HETEROCYCLES, Vol. 89, No. 6, 2014, pp. 1369 - 1391. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 14th March, 2014, Accepted, 11th April, 2014, Published online, 15th April, 2014
DOI: 10.3987/REV-14-795

REDUCTIVE CYCLIZATION REACTIONS TO BICYCLIC COMPOUNDS USING SAMARIUM DIIODIDE

Motoo Tori* and Masakazu Sono

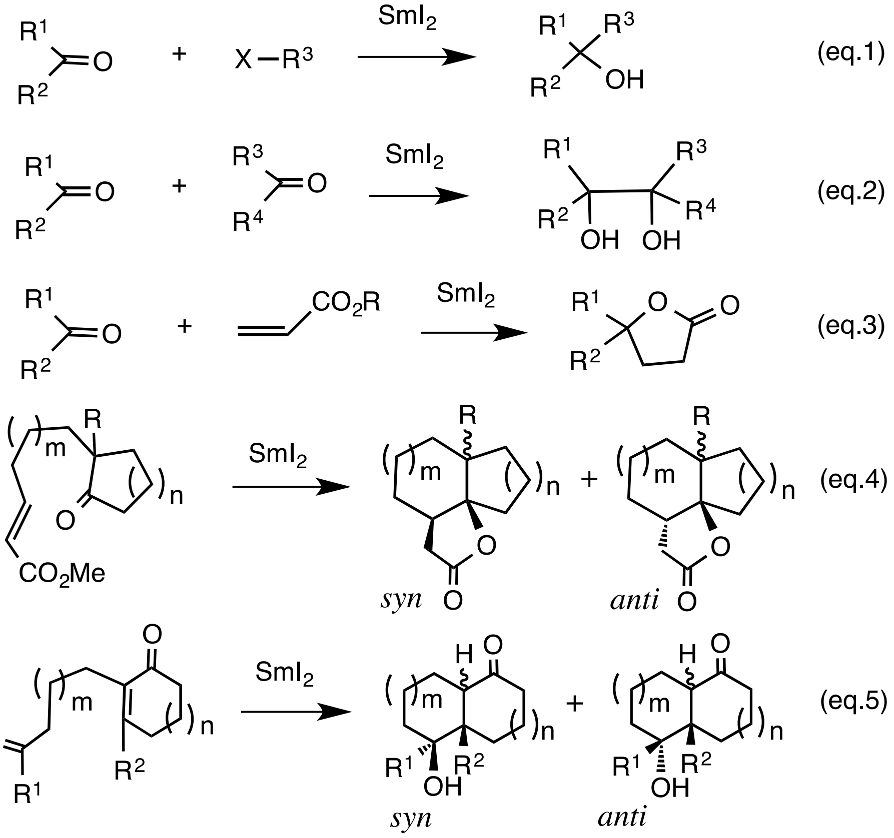
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan

Abstract – This review covers reports on the one-electron reductive cyclization reactions affording bicyclic compounds, such as hydrindans, perhydronaphthalenes, perhydroguaianes, and other systems including five-, six-, seven-, and eight-membered carbocycles using SmI_2. The substrate is aldehyde, ketone, or ester. The effect of additives, such as H_2O, MeOH, HMPA, and NiI_2, was studied. The mechanistic aspects recently investigated are also introduced.

CONTENTS

1. INTRODUCTION

Samarium diiodide (SmI_2) has been used in organic synthesis because it is easy to use, highly selective, very powerful, and because its power can be changed by the use of additives, such as H_2O, MeOH, *t*-BuOH, HMPA, and NiI_2.[1] SmI_2 has been utilized for carbon-carbon bond-forming reactions such as between ketone and halide (eq. 1, Scheme 1), between ketones (eq. 2), or between ketone and α,β-unsaturated carbonyl to afford lactone (eq. 3).[1]



Scheme 1. Major reactions of SmI_2

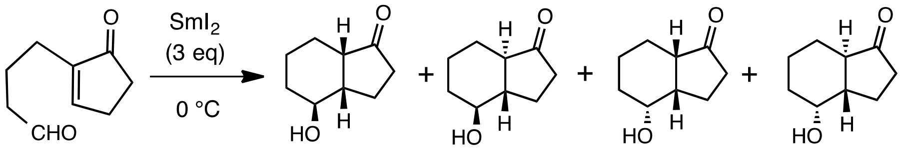
We are especially interested in carbon-carbon bond-forming reactions at both the α- and β-positions of α,β-unsaturated carbonyl compounds. The intramolecular versions of these types of reactions (eqs. 4 and 5) are the main topic of this review. Depending on the size of 'm' and/or 'n', hydrindans, perhydronaphthalenes, perhydroguaianes, and other systems can be established. These reactions can also be applicable to the synthesis of natural products, such as eremophilanes and guaianes. One-electron reduction of a carbonyl group by SmI_2 affords a radical anion, which adds to a double bond or a carbonyl group ('carbonyl-first mechanism').[1] However, in the case of α,β-unsaturated carbonyl compounds, substrates can be recognized as an alkene substituted with an alkoxycarbonyl group. Therefore, it is thought that the carbonyl is first reduced to afford a radical anion and is then added to the double bond of the alkene substituted with an alkoxycarbonyl group at the β-position of the carbonyl group. On the other hand, if the α,β-unsaturated carbonyl compound is first reduced, a radical is formed at the β-position of the carbonyl group. This radical can attack the carbonyl group to form a new carbon-carbon bond. This is called the 'alkene-first mechanism' by Procter.[1] These points will be discussed later. Special attention should be paid to the stereochemistry of the products in eq. 5. When the newly created hydroxy group (OH) and R^2 (H or Me) are in the same direction, this is called a *syn* relationship, while in the opposite direction, an *anti* relationship. Please note that this is not due to the relation of a fused-ring, for example, *cis*- or *trans*-hydrindan. Most reactions were conducted at rt or 0 ˚C and 3 equivalents of SmI_2 were used in general. The amount of SmI_2 was increased when the reaction was slow.

Kagan,[2-5] Curran,[6-8] Molander,[9-12] Little,[13] Flowers, II,[14,15] and Procter[1,16,17] have published reviews on similar subjects. These authors concentrated on a narrow area, cyclization to bicyclic systems, covering reports published in approximately the past ten years, and touched on the mechanism obtained recently by DMPO and ESR methods. The ring-opening fragmentation reaction was not included.[18]

2. CYCLIZATION TO HYDRINDANS

Hydrindans are synthesized by coupling between enone and aldehyde moieties, as shown in Table 1.[19] Three chiral centers are created from **1** by this reaction in one step to afford four kinds of products. When the reaction was conducted without additives, *syn* compound **2**, the configurations of which were all β-oriented, was the predominant product. When MeOH was added as the additive, the ratio of compound **2** slightly decreased. However, the product ratio was almost the same as without the additive. Addition of HMPA decreased the yield of these products, presumably due to the isolation procedure. In any case the ratio of *syn* (**2** and **3**):*anti* (**4** and **5**) was *ca*. 9:1.

Table 1. The reaction of compound **1** with SmI_2



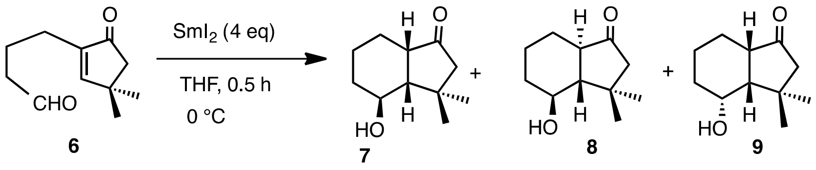
1 **2** **3** **4** **5**

entry	additives	yield (%)	ratio				*syn* : *anti*
			2	**3**	**4**	**5**	
1	none	98	81	13	4	2	94 : 6
2	MeOH (4 eq)	90	75	12	11	2	87 : 13
3	HMPA	64	66	22	9	3	88 : 12

Two methyl groups were added to the cyclopentanone ring and similar reactions were carried out (Table 2).[19] The stereochemistries of the products were almost the same as those in Table 1. Without an additive, *syn* compounds **7** and **8** predominated, and with MeOH as the additive, the ratio of compound **9** increased. The tendency was for the major product to have a *syn* configuration involving the hydroxy group and the hydrogen at the juncture position, while in the case of compound **9**, the relationship was *anti*. Compounds

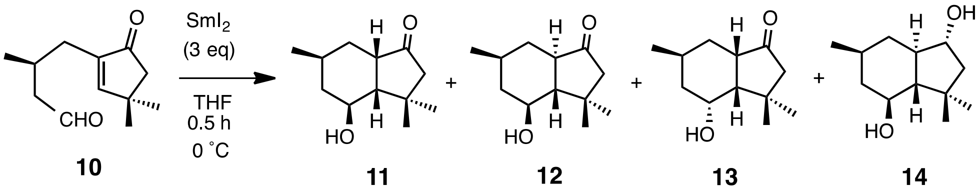
7 and **8** belong to the same group because the juncture position next to the carbonyl group is created on the quenching of samarium enolate. *cis*-Fused hydrindans are usually produced rapidly due to their stability. The ratio of *syn*:*anti* was *ca*. 7:3–9:1.

