CHEMICAL REVIEWS

REVIEW

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Synthetic Routes to Chiral Nonracemic and Racemic Dihydro- And Tetrahydrothiophenes

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1. INTRODUCTION

Natural and man-made organosulfur compounds play important roles in biological and medicinal chemistry.[1] Among the various classes of organic sulfur compounds, dihydro- and especially tetrahydrothiophenes have attracted particular attention because of the widespread occurrence as ring system motifs in natural and non-natural products displaying a broad spectrum of biological activities.

Tetrahydrothiophene-based compounds include the essential coenzyme biotin **1**, a water-soluble vitamin involved in important biological functions,[2] and the potent α-glucosidase inhibitors salacinol **2**[3−6] and kotalanol **3**,[7] isolated from several *Salacia* plant species. Recently, the related compounds salaprinol **4** and ponkoranol **5** were isolated from *Salacia prinoides*,[8,9] and significant efforts to prepare these cyclic sulfonium salts and synthetic analogues,[10] including **6**[11] and **7**,[12] have been made in the past few years (Figure 1).

Further representative compounds are the 4′-thioadenosine derivative **8**, a highly potent and selective A_3 adenosine receptor antagonist;[13] the 4′-thiocytidine nucleoside **9**, active against HSV-1 and HSV-2;[14] the cholecystokinin type-B receptor antagonist tetronothiodin **10**;[15] and (*R*)-tetrahydrothiophen-3-ol **11**,[16−18] a pivotal intermediate to obtain the potent antibacterial Sulopenem **12**[16] (Figure 2).

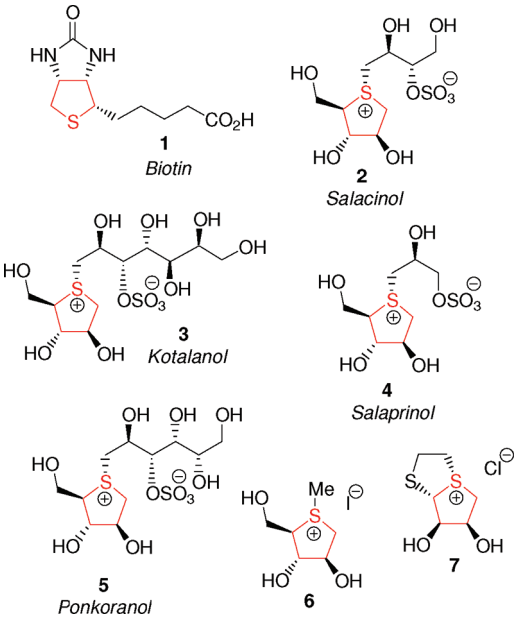

Figure 1.

The field of applications of tetrahydrothiophenes is impressively wide in scope: these compounds have been employed as templates to assist and control various chemical transformations, including asymmetric hydrogenation,[19] catalytic asymmetric epoxidation,[20] and catalytic intramolecular cyclopropanation.[21] Moreover, adsorption of tetrahydrothiophene on gold has emerged as a powerful tool to obtain self-assembled monolayers (SAMs), which can be used to control physical and chemical properties of surfaces for various technological purposes.[22]

The dihydrothiophene ring system is a common structural feature of many bioactive compounds, some of which are shown in Figure 3. In particular, (*S*)-ethyl 4-amino-4,5-dihydrothiophene-2-carboxylate **13**[23] inhibits copper amine oxidases (CAOs), the unnatural L-nucleoside **14** displays potent anti-HIV activity without significant toxicity,[24] and 4,5-dihydrothiophene-3-carbonitrile **15**[25] exhibits antibacterial and antifungal properties. Interestingly, it has been demonstrated that calicheamicin becomes active

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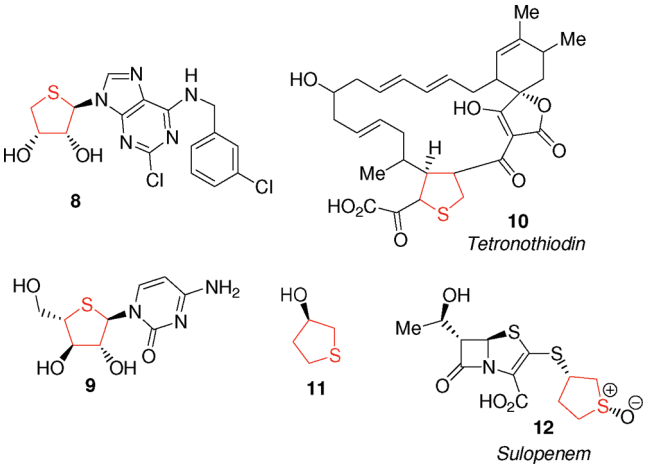


Figure 2.

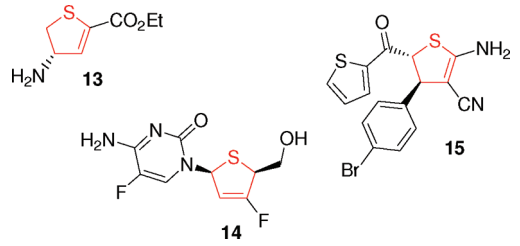


Figure 3.

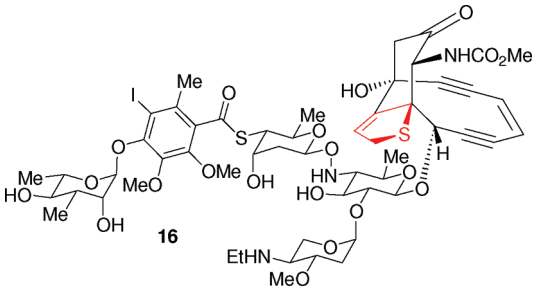


Figure 4.

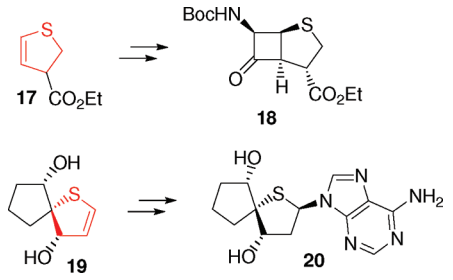


Figure 5.

once it is converted into the triggered form **16** (Figure 4), the dihydrothiophene heterocycle contributing to the overall calicheamicin activation for DNA cleavage.[26]

On the other hand, dihydrothiophene compounds have proven to be versatile intermediates for synthetic applications. For example, 2,3-dihydrothiophene **17**[27] was conveniently used to obtain the penicillin analogue **18**, whereas **19**[28] served as synthon for an enantioselective approach to 2′-deoxy-4′-thiaspirocyclic nucleosides, such as **20** (Figure 5).

However, despite the importance of dihydro- and tetrahydrothiophene scaffolds and the high benefits in a variety of applications, few methods for their asymmetric synthesis have been reported, and only over the past decade has this topic emerged as an important research area. Asymmetric organosulfur chemistry has been reviewed almost exclusively in connection with sulfur species with chirality at sulfur,[29] with particular regard to sulfoxides.[30]

This review will provide a comprehensive survey of the methods available for the asymmetric synthesis of dihydro- and tetrahydrothiophene compounds with chirality at carbon that have been published since the 1990s up to present, also updating the important contributions to the field given by De Clercq[31] and Seki[32] through their overviews of the synthetic approaches to biotin.

The synthetic routes to chiral nonracemic dihydro- and tetrahydrothiophenes have been divided according to the way the asymmetry has been introduced. Thus, chiral auxiliary-assisted approaches are discussed in section 2.1, whereas examples of syntheses using chiral pool and alternative enantiopure sources are discussed in section 2.2. Asymmetric organocatalytic transformations are covered in section 2.3, whereas section 2.4 is dedicated to desymmetrization routes. Moreover, the final section 3, containing a selection of the most recent approaches to racemic dihydro- and tetrahydrothiophenes, also has been included owing to the lack of recent reviews on this topic.

2. SYNTHESIS OF CHIRAL NONRACEMIC DIHYDRO- AND TETRAHYDROTHIOPHENES

The asymmetric synthesis of dihydro- and tetrahydrothiophenes represents a flourishing area in organic synthesis, as documented by the enourmous number of publications that have appeared in the last 20 years. In this context, chiral nonracemic dihydro- and tetrahydrothiophenes have been obtained either from chiral auxiliaries and chiral synthons or by application of organocatalytic and desymmetrization processes.

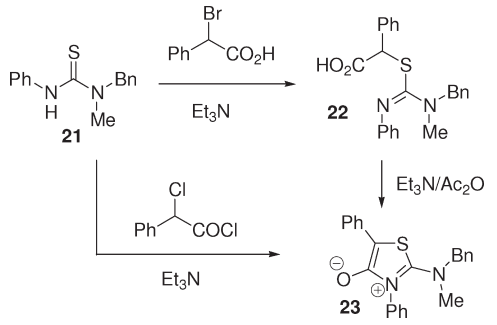
2.1. Chiral Auxiliary-Assisted Approaches

The use of chiral auxiliaries for the preparation of enantiomerically pure compounds has found wide application for a variety of reactions over the last four decades.[33] This strategy has been successfully utilized for the preparation of chiral dihydro- and tetrahydrothiophene compounds, with asymmetry being introduced through the use of carbohydrates, camphorsultams, menthyl derivatives, and 1-phenylethylamine as auxiliaries.

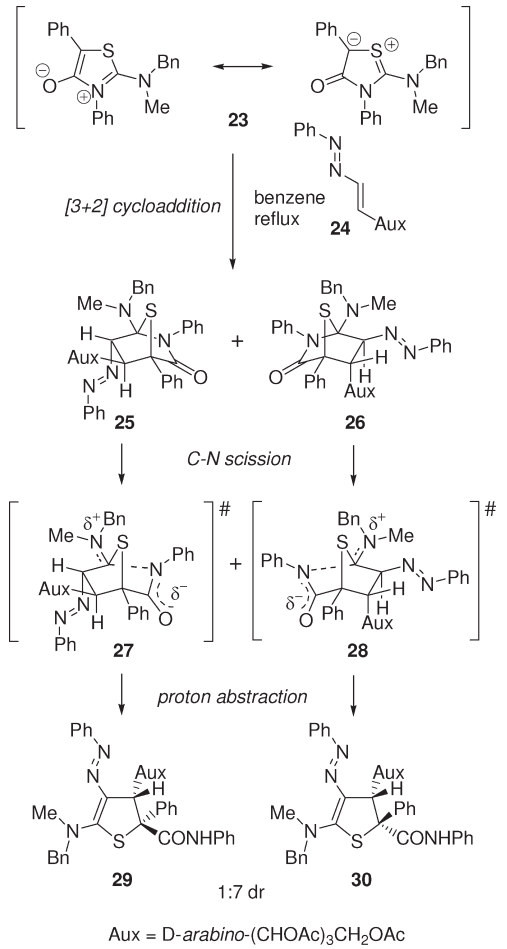
The 1,3-dipolar cycloaddition reaction between achiral sulfur-containing 1,3-dipoles and dipolarophiles with embedded carbohydrate or camphorsultam auxiliaries has emerged as a powerful tool for preparing either dihydro- or tetrahydrothiophene chiral derivatives in a stereoselective fashion. In this context, thioisomünchnones, 1,3-dipoles containing a thiocarbonyl ylide within their backbone,[34] have been successfully utilized for the construction of dihydrothiophene scaffolds.

