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REVIEW ARTICLE

The synthetic versatility of oxazolidinethiones

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Different methods for the preparation of oxazolidinethiones and their more recent applications are reviewed. In this review, novel rearrangements and new reactions have also been summarized which for their homologous oxazolidinones have not been observed. The principal application of oxazolidinethiones has been as chiral auxiliaries in asymmetric aldol addition reactions for the obtention of chiral fragments containing one or two stereogenic centres with the stereochemistry required for the preparation of complex natural products.

Keywords: Oxazolidinethiones; Chiral auxiliary; Applications; Asymmetric synthesis

1. Introduction

Oxazolidinethiones have been the subject of extensive studies because of their important biological activity. For example, 5-(α, α, α-trifluoro-*m*-tolyloxymethyl)-2-oxazolidinethione has been demonstrated to be an antifertility agent [1, 2] and shows thyroid toxicity in chronic studies both in rats and dogs [3]. At the present time, the syntheses of oxazolidinethiones have been directed to the preparation of efficient chiral auxiliaries and their application in asymmetric synthesis. It has been found that under certain conditions, chiral oxazolidinethiones can carry out rearrangements, which have not been observed for the homologous oxazolidinones. Furthermore, in a large number of asymmetric transformations, chiral oxazolidinethiones give better yields and better diastereomeric ratios than the homologous oxazolidinones.

This review will summarize some important and recent advances of the applications of chiral oxazolidinethiones in the asymmetric synthesis of complex natural products. Since the applications of chiral oxazolidinethiones and thiazolidinethiones in asymmetric synthesis have been covered in a previous review [4], only more recent applications will be considered

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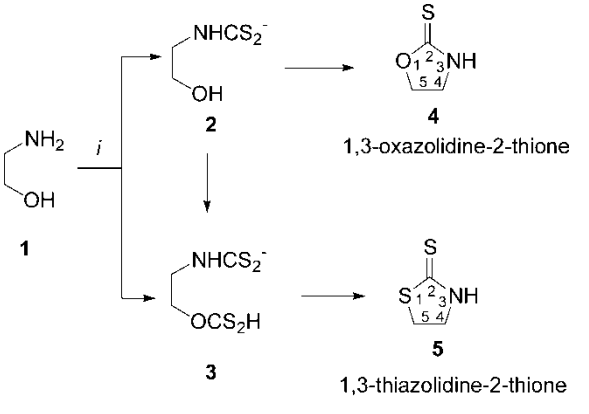
here. The first part of this review covers a brief description of procedures used to prepare oxazolidinethiones. In the second section, the applications of oxazolidinethiones will be covered, where many examples are organized according to the different kinds of reactions used.

2. Methods for the preparation of oxazolidinethiones

2.1 *Some general methods*

A simple, general procedure used to prepare oxazolidinethiones has been the condensation of β-aminoalcohols – which are commercially available or readily obtained by reduction of α-amino-acids [5] – with carbon disulfide under basic conditions. Ettlinger [6] reported that sterically hindered aminoalcohols, when heated with carbon disulfide and alcoholic alkali, provided the heterocyclic oxazolidinethione. However, ethanolamine **1** (scheme 1) treated similarly or with carbon disulfide alone afforded a mixture of oxazolidinethione **4** and thiazolidinethione **5** in the same amount. The obtention of oxazolidinethione **4** can be rationalized by the initial formation of the dithiocarbamate **2** and a subsequent nucleophilic attack on the thiocarbonyl moiety to provide **4**. On the other hand, the unhindered primary hydroxyl of **2** attacked to another molecule of carbon disulfide to give the xanthate **3** which underwent an intramolecular cyclization to give **5**.

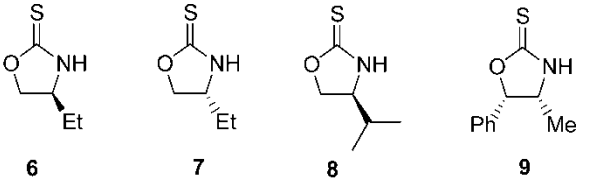


SCHEME 1 *Reagents and conditions*: *i*) CS_2, KOH, EtOH, H_2O, reflux, 6 h or CS_2.

Ettlinger [6] applied mild reaction conditions to favour the formation of oxazolidinethione heterocycle **4** by combination of the ethanolamine with carbon disulfide at low temperature. A thermal decomposition of **2** employing lead nitrate as a dehydrosulfurization reagent, afforded **4** and other chiral oxazolidinethiones in moderated yields.

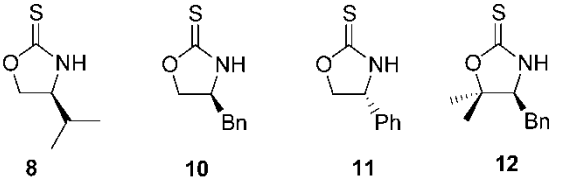
Nagao [7] obtained a series of chiral oxazolidinethiones **6-9** by condensation of the corresponding β-amino alcohols with carbon disulfide in the presence of Et_3N (CH_2Cl_2, r.t., 4 h) or KOH ($EtOH/H_2O$, 70–80 °C, 6 h). In both cases the presence of the thiazolidinethione heterocycle was not mentioned. Nagao described another advantage of the oxazolidinethiones compared to their 2-oxo-analogues: the compounds can be more readily analyzed by HPLC

with UV detector because these heterocycles show a strong UV absorption ($\pi - \pi^*$) with a high ε value.



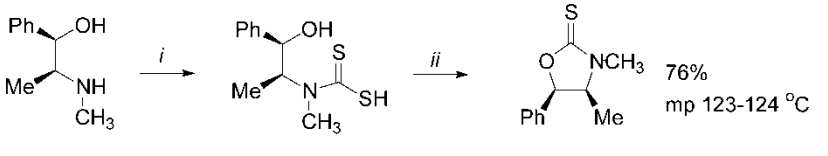
	6	**7**	**8**	**9**
mp (°C)	oil	oil	45-46	81-82
yield (%)	58.4	58.0	46.5	69.0

Another method to prepare oxazolidinethiones was reported by Le Corre [8] who proposed a mechanism consistent with the stoichiometry, nature of the β-aminoalcohol and the stereochemistry of the reaction. For this study, oxazolidinethiones **8** and **10–12** were prepared from the aminoalcohols containing a primary, secondary, or tertiary hydroxyl group and a primary or secondary amine. The reaction conditions that favoured the formation of the oxazolidinethiones in good yields were a stoichiometric quantity of CS_2, a low basic medium and reduced reaction time [8].



	8	**10**	**11**	**12**
mp (°C)	45-46	oil	121-122	142-143
yield (%)	62.0	63.0	50.0	60.0

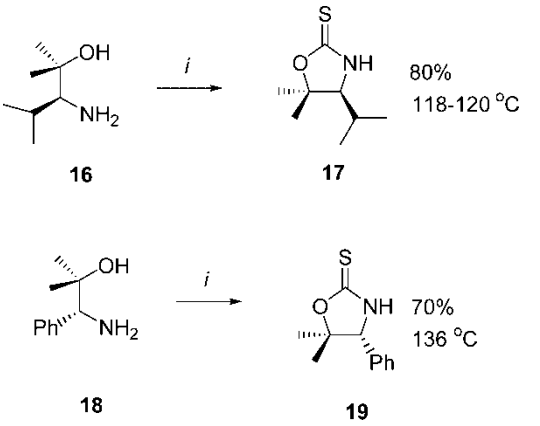
The formation of oxazolidinethione **15** from an aminoalcohol bearing a secondary amine group **13** (scheme 2) was achieved by formation of the dithiocarbamic acid **14** which suffered an internal cyclization by treatment with sodium hydroxide in water-THF [9].



13 **14** **15**

SCHEME 2 *i*) CS_2, NEt_3, CH_2Cl_2, *ii*) NaOH, H_2O, THF.

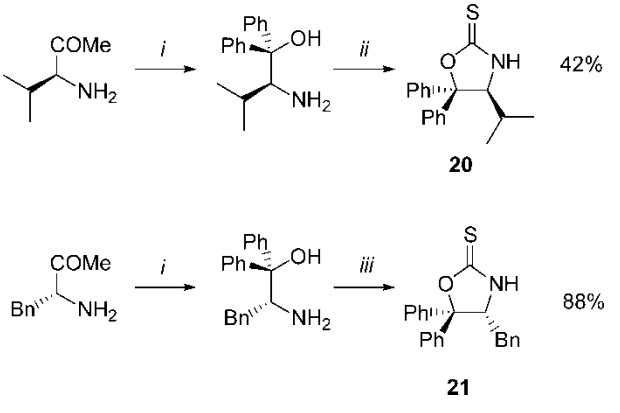
Aminoalcohols **16** and **18** (scheme 3) contain a tertiary hydroxyl group and can provide oxazolidinethiones **17** and **19** in high yields when a medium of low basicity (solution 1 M of Na_2CO_3) is used together with a long reflux time. The advantage is that in this case the thiazolidinethione heterocycle is not formed [10, 11].



SCHEME 3 Chiral trisubstituted oxazolidinethiones. *i*) CS_2 (4 equiv), Na_2CO_3 1 M, reflux, 16 h, CS_2 (2 equiv), reflux, 4 h.

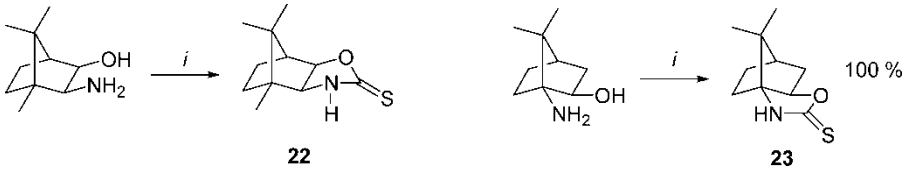
2.2 *Syntheses of highly hindered oxazolidinethiones*

Another group of interesting oxazolidinethiones are those that are highly hindered. These are prepared using similar methods to those described above. For example, oxazolidinethiones **20** and **21** (scheme 4) were obtained by a method that employed aminoalcohols containing a tertiary, sterically hindered hydroxyl group. These aminoalcohols were prepared from the α-aminoacid methyl esters L-valine and D-phenylalanine by a double phenyl Grignard addition. Oxazolidinethione **20** was prepared in 42% yield by cyclization of the 1,2-aminoalcohol with CS_2 in the presence of Et_3N [12], while oxazolidinethione **21** was achieved in 88% yield by cyclization with thiophosgene [13].



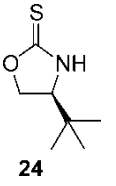
SCHEME 4 *i*) PhMgBr (5 equiv), Et_2O, *ii*) CS_2, Et_3N, THF, reflux, *iii*) $CSCl_2$.

The 1,2-aminoalcohol derivatives of camphor have been employed to obtain the rigid heterocyclic oxazolidinethiones **22** [14] (yield was not mentioned) and **23** [15] in 100% yield. These compounds were achieved in the presence of carbon disulfide, Et_3N and applying 15 h reflux (scheme 5).



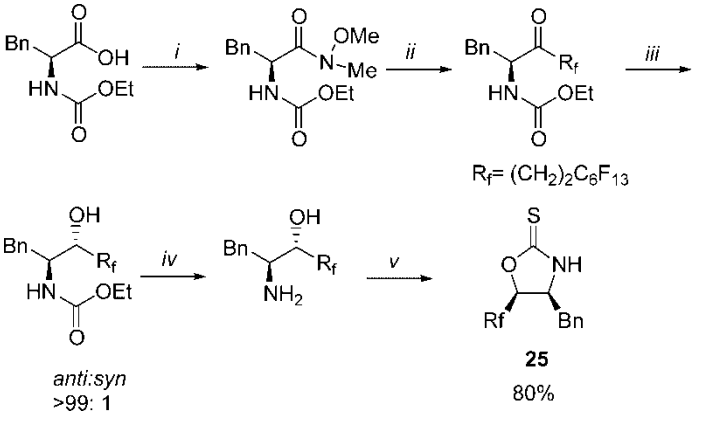
SCHEME 5 *i*) CS_2, Et_3N, THF, reflux.

A highly hindered oxazolidinethione **24** derived from L-*tert*-leucinol was also described, although the methodology employed for the cycle formation was not mentioned [16].



24

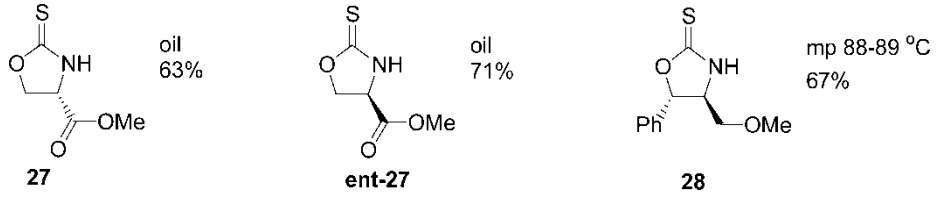
The chiral fluorous oxazolidinethione **25** was synthesized from L-phenylalanine using a general five-step methodology (scheme 6). The key feature in this synthesis was the efficient generation of the perfluoroalkyllithium species. For the preparation the aminoalcohol was treated with CS_2 in the presence of DIPEA generating **25** in 80% yield after 36 h of reaction time [17].



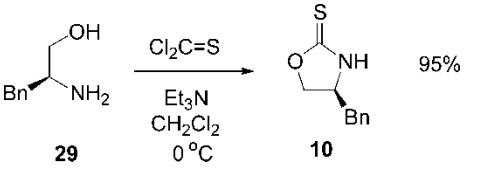
SCHEME 6 *i*) DIPEA, isobutyl chloroformate, −30 °C, CH_2Cl_2, $CH_3ONH_2CH_3Cl$, DMF, 3 h, rt, *ii*) *t*-BuLi, $C_6F_{13}(CH_2)_2I$, Et_2O/Hex, −78 °C, *iii*) $LiAlH(OtBu)_3$, EtOH, −78 °C to rt, *iv*) KOH, EtOH, H_2O, *v*) CS_2, DIPEA, THF.

Oxazolidinethiones with hetero-substituents have been easily prepared from inexpensive L-serine with carbon disulfide in the presence of Et_3N providing **27** in 63% yield as oil. Using D-serine **ent-27** is obtained in 71% yield as oil [18]. The oxazolidinethione **28** was prepared in

a 67% yield from (1*S*, 2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol and CS_2 employing dry DMF as solvent and without using base [19].



Crimmins [20] reported oxazolidinethione **10** (scheme 7) that was derived from (*S*)-phenylalaninol **29**. In this case aminoalcohol **29** was treated with thiophosgene in the presence of triethylamine applying a short reaction time to give **10** as an oil in a high yield (95%). The author described that the oil crystallized after approximately one month at 0 °C.



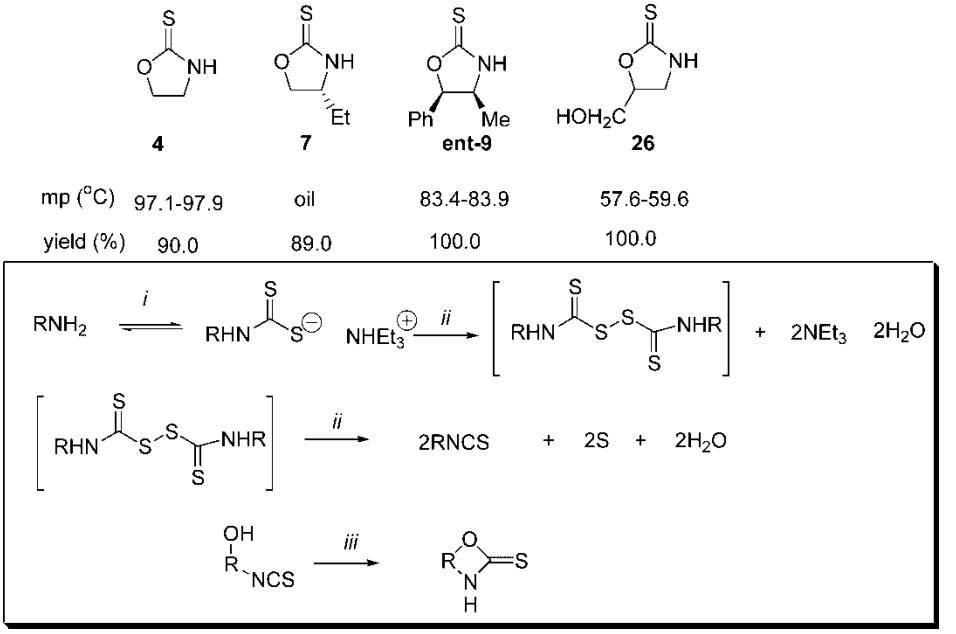
SCHEME 7 Chiral oxazolidinethione obtained with thiophosgene.

Another procedure was reported by Li and Ohtani [21] who described a general method for the preparation of oxazolidinethiones in high yields through the reaction of hydrogen peroxide with a mixture of aminoalcohol, carbon disulfide and a base in a water-miscible organic solvent. The syntheses of oxazolidinethiones **4**, **7**, **ent-9** and **26** (scheme 8) were achieved by previous formation of the isothiocyanates using hydrogen peroxide as dehydrosulfurization reagent and a subsequent internal cyclization. A possible mechanism was described for primary amines but can be also applied to aminoalcohols [22].

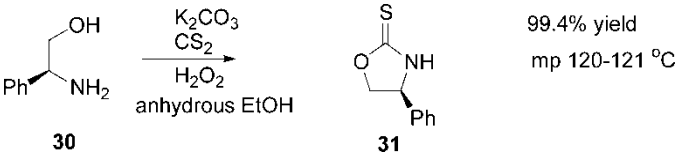
Subsequently, Palomo [23] described the preparation of two chiral oxazolidinethiones from *S*-valinol and *R*-phenylglycinol under reaction conditions described above to afford oxazolidinethiones **8** and **11**, respectively, in high yields. Furthermore, a modification of Li and Ohtani's [24] methodology consisted in changing the organic base for an inorganic base. The application of this methodology produced chiral oxazolidinethiones in high yield and particularly **31** was easily isolated in the form of white crystals in >99% yield (scheme 9 and 10).