Table 2. The reaction of compound **6** with SmI_2



entry	additives	yield (%)	ratio 7	ratio 8	ratio 9	*syn* : *anti*
1	none	77	48	47	5	95 : 5
2	MeOH (2 eq)	96	14	59	27	73 : 27
3	HMPA	87	52	40	8	92 : 8

Table 3. The reaction of compound **10** with SmI_2

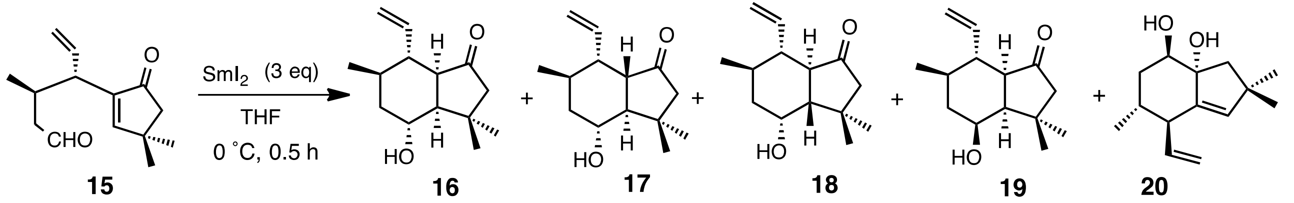


entry	additives	yield (%)	ratio **11** : **12** : **13** : **14**	*syn* : *anti*
1	none	60	56 : 25 : 14 : 5	86 : 14
2	MeOH (2 eq)	79	36 : 42 : 17 : 5	83 : 17
3	HMPA	81	47 : 26 : 16 : 11	84 : 16

One methyl group was introduced at the side chain because the substrate was chosen aiming at the synthesis of botrydial.[19] Compound **10** was subjected to the reaction with SmI_2 (Table 3). The major product was compound **11**, which again had a *syn* relationship involving the hydroxy group and the hydrogen at the juncture position. When MeOH was added, the ratio of compound **11** decreased and that of compound **12** increased. Compounds **11** and **12** have different stereochemistry of the hydrogen adjacent to the carbonyl group. It is interesting to note that over reduction to product **14** also occurred in this case. This means that SmI_2 can reduce ketone to alcohol under these conditions. The ratio of *syn*:*anti* was *ca*. 4:1.

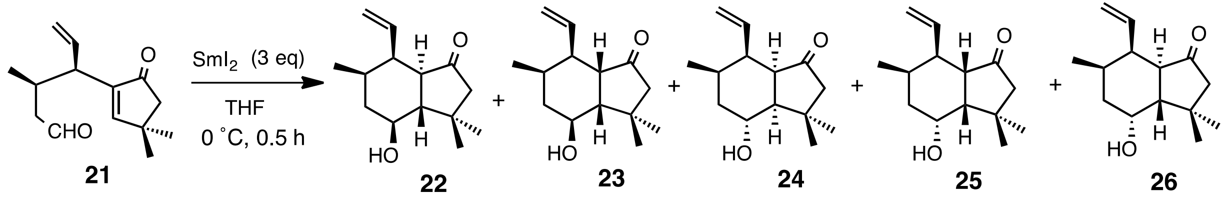
Two substrates, **15** and **21**, bearing a vinyl group on the side chain were next studied (Tables 4 and 5).[19] In these examples the products are complicated because they have many chiral centers. The products were separated carefully using HPLC and the ratio was determined by GC. In the case of compound **15**, the situation was much more complex. The major products, **16** and **17**, had a *syn* configuration and compound **20** arose from the coupling between ketone and aldehyde (Table 4). The product ratio of *syn*:*anti* was *ca*. 1:1–4:1. For compound **21**, it was slightly simpler. These results depended on the difference of the substitution pattern of both vinyl and methyl groups. Only *syn* products were formed in entries 1 and 3, while with MeOH as an additive, the ratio of *syn*:*anti* was *ca*. 1:2 (Table 5). The transition state affording these isomers was considered (Scheme 2).

Table 4. The reaction of compound **15** with SmI_2

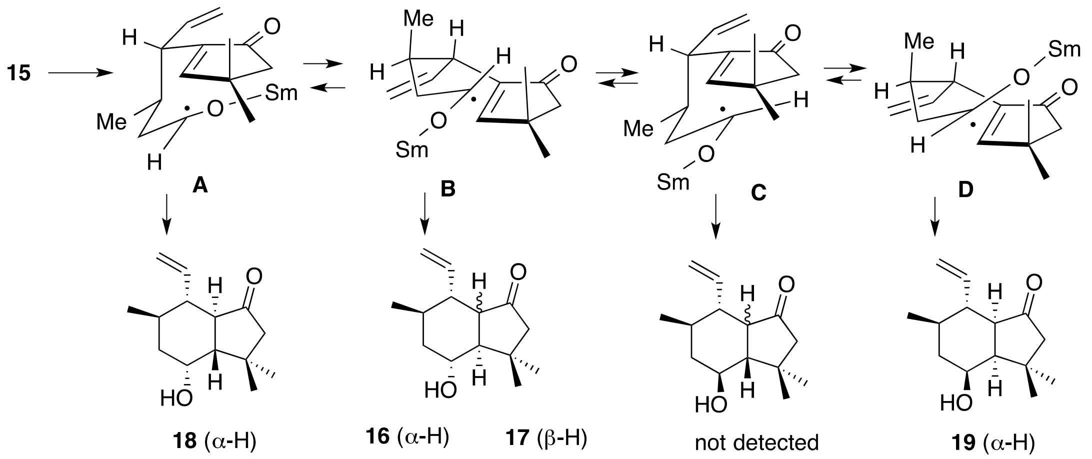


entry	additives	yield (%)	ratio **16** : **17** : **18** : **19** : **20**	*syn* : *anti*
1	none	68	58 : 19 : 16 : 7 : 0	77 : 23
2	MeOH	83	49 : 16 : 20 : 15 : 0	65 : 35
3	HMPA	52	30 : 9 : 26 : 21 : 14	45 : 55

Table 5. The reaction of compound **21** with SmI_2



entry	additives	yield (%)	ratio **22** : **23** : **24** : **25** : **26**	*syn* : *anti*
1	none	55	84 : 10 : 6 : 0 : 0	100 : 0
2	MeOH	70	31 : 2 : 5 : 56 : 6	38 : 62
3	HMPA	73	94 : 6 : 0 : 0 : 0	100 : 0



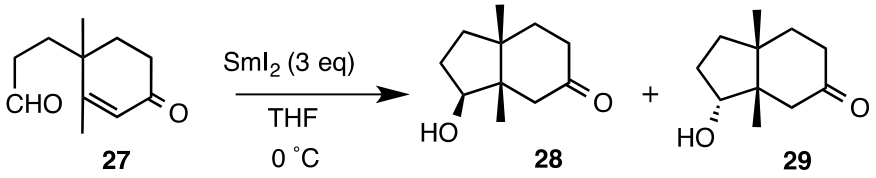
Scheme 2. A plausible mechanism of compound **15**

Conformations B and C must be more stable than A and D because samarium is outside the molecule. It was not clear why the product from conformer C was not produced.

The intramolecular reaction between six-membered enone and aldehyde or ketone was next investigated. Compound **27** had a methyl group at the β-position of the α,β-unsaturated carbonyl group (Table 6). The major product was *syn* compound **28** and the ratio of *syn*;*anti* was *ca.* 7:3–8:2. The yield was good without an additive or with NiI_2. However, in the presence of MeOH or HMPA, yields were not high.[20]

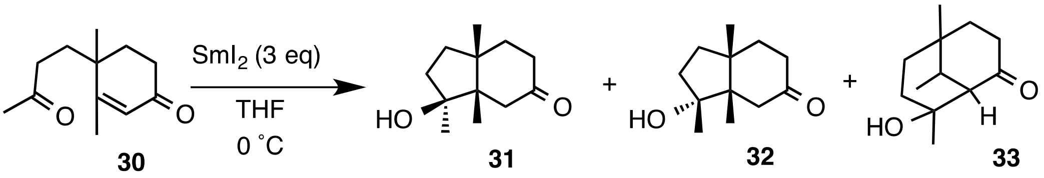
In the reaction between the ketone and enone in compound **30**, yields were also very high in most cases (Table 7).[20] The major product was *syn* compound **31**. With HMPA as an additive, the α-position of the α,β-unsaturated carbonyl group reacted to give **33**. It was quite surprising that the yields were very high in spite of the coupling between the ketone and the quaternary position. This is presumably because the conformation at the transition state benefited the bond formation in this substrate. The substrates described in Tables 1–5 had no functional group at the juncture position of the products, while compounds in Tables 6 and 7 had methyl groups there.

Table 6. The reaction of compound **27** with SmI_2



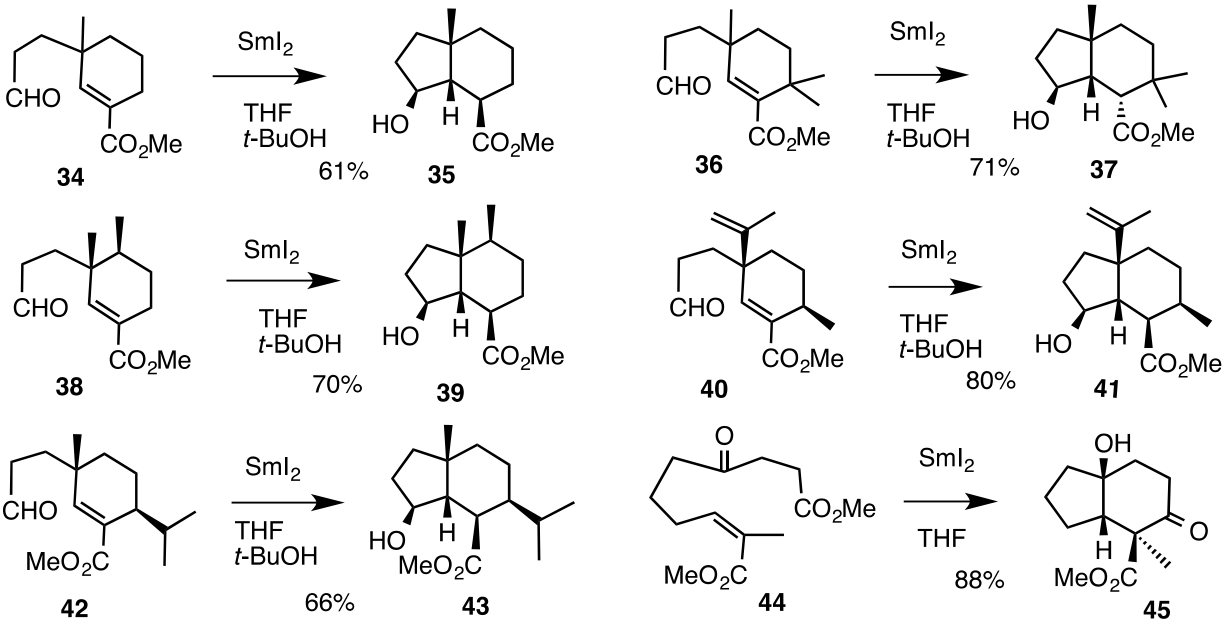
entry	additives	yield (%)	ratio	
			28	**29**
1	none	100	87	13
2	MeOH (2 eq)	58	72	28
3	HMPA (12 eq)	50	82	18
4	NiI_2	100	75	25