Thus, triethylamine-promoted reaction of α-bromophenylacetic acid with *N,N,N′*-trisubstituted thiourea **21** gave rise to the intermediate **22**, which underwent cyclodehydration in the presence of the Et_3N/Ac_2O system, producing thioisomünchnone **23**. The same compound also could be obtained by reaction of thiourea

Scheme 1

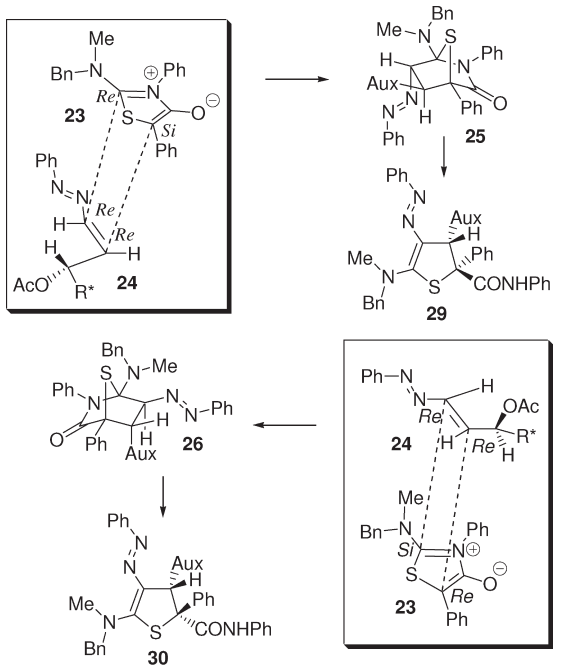


Scheme 2



Aux = D-*arabino*-$(CHOAc)_3CH_2OAc$

Scheme 3



Aux = D-*arabino*-$(CHOAc)_3CH_2OAc$
R* = D-*erythro*-$(CHOAc)_2CH_2OAc$

21 with α-chlorophenylacetic acid chloride in the presence of Et_3N (Scheme 1).

Model studies indicated that mesoionic compound **23** could react with several electrophilic alkenes, such as *trans*-β-nitrostyrene,[35−37] acrylonitrile, and methyl vinyl ketone,[38] to provide transient cycloadducts progenitors of dihydrothiophene compounds. The asymmetric version of this methodology was achieved by reaction of **23** with chiral nitroalkenes[35−37] and 1,2-diaza-1,3-butadienes[39−41] derived from carbohydrates.

For example, as shown in Scheme 2, heating a benzene solution of **23** in the presence of 1,2-diaza-1,3-butadiene **24** bearing an acyclic carbon chain of D-arabino configuration produced a 1:7 diastereomeric mixture of 4,5-dihydrothiophenes **29** and **30** via nonisolated cycloadducts **25** and **26**.[39] Compounds **29** and **30** were recovered by a combination of crystallization and chromatographic techniques in 6% and 88% yields, respectively, with their structures being unambiguously assigned by X-ray diffractometry.

The formation of **29** and **30** has been explained assuming that the initially formed cycloadducts **25** and **26** underwent C−N bond cleavage leading to zwitterionic-like intermediates **27** and **28**, which collapsed to the dihydrothiophene products by a rapid inter- or intramolecular proton abstraction. The stereochemical outcome of the whole process is likely to be controlled by the [3 + 2]-cycloaddition step (Scheme 3).

Thus, in compounds **29** and **30** the (*R*)-configuration of the carbon β to the sulfur atom results from the regioselective approach of the mesoionic compound **23** to the less hindered *Re*,*Re* face of **24**, whereas the prevalent (*R*)-configuration at the carbon α arises from preferential formation of the cycloadduct **26** with the exo-oriented azo group. Similar results have been obtained by using differently substituted mesoionic compounds and 1,2-diaza-1,3-butadiene partners, leading to the formation of dihydrothiophenes **31**−**38** as the major products in good yields (Figure 6).

Karlsson and Högberg[42] established 1,3-dipolar cycloaddition of a sulfur-containing 1,3-dipole and α,β-unsaturated camphorsultam amides as a convenient tool for the synthesis of *trans*-3,4-disubstituted tetrahydrothiophenes in high yields and high diastereomeric ratios (up to 90:10), as illustrated in Scheme 4 for a selected example.

Thus, *trans*-cinnamoyl amide **41**, prepared by *N*-acylation of camphorsultam **39** with acryloyl chloride **40**, reacted as dipolarophile with in situ formed **43**, leading to diastereomeric tetrahydrothiophene compounds **44** and **45** (95% yield, 90:10 diastereomeric ratio (dr)),

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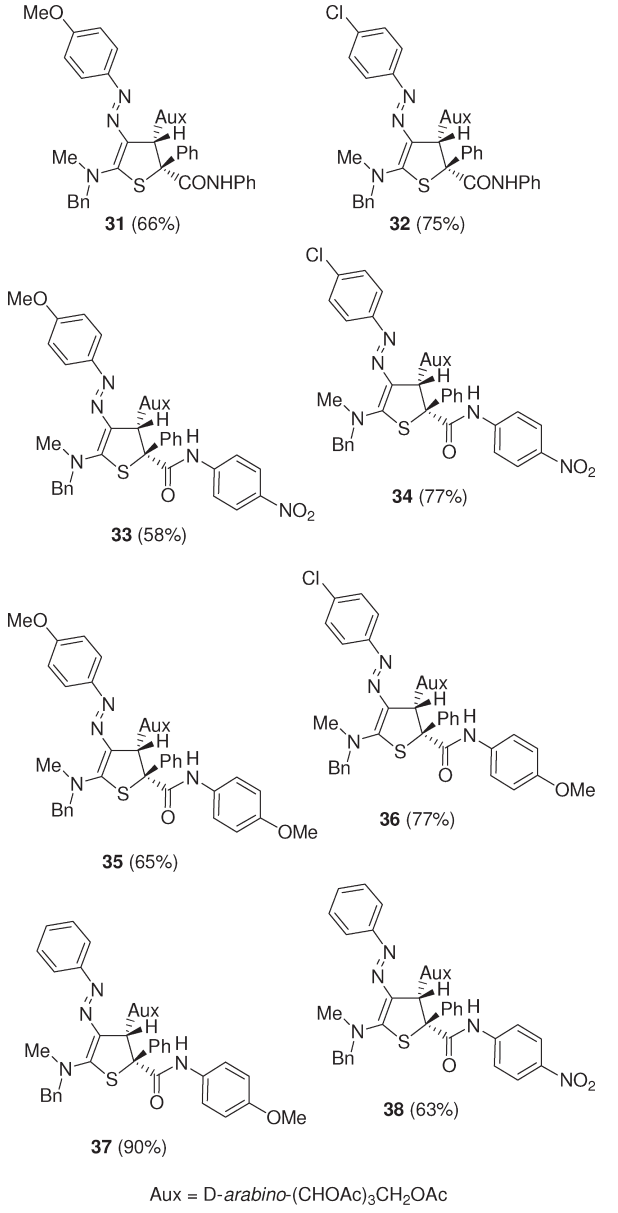


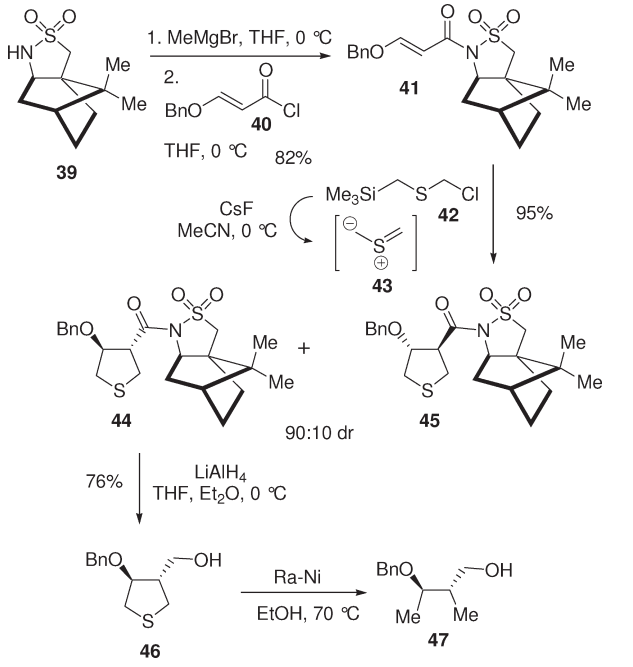
Figure 6.

which were easily separated by column chromatography. Subsequent $LiAlH_4$ reduction of the major isomer **44** gave access to the corresponding enantiopure alcohol **46**, which underwent reductive desulfurization into the known compound **47**.[43] Interestingly, compound **46** has been later used by Corsaro and coworkers[44] to produce different 4′-thionucleosides.

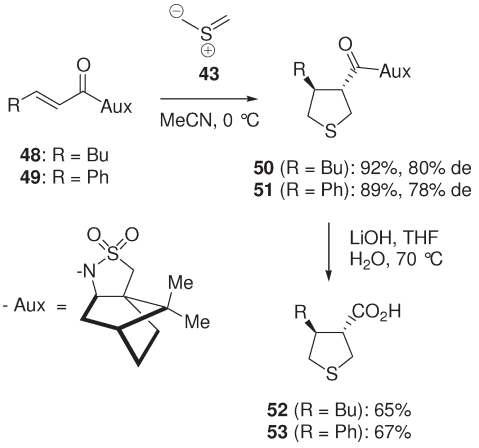
Similarly, asymmetric cycloadditions of camphorsultam amides **48** and **49** with ylide **43** under the same reaction conditions gave rise to tetrahydrothiophenes **50** and **51** in high yield and diastereoselectivity (Scheme 5). Chromatographic separation of the major diastereomer followed by removal of the chiral auxiliary gave the corresponding carboxylic acids **52** and **53**, respectively.

A readily available dimenthylphosphonyl ester group proved to be a highly effective chiral auxiliary in [2,3]-sigmatropic rearrangements of (allylthiomethyl)phosphonates to α-mercapto γ,δ-unsaturated phosphonates, precursors of chiral nonracemic 2-phosphonothiolanes.[45] As shown in Scheme 6, L-dimenthyl phosphite **54** was converted into

Scheme 4



Scheme 5



phosphonodithioformate **55**, which was then reduced and treated with allyl bromide to give (allylsulfanyl)methylphosphonate **56** in 95% yield.

Treatment of **56** with 5 equiv of *sec*-BuLi/HMPA in tetrahydrofuran (THF) at −75 °C for 75 min followed by acidic hydrolysis and extraction with pentane gave a 94:6 mixture of the rearranged α-mercaptophosphonates **57** and **58** in 95% yield. UV irradiation of crude thiols **57** and **58** in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) triggered a radical intramolecular cyclization producing the 2-phosphonothiolanes **59** and **60** in 60% isolated yield, without any epimerization.

(−)-*p*-Menthane-3-carboxaldehyde **61** has been efficiently used to install a chiral auxiliary appendage on alkylthionocarbamate derivatives involved in [3,3]-sigmatropic rearrangements leading to *S*-alkylthiocarbamates, eventually converted into chiral nonracemic 2,5-dihydrothiophene compounds.[46]

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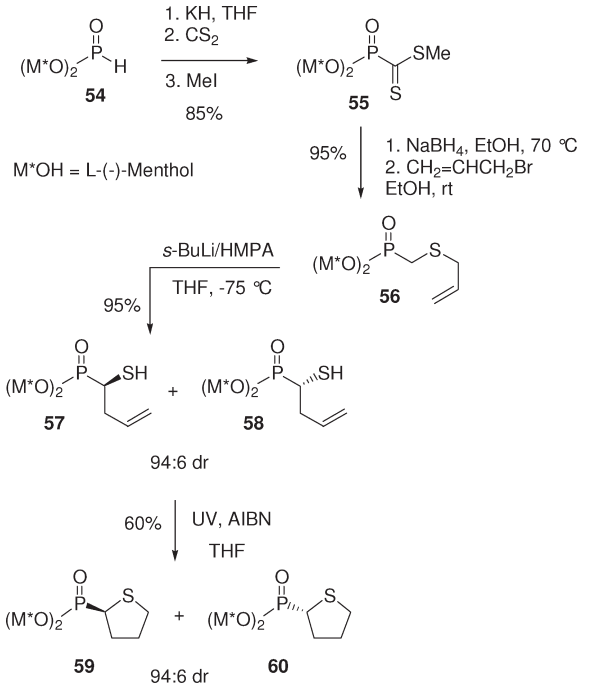
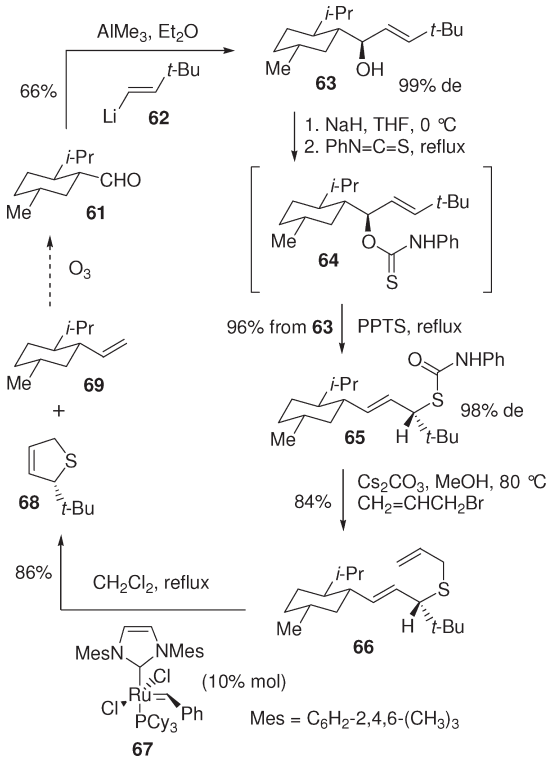
Scheme 6