2.3 *Syntheses of oxazolidinethiones from isothiocyanates derivatives*

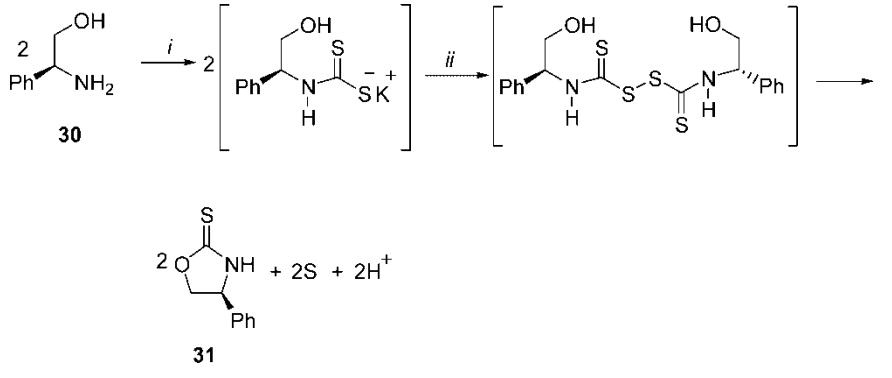
5-Mono-and di-substituted oxazolidinethiones were prepared by the addition reaction of an isothiocyanate carbanion **33** to aldehydes and ketones [25]. The carbanion **33** (scheme 11) was generated by the fluoride-catalyzed reaction of the trimethylsilylmethyl isothiocyanate **32** in the presence of a catalytic amount of tetrabutylammonium fluoride. The carbanion **33** was then reacted with a carbonyl compound to provide adduct **34** which underwent intramolecular cyclization and subsequent fluoride ion regeneration by reaction of **35** with trimethylsilyl fluoride. The oxazolidinethiones were obtained after an easy hydrolysis reaction in **36**. While the aldehydes employed afforded the oxazolidinethiones in good yields, the ketones produced the oxazolidinethiones only in low yields (table 1).



SCHEME 8 *i*) CS_2, NEt_3, *ii*) H_2O_2, *iii*) cyclization.

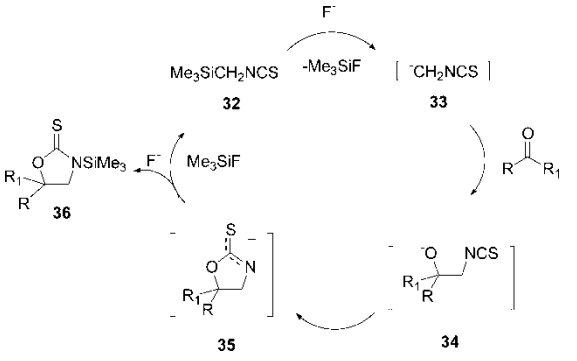


SCHEME 9 One example of a rapid and efficient synthesis of chiral oxazolidinethione.



SCHEME 10 A plausible reaction mechanism of oxazolidinethione formation. *i*) CS_2 (2 equiv), K_2CO_3 (0.5 equiv), *ii*) H_2O_2.

An asymmetric aldol addition reaction has been employed to furnish a series of interesting chiral oxazolidinethiones **39** (scheme 12). They were prepared in good yields by a diastereoselective aldol addition reaction of the respective stannous enolate of the *N*-isothiocyanoacetyloxazolidinone **37** with different aldehydes [26]. The *syn* aldol adducts **38**



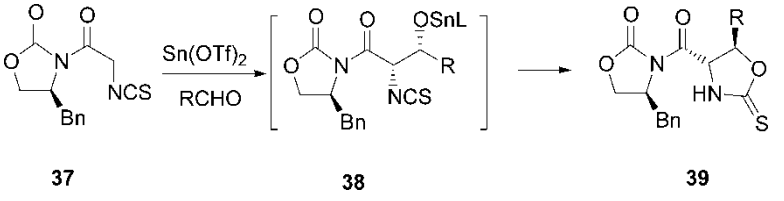
SCHEME 11 Formation of 5-mono and di-substituted oxazolidinethiones.

Table 1. Preparation of oxazolidinethiones derived from **36**.

R	R_1	F^- (equiv)	Time (h)	OZT[a] (%)
Ph	H	*n*-Bu_4NF (0.1)	8	74
Ph	H	KF (1.0), TEBA.Cl (0.1)	2	74
Ph	H	KF (1.0), 18-Crown-6 (0.1)	5	65
Et	H	*n*-Bu_4NF (0.1)	5	63
i-Pr	H	*n*-Bu_4NF (0.1)	10	67
Ph	Ph	*n*-Bu_4NF (0.1)	40	25
Ph	Me	*n*-Bu_4NF (0.1)	23	35

[a]OZT (oxazolidinethione).

were obtained with high diastereoselectivity, which were isolated finally as the internally cycled heterocycles **39**. The results of these reactions are summarized in table 2.

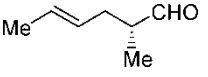
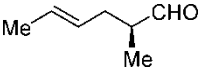
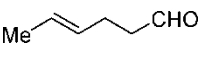


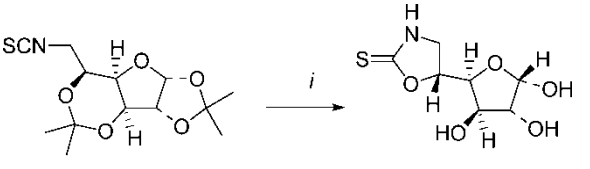
SCHEME 12 Chiral oxazolidinethione generated from chiral oxazolidinone.

The preparation of spirooxazolidinethiones from sugars has been widely studied by Fuentes, and others [27, 28] who established the conditions for the preparation of oxazolidinethione derivatives either from protected deoxyisothiocyanate **40** (scheme 13) or from fully unprotected 6-amino-6-deoxy sugars. Both routes for the synthesis of oxazolidinethiones involved replacement of one hydroxyl group by an amino group and subsequent formation of the isothiocyanate or the chlorothioformamide derivatives. The protected deoxyisothiocyanate **40** was hydrolyzed with TFA-H_2O under careful control of the temperature. Removal of the solvent afforded the spirooxazolidinethione **41**.

The 5-(L-tetrafuran-4-yl)oxazolidinethione **45** (scheme 14) was obtained in good yield by the reaction of unprotected 6-amino-6-deoxy galactose **42** with thiophosgene. This reaction provided the chlorothioformamide **43** intermediate, which underwent an intramolecular nucleophilic attack of the α-hydroxyl group displacing chloride to afford spirooxazolidinethione **45**.

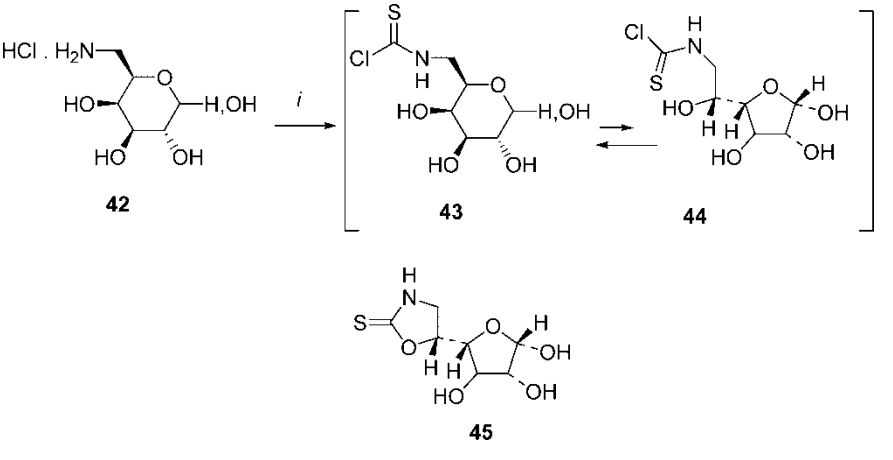
Table 2. Asymmetric aldol addition reactions of **37** with different aldehydes.

RCHO	Ratio	Yield, %	Adduct
	94:6	73	**39a**
	97:3	71	**39b**
	93:7	81	**39c**
Me_2CHCHO	99:1	92	**39d**
MeCHO	91:9	75	**39e**
PhCHO	99:1	91	**39f**



40 **41**

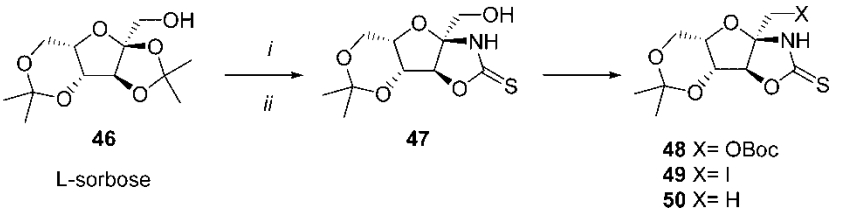
SCHEME 13 *Reagents and conditions. i*) 50% TFA-H_2O, 10 °C, evaporation at 40–50 °C.



42 **43** **44** **45**

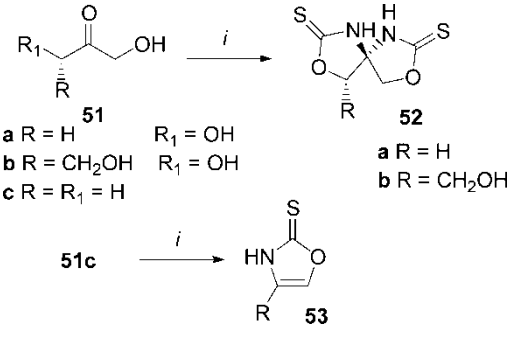
SCHEME 14 *Reagents and conditions. i*) $CaCO_3$, $CSCl_2$, $CHCl_3/H_2O$, 3 h.

Tatibouët's group has widely investigated the preparation of fused oxazolidinethiones on ketohexose backbones [29–33]. When L-sorbose **46** was treated with potassium thiocyanate under acidic conditions the carbohydrate oxazolidinethione **47** was achieved. Functionalization of the hydroxyl group allowed the production of diverse functionalized oxazolidinethiones **48–50** (scheme 15).



SCHEME 15 *i*) KSCN, HCl, H_2O, *ii*) acetone, cat. H_2SO_4.

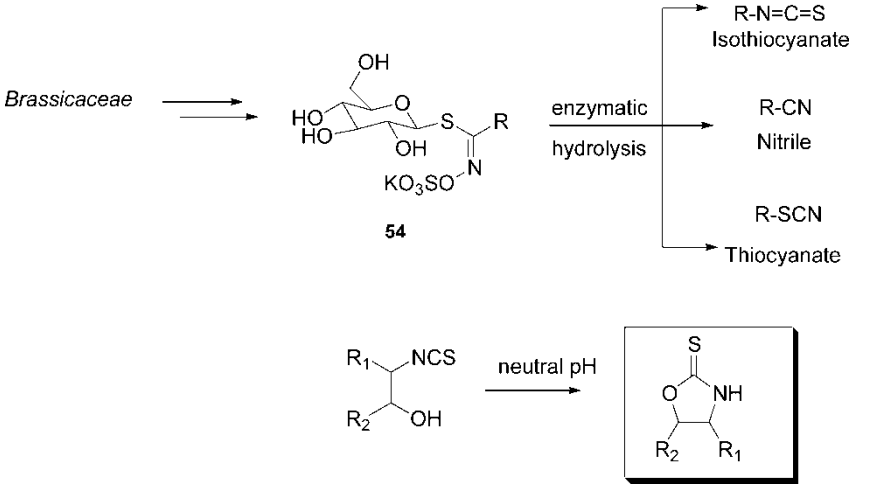
Leconte *et al.* [34] described the preparation of the bis-oxazolidinethiones **52** and oxazolinethiones **53** through the condensation of α-hydroxyketones **51** with thiocyanic acid (scheme 16).



SCHEME 16 *i*) KSCN, HCl, H_2O.

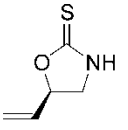
2.4 *Chemo-enzymatic preparation*

Leoni and co-workers [35–39] reported an interesting chemo-enzymatic process to furnish miscellaneous enantiopure oxazolidinethiones **55–61** from vegetal sources. Glucosinolates **54** (scheme 17) represent a specific group of natural compounds (secondary plant metabolites)



SCHEME 17 Enzymatic pathways of the hydrolysis of glucosinolates.

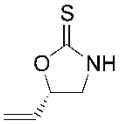
occurring predominantly in vegetables of the family Brassicaceae – Mustard, cabbage, broccoli, turnip, radish, Brussel sprouts, cauliflower, kale, rutabaga and rape. Glucosinolates are found throughout the roots, stems, leaves and seeds in the cruciferae family and can be hydrolyzed by the myrosinase (β-thioglucosidase) enzyme to D-glucose, the sulphate anion and a series of sulfur and nitrogen-containing compounds principally isothiocyanate. When the side-chain R carries a hydroxyl group in β-position to the isothiocyanate function, spontaneous cyclization occurs to yield enantiopure oxazolidinethiones.



55

mp (°C) 48

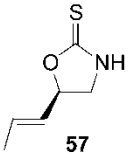
Brassica napus
Rape



56

48

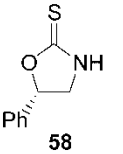
Crambe abyssinica
Crambe



57

60

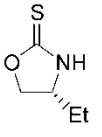
Brassica napus
Rape



58

116

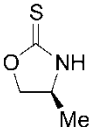
Barbarea vulgaris
Winter cress



7

mp (°C) 32

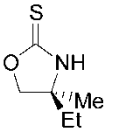
Sisymbrium loeselii
small tumbleweed mustard



59

60

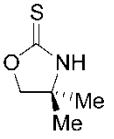
Sisymbrium loeselii
small tumbleweed mustard



60

43

Cleome spinosa
Spider flower



61

106

Conringia orientalis
Hare´s-ear mustard

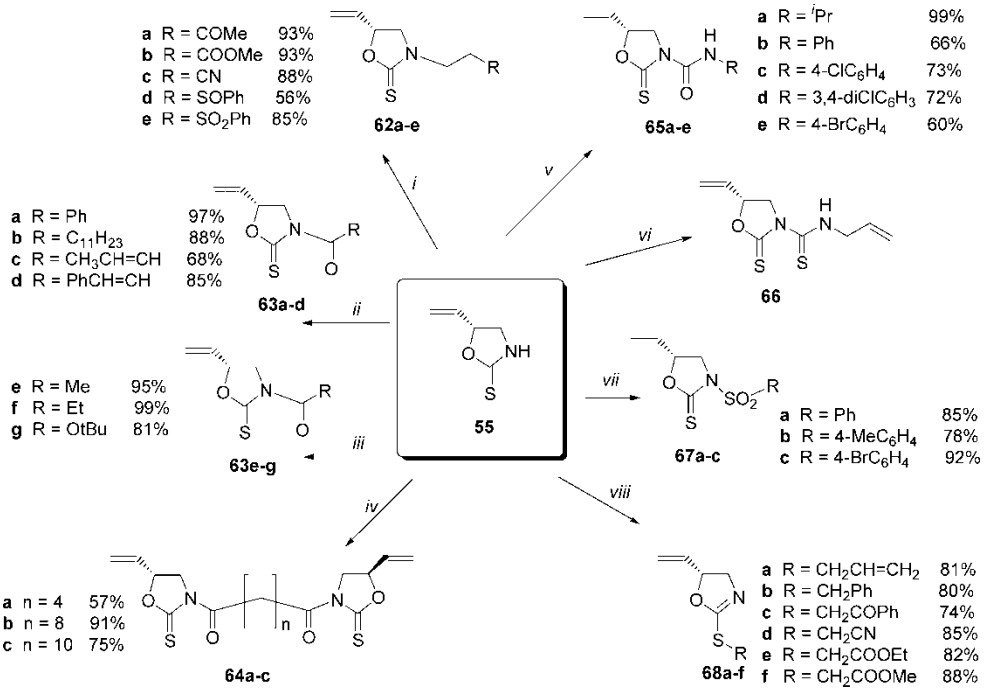
Epi-goitrin **55** was exposed to different reaction conditions [40] such as *N*-alkylation with Michael acceptors in the presence of Et_3N to afford compounds **62a–e**, *N*-acylation with acyl chlorides or carboxylic anhydrides to achieve **63a–d** and **63e–g** and *N*-acylation with diacyl chlorides to obtain bis-*N*-acyloxazolidinethiones **64a–c**. When compound **55** was exposed to other acylating agents such as isocyanates isothiocyanates, ureas **65a–e** and thioureas **66** were obtained respectively. Other reaction conditions that were applied to compound **55** were the *N*-sulfonylation to afford sulfonamido derivatives **67a–c** and *S*-alkylation to produce oxazolines **68a–f** (scheme 18).

The *N*-acyloxazolidinethiones **63a** and **63g** (scheme 19) were exposed to oxidative desulfurization conditions with *m*CPBA to give **69a** and **69g** [40].

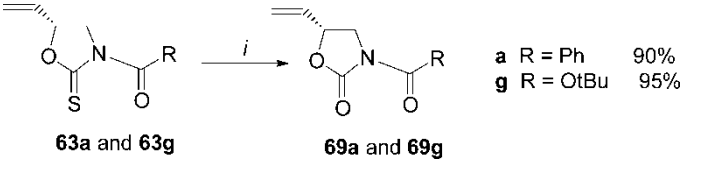
3. Application and synthetic versatility of oxazolidinethiones

3.1 *Novel rearrangements*

Meyer and Ford [19] described the preparation of a series of chiral thiirane derivatives in 48–70% yields and in enantiomeric excesses of 19–32%, using the chiral 2-thiomethyloxazoline **70** (scheme 20), which was prepared by methylation of oxazolidinethione **28** with sodium hydride and methyl iodide. Subsequent treatment of **70** with lithium diisopropylamide gave the lithium salt **71** and addition of carbonyl compounds at −95 °C furnished the chiral thiiranes **74**. Thiiranes have been employed in numerous commercial and industrial applications, in particular as disinfectants, as precursors for synthetic



SCHEME 18 *i*) CH_2=CH−EWG, Et_3N, *ii*) RCOCl, Et_3N, CH_2Cl_2, *iii*) $(RCO)_2O$, pyridine, *iv*) RCOCl, Et_3N, CH_2Cl_2, *v*) RNCO, Et_3N, CH_2Cl_2, *vi*) CH_2=$CHCH_2NCS$, NaH, DMF, *vii*) RSO_2Cl, Et_3N, CH_2Cl_2, *viii*) RBr, Et_3N or NaH (**a** and **b**), CH_2Cl_2.

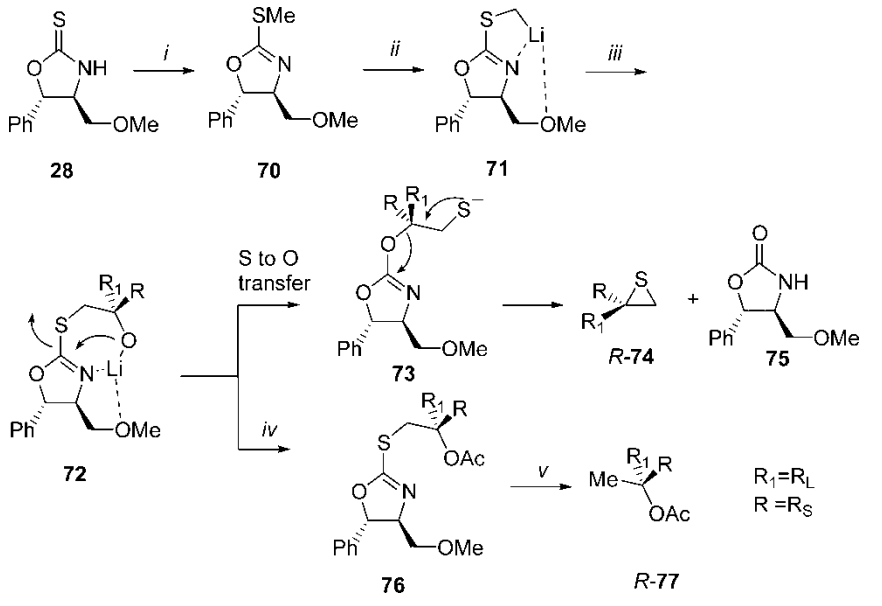


SCHEME 19 *i*) *m*CPBA, CH_2Cl_2.

