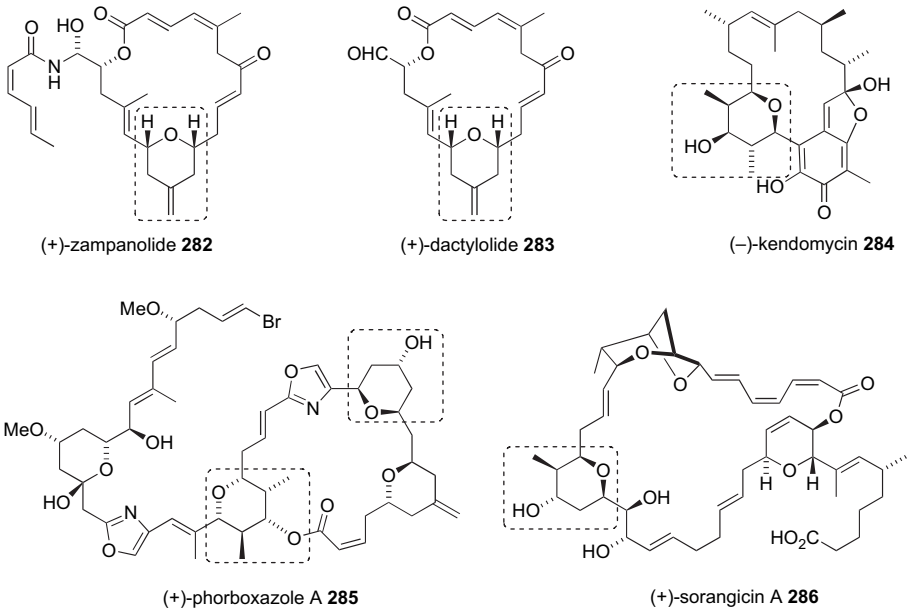
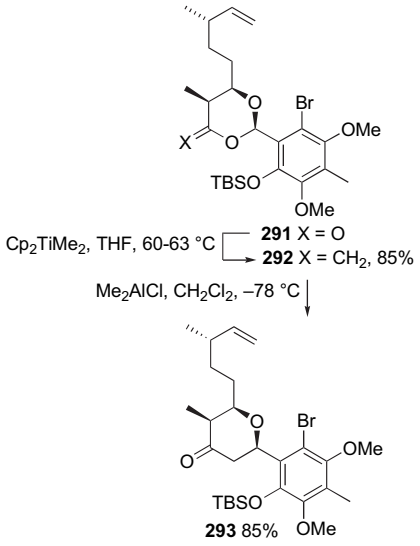


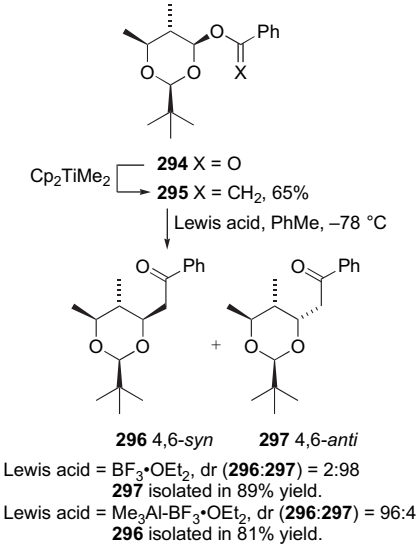
Figure 9.

pseudo-equatorial orientation of the side chain in oxonium ion **289**. Another illustrative example showing both high stereoselectivity and good functional-group compatibility is the conversion of dioxanone **291** into tetrahydropyranone **293** via ketene acetal **292**, which was as a key step in Smith and co-workers' preparation of (−)-kendomycin **284** (Scheme 102).[220]



Scheme 102.

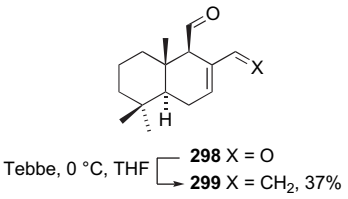
Building on the work of Ley and co-workers,[222] Zhang and Rovis converted ester **294** into an enol ether **295**, which rearranged to give either 4,6-*syn*-dioxane **296** or 4,6-*anti*-dioxane **297**, depending on the Lewis acid used to mediate the rearrangement (Scheme 103).[223]



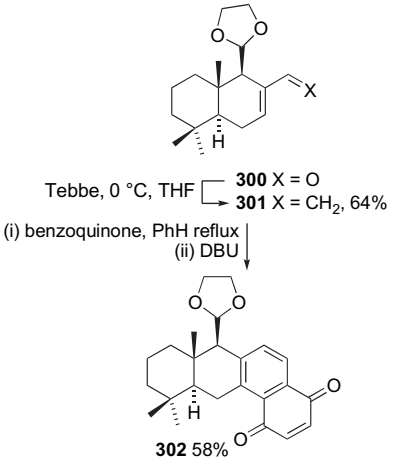
Scheme 103.