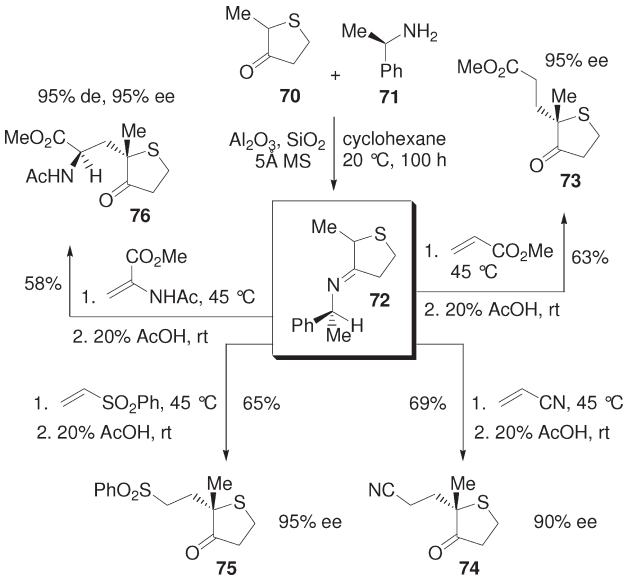
Scheme 7



This strategy called for the synthesis of suitable allylic alcohols, incorporating the bulky menthyl chiral auxiliary, as precursors of the required alkylthionocarbamates. Thus, (−)-*p*-menthane-3-carboxaldehyde **61** was treated with vinyllithium **62** in the presence of trimethylaluminum to give the Felkin adduct **63** as the sole diastereomer (>99% diastereomeric excess (de)) (Scheme 7).

Treatment of **63** with *N*-phenylisothiocyanate in basic medium produced the intermediate allylic thionocarbamate **64**, which rearranged to the thiocarbamate **65** upon acidification of the reaction mixture with pyridinium *p*-toluenesulfonate (PPTS). Subsequent one-pot hydrolysis of the carbamate functionality and alkylation of the resulting thiol with allyl bromide gave 84% yield of the *S*-allylated derivative **66**. The latter underwent ring-closing metathesis in the presence of Grubbs−Nolan catalyst **67**,[47,48] producing dihydrothiophene **68** in 86% isolated yield together with compound **69**, which was reconverted into the starting aldehyde **61** by ozonolysis.

Scheme 8



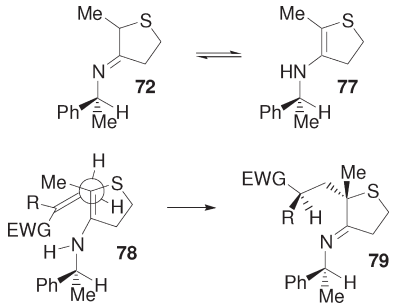


Figure 7.

Treatment of **72** with methyl acrylate for 70 h and hydrolytic workup, provided the adduct (*S*)-**73** in 63% overall yield and ≥95% enantiomeric excess (ee) (Scheme 8).

The asymmetric Michael addition of chiral imine **72** to electrophilic alkenes served as a versatile tool for the preparation of the enantiopure 2,2-disubstituted tetrahydrothiophen-3-ones **73**−**76**,[49] convenient building blocks for the synthesis of a large variety of target molecules possessing biological and pharmacological activities. Thus, condensation of the commercially available 2-methyltetrahydrothiophen-3-one **70** and (*R*)-1-phenylethylamine **71**, followed by heating of the derived imine **72** with methyl acrylate for 70 h and hydrolytic workup, provided the adduct (*S*)-**73** in 63% overall yield and ≥95% enantiomeric excess (ee) (Scheme 8).

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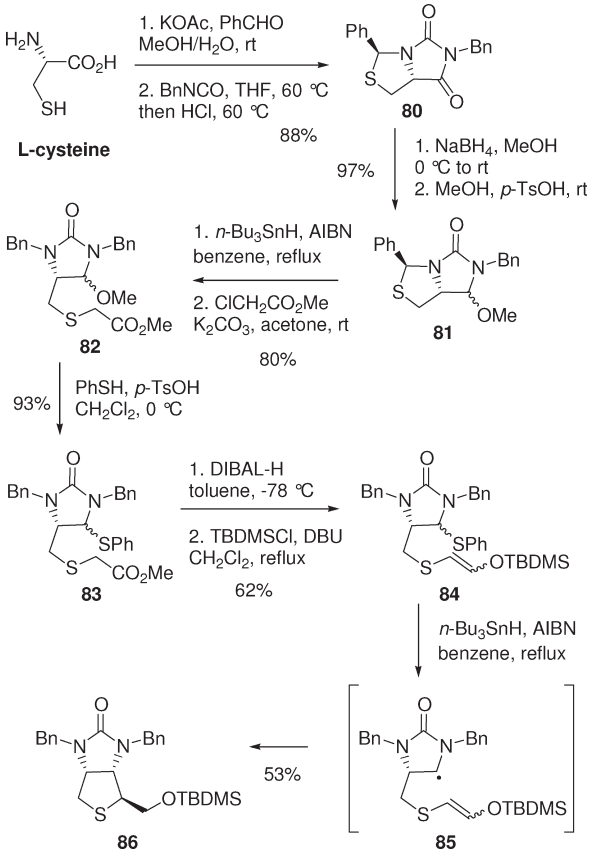
Scheme 9



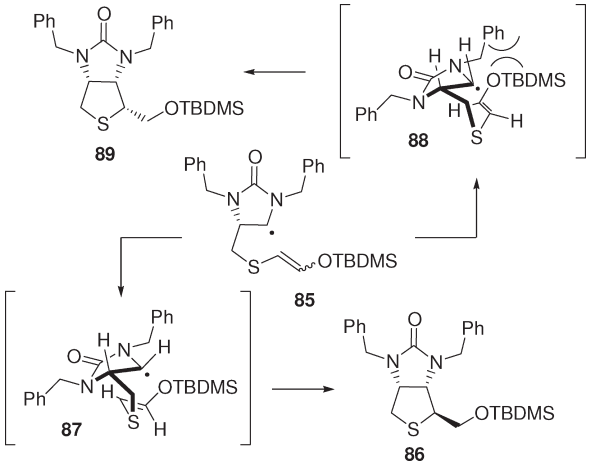
Similarly, reactions of imine **72** with acrylonitrile, phenyl vinyl sulfone, and methyl 2-acetamidoacrylate afforded the corresponding adducts **74**, **75**, and **76**, respectively, in good yield and excellent stereoselectivity. The high-ordered, six-membered transition state **78** derived by interaction of the electrophilic alkenes with the enamine **77**, in tautomeric equilibrium with imine **72**, is thought to be responsible for the high level of stereoselectivity (Figure 7). It is likely that the alkylation took place anti to the bulky phenyl group of the chiral amine moiety,[50] producing the (*S*)-configuration at the newly created quaternary carbon centers in the adducts of general structure **79**, precursors of **73**−**76**.

2.2. Asymmetry from Chiral Pool and Alternative Enantiopure Sources

2.2.1. From Chiral Pool. Enantiopure chiral pool-derived precursors have been widely used to import stereogenic centers and functionalities suitable to further transformation to the required targets.[33] In this context, tetrahydrothiophene ring systems have been efficiently synthesized starting from α-amino acids, sugars, α-hydroxy acid esters, glycidols, and terpenes.

2.2.1.1. From α-Amino Acids. The Chavan group has conveniently used naturally available cysteine as the chiral starting material to prepare the silyl enol ether **84**,[51] a key intermediate for setting up the tetrahydrothiophene core of (+)-biotin via radical cyclization. As shown in Scheme 9, L-cysteine was converted through a well-established procedure into the hydantoin **80**, which was transformed into methoxy imidazothiazolone **81** by sequential reduction and acid-catalyzed methoxylation (85% overall yield).

Scheme 10



Reductive cleavage of the benzylic carbon−sulfur bond of **81** with the *n*-Bu_3SnH/AIBN system in benzene at reflux temperature produced a nonisolated tin thiolate that was alkylated with methyl chloroacetate to give **82** in 80% yield. Reduction of the ester group of the derived thiophenyl derivative **83** to the corresponding aldehyde and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated silyl enol etherification with *tert*-butyl dimethyl chlorosilane gave **84** in 58% overall yield. Treatment of the latter with *n*-Bu_3SnH and a catalytic amount of AIBN in refluxing benzene promoted an intramolecular 1,5-exo-trig cyclization of transient α-amido radical **85** onto the silyl enol ether moiety, producing exclusively the *cis*−*trans* product **86**.

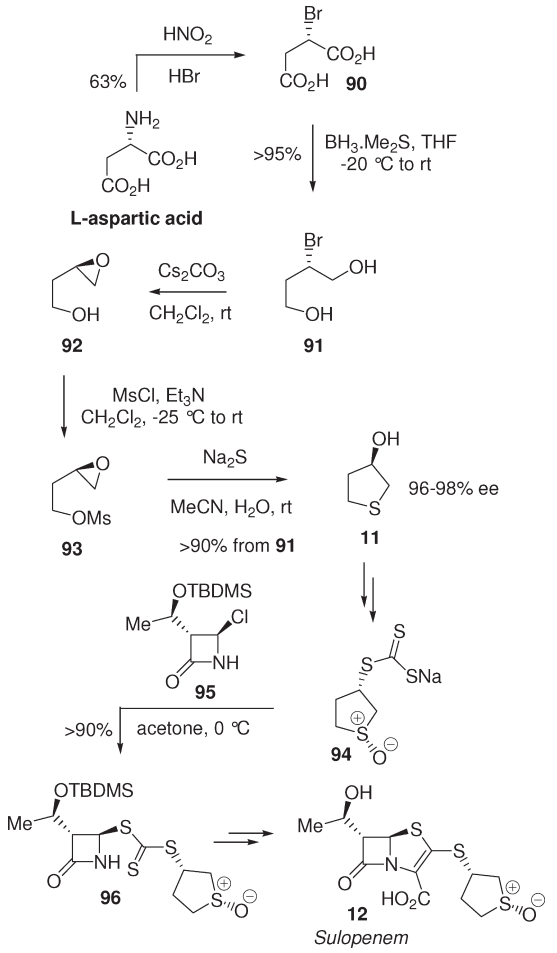
It is noteworthy that the failure to form the *cis*−*cis* isomer **89** appears to be unprecedented in cyclization of structurally related radicals.[52] The formation of **86** could be explained by assuming that cyclization of α-amido radical **85** onto the enol ether carbon−carbon double bond proceeded via the boatlike transition state **87** rather than the chairlike one **88** leading to **89** (Scheme 10). In this way, there is less steric compression between the quasi-equatorial *N*-benzyl substituent and the bulky *O*-tert-butyldimethylsilyl (OTBDMS) group.

Pfizer's group was able to obtain (*R*)-tetrahydrothiophen-3-ol **11** from the readily available and inexpensive L-aspartic acid via a high-yielding five-step sequence (Scheme 11).[16] Accordingly, the bromo diacid **90**, obtained in 63% yield by diazotization of L-aspartic acid in the presence of HBr, was reduced with diborane to the bromo diol **91**, efficiently isolated in >95% yield by a nonaqueous workup of the reaction mixture.Treatment of **91** with cesium carbonate in dichloromethane followed by mesylation of the derived epoxide **92** afforded epoxymesylate **93**. Subsequent treatment of the latter with sodium sulfide produced the optically pure **11** (96−98% ee), eventually taken to sulopenem **12** via sulfoxide **94**.