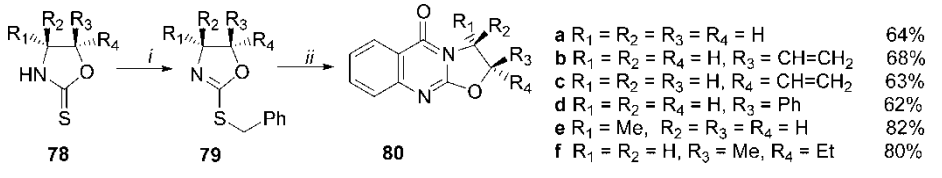
polymers, as stabilizers for plastics, and as pharmacologically active substances [41]. The rearrangement-fragmentation (**72** to **73** to **74**) occurred above 0 °C, first by an intramolecular nucleophilic substitution reaction followed by a nucleophilic attack of the sulfide in **73**. On the other hand, compound **72** was trapped as its acetate **76** which was treated with Raney nickel furnishing the chiral acetate **77** without racemization. It was found that the absolute configuration of the acetates was equal to that of the corresponding thiiranes, which were assigned as *R*.

Gueyrard *et al.* [42] described a concise and practical synthesis of the homochiral 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-one derivates **80a–f**. These compounds were obtained by reaction of the oxazolidinethiones **78** with benzyl bromide leading to the formation of 2-benzylthio-1,3-oxazolines **79** and a subsequent cyclization with anthranilic acid to give **80a–f** in good yields (scheme 21).

Adamczyk [43] described a rearrangement that transformed the aldol products **82** (scheme 22) to the tetrahydro-3-(3-hydroxy-2-carbomethoxypropyl)-2-thioxo-4H-1,3-oxazin-4-ones **83** via attack of the hydroxyl side chain on the thiocarbonyl group of the

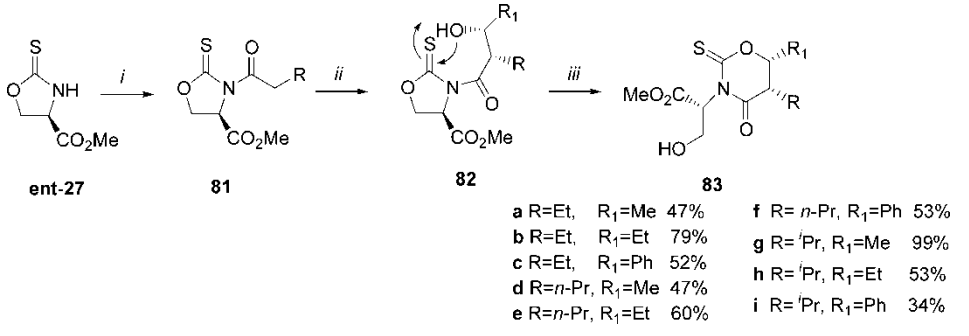


SCHEME 20 *i*) NaH, CH_3I, *ii*) LDA, −78 °C, *iii*) R_1COR, *iv*) AcCl −78 °C, *v*) Raney Ni, benzene.



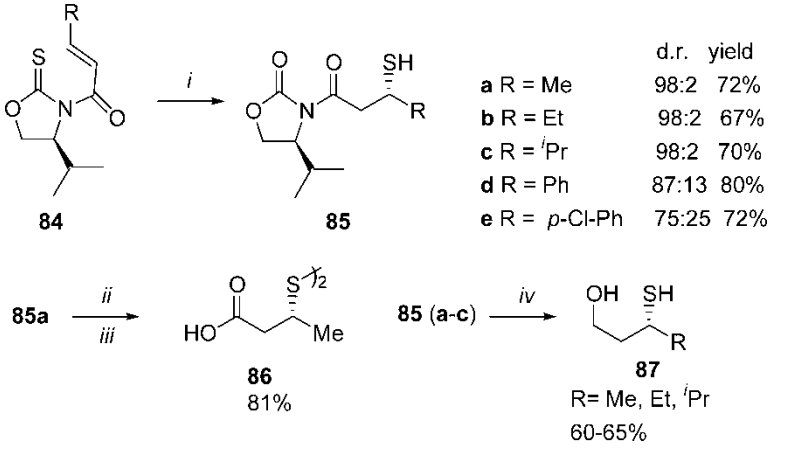
SCHEME 21 *i*) BnBr (1.2 equiv), NaH (1.1 equiv), MeCN, *ii*) Anthranilic acid, 4 Å molecular sieves, EtOH, 18 h, reflux.

oxazolidinethione. The rearrangement could be accelerated by treatment of the *syn*-aldol products with diisopropylethylamine in dichloromethane at room temperature, proceeding to completion after only 14 hours. This rearrangement was facile when the α-substituent was sterically more demanding.



SCHEME 22 *i*) RCOCl, Py, CH_2Cl_2, *ii*) (n-Bu)$_2$BOTf, DIPEA, CH_2Cl_2, 0 °C, R_1COH, −78 °C to 0 °C, *iii*) DIPEA, CH_2Cl_2.

Palomo [14] described an interesting reaction that promoted by Lewis acids, in which *N*-enoyl oxazolidinethiones provided β-mercapto carbonyl adducts in 67–80% yield. The reactions proceeded with high diastereoselectivity in the presence of aliphatic R groups and moderate diastereoselectivity with aromatic R groups. The reaction involved an intramolecular sulfur transfer at Cβ in *N*-enoyl oxazolidinethione **84** (scheme 23) promoted by a Lewis acid and a subsequent water addition to afford the β-mercapto carbonyl adducts **85**. Removal of the chiral auxiliary from adducts **85** provided the β-disulfide carbonyl compounds **86** and β-mercapto alcohols **87** in very good yields. In this reaction, the chiral auxiliary played a dual action as the agent inducing chirality and at the same time as reagent.

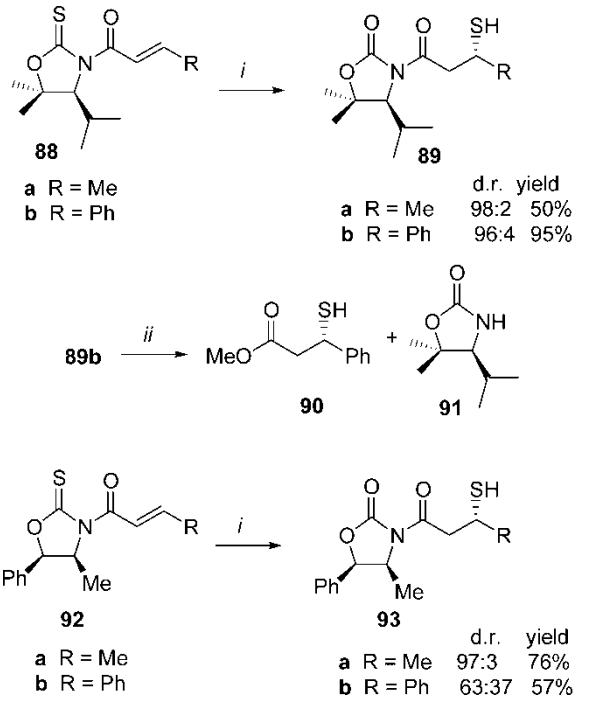


SCHEME 23 *i*) $SnCl_4$, CH_2Cl_2, −78 °C, H_2O, *ii*) I_2, CCl_4, rt., 1 h, *iii*) LiOH, H_2O_2, THF/H_2O, 0 °C, 1 h, *iv*) $NaBH_4$, THF/H_2O, rt., 1 h.

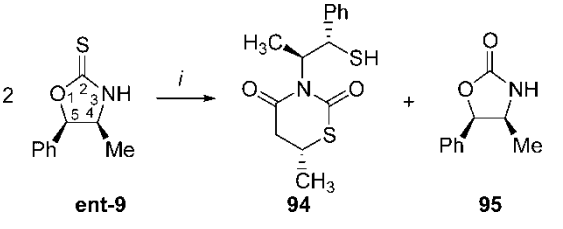
The asymmetric intramolecular sulfur transfer reaction was also investigated [10], in the *N*-enoyl oxazolidinethiones **88** and **92** (scheme 24), using $NbCl_5$ and TMSCl as promoter reagents to afford the β-mercapto adducts **89** and **93** in good yields and good diastereomeric ratios. $NbCl_5$ was easy to handle and it was possible to follow the course of the reaction by the colour change, from red to yellow. The removal of the chiral auxiliary from adduct **89b** with $Sm(OTf)_3$ in methanol provided the β-sulfide carbonyl compound **90** and oxazolidinone **91** which was subsequently recovered. The chiral auxiliary was not removed on **93**.

Ortiz [44] described a rearrangement that was carried out with oxazolidinethione **ent-9** (scheme 25). Treating **ent-9** under *N*-acylation conditions with sodium hydride and in the presence of (1 equiv) *trans*-crotonyl chloride followed by addition of water, thiazine **94** was afforded with high selectivity (>99%), and oxazolidinone **95** was obtained as subproduct of the reaction. In this rearrangement, two oxazolidinethiones **ent-9** were involved, one acted as chiral auxiliary producing an *N*-enoyl oxazolidinethione. The other one acted as chiral nucleophile thiolate, which attacked at the C-5 position of the *N*-enoyl oxazolidinethione, followed by cyclization and hydrolysis to provide thiazine **94** in 65% yield.

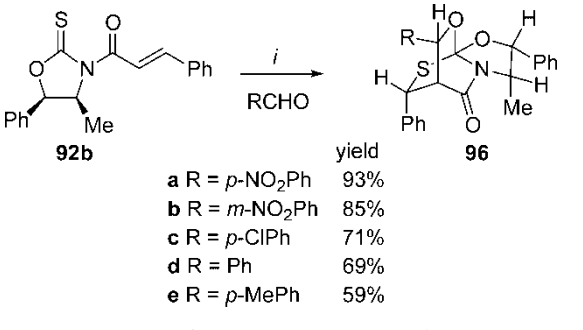
A novel tandem Michael-aldol reaction was employed to produce unusual heterotricyclic compounds **96** (scheme 26) with three consecutive chiral centres and a chiral carbon centre bound to four heteroatoms [45]. These interesting compounds were achieved by condensation of *N*-enoyl oxazolidinethiones **92b** with aldehydes in the presence of BF_3Et_2O as promoter. Compounds **96** were obtained in 59–93% yield and with high selectivity (95:5) with some of the aldehydes.



SCHEME 24 *i*) TMSCl or $NbCl_5$, CH_2Cl_2, −78 °C, H_2O, *ii*) $Sm(OTf)_3$, MeOH, rt.



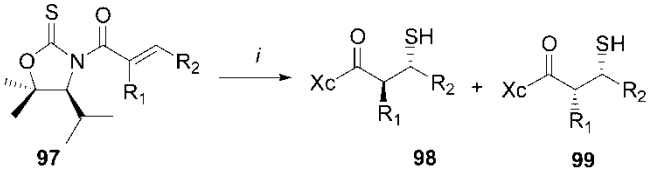
SCHEME 25 *i*) NaH, *trans*-crotonyl chloride, THF, 0 °C, H_2O.



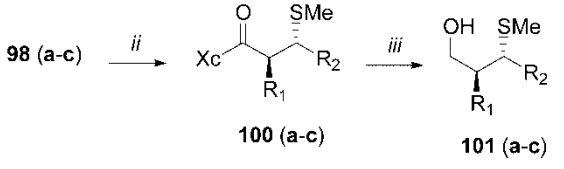
SCHEME 26 *i*) BF_3Et_2O, CH_2Cl_2, 0 °C.

The chiral 3-methylthio alcohols **101** were prepared through an intramolecular sulfur transfer reaction [46] which was applied to trisubstituted α,β-unsaturated *N*-enoyl oxazolidinethiones **97** in the presence of $SnCl_4$ or $NbCl_5$ as promoters to provide the β-mercapto carbonyl adducts **98** and **99** (scheme 27) with two consecutive chiral centres. Adducts **98**

were obtained in 40–93% yield and with good diastereoselectivity. The thiol group on the β-mercapto adducts **98** was protected with CH_3I in the presence of Et_3N to afford the products **100**. The removal of oxazolidinone in **100** was carried out by reduction with $LiAlH_4$ to produce the chiral 3-methylthio alcohols **101**.

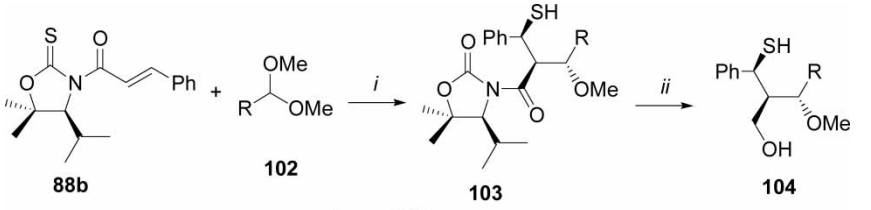


			anti/*syn*	yield
a R_1 = Me, R_2 = Me	**94a** = **95a**	R_1=Me, R_2=Me	98:2	40%
b R_1 = Me, R_2 = Ph	**94b** = **95b**	R_1=Me, R_2=Ph	84:16	93%
c R_1 = R_2= -$(CH_2)_4$-	**94c** = **95c**	R_1=R_2= -$(CH_2)_4$-	96:4	52%



SCHEME 27 *i*) $SnCl_4$ or $NbCl_5$, CH_2Cl_2, H_2O, *ii*) CH_3I, Et_3N, MeOH, *iii*) $LiAlH_4$, THF, 0 °C.

The tandem Michael–aldol reaction was described [47] also for the *N*-enoyl oxazolidinethione **88b**, using acetals **102** (scheme 28) and $SnCl_4$ as promoter to provide the β-mercapto adducts **103** with three consecutive chiral centres. The adducts were obtained in 45–87% yield and with a de > 95%. The removal of the oxazolidinone was carried out by reduction with $LiAlH_4$ to afford the chiral alcohols **104**.

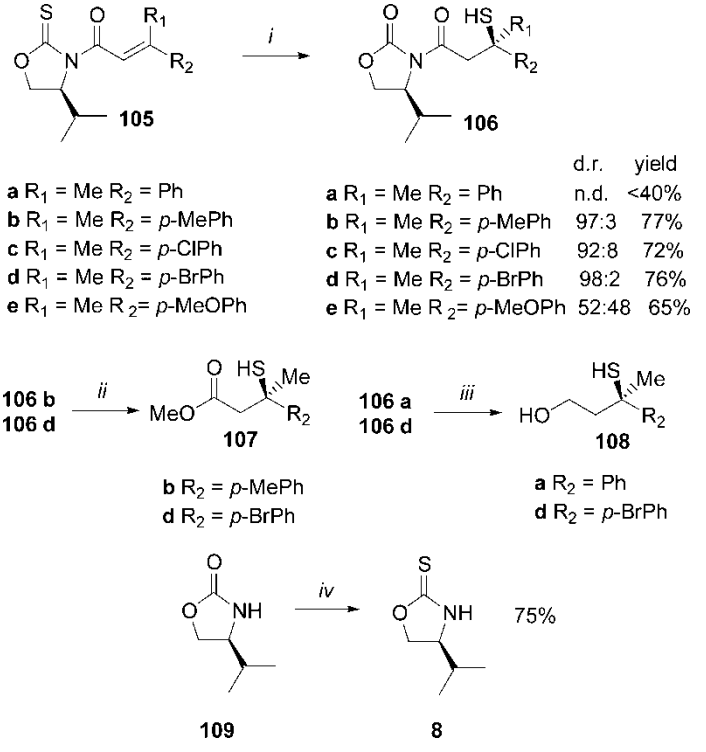


	de	yield
a R = Ph	>95%	79%
b R = *p*-ClPh	>95%	87%
c R = *p*-MeOPh	>95%	66%
d R = *p*-NO_2Ph	>95%	45%

SCHEME 28 *i*) $SnCl_4$, CH_2Cl_2, −40 °C, 24 h, H_2O, *ii*) $LiAlH_4$, THF, 0 °C.

Palomo [23] reported that the β,β-disubstituted *N*-enoyl oxazolidinethiones **105** (scheme 29) react in the presence of BF_3Et_2O in a highly stereoselective intramolecular Michael-type process to produce adducts **106** in high yields and with excellent

diastereoselectivities. This transformation allowed the construction of C-S bonds with a quaternary stereocentre. The oxazolidinone was removed with $Sm(OTf)_3$ in MeOH to provide the β,β-disubstituted β-sulfanyl carboxylic esters **107** and the 1,3-hydroxythiols **108** with 94% and 96% e.e. after reduction with $NaBH_4$. The oxazolidinone **109** recovered in each reaction was transformed into the oxazolidinethione **8** by treatment with Lawesson's reagent [48].

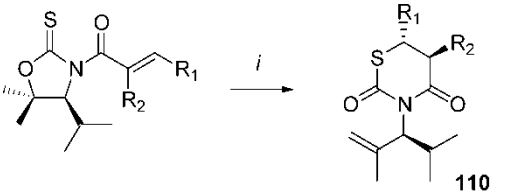


SCHEME 29 *i*) BF_3Et_2O, CH_2Cl_2, H_2O, *ii*) $Sm(OTf)_3$, MeOH, rt., *iii*) $NaBH_4$,THF/H_2O, *iv*) Lawesson's reagent, 1,4-dioxane, reflux.

The *N*-enoyl oxazolidinethiones **88** and **97** (scheme 30) were transformed to their corresponding *N*-substituted 1,3-thiazine-2,4-diones **110** through a novel rearrangement promoted by $NbCl_5$ [49]. This rearrangement allowed the preparation of the chiral thiazines **110** with one or two chiral centres. The formation of thiazines **110** occurred in competition with the formation of their respective β-mercapto adducts **89** and **99** (schemes 24 and 27). The formation of one or the other product was subject to the employed reaction conditions.

