Samarium(II)-Iodide-Mediated Cyclizations in Natural Product Synthesis

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1. Introduction

Since its introduction as a reagent for organic synthesis by Kagan in 1977,[1,2] samarium(II) iodide (SmI_2) has been widely embraced by the synthetic chemical community. Previous reviews have dealt with the application of this reagent in general organic chemistry,[3−8] specific organic transformations,[9] sequential reactions,[10−12] and polymer chemistry.[13,14] This review will deal with the application of SmI_2-mediated *cyclization* reactions in the synthesis of natural products.

Natural product synthesis remains the arena in which new synthetic methods and reagents are put to the test. The challenging structures and complex functionality of many natural product targets ensures that only robust and selective methods and reagents come through such a trial. The mild and selective nature of SmI_2 has led to its widespread application in target synthesis, and an array of cyclization protocols have been employed successfully to assemble many different ring systems. This review pays testament not only to the power of SmI_2 as a reagent for synthesis, but also to the creativity and ingenuity of the organic chemist.

Examples have been ordered according to the size of the ring formed in the SmI_2-mediated cyclization. Additionally, a brief introduction to the reagent and the classes of transformation possible has also been included, although the reader is referred to previous reviews for a complete discussion of this area.[3−12]

1.1. The Reagent

Due to the propensity for Sm(II) to revert to the more stable Sm(III) oxidation state, SmI_2 is a one-electron-transfer reagent. The reduction potential has been measured.[15−17] The reagent is commercially available as a solution in THF; however, it can be prepared readily, and several straightforward methods have been described. The reaction of Sm metal with diiodoethane[2] and diodomethane[18] remain the most popular methods for preparing SmI_2 as a

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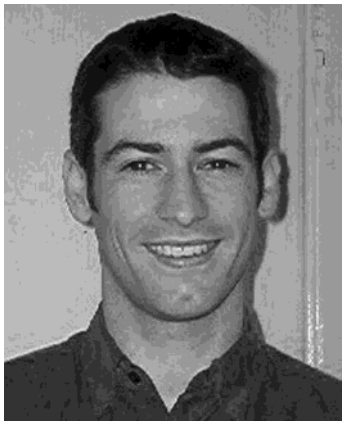

Derek Johnston was born in Irvine in Ayrshire, Scotland, and educated at Girvan Academy before leaving to study Chemistry at Glasgow University in 1994. After graduating in 1998, he carried out Ph.D. studies with David J. Procter at Glasgow, working on new, stereoselective cyclization reactions using SmI_2. In 2001 he took a position as Senior Research Chemist at OSI Pharmaceuticals in Oxford, England, before returning to Scotland in 2002 as a postdoctoral fellow in Medicinal Chemistry with Dave Adams at Heriot–Watt University, Edinburgh. In January 2004 he took a position with Scottish Biomedical in Glasgow. Outside of chemistry, Derek enjoys playing and watching football.

solution in THF, although the reaction of the metal with iodine is arguably more convenient.[19] Recently, the preparation of the reagent from Sm metal and a variety of iodine sources, including iodoform, using sonication has been described.[20] The preparation of the reagent in acetonitrile from the reaction of Sm metal with TMSCl and NaI is also possible.[21] SmI_2 is air-sensitive but tolerant of water and can be handled using standard syringe techniques. Reactions are typically carried out in THF, although the use of other solvents has been investigated.[22]

Part of the reagent's popularity arises from its ability to mediate both radical and anionic processes and sequences involving both.[10−12] It has been utilized in a wide range of synthetic transformations ranging from functional group interconversions to carbon−carbon bond-forming reactions. The reagent is often

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highly chemoselective, and transformations instigated by SmI_2 tend to proceed with high degrees of stereoselectivity. Adding to its appeal, the reactivity, chemoselectivity, and stereoselectivity of SmI_2 can be manipulated and fine-tuned by the addition of various salts and cosolvents to the reaction mixture (section 1.2).

1.2. Effect of Additives and Cosolvents

Additives and cosolvents often have a profound effect on reactions mediated by SmI_2. Although the influence of solvents or additives has recently been summarized by Kagan,[22] this is still a poorly understood area. A full discussion of additive effects in SmI_2 chemistry is beyond the scope of this review; however, the effects of the most commonly employed additives are discussed briefly below.

1.2.1. Lewis-Basic Additives and Cosolvents

A number of additives containing Lewis-basic oxygen and nitrogen functionality have been used in SmI_2 reactions. The reduction potential of the reagent is increased significantly by such additives.[23] The most commonly employed Lewis base is HMPA,[24] the effects of which have been extensively studied.[15−17,25] Flowers has shown that the reduction potential of the reagent increases with increasing HMPA up to a plateau after the addition of four equivalents with respect to samarium.[15] This is in agreement with the isolation and X-ray characterization of $SmI_2(HMPA)_4$ from the purple solution obtained when toluene is added to SmI_2 in THF−HMPA.[26,27] Flowers suggested that this is the active species in reactions involving SmI_2 in THF−HMPA.[25] Daasbjerg and Skrydstrup, however, suggested that the active species in solution may be more closely represented by the formula $[Sm(HMPA)_4(THF)_2]I_2$.[17] Also, $[Sm(HMPA)_6]I_2$ has been isolated in the solid state,[27] and Daasbjerg and Skrydstrup provided some evidence for the presence of this species in solutions containing an excess of HMPA.[17]

The use of less-toxic DMPU as an additive also increases the reduction potential of the reagent, although more equivalents are required to achieve the same level of activation.[23] The insolubility of the SmI_2−DMPU complexes in THF can be a problem in some cases; however, this can be overcome through the use of acetonitrile as solvent.[28,29]

1.2.2. Proton Sources as Additives

Low molecular weight alcohols such as MeOH and *t*-BuOH are frequently used as additives in SmI_2 reactions to protonate anionic intermediates formed during the processes.[22] It is also becoming increasingly clear that additives such as MeOH and water, in particular, do not solely act as proton sources but also lead to activation of the reagent in some way, perhaps through coordination to the metal center.[28] Very recently, Flowers has shown that water has a significant effect on the mechanism and rate of the SmI_2-mediated reduction of ketones, indicating that water coordinates to Sm(II), generating a new reactive species. A similar effect may arise with high concentrations of MeOH. This study also indicated that the pK_a of the added proton source can affect the degree of rate enhancement.[30]

1.2.3. Other Promoters

Irradiation of SmI_2 reactions in the visible range has been used to increase the rate of a range of SmI_2-mediated reactions, including sequential radical−anionic processes and carbonylations.[31] The reduction of alkyl chlorides with SmI_2 is also promoted by irradiation.[32]

Various inorganic salts have been used as additives in SmI_2-mediated reactions. Lithium chloride and bromide have been shown to give a notable increase in reactivity.[33] Chemoselectivity has also been shown to be significantly altered by lithium halide additives.[34]

A number of transition-metal salts,[35] such as NiI_2, and iron(III) salts have been used as catalytic additives in SmI_2-mediated reactions, giving increased reaction rates, particularly in Barbier-type processes.

1.3. Carbon–Carbon Bond-Forming Processes Mediated by SmI_2

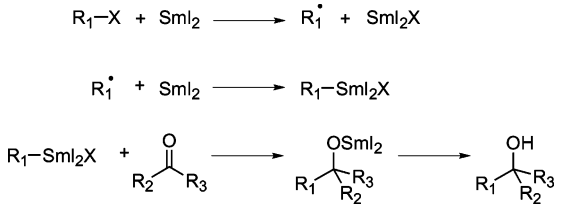
In the following section, the main SmI_2-mediated C−C bond-forming processes are outlined and their mechanisms briefly discussed. The aim of this section is to provide an introduction to the reagent and its reactions prior to discussion of its use in natural product synthesis.

1.3.1. SmI_2-Mediated Barbier Reaction

The SmI_2-mediated Barbier reaction has been the subject of a recent review.[9] This reaction is homogeneous and often highly chemoselective, an advantage when compared with Mg-, Li-, and Zn-mediated Barbier reactions. Primary, secondary, allylic, and benzylic halides as well as 1-iodoalkynes can be used in the transformation, although aryl, vinyl, and tertiary halides do not routinely give satisfactory results. Additives such as HMPA,[36] NiI_2,[35] ferric salts such as $Fe(DBM)_3$,[37] and light activation[38] have been found to increase the rate of Barbier-type reactions.

Ambiguity still surrounds the mechanism of many SmI_2-mediated reactions, and the SmI_2-mediated Barbier reaction is no exception. The mechanism most widely accepted involves the addition of an organosamarium, or carbanion, to a carbonyl group (Scheme 1). Curran provided some evidence for this mechanism.[39,40]

Scheme 1

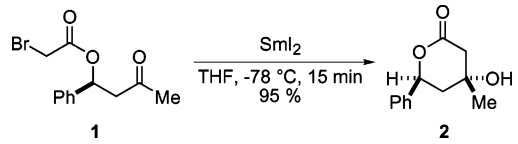


With two reducible groups within the same molecule, the mechanism of the *intramolecular* SmI_2-mediated Barbier reaction is even less clear cut and more difficult to investigate.[41] However, Molander found evidence for the intermediacy of organosamarium species, suggesting a mechanism similar to that described above.[40,42] Despite the mechanistic ambiguity, the SmI_2-mediated Barbier cyclization has been used to great effect in many syntheses.

1.3.2. Reformatsky and Aldol-Type Reactions

The SmI_2-mediated Reformatsky reaction provides a useful alternative to the traditional zinc-mediated reaction.[9] It is generally believed that the intermolecular and intramolecular Reformatsky reactions progress through a samarium(III) enolate. It is in the intramolecular sense that the SmI_2-mediated Reformatsky reaction has been used to greatest effect, with cyclizations giving high yields and proceeding with high levels of stereocontrol. For example, treatment of α-bromo ester **1** with SmI_2 gives lactone **2** as a single diastereoisomer (Scheme 2).[43]

Scheme 2



1 **2**

The intramolecular reaction has been used to access medium and large carbocycles and lactones. Inanaga suggests that the successful formation of such rings could be assisted by the large ionic radius of samarium, its flexible coordination number, and its high oxophilicity; the lanthanide center effectively brings the two reacting centers together through chelation.[44]

1.3.3. Radical–Alkene/Alkyne Cyclizations

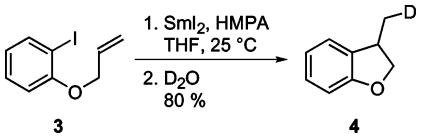
SmI_2-mediated radical cyclizations where radical generation is achieved by the reduction of halides and sulfonates, for example, have been used in natural product synthesis. In the majority of these cyclizations, the radical acceptor is either an alkene or alkyne. The methodology has been extended to

involve conjugate addition reactions, with α,β-unsaturated esters, amides, nitriles, lactones, and lactams being used as the radical acceptor.[45−48]

Reductive radical cyclizations mediated by SmI_2 provide an attractive alternative to Bu_3SnH-mediated reactions. With the ability of SmI_2 to further reduce carbon-centered radicals to carbanions, it is important that the rate of cyclization is faster than the rate of the second reduction. To promote cyclization, reactions are often performed at low concentration of reagent.

These cyclizations typically proceed via a mechanism analogous to that of tin-hydride-mediated reactions; however, whether hydrogen-atom capture or proton capture terminates the sequence depends on the type of radical formed after cyclization and the specific reducing conditions. For example, in studies by Curran on the cyclization of iodide **3**, deuterium incorporation in **4** after quenching with D_2O illustrates that a second SmI_2 reduction is occurring before hydrogen-atom capture by the radical intermediate (Scheme 3).[49]

Scheme 3



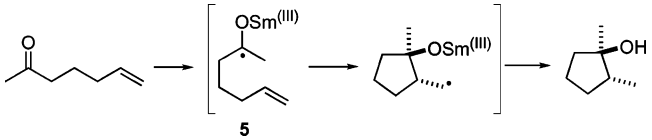
3 4

1.3.4. Carbonyl–Alkene/Alkyne Reductive Couplings

SmI_2-mediated carbonyl−alkene/alkyne reductive couplings are widely documented, with a wealth of precedent for both intermolecular and intramolecular reactions.[4−7,10−12] The intramolecular reaction is particularly useful and allows a variety of cyclic alcohols of varying ring sizes to be assembled under mild conditions with high stereoselectivities.

Both aldehydes and ketones can be employed in the cyclizations, and both activated[50] and unactivated[51] alkenes and alkynes have been employed as the coupling partners. Mechanistically, these reactions have been described as ketyl−olefin couplings, involving reduction of the aldehyde or ketone carbonyl with SmI_2 to give a samarium ketyl radical anion **5,** which then adds to the carbon−carbon multiple bond (Scheme 4).[51]

Scheme 4



5

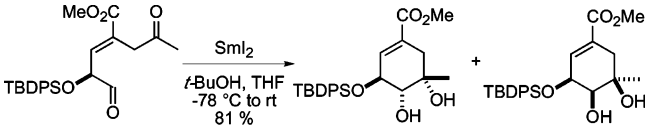
In cases where the acceptor is itself reducible, for example, in α,β-unsaturated esters, it now seems clear that alternative mechanisms may operate. For example, a mechanism involving conjugate reduction of the electron-deficient double bond, followed by anionic cyclization onto the carbonyl group, has been shown to occur for some substrates.[52] A dependence of stereochemical reaction outcome on the olefin geometry in the starting material is perhaps the best indication that a ketyl−olefin mechanism is operating.[53,54]

1.3.5. Pinacol-Type Couplings

SmI_2 is routinely used to mediate the pinacol coupling reactions of both aldehydes and ketones.[4−7] The coupling of aldehydes or ketones with oximes,[55,56] hydrazones,[57,58] and nitriles[59] has also been reported.

The SmI_2-mediated intramolecular pinacol couplings generally progress with significant selectivity to form cis diols. Furthermore, when the carbonyl has an alkoxy group in the α-position, the orientation of the hydroxyls is predominately 'anti' relative to that substituent; for example, keto−aldehyde **6** cyclizes to give *cis*-1,2-diol **7** with excellent selectivity (Scheme 5).[60]

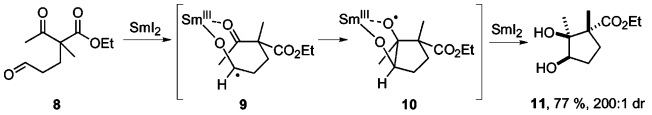
Scheme 5



6 7 96 : 4

The mechanism for the intramolecular pinacol coupling is thought to proceed via reduction of one of the carbonyl groups by SmI_2 to give a ketyl radical anion. The Sm(III) center then coordinates to, and activates, the second carbonyl before attack by the ketyl radical anion. The resultant oxygen-centered radical is then reduced further before protonation to form the diol.[61] Coordination of the Sm(III) center to the second carbonyl following the initial reduction explains the frequently observed cis stereoselectivity of the cyclization.[60] For example, keto−aldehyde **8** undergoes reduction to give ketyl radical anion **9**. Cyclization then forms oxy−radical **10,** which after reduction and protonation, gives *cis*-diol **11** with excellent selectivity (Scheme 6).[61]

Scheme 6



8 9 10 11, 77 %, 200:1 dr

2. Cyclization Reactions in Natural Product Synthesis

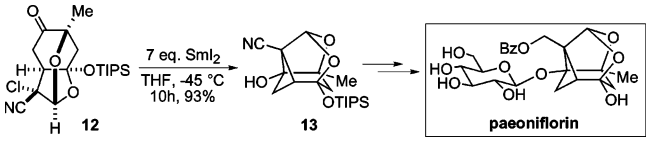
2.1. Four-Membered Rings

2.1.1. Reformatsky Reactions

Despite the extensive literature surrounding SmI_2 transformations, few examples of four-membered ring formation using the reagent have been reported. In 1993, Corey reported the first total synthesis of paeoniflorin.[62] In his approach to the natural product, protected paeoniflorigenin **13** was first prepared, with subsequent glycosylation then giving paeoniflorin. The caged structure of **13** was prepared using a multistep reaction sequence, which featured a SmI_2-mediated Reformatsky reaction. The reaction of chloride **12** proceeded smoothly in the absence of

additives at −45 °C to give cyclobutanol **13** in excellent yield (Scheme 7). An aldol-type cyclization

Scheme 7

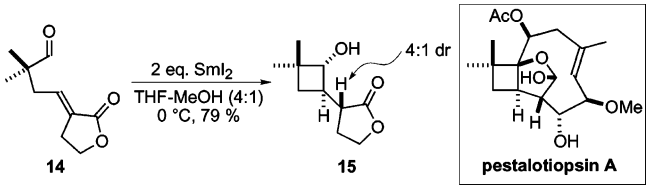


could not be used to effect the transformation as the cyclobutanol products were found to be extremely base sensitive.

2.1.2. Carbonyl–Alkene Reductive Couplings

Procter constructed the bicyclic core of pestalotiopsin A using a SmI_2-mediated 4-*exo*-trig cyclization of an unsaturated aldehyde. In model studies, treatment of aldehyde **14** with two equivalents of SmI_2 in THF−MeOH (4:1) gave the *anti*-cyclobutanol **15** in good yield and with complete *anti*-selectivity and modest diastereocontrol at the third new stereocenter α to the lactone carbonyl group (Scheme 8).[63] Inter-

Scheme 8



estingly, the double-bond stereochemistry in the substrate was found to have a profound effect on selectivity of the cyclization.[63,64]

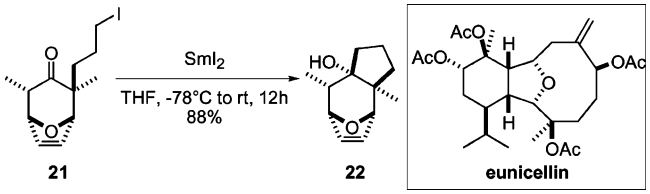
An extension of this work utilized a remote stereocontrol element in the substrate to control the facial selectivity in the cyclization. Treatment of aldehyde **16** with SmI_2 in THF−MeOH gave poor results; however, use of 2,2,2-trifluoroethanol as a cosolvent led to good yields of cyclobutanols **17** and **18,** with moderate selectivity. The stereochemical outcome is explained by an unusual coordination of the TBDMS ether to the Sm(III) center of the ketyl radical anion **20**. Further manipulation of cyclobutanol **17** gave access to **19**, representing the functionalized core of the natural product (Scheme 9).[65]

2.2. Five-Membered Rings

2.2.1. Barbier Reactions

The eunicellins possess an interesting α,α′-bridged nine-membered ring ether, a framework which Hoffmann has attempted to construct in model studies using a cerium(IV) ammonium nitrate (CAN) oxidative fragmentation process.[66] In the preparation of the tricyclic substrate for CAN-mediated fragmentation, Hoffmann employs a SmI_2-mediated Barbier reaction to form the tertiary cyclopentanol **22** necessary for the oxidative fragmentation step (Scheme 10). The cyclization of **21** proceeds very efficiently

Scheme 10



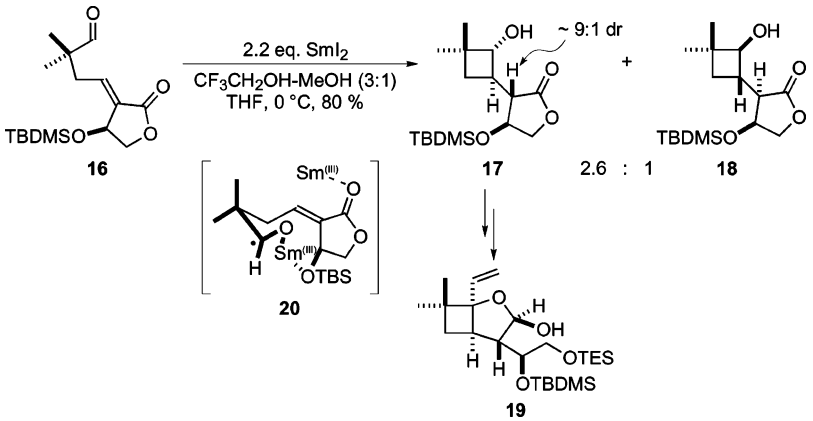
under mild conditions in the absence of additives to give **22** as a single diastereoisomer.