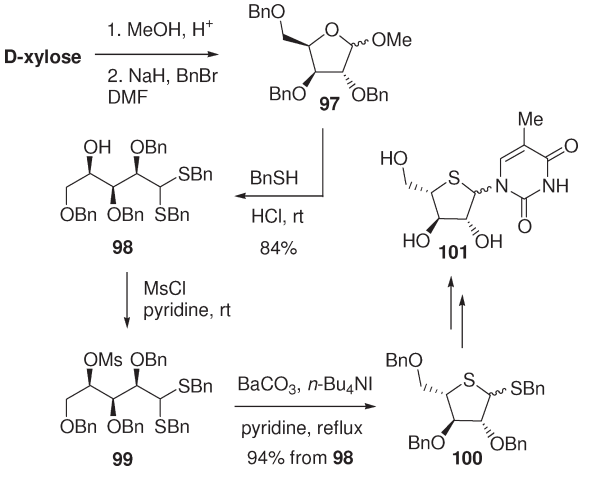
2.2.1.2. From Sugars. Natural and unnatural carbohydrates have been extensively used to obtain chiral polyhydroxylated tetrahydrothiophenes, which may act as building blocks for the synthesis of thionucleosides, either in the D- or L-series. Owing to the large collection of publications reported after 1990 on this subject, we focused our attention on the few selected approaches not previously covered in review accounts on the synthesis of 4′-thionucleosides[53] and biotin.[31,32]

For the sake of clarity, the content of this section has been divided into three general subsections, according to the way the tetrahydrothiophene backbone has been assembled. Thus, syntheses

Scheme 11

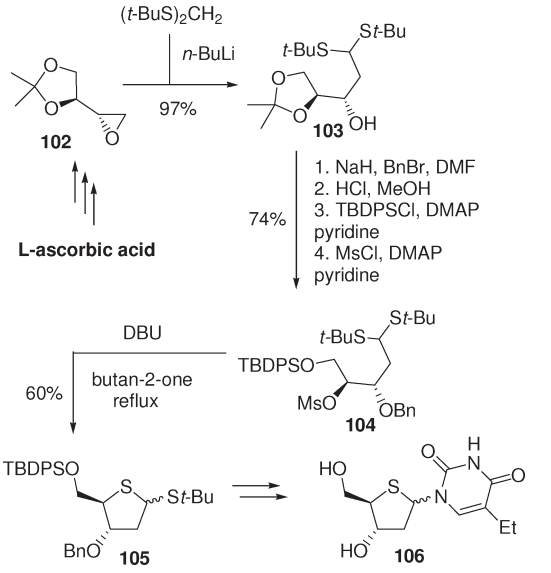


Scheme 12

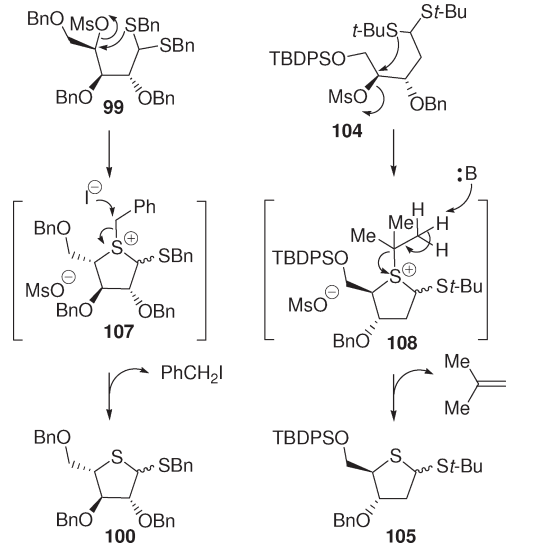


involving ring-closure of dithioacetals or thioaminals are discussed in subsection 2.2.1.2.1; subsection 2.2.1.2.2 is dedicated to thiolane ring formation through cyclization by *S*-centered anions; and ring-contraction reactions are collected in the final subsection 2.2.1.2.3.

Scheme 13



Scheme 14



2.2.1.2.1. Thiolane Ring-Closure of Dithioacetals and Thioaminals. A well-established method for building up the tetrahydrothiophene core of 4′-thiofuranoses is based on cyclization of dibenzyl dithioacetal intermediates derived from carbohydrate precursors.[54] As a typical case in point,[55] reaction of D-xylose-derived methyl 2,3,5-tri-*O*-benzyl-D-xylofuranoside **97** with phenylmethanethiol in the presence of concentrated hydrochloric acid provided the open-chain dibenzyl dithioacetal **98**, which was mesylated at room temperature in pyridine to afford **99** (Scheme 12). Subsequent treatment with $BaCO_3$/*n*-Bu_4NI in refluxing pyridine set the stage for the key cyclization step, giving rise to a 6.7:1 anomeric mixture of 1-*S*-benzylfuranose **100**, which has found application in the synthesis of pyrimidine 4′-thionucleosides, such as **101**.

Alternatively, di-*tert*-butyl dithioacetal cyclization has been employed to achieve a 2′-deoxy-4′-thionucleoside synthesis

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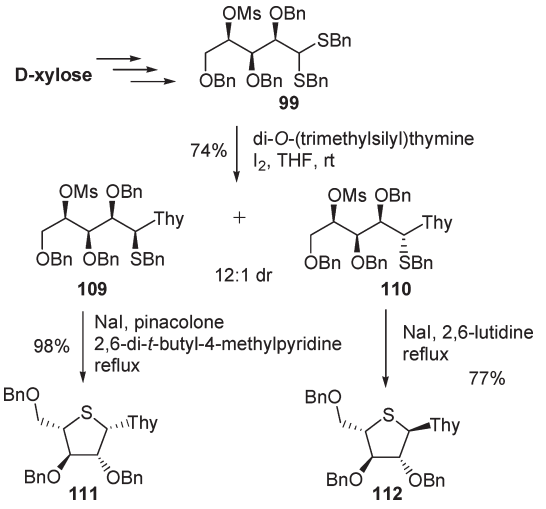
Scheme 15



starting from the readily available epoxide **102**[56] derived from L-ascorbic acid.[57] As depicted in Scheme 13, the formaldehyde di-*tert*-butyl dithioacetal anion reaction[58,59] on the epoxide **102** afforded compound **103**. A standard protection−deprotection sequence was used to prepare the mesylate **104**, which, when heated in butan-2-one containing excess DBU (4 equiv), produced the protected thiosugar **105**, a suitable starting material for the synthesis of the known thionucleoside **106**.[60]

It was assumed that the open-chain derivatives **99** and **104** underwent an intramolecular nucleophilic substitution producing transient sulfonium ions **107** and **108**, from which compounds **100** and **105** were obtained through *S*-dealkylation (Scheme 14). Thus, nucleophilic attack of iodide ion at the benzylic carbon of **107** released **100**, whereas a facile DBU-promoted *S*-de-*tert*-butylation of **108** gave the protected thiosugar **105**.

Remarkably, the di-*tert*-butyl dithioacetal cyclization method proved to be superior, in terms of yield, in comparison to similar routes based on the use of dibenzyl dithioacetals and iodide ion as the debenzylating agent.[61] The ring-closure of 4-mesyloxy-1-benzylthio frameworks bearing a nucleobase at C-1 has been successful for the direct access to L-thionucleosides in good to excellent yields.[62]

A representative example of this strategy is outlined in Scheme 15. Thus, the iodine-promoted glycosylation of di-*O*-(trimethylsilyl)thymine with the D-xylose derivative **99** gave a 12:1 mixture of diastereomeric thioaminals *syn*-**109** and *anti*-**110**.

The formation of 1,2-*cis*-thiosugar **111** has been efficiently accomplished in 98% isolated yield by refluxing a solution of *syn*-**109** in pinacolone in the presence of 2,6-di-*tert*-butyl-4-methylpyridine and an excess of sodium iodide. Similarly, the 1,2-*trans* compound **112** could be obtained in 77% yield by ring-closure of *anti*-**110** in boiling 2,6-lutidine containing an excess of sodium iodide. Analogously, treatment of thioaminal congeners derived from D-ribose, D-lyxose, and D-arabinose provided the corresponding thiothymidine analogues **113**−**118** in very good yields (Figure 8).

2.2.1.2.2. Thiolane Ring-Closure by S-Centered Anions. The most common procedure for obtaining polyhydroxylated tetrahydrothiophenes from carbohydrate precursors entailed a nucleophilic attack of sulfide anion to dielectrophilic partners. Thus, Matsuda and co-workers[63] accomplished a facile, large-scale synthesis of the

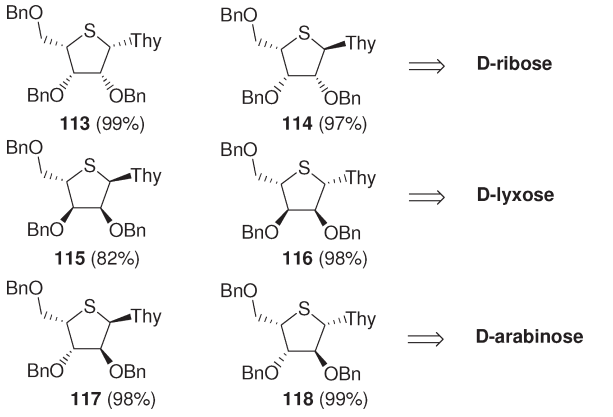
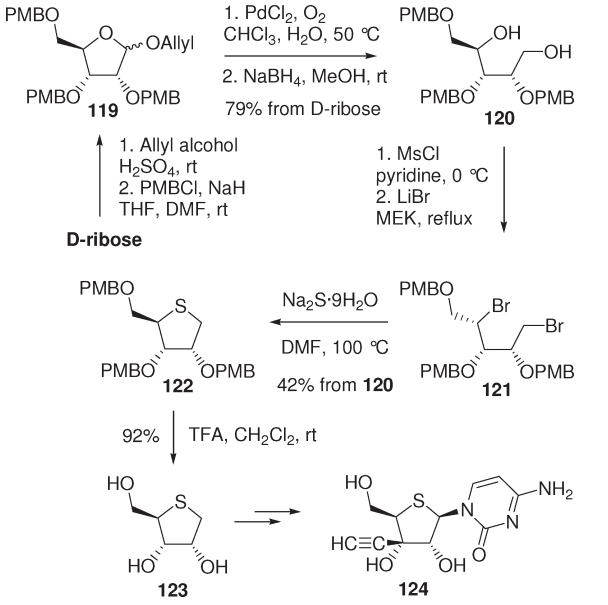


Figure 8.

Scheme 16



thiosugar **123** via sodium sulfide-promoted cyclization of dibromo derivative **121**, in turn obtained from D-ribose (Scheme 16).

In detail, allyl glycosidation of D-ribose, followed by protection of the remaining hydroxyl groups as the corresponding *p*-methoxybenzyl (PMB) ethers, provided the furanose derivative **119**, eventually taken to diol **120** by a two-step sequence calling for deallylation and reduction of the released hemiacetal moiety. Mesylation of **120** and treatment of the resulting dimesylate with well-dried lithium bromide (10 equiv) in refluxing methyl ethyl ketone (MEK) gave rise to the dibromo compound **121** that underwent sodium sulfide-assisted cyclization in dimethylformamide (DMF) at 100 °C, providing **122** in 42% isolated yield over three steps. The latter compound was finally deprotected to give a 92% yield of 1,4-anhydro-4-thio-D-ribitol **123**, a useful precursor of a range of 4′-thionucleosides, such as 1-(3-*C*-ethynyl-4-thio-β-D-ribofuranosyl)cytosine **124**.[64]

The cyclization of a disulfonate intermediate has been extensively applied to assemble the core ring system of natural and non-natural tetrahydrothiophene compounds. Thus, the synthesis of 1,4-dideoxy-1,4-epithio-D-arabinitol **129** from D-xylose[65] called for the preparation of the key dimesylate intermediate **127** (Scheme 17).