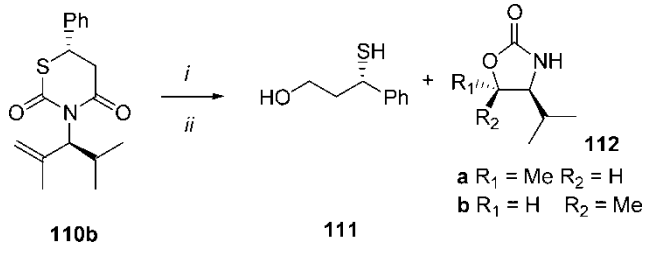
The olefinic bond in thiazine **110b** could be oxidized to the corresponding ketone which under reductive conditions with $NaBH_4$ provided the 1,3-hydroxythiol **111** and a mixture of oxazolidinones **112** (scheme 31).

The heterocyclic oxazolidinethione **17** (scheme 32) was transformed through an intramolecular nucleophilic substitution reaction to the *N*-substituted 2,4-thiazolidinedione **113**, exercising a novel reaction carried out between oxazolidinethione **17** and bromoacetyl bromide [11]. The trisubstituted oxazolidinethione **17** showed an interesting elimination reaction to form a double bond in **113**, which could be transformed to its respective alcohol **114**, first realizing



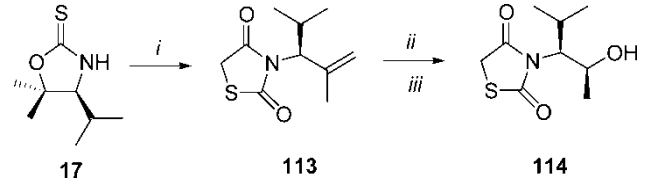
		d.r	yield
88a R_1 = Me R_2 = H	**a** R_1 = Me R_2 = H	98:2	60%
88b R_1 = Ph R_2 = H	**b** R_1 = Ph R_2 = H	98:2	87%
97a R_1 = Me R_2 = Me	**c** R_1 = Me R_2 = Me	83:17	16%
97b R_1 = Ph R_2 = Me	**d** R_1 = Ph R_2 = Me	60:40	55%
97c R_1 = R_2 = -$(CH_2)_4$-	**e** R_1 = R_2 = -$(CH_2)_4$-	96:4	82%

SCHEME 30 *i*) $NbCl_5$, CH_2Cl_2, H_2O.



SCHEME 31 *i*) $NaIO_4$, OsO_4, THF/H_2O, *ii*) $NaBH_4$, MeOH.

an oxidation reaction with OsO_4−$NaIO_4$ and then a stereoselective reduction reaction with L-selectride.

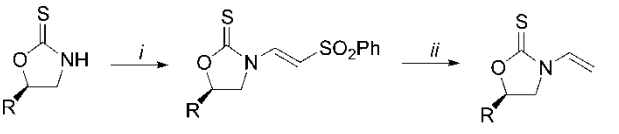


SCHEME 32 *i*) NaH, $BrCOCH_2Br$, CH_2Cl_2, 0 °C to rt., *ii*) $NaIO_4$, OsO_4, THF/H_2O, *iii*) L-selectride, THF, −78 °C.

The oxazolidinethiones **4** and **55** (scheme 33) were converted into their respective *N*-vinyl oxazolidinethiones **116** in good yields [50]. A regioselective Michael-type *N*-phenylsulfonylvinylation provided compounds **115** and a subsequent chemoselective reduction gave rise to *N*-vinyl oxazolidinethiones **116**, which are useful synthons for the development of stereoselective cycloadditions.

Tardy *et al.* [51] recently described the use of *N*-vinyloxazolidinethiones **116** as new chiral dienophiles in $Eu(fod)_3$-catalyzed inverse hetero-Diels-Alder reactions involving the benzylidene pyruvic acid methyl ester **117**. This reaction furnished heteroadducts **118** and **119** with good yields and good diastereocontrol (scheme 34).

Evans [52] described an important application of the bis(imine)-copper(II) **121** as chiral Lewis acid catalyst for the Diels-Alder reaction employing *N*-enoyl oxazolidinethione

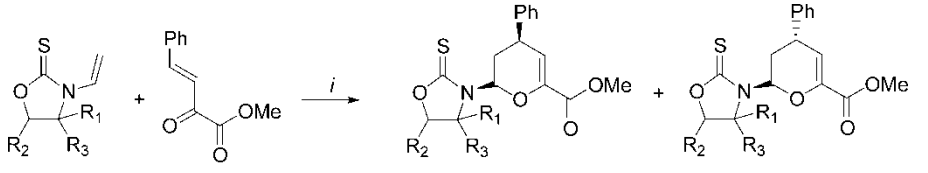


4 R=H
55 R=CH=CH$_2$

115
a R=H 80%
b R=CH=CH$_2$ 93%

116
a R=H 86%
b R=CH=CH$_2$ 75%

SCHEME 33 *i*) 1,2-Bis-(phenylsulfonyl)ethylidene (BPSE), DIPEA, Bu_4NBr, DMF, *ii*) Na/Hg, NaH_2PO_4, THF-MeOH.



116 **117** **118** *endo* **119** *exo*

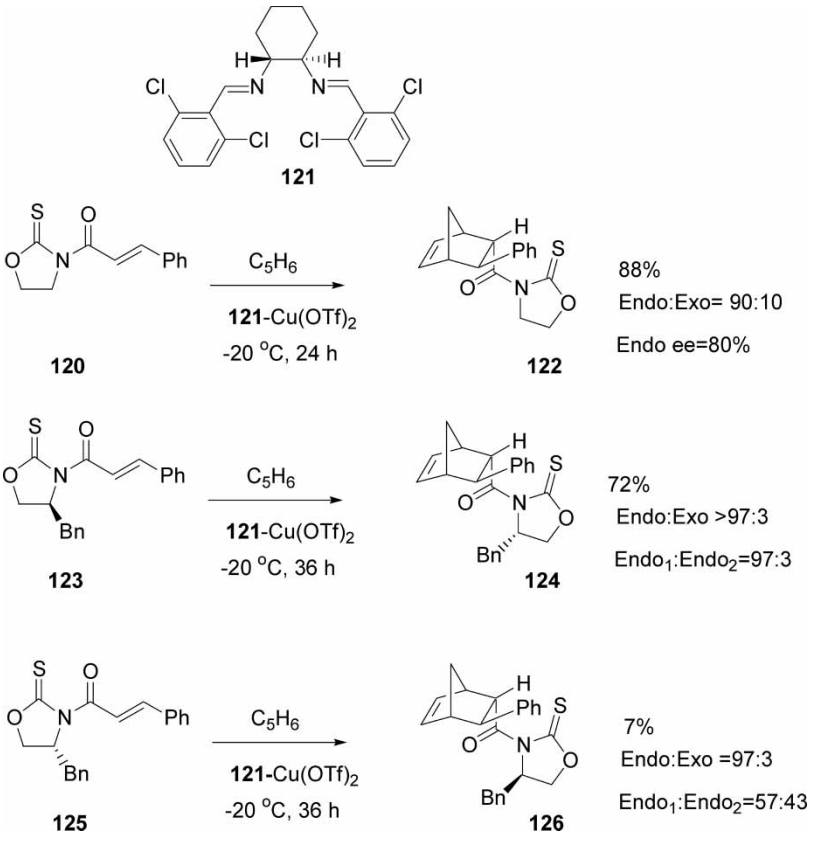
		endo/*exo*	yield
a	$R_1 = R_2 = R_3 = H$	86:14	56%
c (4*R*)	R_1 = Et $R_2 = R_3 = H$	78:22	75%
d(4*S*)	R_1 = Bn $R_2 = R_3 = H$	81:19	78%
e (4*R*)	R_1 = Bn $R_2 = R_3 = H$	86:14	87%
f (4*S*)	R_1 = Ph $R_2 = R_3 = H$	80:20	75%
g (4*R*)	R_1 = Ph $R_2 = R_3 = H$	75:25	82%
h (4*S*,5*R*)	R_1 = Me R_2 = Ph R_3 = H	89:11	77%
i	R_1 = H R_2 = Me R_3 = Me	70:30	20%

SCHEME 34 *i*) Eu(fod)$_3$ 5 mol%, cyclohexane, 48 h reflux.

120 and the chiral *N*-enoyl oxazolidinethiones **123** and **125** as dienophiles (scheme 35). The enantioselective Diels-Alder reaction of imide **120** with cyclopentadiene catalyzed by **121** Cu(OTf)$_2$ provided the product **122** with high selectivity. The stereochemical course of the reaction was dictated by the geometry of the catalyst-dienophile complex at the metal centre where the square planar and tetrahedral complexes shielded opposite faces of the dienophile. The sense of asymmetric induction in this reaction was rationalized by assuming that the reaction proceeded via the more reasonable square-planar intermediate rather than the tetrahedral Cu(II) dienophile complex. The chiral oxazolidinethiones **123** and **125** were treated under the same reaction conditions. In the matched case, the chirality of the ligand and substrate had a cooperative effect and product **124** was obtained with high selectivity. In the mismatched case, the stereochemical elements imposed by catalyst and substrate favoured the formation of different products and **126** was obtained in low yield as a mixture of diastereomers.

3.2 *Asymmetric aldol addition reactions*

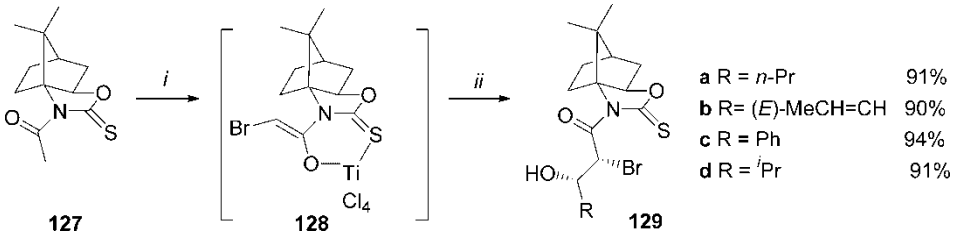
The chiral auxiliary mediated asymmetric aldol addition is one of the most general and widely used methods for asymmetric carbon-carbon bond formation. Removal of the chiral auxiliary produces chiral alcohols, aldehydes, acids and esters containing one or two stereogenic centres which have been applied to a multitude of organic syntheses. In this part of the review, the



SCHEME 35 Asymmetric catalytic Diels-Alder reactions with *N*-enoyl oxazolidinethiones.

asymmetric aldol addition reactions are classified, based on the *N*-substituent as aldol additions with *N*-acetyl oxazolidinethiones, aldol additions with *N*-propionyl oxazolidinethiones and aldol additions with *N*-glycolyl oxazolidinethiones.

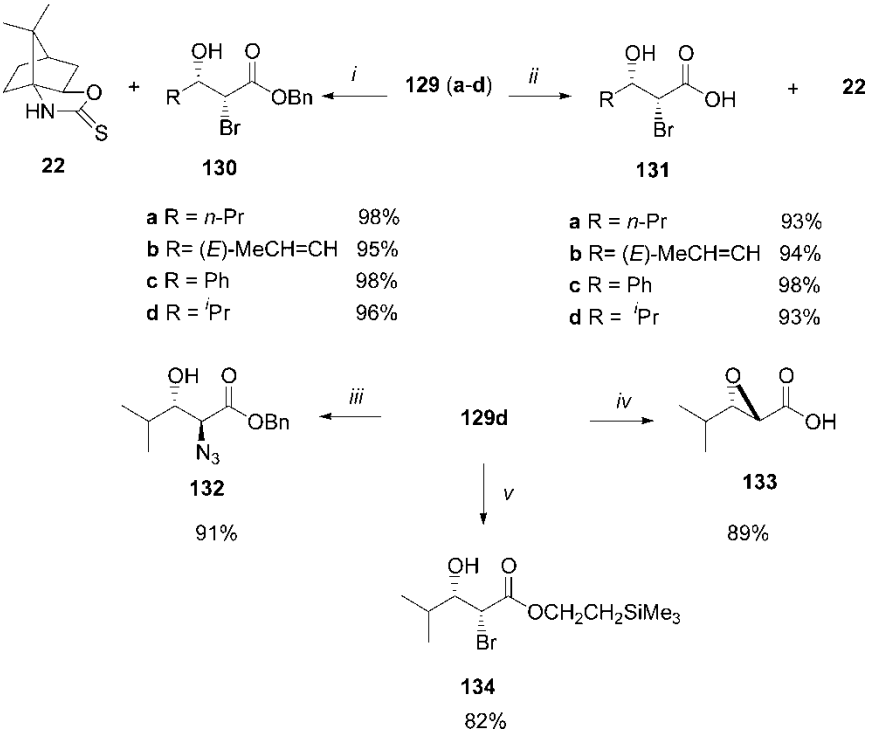
3.2.1 Aldol addition reactions with chiral *N*-acetyl oxazolidinethiones and their applications. Yan *et al.* [53] reported the asymmetric bromination-aldolization of a chiral titanium enolate derived from *N*-acetyl oxazolidinethione **127** as described in scheme 36. First, enolate of **127** was formed with $TiCl_4$ and DIPEA in CH_2Cl_2 at 0 °C, which was then treated with bromine to afford the bromoacetate carboxythioimide type intermediate **128**. After treatment



SCHEME 36 *i*) $TiCl_4$, DIPEA, Br_2, DIPEA, CH_2Cl_2, *ii*) RCHO, −78 °C,

with additional DIPEA at −78 °C and subsequent condensation with representative aldehydes the *syn* bromohydrin aldol adducts **129** were produced in excellent yields and with high diastereoselectivity.

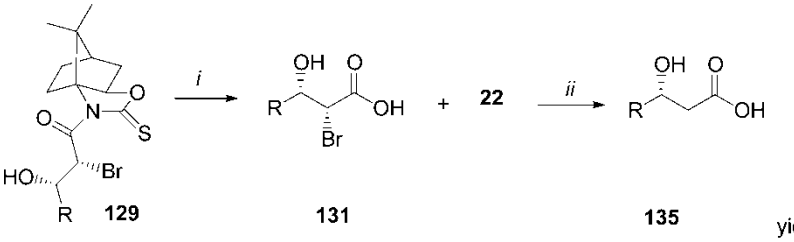
Adducts **129** were converted to the benzyl α-bromo-β-hydroxy esters **130** in high yields with no apparent loss of stereochemistry and no detectable elimination product with the recovery of the chiral auxiliary **22**. Compounds **129** were transformed furthermore to α-bromo-β-hydroxy carboxylic acids **131** in high yields. The *syn* bromohydrin aldol **129d** was also transformed into the α-β-difunctional compounds **132**, **133** and **134** in high yields (scheme 37) [54].



SCHEME 37 *i*) DMAP, BnOH, 0 °C, CH_2Cl_2, *ii*) Et_3N, H_2O, CH_2Cl_2, 0 °C, *iii*) DMAP, BnOH, 0 °C, CH_2Cl_2, NaN_3, n-$Bu_4N^+-HSO_4^-$, *iv*) KF, LiF, n-$Bu_4N^+-HSO_4^-$, 25 °C, CH_2Cl_2, *v*) DMAP, 2-(trimethylsilyl) ethanol, 0 °C, CH_2Cl_2.

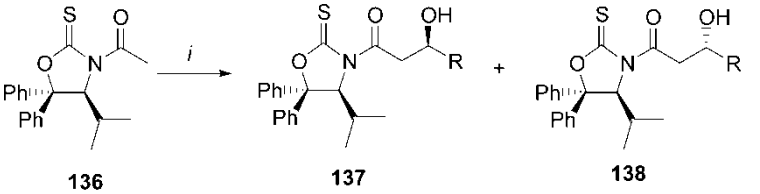
Yan and Wang [55] reported a chemoselective cleavage of the C−Br bond in bromohydrin aldols **129** (scheme 38) by a standard one-pot procedure which involved deacylation with H_2O and Et_3N (or DMPA) and mild and rapid reduction reaction with Al-Hg to give rise to the β-hydroxy acids **135** in high yields and with high enantiopurity. The reduction was carried out successfully in the presence of sensitive substituents.

Guz and Phillips [12] described that the condensation of aldehydes with the *N*-acetyl oxazolidinethione **136** (scheme 39) under Crimmims' conditions ($TiCl_4$, (−)-sparteine, NMP) gave rise to the acetate aldol adducts **137** and **138** in excellent yield and with high levels of diastereoselection. Using $TiCl_4$ and the amine with an exact 1:1 stoichiometry aldol **137** was obtained in high yield and with excellent diastereoselectivity.



		yield
c R = Ph	**c** R = Ph	92%
d R = ^{i}Pr	**d** R = ^{i}Pr	96%
e R = -CH=CH$_2$	**e** R = -CH=CH$_2$	83%

SCHEME 38 *i*) H_2O, CH_2Cl_2, NEt_3, 0 °C, *ii*) Al−Hg, 0 °C.



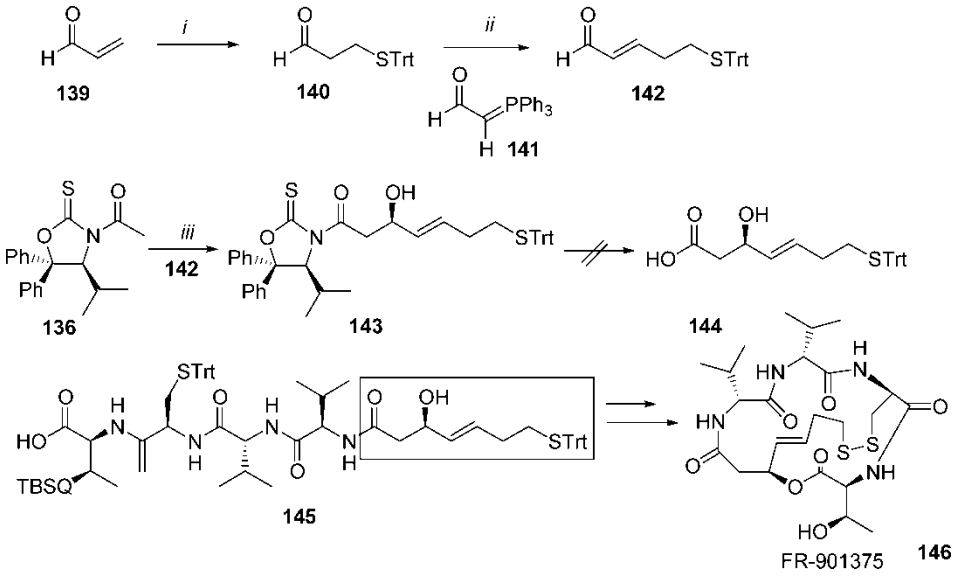
	dr (**137:138**)	yield (%)
a R = $(CH_3)_2CHCH_2$	96:4	82
b R = *trans*-CH_3CH=CH	99:1	85
c R = $PMBOCH_2$	97:3	55
d R = $TBDPSOCH_2CH_2$	99.1	56

SCHEME 39 *i*) $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, 0 °C, RCHO, −78 °C.