The isomeric sesquiterpenes (±)-isocaryophyllene and (±)-caryophyllene contain nine-membered rings fused to cyclobutane rings. In a similar strategy to the one discussed in the previous example, Suginome utilized a mercury(II)-oxide-mediated oxidative fragmentation to access the nine-membered ring in his approach to caryophyllene.[67]

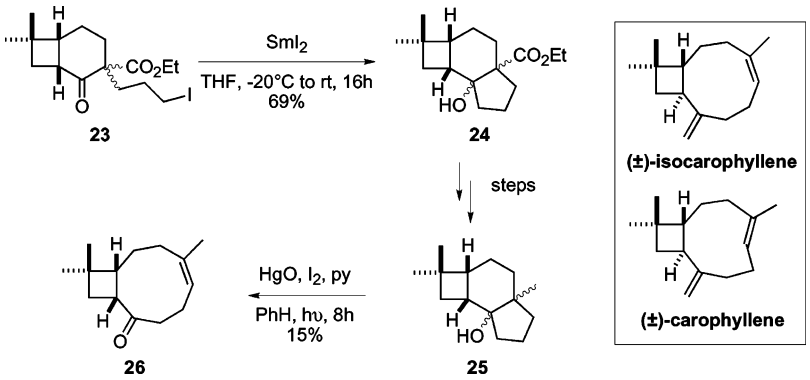
Substrate **25** for oxidative fragmentation was prepared using a SmI_2-mediated intramolecular Barbier reaction (Scheme 11). Cyclization of iodoketone **23** was achieved under mild conditions in the absence of additives to give the tertiary alcohol **24** in good yield. In this transformation, the stereochemistry of the tertiary alcohol and the quaternary center bearing the ethyl ester in **24** is unimportant as the stereochemistry at both centers is lost during the subsequent fragmentation to give **26**.[67]

In an earlier paper, Suginome used SmI_2 in HMPA to mediate a Barbier reaction to form the intermediate cyclopentanol **28**, followed by a similar mercury(II) oxide *β*-scission of an alkoxy radical, in an approach to (±)-muscone (Scheme 12).[68]

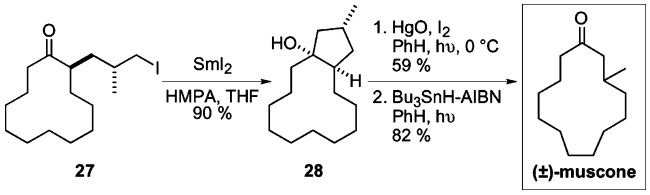
Scheme 9



Scheme 11

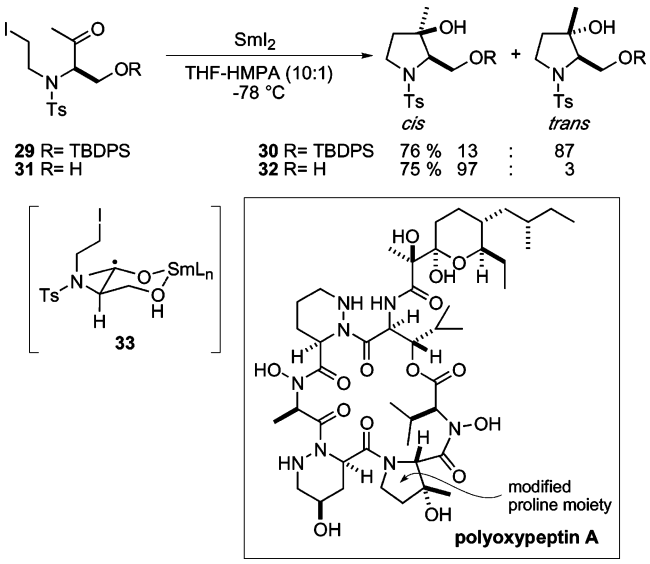


Scheme 12



Hamada constructed the novel, substituted proline moiety of polyoxypeptin A, a hexacyclic depsipeptide antibiotic, using a SmI_2-mediated Barbier reaction (Scheme 13).[69] As outlined in section 1.3.1, several

Scheme 13



mechanisms have been proposed for the SmI_2-mediated Barbier reaction. While an organosamarium addition to the carbonyl is the most widely accepted mechanism for the intermolecular reaction,[40] the mechanism is harder to define in the intramolecular sense, and this example is particularly ambiguous. In this case, generation of an organosamarium species from the iodide moiety in **29**/**31** might be expected to result in elimination aided by the electron-withdrawing tosyl group on nitrogen. Similarly, reduction of the carbonyl group in **29**/**31** could lead to fragmentation via elimination of the α-amino group.[70−72] The authors propose a mechanism involving displacement of the iodide by a ketyl radical such as **33**. This mechanism has been discounted for the intermolecular reaction[39] and seems unlikely in this case. A radical−radical coupling may be a more likely mechanism for the transformation of these substrates. Despite the potential complications outlined above, the reactions proceed in high yield (Scheme 13).

The stereochemical outcome of the cyclization was found to be highly dependent on the substrate. For example, treatment of TBDPS-protected substrate **29** with SmI_2 in the presence of HMPA gave the trans diastereoisomer of pyrrolidine **30** as the major product. Conversely, cyclization of the unprotected substrate **31** gave the cis diastereoisomer of pyrrolidine **32** as the major product (Scheme 13).[69] The switch in the selectivity of the cyclization can be explained by formation of a samarium chelate **34** between the ketone carbonyl and the unprotected alcohol (Figure 1). Such chelation is not possible in reactions of the

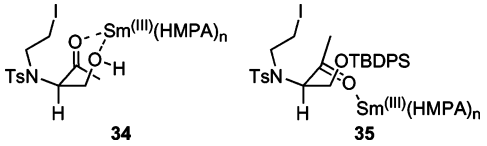


Figure 1.

protected substrate, and the coordination of a bulky Sm−HMPA complex to the carbonyl combined with the use of a large protecting group would result in a transition state resembling **35**.

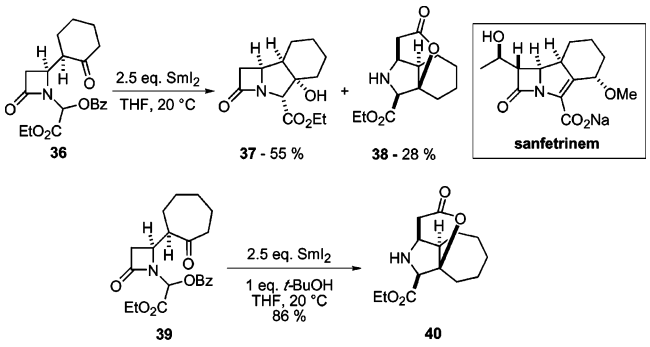
2.2.2. Reformatsky-Type Reactions

Skrydstrup prepared the tricyclic core of the antibiotic drug sanfetrinem via the SmI_2-mediated intramolecular Reformatsky-type reaction of β-lactam **36**. It is well known that SmI_2 reduces a variety of α-heteroatom-substituted carbonyl compounds to generate Sm(III) enolates.[5,6] Reduction of the α-benzoyloxyglycine moiety in **36** and cyclization of the resultant enolate onto the pendant cyclohexanone gave the tricyclic product **37** (Scheme 14). Byproduct **38** is also observed in appreciable yield and is formed via acyl transfer from the β-lactam to the newly formed samarium alkoxide. In other similar substrates, such as **39**, the acyl transfer predominates, with high yields of the proline derivative **40** obtained.[73]

2.2.3. Radical–Alkene/Alkyne Cyclizations

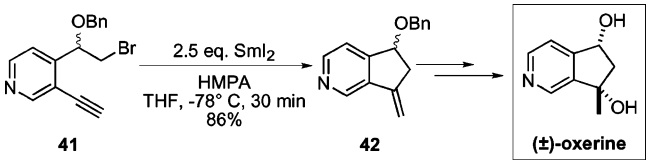
A number of examples of five-membered ring formation via SmI_2-mediated radical alkene/alkyne cyclizations in natural product synthesis have been

Scheme 14



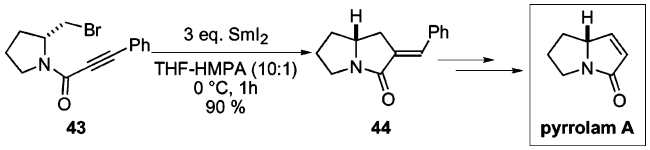
reported. In Ohta's racemic synthesis of the monoterpene alkaloid, oxerine, a SmI_2-mediated 5-*exo*-dig cyclization, was used to form the cyclopentane ring.[74] Reduction of bromide **41** gave a primary radical, which cyclized onto the triple bond to close the five-membered ring and form **42** (Scheme 15). No products from the elimination of the benzyloxy group were observed. Ozonolysis, Grignard addition, and deprotection furnished racemic oxerine.

Scheme 15



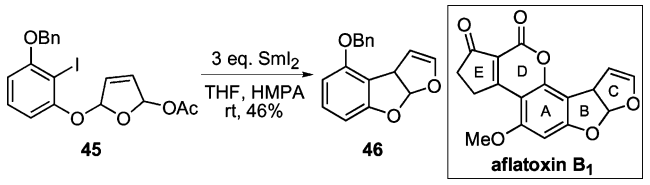
Ohta used a similar strategy in the synthesis of pyrrolam A. Treatment of primary bromide **43** with SmI_2 in THF−HMPA gave a primary radical which underwent clean 5-*exo*-dig cyclization to give **44** in high yield (Scheme 16). Only the *E*-olefin product was observed.[75]

Scheme 16



The ABC ring system of aflatoxin B_1 has been prepared by the SmI_2-mediated cyclization of aryl iodide **45** to give **46** in moderate yield (Scheme 17).[76]

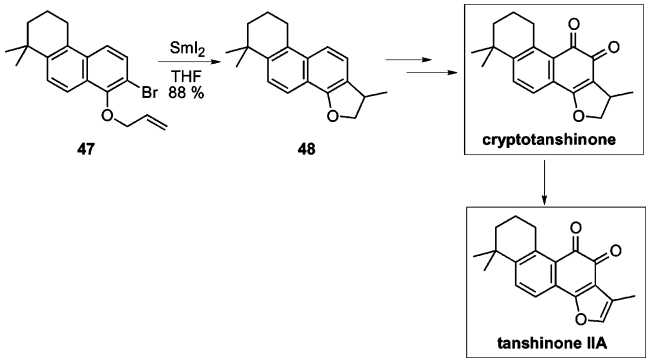
Scheme 17



The reaction proceeds via a 5-*exo*-trig radical cyclization, reduction of the resultant radical to the anion, and elimination of acetate.

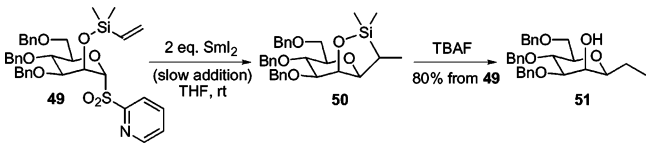
Cai and Lu formed the furan moiety of the biologically active diterpenoid quinines, cryptotanshinone and tanshinone IIA, using a SmI_2-mediated 5-*exo*-trig cyclization. Treatment of aryl bromide **47** with SmI_2 in THF promoted radical cyclization onto the pendant olefin acceptor, giving the dihydrobenzofuran **48** in high yield (Scheme 18). This intermediate was subsequently converted into both the target natural products.[77]

Scheme 18



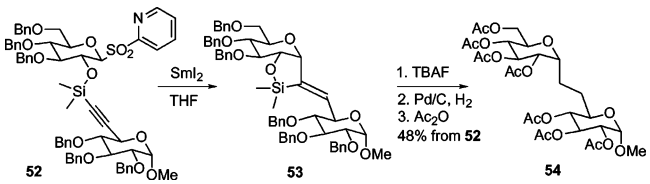
C-Disaccharides, in which the interglycosidic oxygen atom of a disaccharide has been replaced by a methylene group, are powerful tools for glycobiology. Of the many methods for *C*-glycoside formation, Stork's intramolecular free-radical cyclization employing a temporary silicon tether has attracted much attention. Beau and Skrydstrup prepared simple *C*-glycosides by SmI_2-mediated 5-*exo*-*trig* cyclization onto a silicon-tethered alkene. The cyclization of glycosyl phenyl sulfones required the use of HMPA as an additive and gave low yields. Lowering the LUMO energy of the aryl sulfone group by employing 2-pyridyl sulfones allowed the cyclizations to be carried out more efficiently and in the absence of HMPA. Thus, slow addition of SmI_2 to mannosyl 2-pyridyl sulfone **49** gave the β-*C*-glycoside **51** in 80% overall yield after desilylation (Scheme 19).[78]

Scheme 19



This approach was extended to the first stereoselective synthesis of a *C*-disaccharide.[78] Glycosylpyridyl sulfone **52** undergoes 5-*exo*-dig cyclization on treatment with SmI_2 to give **53**. Subsequent desilylation and further transformation gave the peracetylated *C*-disaccharide **54** in 48% overall yield (Scheme 20).

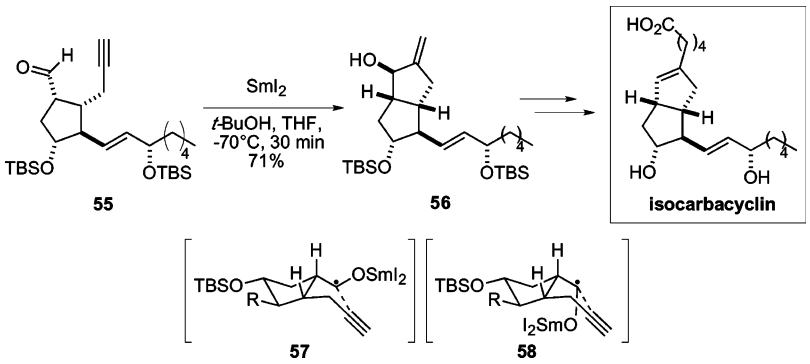
Scheme 20



2.2.4. Carbonyl–Alkene/Alkyne Reductive Couplings

Kurozumi's approach to isocarbacyclin employed the SmI_2-mediated 5-*exo*-dig cyclization of alkynyl aldehyde **55** to form the second five-membered ring

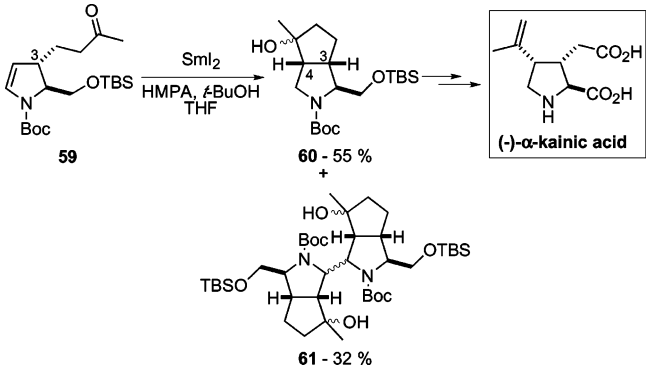
Scheme 21



in the bicyclo[3.3.0]octane ring system (Scheme 21).[79] Several reagents for the transformation were examined, such as Zn/TMSCl and lithium naphthalide; however, SmI_2 gave the highest yield and rate of cyclization. The 5-*exo*-dig aldehyde-alkyne reductive coupling gave a 9:1 ratio of diastereoisomers, **56** being the major product. The stereoselectivity of the cyclization can be explained by the Sm(III)−ketyl taking up an *exo* orientation in the transition state **57**. In transition state **58**, the Sm(III) complex is subject to unfavorable steric interactions with the pseudoaxial protons of the existing carbocycle. Byproducts resulting from intermolecular pinacol coupling and simple reduction of the aldehyde were also formed in the reaction.

(−)-α-Kainic acid has attracted the attention of many groups due to the challenge of installing three contiguous stereocenters on the pyrrolidine ring and the potent neuroexcitatory activity of the natural product. In Cossy's formal synthesis of (−)-α-kainic acid, the SmI_2-mediated cyclization of ketone **59** was used as a key step.[80] The ketyl radical anion derived from **59** cyclizes to form the *cis*-bicyclic product **60** (Scheme 22), thus establishing the cis stereochemical

Scheme 22

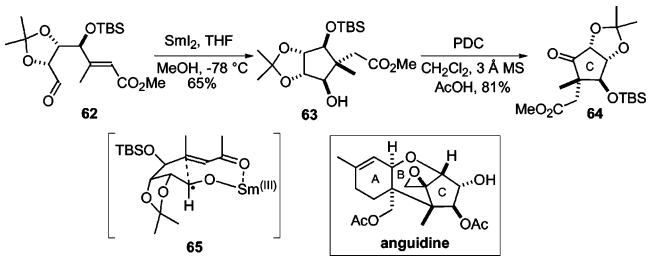


relationship between C3 and C4 in the natural product.

A 55% yield of the desired bicyclic pyrrolidine **60** was obtained, although a significant quantity of the dimer byproduct **61** was also isolated. The formation of **61** is due to dimerization of the stabilized radical formed upon cyclization competing with further reduction−protonation to give **60**. The stereochemistry of the newly generated tertiary alcohol was not discussed and lost during the formation of the propenyl group of the target.

Enholm utilized a SmI_2-mediated carbonyl−olefin reductive coupling in a synthesis of the C ring of anguidine. Carbohydrate-derived aldehyde **62** undergoes cyclization on treatment with SmI_2 to give functionalized cyclopentanol **63**. Oxidation then gives ketone **64**, a precursor to the C ring of the target (Scheme 23).[81] The anti stereochemistry at the newly

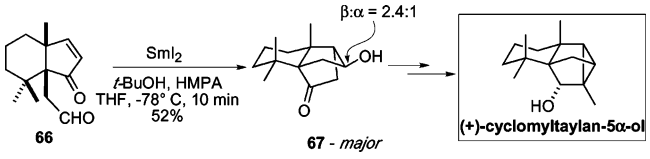
Scheme 23



formed carbon−carbon bond can be rationalized by the formation of a Sm(III)−chelate **65**.

In Hagiwara's enantioselective total synthesis of (+)-cyclomyltaylan-5-α-ol, a tetracyclic sesquiterpenoid, a SmI_2-mediated reductive cyclization was used to form a tricyclic intermediate.[82,83] The cyclization of aldehyde **66** in the presence of HMPA gave cyclopentanol **67** in moderate yield and with moderate diastereocontrol (Scheme 24).

Scheme 24



The authors rationalized the product stereochemistry by invoking a vinylogous pinacol coupling mechanism, arguing that the alternative ketyl−olefin coupling mechanism would result in the α-diastereoisomer being formed preferentially due to the formation of a seven-membered chelate **68** between the ketyl radical anion and the enone carbonyl (Figure 2).[82,83] However, as the reaction is carried out in the

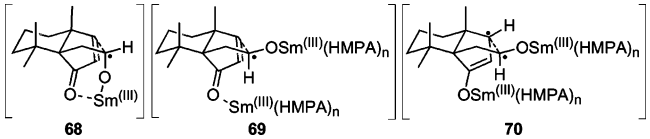
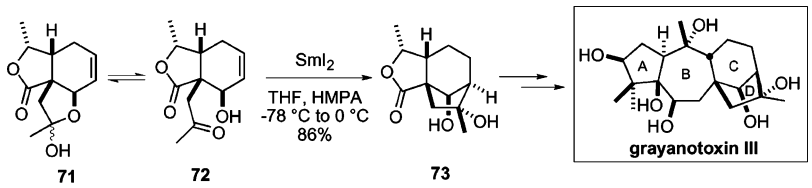


Figure 2.

Scheme 25

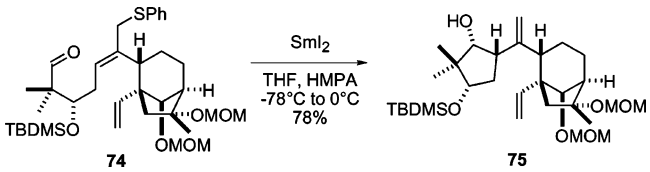


presence of HMPA, chelation in the transition state would be disfavored. Transition state **69**, representing a ketyl−olefin coupling mechanism, would also explain the observed stereochemical outcome. Here, the anti stereochemical relationship across the new carbon−carbon bond minimizes electrostatic repulsion between the ketyl anion and the developing electron density α to the ketone. This explanation has been used to rationalize the anti stereochemistry often observed in ketyl−olefin cyclizations.[84] An analogous argument can also be used to explain the stereochemical outcome of the reaction if a vinylogous pinacol mechanism is operating (Figure 2, transition state **70**). Therefore, neither mechanism can be discounted.

In his approach to grayanotoxin III, Matsuda used SmI_2 for the three key carbocycle-forming steps.[85] In the first SmI_2-mediated step, to form the CD rings of the natural product, the hemi−ketal **71**, which is in equilibrium with the hydroxy−ketone **72**, was treated with SmI_2 in the presence of HMPA (Scheme 25). Addition of the ketyl−radical anion to the unactivated olefin proceeded well to give **73** in high yield.