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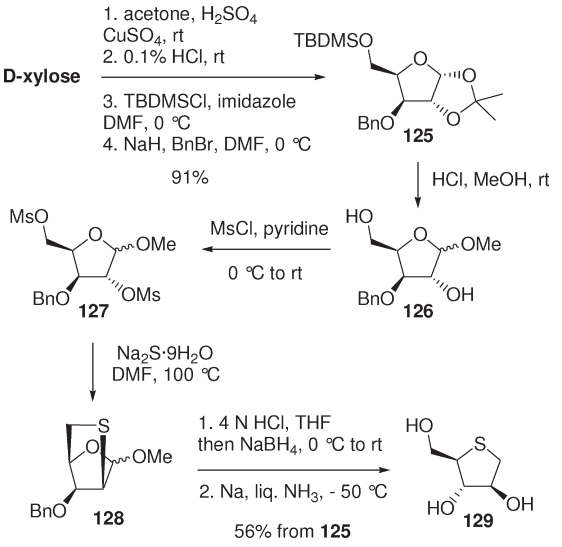
Scheme 17



Conversion of D-xylose into acetonide **125** followed by deacetalization and concomitant methyl glycoside formation gave rise to xylofuranoside **126** (1:1 anomeric mixture), which was directly treated with methanesulfonyl chloride under standard conditions to afford the corresponding dimesylate **127**. Its treatment with sodium sulfide in DMF at 100 °C produced the bicyclic derivative **128**, which furnished the target compound **129** by sequential acid hydrolysis, reduction of the released aldehyde group, and debenzylation. Interestingly, the polyhydroxylated tetrahydrothiophene **129** served as the starting material for the synthesis of the biologically active compounds **2**−**4** and **6**, as outlined in Scheme 18.

In detail, salacinol **2**[66,67] and kotalanol **3**[68] have been obtained in 75 and 56% overall yields, respectively, by conversion of **129** into the corresponding *p*-methoxybenzyl-protected derivative **130**, followed by regioselective *S*-alkylation with the enantiopure cyclic sulfates **131** and **132** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and removal of the protecting groups.

Similarly, salaprinol **4** was efficiently prepared via the ring-opening reaction of the cyclic sulfate **133**[9] with unprotected **129**. Moreover, reaction of the latter with methyl iodide and $NaHCO_3$ provided the cyclic sulfonium salt **6** as an unseparable 7:1 stereoisomeric mixture.[11]

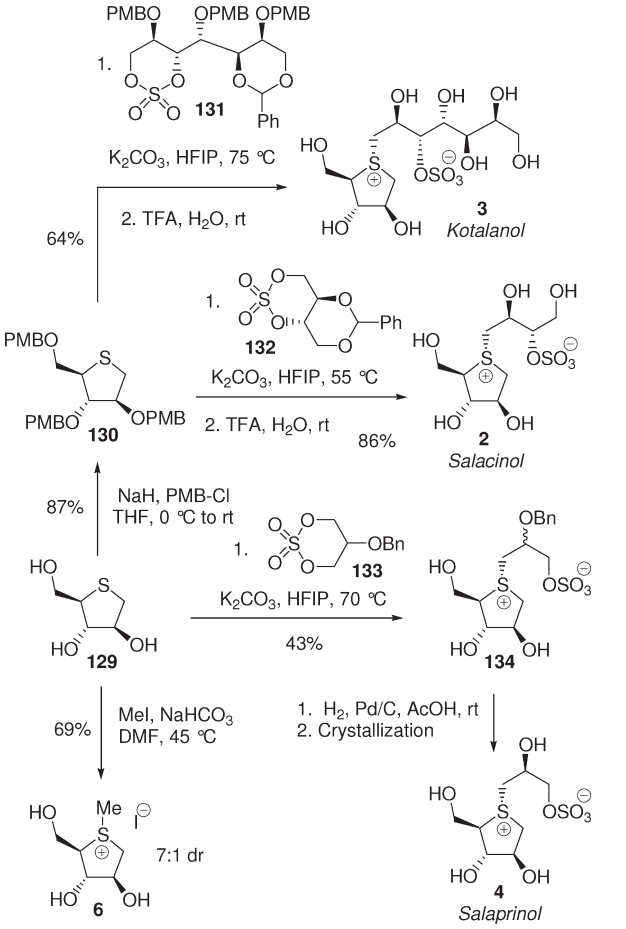
The 4′-thionucleoside **9** has been prepared starting from D-xylose, conveniently transformed in two steps into the fully protected intermediate **97** (Scheme 19).[14] Acid hydrolysis of the acetal group, followed by $LiBH_4$ reduction produced the diol **135**, which was then taken to the per-benzylated thioether **137** by sodium sulfide-promoted cyclization of the corresponding dimesylate **136**.

Interestingly, *ent*-**137**, prepared from L-xylose, was transformed into ponkoranol **5** by *S*-alkylation with D-glucose-derived cyclic sulfate **138** followed by protective groups removal and reduction of the hemiacetal moiety (Scheme 20).[69]

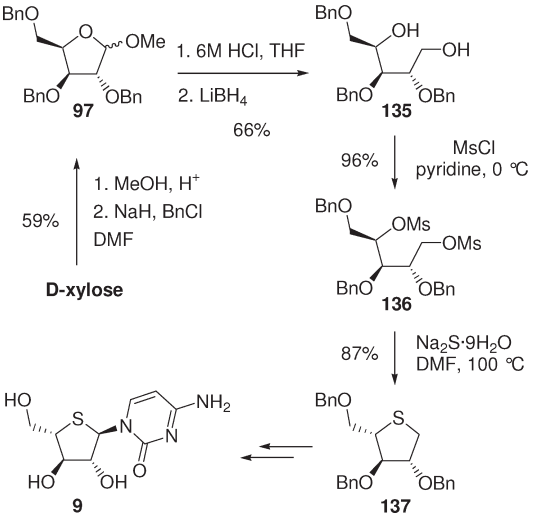
The synthesis of thiosugar **141**,[13] precursor of D-4′-thioadenosine derivatives endowed with antagonist activity on human A_3 adenosine receptor, was easily accomplished through cyclization of dimesylate **140**, in turn prepared from D-mannose (Scheme 21).

Thus, D-mannose was converted by standard chemistry into the protected diol **139** and the corresponding dimesylate **140** cyclized to tetrahydrothiophene **141** on treatment with sodium

Scheme 18



Scheme 19



sulfide. Selective hydrolysis of the 5,6-acetonide residue and oxidative cleavage of the resulting diol unexpectedly gave access to acetate **142**, indicating that oxidative cleavage of diol, oxidation of the resulting aldehyde to the acid, and oxidative decarboxylation of the acid occurred simultaneously.[70]

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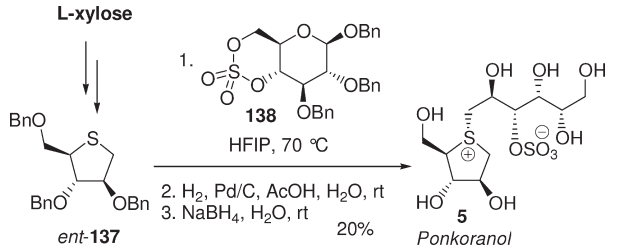
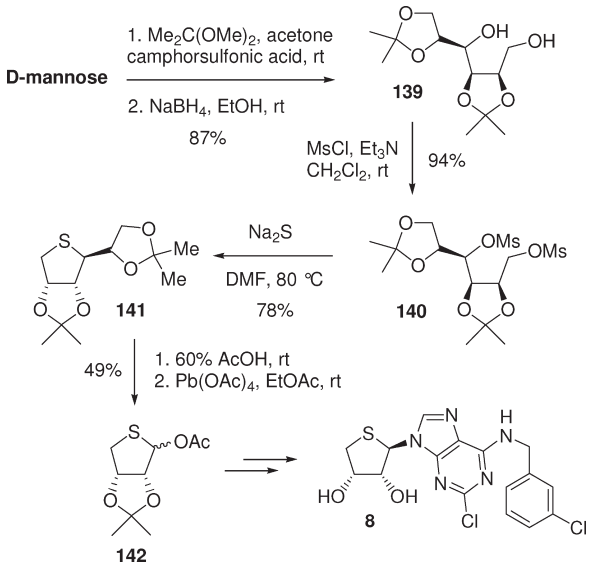
Scheme 20



Scheme 21



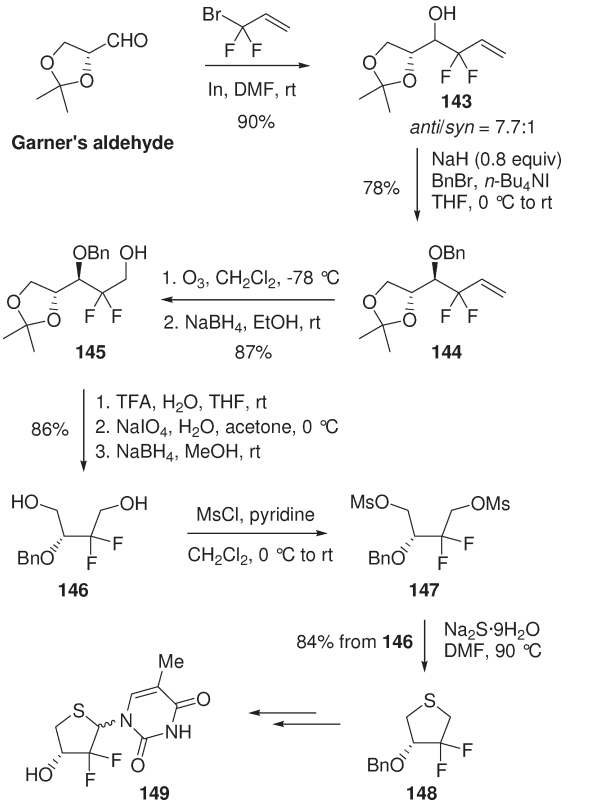
Compound **142** was eventually used to prepare a series of N^6-substituted D-4′-thionucleosides, including **8**. The cyclization of a dimesylate intermediate was the key step for the preparation of *gem*-difluorinated thionucleosides starting from 1-(*R*)- or 1-(*S*)-glyceraldehyde acetonide.[71−75]

As an example,[75] 3,3-difluorotetrahydrothiophene **148** was prepared according to the synthetic sequence outlined in Scheme 22. Thus, 1-(*R*)-glyceraldehyde acetonide (Garner's aldehyde) was coupled with the *gem*-difluoroallylindium reagent generated in situ from 3-bromo-3,3-difluoropropene and indium in DMF at room temperature to provide the allyl alcohol **143** (*anti/syn* ratio = 7.7:1) in 90% yield. Noteworthy is that benzylation of **143** with benzyl bromide and catalytic *n*-Bu_4NI in THF at room temperature with <1.0 equiv of sodium hydride afforded *anti*-**144** in 78% yield.

At this stage, a multistep sequence was set up to remove one carbon atom at both ends. Thus, an oxidation−reduction sequence, followed by sequential isopropylidene deprotection, oxidative scission of the resulting diol, and reduction of the released aldehyde, produced diol **146** in 75% overall yield.

The latter was transformed by mesylation under standard conditions into the pivotal intermediate **147**, which subsequently took part in a ring-closure reaction upon treatment with sodium sulfide in DMF at 90 °C for 30 min. This operation produced thiofuranose **148** (84% yield), which was utilized to prepare 4′-thionucleosides, including **149**. Benazza and co-workers have

Scheme 22



achieved the synthesis of polyhydroxylated chiral thiolanes[76−78] via electrophilic activation of polyols as the corresponding thionocarbonates, as shown in Scheme 23 for a typical example.

Thus, dibenzyldithioacetal **150** with D-xylo configuration was transformed into the corresponding bis-cyclic thionocarbonate **151** in 73% yield by treatment with diimidazolyl thione (Im_2CS) reagent. Subsequent reaction with sodium sulfide in dimethyl sulfoxide (DMSO) at 80 °C and acetylation of the crude reaction mixture produced thiofuranose analogue **152** in 60% yield over two steps.[77,78]

This approach was also applied to aldose dibenzyldithioacetals with L-arabino, D-lyxo, D-galacto, and D-gluco configurations, as well as to D-arabino- and D-lyxo-configured 1-*O*-benzylpentitols, producing polyhydroxylated thioanhydropentitols **153**−**158** in good yields (Figure 9).

To explore the glycosidase inhibitory activity of synthetic thiosugars structurally related to australine and alexine, Grierson and co-workers[12] synthesized the pyrrolizidine analogue **7**, starting from the dithiolane **159** derived from D-erythrose (Scheme 24). Selective protection of the primary hydroxyl group as the corresponding tosylate **160** proceeded with concomitant cyclization providing the bicyclic sulfonium salt **7** as the only reaction product, with its structure being unequivocally determined by NMR and X-ray analysis.