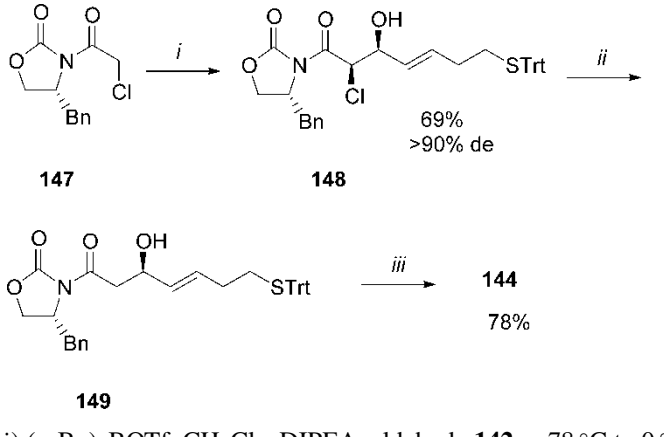
The protocol reported by Phillips was employed in the synthesis of (3*S*, 4*E*)-hydroxy-7-mercapto-4-heptenoic acid **144** [56], a fragment employed in the first total synthesis of FR-901375 **146** (scheme 40), a novel bicyclic depsipeptide isolated from the fermentation broth of *Pseudomonas chloroaphis* No 2522. The synthesis of **144** was tried through the aldol condensation of aldehyde **142** and *N*-acetyl oxazolidinethione **136**. Aldehyde **142** was obtained by conjugate addition of triphenylmethanethiol to acrolein **139** to afford the aldehyde **140**, which, upon subsequent treatment of **140** with **141**, yielded the α,β-unsaturated aldehyde **142**. Condensation of **142** with the *N*-acetyl oxazolidinethione **136** in the presence of $TiCl_4$, (−)-sparteine and NMP provided the aldol product **143** in poor yield (35%), and moderated diastereoselectivity (6:1). Because of this **144** was achieved according to Yan's method with high diastereoselectivity [55].

The dibutylboron enolate derived from chloroacetyl-oxazolidinone **147** and aldehyde **142** provided the chlorohydrin **148**. The subsequent dechlorination of **148** was achieved with Al-Hg to give **149** in quantitative yield. The hydrolysis of the chiral auxiliary of **149** with $LiOH/H_2O_2$ furnished **144** in 78% yield (scheme 41) [55].

Another interesting application of *N*-acetyl oxazolidinethione was shown by Crimmins [57] in the enantioselective total synthesis of (+)-rogioloxepane A **153** (scheme 42). The rogioloxepane A **153** is a representative member of the *Laurencia*-derived C15 acetogenins containing an α,α'-*trans*-disubstituted oxepene ring. For this synthesis, the protocol reported by Phillips was employed to generate the C6 stereogenic centre with the required stereochemistry. The aldol addition reaction of the chlorotitanium enolate of the *N*-acetyl oxazolidinethione



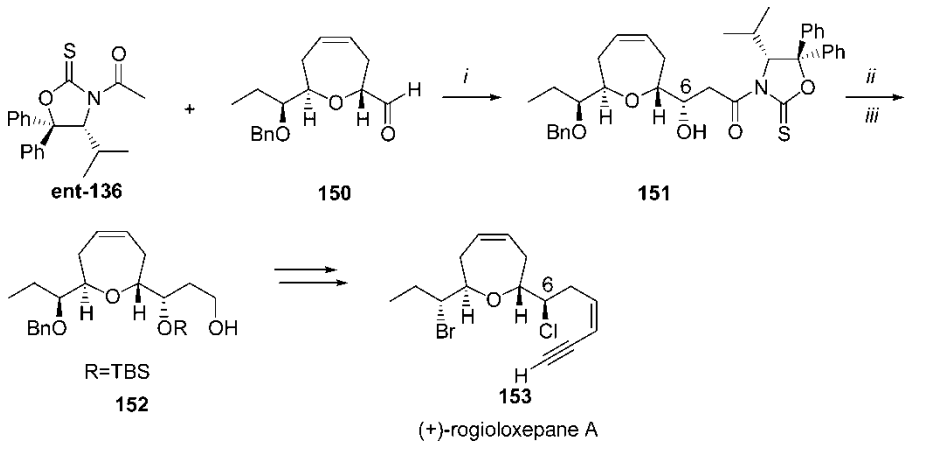
SCHEME 40 *i*) $HSCPh_3$, Et_3N, CH_2Cl_2, rt., 0.5 h, *ii*) benzene, reflux, 7 h, *iii*) $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, 0 °C, **142**, −78 °C.



SCHEME 41 *i*) $(n\text{-}Bu)_2BOTf$, CH_2Cl_2, DIPEA, aldehyde **142**, −78 °C to 0 °C, *ii*) Al−Hg, THF−H_2O, *iii*) LiOH, H_2O_2, THF.

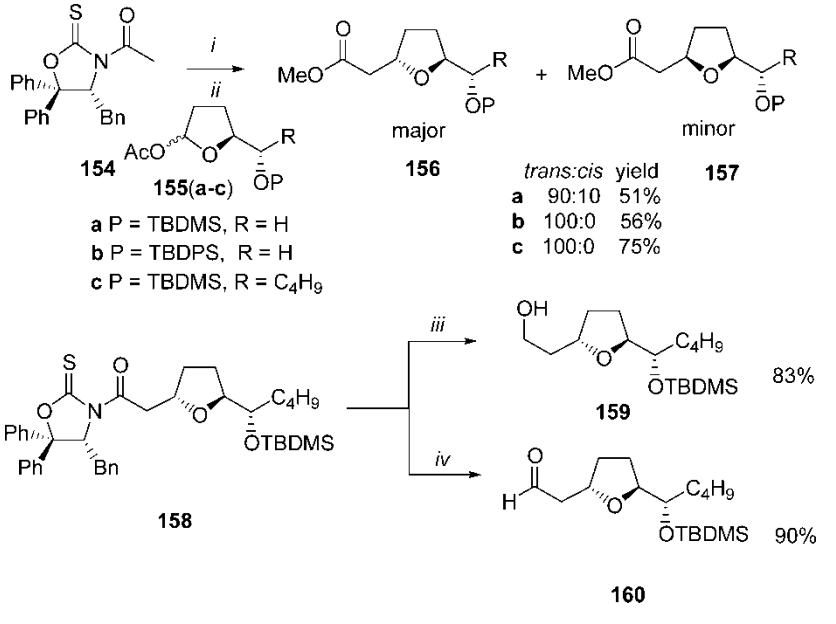
ent-136 provided in the presence of aldehyde **150** the aldol adduct **151** in 92% yield and with a diastereoselectivity of 5:1. Silylation of the mixture of diastereomers followed by reductive removal of the oxazolidinethione afforded the primary alcohols, which were separated by flash chromatography to obtain **152**. Alcohol **152** was then manipulated in several steps to achieve the desired (+)-rogioloxepane A **153**.

A highly diastereoselective synthesis of *trans*-2,5-disubstituted tetrahydrofurans **156** (scheme 43) was described, which is based on the condensation of the lactol acetate **155** with the chlorotitanium enolate of *N*-acetyl oxazolidinethione **154** using $TiCl_4$ and DIPEA [13]. The adducts formed were transesterified *in situ* to the methyl esters **156** and **157** in yields of 51–75% and with high diastereoselectivity. It is important to note that the intermediate



SCHEME 42 *i*) $TiCl_4$, (−)-sparteine, NMP, *ii*) TBSOTf, *iii*) $NaBH_4$.

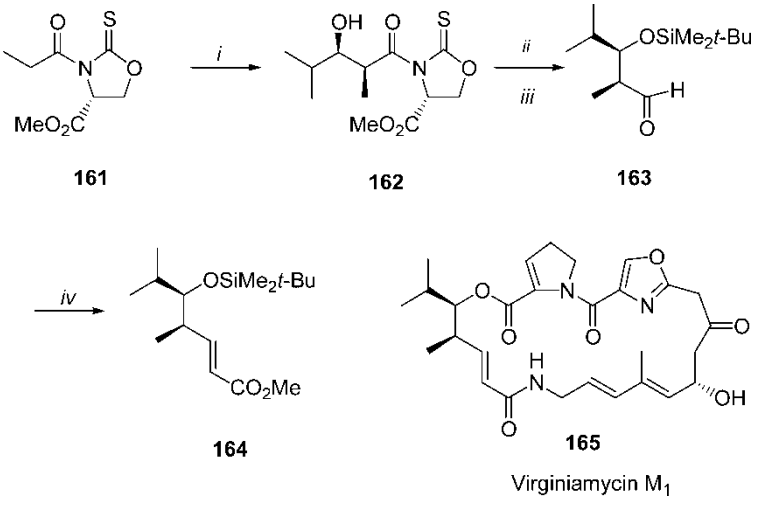
trans adduct **158** could be isolated and further transformed into the primary alcohol **159** and aldehyde **160**. The chiral auxiliaries were recovered in 91% and 93% yield, respectively.



SCHEME 43 *i*) $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C to −20 or −40 °C, *ii*) K_2CO_3, MeOH, *iii*) $LiBH_4$, 0 °C, *iv*) DIBAL-H, −78 °C.

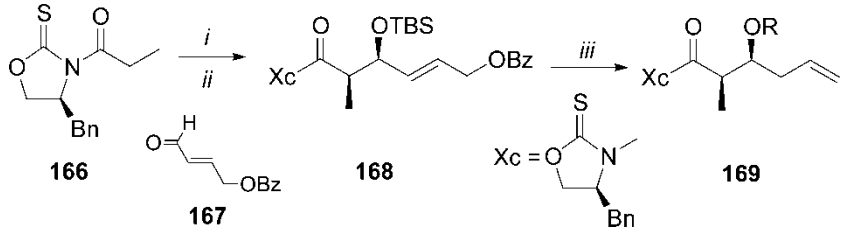
3.2.2 Aldol addition reactions with chiral *N*-propionyl oxazolidinethiones and their applications. The condensation of an aldehyde with *N*-propyl oxazolidinethione enolates produces an aldol adduct with two new stereogenic centres in high yield and with excellent diastereoselectivity. This methodology has been widely applied to the synthesis of complex natural products.

In this review, some recent advances are considered. Kazmierczak and Helquist [58] reported a straightforward asymmetric synthesis of the structural unit **164**, which is present in several important natural products such as Virginiamycin M_1 **165** (scheme 44). The synthesis of **164** was achieved by the condensation of isobutyraldehyde with *N*-propionyl oxazolidinethione **161** under Miller's conditions ($(n\text{-Bu})_2$BOTf, DIPEA) to provide the *syn* adduct **162**. Protection of the hydroxyl group and removal of the chiral auxiliary from adduct **162** with diisobutylaluminum hydride provided the aldehyde **163**. Condensation of **163** with the phosphonium ylide afforded product **164** mainly as *Z* isomer. The enantiomeric excess of the final product (4*R*, 5*R*)-**164** was 99%.

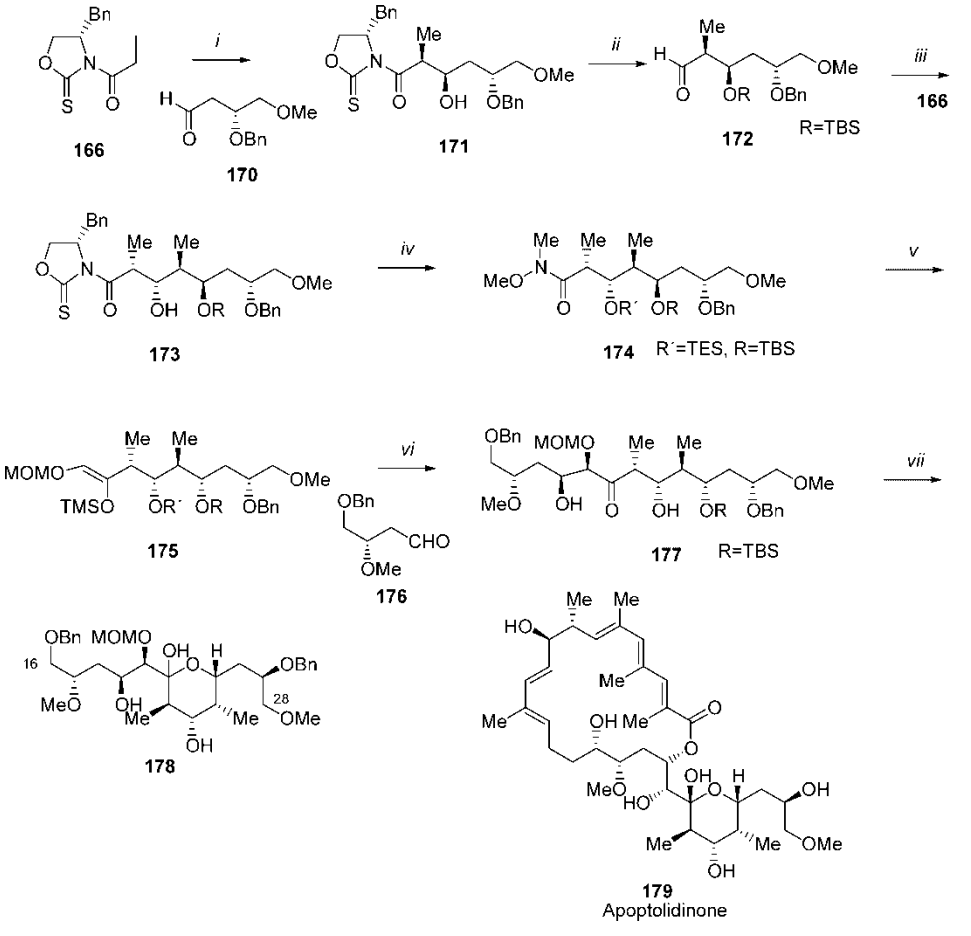


SCHEME 44 *i*) $(n\text{-Bu})_2BOSO_2CF_3$, DIPEA, $(Me)_2CHCHO$, CH_2Cl_2, *ii*) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, *iii*) $(^i Bu)_2AlH$, CH_2Cl_2, −78 °C, *iv*) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2.

Lautens [59] described a new methodology for the conversion of the α,β-unsaturated aldehyde **167** to the β,γ-unsaturated carboxylic derivative **169** (scheme 45). The condensation of aldehyde **167** with *N*-propionyl oxazolidinethione **166** under aldol addition conditions ($TiCl_4$, DIPEA) provided the *syn*-aldol adduct **168** in 84% yield. Then adduct **168** was protected with TBSOTf and exposed to a regioselective Pd-catalyzed formate reduction to obtain the desired terminal olefin **169** in excellent yield (85%).



SCHEME 45 *i*) $TiCl_4$ (2 equiv), DIPEA (1.1 equiv), CH_2Cl_2, 0 °C, aldehyde **167**, −78 °*C*, *ii*) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10°C, *iii*) HCO_2NH_4, $Pd_2(dba)_3$, n-Bu_3P, toluene, 100 °C.

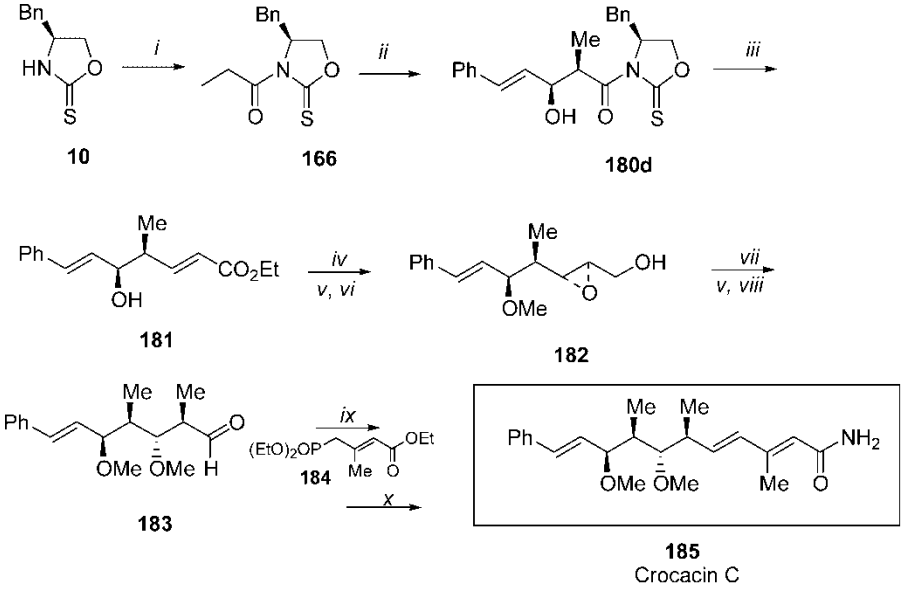


SCHEME 46 *i*) $TiCl_4$, (−)-sparteine, CH_2Cl_2, −78 °C to 0 °C, aldehyde **170**, *ii*) 1. TBSOTf, 2,6-lutidine, 2. $NaBH_4$, EtOH, 3. $(COCl)_2$, DMSO, Et_3N, *iii*) $TiCl_4$ (2.1 equiv), (−)-sparteine (2.1 equiv), CH_2Cl_2, −78 °C to 0 °C, *N*-propionyl oxazolidinethione **166**, *iv*) 1. Me(MeO)NH·HCl, Me_3Al, −15 °C to 0 °C, 2. TESCl, ImH, 0 °C, *v*) 1. *n*-BuLi, Bu_3SnCH_2OMOM, THF, −78 °C, 2. $LiN(SiMe_2Ph)_2$, TMSCl, *vi*) $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C, *vii*) TBAF, THF, −10 °C.

Sulikowski [60] described another application of chiral *N*-propionyl oxazolidinethione **166** during the synthesis of the C(16)–C(28) fragment **178**, which is present in the structure of apoptolidinone **179** (scheme 46). The use of two consecutive *syn* propionate aldol reactions and a Mukaiyama aldol addition allowed the successful elaboration of the stereocontrolled assembly of the C(16)–C(28) fragment **178**. Condensation of aldehyde **170** with ***N***-propionyl oxazolidinethione **166** under Crimmins' conditions gave rise to the *syn* aldol adduct **171** in 96% yield (>95:5 diastereoselectivity). The aldol adduct **171** was converted to aldehyde **172** after hydroxyl protection and removal of the chiral auxiliary with $NaBH_4$ followed by Swern oxidation. In the second aldol reaction, **166** was treated with 2.1 equiv of $TiCl_4$ in the presence of 2.1 equiv of (−)-sparteine followed by addition of **172** to afford the non-Evans *syn* aldol adduct **173** in 93% yield and with excellent diastereoselectivity (>95:5). Removal of the chiral auxiliary with *N*, *O*-dimethylhydroxylamine provided the corresponding Weinreb amide **174**. Subsequent silyl protection (TESCl, imidazole) of the remaining hydroxyl group and addition of (methoxymethoxy)methyllithium, generated by

the *in situ* transmetalation of (methyloxymethyoxy)methyltributylstannane, afforded (*Z*)-enolsilane **175**. A double diastereoselective Mukaiyama aldol addition reaction was employed coupling **175** and the aldehyde **176** using BF_3 OEt_2 as promoter, to furnish the *syn* aldol adduct **177**. The removal of the C(25) TBS protecting group and treatment with TBAF gave pyran **178** in 94% yield.