In the second SmI_2-mediated cyclization in Matsuda's approach, an allylic sulfide was used as a radical acceptor in a cyclization to form the A ring of the natural product (Scheme 26).[85] The cyclization

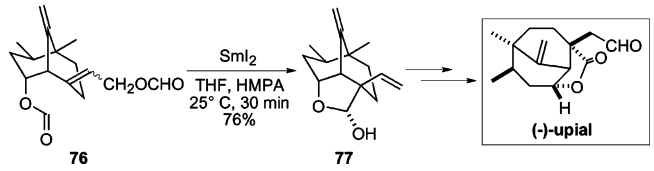
Scheme 26



of **74** resulted in elimination of the sulfide to generate a new double bond, which was then epoxidized and reduced to form the tertiary alcohol found in the B ring of the target. The cyclization proceeded to form exclusively the *syn*-cyclopentanol **75** in good yield. Interestingly, in model studies, related cyclization substrates without geminal disubstitution α to the aldehyde gave exclusively *anti*-cyclopentanol products.[86] Also noteworthy is the fact that the stereochemistry and yield of the cyclization are independent of the initial olefin geometry of the allyl sulfide. The third SmI_2-mediated cyclization in Matsuda's approach will be discussed in a later section.

The unusual bicyclo[3.3.1]nonane framework and the stereochemical complexity of the monoisoprenoid sesquiterpene (−)-upial renders it an interesting target for synthetic chemists. In his approach to the natural product, Yamada used an interesting 5-*exo*-trig cyclization to prepare tricyclic lactol **67** (Scheme 27).[87] Treatment of allylic formate **66**, used as a 2:1

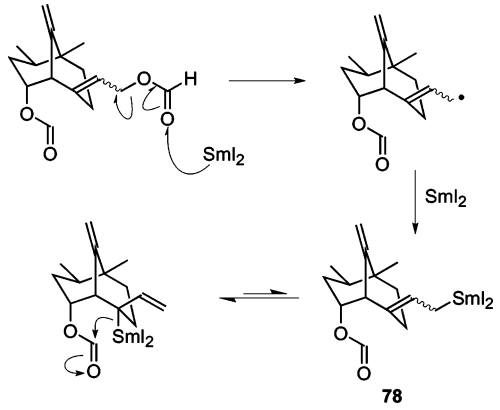
Scheme 27



mixture of double-bond isomers, with SmI_2 in the presence of HMPA gave **67** as a single diastereoisomer.

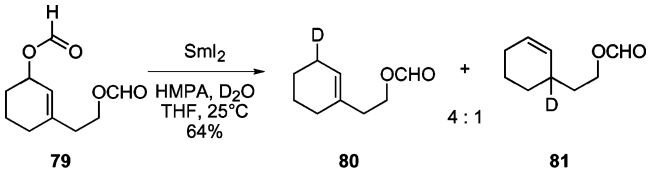
At first glance, the reaction appears to be analogous to Matsuda's second SmI_2 cyclization in his approach to Grayanotoxin III (see Scheme 26), i.e., ketyl−olefin addition followed by *β*-elimination; however, the mechanism here is quite different (Scheme 28).

Scheme 28



Model studies have shown that the reaction proceeds by the allylic organosamarium **78**.[88] For example, reaction of model substrate **79** in the presence of D_2O led to the formation of products **80** and **81**, in which deuterium is incorporated in the allylic positions (Scheme 29).

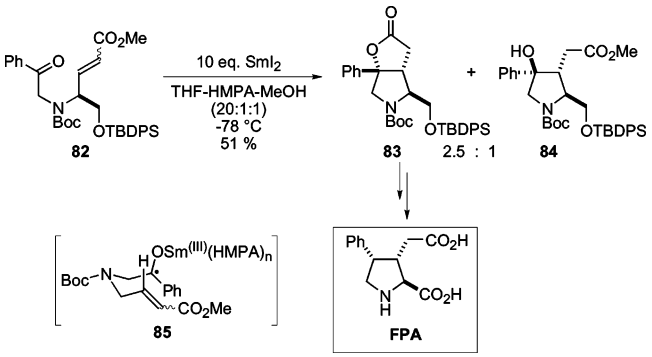
Scheme 29



Shirahama and Hashimoto completed a formal synthesis of the kainoid amino acid FPA using a SmI_2-induced cyclization to construct the pyrrolidine moiety. Cyclization substrate **82**, used as a mixture of *E* and *Z* isomers, was treated with SmI_2 in the presence of HMPA to give **84** as the only product in moderate yield. With MeOH also present however, the reaction proceeded to give a 1:2.5 mixture of **84**

and the desired bicyclic product **83**, which was converted to a known precursor to FPA (Scheme 30).[89] The formation of **84** in the absence of MeOH

Scheme 30



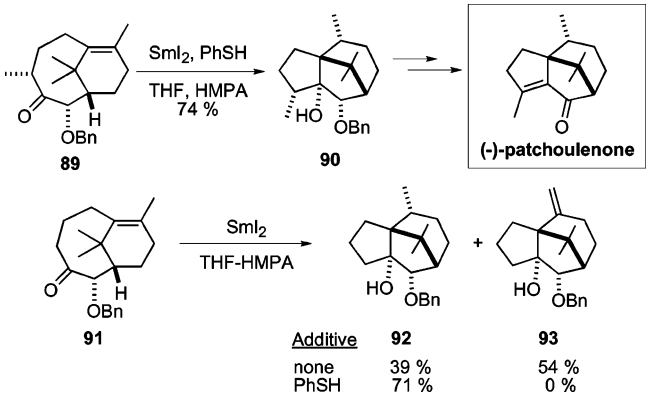
can be explained by the anti transition state **85**. The switch in selectivity on the addition of MeOH is difficult to explain but may arise from an alternative mechanistic pathway in which the α,*β*-unsaturated ester is reduced leading to cyclization.

Sinaÿ used a SmI_2-mediated 5-*exo*-dig ketyl−alkyne cyclization to form the bicyclic core of the miharamycin antibiotics.[90] The reaction of α-propargyloxy ketone **86** proceeds in the presence of HMPA and *t*-BuOH to give bicyclic ether **87** in high yield and as a single diastereoisomer (Scheme 31). The potential reductive cleavage of either the α-propargyloxy group or the α-acetal group was not observed. Oxidative cleavage of the exocyclic olefin, followed by reduction, gave **88** the core of the natural products.

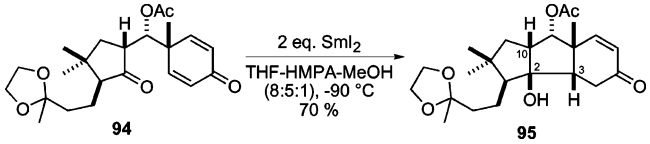
Banwell used a SmI_2-mediated 5-*exo*-trig ketyl−olefin transannular cyclization in an approach to (−)-patchoulenone. Ketone **89** was treated with SmI_2 in the presence of HMPA and thiophenol to give tricyclic tertiary alcohol **90** as a single diastereoisomer (Scheme 32).[91] In the cyclization of a simpler substrate **91**, the unsaturated isomerization product **93** was obtained as the major product in the absence of thiophenol, presumably due to disproportionation of the tertiary carbon-centered radical. The inclusion of thiophenol as a hydrogen-atom donor successfully overcame this problem, giving **92** in high yield.[91]

Arseniyadis investigated the use of SmI_2-mediated ketyl−olefin cyclizations in a fragmentation-based approach to the BC ring system of the taxane skeleton. For example, treatment of ketone **94** with SmI_2 in the presence of HMPA and MeOH gave tricyclic product **95** in good yield (Scheme 33).[92,93] The

Scheme 32



Scheme 33

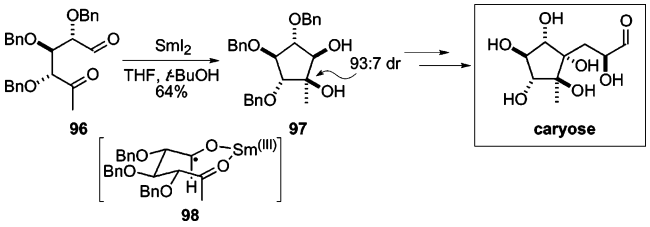


cyclization corresponds to formation of the C2−C3 bond (taxane numbering system, see Figure 4, section 2.5.2). The proposed fragmentation of the C2−C10 bond would generate the taxane BC ring system.

2.2.5. Pinacol-Type Reactions

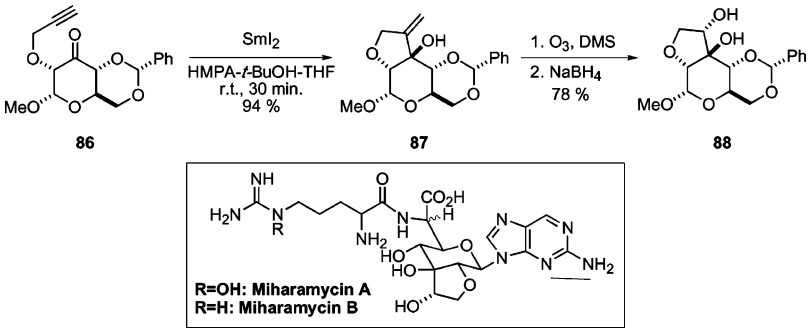
In Iadonisi's approach to the carbocyclic monosaccharide caryose, a SmI_2-mediated pinacol cyclization of keto−aldehyde **96** has been used as the key step.[94] In common with a number of related pinacol cyclizations, the major *cis*-diol **97** arising from the reaction contains the newly formed diol hydroxyl groups anti to the 'directing' α-benzyloxy substituents in the transition state **98** (Scheme 34).

Scheme 34

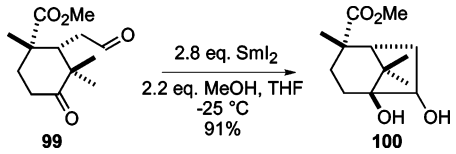


Arseniyadis utilized a SmI_2-mediated pinacol cyclization of keto−aldehyde **99** in the synthesis of **100**, a precursor to the A ring of taxol and its derivatives (Scheme 35).[95]

Scheme 31



Scheme 35



Sinaÿ prepared calditol via a SmI_2-mediated pinacol coupling to form the central cyclopentane moiety. Diol **87** was subjected to Swern oxidation to give the sensitive keto aldehyde **88,** which was immediately treated with SmI_2 (Scheme 36).[96] This gave mixture of diols **89** and **90** in high yield, which were separated via transient protection as the corresponding cyclic carbonates. Subsequent transformation of the pinacol products gave a range of diastereoisomers of the proposed structure, one of which was found to be identical with natural calditol. While the correct product arose from the minor cyclization product **89**, this synthesis resolved a long-running dispute regarding the true structure of the natural product.[96]

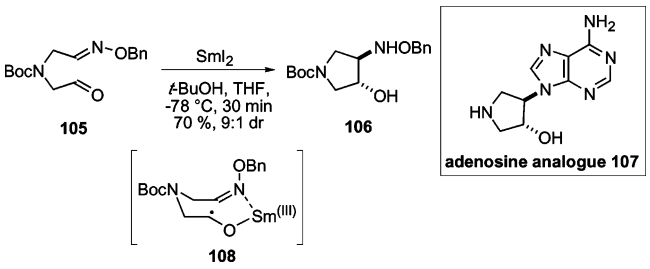
The SmI_2-mediated coupling of aldehydes and ketones with oximes has also been employed to access five-membered rings in approaches to natural products. Naito used an aldehyde−oxime coupling reaction to form the functionalized pyrrolidine ring in their approach to 4-pyrimidinyl and 4-purinylpyrrolidin-3-ol nucleoside analogues.[97] The synthesis of uridine, thymidine, and adenosine analogues, for example, **107**, has been reported. The SmI_2-mediated aldehyde−oxime coupling of **105** proceeded efficiently in the presence of *t*-BuOH to afford the cyclic product in 70% yield and with good stereoselectivity for the anti product **106** (Scheme 37). The analogous Bu_3-SnH-mediated cyclization proceeded in 66% yield but gave only a 3:1 ratio of diastereoisomers.

The anti selectivity is thought to arise from steric and electronic effects favoring transition state **108**. Both the stereoselectivity and overall yield of the cyclization were found to depend on the reaction temperature. In addition, no reaction was observed in the absence of *t*-BuOH.[97]

In Giese's synthesis of trehazolin, the SmI_2-mediated ketone−oxime reductive coupling of **109** was used to form the intermediate **110** as a single diastereoisomer (Scheme 38).[98]

The substrate **109**, which was derived from D-glucose, has three stereocenters already established. The authors found it necessary to protect the hydroxyls at C6 and C4 as a benzylidene acetal to

Scheme 37



obtain the desired stereochemistry from the cyclization. When these hydroxyls were protected as benzyl ethers, the product formed on cyclization had the wrong stereochemistry at C5. The authors propose that this is due to a normal preference (when P_1 and $P_2 = -CH_2Ph$) for the chairlike transition structure A over B (Scheme 39). The use of a cyclic acetal precludes conformation A and the cyclization proceeds through conformation B, thus leading to the product having the correct stereochemistry at C5. The stereochemistry at C1 was inverted in a subsequent step.[98]

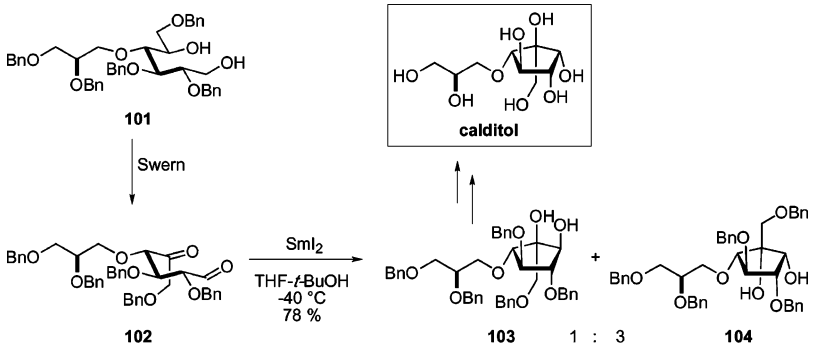
Chiara also used a ketone−oxime reductive cyclization in an approach to trehazolin.[99,100] The cyclization substrate **111** was obtained from D-mannose in 9 steps but possessed the wrong configuration at C2 for the natural product. This stereocenter, however, behaves as a stereocontrol element in the cyclization and was elegantly inverted later in the synthesis via an intramolecular S_N2 cyclization. In stark contrast to Giese's observed syn selectivity across the newly generated C−C bond, Chiara obtains the anti product exclusively via intermediate **113**. An excess of SmI_2 was used in the cyclization of **111** such that, after cyclization, the addition of a large excess of H_2O activated the remaining reagent, allowing reduction of the initially formed benzyloxyamine to the amine (Scheme 40). In situ treatment with aqueous LiOH then removed the acetate protecting group, giving amine **112** in almost quantitative yield.[99,100]

2.3. Six-Membered Rings

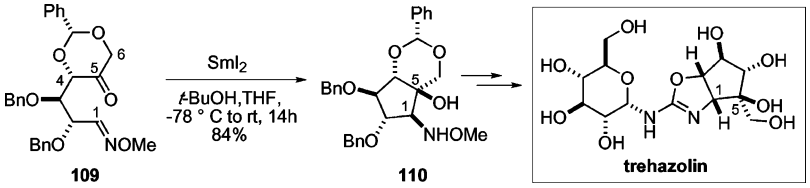
2.3.1. Barbier Reactions

Nakata utilized the SmI_2-mediated Barbier-type cyclization of a primary iodide with an ester as part of a convergent synthesis of a *trans*-fused 6,6,6,6-tetracyclic ether, typically found in marine polycyclic

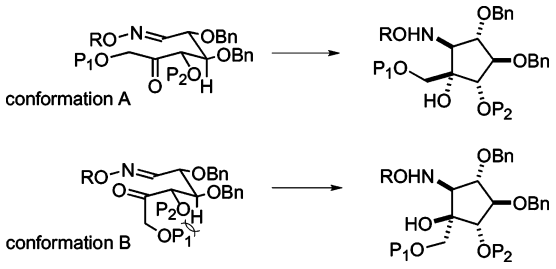
Scheme 36



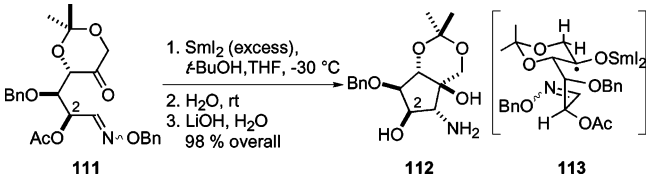
Scheme 38



Scheme 39

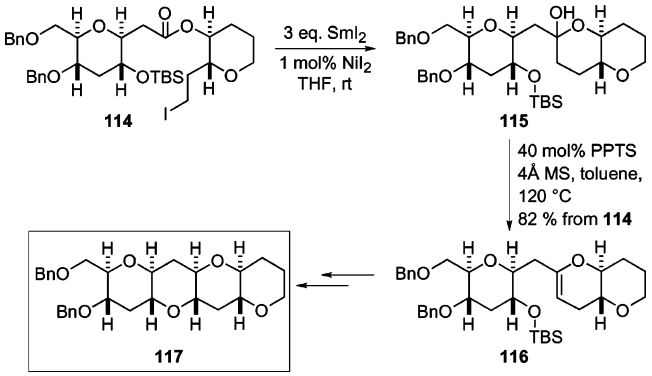


Scheme 40



ethers. Treatment of iodide **114** with excess SmI_2 in the presence of 1 mol % of NiI_2 led to the smooth formation of intermediate hemiacetal **115**, which was dehydrated to give dihydropyran **116** in excellent overall yield (Scheme 41). Further elaboration gave the tetracycle **117**.[101]

Scheme 41



SmI_2-mediated Barbier reactions have been extended to include additions to imide carbonyls. Such a process has been applied in the synthesis of (+)-lentiginosine, an indolizidine alkaloid that is a selective inhibitor of amyloglucosidase. Ha described the synthesis of the natural product starting from L-malic acid using SmI_2 in the key step to mediate the Barbier cyclization of *N*-(iodobutyl)succinimide **118** (Scheme 42).[102] The cyclization proceeded efficiently in the presence of a catalytic amount of $Fe(DBM)_3$, and after subsequent dehydration, indolizidine **119** was obtained in good yield. Pyrrolizidine and quinolizidine heterocyclic systems, which are found extensively in biologically important molecules, have also been prepared.[102]

Yamada completed a formal synthesis of eleman-8β,12-olide using a SmI_2-mediated Barbier−Michael process. Treatment of allylic bromide **120** with SmI_2 in THF−HMPA gave ester **121** in good yield as a 5:2 mixture of diastereoisomers (Scheme 43).[103] An identical ratio of products and similar yield were obtained when the *Z*-allylic bromide was employed, indicating the presence of a common allylsamarium intermediate.

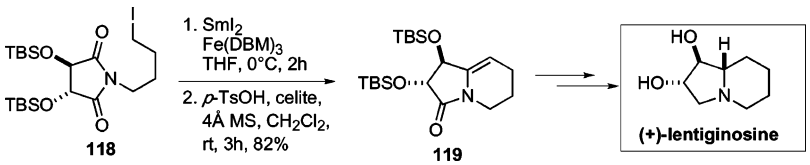
2.3.2. Reformatsky-Type Reactions

The SmI_2-mediated intramolecular Reformatsky reaction has been used extensively in natural product synthesis. In many cases, the use of SmI_2 proves superior to the use of other metal reductants. Xu used such a cyclization in a model approach to clavulactone (Scheme 44).[104] Formation of bromopropionate **122** and cyclization gives lactone **123** in modest yield. A related model approach to the same target has also been described by Wu.[105]

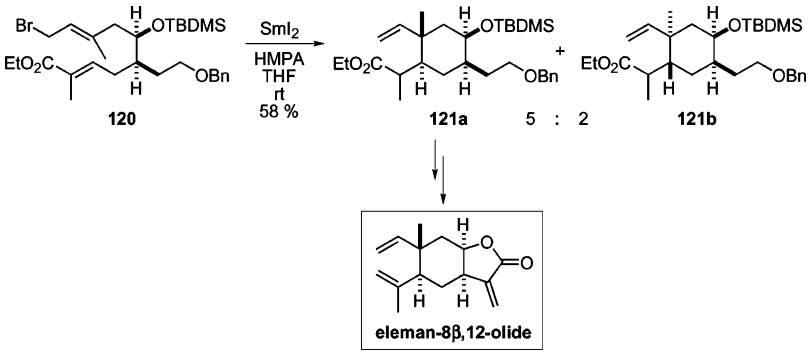
3′-β-Branched ribonucleosides are of interest as potential antitumor agents. Matsuda reported the synthesis of uridine derivative **126** from 3′-keto−nucleoside **124** using a SmI_2-mediated Reformatsky reaction.[106] Although 3′-keto−nucleosides are known to be unstable, especially under basic conditions, the mild, neutral conditions of the SmI_2 cyclization allows lactone **125** to be isolated in excellent yield (Scheme 45). Zinc metal was found to be ineffective in the cyclization. Interestingly, attempts to carry out the cyclization using SmI_2 and HMPA led to decompostion due to reduction of the ketone carbonyl group to the dianion, followed by eliminative cleavage of the endocyclic carbon−oxygen bond.