The enantiospecific synthesis of polyhydroxythiolanes by the use of simple sugar derivatives as starting chiral templates has been extensively studied by Izquierdo and co-workers.[79−82] The seven-step enantiospecific synthesis of 1,4-anhydro-4-thio-D-mannitol **167**,[82] key intermediate for the preparation of glycosidase inhibitors bearing inner thiosulfonium salt, starting from methyl 4,6-*O*-benzylidene-α-D-altropyranoside **161**, offered a recent example of this chemistry.

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

Scheme 23

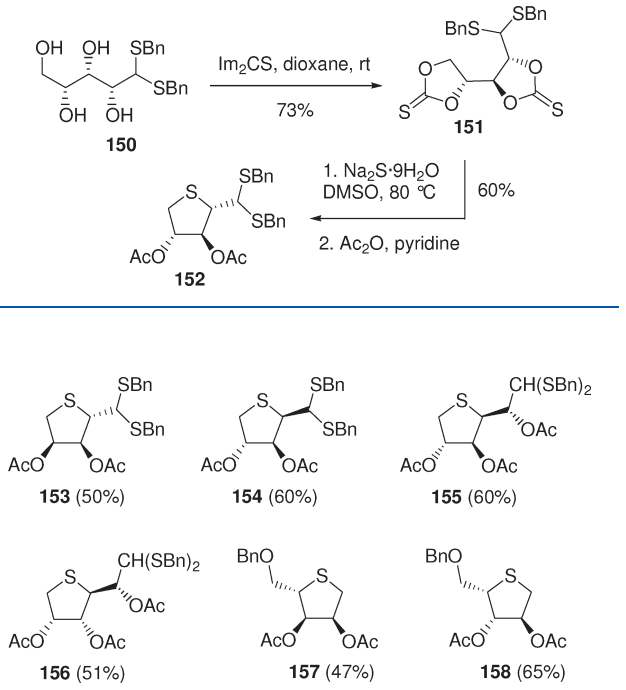
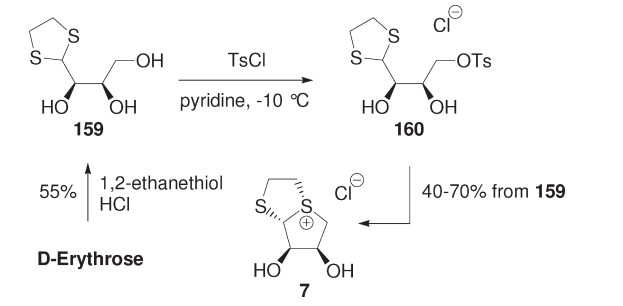
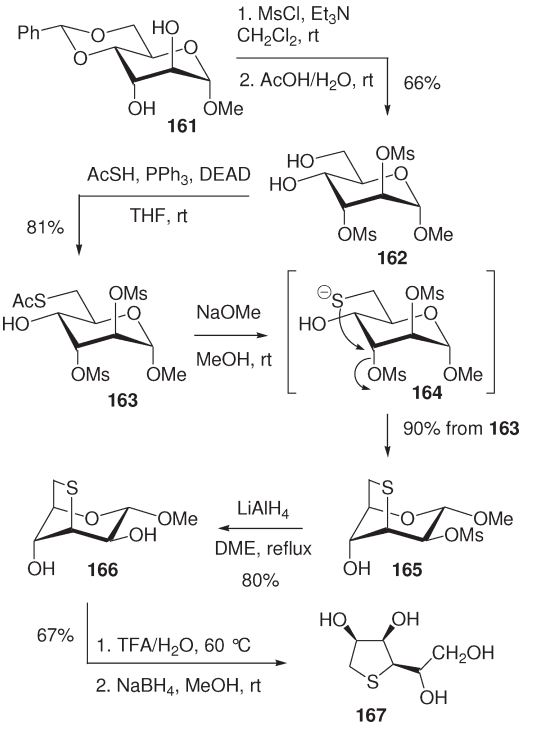


Figure 9.

Scheme 24



Scheme 25



According to Scheme 25, compound **161** was transformed into the corresponding methanesulfonate ester **162** by sequential mesylation and acidic removal of the benzylidene acetal protecting group. An efficient thio-Mitsunobu reaction afforded regioselectively *S*-acetyl derivative **163**, which was subsequently treated with the NaOMe/MeOH system to effect a clean removal of the acetyl group. This operation released the mercaptide anion **164**, which took part in a C-3 regioselective intramolecular nucleophilic substitution affording **165**. Subsequent *O*-demesylation produced alcohol **166**, which was eventually taken to the target compound **167** by a two-step hydrolysis−reduction sequence.

The preparation of polyhydroxylated chiral thiolanes as potential enzyme inhibitors has been successfully accomplished by introduction of a thiol group in a sugar moiety through conjugate addition followed by nucleophilic internal displacement of a sulfonyloxy group.[83] As an example, the reaction between NaSH and the (*E*)-alkene **169**, in turn derived from 2,3-*O*-isopropylidene-L-erythrose **168**, produced an 80% yield of the epimeric thiolanes **170** and **171** (Scheme 26). Treatment of the mixture of **170** and **171** with aqueous trifluoroacetic acid (TFA) removed the acetonide protecting group, giving rise to lactone **172** along with unprotected thiolane **173**. A two-step reduction−acetylation sequence allowed the conversion of **172** into the triacetate **174** (52% yield), which was eventually transformed into trihydroxylated thiolane **175** in 66% yield by treatment with NaOMe/MeOH.

These results compare well with those obtained in related studies dealing with the synthesis of homochiral hydroxylated pyrrolidines via reaction of **169** with ammonia.[84] However, due to a facile interconversion of tetrahydrothiophenes **170** and **171** via a retro-Michael−Michael reaction, the thiophane synthesis was less efficient in terms of diastereoselectivity with respect to the analogue pyrrolidine approach. Similarly, the synthetic sequence has been conveniently applied to prepare thiolanes **178** and **179** from mesylate **177**, derived from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **176** (Scheme 27).

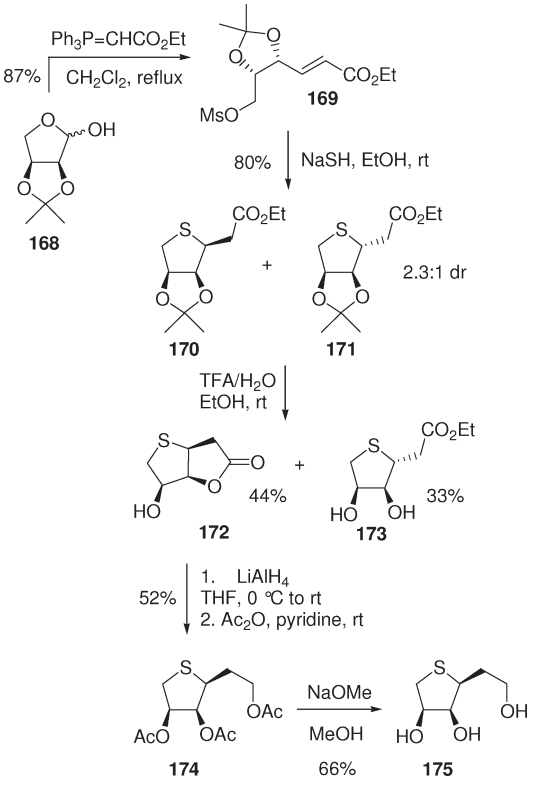
Commercially available tri-*O*-acetyl-D-glucal **180** has been recently used as the chiral starting material toward the stereoselective synthesis of highly substituted chiral tetrahydrothiophenes.[85] As shown in Scheme 28, conversion of **180** to furan derivative **182** followed by treatment with potassium thioacetate produced the chiral furan **183** in 50% overall yield.

Oxidation of **183** with singlet oxygen in a 1:1 $MeOH/CH_2Cl_2$ mixture containing diisopropylethylamine afforded a 1.6:1 diastereomeric mixture of 4-hydroxybutenolide **184** in 71% yield. Sequential reduction and acid-catalyzed lactonization gave a very good yield of enantiomerically pure butenolide **185**, which, when treated with methanolic potassium carbonate, afforded the lactone **187** via an intramolecular thia-Michael reaction. Subsequent $LiAlH_4$ reduction and acetylation of the intermediate diol gave tetrahydrothiophene **188**.

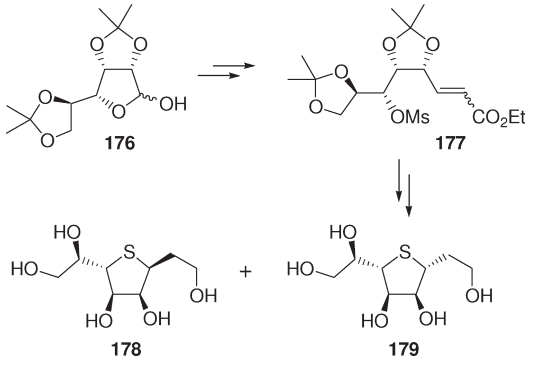
2.2.1.2.3. Ring Contraction. The preparation of chiral tetrahydrothiophenes has been also achieved through ring-contraction of sugar-derived thiepane and thiane derivatives by nucleophilic transannular substitution. Thus, treatment of Me_3SiI with

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

Scheme 26



Scheme 27

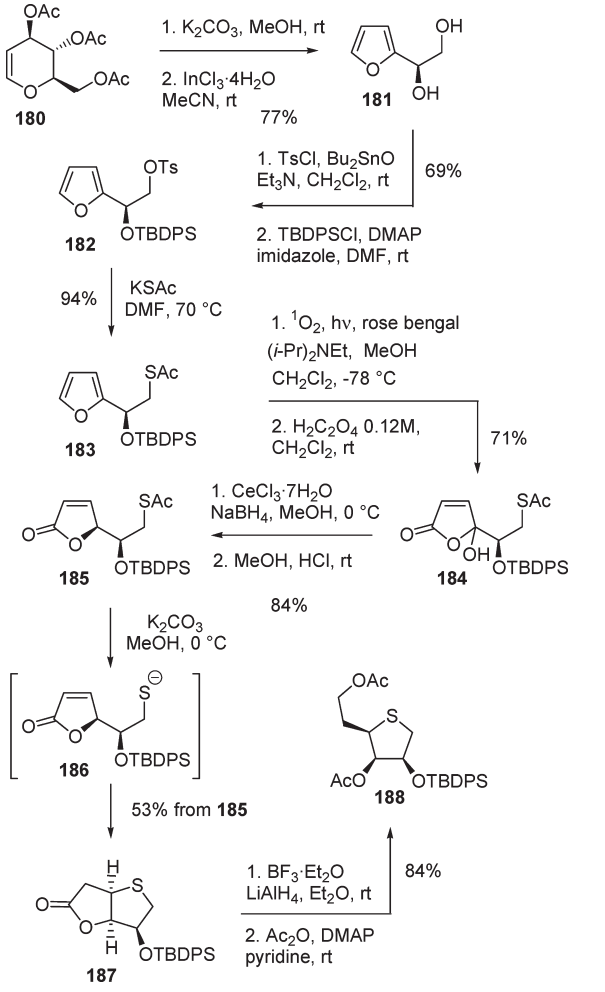


(4*R*,5*R*)-dihydroxythiepane **190**,[86] in turn obtained from D-mannitol-derived dibromo derivative **189**,[87] produced the oxonium intermediate **191** (Scheme 29).

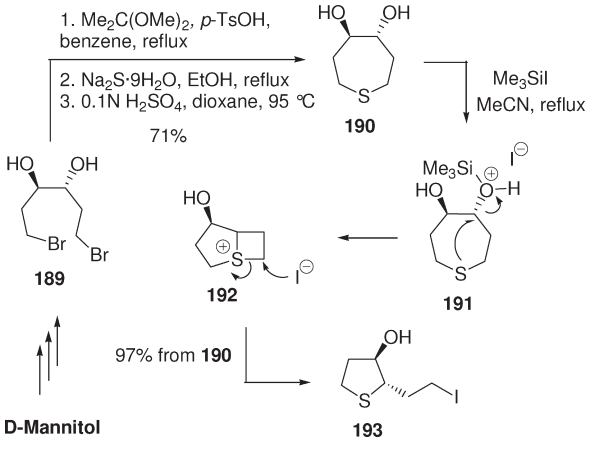
The bicyclic sulfonium salt **192** was ultimately formed through transannular nucleophilic substitution via displacement of the hydroxyl group coordinated with the silicon reagent. Subsequent iodide attack at the α-position of the 4-membered ring moiety gave a 97% yield of the optically pure tetrahydrothiophene **193**.