Table 7. The reaction of compound **30** with SmI_2



entry	additives	yield (%)	ratio		
			31	**32**	**33**
1	none	100	84	16	0
2	MeOH (2 eq)	100	84	16	0
3	HMPA (12 eq)	78	61	17	22
4	NiI_2	100	53	47	0

Another system for constructing hydrindans was reported (Scheme 3).[21,22] The intramolecular carbon-carbon bond formation between aldehyde and α,β-unsaturated ester only produced *cis*-hydrindans, **35**, **37**, **39**, **41**, and **43**. In most cases, a methoxycarbonyl group was oriented on the same side of the juncture hydrogen, presumably due to the requirement of samarium enolate quenching. The proton can easily be taken from the α-equatorial side. Therefore, compounds bearing β-substituents at the adjacent position more easily took the proton from the α-equatorial side, while in the case of **36**, the methyl group on the α-side interfered with the α-attack, and finally a compound bearing a thermodynamically stable α-methoxycarbonyl group was formed. Compound **44** cyclized to hydrindan **45**, making two carbon-carbon bonds, one being Dieckmann-type condensation.[22] In all cases, *sec*-hydroxy groups had a *syn* configuration involving the juncture hydrogen.



Scheme 3. Formation of hydrindan systems in various substrates

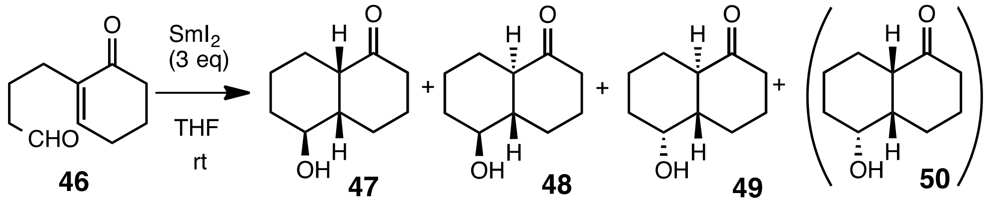
3. CYCLIZATION TO PERHYDRONAPHTHALENES

3.1. Enone in the ring

The intramolecular reaction between the six-membered enone and aldehyde or ketone affords perhydronaphthalenes.[23] The reaction between aldehyde and the enone system was carried out to form both *syn* and *anti* products involving the newly created hydroxy group and the hydrogen at the juncture position (Table 8). Compound **48** was always the major product. The ratio of the product hardly changed depending on the conditions employed. The ratio of *syn*:*anti* was *ca*. 9:1. The fourth isomer **50** was not produced. This tendency was almost the same as that of hydrindans because the predominant transition state was quite similar.

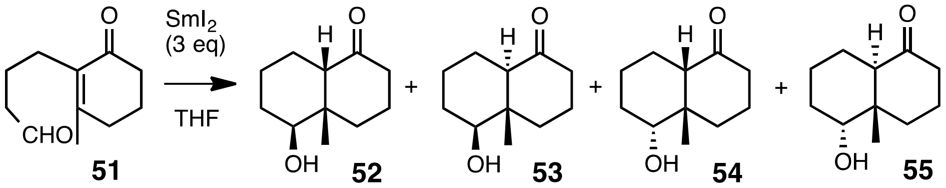
Compound **51** had a methyl group at the β-position of the enone system which was expected to become a juncture substitution in the product.[23] The yield depended on the conditions shown in Table 9 and varied markedly. Compound **52** was the sole product without an additive. *anti* Products, **54** and **55**, involving the hydroxy and methyl groups at the juncture were hardly formed in these cases.

Table 8. The reaction of compound **46** with SmI_2



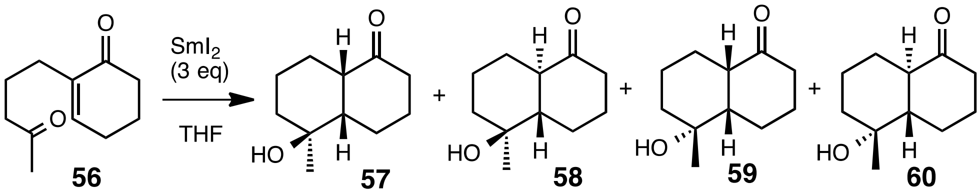
entry	additives	yield(%)	ratio			syn : anti
			47	48	49	
1	none	100	28	61	11	89 : 11
2	MeOH (10 eq)	91	20	66	14	86 : 14
3	HMPA (12 eq)	50	30	57	13	87 : 13
4	NiI_2 (2 eq)	95	35	50	15	85 : 15

Table 9. The reaction of compound **51** with SmI_2



entry	additives	temp. (˚C)	yield (%)	ratio				syn : anti
				52	53	54	55	
1	none	0	67	100	0	0	0	100 : 0
2	MeOH (10 eq)	rt	92	53	45	2	0	98 : 2
3	HMPA (12 eq)	rt	64	57	31	0	12	88 : 12
4	NiI_2 (2 eq)	rt	51	100	0	0	0	100 : 0

Table 10. The reaction of compound **56** with SmI_2

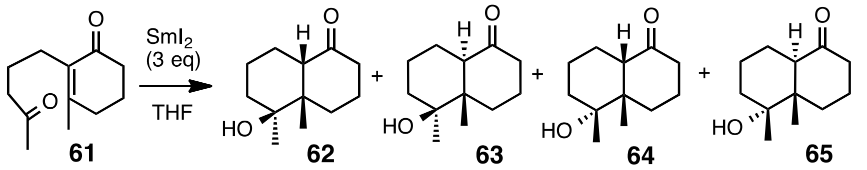


entry	additives	temp.(˚C)	yield (%)	ratio				syn : anti
				57	58	59	60	
1	none	0	100	46	0	19	35	46 : 54
2	MeOH (10 eq)	rt	81	4	86	0	10	90 : 10
3	HMPA (12 eq)	0	33	44	56	0	0	100 : 0
4	NiI_2 (2 eq)	rt	85	38	44	10	18	82 : 18

Compound **56** produced *syn* products **57** and **58** as major isomers with additives (Table 10).

Finally, substrate **61** was treated similarly with SmI_2 (Table 11).[23] Compound **62** was the major product without an additive. However, when MeOH was added, compound **63** was formed predominantly. The transition state must be considered individually to explain these phenomena.

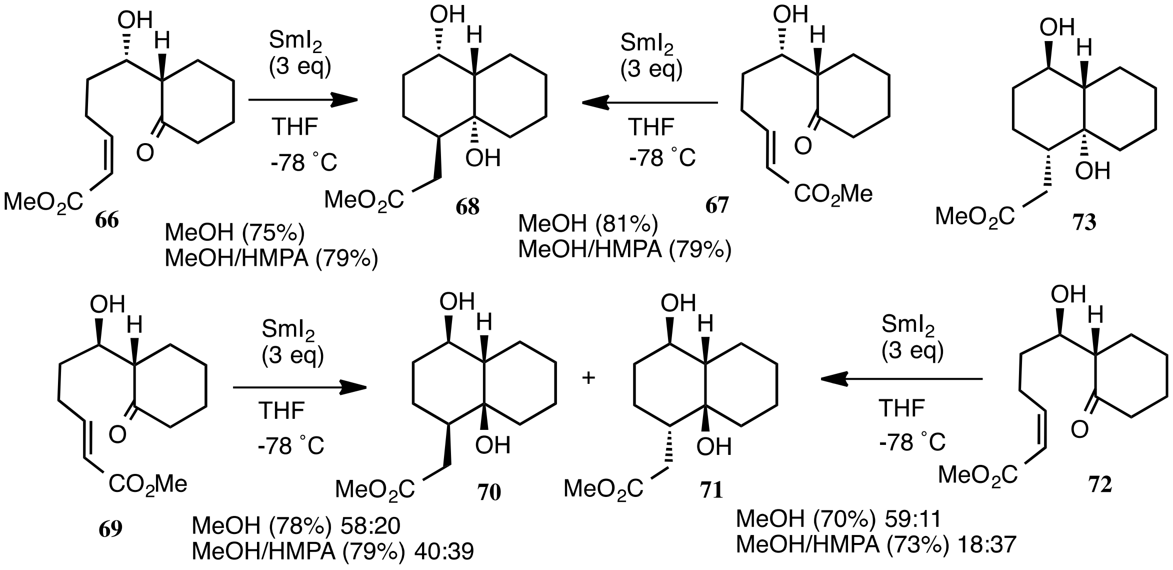
Table 11. The reaction of compound **61** with SmI_2 and the products



entry	additives	temp. (˚C)	yield (%)	ratio 62	63	64	65	*syn* : *anti*
1	none	0	56	52	25	0	23	77 : 23
2	MeOH (10 eq)	rt	76	26	56	15	3	82 : 18
3	NiI_2 (2 eq)	rt	71	64	20	10	6	84 : 16

3.2. Enone in the side chain

Matsuda and Shirahama reported SmI_2-induced cyclization (with MeOH as an additive) to perhydronaphthalenes.[24] They used diastereoisomers with *E* and *Z* isomers, **66**, **67**, **69**, and **72**, and compared their results (Scheme 4). Although the product from compounds **66** and **67** was only one isomer, their diastereoisomers **69** and **72** afforded different results. Compound **69** produced a mixture of isomers, **70** and **71**. Compound **72** afforded **73**, as well as **70** and **71**. These differences were attributed to the different configurations of the hydroxy group, because SmI_2 coordinated both the carbonyl and hydroxy groups in the transition state. This is a marked difference from other cases discussed in this review, especially the compound discussed in Section 6.