Nakata prepared the insect toxin pederin using a SmI_2-mediated Reformatsky reaction to form the six-membered ring of the right half, (+)-benzoylpedamide. The aldehyde substrate **128** is prepared by ozonolysis of ester **127** and was treated directly with

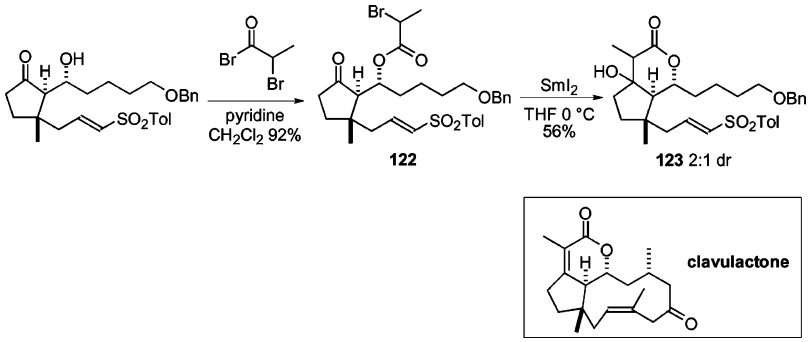
Scheme 42



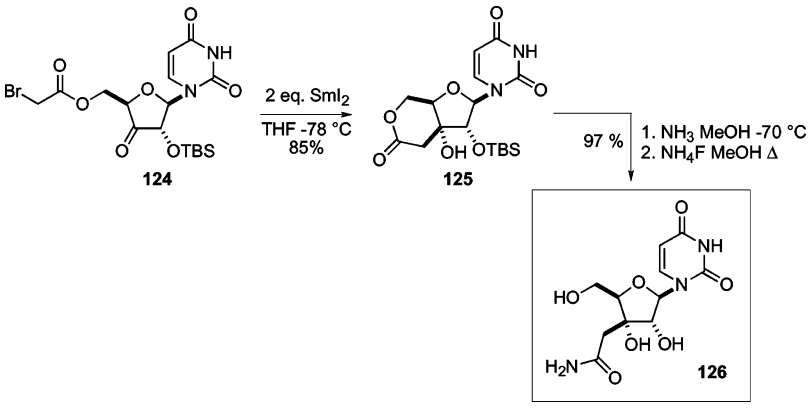
Scheme 43



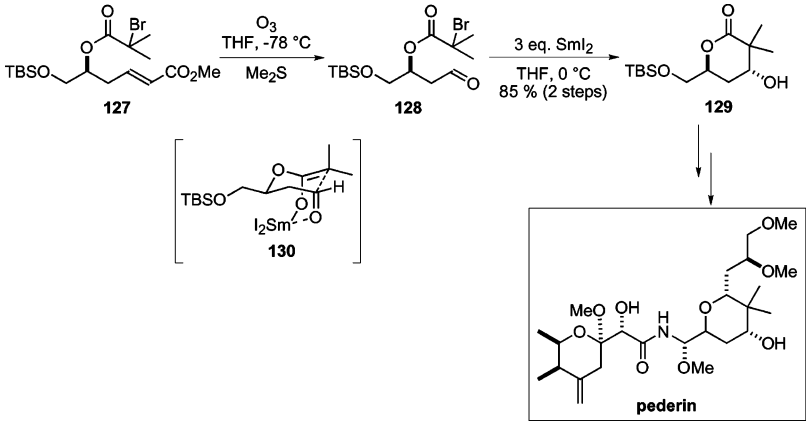
Scheme 44



Scheme 45



Scheme 46



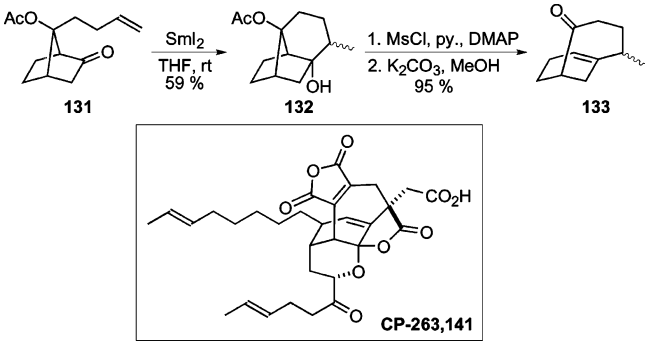
SmI_2 to give the cyclized product **129** in high yield and as a single diastereoisomer (Scheme 46).[107] The selectivity of the reaction is ascribed to the six-membered transition state **130**.

2.3.3. Carbonyl–Alkene/Alkyne Reductive Couplings

SmI_2 has been employed in a variety of ways to access six-membered rings, with the most popular

method involving 6-*exo* ketyl−olefin cyclizations. Wood used a 6-*exo*-trig ketyl−olefin cyclization onto an unactivated olefin in an approach to the bicyclo-[4.3.0]decane core of CP-263,141.[108] Treatment of ketone **131** with SmI_2 gave a moderate yield of tricycle **132**. A facile Wharton fragmentation is then used to introduce the bridgehead olefin, giving **133,** which constitutes the bicyclic core of the target (Scheme 47). Other radical methods for the construc-

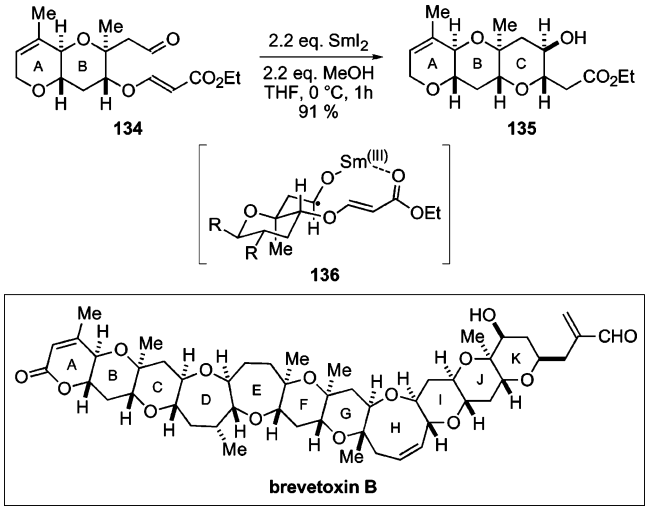
Scheme 47



tion of the fragmentation substrate proved unsuccessful. Related 5-exo-trig cyclizations were also reported using both SmI_2 and tributyltin hydride.

Nakata used a SmI_2-mediated 6-*exo*-trig ketyl−olefin cyclization to form the ABC *trans*-fused tricyclic tetrahydropyran ring system of the neurotoxin brevetoxin B (Scheme 48).[109,110] The reductive cy-

Scheme 48

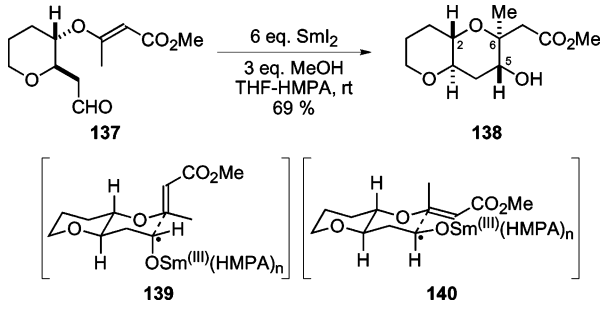


clization of **134**, employing MeOH as an additive, occurred with complete *anti*-selectivity to give **135** in high yield via chelated transition structure **136**.

Nakata used a similar strategy in his synthesis of the ABCDEF ring system common to yessotoxin and adriatoxin. His approach also involves the construction of an oxepane ring and will be dealt with in a subsequent section.[111] Interestingly, similar *anti*-stereoselectivity was observed in the analogous cyclization of a methyl ketone, in the construction of the D ring system of maitotoxin.[112]

SmI_2-mediated ketyl−olefin couplings have been used to construct a range of bicyclic ether systems bearing an angular methyl group. For example, cyclization of aldehyde **137,** which only proceeded in the presence of HMPA, gave the 2,6-*anti*-5,6-*trans*-tetrahydropyran **138** as a single diastereoisomer in moderate yield (Scheme 49).[113] The 2,6-anti selectiv-

Scheme 49



ity in this reaction, compared to the 2,6-syn selectivity observed in the cyclization of **134** (Scheme 48), was attributed to the nonchelated transition state **139**, which is subject to less steric interaction than **140** while maintaining the anti relationship generally observed in such cyclizations.[84]

Takahashi and Nakata employed a similar reductive cyclization strategy to construct tetrahydropyran **142** in their synthesis of mucocin (Scheme 50). Interestingly, an aldehyde group in the substrate **141** survives the reducing conditions provided reaction times are kept short.[114] It has been proposed that the reduction of carbonyl groups with SmI_2 is reversible, with the ketyl radical anion being drained from the equilibrium by cyclization.[40] This could account for the selective transformation of only one aldehyde group. Alternatively, precoordination of samarium to the aldehyde and ester carbonyl groups may increase the reactivity of the proximal aldehyde, as shown in transition structure **143**. A vinylogous pinacol coupling mechanism (cf. Figure 2, section 2.2.3, transition state **70**) can probably be discounted due to the considerably lower reactivity of the β-alkoxy enoate group compared to the aldehyde.

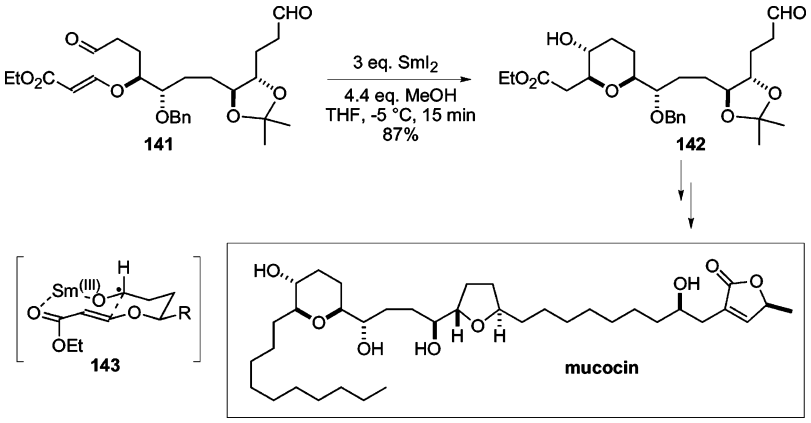
A related 6-*exo*-trig ketyl−olefin cyclization onto a β-alkoxyacrylate has been used to construct the tetrahydropyran ring system in pyranicin. Using MeOH as the proton source, cyclization of **144** proceeds in excellent yield to give the 16,20-*syn*-19,20-anti product **145** (Scheme 49).[115] The cyclization proceeds through chelated *anti*-transition state similar to **143** (Scheme 50).

Yamamoto utilized Nakata's SmI_2-mediated reductive cyclization protocol in the synthesis of the EFGH ring segment **148** of gambierol.[116,117] Thus, treatment of ketone **146** with SmI_2 in THF−MeOH gave **147** in near quantitative yield with complete selectivity (Scheme 52).

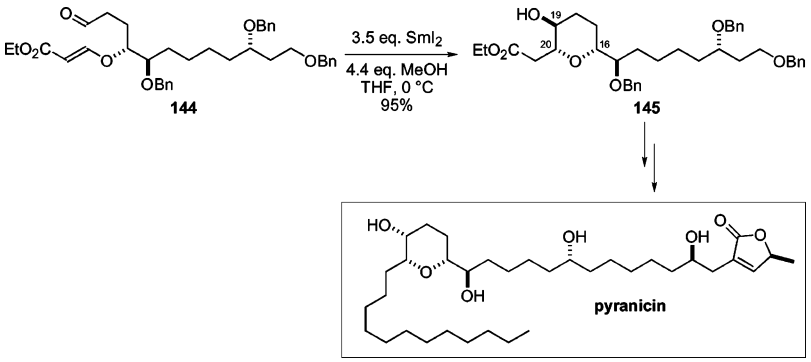
Recently, Yamamoto reported the total synthesis of gambierol using a similar strategy to form the C ring of the target. Treatment of aldehyde **149** with SmI_2 in THF−MeOH gave an excellent yield of **150**, representing the ABC ring system of the target (Scheme 51).[118,119]

In Tadano's approach to the insect pheromones (−)-anastrephin and (−)-epianastrephin, a SmI_2-mediated 6-*exo*-trig ketyl−olefin cyclization, was used in

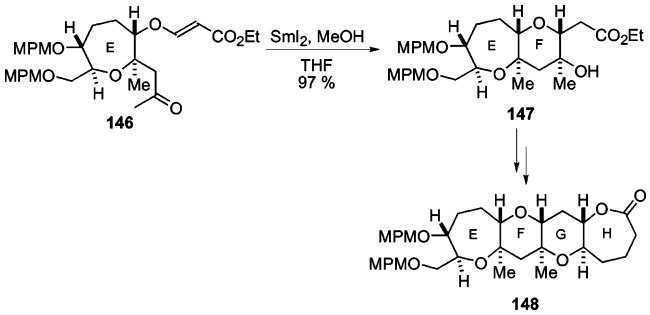
Scheme 50



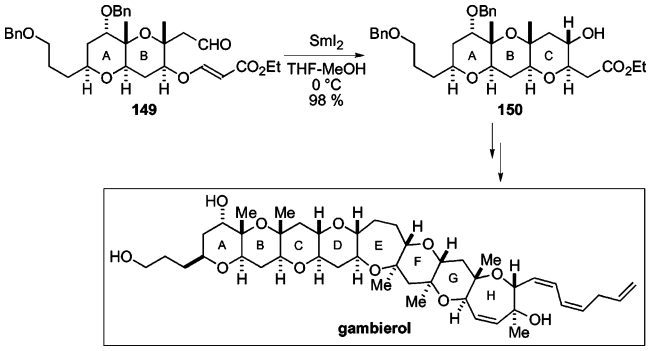
Scheme 51



Scheme 52



Scheme 53



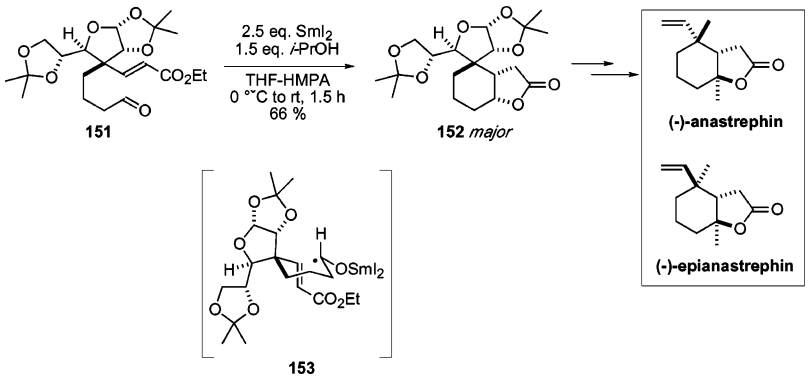
conjunction with a glucose derived "chiral auxiliary" to generate the six-membered ring of the target stereoselectively.[120,121] Treatment of aldehyde **151** with SmI_2 in THF−HMPA gave, after in situ lactonization, a mixture of bicyclic lactones in which **152** was the major product (Scheme 54).

Suprisingly, major product **152** was found to have *cis*-stereochemistry across the new carbon−carbon bond, in contrast to most SmI_2-mediated ketyl−olefin couplings involving aldehydes. The authors propose that the stereochemistry arises from a chairlike transition state. It appears that interactions between the cyclic acetal and the ester group result in the olefin assuming a pseudoaxial orientation and transition structure **153** is favored. Furthermore, the samarium(III) alkoxide adopts an equatorial orientation due to unfavorable 1,3-diaxial interactions when in an axial position. The authors also report differing stereochemical outcomes from related cyclizations involving a *Z*-olefin substrate and a methyl ketone. The glucose-derived fragment of the product was dismantled in a series of transformations en route to the final product.[120,121]

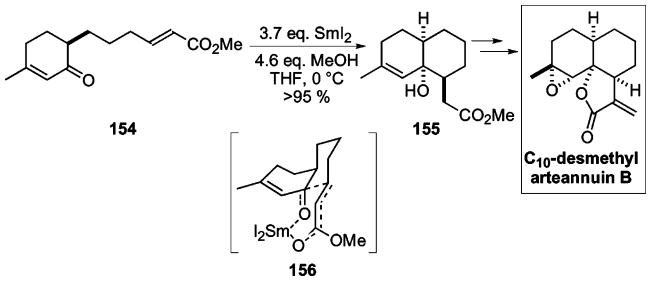
Little used a SmI_2-mediated 6-*exo*-trig ketyl−olefin cyclization as the key step in his approach to the synthesis of (−)-C10-desmethyl arteannuin B.[122] The cyclization of **154** proceeded in excellent yield on treatment with an excess of SmI_2 at 0 °C, with simultaneous but separate addition of MeOH, to give **155** as a single diastereoisomer (Scheme 55). Addition of the proton source in this manner was found to promote cyclization over simple ketone reduction. The authors reason that the observed stereochemical outcome can be explained by an 11-membered ring chelate transition state **156**. Similar ring systems were constructed via electroreductive cyclization, but this method gave poor control of stereochemistry.

Matsuda used a SmI_2-mediated 6-*exo*-trig ketyl−olefin cyclization to form the *cis*-decalin skeleton of the diterpene vinigrol from (+)-dihydrocarvone (Scheme 56).[123] As expected, the reaction of ketone **157** proceeded with *anti*-selectivity across the new

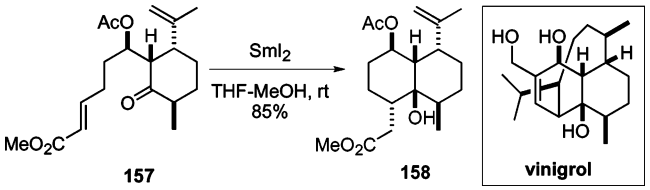
Scheme 54



Scheme 55



Scheme 56



C−C bond, giving the required stereochemistry for vinigrol.

Crucially, in this approach the β-hydroxyl group in substrate **157** was protected as an acetate. When the β-hydroxyl was left unprotected, chelation of the samarium(III) ketyl radical anion and the β-hydroxyl led to transition structure **159** (Figure 3), where the

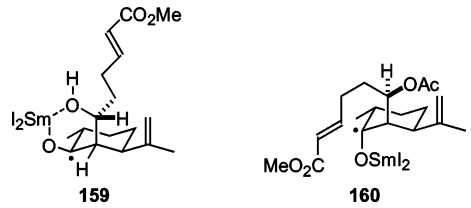
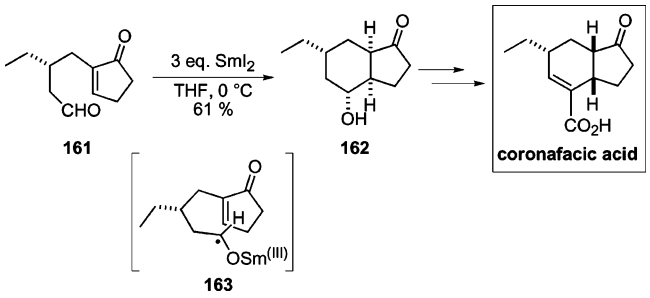


Figure 3.

ketyl radical anion and olefin are held some distance apart. The use of acetate protection in **157** prevented such chelation and allowed the ketyl−radical and olefin to come into closer proximity, as seen in transition structure **160**, thus permitting cyclization to the desired product **158**.[123]

Tori used a SmI_2-promoted 6-*endo*-trig cyclization to construct the hydrindanone skeleton in the synthesis of the natural product coronafacic acid. Treatment of enone−aldehyde **161** with SmI_2 gave the bicyclic ketone **162** as the major diastereoisomer (Scheme 57). The stereochemistry at the ring junction was inverted later in the synthesis.[124]

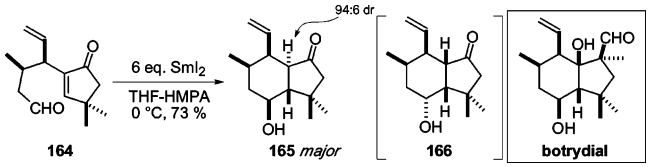
Scheme 57



Isolation of the apparent 6-*endo*-trig product may arise from a ketyl−olefin coupling mechanism proceeding via transition state **163**, with the *endo* cyclization generating a stabilized radical.