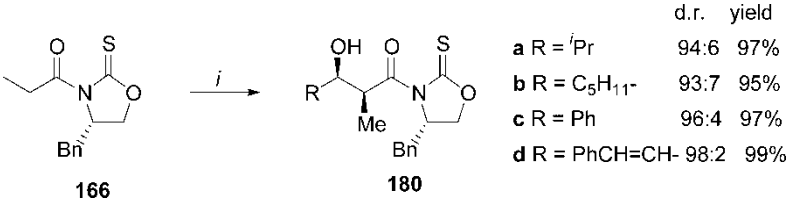
Chakraborty [61] described the total synthesis of (+)-crocacin C **185** (scheme 47), which was isolated from the myxobacterial strains of *Chondromyces crocatus*. The synthesis was achieved employing the following reactions. The *N*-propionyl oxazolidinethione **166** was prepared by *N*-acylation of chiral oxazolidinethione **10** using propionic anhydride in the presence of triethylamine and anhydrous LiCl in THF to furnish **166** in 79% yield. Condensation of *trans*-cinnamaldehyde with *N*-propionyl oxazolidinethione **166** under Crimmins' conditions produced the non-Evans *syn* aldol adduct **180d** as the only diastereomer in 89% yield. Adduct **180d** was obtained with the required stereochemistry at C8 and C9 and the *syn*-relationship between the methyl and hydroxyl groups was indicated by the relatively small value of the vicinal coupling constant of 4.7 Hz. The chiral auxiliary was removed by reduction using DIBAL-H in THF at −78 °C to give the corresponding aldehyde, which was transformed to the α,β-unsaturated ester **181**. The remaining two centres C6 and C7 were constructed by a Sharpless' asymmetric epoxidation using (−)-diisopropyl tartrate in the presence of $Ti(^iPrO)_4$, *t*-butylhydroperoxide and 4 Å molecular sieves in CH_2Cl_2 at −20 °C affording epoxide **182** in 93% yield. Subsequent regioselective opening of the epoxide alcohol **182** with lithium dimethylcuprate in ether at −20 °C gave the required 1,3-diol which was transformed to aldehyde **183**. Finally, a Horner-Wadsworth olefination reaction was carried out between aldehyde



SCHEME 47 *i*) $(CH_3CH_2CO)_2O$, Et_3N, LiCl, THF, *ii*) $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C, *trans*-cinnamaldehyde, *iii*) 1. DIBAL-H, THF, −78 °C, 2. $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, *iv*) DIBAL-H, CH_2Cl_2, −78 °C, *v*) 1. TBDMSCl, imidazole, THF, 0 °C to rt, 2. NaH, MeI, TBAI (cat.), THF, 0 °C to rt, 3. CSA (cat), CH_2Cl_2:MeOH (2:1), 0 °C to rt, *vi*) $Ti(^iPrO)_4$, (−)-DIPT, TBHP, 4 Å MS, CH_2Cl_2, −20 °C, *vii*) Me_2CuLi, Et_2O, −20 °C, *viii*) SO_3−Py, Et_3N, DMSO, CH_2Cl_2, *ix*) **184**, LDA, DMPU, THF, −78 °C, *x*) 1. LiOH, THF:MeOH:H_2O, 0 °C to rt, 2. Et_3N, $ClCO_2Et$, THF, 25% NH_4OH, −20 °C to 0 °C.

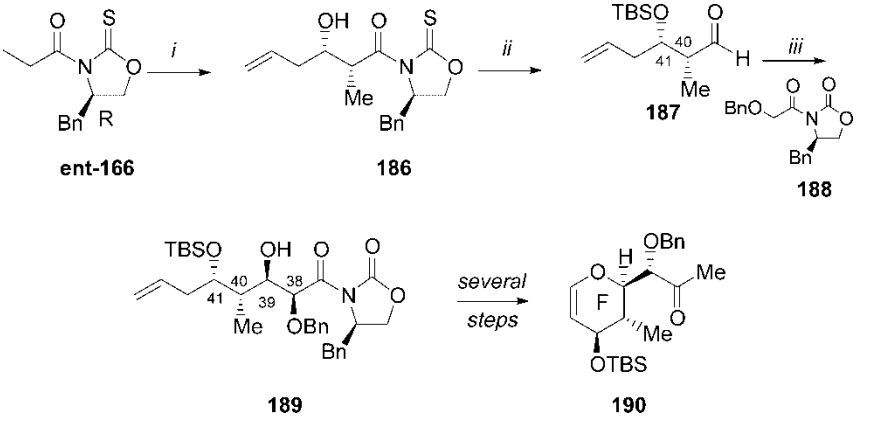
183 and the diethyl phosphonate **184** to provide the desired *E*-olefin, which was converted to the natural product **185**.

Crimmins [62] recently described an improved procedure for the asymmetric aldol addition with the *N*-propionyl oxazolidinethione **166**, which obviated the need to use (−)-sparteine. The improved conditions employed 1.05 equivalents of titanium tetrachloride, 1.1 equivalents of diisopropylethylamine, 1.0 equivalent of *N*-methyl-2-pyrrolidinone and 1.1 equivalents of the desired aldehyde at 0 °C to provide the Evans *syn* aldol adducts **180** (scheme 48) as the major diastereomers with high level of conversion and high selectivity.



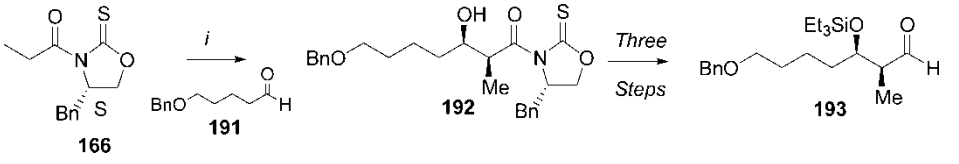
SCHEME 48 *i*) $TiCl_4$, DIPEA, NMP, CH_2Cl_2, RCHO, 0 °C.

Crimmins [63] also reported the asymmetric synthesis of the C29–C51 fragment containing the E and F pyran rings of Spongistatin 1 **196**. The synthesis started with the preparation of the F ring (methyl ketone **190**) (scheme 49). The C40–C41 stereocentres were introduced by an aldol addition reaction that was carried out between the *N*-propionyl oxazolidinethione **ent-166** and 3-butenal in the presence of titanium tetrachloride and (−)-sparteine to produce the *syn* aldol adduct **186** in 94% yield with >98:2 diastereoselectivity. Protection of the hydroxyl group, followed by removal of the chiral auxiliary from adduct **186** with $LiBH_4$ provided the corresponding primary alcohol, which was immediately oxidized to aldehyde **187** with Dess-Martin periodinane. Then aldehyde **187** was treated with dibutylboryl enolate derived from **188** to provide the *syn* aldol adduct **189** in 74% yield as a single observable diastereomer containing the other two new C38–C39 stereocentres. Adduct **189** was manipulated under different reaction conditions to obtain the desired methyl ketone **190**.



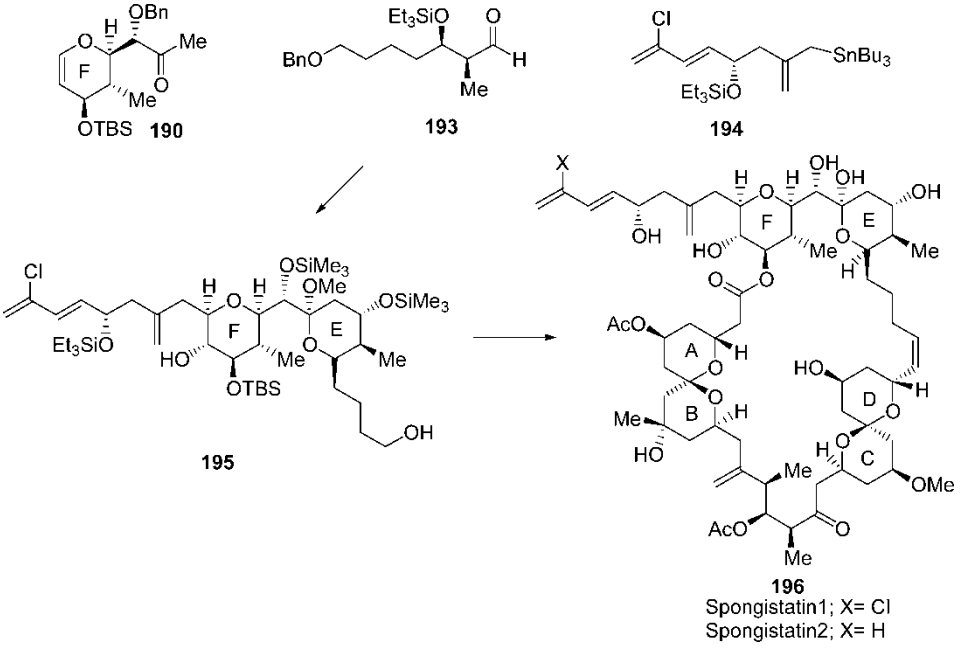
SCHEME 49 *i*) $TiCl_4$, (−)-sparteine, CH_2Cl_2, −78 °C to 0 °C, 3-butenal, *ii*) 1. *t*-$BuMe_2SiOTf$, 2,6-lutidine, 2. $LiBH_4$, MeOH, Et_2O, 3. Dess-Martin periodinane, *iii*) Bu_2BOTf, DIPEA, CH_2Cl_2, −78 °C.

The *N*-propionyl oxazolidinethione **166** was utilized for the generation of aldehyde **193** (scheme 50). The synthesis was achieved by condensation of aldehyde **191** with *N*-propionyl oxazolidinethione **166** under Crimmins' conditions to furnish the *syn* aldol adduct **192** in 85% yield and with high diastereoselectivity (98:2). Three subsequent reactions afforded the C29–C35 aldehyde **193**.



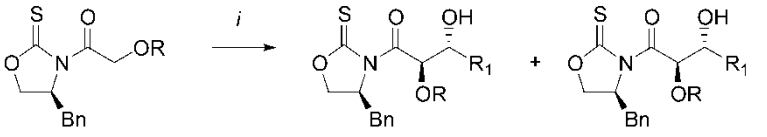
SCHEME 50 *i*) $TiCl_4$, (−)-sparteine, CH_2Cl_2, −78 °C to 0 °C.

The three subunits **190**, **193** and **194** were assembled to the desired EF fragment **195** of Spongistatin 1 **196** (scheme 51) [63]. The asymmetric total synthesis of Spongistatin 1 and 2 is described in reference 64.



SCHEME 51 Asymmetric synthesis of the fragment containing the E and F pyran rings.

3.2.3 Aldol addition reactions with chiral *N*-glycolyl oxazolidinethiones and their applications. A series of *N*-glycolyl oxazolidinethiones **197–199** (scheme 52) were treated with titanium (IV) chloride and (−)-sparteine [65]. Addition of an aldehyde, activated with additional titanium (IV) chloride, gave rise to the *anti* aldol adducts **200** and **201** in high yields and with high selectivities using a simple one-pot procedure. The degree of *anti* selection was highly dependent on the amount of $TiCl_4$ used to activate the aldehyde, where saturated aldehydes required >2 equiv of $TiCl_4$ and α,β-unsaturated aldehydes required >3 equiv of $TiCl_4$



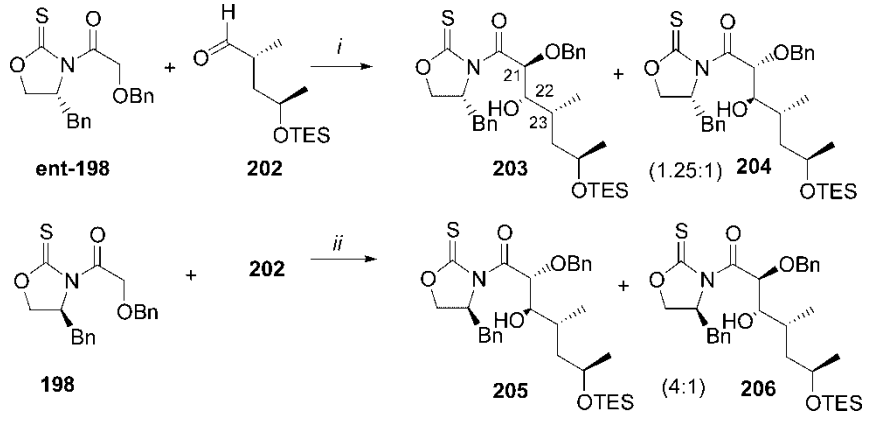
197 R=$CH_2CH{=}CH_2$
198 R=Bn
199 R=Me

	R_1CHO	**200:201**: *syn*	yield(%)
R= $CH_2CH{=}CH_2$	R_1= Me	94:6:0	84
	R_1 = *n*-Pr	*97:3*:0	74
	R_1 = *n*-C_5H_{11}	94:6:0	74
	R_1 = ^{i}Pr	87:13:0	61
	R_1 = $CH{=}CH_2$	95:5:0	58
	R_1 = $CH{=}CHCH_3$	73:23:4	56
	R_1= Ph	65:24:11	56
R= Bn	R_1= *n*-C_5H_{11}	88:12:0	64
	R_1 = $CH{=}CH_2$	74:26:0	48
R = Me	R1 = Me	86:4:10	62
	R1 = C_5H_{11}	84:11:5	63
	R1 = $CH{=}CH_2$	88:12:0	59

SCHEME 52 *i*) $TiCl_4$, (−)-sparteine, $TiCl_4$, R_1CHO.

for optimum results. Selective formation of the Evans *syn* diastereomer occurred upon addition of the free aldehyde to the enolate without prior activation.

Zhang *et al.* [66] demonstrated that there are several advantages of the Crimmins' aldol methodology such as: the use of $TiCl_4$ enables an easy formation of the titanium enolate and the flexibility imparted by Crimmins' chelated and nonchelated models is dependent on the amount of $TiCl_4$ and amine base used. These modifications provided access to both the Evans-*syn* aldol adduct via the nonchelated model and the non-Evans-*syn* adduct via the chelated model with high level of *syn*/*anti* selectivity. Zhang *et al.* applied the protocol of Crimmins for the construction of the subunit **208** within the cytotoxic macrolide B1 **209**. The first step was the condensation of aldehyde **202** with *N*-glycolyloxazolidinethione **ent-198** (scheme 53)

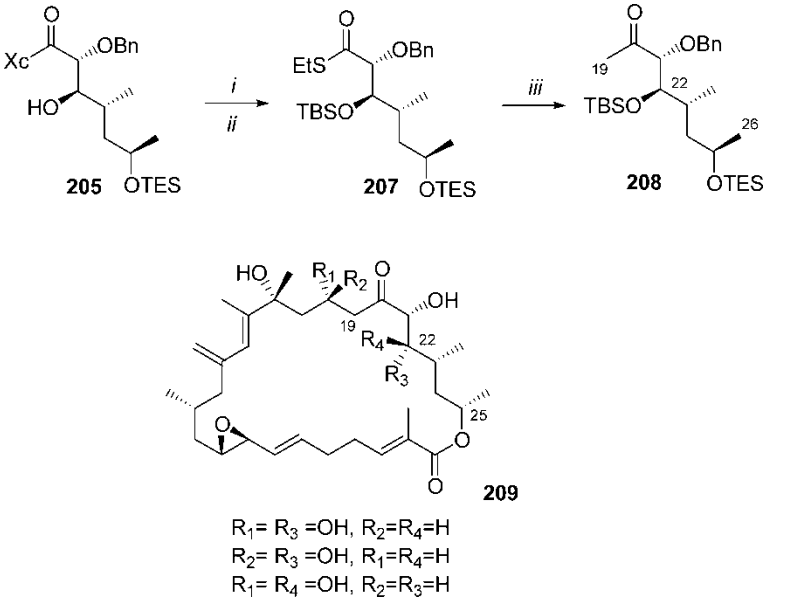


ent-198 **202** **203** **204**

SCHEME 53 *i*) $TiCl_4$ (1 equiv), (−)-sparteine (2.5 equiv), aldehyde **202**, CH_2Cl_2, −78 °C, *ii*) $TiCl_4$ (1 equiv), (−)-sparteine (1 equiv), aldehyde **202**, CH_2Cl_2, −78 °C.

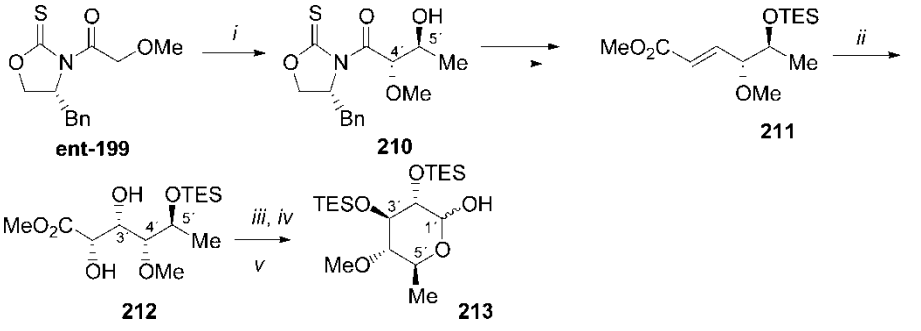
under the conditions for obtaining non-chelation or Evans-*syn* aldol adduct. This chemistry, however, provided unexpectedly the diastereomeric *anti* aldol adducts **203** and **204** in yields of 44% and 30%, respectively, and in a ratio 1.25:1. The *anti*-relationship was supported by the values of the vicinal coupling constant for **203** $H_{21} - H_{22} J = 9.3$ Hz and for **204** $H_{21} - H_{22} J = 8.4$ Hz. The addition of additives such as NMP or alternative bases (TMEDA) did not affect the observed stereochemical outcome. On the other hand, condensation of aldehyde **202** with *N*-glycolyloxazolidinethione **198** under chelation conditions provided the *anti* aldol adducts **205** and **206** with a diastereomeric ratio of 4:1 in low yields.

The aldol adduct **205** was converted to ketone **208** after hydroxyl protection and removal of the chiral auxiliary with a catalytic amount of KH (30 wt. % in mineral oil) and EtSH (3 equiv) to produce the thioester **207** in 89% yield. The thioester **207** was treated with Me_2CuLi to give the methyl ketone **208** [66] (scheme 54). The C19-C26 subunit forms part of the cytotoxic macrolide B1 **209**.