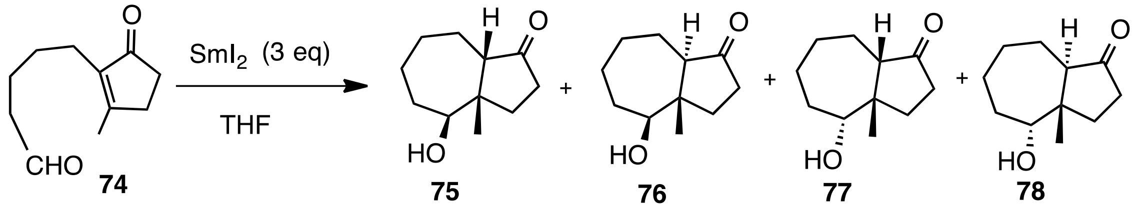


Scheme 4. Formation of perhydronaphthols from four diastereoisomers, **66**, **67**, **69**, and **72**

4. PERHYDROGUAIANES

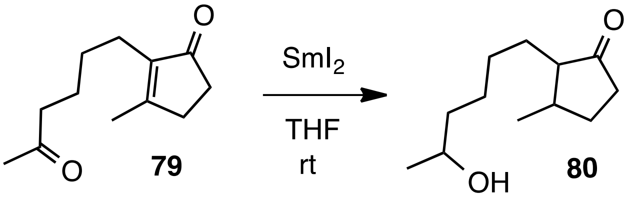
Four methylenes were introduced in the side chain to obtain a seven-membered carbocycle. Compound **74** afforded compound **78** as the major product without an additive (Table 12).[25] Even when MeOH was added, compound **78** was the major product, which was *anti* involving the hydroxy group and methyl group at the ring junction. The ratio of *syn*:*anti* was *ca*. 1:1–1:4.

Table 12. The reaction of compound **74** with SmI_2 and the products



entry	additives	temp. (˚C)	yield (%)	ratio				*syn* : *anti*
				75	**76**	**77**	**78**	
1	none	0	79	19	16	12	53	35 : 65
2	MeOH (10 eq)	rt	82	10	12	28	50	22 : 78
3	HMPA (12 eq)	rt	78	24	31	20	25	55 : 45
4	NiI_2 (0.1 eq)	0	69	13	18	24	45	31 : 69

When the carbonyl group was changed to a ketone from an aldehyde, compound **79** did not cyclize, but instead various reduction products were formed (Scheme 5).[25]



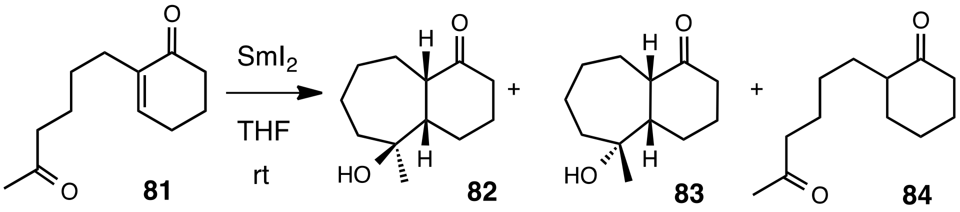
Scheme 5. The reaction of compound **79** with SmI_2

5. OTHER SYSTEMS

5.1. 6,7-Fused ring systems

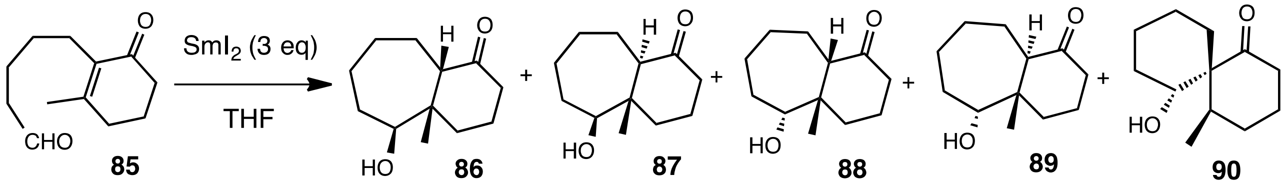
When compound **81**, bearing a ketone and enone, was subjected to the reaction with SmI_2, compounds with the ring system 6/7 (**82** and **83**) were produced in 74% yield (6 eq. of SmI_2) (Table 13).[25] Unfortunately, the yield did not increase when MeOH was added. When the methyl group was substituted at the β-position of the substrate, five products were formed depending on with or without an additive (Table 14).[25] The major product was **86** without an additive or with MeOH. When HMPA was added, a spiro ketol **90** was also formed. This is the product of an anionic aldol-type reaction.

Table 13. The reaction of compound **81** with SmI_2



entry	additive	SmI_2 (eq)	yield (%)		
			82	**83**	**84**
1	none	6	19	55	16
2	MeOH (10 eq)	3	0	6	38

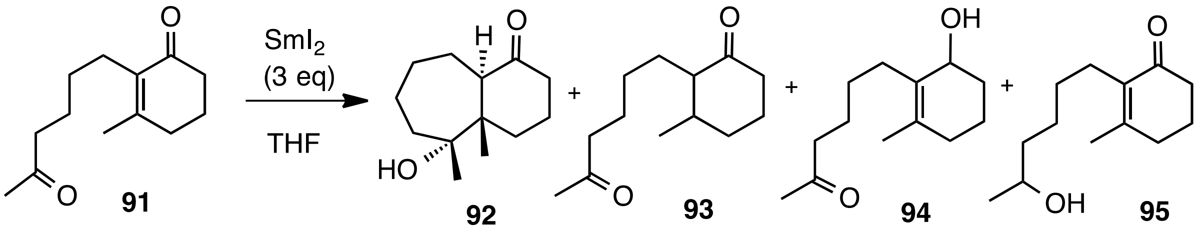
Table 14. The reaction of compound **85** with SmI_2



entry	additives	temp. (˚C)	yield (%)	ratio					*syn* : *anti*
				86	**87**	**88**	**89**	**90**	
1	none	0	82	64	10	9	17	0	74 : 26
2	MeOH (10 eq)	rt	84	59	0	34	7	0	59 : 41
3	HMPA (12 eq)	rt	45	28	0	34	5	33	42 : 58

When the substrate was changed to compound **91**, cyclization product **92** was obtained in very low yield (Table 15).[25] The structure was elucidated by X-ray crystallogrpahy. Other products were various reduction products.

Table 15. The reaction of compound **91** with SmI_2

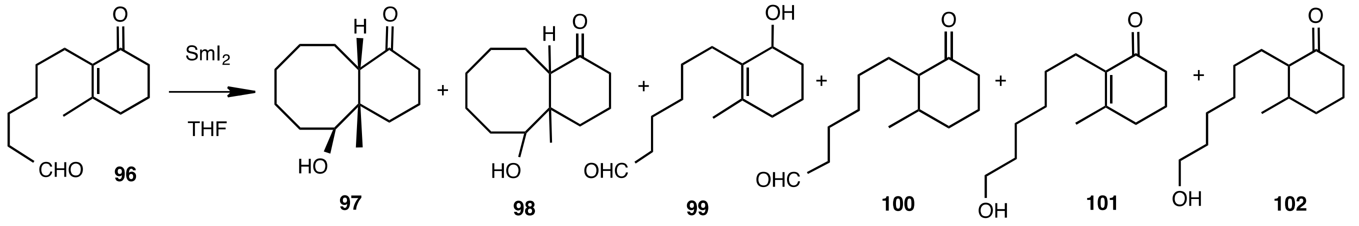


entry	additives	temp (°C)	yield (%)			
			92	**93**	**94**	**95**
1	none	rt	9	42	35	0
2	MeOH (10 eq)	rt	4	18	0	50
3	HMPA (12 eq)	0	0	53	0	0

5.2. 6,8-Fused ring systems

Challenges to eight-membered compounds were conducted using substrate **96**.[25] Although the yield was quite low, cyclized compounds **97** and **98** were produced (Table 16). Otherwise, various reduction products were formed.

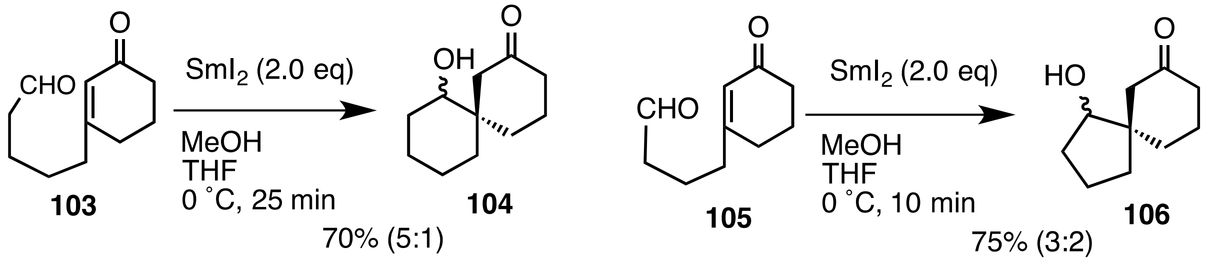
Table 16. The reaction of compound **96** with SmI_2



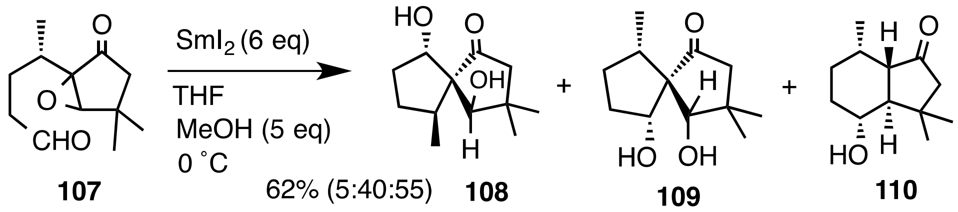
entry	SmI_2 (eq)	additives	temp (°C)	yield (%)					
				97	98	99	100	101	102
1	6	none	rt	10	7	5	0	0	26
2	3	MeOH (10 eq)	0	0	0	14	13	14	0
3	3	HMPA (12 eq)	rt	26	0	30	0	4	39

5.3. Spiro systems

When the side chain is substituted at the β-position of the carbonyl group, such as **103**, the product may be a spiro cyclic compound (Scheme 6).[26] Compound **103** afforded **104** in 70% yield with diastereoselectivity of 5:1. The substrate with one carbon less substance **105** gave **106** in 75% yield in the ratio of 3:2. The configurations of each hydroxy group were determined by NMR spectroscopy. Several other systems were also described in this paper.