Tori also used a similar SmI_2-promoted aldehyde−enone coupling to construct the hydrindanone skeleton of the metabolite botrydial. Treatment of **164** with SmI_2 in the presence of HMPA gave the hydrindanone **165** in good yield, with excellent diastereocontrol at three new chiral centers (Scheme 58).[125]

Scheme 58

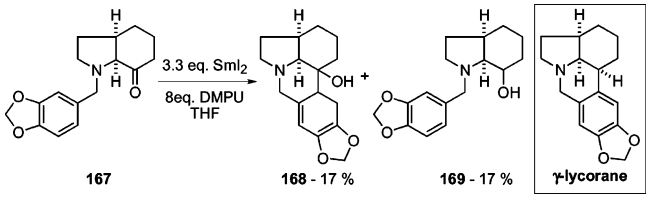


The use of MeOH in place of HMPA gave a more complex mixture of products and only moderate control, with diastereoisomer **166** being the major product.

In his approach to the polycyclic ring systems of the *Amaryllidaceae* and *Erythrina* families of alkaloids, Parsons used a SmI_2-mediated cyclization of ketone **167**.[126] Treatment of **167**, bearing a methylenedioxy-substituted aromatic, with SmI_2 in the presence of DMPU gave cyclohexadiene **168** in low yield (Scheme 59). This readily oxidized in air to give the γ-lycorane ring system. The diastereoselectivity of the cyclization is not discussed.

The authors suggest that either a ketyl−olefin cyclization or an intramolecular Friedel−Crafts reaction could be responsible for product formation. If a Sm(II)/Sm(III) Friedel−Crafts process is occurring, then the formation of the cyclohexadiene can only be explained by reduction of the intermediate cation by

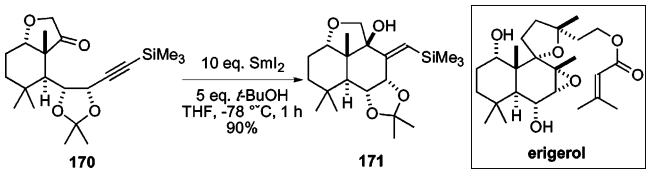
Scheme 59



SmI_2. A ketyl−olefin cyclization is perhaps a more likely explanation, despite the electron-rich nature of the aromatic ring. This possible mechanism is given some support by the isolation of a similar quantity of the secondary alcohol **169**,[126] although it is important to note that **169** may derive from an independent reaction pathway. The SmI_2-mediated intramolecular addition of ketyl radical anions to aromatics bearing ester substituents has been shown to occur efficiently, giving cyclohexadienes in good yields.[127−129] Analogous intramolecular additions to electronically neutral aromatics have also been observed.[130]

A SmI_2-mediated 6-*exo*-dig ketyl-alkyne cyclization has been used to form the *trans*-decalin skeleton of (±)-erigerol (Scheme 60).[131] The cyclization of ketone

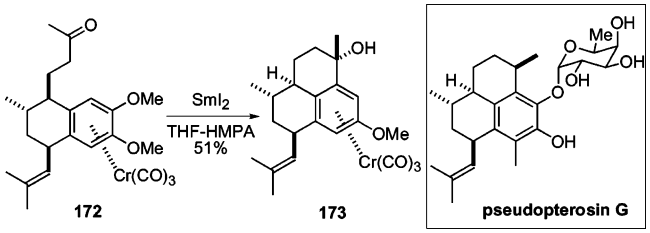
Scheme 60



170 proceeded to give **171** as a single diastereoisomer, in excellent yield.

Schmalz carried out extensive studies on chiral tetralin−$Cr(CO)_3$ complexes and reported the first examples of radical additions to arene $Cr(CO)_3$ complexes.[132,133] In the cyclization of **172**, the bulky $Cr(CO)_3$ group serves to control the stereoselectivity of the cyclization but the electron-withdrawing nature of the group activates the aromatic ring to ketyl radical addition in a system that would otherwise be deactivated by the electron-donating methoxy substituents (Scheme 61). On treatment with SmI_2, **172**

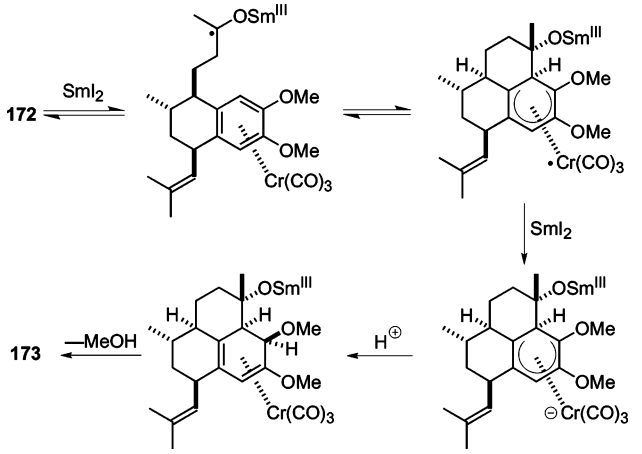
Scheme 61



undergoes stereoselective cyclization to give **173**, representing the skeleton of pseudopterosin G and helioporin E (not shown), in moderate yield.

A proposed mechanism for the cyclization involves ketyl radical anion formation and addition to the top face of the complexed aryl ring. Following a second electron reduction by SmI_2, regioselective elimination of a methoxy group gave **173** (Scheme 62).[132,133]

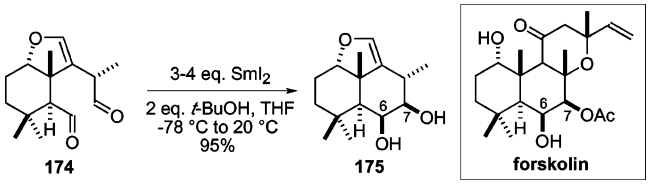
Scheme 62



2.3.4. Pinacol-Type Couplings

SmI_2-mediated pinacol coupling reactions have also been used to generate six-membered rings in natural product synthesis. In an approach to forskolin, Pancrazi employed a SmI_2-mediated pinacol coupling of dialdehyde **174** to give **175** with the *cis*-diol motif required for the natural product (Scheme 63).[134] A

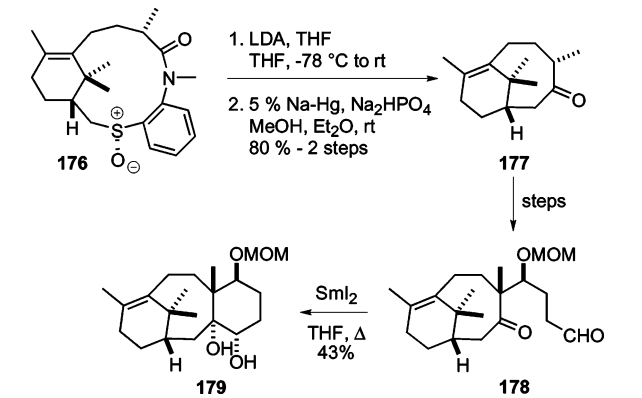
Scheme 63



formal synthesis of (±)-forskolin has been achieved using this approach.[135]

Kajiwara used a SmI_2-mediated pinacol reaction as a key step in his preparation of the taxane ABC ring system.[136] Having previously established the AB ring system of substrate **178** using a lactam−sulfoxide ring contraction, Kajiwara then explored the use of SmI_2 to construct the C ring. The cyclization of keto−aldehyde **178** was carried out in refluxing THF. The syn diol **179**, possessing the necessary trans stereochemistry at the BC ring junction, was obtained in moderate yield (Scheme 64).

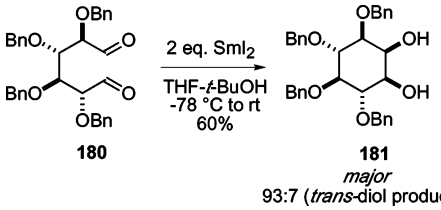
Scheme 64



The importance of inositol phosphates as second messengers in a variety of cellular signal transduc-

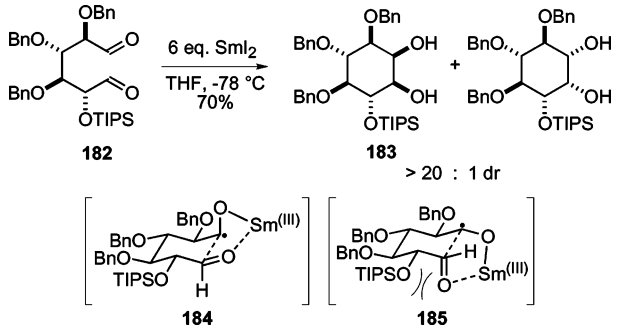
tion systems has led to extensive studies into the synthesis of inositol derivatives. Guidot employed a SmI_2-mediated pinacol cyclization of C_2-symmetrical dialdehyde **180** to prepare protected inositol derivative **181** (Scheme 65).[137]

Scheme 65



Similarly d'Alarcao used a SmI_2-mediated pinacol cyclization of non-C_2-symmetrical dialdehyde **182** to prepare *myo*-inositol derivative **183**. The reaction proceeded with good diastereoselectivity provided low temperatures were employed (Scheme 66).[138] The

Scheme 66



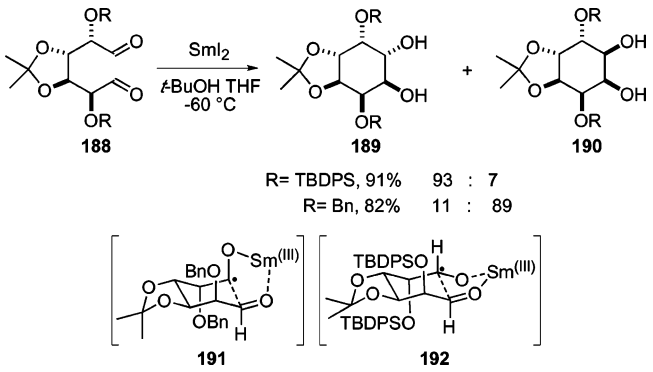
selectivity can be ascribed to the importance of transition state **184**, in which the preferred *cis*-diol forms anti to the bulky TIPS ether protecting group.

d'Alarcao constructed the inositol ring of a disaccharide isolated from the jojoba bean, using a similar SmI_2-mediated pinacol coupling of a dialdehyde derived from L-xylose. The diene precursor **186** was ozonolyzed to give a dialdehyde, which was directly treated with SmI_2 in THF and *t*-BuOH to give the *cis*-diol **187** in moderate overall yield (Scheme 67).[139]

Chiara employed a SmI_2-mediated pinacol coupling to prepare *myo*-inositol from D-mannitol.[140] This strategy was later employed for the synthesis of cyclitols **189** and **190** en route to *C*-fucopyranosides (Scheme 68). The stereoselectivity of the cyclization was found to be dependent upon the protecting group used to mask the hydroxyls α to the aldehyde groups.[141]

The use of benzyl ether protecting groups led to the isolation of the *cis*-diol **190** as the major product. This can be rationalized in the usual way by invoking

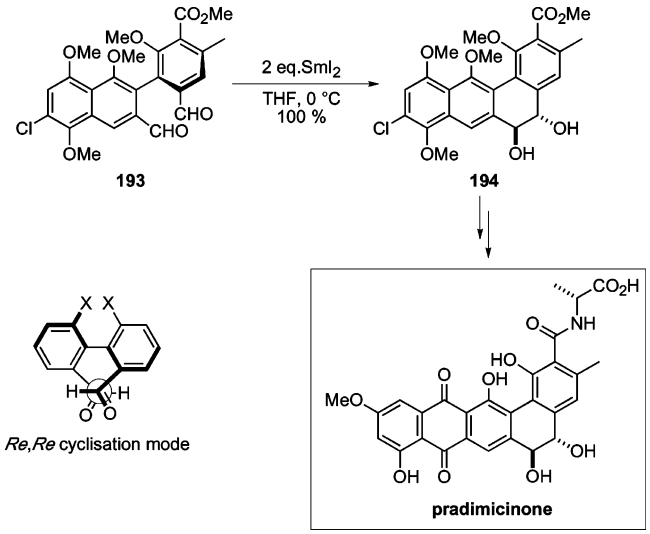
Scheme 68



coordination of the Sm(III) of the ketyl radical anion to the aldehyde as in transition structure **191**. The use of bulky TBDPS protecting groups, which are held in a pseudoaxial orientation, prevents the formation of an analogous transition structure due to prohibitive 1,3-diaxial interactions. Rather, the formation of the *trans*-diol via transition structure **192** is favored.

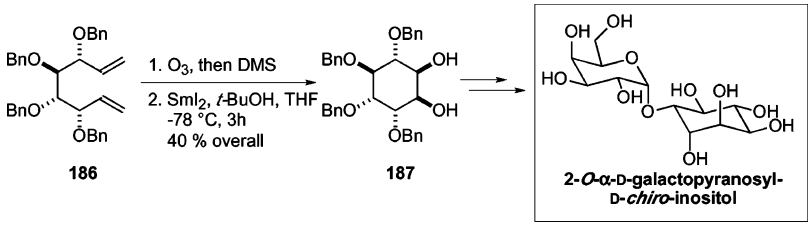
Suzuki completed the synthesis of pradimicinone,[142] the aromatic pentacyclic aglycone moiety common to both the pradimicin and benanomicin antibiotic classes. The key step in the approach involves a SmI_2-mediated pinacol cyclization of an axially chiral 2,2′-biaryldicarbaldehyde (*M*)-**193** (Scheme 69).

Scheme 69



This cyclization proceeds to give the *trans*-1,2-diol **194** in quantitative yield, with complete transfer of the axial chirality in the starting material to the central chirality of the product, which is obtained in enantiomerically pure form. The *trans*-selectivity

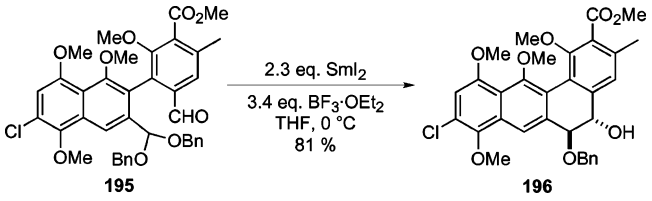
Scheme 67



observed is in contrast with the *cis*-selectivity observed in aliphatic 1,6-dicarbonyl pinacol reactions and was unchanged by the addition of HMPA in model studies.[143] The selectivity and chiral transfer were attributed to a *Re,Re* cyclization mode, giving the diequatorial product.

Having completed the synthesis of pradimicinone, Suzuki found that discriminating between the hydroxyl groups was virtually impossible due to the pseudo-C_2-symmetric nature of the 1,2-diol. To address this problem, they developed the first intramolecular semi-pinacol reaction mediated by SmI_2.[144] The cyclization of acetal−aldehyde **195** was investigated using a number of reductant−Lewis-acid combinations. The combination of SmI_2 and $BF_3{\cdot}OEt_2$ proved most effective, giving the mono-benzylated 1,2-diol **196** in high yield (Scheme 70), with the

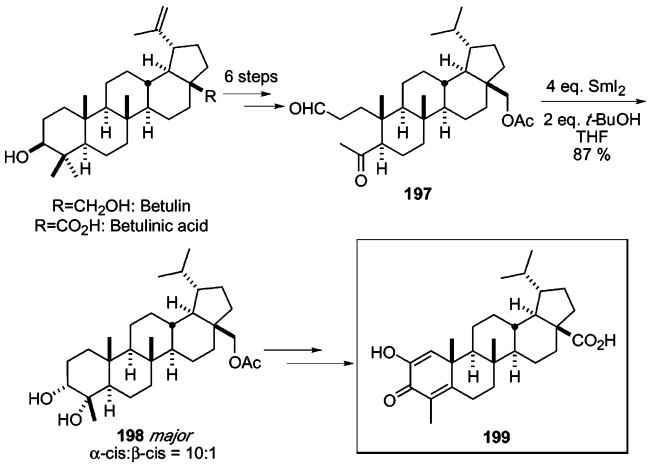
Scheme 70



complete trans selectivity also observed in the conventional pinacol reaction.[142,143]

Snyder used a SmI_2-mediated pinacol coupling to prepare betulinic acid analogue **199**. Triterpene betulin was converted in six steps into the keto aldehyde **197**, which was subjected to SmI_2-mediated pinacol reaction. The coupling proceeded in high yield and with high selectivity (Scheme 71). McMurry coupling

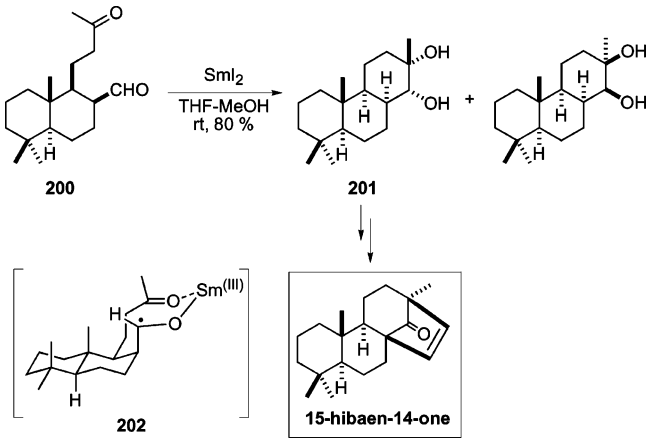
Scheme 71



procedures proved unsuccessful in this case. The major α-diol **198** was transformed to give the target 24-nortriterpene **199**.[145]

Marcos used keto−aldehyde **200**, prepared from the natural diterpene zamoranic acid, to prepare the tetracyclic diterpene 15-hibaen-14-one. Treatment of **200** with SmI_2 in THF−MeOH gave **201** as a 25:1 mixture of *cis*-diols. The selectivity is thought to arise from the formation of chairlike transition state **202** (Scheme 72).[146]

Scheme 72



In Krohn's synthesis of the aquayamycin, 8-deoxy WP 3688-2, SmI_2 is used to form the six-membered B ring via an intramolecular 'pinacol-type' coupling reaction.[147] The cyclization of **203** progressed under mild conditions to afford the diol **204** in good yield and as a 9:1 ratio of diastereoisomers, the desired cis diol being the major product (Scheme 73).

The proposed mechanism involves the intramolecular aldol reaction of a Sm(III) enolate **206** (Scheme 74).[147] The authors observed a dependence of diastereoselectivity on reaction temperature. When the reaction was cooled to −100 °C, the formation of the trans diol was the major product. The diol **204** was converted to 8-deoxy WP 3688-2 in three steps.

When the carbonyl of the methyl ketone was protected, as in ketal **207**, instead of the desired cyclization, elimination to form enolate **208** followed by an intramolecular aldol reaction occurred to form seven-membered carbocycle **209** (Scheme 75).[147]

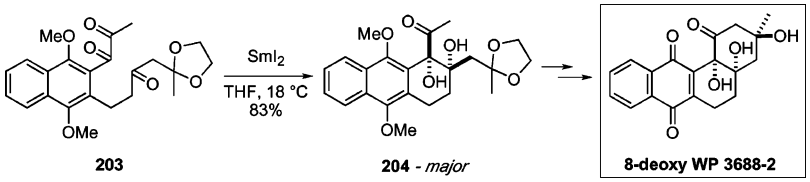
Pinacol-type cyclizations of aldehyde−oximes have also been used to form six-membered rings. L-Aspartic-acid-derived cyclization substrate **210** underwent cyclization on treatment with SmI_2 in the presence of *t*-BuOH at −50 °C to give a diastereoisomeric mixture of piperidines in modest yield (Scheme 76).[148] Subsequent transformation of the major anti-trans product **211** gave **212**, a building block for the preparation of the pseudodistomins and neuraminidase inhibitors.