3.9. Cycloadditions

Methylenation of aldehydes, ketones, esters and lactones has been used to prepare substrates for a range of cycloadditions. Preite and co-workers found that using 1 equiv of the Tebbe reagent allowed selective methylenation of the less sterically hindered α,β-unsaturated aldehyde in dial **298** to give the diene **299** without any observable epimerization or methylenation of the other aldehyde, albeit in low yield (Scheme 104).[224] Unfortunately, epimerization did occur during the subsequent Diels–Alder reaction with benzoquinone. Acetal protection of the unconjugated aldehyde prior to the methylenation–cycloaddition sequence avoided this complication and Diels–Alder reaction between diene **301**, derived from aldehyde **300**, and benzoquinone gave acetal **302** after base-catalysed oxidation in air (Scheme 105).



Scheme 104.

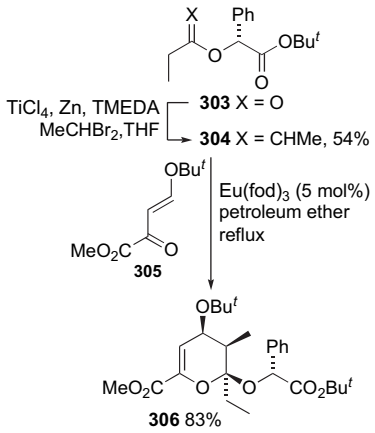


Scheme 105.

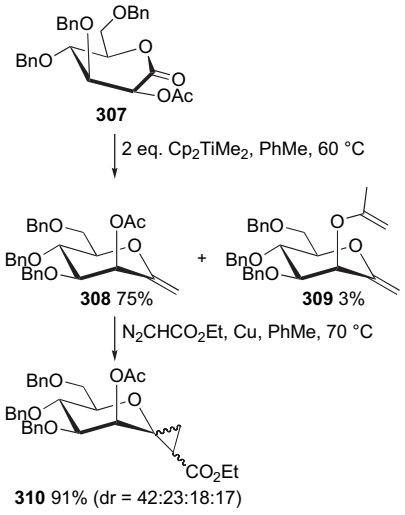
In Dujardin and co-workers' syntheses of 1,2,3,5-tetrasubstituted tetrahydropyrans, a chiral enol ether **304** was used as the dienophile to facilitate an asymmetric hetero-Diels–Alder reaction with remarkable stereocontrol.[225] A completely regiocontrolled Takai mono-ethylidenation of diester **303** afforded enol ether **304**, which was isolated as a 9:1 *Z*/*E* mixture. Reaction of enol ether **304** with heterodiene **305** proceeded with total *endo* and facial selectivity to give only functionalized dihydropyran **306** in high yield, as the minor *E*-enol ether isomer failed to react (Scheme 106). The dihydropyran was later hydrogenated to give tetrahydropyrans.

Vasella and co-workers explored a route to monosaccharide cyclopropanes **310** through methylenation of the sugar-derived lactone **307** (Scheme 107).[54] Treating the lactone **307** with the Petasis reagent led to selective methylenation of the lactone giving enol ether **308** in 75% yield along with only 3% of the doubly methylenated product **309**. Unselective cyclopropanation of the enol ether **308** then gave a mixture of monosaccharide cyclopropanes **310**.

Methylenation of *syn*-substituted ketone **311** using a Wittig reagent led to substantial epimerization to the *anti* isomer, and Bach and Speigel found that this could be minimised

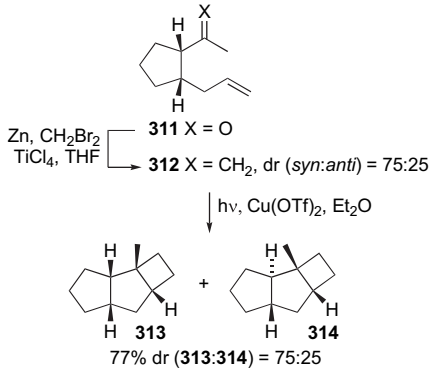


Scheme 106.



Scheme 107.

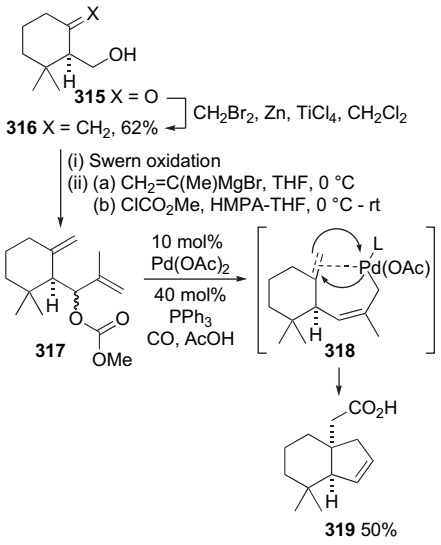
if the Takai–Lombardo reagent was used instead, so that a 75:25 *syn–anti* mixture of dienes **312** was isolated (Scheme 108).[226] Irradiating this mixture in the presence of $Cu(OTf)_2$ led to [2+2] cycloaddition to give the cyclobutanes **313** and **314** in good yield and with the same dr.



Scheme 108.