Later, the same authors used the D-sorbitol-derived thiepane **194** as a convenient starting material for the preparation of new polyfunctionalized thiolane derivatives,[88,89] to elucidate their role as potential glycosidase inhibitors. As shown in Scheme 30, acid-promoted deprotection of **194** and subsequent double mesylation of the intermediate diol produced compound **195**, which was heated at 120 °C in DMSO in the presence of sodium

Scheme 28



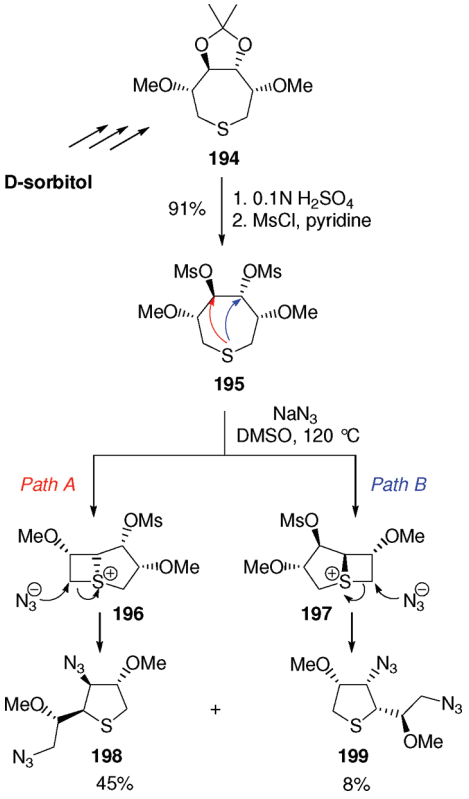
Scheme 29



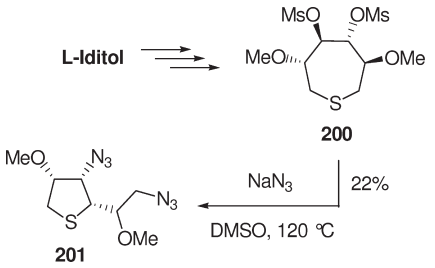
azide to yield chromatographically separable tetrahydrothiophenes **198** and **199**. This result has been explained by assuming that nucleophilic transannular substitution produced the diastereomeric bicyclic sulfonium salt intermediates **196** (*path A*) and **197** (*path B*), precursors of thiolane derivatives **198** and **199**, respectively, upon azide anion attack.

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

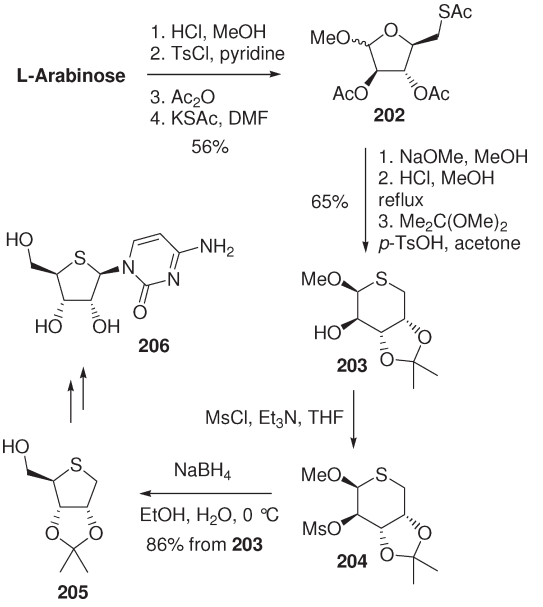
Scheme 30



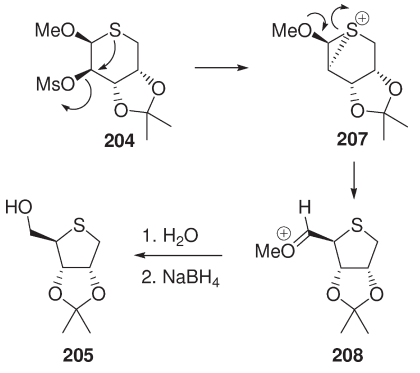
Scheme 31



Scheme 32



Scheme 33



On the other hand, the tetrahydrothiophene **201** has been obtained as the sole product when using the C_2-symmetric dimesylthiepane **200**, prepared from L-iditol[90] as the starting material (Scheme 31). The chiral polyhydroxylated tetrahydrothiophene **205** has been prepared from the L-arabinose-derived tetrahydrothiopyran compound **204** via a reductive ring-contraction reaction (Scheme 32).[91]

Thus, the 5-thioacetate **202** was submitted to sequential deacetylation, acid-catalyzed recyclization, and acetonide protection to produce the isopropylidene derivative **203**. The latter was taken to the corresponding mesylate **204**, which was directly treated with $NaBH_4$ in aqueous EtOH to give protected 1,4-anhydro-4-thio-D-ribitol **205**, used as a starting material for the synthesis of 4′-thioribonucleosides, such as **206**. It is likely that episulfonium ion **207**, resulting from the transannular cyclization of **204**, rearranged to intermediate **208**, which furnished the target compound **205** by hydrolysis and reduction (Scheme 33).

2.2.1.3. From α-Hydroxy Acid Esters. Optically pure α-hydroxy acid esters, namely, (*S*)-dimethyl malate[92] and (*S*)-ethyl lactate,[93] have been successfully used as synthetic precursors of chiral tetrahydrothiophene compounds. Thus, (*S*)-tetrahydrothiophen-3-ol *ent*-**11** has been prepared in five steps starting from (*S*)-dimethyl malate in ∼37% overall yield (Scheme 34).[92]

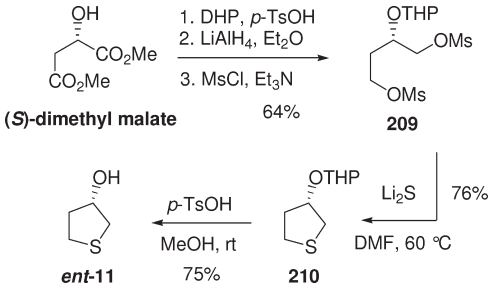
In detail, protection of the hydroxyl group of (*S*)-dimethyl malate as the corresponding tetrahydropyranyl (THP) ether followed by ester groups reduction and mesylation of the resulting diol provided the bismesylate **209** in 64% yield. Subsequent treatment with an excess of lithium sulfide in DMF at 60 °C produced the protected tetrahydrothiophene **210**, which was taken to *ent*-**11** in 57% overall yield by acidic removal of the tetrahydropyranyl protecting group.

Similarly, (*R*)-tetrahydrothiophen-3-ol **11** was prepared starting from optically pure (*R*)-dimethyl malate. A new tetrahydrothiophene synthesis featuring an unusual carbon−carbon bond-forming reaction to form the cyclic thioether nucleus has been achieved by acid-promoted rearrangement of 5-alkenyl oxathiolanes.[93]

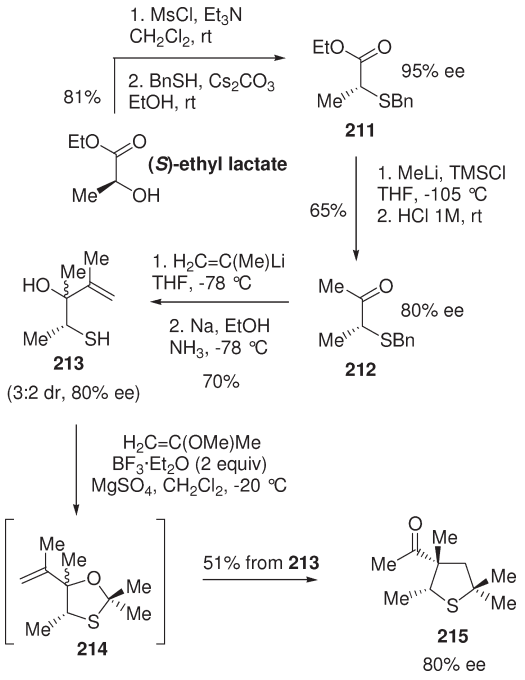
This chemistry was applied to the enantioselective synthesis of tetrahydrothiophene **215**, by the use of (*S*)-ethyl lactate as the chiral source (Scheme 35). Thus, mesylation of the hydroxyl

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

Scheme 34



Scheme 35

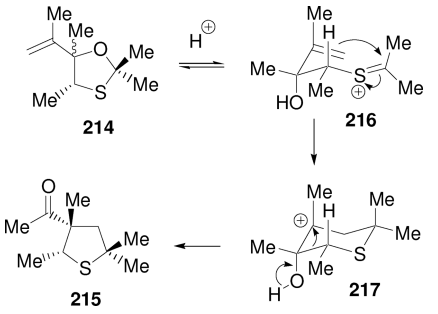


group of (*S*)-ethyl lactate and subsequent displacement with benzyl sulfide anion of the derived mesylate derivative provided the enantiomerically pure α-thioester **211** (81% yield, 95% ee), which was taken to the methyl ketone **212** by careful treatment with excess methyllithium in the presence of trimethylsilyl chloride. Its condensation with 2-propenyllithium followed by removal of the benzyl protecting group furnished thiol **213** as a 3:2 mixture of C-3 epimers in 80% ee. Reaction of **213** with 2-methoxypropene in the presence of $BF_3 \cdot Et_2O$ and excess $MgSO_4$ at −20 °C in CH_2Cl_2 afforded predominantly 3-acyltetrahydrothiophene **215** (51% yield, 80% ee) via 5-alkenyl oxathiolane intermediate **214**.

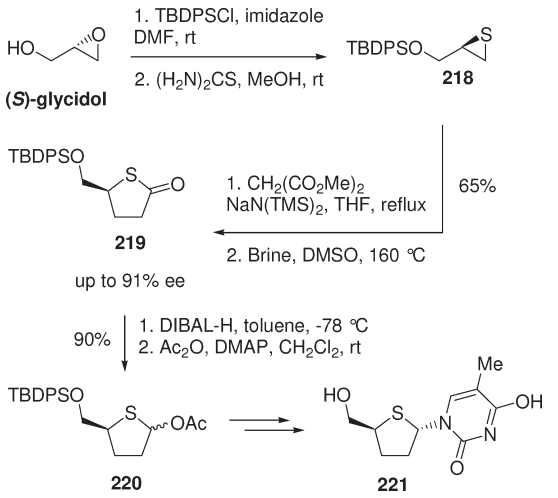
The formation of **215** is likely to require ring-opening of oxathiolane **214** as the starting move. The produced thionium ion **216** may evolve to the tetrahydrothiopyranyl carbenium ion **217**, which successively takes part in a pinacol rearrangement (Scheme 36). As a result, the conversion of **214** to **215** would occur with retention of configuration at the homoallylic stereogenic center, as previously observed in related transformations in the nitrogen and oxygen series.[94]

2.2.1.4. From Glycidols. (*S*)- and (*R*)-Glycidol were successfully employed as the chiral sources for a large-scale synthesis of

Scheme 36



Scheme 37



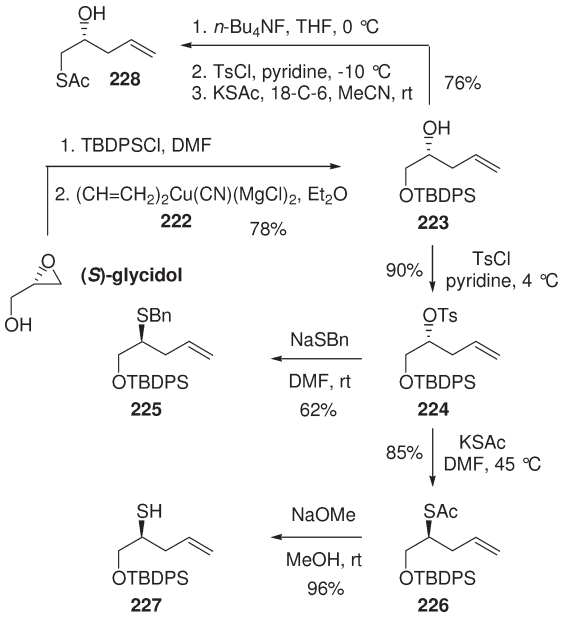
enantiomerically pure thiolactones, useful precursors of uracil and cytosine 4′-thionucleosides.[95] As shown in Scheme 37, (*S*)-glycidol was converted into the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether and treated with thiourea to give the (*R*)-thiirane **218**. Its reaction with dimethyl malonate anion in refluxing THF followed by Krapcho demethoxycarbonylation provided thiolactone **219** in 65% overall yield, with an enantiomeric excess of up to 91%. Finally, compound **219** was converted into the corresponding thiolactol acetate **220**, a suitable starting material to prepare a wide range of 2′,3′-dideoxy-4′-thionucleosides, such as the uridine derivative **221**, for antiviral testing.