2.4. Seven-Membered Rings

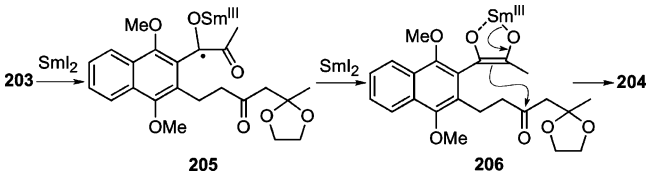
2.4.1. Barbier Reactions

Little used SmI_2 in two key carbon−carbon bond-forming transformations in his preparation of the carbon framework of the diterpene phorbol (Scheme 77).[149] The first SmI_2-mediated step involved a chelation-controlled intermolecular ketyl−olefin coupling which formed the tricyclic structure **216**. The authors propose that the reaction progressed through the Sm(III) chelate intermediate **215** to give the observed stereochemistry in the product. Epimerization, which triggered lactonization, and manipulation of the hydroxyl group gave iodide **217**. Treatment with SmI_2 in the presence of catalytic NiI_2[35,38] gave the seven-membered carbocycle **218** in good yield and as a

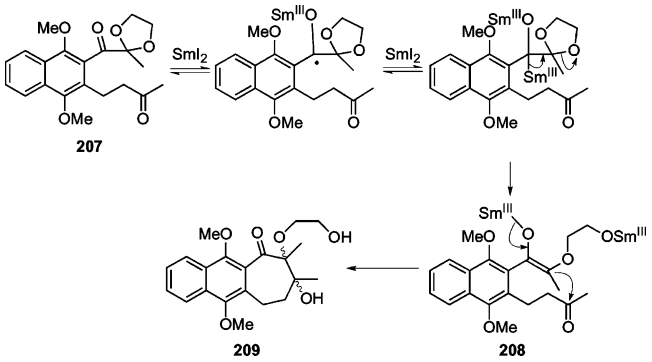
Scheme 73



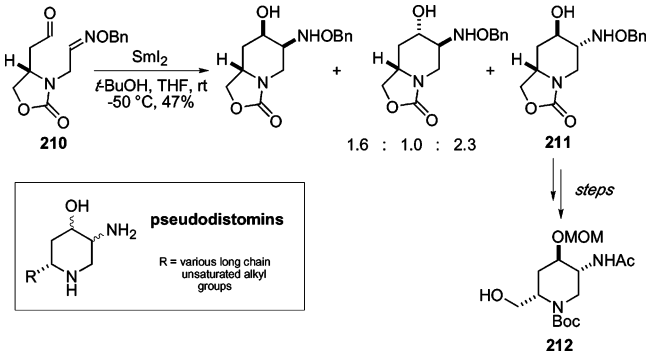
Scheme 74



Scheme 75



Scheme 76



single diastereoisomer. In the absence of NiI_2, the reaction was sluggish and gave poor yields.

2.4.2. Carbonyl–Olefin Reductive Couplings

Ciguatoxin is a complex polycyclic ether believed to be the cause of many reported cases of ciguatera (sea food poisoning). In the convergent preparation of the GHIJKLM fragment, Sasaki used a SmI_2-mediated 7-*exo*-trig ketyl−olefin cyclization to generate the seven-membered oxacyclic G ring.[150] The cyclization of **219** proceeded selectively to give the anti cycloheptanol product. The crude product was reduced directly with $LiAlH_4$ to give diol **220** (Scheme 78).

An explanation for the high diastereoselectivity of the cyclization was not postulated by the authors; however, in a report by Nakata, in which he describes a similar SmI_2-mediated 7-*exo*-trig ketyl−olefin cyclization of aldehyde **221** to give the anti product **222** (Scheme 79), a 12-membered chelate transition state was used to explain the complete diastereocontrol in the reaction.[151,152] Whether such chelation is responsible for the diastereoselectivity in the cyclization of **219** (Scheme 78) is unclear, as the reaction was carried out in the presence of HMPA, a cosolvent that might be expected to disrupt chelation.

In a convergent approach to the ABCDEF ring fragment common to the marine polyethers yessotoxin and adriatoxin, Nakata used a SmI_2-mediated ketyl−olefin cyclization to construct the seven-membered E ring. The cyclization of keto−enoate **223** proceeds with complete stereoselectivity and concomitant lactonization to give **224** in high yield (Scheme 80).[111] The six-membered D ring was also formed by a SmI_2-mediated ketyl−olefin cyclization (cf section 2.3.4).

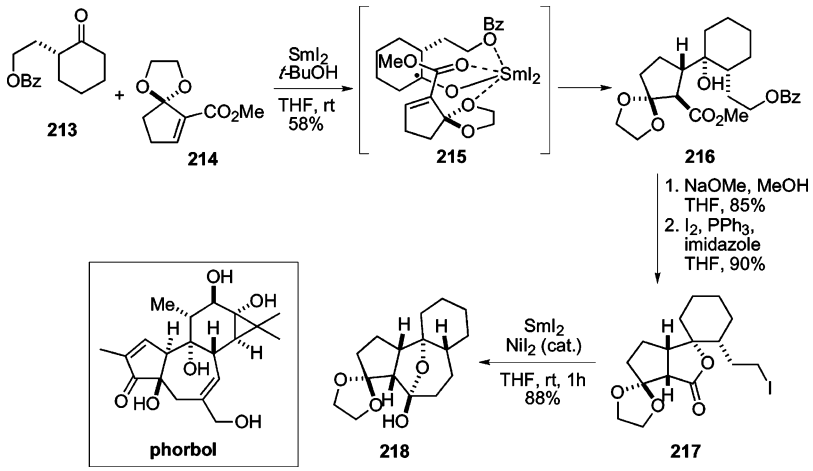
The diterpene guanacastepene A has attracted synthetic interest due to its promising antibacterial activity. In model studies, Lee constructed the carbon skeleton of the natural product using a SmI_2-mediated 7-*exo*-trig cyclization to form the central B ring (Scheme 81).[153] Cyclization of **225** in THF and *t*-BuOH gave the tricyclic system **226** in moderate yield as a mixture of two diastereoisomers, which were not assigned.

2.4.3. Pinacol-Type Couplings

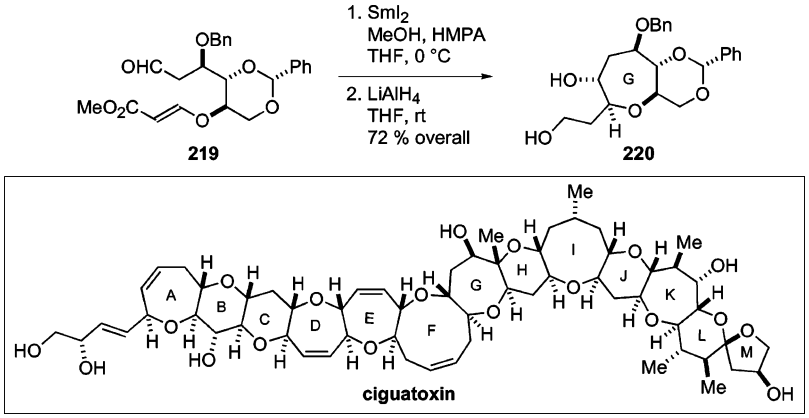
We previously discussed the use of SmI_2-mediated ketyl−olefin couplings in the formation of the two five-membered rings of grayanotoxin (section 2.2.4). The final ring-forming step in Matsuda's synthesis of this natural product involves a SmI_2-mediated pinacol coupling to close the seven-membered carbocycle.[85] Initially, Matsuda examined the use of a titanium-mediated pinacol cyclization to form this ring; however, undesired side reactions were observed. However, the cyclization of dicarbonyl **227** with SmI_2 in the presence of HMPA gave the triol **228** in good yield, with no other stereoisomers being detected (Scheme 80). Interestingly the hydroxyl at C3 of **227** appears to play an important role in the cyclization as when the reaction was attempted with the hydroxyl protected as the MOM ether, no cyclization took place.

In Naito's asymmetric approach to balanol, SmI_2 was used to form the hexahydroazepine ring via the cyclization of ketyl−oxime **229**. Initially, attempts to carry out the cyclization using Bu_3SnH led to moderate yields of the hexahydroazepine ring in an approximately 3:1 ratio, favoring the anti cyclization product **229**. The use of SmI_2 in the presence of HMPA gave an improved yield with a marked increase in diastereoselectivity, again favoring the anti product **230** but now by nearly 7:1 (Scheme 83). Such stereoselectivity was explained by invoking an 11-membered Sm(III) chelate intermediate **231**.[154,155]

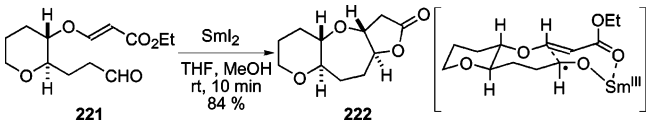
Scheme 77



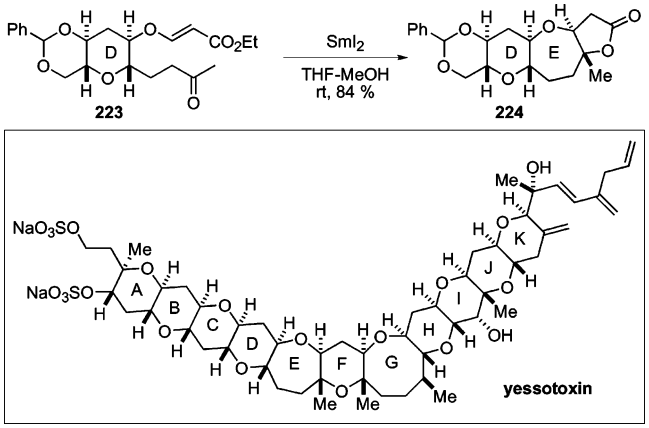
Scheme 78



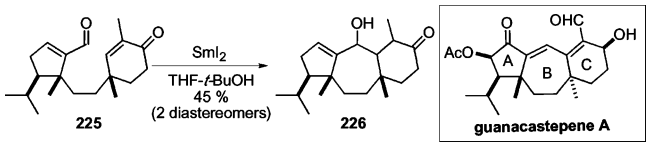
Scheme 79



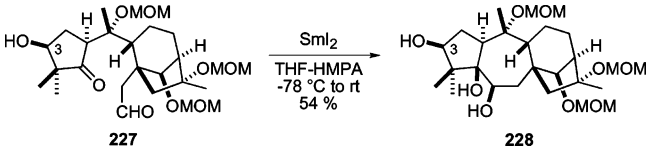
Scheme 80



Scheme 81



Scheme 82

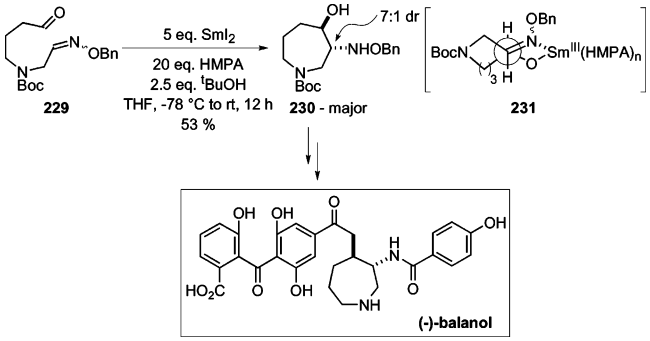


The important role of HMPA in the cyclization was highlighted when in its absence treatment of **229** with SmI_2 failed to give any of the desired product. Further studies by Naito also revealed that the initial geometry of the oxime had no influence on the yield or stereoselectivity of the cyclization.

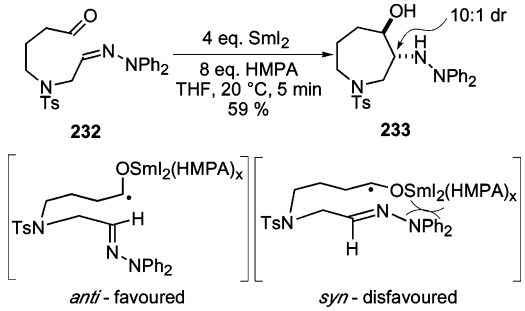
Work by Skrydstrup on the synthesis of balanol also employs a radical cyclization to form the hexahydroazepine ring.[156] SmI_2 was used to mediate the intramolecular ketyl−hydrazone coupling of **232** to form the seven-membered ring of the target (Scheme 84). Hexahydroazepine **233** was formed in good yield and with high diastereoselectivity. Skrydstrup proposed that HMPA is playing a key role in promoting the cyclization simply by discouraging competitive processes such as intermolecular pinacol coupling reactions.

Unlike Naito, Skrydstrup does not invoke an 11-membered chelate intermediate to explain the observed stereoselectivities. Instead, he ascribes the anti stereoselectivity to steric repulsions between the complexed Sm(III)−ketyl and the bulky diphenylhydrazone group in the intermediate transition structure, with the substituents taking up pseudoaxial positions.

Scheme 83

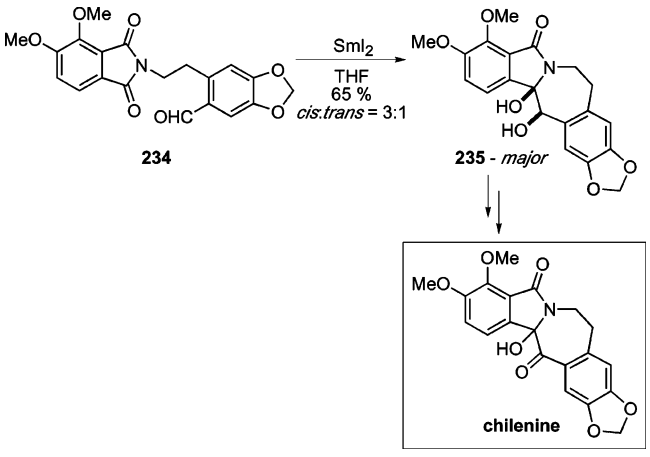


Scheme 84



Yoda employed an unusual SmI_2-induced pinacol coupling to form the benzazepine moiety of the aporhoedane alkaloid chilenine. Treatment of the phthalimide substrate **234**, bearing a distal formyl group, with SmI_2 yielded the pinacol product **235** as a 3:1 mixture of diastereoisomers (Scheme 85).[157] The

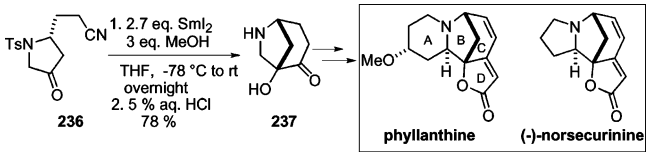
Scheme 85



cyclization proceeded with complete regioselectivity. Notably, no additives were required. Both diastereoisomers can be converted to the natural product via a common intermediate enol acetate, and hence, the preparation of the pinacol product constitutes a formal synthesis of chilenine.

Weinreb's approach to the securinine alkaloids involved a pinacol-type coupling between a ketone carbonyl group and a pendant nitrile. Treatment of **236** with SmI_2 in the presence of MeOH gave an intermediate imine, which was hydrolyzed on workup to give bicyclic ketone **237** in high yield (Scheme 86).[158] Phyllanthine, (−)-norsecurinine, and (+)-

Scheme 86



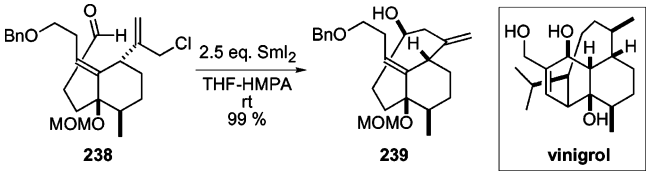
14,15-dihydronorsecurinine (not shown) were subsequently accessed from this BC ring fragment.

2.5. Eight-Membered Rings

2.5.1. Barbier Reactions

SmI_2 has been used to great effect for the formation of eight-membered rings. In an alternative approach to vinigrol to that previously discussed (see Scheme 56, section 2.3.4), Matsuda has shown the SmI_2-mediated intramolecular Barbier coupling of an aldehyde and an allylic chloride to be a viable method for generating the eight-membered ring of the target (Scheme 87).[159,160] Treatment of chloride **238** with

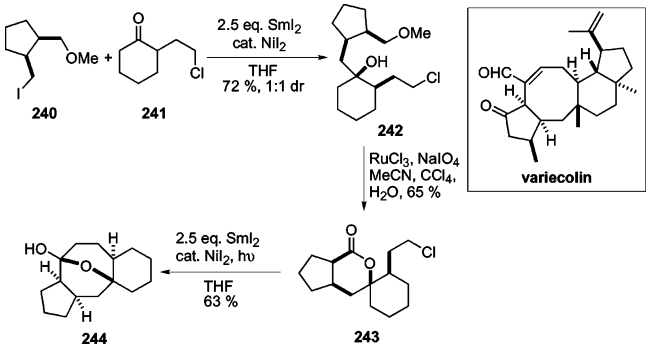
Scheme 87



SmI_2 in the presence of HMPA gave cyclooctanol **239** in excellent yield under non-high dilution conditions.

Molander constructed the ABC ring system of the sesterterpenoid variecolin. His approach involves two key SmI_2-mediated transformations and exploits the difference in reactivity of alkyl iodides and chlorides with the reagent. The first step involves the intermolecular coupling of **240** and **241** carried out with SmI_2 under Barbier conditions, in the presence of catalytic NiI_2,[35,38] to give **242** in good yield (Scheme 88).[161] The primary alkyl chloride was tolerated in

Scheme 88



the intermolecular coupling. The second SmI_2-mediated step involves the Barbier cyclization of lactone **243**. In this instance, SmI_2 is used with catalytic NiI_2 combined with photochemical activation[31,32] to allow conversion of the primary chloride **243** to the bridged hemiketal **244** in good yield.

2.5.2. Reformatsky Reactions

The biologically important natural product Taxol has provided arguably the greatest challenge to synthetic chemists in recent years (Figure 4).

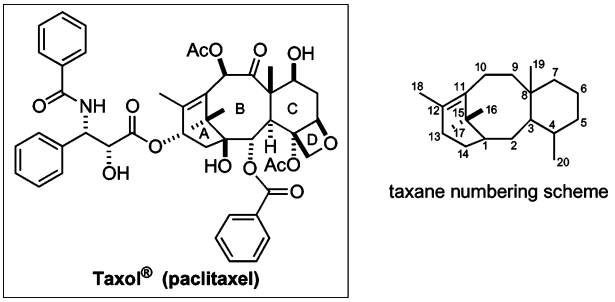
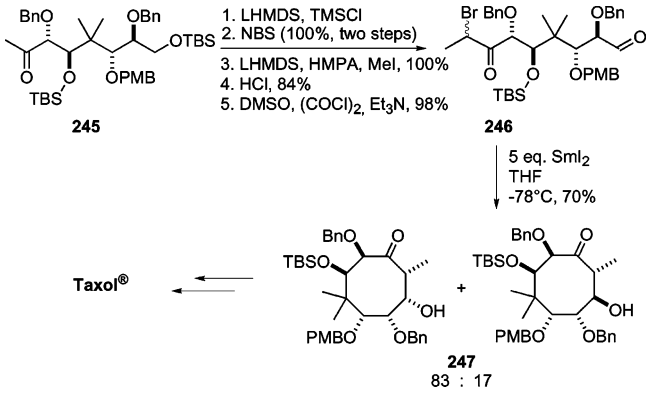


Figure 4.