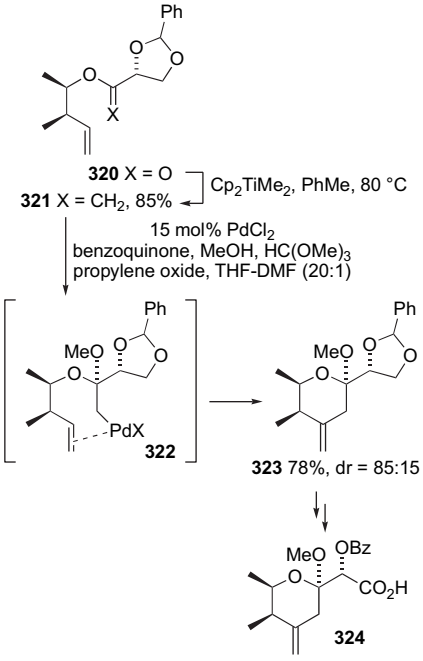
3.10. Metallation and metal-catalysed transformations

In their total synthesis of racemic acanthodoral, Zhang and Koreeda used Takai methylenation of ketone **315** to generate *exo*-methylene compound **316** (Scheme 109).[227] The alkene **316** was elaborated by further steps to give the diene **317**, which was cyclised and carboxylated to give carboxylic acid **319**, presumably via the carbopalladation product **318**.



Scheme 109.

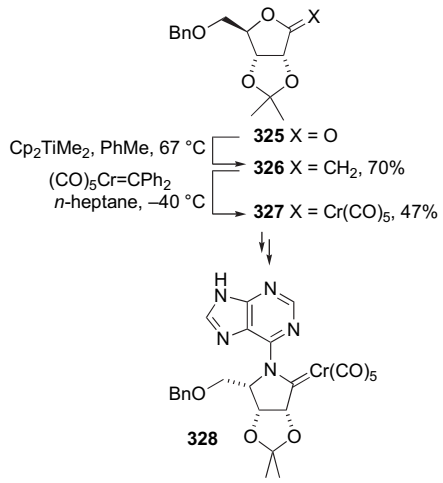
Rawal and co-workers recently synthesised mycalamide A, which is one of a family of natural products from *Mycale* marine sponges.[228] They constructed the benzoyl-protected version **324** of the pederic acid subunit, which is common to the whole family of natural products, by a tandem Wacker–Heck reaction on enol ether **321**, prepared from ester **320** using the Petasis reagent (Scheme 110). This gave predominantly ketal **323**, presumably via a carbopalladated intermediate **322**.



Scheme 110.

Dötz and de Silva generated a Fischer carbene complex as part of the preparation of an adenosine analogue **328** by methylenation of lactone **325** using the Petasis reagent

followed by an alkene metathesis of the enol ether **326** to give the chromium alkylidene complex **327** (Scheme 111).[229]



Scheme 111.

Ring-closing reactions involving metal-mediated alkene metathesis have been used so often in conjunction with titanium carbenoids as to deserve a section of their own (see below).

3.11. Ring-closing metathesis (RCM) and tandem metathesis-intramolecular alkylidenation

A common strategy in total synthesis involves alkenation of carbonyl groups using titanium carbenoids followed by ring-closing metathesis. The carbonyl group may be an aldehyde, a ketone or an ester, and Grubbs' second-generation catalyst **329** is almost invariably the catalyst used for the RCM reaction (Fig. 10). First, we shall consider the reaction sequence when the carbonyl group is a ketone or an aldehyde. Here, titanium carbenoids are the reagent of choice if the group is sterically hindered or if base-induced epimerization of α-chiral centres, retro-Michael reaction or another side reaction is likely when using a Wittig reagent. Employing this strategy, Mulholland and Pattendan converted sugar-derived ketone **330** into diene **331** with the Nysted reagent under Tochtermann–Matsubara conditions, and then used RCM to make cyclopentene **332**, which was then elaborated to give the fully substituted cyclopentane unit of viridenomycin using radical chemistry (Scheme 112).[230] In the methylenation–RCM sequence that completed their approach to the pentacyclic core of vannusal A, Nicolaou's group used Takai methylenation of ketone **333**, rather than Wittig conditions, to avoid potential epimerization of the α-chiral centre or elimination of the OTES group (Scheme 113).[231] RCM of the resulting diene **334** gave pentacycle **335** in high yield.

Gaul and Danishefsky applied a Tebbe methylenation–RCM sequence in a model study, prior to their full synthesis of the

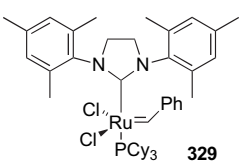
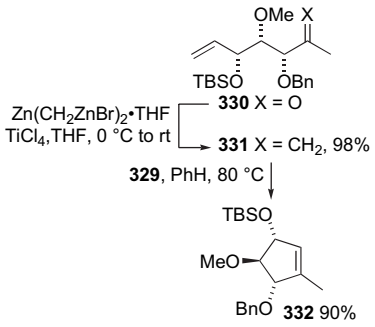
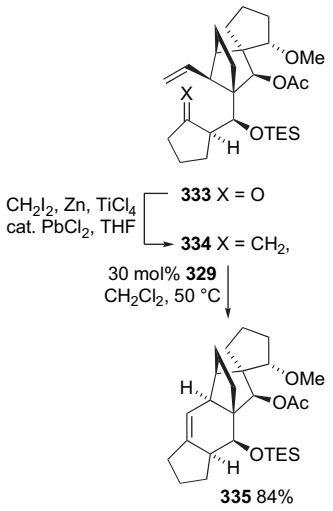


Figure 10.