Scheme 6. Cyclization of **103** and **105** to spiro cyclic compounds



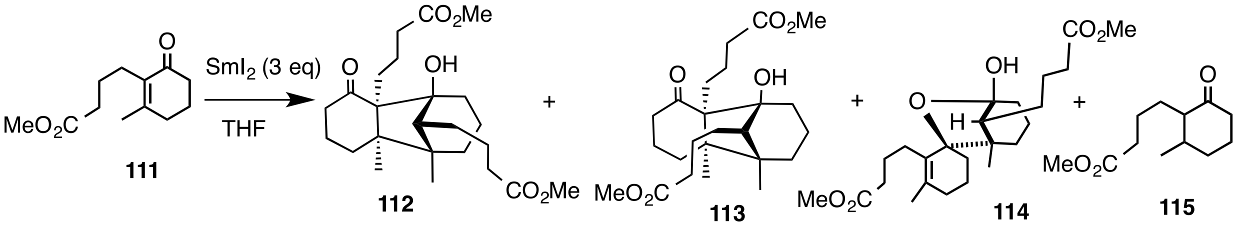
Scheme 7. Cyclization of **107** by SmI_2

The substrate similar to compounds **15** and **21**, but bearing an epoxide instead of enone system, **107**, gave three kinds of products, **108**, **109**, and **110** (Scheme 7).[27] These spiro compounds were apparently derived from two-electron reduction followed by the intramolecular aldol reaction. Compound **107** was a mixture of two diastereoisomers and thus two products, **108** and **109**, were obtained. The hydroxy group oriented to the carbonyl side, presumably due to the coordination of samarium with both oxygen atoms.

5.4. Esters

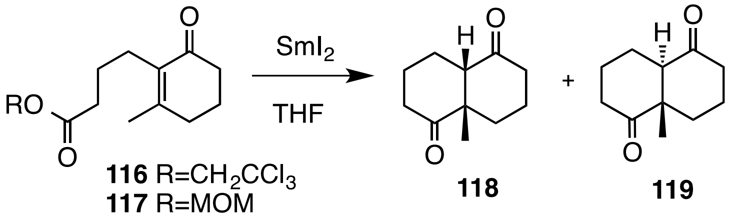
Esters are usually not reduced by SmI_2; however, they can work as acceptors of Claisen-type or Dieckmann-type condensations.[28] When compound **111** was subjected to reduction with SmI_2, a simple reduction product **115** was mostly produced with recovery of the starting material (Table 17). Instead, dimerization of the cyclohexenone moiety occurred at the β-position, and then aldol-type carbon-carbon bond formation followed to give compounds **112** and **113**.

Table 17. The reaction of compound **111** with SmI_2



entry	additive	temp.(˚C)	yield (%)			
			112	**113**	**114**	**115**
1	none	rt	12	12	0	21
2	MeOH (10 eq)	0	8	8	trace	22
3	HMPA (12 eq)	0	0	0	0	26

Table 18. The reaction of compounds **116** and **117** with SmI_2



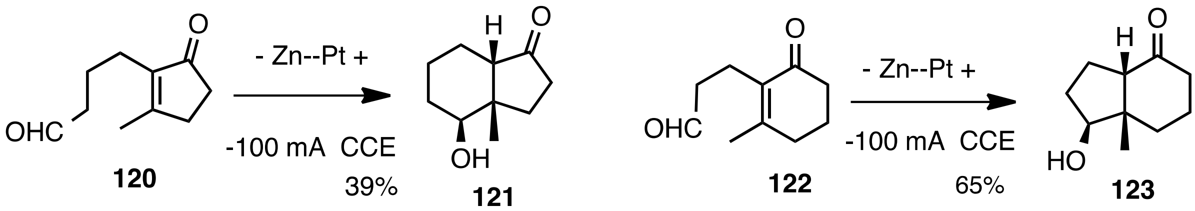
entry	substrate	SmI_2 (eq)	additive	time (h)	yield (%)	
					118	**119**
1	**116**	5	H_2O (8 eq)	0.5	12	6
2	**117**	3	H_2O (8 eq)	0.5	8	3
3	**117**	2	TBDMSCl (1 eq)	2.0	53	11

When the ester was changed to trichloroethyl ester **116**, the products were bicyclic diones **118** and **119**, on the addition of H_2O as an additive, although the yield was 18% (Table 18).[28] These results indicated that the radical formed at the β-position of the cyclohexanone moiety was further reduced by SmI_2 and the resulting anion attacked the ester part.

MOM ester **117** gave a complex mixture without an additive.[28] However, with water as an additive, **118** and **119** were formed in 11% yield (Table 18). The addition of TBDMSCl afforded a better yield of compound **118**.

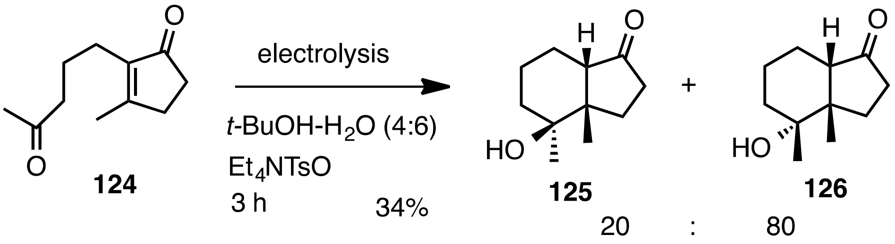
5.5. Comparison with electrolysis

One-electron reduction using SmI_2 was compared with electrolysis.[29] When compound **120** was treated under CCE conditions (Zn-Pt electrode), compound **121** was produced in 39% yield (Scheme 8). However, SmI_2 can give compound **121** in 80% yield as the sole product. In the case of compound **122**, electrolysis gave the cyclized product **123** in 65% yield, which was better than SmI_2 reduction (57%). Other interesting examples are described in this report.



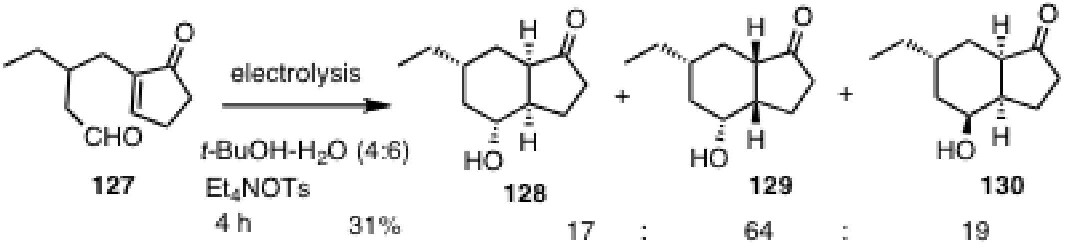
Scheme 8. Cyclization of **120** and **122** to hydrindanones by electrolysis

In the case of compound **124**, compound **126** predominated in electrolysis (Scheme 9).[29] The yield of SmI_2-mediated cyclization was 50% without an additive (**125**:**126** = 11:89), and 100% with MeOH (20 eq) (**125**:**126** = 55:45).



Scheme 9. Cyclization of **124** by electrolysis

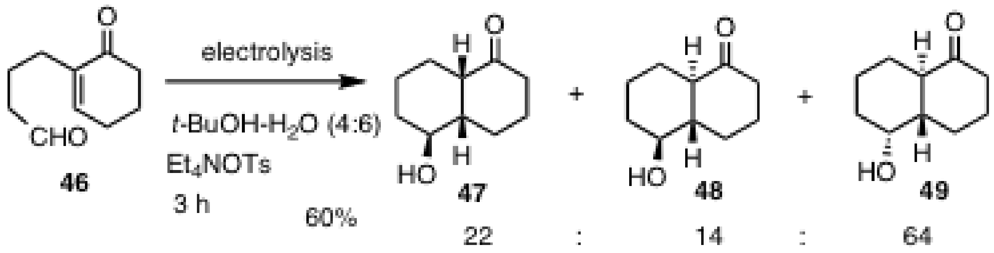
In the complicated example of compound **127**, electrolysis afforded three products, **128**, **129**, and **130**, in 31% yield (Scheme 10).[29] However, with SmI_2, the total yield was either 64 or 69%, depending on whether there was an additive or not (see Table 19). SmI_2-mediated cyclization mainly afforded *syn* products involving the hydroxy group and hydrogen at the juncture position, while electrolysis gave *anti* products as the major products.



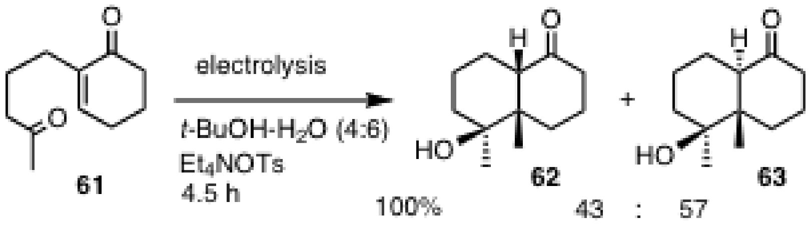
Scheme 10. Cyclization of **127** by electrolysis

In the case of perhydronaphthalenes, SmI_2-mediated cyclization of **46** gave *syn* products **47** and **48** as the major products (see Table 8),[29] while electrolysis afforded *anti* product **49** as the major product (Scheme 11). The yield from electrolysis was less than from SmI_2-mediated cyclization.