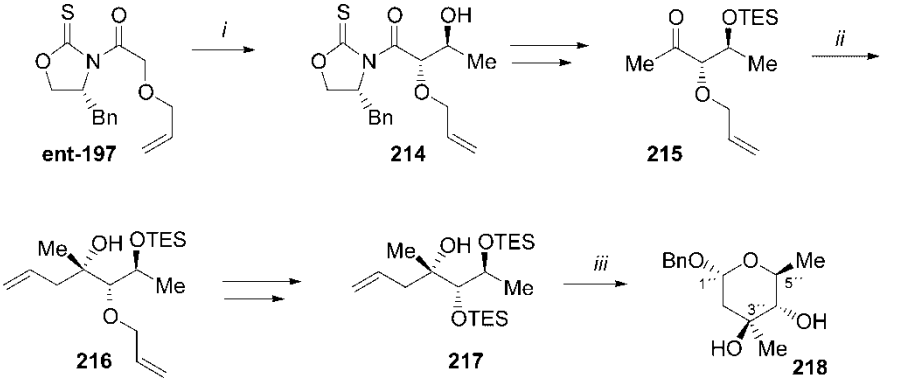
SCHEME 54 *i*) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, *ii*) KH (cat.), EtSH (3 equiv), THF, *iii*) Me_2CuLi, Et_2O, −50 °C.

Crimmins [67] described the enantioselective synthesis of the C9 and C27 sugar subunits **213** (scheme 55) and **225**, respectively, of the potent antitumor agent apoptolidin **226**. For the synthesis of 6′-deoxy-L-glucose **213**, the chlorotitanium enolate of *O*-methyl glycolyloxazolidinethione **ent-199** was treated with acetaldehyde in the presence of excess of $TiCl_4$ at −78 °C to provide the aldol adduct **210** as a 15:1 mixture of diastereomers (scheme 55). Subsequent recrystallization of the product provided the major *anti* diastereomer in 80% yield with the required stereochemistry at C4 and C5. Protection of the hydroxyl group of **210** was followed by reductive removal of the auxiliary and subsequent oxidation to the corresponding primary alcohol. The respective aldehyde intermediate was then treated under Horner-Wadsworth-Emmons' olefination conditions to deliver the **211**-olefin. The C2 and C3 stereocentres were incorporated by a Sharpless asymmetric dihydroxylation yielding a 7:1 mixture of the *syn* diols in 79% yield, with diol **212** as the mayor product. Cyclization and reduction reactions provided the hemiacetal **213** as a 5:1 mixture of anomers.



SCHEME 55 *i*) $TiCl_4$ (3 equiv), (−)-sparteine, CH_2Cl_2, −78 °C, CH_3CHO, *ii*) AD-Mix β, *t*-BuOH, H_2O, *iii*) *n*-Bu_4NF, THF, *iv*) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, *v*) $^{i}Bu_2AlH$, CH_2Cl_2.

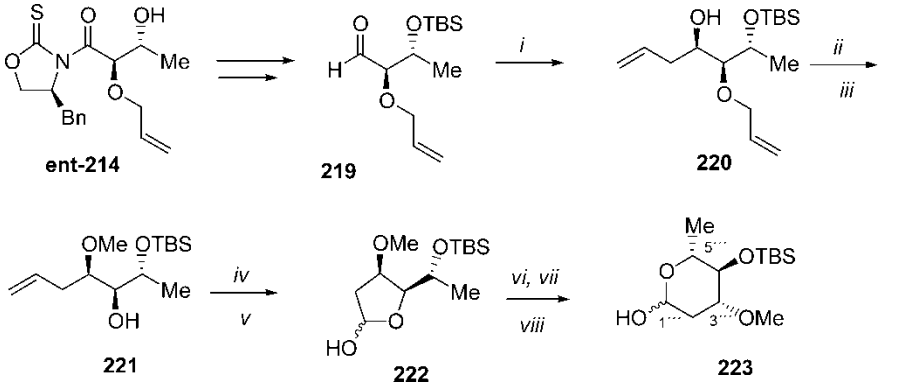
The preparation of the D-oleandrose derivative **218** (scheme 56) was carried out by enolization of *N*-acyl oxazolidinethione **ent-197** with $TiCl_4$ (3 equiv), (−)-sparteine and acetaldehyde to give the *anti* aldol adduct **214** in 90% yield and 13:1 dr. Aldol adduct **214** was then transformed to ketone **215** through the corresponding Weinreb amide, which was manipulated to obtain acetal **218**.



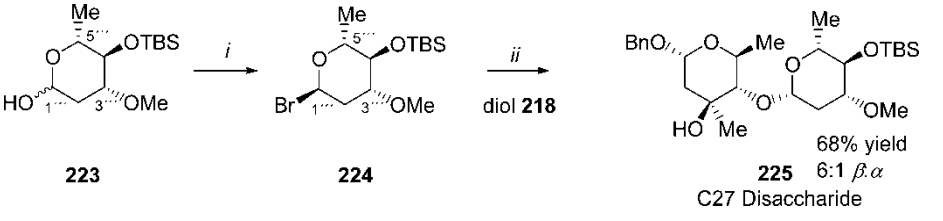
SCHEME 56 *i*) $TiCl_4$ (3 equiv), (−)-sparteine, CH_2Cl_2, −78 °C, CH_3CHO, *ii*) $CH_2CHCH_2SnBu_3$, $MgBr_2{-}OEt_2$, CH_2Cl_2, −78 °C to 25 °C, *iii*) 1. OsO_4, NMO, THF, H_2O, 2. $Pb(OAc)_2$, C_6H_6, 3. PPTS, BnOH, CH_2Cl_2, 4. *n*-Bu_4NF, THF.

The third sugar unit **223** (scheme 57) (an L-olivomycose derivative) was obtained by the condensation of acetaldehyde with the *N*-acyl oxazolidinethione **ent-214** under the same reaction conditions described above. Protection of the secondary hydroxyl group, reductive removal of the oxazolidinethione and oxidation of the primary alcohol under Swern conditions produced aldehyde **219** which was manipulated to obtain the six-membered ring acetal **223**.

The completion of the C27 disaccharide unit **225** (scheme 58) required a stereoselective glycosidation reaction between hemiacetal **223** as the glycosyl donor and sugar **218** as the glycosyl acceptor [67]. This reaction was carried out using a glycosidation reported by Binkley, transforming **223** to its glycosyl bromide **224**. An immediate treatment of the glycosyl bromide **224** with Ag_2O-silica gel in the presence of diol **218** produced the desired glycoside **225** as a 6:1 mixture of anomers with the β-anomer as the major isomer.

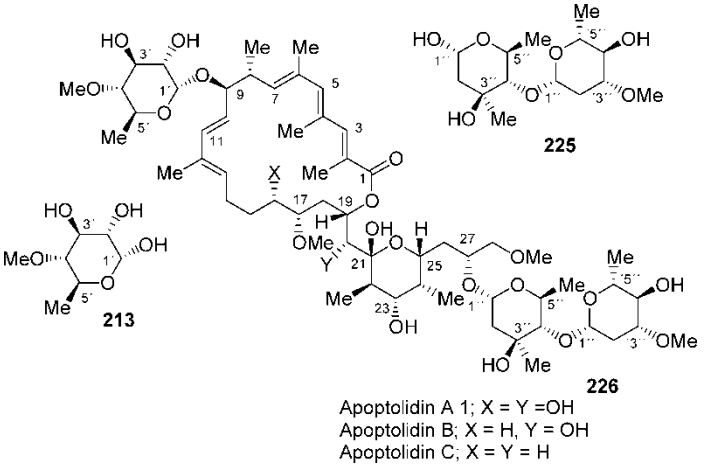


SCHEME 57 *i*) $CH_2CHCH_2SnBu_3$, $MgBr_2-OEt_2$, CH_2Cl_2, −78 °C to 25 °C, *ii*) Me_3OBF_4, proton sponge, CH_2Cl_2, *iii*) $Ti(O-^iPr)_4$, *n*-BuMgCl, THF, 0 °C, *iv*) OsO_4, NMO, THF, H_2O, *v*) $NaIO_4$, THF, H_2O, *vi*) *p*-TsOH, BnOH, *vii*) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, *viii*) H_2, Pd/C, EtOH.



SCHEME 58 Stereoselective glycosidation reaction. *i*) Me_3SiBr, C_6H_6, *ii*) Ag_2O-SiO_2, CH_2Cl_2, −78 °C.

The three monosaccharide subunits **213**, **218** and **223** of the potent antitumor agent, apoptolidin **226** (scheme 59), were synthesized using an asymmetric *anti* glycolate aldol as the critical step in the synthesis of each sugar.

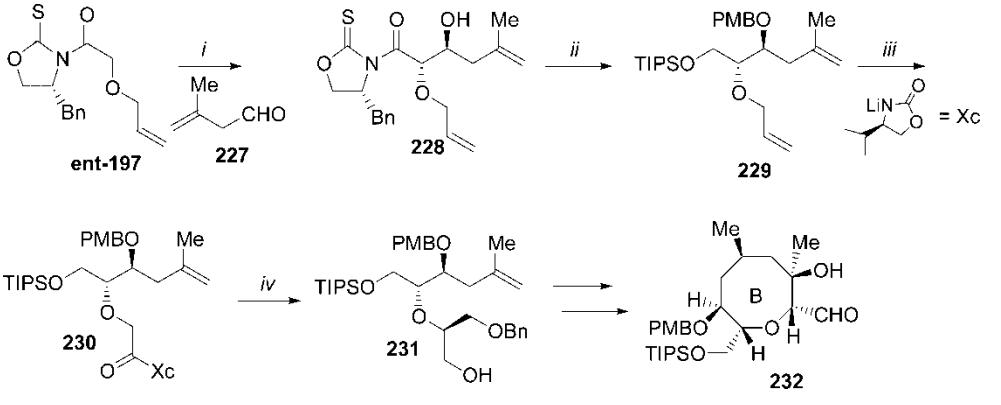


SCHEME 59 C9 and C27 sugar subunits **213** and **225** of the potent antitumor agent apoptolidin **226**.

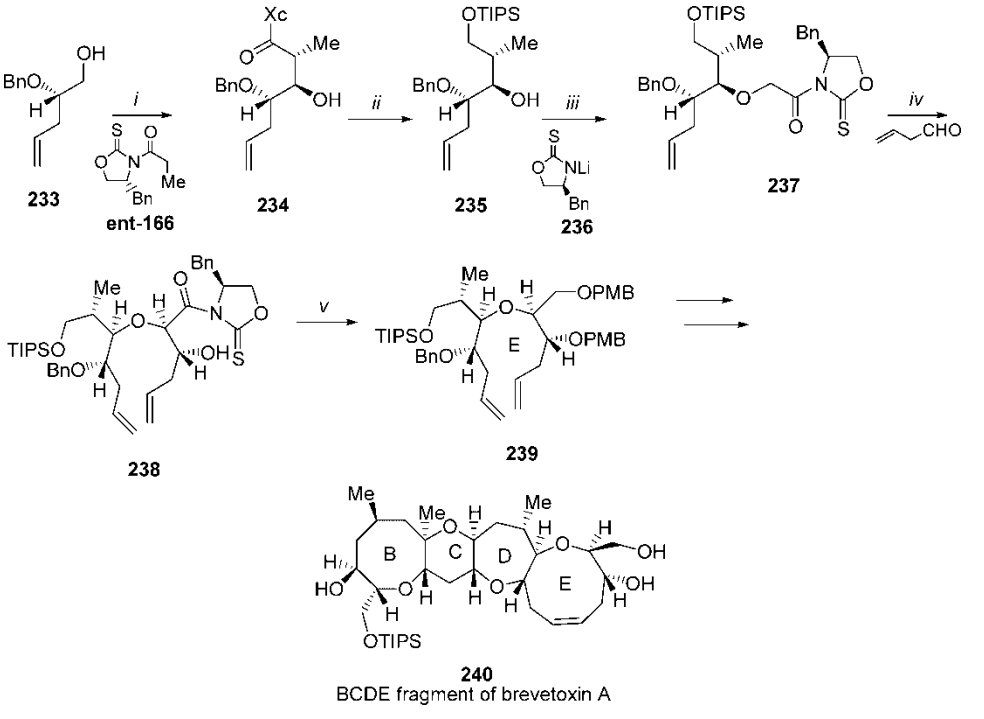
Crimmins [68] described a stereoselective synthesis of the BCDE fragment of Brevetoxin A **240**. For the BCDE fragment of brevetoxin A **240**, suitably functionalized B and E ring units were required to implement the planned assembly. Synthesis of the B ring **232** (scheme 60) commenced with an aldol addition of the chlorotitanium enolate of the *N*-acyl oxazolidinethione **ent-197** with 3-methyl-3-butenal **227** to provide the *anti* adduct **228** in 65% yield and 5:1 dr. Reductive removal of the chiral auxiliary followed by protection of hydroxyl group gave the allyl ether **229**. The allyl ether **229** was transformed to imide **230**, which was submitted to an asymmetric alkylation reaction with benzyl iodomethyl ether (prepared in *situ*) to provide a single diastereomer in 93% yield. The chiral auxiliary was removed by a reduction reaction with $LiBH_4$ to give the primary alcohol **231**. Subsequent manipulations of **231** afforded the desired aldehyde **232**.

For the synthesis of the E ring precursor of brevetoxin A [68], two aldol addition reactions were employed to achieve four stereogenic centres. The primary aldol addition was carried out with the alcohol **233** (scheme 61) which was transformed to its respective aldehyde. Condensation of this aldehyde with *N*-propionyl oxazolidinethione **ent-166** gave the Evans *syn* adduct **234** in high yield (92%) and with excellent diastereoselectivity (>98:2). The chiral auxiliary was removed by reduction with $LiBH_4$ and selective protection of the primary alcohol as the TIPS ether provided alcohol **235**. Alkylation of the secondary alcohol with sodium bromoacetate and coupling of the resultant acid to (*R*)-4-benzyl-2-oxazolidinethione **236** gave *N*-glycolyl oxazolidinethione **237**. Condensation of 3-butenal with **237** using $TiCl_4$ (3 equiv) and (−)-sparteine in CH_2Cl_2 provided the *anti* aldol adduct **238** in modest yield (50%) and with modest diastereoselectivity of 5:1. This complex system provided the diene **239** precursor of the E ring. Subsequent transformations afforded the enantioselective synthesis of the BCDE fragment **240** of brevetoxin A.

In a recent communication [69], Crimmins and Ellis reported the enantioselective total synthesis of 11-acetoxy-4-deoxyasbestinin D **247** (scheme 62). The tetracyclic framework of 11-acetoxy-4-deoxyasbestinin D **247** includes nine contiguous stereocentres in a fully substituted tetrahydrofuran. The synthesis of the oxonene core began with the addition of isoprenylmagnesium bromide to (*R*)-benzyl glycidyl ether **241** to afford a secondary alcohol, which was *O*-alkylated with sodium bromoacetate. The resultant glycolic acid **242** was coupled with (*S*)-4-benzyloxazolidinethione **10** to provide *N*-glycolyl oxazolidinethione



SCHEME 60 *i*) $TiCl_4$ (>3 equiv), (−)-sparteine, CH_2Cl_2, −78 °C, *ii*) 1. $LiBH_4$, Et_2O, MeOH, 2. $^iPr_3SiCl$, imidazole, DMF, 3. PMBBr, NaH, DMF, *iii*) 1. $Ti(O{-}^iPr)_4$, BuMgCl, Et_2O, 0 °C, 2. NaH, $BrCH_2CO_2H$, THF, DMF, 3. Me_3CCOCl, Et_3N, THF, −78 °C, *iv*) 1. $NaN(SiMe_3)_2$, THF, $(BnO)_2CH_2$, TMSI, −78 °C, 2. $LiBH_4$, MeOH, Et_2O.

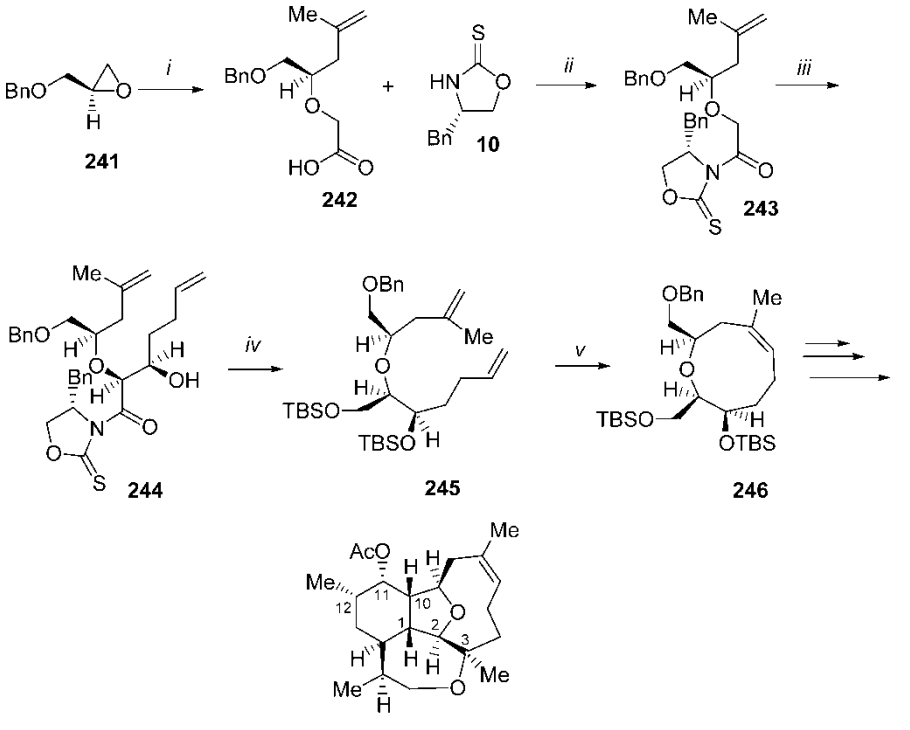


SCHEME 61 *i*) 1. $(COCl)_2$, DMSO, Et_3N, 2. $TiCl_4$ (>3 equiv), (−)-sparteine, NMP, *ii*) 1.$LiBH_4$, MeOH, Et_2O, 2. $^iPr_3SiCl$, imidazole, CH_2Cl_2, *iii*) $BrCH_2CO_2H$, NaH, 2. Me_3CCOCl, Et_3N, THF −78 °C to 0 °C, *iv*) $TiCl_4$ (3 equiv), (−)-sparteine, CH_2Cl_2, −78 °C, *v*) 1. $LiBH_4$, MeOH, Et_2O, 2. Na, naphthalene, THF, 3. NaH, PMBBr, DMF.