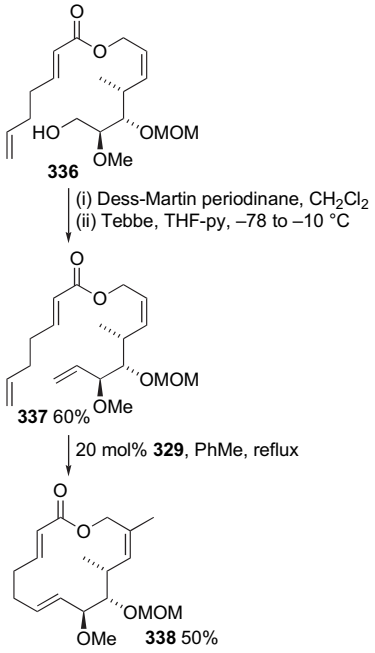


Scheme 112.



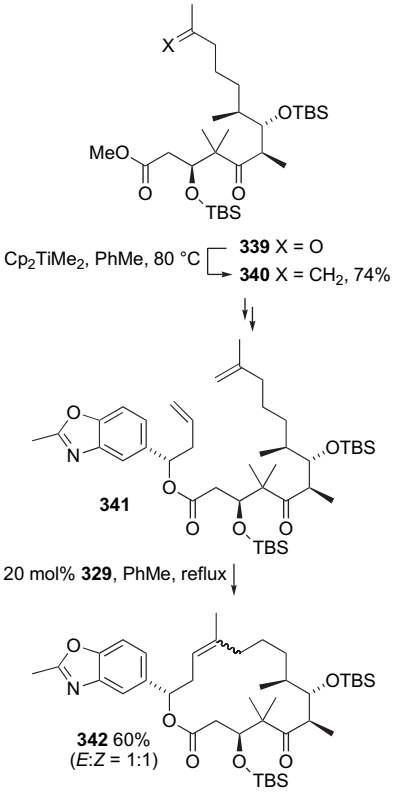
Scheme 113.

macrolide natural product migrastatin.[232,233] Thus, alcohol **336** was oxidised to the aldehyde and Tebbe methylenation afforded tetraene **337**, which was then cyclised to give macrolide **338** (Scheme 114).



Scheme 114.

Dong and co-workers applied a similar strategy to prepare epothilone analogues. Degradation of epothilone D gave ketone **339**, which was methylenated to give alkene **340**, before epothilone-like structures were reconstructed by conversion of the methyl ester into the ester of an alkene-bearing group and RCM (Scheme 115).[234] In one example, alkene **340** was converted into diene **341**, which cyclised to give an *E*–*Z* mixture of protected epothilone analogues **342**.

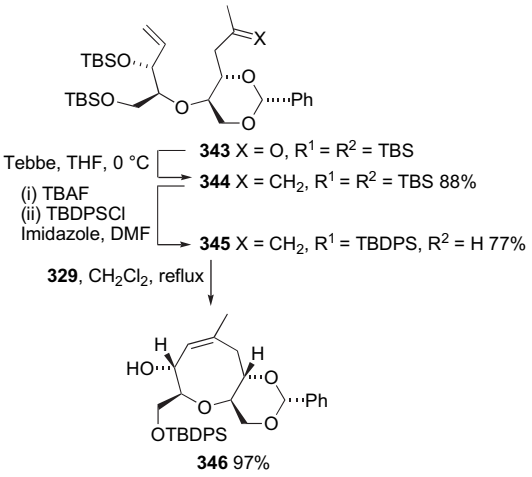


Scheme 115.

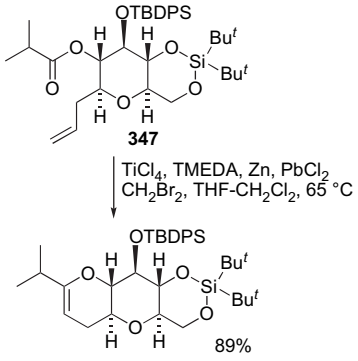
A common method for the preparation of polycylic ether natural products is an iterative sequence of alkylidenation followed by RCM. Fujiwara et al. used this type of procedure to form the eight-membered I-ring portion of ciguatoxin **161** (Fig. 5).[235] Ketone **343** was methylenated to give diene **344**, which after a change of protection to give alcohol **345** was smoothly cyclised to give the medium-ring ether **346** (Scheme 116).

Majumder and Rainier used modified Takai alkylidenation conditions to cyclise isobutyrate ester **347** in excellent yield during their investigations into the synthesis of polycyclic ether natural products (Scheme 117).[136] The mechanism of this unusual cyclisation has already been discussed in Section 2.4. This procedure, like the tandem methylenation–RCM using Tebbe or Petasis reagents introduced by Nicoloau (Scheme 31, Section 2.4),[19] is very substrate dependent. Thus, the same conditions led to simple methylenation of ester **348** and the resulting enol ether **349** was therefore cyclised with Grubbs' second-generation catalyst **329** to give the seven-membered enol ether **350** (Scheme 118).[135]

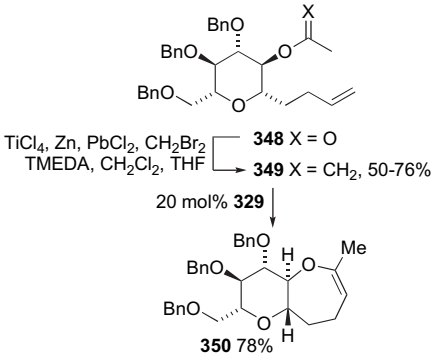
Rainier and co-workers used both of these types of alkylidenation–RCM sequences in their total synthesis of (−)-



Scheme 116.