A compound bearing a ketone and an enone, **61**, gave cyclization products, **62** and **63**, by electrolysis in the ratio of 43:57 in total 100% yield. Although this is the coupling of an enone and a ketone, perhydronaphthalene was achieved in better yield by electrolysis (Scheme 12).[29] These products both had *syn* configurations involving the hydroxy group and methyl group at the juncture position. In the case of SmI_2, two more diastereoisomers were produced, although the ratio was not very high (see Table 11).



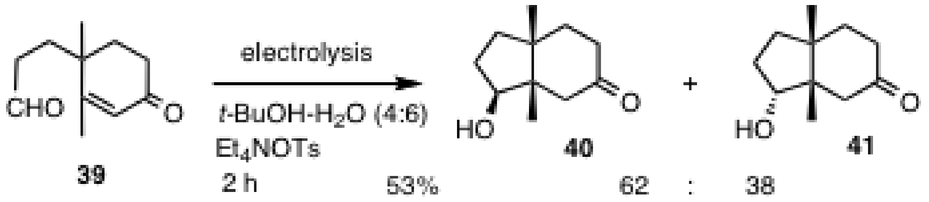
Scheme 11. Cyclization of **46** by electrolysis



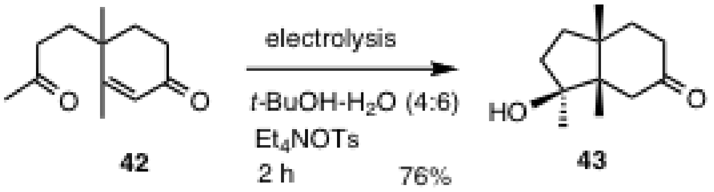
Scheme 12. Cyclization of **61** by electrolysis

Substrate **39** was subjected to electrolysis (Scheme 13).[29] The *syn* product **40** always predominated with both electrolysis and SmI_2 (see Table 6).

Ketone **42** gave only **43** with electrolysis (Scheme 14).[29] Cyclization mediated by SmI_2 with or without MeOH gave **43** as a major product (see Table 7). For compounds **39** and **42**, the transition state affording the *syn* product might be advantageous both in aqueous and THF solutions.



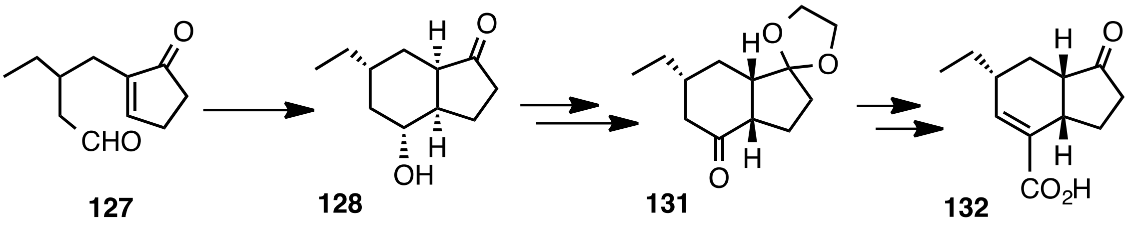
Scheme 13. Cyclization of **39** by electrolysis



Scheme 14. Cyclization of **42** by electrolysis

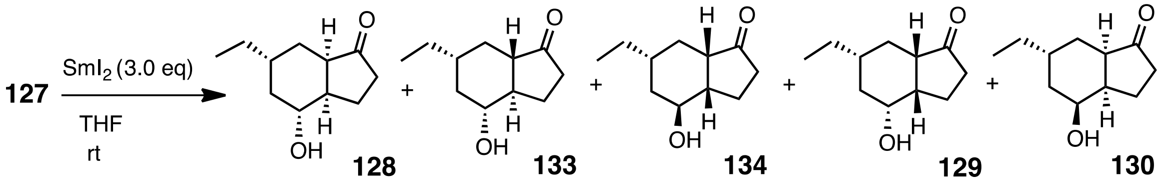
5.6. Application to the synthesis of coronafacic acid

The SmI_2-mediated cyclization reaction was applied to the synthesis of coronafacic acid (**132**) (Scheme 15).[30] Substrate **127** had one chiral center, and therefore the products were very complicated (Table 19). In most cases, three or four products were obtained depending on the conditions. However, the authors treated the whole mixture under isomerization conditions with alkaline, and thermodynamically stable products were separated. This method can be used for synthesis if one stable isomer predominates over the other.



Scheme 15. Total synthesis of coronafacic acid (**132**) from aldehyde **127**

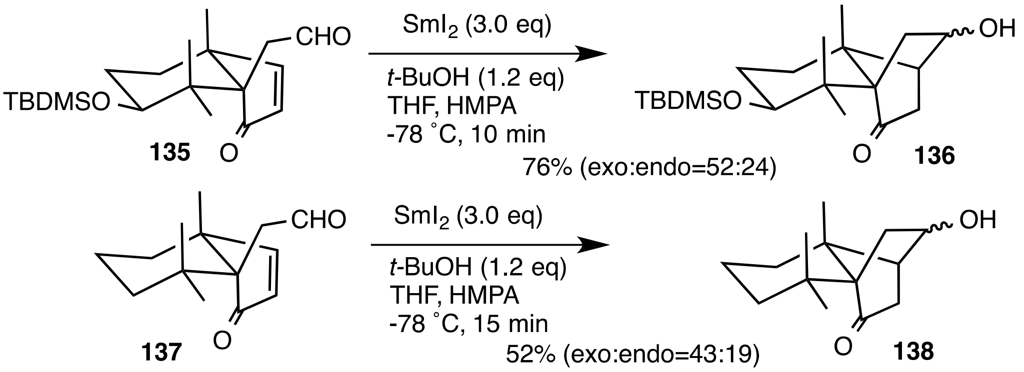
Table 19. The reaction of compound **127** with SmI_2



entry	additives	yield (%)	ratio					syn : anti
			128	**133**	**134**	**129**	**130**	
1	none	64	47	20	21	12	0	88 : 12
2	MeOH (10 eq)	69	32	12	0	17	39	44 : 56
3	HMPA	61	48	16	25	11	0	89 : 11
4	NiI_2	78	61	28	11	0	0	100 : 0

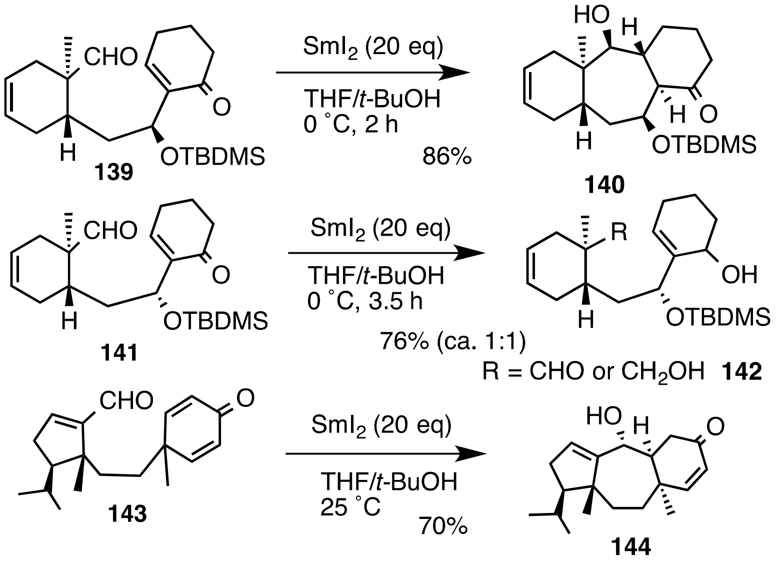
5.7. Tricyclic systems

Hagiwara reported SmI_2-induced cyclization of the bicyclic enone **135** (Scheme 16).[31] The reaction without an additive gave a retro-aldol product. However, successful cyclization to **136** was accomplished with *t*-BuOH and HMPA at low temperature in 76% yield (exo:endo = 52:24). The compound without TBDMSO group **137** afforded **138** under similar conditions. This cyclization can be considered 5-*Exo* Trig cyclization. They proposed the 'carbonyl-first' mechanism, because the exo product predominated.



Scheme 16. The reaction of compounds **135** and **137** with SmI_2 by Hagiwara

Two groups reported the cyclization to seven-membered carbocycles, making tricyclic compounds. Arimoto conducted SmI_2-induced cyclization of compound **139** with *t*-BuOH as an additive and the desired tricyclic compound **140** was obtained in 86% yield as the sole isomer (Scheme 17).[32] Interestingly, its diastereoisomer **141** did not afford a cyclized product, but only reduction products were isolated. This is a marked difference in conformation at the transition state of both compounds. Lee reported synthesis toward guanacastepene (Scheme 17).[33] Compound **143** successfully afforded compound **144** in 70% yield as the sole product. Again, in this system the transition state highly predominated for cyclization, affording only one product.