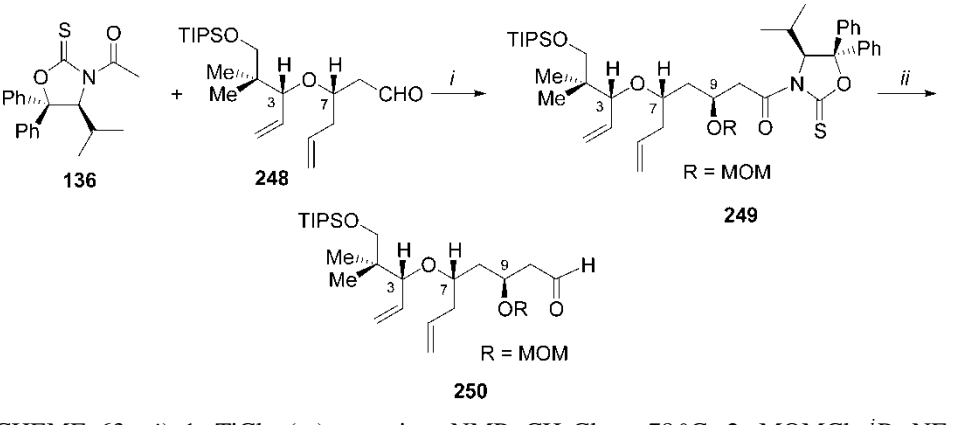
243. Condensation of 4-pentenal with the chlorotitanium enolate of oxazolidinethione **243** in the presence of NMP gave *syn*-aldol adduct **244** in 70% yield (>95:5 dr). The chiral auxiliary was removed by reduction with $LiBH_4$ and the protection of the diol afforded diene **245**, which was treated with Grubbs' catalyst leading to the formation of oxonene **246** in 99% yield. Subsequent manipulations of **246** provided the desired natural product **247**.

In a more recent communication [70], Crimmins and Vanier described a stereoselective synthesis for SCH 351448 **256**. In this synthesis, two aldol condensation reactions were employed using two different oxazolidinethiones to achieve the C9, C11 and C12 stereocentres, respectively. The primary aldol addition was carried out combining the Phillips *N*-acetyl oxazolidinethione **136** with aldehyde **248** (scheme 63). Immediate protection of the alcohol of the aldol adduct as its MOM ether gave the imide **249** in 84% yield in two steps with 10:1 dr. The C1-C11 fragment was completed by reductive removal of the auxiliary and subsequent oxidation of the alcohol under Swern conditions to provide aldehyde **250** in good yield.

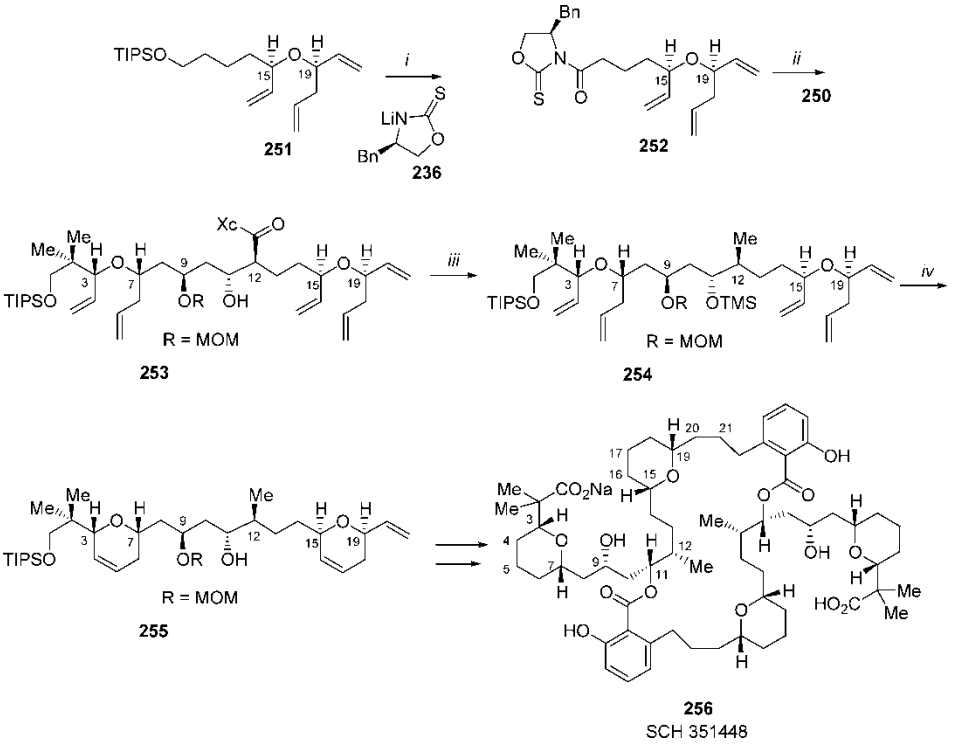
The second aldol addition was carried out with excellent stereocontrol through a diastereoselective *syn* aldol addition between the chlorotitanium enolate of thioimide **252** (scheme 64) and aldehyde **250** using $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2 to give rise to the *syn*-aldol adduct **253** in 81% yield and with 15:1 dr. The aldol adduct **253** was protected as the TMS ether, followed by the removal of the chiral auxiliary by reduction with $NaBH_4$ to give a primary alcohol which was deoxygenated by conversion to its mesylate. Reduction with $LiEt_3BH$ gave the desired C1–C20 fragment **254**. Silyl ether **254** was converted to the alcohol by removal of the TMS ether with mild acid



SCHEME 62 *i*) 1. $CH_2{=}C(CH_3)MgBr$, CuI, THF, −40 °C, 2. NaH, $BrCH_2CO_2H$, THF, DMF, *ii*) DCC, DMAP, CH_2Cl_2, *iii*) $TiCl_4$ (>3 equiv), $^{i}PrNEt_2$, NMP, 4-pentenal, CH_2Cl_2, −78 °C, *iv*) 1. $LiBH_4$, MeOH, Et_2O, 0 °C, 2. TBSCl, imidazole, DMAP, DMF, 50 °C, *v*) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C.



SCHEME 63 *i*) 1. $TiCl_4$ (−)-sparteine, NMP, CH_2Cl_2, −78 °C, 2. MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, *ii*) 1. $LiBH_4$, MeOH, Et_2O, 2. $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.

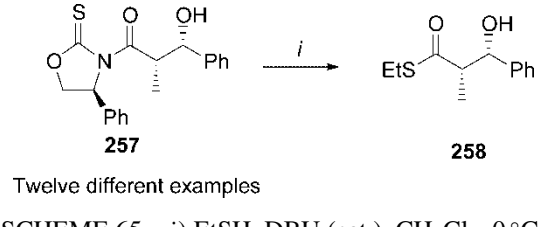


SCHEME 64 *i*) 1 *n*-Bu_4NF, THF, 2. H_2CrO_4, acetone, 3. $(COCl)_2$, DMF, CH_2Cl_2, *ii*) $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, −78 °C, *iii*) 1. TMSCl, Et_3N, DMPA, CH_2Cl_2, 2. $NaBH_4$, THF, H_2O, 3. MsCl, Et_3N, CH_2Cl_2, 4. $LiEt_3BH$, THF, *iv*) 1. PPTS, MeOH, 0 °C, 2. $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C.

and the polyene was exposed to Grubbs' catalyst to produce the bishydropyran **255**. Subsequent reactions afforded the desired enantioselective total synthesis of (+)-SCH 351448 **256** [70].

4. Cleavage of the chiral auxiliary

Wu and co-workers [71] described a novel very mild and convenient procedure for the removal of the chiral auxiliary in *N*-acyl-β-hydroxy-4-phenyl-oxazolidinethione **257** to provide the



SCHEME 65 *i*) EtSH, DBU (cat.), CH_2Cl_2, 0 °C.

corresponding ethyl thioester **258** in high yield, using a treatment with EtSH in the presence of a catalytic amount of DBU (scheme 65). Thioesters are more reactive than the corresponding carbon esters. They can be converted into esters by treatment with an alcohol in the presence of NBS or $Ag(OCOCF_3)$, or reduced to aldehydes with DIBAL-H or Me_2SiH_2/Pd-C. Thioesters can also be reduced to alcohols with $NaBH_4$ or transformed to ketones through reactions with organo-zinc, copper or boron reagents in the presence of a proper palladium catalyst.

5. Conclusion

In summary, chiral oxazolidinethiones demonstrate interesting rearrangement reactions. Furthermore, the oxazolidinethione moiety can be applied as a chiral auxiliary and nucleophile thiolate carrier molecule. The homologous chiral oxazolidinones have not shown these types of rearrangements. Chiral oxazolidinethiones have been widely employed as efficient chiral auxiliaries in asymmetric aldol addition reactions. These reactions have been improved using *N*-acetyl, *N*-propionyl and *N*-glycolyl oxazolidinethiones to obtain *syn*- and *anti*-adducts, used in the stereoselective total syntheses of a wide variety of natural products. The interest of oxazolidinethiones as chiral auxiliaries has led to trisubstituted oxazolidinethiones with bulky substituents. In spite of this there are many relevant contributions with oxazolidinethiones, and it is expected that their asymmetric reactions will be more explored. In this spirit, we hope that our timely review will stimulate chemists to become active in this fascinating and challenging research field of sulfur chemistry.

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References

[1] G.A. Youngdale, G.W. Duncan, D.E. Emmert, D. Lednicer. *J. Med. Chem.*, **9**, 155 (1966).
[2] D. Lednicer, D.E. Emmert. *J. Med. Chem.*, **11**, 1258 (1968).
[3] G.A. Johnson, E.G. Kim, S.J. Boukma, D. Lednicer, G.A. Youngdale. *J. Med. Chem.*, **15**, 327 (1972).
[4] F. Velázquez, H.F. Olivo. *Curr. Org. Chem.*, **6**, 303 (2002).
[5] M.J. McMKennon, A.I. Meyers. *J. Org. Chem.*, **58**, 3568 (1993).
[6] M.G. Ettlinger. *J. Am. Chem. Soc.*, **72**, 4792 (1950).
[7] Y. Nagao, T. Kumagai, S. Yamada, E. Fujita. *J. Chem. Soc. Perkin Trans.* I, 2361 (1985).
[8] D. Delaunay, L. Toupet, M. Le Corre. *J. Org. Chem.*, **60**, 6604 (1995).
[9] M. Moreno-Mãnas, I. Prados. *J. Heterocyclic. Chem.*, **30**, 1235 (1993).
[10] A. Ortiz, L. Quintero, H. Hernández, S. Maldonado, G. Mendoza, S. Bernès. *Tetrahedron Lett.*, **44**, 1129 (2003).
[11] G. Mendoza, H. Hernández, L. Quintero, M.S. Rivadeneyra, S. Bernès, E. Sansinenea, A. Ortiz. *Tetrahedron Lett.*, **46**, 7867 (2005).
[12] N.R. Guz, A.J. Phillips. *Org. Lett.*, **4**, 2253 (2002).
[13] G. Jalce, M. Seck, X. Franck, R. Hocquemiller, B. Frigadère. *J. Org. Chem.*, **69**, 3240 (2004).
[14] C. Palomo, M. Oiarbide, F. Dias, A. Ortiz, A. Linden. *J. Am. Chem. Soc.*, **123**, 5602 (2001).
[15] T.-H. Yan, C.-W. Tan, H.-C. Lee, H.-C. Lo, T.-Y. Huang. *J. Am. Chem. Soc.*, **115**, 2613 (1993).
[16] Y. Zhang, A.J. Phillips, T. Sammakia. *Org. Lett.*, **6**, 23 (2004).
[17] J.E. Hein, L.M. Geary, A.A. Jaworski, P.G. Hultin. *J. Org. Chem.*, **70**, 9940 (2005).
[18] C.-N. Hsiao, L. Liu, M.J. Miller. *J. Org. Chem.*, **52**, 2201 (1987).
[19] A.I. Meyers, M.E. Ford. *J. Org. Chem.*, **41**, 1735 (1976).
[20] M.T. Crimmins, B.W. King, E.A. Tabet, K. Chaudhary. *J. Org. Chem.*, **66**, 894 (2001).
[21] G. Li, T. Ohtani. *Heterocycles*, **45**, 2471 (1997).

[22] G. Li, H. Tajima, T. Ohtani. *J. Org. Chem.*, **62**, 4539 (1997).
[23] C. Palomo, M. Oiarbide, F. Dias, R. López, A. Linden. *Angew. Chem. Int. Ed.*, **43**, 3307 (2004).
[24] Y. Wu, Y.-Q. Yang, Q. Hu. *J. Org. Chem.*, **69**, 3990 (2004).
[25] T. Hirao, A. Yamada, K.-I. Hayashi, Y. Ohshiro, T. Agawa. *Bull. Chem. Soc. Jpn.*, **55**, 1163 (1982).
[26] D.A. Evans, A.E. Weber. *J. Am. Chem. Soc.*, **108**, 6757 (1986).
[27] J.M. García Fernández, C. Ortiz Mellet, J. Fuentes. *Tetrahedron Lett.*, **33**, 3931 (1992).
[28] J.M. García Fernández, C. Ortiz Mellet, J. Fuentes. *J. Org. Chem.*, **58**, 5192 (1993).
[29] J. Girniene, D. Gueyrard, A. Tatibouët, A. Sackus, P. Rollin. *Tetrahedron Lett.*, **42**, 2977 (2001).
[30] A. Tatibouët, S. Lawrence, P. Rollin, G.D. Holman. *SYNLETT*, **11**, 1945 (2004).
[31] A. Tatibouët, A.C. Simao, P. Rollin. *Lett. Org. Chem.*, **2**, 47 (2005).
[32] J. Girniene, G. Apremont, A. Tatibouët, A. Sackus, P. Rollin. *Tetrahedron*, **60**, 2609 (2004).
[33] J. Girniene, A. Tatibouët, A. Sackus, J. Yang, G.D. Holman, P. Rollin. *Carbohydr. Res.*, **338**, 711 (2003).
[34] N. Leconte, S. Silva, A. Tatibouët, A.P. Rauter, P. Rollin. *SYNLETT*, **2**, 301 (2006).
[35] O. Leoni, R. Bernardi, D. Gueyrard, P. Rollin, S. Palmieri. *Tetrahedron Asymmetry*, **10**, 4775 (1999).
[36] S. Galletti,. R. Bernardi, O. Leoni, P. Rollin, S. Palmieri. *J. Agric. Food Chem.*, **49**, 471 (2001).
[37] C.G. Tsiafoulis, M.I. Prodromidis, M.I. Karayannis. *Anal. Chem.*, **75**, 927 (2003).
[38] L. Lazzeri, G. Curto, O. Leoni, E. Dallavalle. *J. Agric. Food Chem.*, **52**, 6703 (2004).
[39] O. Leoni, C. Marot, P. Rollin, S. Palmieri. *Tetrahedron Asymmetry*, **5**, 1157 (1994).
[40] D. Gueyrard, V. Grumel, O. Leoni, S. Palmieri, P. Rollin. *Heterocycles*, **52**, 827 (2000).
[41] W. Adam, R.M. Bargon. *Chem. Rev.*, **104**, 251 (2004).
[42] D. Gueyrard, O. Leoni, S. Palmieri, P. Rollin. *Tetrahedron Asymmetry*, **12**, 337 (2001).
[43] M. Adamczyk, P.G. Mattingly, Y. Pan. *Tetrahedron Lett.*, **36**, 5303 (1995).
[44] A. Ortiz, L. Quintero, G. Mendoza, S. Bernés. *Tetrahedron Lett.*, **44**, 5053 (2003).
[45] T. Kataoka, H. Kinoshita, S. Kinoshita, T. Osamura, S. Watanabe, T. Iwamura, O. Muraoka, G. Tanabe. *Angew. Chem. Int. Ed.*, **42**, 2889 (2003).
[46] A. Ortiz, H. Hernández, G. Mendoza, L. Quintero, S. Bernés. *Tetrahedron Lett.*, **46**, 2243 (2005).
[47] H. Kinoshita, N. Takahashi, T. Iwamura, S-I, Watanabe, T. Kataoka, O. Muraoka, G. Tanabe. *Tetrahedron Lett.*, **46**, 7155 (2005).
[48] M.V. Lakshmikantham, W. Chen, M.P. Cava. *J. Org. Chem.*, **54**, 4746 (1989).
[49] H. Hernández, S. Bernès, L. Quintero, E. Sansinenea, A. Ortiz. *Tetrahedron Lett.*, **47**, 1153 (2006).
[50] J. Girniene, S. Tardy, A. Tatibouët, A. Sackus, P. Rollin. *Tetrahedron Lett.*, **45**, 6443 (2004).
[51] S. Tardy, A. Tatibouët, P. Rollin, G. Dujardin. *SYNLETT*, **9**, 1425 (2006).
[52] D.A. Evans, T. Lectka, S.J. Miller. *Tetrahedron Lett.*, **44**, 7027 (1993).
[53] Y.-C. Wang, D.-W. Su, C.-M. Lin, H.-L. Tseng, C.-L. Li, T.-H. Yan. *Tetrahedron Lett.*, **40**, 3577 (1999).
[54] Y.-C. Wang, D.-W. Su, C.-M. Lin, H.-L. Tseng, C.-L., Li, T.-H. Yan. *J. Org. Chem.*, **64**, 6495 (1999).
[55] Y.-C. Wang, T.-H. Yan. *J. Org. Chem.*, **65**, 6752 (2000).
[56] Y. Chen, C. Cambs, Y. Abe, P. Wentworth, Jr., K.D. Janda. *J. Org. Chem.*, **68**, 8902 (2003).
[57] M.T. Crimmins, A.C. DeBaillie. *Org. Lett.*, **5**, 3009 (2003).
[58] F. Kazmierczak, P. Helquist. *J. Org. Chem.*, **54**, 3988 (1989).
[59] G. Hughes, M. Lautens, C. Wen. *Org. Lett.*, **2**, 107 (2000).
[60] G.A. Sulikowski, W.-M. Lee, B. Jin, B. Wu. *Org. Lett.*, **2**, 1439 (2000).
[61] T.K. Chakraborty, S. Jayaprakash, P. Laxman. *Tetrahedron*, **57**, 9461 (2001).
[62] M.T. Crimmins, J. She. S*ynlett*, **8**, 1371 (2004).
[63] M.T. Crimmins, J.D. Katz, L.C. McAtee, E.A. Tabet, S.J. Kirincich. *Org. Lett.*, **3**, 949 (2001).
[64] M.T. Crimmins, J.D. Katz, D.G. Washburn, S.P. Allwein, L.F. McAtee. *J. Am. Chem. Soc.*, **124**, 5661 (2002).
[65] M.T. Crimmins, P.J. McDougall. *Org. Lett.*, **5**, 591 (2003).
[66] W. Zhang, R.G. Carter, A.F.T. Yokochi. *J. Org. Chem.*, **69**, 2569 (2004).
[67] M.T. Crimmins, A. Long. *Org. Lett.*, **7**, 4157 (2005).
[68] M.T. Crimmins, P.J. McDougall, K.A. Emmitte. *Org. Lett.*, **7**, 4033 (2005).
[69] M.T. Crimmins, J.M. Ellis. *J. Am. Chem. Soc.*, **127**, 17200 (2005).
[70] M.T. Crimmins, G.S. Vanier. *Org. Lett.*, **8**, 2887 (2006).
[71] Y. Wu, Q. Hu, Y.-P. Sun,Y.-Q. Yang. *Tetrahedron Lett.*, **45**, 7715 (2004).