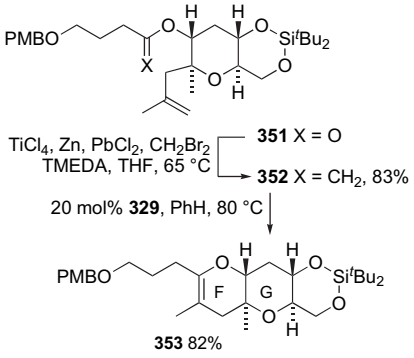


Scheme 117.



Scheme 118.

gambierol **149**. Thus, Takai methylenation of ester **351** gave enol ether **352**, which was cyclised using Grubbs' catalyst **329** to give tetrasubstituted alkene **353** constructing ring F (Scheme 119).[236] On the other hand, in the final stages of the synthesis, completion of the carbon backbone was achieved by coupling fragments **354** and **355** corresponding to the two halves of the molecule by esterification and then Takai ethylidenation conditions caused ester **356** to cyclise directly to enol ether **357** (Scheme 120).[237] Presumably alkene metathesis generated a titanium alkylidene complex from the methylene unit and this then alkylidenated the ester intramolecularly (see Section 2.4).

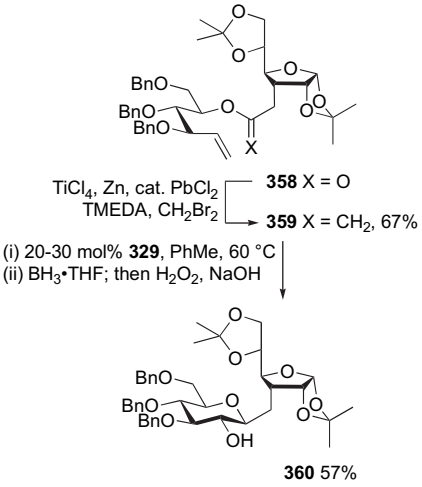


Scheme 119.

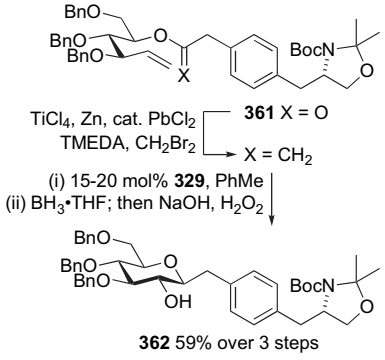
Postema and co-workers have used a methylenation–RCM–hydroboration–oxidation sequence extensively to form many different kinds of β-C-glycosides.[238–243] In a typical example, Takai methylenation of ester **358** gave enol ether **359**, which underwent RCM followed by hydroboration and oxidative work-up to give a C-disaccharide **360** in a stereoselective fashion (Scheme 121).[238] Similarly, the C-glycoside analogue **362** of an O-linked amino-acid glycoside was synthesised in 59% overall yield from ester **361** using the same strategy (Scheme 122).[239]

Several rings can be closed simultaneously using this procedure and it has been applied to the synthesis of differentially linked trisaccharides in good-to-excellent overall yield (Scheme 123).[240] In one particular case, the diester **363** was methylenated to give the bis-enol ether **364** that could be converted into trisaccharide **365** by double RCM, hydroboration and oxidation. Indeed, even three rings can be closed simultaneously using the same Takai methylenation–RCM strategy.[242]

Overhand and co-workers used a methylenation–RCM sequence in a synthetic approach to pyranopyran amino acids.[244] Thus, Petasis methylenation of ester **366** gave enol ether **367**, which was cyclised to the heterocyclic enol ether **368** in excellent yield (Scheme 124).

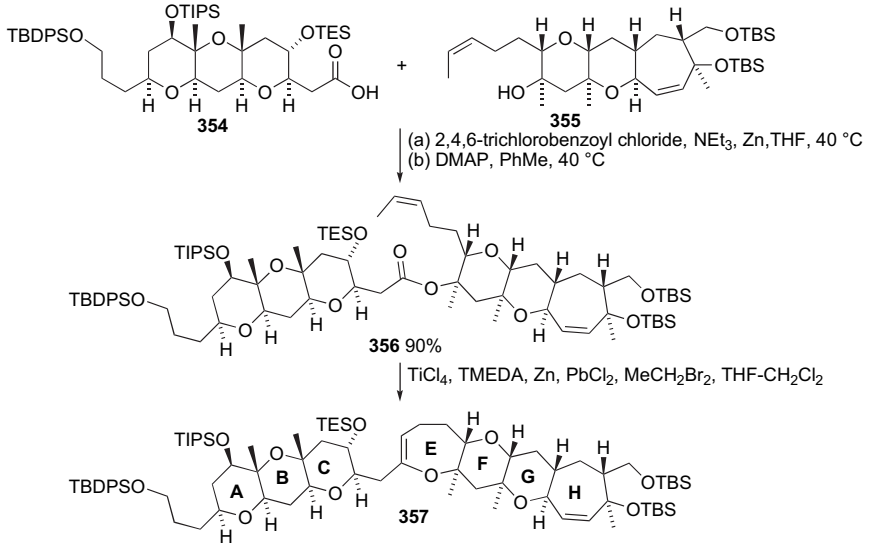


Scheme 121.