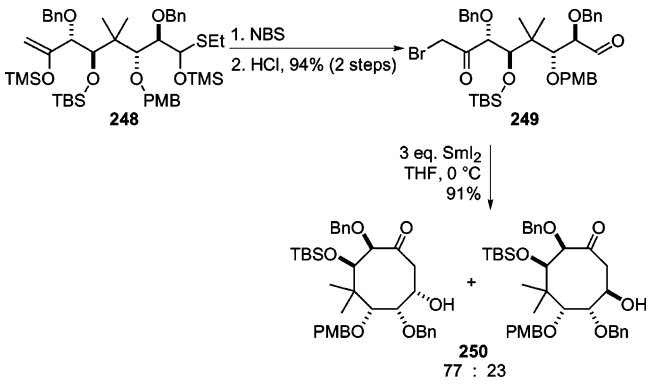
Mukaiyama's approach to the complex target involved initial construction of the B ring using a range of SmI_2-mediated Reformatsky reactions to form the C3−C8 bond. Efficient construction of bromide **246**, followed by treatment with SmI_2 at −78 °C, gave the product **247** in high yield and with good diastereoselectivity (Scheme 89).[162,163]

Scheme 89



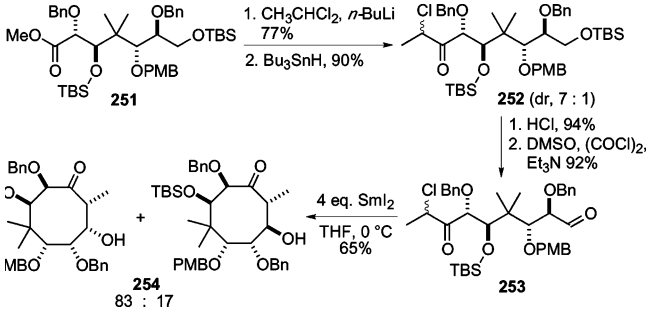
In an alternative approach, Mukaiyama originally planned to employ a sulfonium-ion-mediated cyclization of mixed acetal/silyl enol ether **248** for construction of the eight-membered ring. After several failed attempts, a different strategy was adopted. Conversion of **248** into primary α-bromoketone **249** and treatment with SmI_2 gave *β*-hydroxy ketones **250** in excellent yield (Scheme 90).[163−165]

Scheme 90



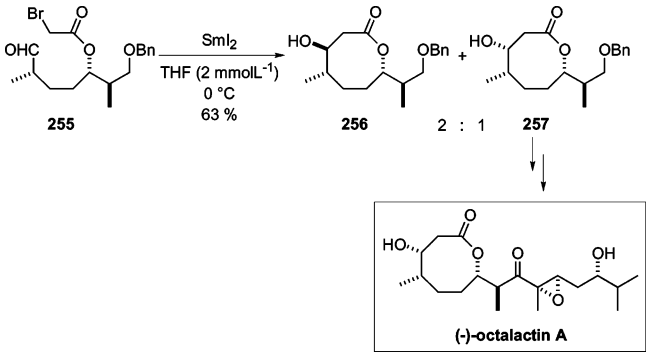
More recently, Mukaiyama has shown that α-chloroketones can also be employed in analogous cyclization reactions. α-Chloroketone **253** was contructed via partial reduction of a dichloro intermediate. Treatment of **253** with SmI_2 at 0 °C gave products **254** in good yield, with similar selectivity to previous examples (Scheme 91).[166,167]

Scheme 91



A formal synthesis of the marine natural product (−)-octalactin A, using a SmI_2-mediated Reformatsky reaction, has been reported. Treatment of *δ*-(bromoacetoxy)aldehyde **255** with SmI_2 at 0 °C under high dilution conditions gave a 2:1 mixture of diastereoisomeric lactones **256** and **257** in good yield (Scheme 92).[168] The undesired major product **256**

Scheme 92

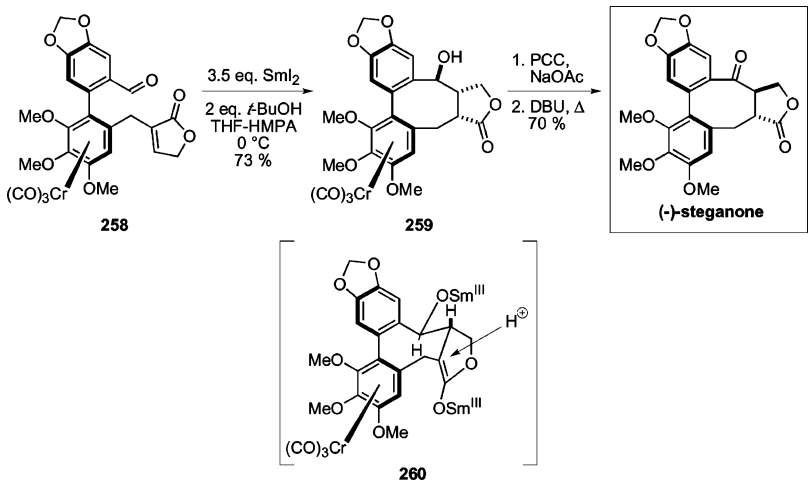


could be converted cleanly to the required minor diastereoisomer **257** via an oxidation−reduction protocol.

2.5.3. Carbonyl–Alkene Reductive Couplings

Molander employed an 8-*endo*-trig ketyl−olefin cyclization for the formation of the eight-membered ring system of (−)-steganone (Scheme 93).[169] Formation of the large carbocycle was assisted by the biaryl system, which held four of the carbon atoms in a suitable arrangement for cyclization. Furthermore, the presence of the electron-donating methylenedioxy group on the same aromatic ring as the aldehyde was beneficial as it served to raise the SOMO of the ketyl−radical and so encourage cyclization of **258**. The main feature of this approach, however, was the use of a chromium tricarbonyl complex to control the stereochemistry of the cyclization. In what would normally be a labile biaryl system, the chromium tricarbonyl group forces the formyl group to occupy a distal position. This holds cyclic intermediate **260** in a conformation which leads to the desired stereo-

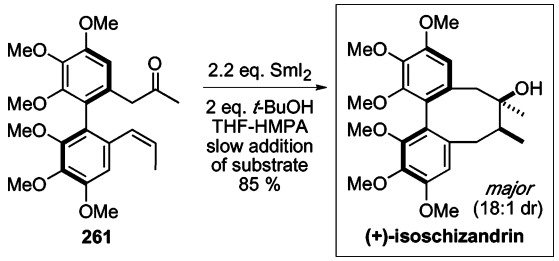
Scheme 93



chemistry at the stereocenter α to the lactone carbonyl.[169] The synthesis was finished in two steps from cyclooctanol **259**. Oxidation of the alcohol using PCC also removed the chromium complex, and epimerization of the stereocenter α to the newly formed ketone carbonyl group gave the enantiopure natural product.

Using a similar strategy, Molander recently reported the total synthesis of (+)-isoschizandrin. In this example, ketone **261** cyclizes in an 8-*endo*-trig fashion to give the target compound (Scheme 94).[170]

Scheme 94



The axial chirality of the biaryl system efficiently controls the central chirality of the product. The *Z*-olefin geometry is also vital to the stereochemical outcome, and the presence of HMPA in the reaction mixture helps control the conformation of the transition state by increasing the steric demands of the alkoxysamarium substituent.

Clearly, not all SmI_2-mediated approaches to natural product targets have been successful. In an ambitious approach to the eight-membered B ring of Taxol, Férézou and Prangé attempted the SmI_2-mediated 8-*exo*-dig cyclization of the aldehyde−alkyne precursor **262**, but unfortunately, the reaction failed to give any ring-closed product (Figure 5).[171]

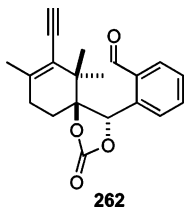
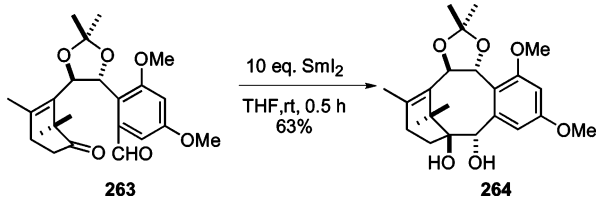


Figure 5.

2.5.4. Pinacol Cyclizations

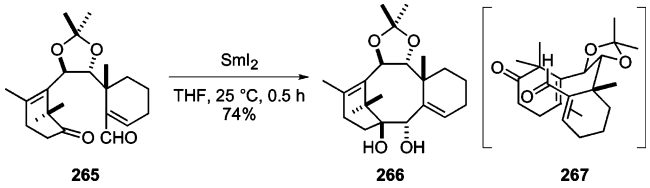
In another approach to the B ring of the taxane skeleton, Swindell used a SmI_2-mediated pinacol coupling to close the ring between C1 and C2 (for taxane numbering scheme, see Figure 2). In the cyclization of **262**, SmI_2 was found to be superior to the $TiCl_4$−Zn reagent system.[172] Aromatic aldehyde **263** cyclized on treatment with SmI_2 to give diol **264** in moderate yield (Scheme 95).

Scheme 95



Swindell later showed that the presence of an aromatic C ring was not essential as α,β-unsaturated aldehyde **265** cyclized in good yield on treatment with SmI_2 (Scheme 96).[173] The use of nonaromatic substrate **265** allowed the methyl group at C8 to be introduced prior to the cyclization. Swindell suggests that the formation of the anti diol product **266** can be rationalized by invoking an *endo* boat−chair transition structure **267**.

Scheme 96

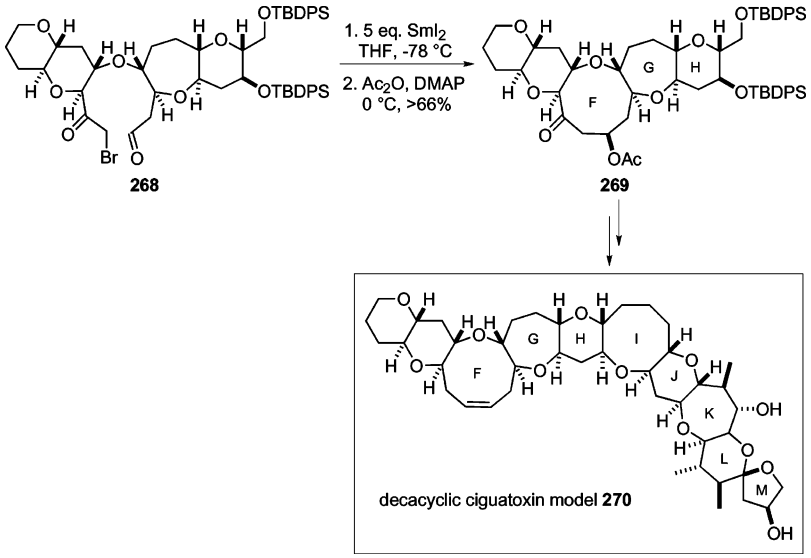


2.6. Nine-Membered Rings

2.6.1. Reformatsky Reactions

Tachibana used SmI_2-mediated Reformatsky reactions to great effect in forming the nine-membered oxonone F ring of ciguatoxin (see Scheme 78). Treatment of bromide **268** with SmI_2 gave **269** as a single

Scheme 97



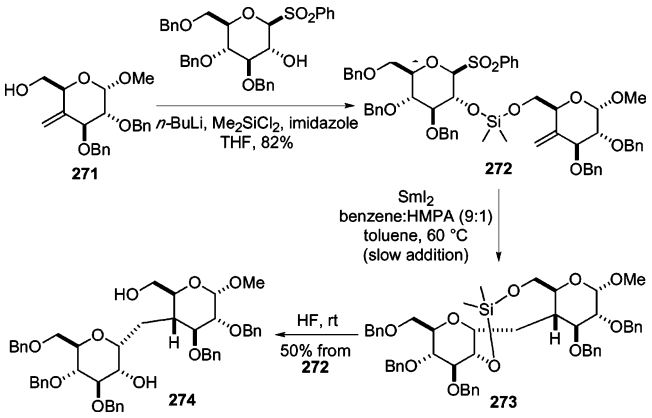
diastereoisomer after in situ acetylation (Scheme 97).[174,175] The product was converted to decacyclic polyether **270**, representing the F−M rings of ciguatoxin.

In earlier model studies, over-reduction of the cyclization products leading to cleavage of the C−O bond α to the ketone was a significant problem at 0 °C. This was overcome by adding the substrate at a faster rate to the SmI_2 in THF at −78 °C.[176,177]

2.6.2. Radical–Alkene Cyclizations

Sinaÿ employed SmI_2 in an intramolecular delivery approach to the synthesis of *C*-disaccharides (see also Scheme 20, section 2.2.3). Glycosyl sulfone **272** bearing a tethered unsaturated sugar acceptor undergoes a radical 9-*endo*-trig cyclization on the slow addition of SmI_2 in benzene and HMPA. The target *C*-disaccharide **274** was formed in 50% overall yield after cleavage of the silicon tether (Scheme 98).[178]

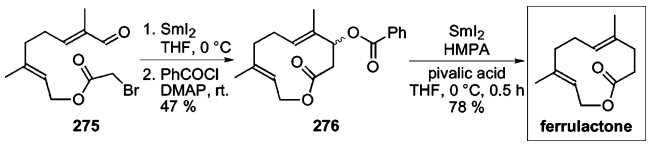
Scheme 98



2.7. Larger Rings

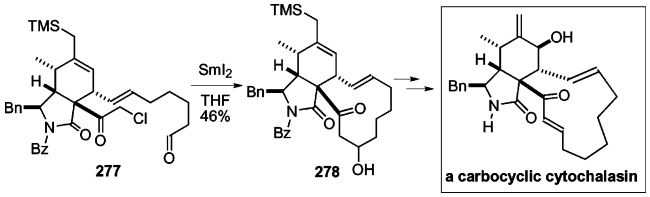
This section will deal with the use of SmI_2 in the construction of larger rings. Inanaga utilized a SmI_2-promoted Reformatsky reaction to generate the 11-membered ring of ferrulactone. Cyclization of bromide **275** onto an α,β-unsaturated aldehyde formed an unstable β-hydroxydecadienolide, which was isolated as the corresponding benzoate **276** (Scheme 99). The next and final step involved the SmI_2-mediated reduction of the allylic benzoate.[179]

Scheme 99



Vedejs employed a SmI_2-mediated Reformatsky reaction to form the 11-membered ring of a carbocyclic cytochalasin. Treatment of α-chloroketone **277** with SmI_2 gave **278** as a single diastereoisomer. The stereochemistry at the newly formed stereocenter was not determined (Scheme 100).[180]

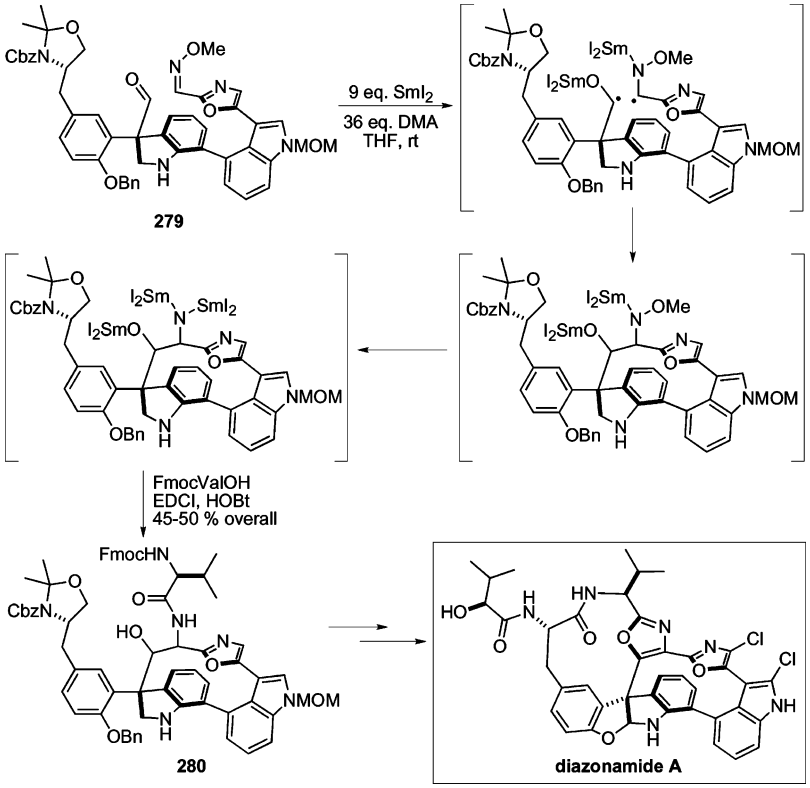
Scheme 100



Nicolaou used a SmI_2-mediated heteropinacol coupling to close the 12-membered 'aromatic' macrocycle in his second total synthesis of diazonamide A. Treatment of oxime−aldehyde **279** with SmI_2 in the presence of DMA (dimethyl acetamide) as an activating ligand led to sequential C−C bond formation and N−O bond cleavage. Nicolaou proposes a diradical mechanism for the pinacol coupling stage. The amine intermediate was not isolated but rather coupled in situ with Fmoc-protected valine to give amide **280** (Scheme 101).[181] HMPA has been used in place of DMA in similar transformations but gave lower yields.[182]

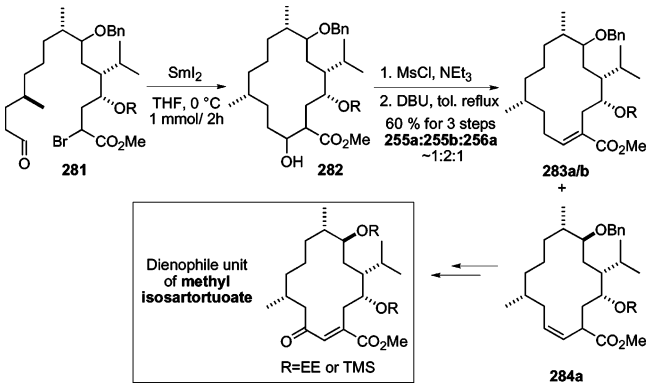
Xu closed the 14-membered ring of the dienophile portion of the tetracyclic tetraterpene isosartortuoate using a SmI_2-mediated Reformatsky reaction. Bromoaldehyde **281** (a mixture of diastereoisomers at the center bearing the benzyloxy substituent) underwent

Scheme 101



cyclization on treatment with SmI_2 at 0 °C to give the macrocycle **282**, as a mixture of several diastereoisomers. This mixture was mesylated and treated with DBU to afford three products: two diastereoisomers of the α,β-unsaturated product **283a/b** (a mixture at the center bearing the benzyloxy substituent) in addition to regioisomer **284a**, formed as a single diastereoisomer by rearrangement of **283a** under the elimination conditions (Scheme 102). While

Scheme 102

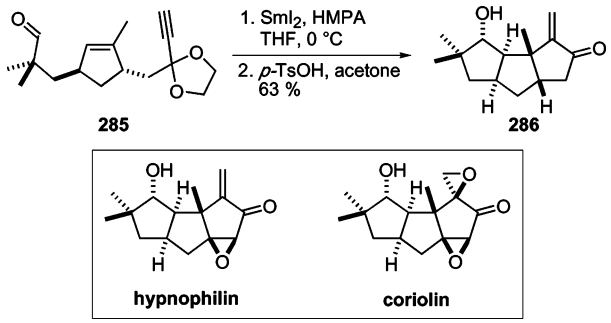


283a could be converted to **284a** by equilibration with DBU in refluxing toluene, only **284a** is carried forward in the synthesis.[183]

3. Sequential Reactions

SmI_2 has been used to great effect in mediating sequential reactions where complex polycyclic systems are constructed in one synthetic operation. Curran used a SmI_2-mediated sequential process in his total synthesis of (±)-hypnophilin and the formal synthesis of (±)-coriolin. Treatment of aldehyde **285** with SmI_2 in the presence of HMPA gave **286** after ketal hydrolysis (Scheme 103). Aldehyde **285** failed

Scheme 103

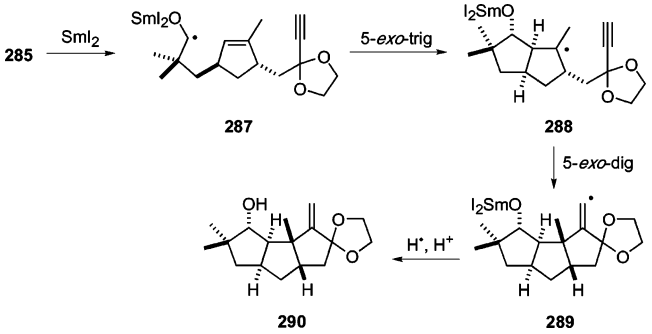


to give any desired product on treatment with Zn/TMSCl or exposure to photochemical conditions. The SmI_2-mediated reaction proceeded with complete diastereocontrol, generating three new stereocenters in the sequence and giving the cis, trans, cis stereochemistry of the tricyclic product. Interestingly, when DMPU was used as cosolvent, the stereoselectivity of the reaction decreased and a 10:1 ratio of diastereoisomers of the tricyclic product was obtained. When using either HMPA or DMPU, a small amount of the uncyclized, reduced aldehyde was also isolated.[184]

The mechanism of the reaction involves the generation of a ketyl−radical anion **287** which cyclizes in a 5-*exo*-trig manner to form the tertiary cyclopentyl radical **288**, which adds to the alkyne in a 5-*exo*-dig cyclization to form the final five-membered ring. As less than two equivalents of SmI_2 is necessary for the sequential reaction and no deuterium incorporation

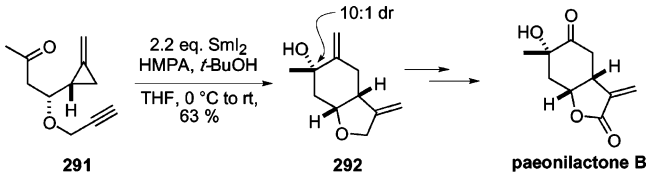
was observed upon quenching with D_2O, the authors concluded that the final radical species **289** undergoes hydrogen-atom capture from the solvent rather than reduction to generate an organosamarium species (Scheme 104).[184]

Scheme 104



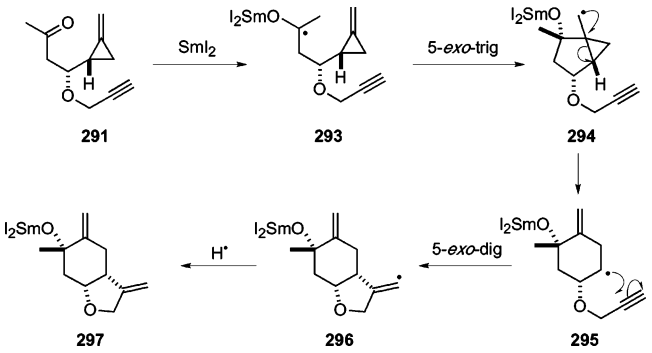
Kilburn employed a SmI_2-mediated sequential radical cyclization of a methylenecyclopropyl ketone in the preparation of paeonilactone B.[185,186] In Kilburn's synthesis of the natural product, the six- and five-membered rings are generated stereoselectively in one synthetic operation. Treatment of methylenecyclopropyl ketone **291** with SmI_2, in the presence of HMPA and *t*-BuOH, gave the bicyclic lactone **292** as a 10:1 mixture of diastereoisomers (Scheme 105).