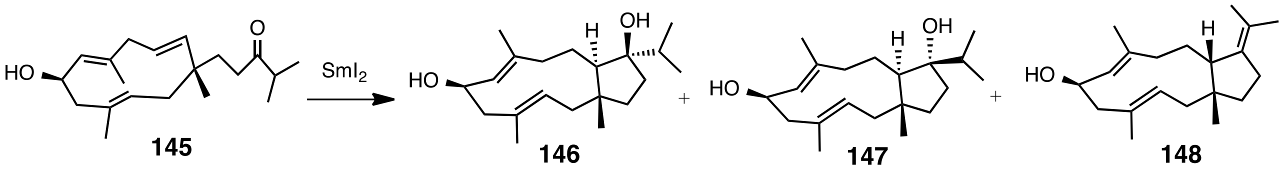


Scheme 17. The reaction of compounds **139**, **141**, and **143** with SmI_2 by Arimoto and Lee, respectively

5.8. 5,11-Fused ring systems

Five-membered carbocycles fused with the large ring can also be formed. A natural product **145** could be correlated with another natural product.[34] Compound **145** was treated with SmI_2 (with a large excess) without an additive, but no reaction occurred (Table 20). Water was added to the mixture and compound **146** was isolated as a major product with a small amount of **147** and **148**. This tendency was almost the same as with HMPA. With DBU, only **146** was produced. The stereochemistry of the juncture in the major product was *trans* because of the strain of the large ring.

Table 20. The reaction of compound **145** with SmI_2

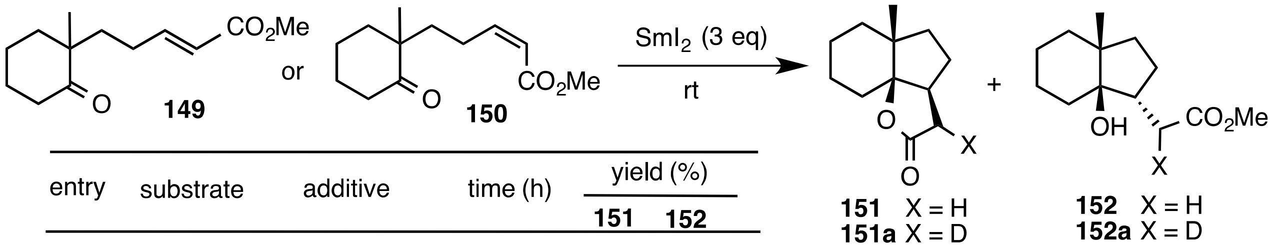


entry	SmI_2 (eq)	time (h)	additive	yield (%)		
				146	**147**	**148**
1	24	23	none	0	0	0
2	6	4.5	H_2O (30 eq)	34	3	5
3	4	6	HMPA (12 eq)	31	7	9
4	3.5	5.5	DBU (12 eq)	26	0	0

6. MECHANISTIC STUDIES

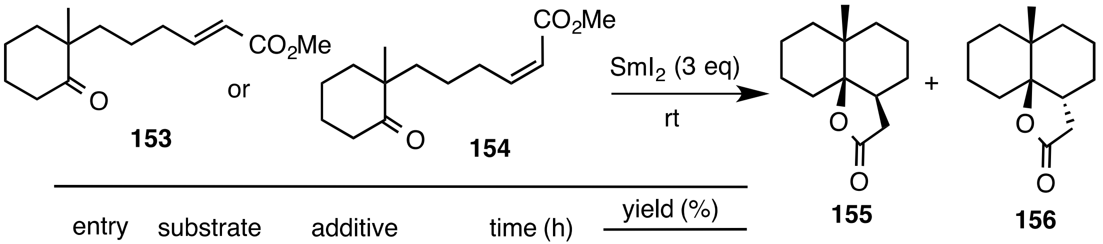
Cyclization between a ketone and an α,β-unsaturated system was next investigated (such as **149** and **150**).[35] This system resembles Matsuda and Shirahama's experiments (see Scheme 4), but lacks a hydroxy group. *anti* Hydroxy ester **152** was produced starting from *E*-**149** by treating with SmI_2 without an additive (Table 21). The same result was obtained on the addition of *t*-BuOH. However, in the presence of HMPA, both **151** and **152** were obtained. This phenomenon was completely reversed when *Z*-**150** was used as the starting material. The major product was *syn* lactone **151** under most of the conditions, except with HMPA. The mechanism will be discussed later (vide infra).

Table 21. The reaction of compounds **149** and **150** with SmI_2

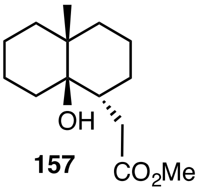


entry	substrate	additive	time (h)	yield (%)	
				151	**152**
1	**149**	none	3	0	75
2		*t*-BuOH (1 eq)	3	0	77
3		HMPA (12 eq)	1	20	74
4	**150**	none	3	88	9
5		*t*-BuOH (1 eq)	3	85	12
6		HMPA (12 eq)	1	7	92

Table 22. The reaction of compounds **153** and **154** with SmI_2



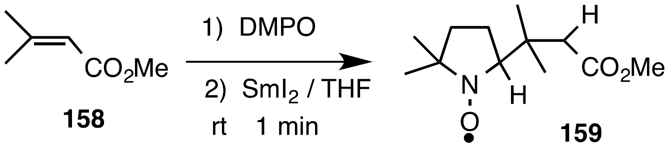
entry	substrate	additive	time (h)	yield (%)	
				155	156
1	153	none	3	0	72
2		*t*-BuOH (2 eq)	3	0	98
3		HMPA (12 eq)	1	0	82
4	154	none	3	90	0
5		*t*-BuOH (2 eq)	3	74	0
6		HMPA (12 eq)	1	75	17



157

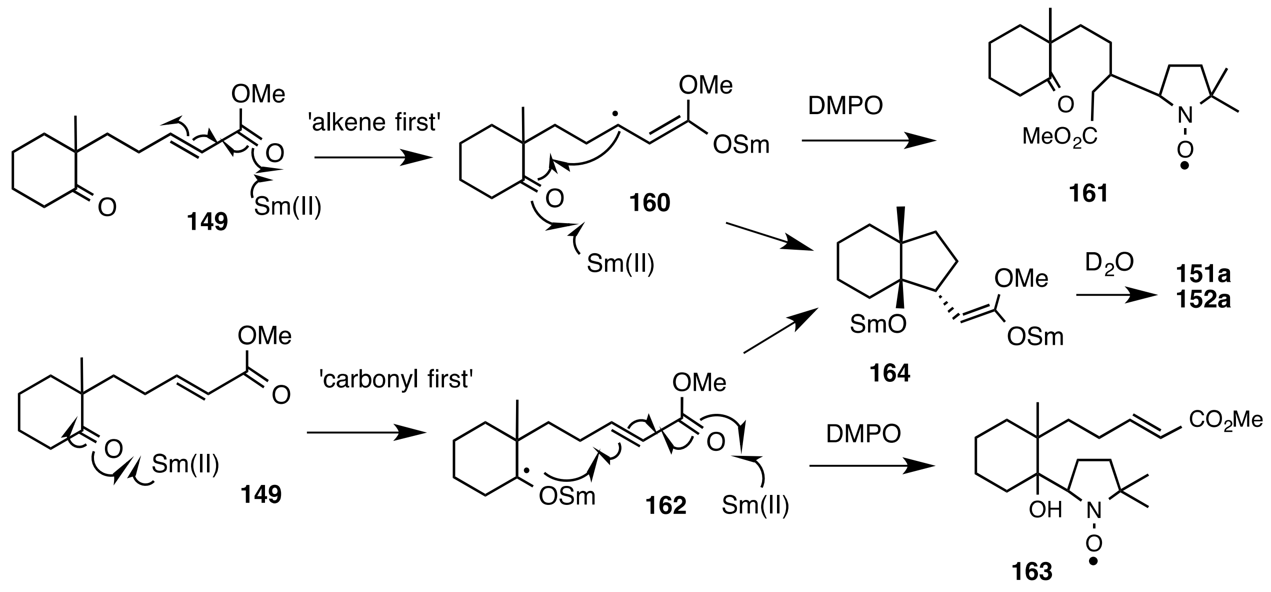
One methylene in the side chain of α,β-unsaturated ester was elongated. When *E*-**153** was treated with SmI_2, *anti* lactone **156** was produced predominantly under most of the conditions employed (Table 22). *Z*-**154** afforded *syn* lactone **155** in high yield. When 10 equivalents of *t*-BuOH were used for **153**, compound **157** was produced (**156**:**157** = 70:13) in 13% yield. The mechanism will be discussed later.

The mechanisms of SmI_2-induced reactions have long been investigated by many scientists.[1] Direct evidence to identify the radical using ESR has been sought and applications to nitroxyl radicals have been reported.[36,37] Sono and Tori used a radical trapping method with DMPO and ESR.[31] Compound **158** was treated with SmI_2 in the presence of DMPO, and radical **159** was shown by ESR signals (Scheme 18). In this case, the only possible radical should be **159**; therefore, the signals should be due to this radical **159**, whose splitting pattern was reasonable. Therefore, this experiment indicates that the α,β-unsaturated carbonyl system can be reduced by SmI_2 to afford a radical, **159**.