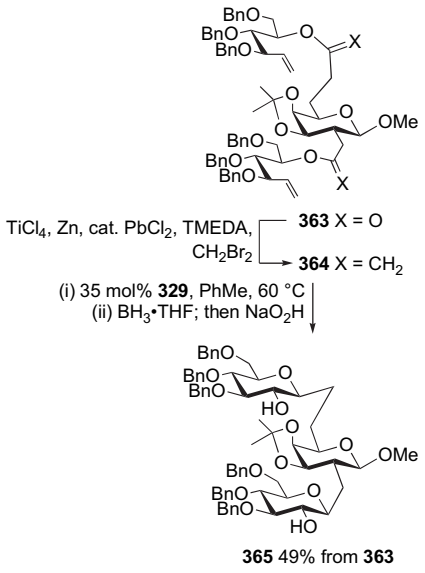


Scheme 122.

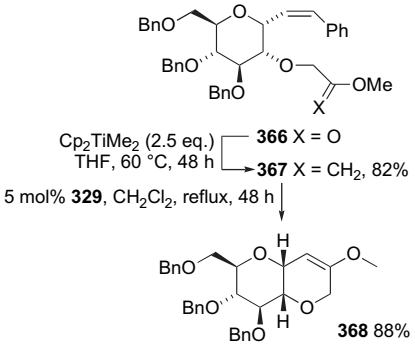
Holson and Roush[245] initially tried using titanocene methylidene to induce tandem methylenation–RCM (see Section 2.4 for a discussion)[19] in a synthetic route to the CD-spiroketal of spongistatin 1 **104** (Fig. 4). Unfortunately, no ring-closed product was observed and ester **369** was cyclised by a two-step procedure using the Tebbe reagent for the



Scheme 120.

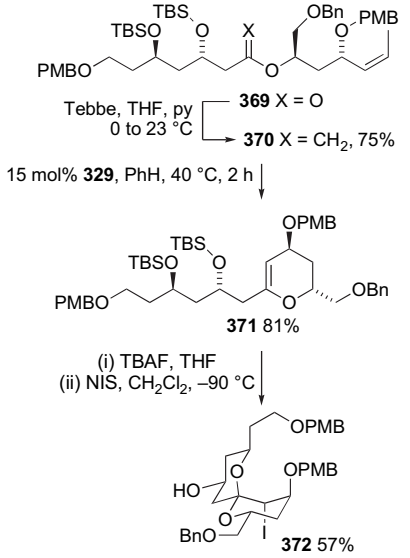


Scheme 123.



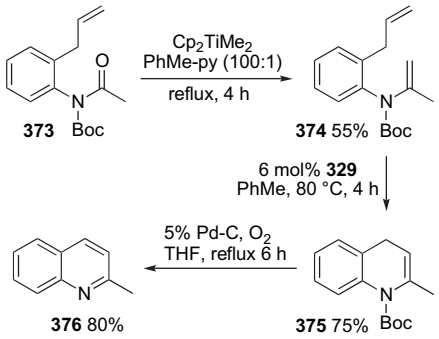
Scheme 124.

methylenation reaction and Grubbs' second-generation catalyst **329** for RCM of the enol ether **370** (Scheme 125). After removal of the silyl protecting groups from the enol ether **371**, spiroketalisation was achieved with *N*-iodosuccinimide to give spiroketal **372**.



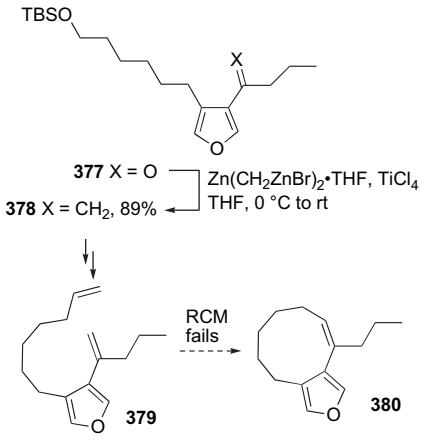
Scheme 125.

Bennasar and co-workers have shown that *N*-Boc-anilide **373** can be methylenated to give enamine **374**, which will undergo RCM to give a 1,4-dihydroquinoline **375** that is easily oxidised to quinoline **376** (Scheme 126).[62] An *N*-Boc-*N*-aryl formamide can also be cyclised in this way.



Scheme 126.