Scheme 105



The reaction mechanism involves the cyclization of ketyl−radical anion **293** onto the methylenecyclopropane moiety in a 5-*exo*-trig manner (Scheme 106).

Scheme 106



Ring opening of cyclopropane intermediate **294** gives rise to the cyclohexyl radical **295**, which then cyclizes in a 5-*exo*-dig fashion to form the second ring.

The presence of HMPA was found to have a dramatic effect on the diastereoselectivity of the reaction. When HMPA was replaced with the less coordinating solvent DMPU, the yield and diastereoselectivity of the sequence decreased. In the absence of any additive, the yield decreased further, and in addition, a switch in diastereoselectivity was observed. The authors explain the diastereoselectivity of the cyclization by invoking the transition structures shown in Figure 6. In the presence of a strongly coordinating solvent such as HMPA, the effective steric bulk of the samarium alkoxide results in it taking up a more favorable pseudoequatorial position to minimize 1,3-diaxial interactions (**298**). In a less coordinating solvent such as DMPU or in the absence of any additive, the effective steric bulk of the samarium alkoxide is less and the methyl group adopts a pseudoequatorial position (**299**).

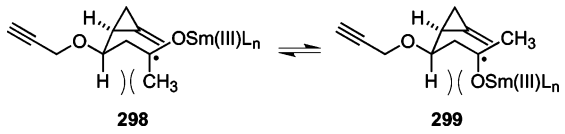
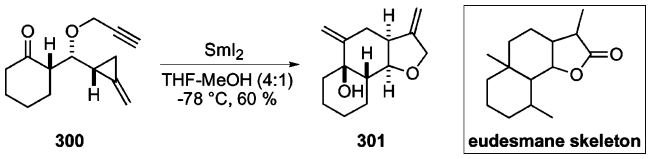


Figure 6.

A related sequential radical cyclization has been used by Kilburn to access the tricyclic ether skeleton of the eudesmanes.[187] It was found that SmI_2 in THF−MeOH (4:1) gave the most efficient conversion of substrate **300** to tricyclic **301** (Scheme 107). Again, it was found that cosolvent played a crucial role in determining the stereochemical outcome of the sequence.

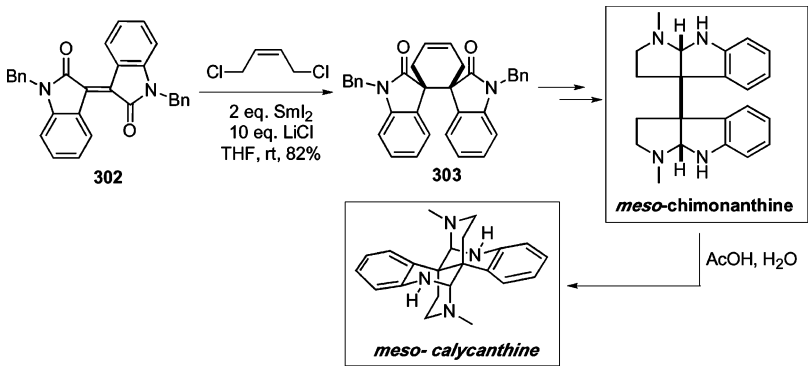
Scheme 107



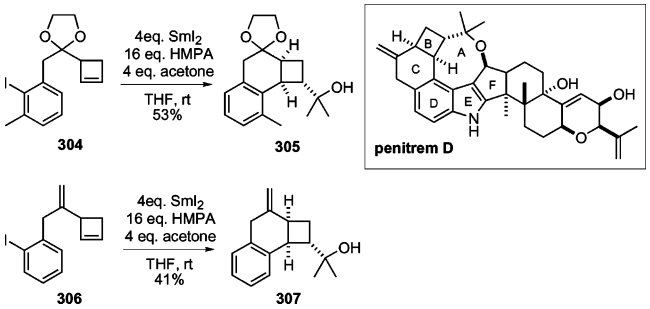
Overman employed a sequential SmI_2-mediated reduction−dialkylation in the stereocontrolled synthesis of *meso*-chimonanthine and *meso*-calycanthine. Treatment of **302** with SmI_2 in the presence of LiCl is thought to first generate a dienolate, which then reacts with *cis*-1,4-dichloro-2-butene, giving **303** in high yield. The dialkylation did not proceed in the absence of LiCl even after the addition of HMPA (Scheme 108).[188] The authors suggest LiCl may act by forming a more reactive samarium complex or by changing the degree of aggregation of the reagent. Flowers has since studied the effect of LiCl on SmI_2 reactions.[33,34] He showed that SmI_2 is monomeric in THF[25] and suggested that LiBr or LiCl react with SmI_2 to produce $SmBr_2$ or $SmCl_2$ in situ. These modified reductants have been found to preferentially reduce carbonyls in the presence of alkyl halides,[34] thus supporting the dienolate mechanism proposed by Overman.[188]

Curran described an efficient, sequential approach to the BCD ring system of the penitrem indole alkaloids. SmI_2-mediated cyclization of an aryl radical in a 6-*exo*-trig fashion onto a cyclobutene acceptor is followed by reduction of the product radical to an organosamarium intermediate, which is quenched by acetone in a Barbier-type reaction. The sequence was found to be quite general. Cyclization of ketal **304**, in which the protected ketone moiety provides a synthetic precursor to the *exo*-methylene group of the penitrems, gave **305** in satisfactory yield. Alternatively, it was found that the process tolerated the *exo*-

Scheme 108



Scheme 109

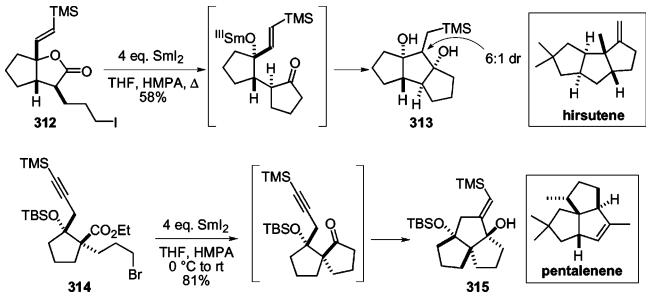


methylene group in substrate **306,** giving direct access to the desired systems albeit in slightly lower yield (Scheme 109).[189]

Molander developed SmI_2-mediated sequential processes for rapid access to a number of bicyclic and tricyclic ring systems in excellent yield and with good diastereoselectivity. Some of the accessible ring systems constitute the core of natural product targets. For example, treatment of lactone **308** with SmI_2 triggers a sequence which involves nucleophilic acyl substitution/ring expansion to give ketone **310**, followed by Barbier cyclization to give **311**, representing the tricyclic ring system of ophiobolin F. As seen previously (Scheme 88, section 2.5.1), the sequence exploits the different rates of reduction of alkyl halides to alkylsamariums (Scheme 110).[190]

Molander also developed SmI_2-mediated sequential processes involving nucleophilic acyl substitution/ketyl−olefin couplings, which allow rapid access to angular and linear triquinane ring systems found in natural products such as hirsutene and pentalenene. For example, treatment of lactone **312** with SmI_2 in HMPA gives linear triquinane skeleton **313** in good yield. Similarly, ester substrate **314** gave angular triquinane framework **315** in excellent yield (Scheme 111).[191]

Scheme 111

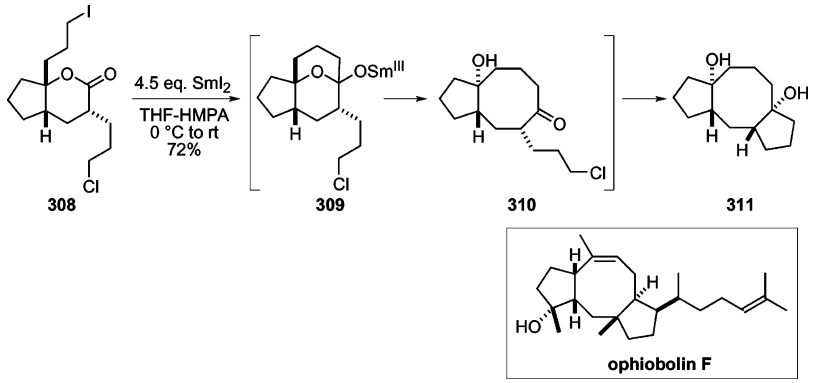


4. Heterocyclizations

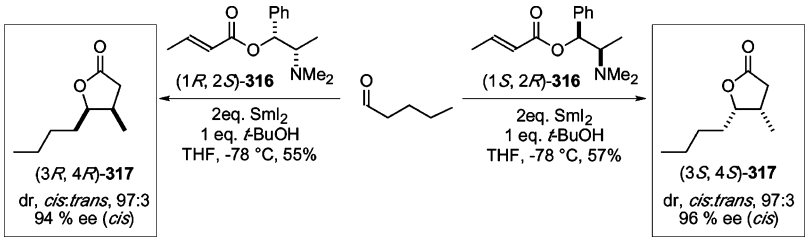
While many of the cyclizations described previously form heterocyclic rings, the heteroatom is not critical to the cyclization step. This section will cover cyclizations in which a carbon−heteroatom bond is formed in the SmI_2-mediated process. For example, Fukuzawa developed an efficient, enantioselective synthesis of chiral γ-butyrolactones via the intermolecular reductive coupling of ketones and aldehydes with ephedrinyl acrylates and crotonates mediated by SmI_2. The reaction of pentanal with ephedrinyl crotonates (1*R*, 2*S*)-**316** and (1*S*, 2*R*)-**316** gave whisky lactones (3*R*, 4*R*)-**317** and (3*S*, 4*S*)-**317,** respectively, in moderate yield and with excellent diastereoselectivity and enantioselectivity (Scheme 112).[192]

The origin of the diastereoselectivity in the reaction is not yet clear, although Fukuzawa observed that

Scheme 110



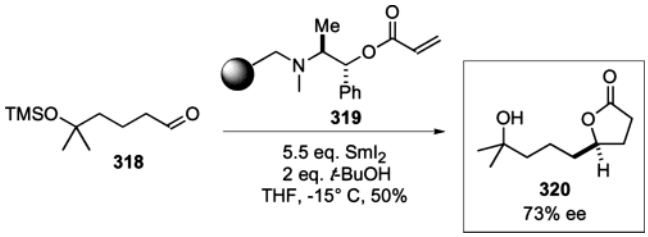
Scheme 112



the addition of HMPA resulted in the formation of racemic lactone product. It is therefore likely that the samarium(III) ion coordinates to the ester and the ephedrine auxiliary, locking the substrate in a conformation in which one face of the crotonate is blocked, possibly by the phenyl group of the ephedrine moiety.

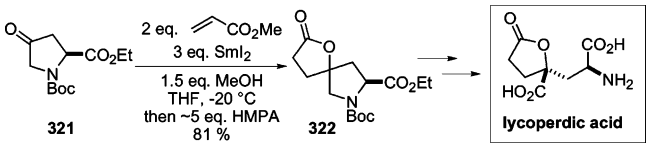
Procter used pseudoephedrine and ephedrine as 'chiral linkers' for asymmetric solid-phase organic synthesis and adapted Fukuzawa's work in an 'asymmetric catch-release' approach to γ-butyrolactones. Thus, an α,β-unsaturated ester linked to resin through an ephedrine 'chiral link' captures a samarium(III) ketyl−radical anion from solution. The ephedrine link controls the stereochemistry of the reductive coupling, and the resulting product undergoes spontaneous, cyclative cleavage from the resin. Simply stirring ephedrinyl acrylate **319** with aldehyde **318**, prepared in four steps from δ-valerolactone, in the presence of SmI_2 and *t*-BuOH, gave γ-butyrolactone **320**, a moderate DNA-binding metabolite isolated from Streptomyces GT61115, in moderate yield and good enantiomeric excess (Scheme 113).[193]

Scheme 113



Yoshifuji prepared the naturally occurring nonproteogenic amino acid lycoperdic acid via a SmI_2-mediated spirolactonization. Addition of SmI_2 to a mixture of ketone **321**, methyl acrylate, followed by addition of HMPA, gave the spirolactone **322** in high yield, as an approximately 1.2:1 mixture of diastereoisomers (Scheme 114). In the absence of HMPA,

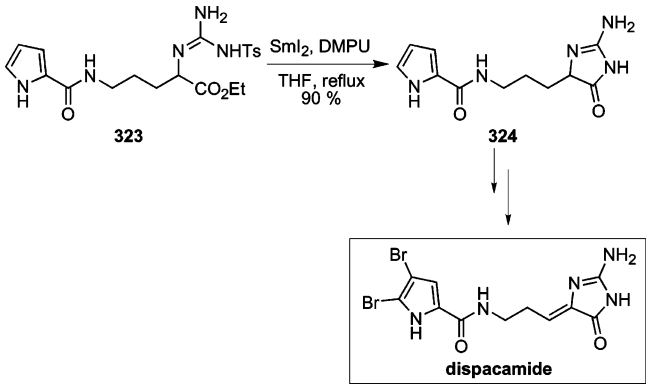
Scheme 114



the reaction was slow and no increase in diastereoselectivity was observed.[194]

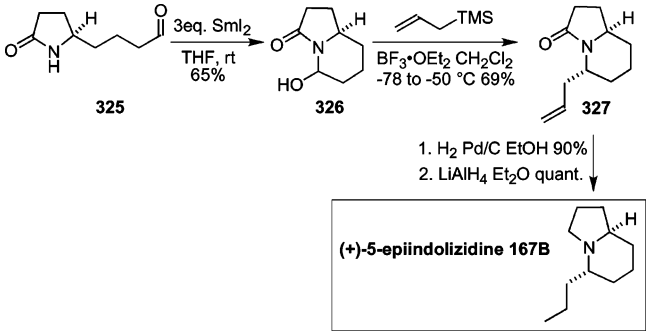
Fresneda utilized a SmI_2-mediated deprotection/cyclization procedure to introduce the 2-amino-imidazolinone moiety in their approach to pyrrole−imidazole marine alkaloid dispacamide. The removal of the *N*-tosyl group from **323** was affected with excess SmI_2 in the presence of the additive DMPU, in refluxing THF. The resulting anion cyclizes to form **324** in high yield (Scheme 115).[195]

Scheme 115



Yoda employed an unusual SmI_2-mediated intramolecular heterocoupling reaction of lactams with tethered aldehydes in the synthesis of indolizidine alkaloids. For example, treatment of **325** with SmI_2 in THF at room temperature gives hemiaminal **326,** which was converted to (+)-5-epiindolizidine 167B in three steps (Scheme 116).[196] The authors suggest a

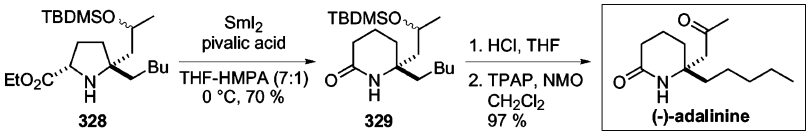
Scheme 116



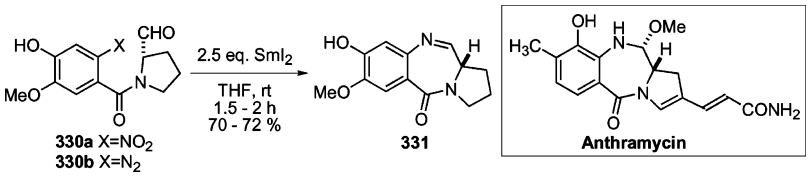
radical mechanism may be responsible for the transformation; however, a Sm(II) or, perhaps more likely, Sm(III) Lewis-acid-mediated hemi-lactam formation seems more plausible.

Honda used a SmI_2-mediated ring expansion reaction as the key step in an approach to the piperidine alkaloid (−)-adalinine. Treatment of the proline derivative **328** with SmI_2 resulted in cleavage of the carbon−nitrogen bond α to the ester to give an acyclic amino ester intermediate, which then underwent lactamization to form **329** in good yield (Scheme 117). HMPA was used to increase the reaction rate and yield, and pivalic acid was employed as a proton

Scheme 117



Scheme 118

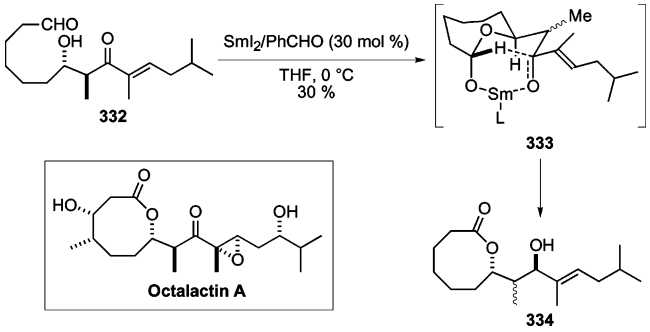


source. Removal of the silyl protecting group in *δ*-lactam **329** and TPAP oxidation gave the target alkaloid in good yield.[197]

Kamal prepared analogues of the DNA-binding antitumor antibiotic anthramycin, using a SmI_2-mediated reductive cyclization. Reduction of an aryl azide or nitro group in substrates **330** followed by condensation with the tethered aldehyde gave **331** in good yield (Scheme 118).[198]

Hulme used a samarium-catalyzed Evans−Tischenko reaction to construct the eight-membered lactone skeleton of octalactin A. Treatment of hydroxy keto−aldehyde **332** with a premixed SmI_2−benzaldehyde catalyst (30 mol %) gave the lactone **334** as a 1:1 mixture of diastereoisomers (Scheme 119).[199] The reaction proceeds via formation of a

Scheme 119



hemiacetal followed by intramolecular hydride transfer to simultaneously form the lactone and reduce the enone carbonyl group. The reaction gave complete 1,3-anti diastereoselectivity. Scrambling of the stereochemistry at the center bearing the methyl substituent was attributed to epimerization prior to cyclization, presumably due to the Sm(III) Lewis acid.

5. Conclusions

In the 25 years since its introduction to organic chemistry, SmI_2 has captured and held the imagination of synthetic organic chemists working in many different areas of the discipline. The versatility of the reagent is perhaps the single most important factor contributing to its popularity. The wide variety of functional group interconversions, carbon−carbon bond-forming reactions, cyclizations, fragmentations, and rearrangements mediated by SmI_2 have led to a wealth of literature on the subject. Despite this, the mechanisms of some SmI_2-mediated reactions are still uncertain and the role of additives and cosolvents is poorly understood.

This review has showcased the use of SmI_2-mediated cyclization reactions in natural product synthesis. The full armory of ring-forming reactions conducted by the reagent has been applied in approaches to a wide range of targets. Indeed, some of the most challenging targets of recent years, such as Taxol, gambierol, and diazonamide A, have been prepared using key cyclization steps mediated by the reagent. Despite the impressive array of examples presented here, many challenges remain in the field of SmI_2 chemistry. The development of new, stereoselective cyclizations, powerful sequential cyclizations, and efficient asymmetric processes are key areas where significant contributions can be made. More generally, further studies on the mechanism of SmI_2 reactions and the role of additives and cosolvents will improve our understanding of the reagent and its chemistry at a more fundamental level.

6. Abbreviations

AIBN	2,2′-azobis(2-methylpropionitrile)
Boc	*tert*-butoxycarbonyl
CAN	cerric ammonium nitrate
Cbz	benzyloxycarbonyl
DBM	dibenzoylmethanato
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	*N*,*N*-dimethyl acetamide
DMAP	4-(dimethylamino)pyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EE	1-ethoxyethyl
Fmoc	9-fluorenylmethyoxycarbonyl
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
PCC	pyridinium chlorochromate
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
SOMO	singly occupied molecular orbital
TBAF	tetrabutylammonium fluoride

TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
Val	valine

7. Acknowledgments

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