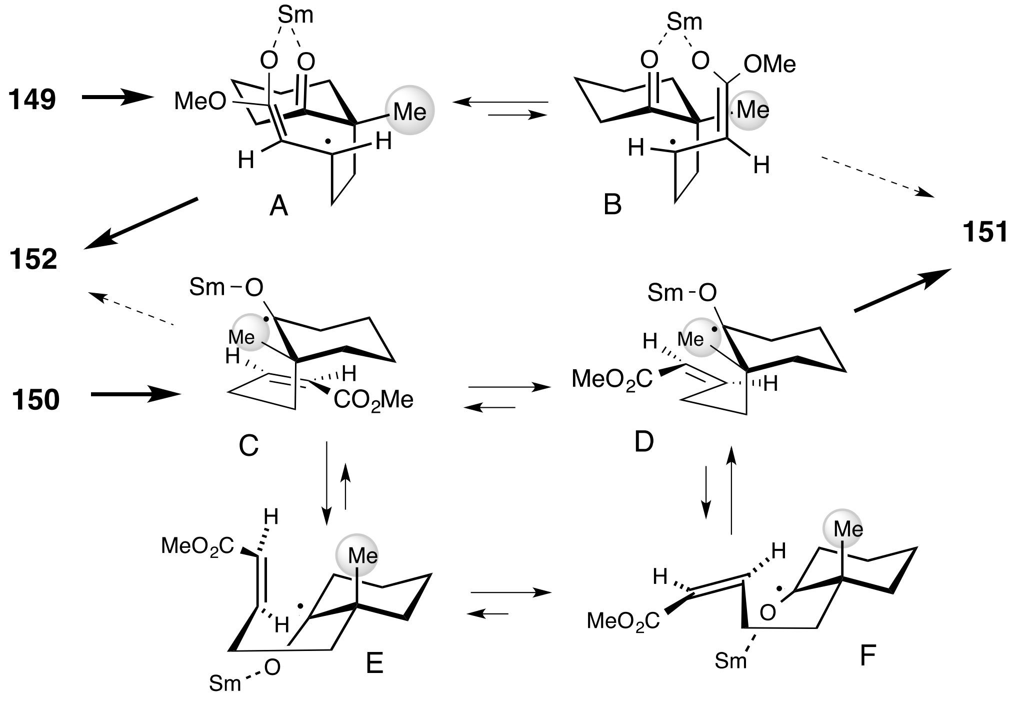
Scheme 18. The spin trapping experiment of **158** with DMPO

Compound **149** was similarly treated with SmI_2 in the presence of DMPO. The resulting ESR spectrum was derived from the sum of radicals **161** and **163** in the ratio of 100:12, demonstrated by simulation of the ESR spectra. Therefore, these results indicated that the α,β-unsaturated carbonyl system could be reduced faster than the isolated ketone. The mechanisms shown in Scheme 19 ('alkene-first mechanism') are possible, although they depend on the functionality in the molecule, because the difference between *E* and *Z* double bonds can also affect the results.



Scheme 19. The reaction mechanism of **149**

The finding that products from **149** and **150** were different could be explained by the conformation in the transition state, shown in Scheme 20. Samarium can coordinate both the carbonyl groups and hence the difference of the geometry of the double bond can change the shape of the transition state.



Scheme 20. The reaction mechanisms for the reaction of **149** and **150**

7. CONCLUSION

This review covers the cyclization reactions to bicyclic systems through either one- or two-electron reduction by SmI_2. As demonstrated in the final section, samarium can pass one electron to the carbonyl group of the α,β-unsaturated system.[38] This is presumably because the reduction potential of α,β−unsaturated carbonyl should be lower. In other words, it is reduced faster than the isolated ketone. Of course, this depends on the functionality and it is not always the fastest route. Procter described that the ‘alkene-first mechanism’ may also be considered, as well as the ‘carbonyl-first mechanism,’ which is widely accepted.[1] Thus two-electron pathways sometimes work and cyclization due to this mechanism occurs frequently. SmI_2 are easy to use and not toxic, but are sensitive to oxygen. As it can be coordinated with the carbonyl groups near the reaction site, the reaction using SmI_2 can be controlled by the addition of various additives. The use of the SmI_2 reagent will be further widened by developing synthetic methods in the future.

ACKNOWLEDGEMENTS

The authors express their sincere thanks to the students in their laboratory engaged in these projects and also to Dr. Katsuyuki Nakashima for his help. They are also grateful for the financial support from Tokushima Bunri University as well as a Grant-in-Aid for Scientific Research from JSPS.

REFERENCES

1. D. J. Procter, R. A. Flowers, II, and T. Skrydstrup, '*Organic Synthesis Using Samarium Diiodide: A Practical Guide*,' Royal Society of Chemistry Publishing, UK, 2010.
2. H. B. Kagan, L. J. Namy, and P. Girard, *Tetrahedron, Suppl. 1,* 1981, **37**, 175.
3. L. J. Namy, J. Collon, C. Bied, and H. B. Kagan, *Synlett,* 1992, 733.
4. H. B. Kagan, *Tetrahedron,* 2003, **59**, 10351.
5. P. Girard, L. J. Namy, and H. B. Kagan, *J. Am. Chem. Soc*., 1980, **102**, 2693.
6. D. P. Curran, T. L. Fevig, and M. J. Totleben, *Synlett,* 1990, 773.
7. D. P. Curran, T. L. Fevig, C. P. Jasperse, and M. J. Totleben, *Synlett,* 1992, 943.
8. D. P. Curran, X. Gu, W. Zhang, and P. Dowd, *Tetrahedron,* 1997, **53**, 9023.
9. G. A. Molander, *Chem. Rev*., 1992, **92**, 29.
10. G. A. Molander and C. R. Harris, *Chem. Rev*., 1996, **96**, 307.
11. G. A. Molander, *Acc. Chem. Res*., 1998, **31**, 603.
12. G. A. Molander and C. R. Haris, *Tetrahedron,* 1998, **54**, 3321.
13. R. D. Little, *Chem. Rev*., 1996, **96**, 93.
14. R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, and R. A. Flowers, II, *J. Am. Chem. Soc*., 2000, **122**, 7718.
15. E. Prasad and R. A. Flowers, II, *J. Am. Chem. Soc.,* 2002, **124**, 6895.
16. M. Szostak and D. J. Procter, *Angew. Chem. Int. Ed*., 2012, **51**, 9238.

17. M. Szostak, M. Spain, D. Parmer, and D. J. Procter, *Chem. Comm.*, 2012, **48**, 330.
18. (a) T. Honda, *Heterocycles*, 2010, **81**, 2719; (b) T. Honda, *Heterocycles*, 2011, **83**, 1.
19. M. Sono, Y. Nakashiba, K. Nakashima, and M. Tori, *J. Org. Chem.*, 2000, **65**, 3099.
20. M. Sono, N. Ise, T. Shoji, and M. Tori, *Molecules*, 2012, **17**, 11079.
21. T. J. K. Findley, D. Sucunza, L. C. Miller, D. T. Davies, and D. J. Procter, *Chem. Eur. J.*, 2008, **14**, 6862.
22. A. Kishida and H. Nagaoka, *Tetrahedron Lett.*, 2008, **49**, 6393.
23. M. Sono, S. Onishi, and M. Tori, *Tetrahedron*, 2003, **59**, 3385.
24. M. Kito, T. Sakai, K. Yamada, F. Matsuda, and H. Shirahama, *Synlett*, 1993, 158.
25. M. Sono, Y. Sugimoto, H. Tatara, N. Ise, S. Takaoka, and M. Tori, *Tetrahedron*, 2008, **64**, 11096.
26. D. S. Hsu and C. W. Hsu, *Tetrahedron Lett.*, 2012, **53**, 2185.
27. M. Sono, Y. Nakashiba, K. Nakashima, S. Takaoka, and M. Tori, *Heterocycles*, 2001, **54**, 101.
28. M. Sono, T. Mizutani, M. Nozaki, S. Takaoka, and M. Tori, *Heterocycles*, 2008, **76**, 851.
29. M. Sono, T. Shoji, T. Tamaki, S. Kishi, and M. Tori, *Heterocycles*, 2007, **72**, 517.
30. M. Sono, A. Hashimoto, K. Nakashima, and M. Tori, *Tetrahderon Lett.*, 2000, **41**, 5115.
31. H. Hagiwara, H. Sakai, T. Uchiyama, Y. Ito, N. Morita, T. Hoshi, T. Suzuki, and M. Ando, *J. Chem. Soc., Perkin Trans. 1*, 2002, 583.
32. A. Sato, T. Masuda, H. Arimoto, and D. Uemura, *Org. Biomol. Chem.*, 2005, **3**, 2231.
33. T. M. Nguyen, R. J. Seifert, D. R. Mowrey, and D. Lee, *Org. Lett.*, 2002, **4**, 3959.
34. M. Sono, M. Hanaoka, T. Hashimoto, A. Asakawa, and M. Tori, *Synlett*, 2009, 469.
35. M. Sono, S. Hanamura, M. Furumaki, H. Murai, and M. Tori, *Org. Lett.*, 2011, **13**, 5720.
36. A. R. Katritzky, H. Y. He, and G. Qiu, *Org. Lett.*, 1999, **1**, 1755.
37. A. Alberti, M. Benaglia, and D. Macciantelli, *Org. Lett.*, 2000, **2**, 1553.
38. J. H. Wagenknecht, L. Eberson, and J. H. P. Utley, '*Organic Electrochemistry*,' Third Edition, ed. by H. Lund and M. M. Baizer, Marcel Dekker, Inc., New York, 1991, 453.

Motoo Tori, born in 1948 in Aichi prefecture (Japan), graduated from Department of Chemistry, Shizuoka University in 1972. He received his Ph.D. degree from The Department of Chemistry, School of Science, The University of Tokyo (Professor Takeyoshi Takahashi) in 1977. He spent two and a half year as a postdoctoral fellow at Department of Chemistry, University of Alberta (Canada) (Professors Satoru Masamune and William A. Ayer) from 1977 to 1979, and one and a half year at Institute für Organische Chemie, Universität Basel (Switzerland) (Professor Christoph Tamm) from 1979 to 1981. He joined Faculty of Pharmaceutical Sciences, Tokushima Bunri University as associate professor in 1983 and was promoted as professor in 1995. During 2003 and 2005, he was the Dean of the Faculty. His research interests are the total synthesis of natural products, the development of new reactions using samarium diiodide, the elucidation of absolute configurations of natural and unnatural products based on the spectroscopic methods, and the chemistry of natural products found in especially Asteraceae plants.

Masakazu Sono, born in 1962 in Hyogo prefecture (Japan), graduated from Faculty of Pharmaceutical Sciences, Tokushima Bunri University in 1984. He received his Ph.D. degree from Tokushima Bunri University (Professor Yoshinori Asakawa) in 1991. He joined Faculty of Pharmaceutical Sciences, Tokushima Bunri University as assistant professor in 1989 and was promoted as associate professor in 2007. During 1997 and 1998, he spent a year at the University of Colorado as a visiting researcher with Professor Gary A. Molander. His research interests are the development of new synthetic methods and the total synthesis of natural products. His efforts focus in two broad areas, one involving the radical chemistry, the other involving various one-electron transfer reactions.