The methylenation–RCM strategy is sometimes limited by the efficiency of RCM reactions: high catalyst loadings are required to form cyclic enol ethers, and when the ring size or orientation of the methylene units is unfavourable, or heteroatoms coordinate to the ruthenium in a way that disfavours cyclisation, RCM may fail altogether. Thus, when Clark and co-workers were developing a route to the carbocyclic core of cornexistins, methylenation of ketone **377** was successful using the Nysted reagent and $TiCl_4$, but RCM of a diene **379** derived from the resulting alkene **378** failed to give the cyclic trisubstituted alkene **380** (Scheme 127).[246]

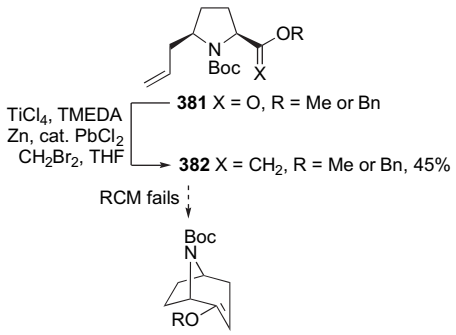


Scheme 127.

Similarly, Aggarwal et al. successfully methylenated esters **381** to give dienes **382** when exploring an RCM route to the tropane alkaloid, ferrugine (Scheme 128),[247] but RCM failed, and recourse to an enyne metathesis route was necessary to complete the total synthesis.

3.12. Solid-phase reactions

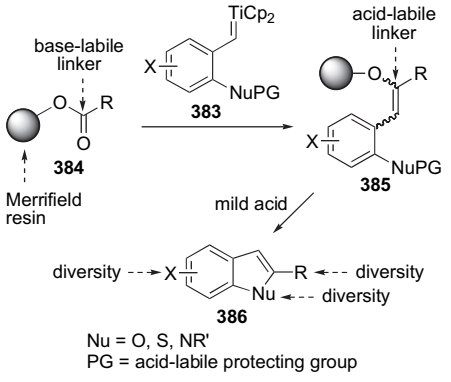
In 1998, Barrett and co-workers demonstrated that Tebbe methylenation of Merrifield-bound esters gave resin-bound



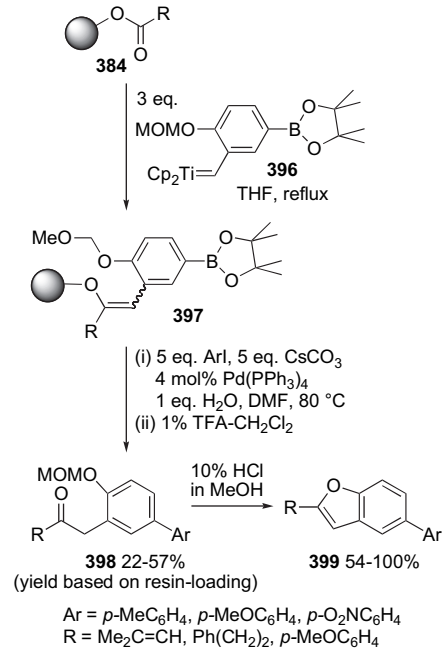
Scheme 128.

enol ethers in good yield.[34] The resin-bound enol ethers could then be subjected to a variety of transformations before cleavage with acid (for more details, see our earlier review[8]).[34,248] Switching the nature of the linkage to the resin in this way had two effects: firstly, it increased the diversity, as different products were available from cleaving at the ester and enol ether stages; and secondly, the switch to a linker cleaved under orthogonal conditions ensured that any unreacted ester remained attached to the resin and the products released from resin-bound enol ethers were clean. The Barrett team introduced the term 'chameleon catch' to describe this switch in the nature of the linker.

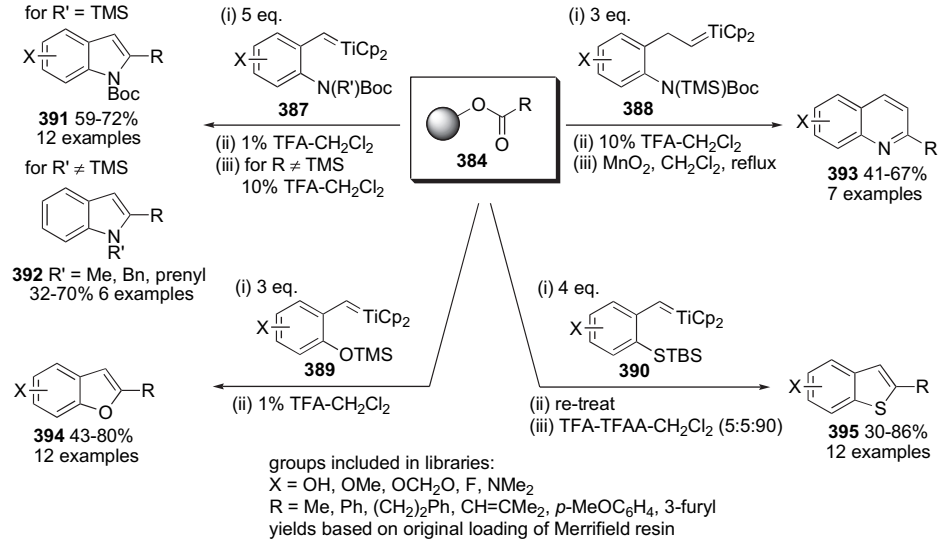
The Tebbe reagent is limited to methylenation and so, in the Barrett work, no extra functionality was introduced during the alkylidenation step. On the other hand, Hartley and coworkers recognised that functionalised titanium carbenoids **383** could be generated from thioacetals (see Section 2.3 and, in particular, Fig. 3) under Takeda's conditions and used to access a range of aromatic heterocycles. The general strategy involves using a titanium carbenoid **383** containing a masked nucleophile to convert resin-bound esters **384** into resin-bound enol ethers **385** (Scheme 129). The use of a solid support overcomes what can be a tedious purification following reaction in solution phase. Treatment with mild



Scheme 129.



Scheme 131.



Scheme 130.

acid leads to cleavage from resin with concomitant cyclisation to generate bicyclic heteroaromatic compounds **386** in high purity (due to the switch in the nature of the linker), and with no trace of the site of attachment to resin. During the review period, the Hartley team have used titanium alkylidene complexes **387**–**390** (derived from thioacetals **35**–**38**, respectively, in Fig. 3) to generate *N*-Boc and *N*-alkyl indoles **391** and **392**,[85,86] quinolines **393**,[89] benzofurans **394**[86] and benzothiophenes **395** (Scheme 130).[88] Of particular interest is the use of titanium benzylidene **396** that bears a boronate group, as this allows the introduction of further diversity after the alkylidenation step by cross coupling the resin-bound boronates **397** with aryl iodides prior to cleavage from resin and cyclisation of the resulting ketones **398** to give benzofurans **399** (Scheme 131).[87]

4. Conclusions

During the review period, a wide range of strategies have been developed that exploit the advantages of methylenation using titanium carbenoids. Petasis methylenation has shown particularly important advances with efficient scale up to 235 kg scale[45] and the introduction of rapid reaction under microwave conditions.[49,50] Although methylenation is widely used, strategies involving other alkylidenation reactions remain surprisingly rare, even though both Takai and Takeda alkylidenation conditions allow the introduction of a wide range of groups.

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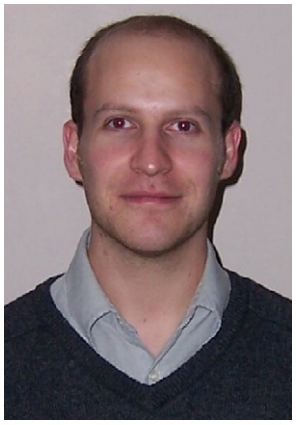
Biographical sketch

Richard Charles Hartley was born in Singapore in 1966 and went on to study Natural Sciences (Chemistry) at Downing College, Cambridge, graduating with a B.A. (honours) degree from the University of Cambridge in 1988. He carried out his Ph.D. research on *Stereospecificity and Stereoselectivity in the [2,3] Sigmatropic Sulfonium Ylide Rearrangement* under the direction of Dr. Stuart Warren at the same university, but having moved to Darwin College. Upon completion of his Ph. D. in 1991, he undertook postdoctoral research in the group of Tak-hang Chan at McGill University, Montreal (Canada), first on enantioselective synthesis of propargyl alcohols using a chiral auxiliary on silicon, and then on the synthesis of oligosaccharides using a soluble polymer support. After nearly two years as the Schering Plough Newman Scholar at University College Dublin, Ireland, he was appointed a lecturer at the University of Glasgow, Scotland, in October 1995, where he is currently a Reader in Organic Synthesis and Chemical Biology. The development of novel titanium carbenoids has been his major research interest, but other interests include the use of small molecules to study and ameliorate oxidative stress.

Jianfeng Li received his B.S. in Chemistry from Peking University, China in 2002. He then undertook an M.Sc. on *Titanium-based Alkylidenating Reagents* under the direction of Dr. Richard C. Hartley at the University of Glasgow, Scotland, completing it in 2005. He is currently a Ph.D. student under the supervision of Prof. Kenneth S. Feldman at Pennsylvania State University, USA. His research now focuses on developing Pummerer methodology for a model study of the total synthesis of Plau'amine.

Calver Amos Main was born in Aldershot, England, in 1980. He received his M.Sc. (honours) degree in Chemistry with Medicinal Chemistry from the University of Glasgow, Scotland, in 2004. He then joined the group of Dr. Richard C. Hartley at the same university for his Ph.D. research, which is a collaboration with Dr. Shahzad S. Rahman at GSK, Harlow, UK. His current research focuses on new titanium carbenoid reagents that allow the diversity-oriented, parallel synthesis of indoles on solid phase.



Gordon J. McKiernan was born in West Dunbartonshire in 1979 and went on to study Chemistry with Medicinal Chemistry at the University of Glasgow, Scotland. He graduated in 2000 and remained there to undertake an EPSRC-funded Ph.D., under the direction of Dr. Richard C. Hartley, on the development of *Novel Titanium(IV) Alkylidenes for the Diversity-based Synthesis of Aromatic Heterocycles*. He graduated in 2004 and after a short period of postdoctoral research with Prof. Amy Howell at the University of Connecticut, Gordon returned to the UK to work for Prof. Adam S. Nelson at the University of Leeds, to help develop a novel solid-phase methodology for the generation of diverse libraries of natural-product-like molecules. Gordon now works as a Development Chemist in the early-phase development facility of Nicolas Piramel Pharmaceuticals (NPIL) in Huddersfield.