Similarly, (*R*)-glycidol was converted into the (*R*)-enantiomer of **219**, eventually taken to thiofuranose analogues in the L-series. Differently protected unsaturated sulfanyl alcohol derivatives have been exploited as precursors of chiral tetrahydrothiophene compounds via electrophile-promoted thioetherification.[96]

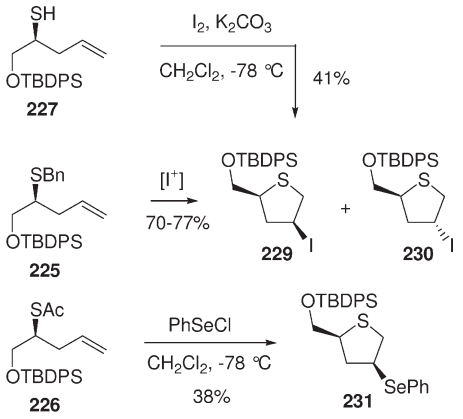
Thus, enantiomerically pure thiols **225**−**228** were prepared from homoallylic alcohol **223**, in turn obtained in 78% yield from enantiopure (*S*)-glycidol by sequential protection and nucleophilic regioselective ring-opening with the vinyl cyanocuprate reagent **222** (Scheme 38). Activation of **223** as the corresponding tosylate **224** followed by S_N2 reactions with benzyl sulfide and thioacetate anions yielded 2-sulfanyl-4-penten-1-ols **225** and **226** in 56 and 76% overall yields, respectively. The latter compound has been eventually converted into the labile thiol **227** by oxygen-free hydrolysis in 96% yield. Furthermore, a desilylation/tosylation sequence followed by nucleophilic displacement with

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

Scheme 38



Scheme 39

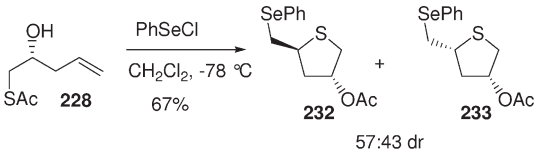


potassium thioacetate provided 1-sulfanyl-4-penten-2-ol **228**, with an overall yield of 76%.

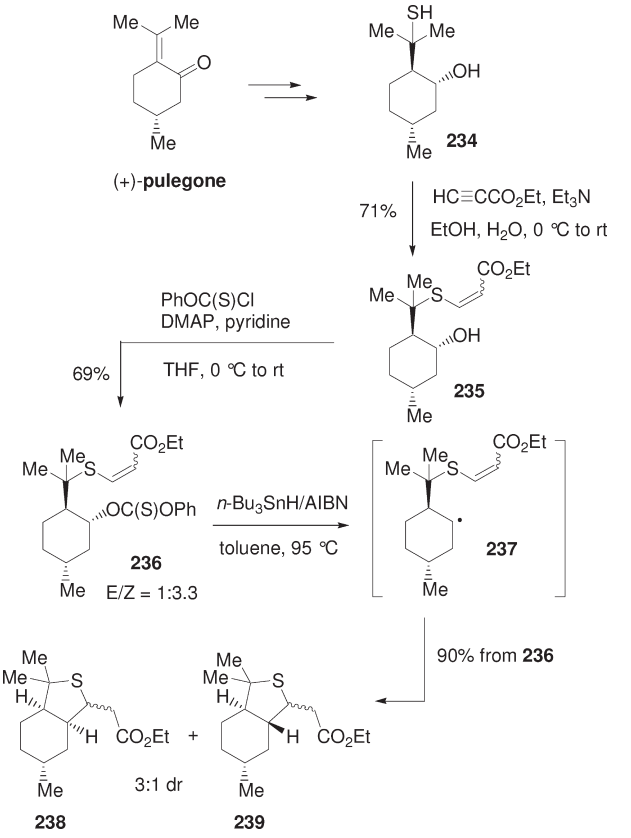
Treatment of unsaturated sulfanyl alcohols **225**−**228** with iodine and selenium electrophiles provided chiral tetrahydrothiophene derivatives via chemoselective cyclothioetherification reactions, which proceeded by endo- or exo-mode depending on the position of the sulfur atom, its protecting group, and the electrophile. In general, 2-sulfanyl-4-penten-1-ols **225**−**227** gave exclusive 5-endo cyclization, independently of the electrophile, with stereoselectivities and yields being strongly affected by the sulfur protecting group, as shown in Scheme 39 for selected examples.

Thus, treatment of thiol **227** with the I_2/K_2CO_3 system in CH_2Cl_2 at −78 °C afforded the compound *cis*-**229** as a single isomer (41% isolated yield), whereas iodothiocyclization of benzyl sulfide **225** with iodine in various experimental conditions led to a 60:40 diastereomeric mixture of **229** and the corresponding isomer *trans*-**230**. Furthermore, selenium-mediated cyclization of thioacetate **226** by action of PhSeCl in CH_2Cl_2 at −78 °C afforded stereoselectively the selenotetrahydrothiophene **231**, though in only 38% yield.

Scheme 40



Scheme 41



Interestingly, selenothioetherification of 1-sulfanyl-4-penten-2-ol **228** proceeded by a 5-exo mode, leading to a 57:43 diastereomeric mixture of tetrahydrothiophenes **232** and **233** in 67% yield (Scheme 40). These compounds are likely to originate from sequential cyclization and acetylation of the hydroxyl group promoted by in situ generated acetyl chloride.

2.2.1.5. From Terpenes. An interesting sulfur connection methodology has been developed by Bachi and co-workers[97] for the construction of some bicyclic sulfur-containing systems through free radical cyclization of β-thioacrylates. As shown in Scheme 41, the reaction of mercaptane **234**, prepared from (+)-pulegone according to known directions,[98] with ethyl propiolate in the presence of catalytic triethylamine, produced β-thioacrylate **235**, which was acylated with *O*-phenyl chlorothionoformate to provide a 1:3.3 *E*/*Z* isomeric mixture of the intermediate **236**. Heating of **236** in toluene at 95 °C in the presence of *n*-Bu_3SnH/AIBN system generated the transient radical **237**, which took part in a 5-exo ring-closure affording C-9 epimeric 8-thiabicyclo[4.3.0]nonane derivatives **238** and **239** (3:1 ratio, 90% yield).

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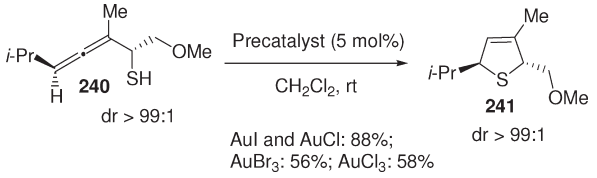
Scheme 42



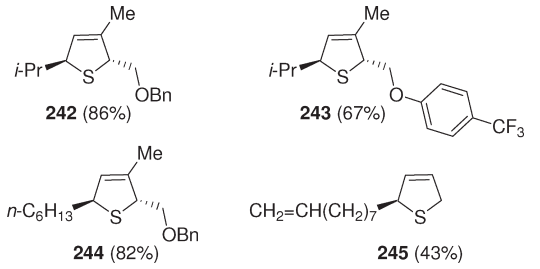
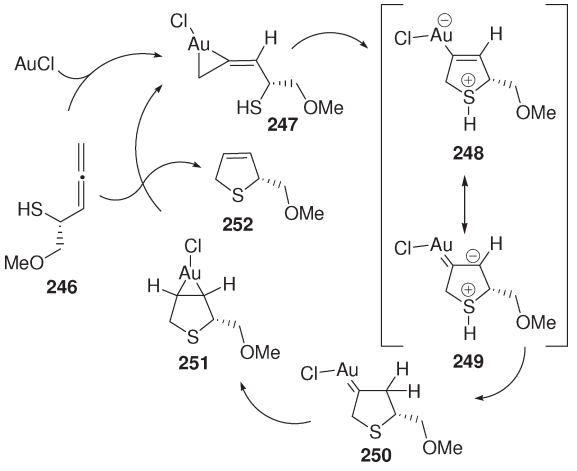


Figure 10.

Scheme 43

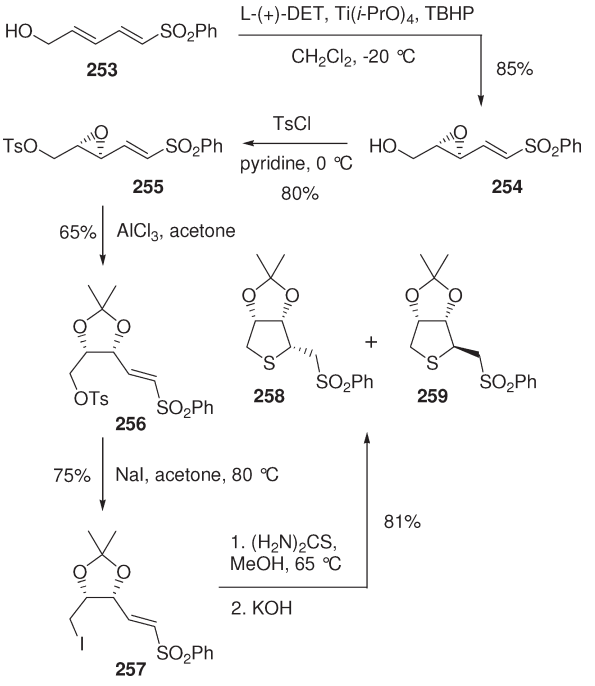


2.2.2. From Alternative Enantiopure Sources. Gold catalysis has been developed in recent years as an innovative strategy to construct a wide range of carbo- and heterocycles.[99] Thus, Krause and co-workers[100,101] opened a new elegant way to five- and six-membered heterocycles through gold-catalyzed cycloisomerization of chiral allenes bearing a nucleophilic substituent in the allylic or homoallylic position.

In this context, the stereoselective endo-cycloisomerization of chiral α-thioallenes to 2,5-dihydrothiophenes represents the first example of a gold-catalyzed carbon−sulfur bond formation.[100] As shown in Scheme 42, treatment of chiral α-thioallene **240**[102] with gold(I) and gold(III) precatalysts, in CH_2Cl_2 at room temperature, provided 2,5-dihydrothiophene **241**, with the chemical yields depending on the gold salt used. Both AuCl and AuI gave **241** with 88% yield, whereas the use of $AuBr_3$ and $AuCl_3$ afforded the same compound in 56 and 58% yields, respectively, due to concomitant oxidation of **240** to the corresponding disulfide, isolated as a side product.

This method allowed the preparation of several other 2,5-dihydrothiophene compounds, such as **242**−**245** (Figure 10), using AuCl as the privileged precatalyst, being less hygroscopic and easier

Scheme 44



to handle than AuI. In all cases, cycloisomerization reactions proceeded smoothly in CH_2Cl_2 solution, whereas slow conversions and low yields were obtained in THF, toluene, or hexane.

These results appeared quite surprising because it is well-known that organosulfur compounds strongly coordinate to transition metals, especially to gold, acting as catalyst poisons.[103] However, recent computational studies on simplified model substrate **246**[104] clearly demonstrated coordination of AuCl to the distal double bond leading to complex **247** (Scheme 43), with coordination to the thiol and the ether groups being energetically less favorable.

An intramolecular attack by the sulfur nucleophile provides the zwitterionic intermediate **248** with the negative charge delocalized between the gold atom and the C-3 carbon atom, as in **249**. A proton transfer from sulfur to the C-3 carbon atom followed by a [1,2]-hydride shift gives the 2,5-dihydrothiophene gold complex **251**. From the latter, the catalytic cycle may restart by a ligand-exchange reaction eventually releasing the heterocyclic product **252**.

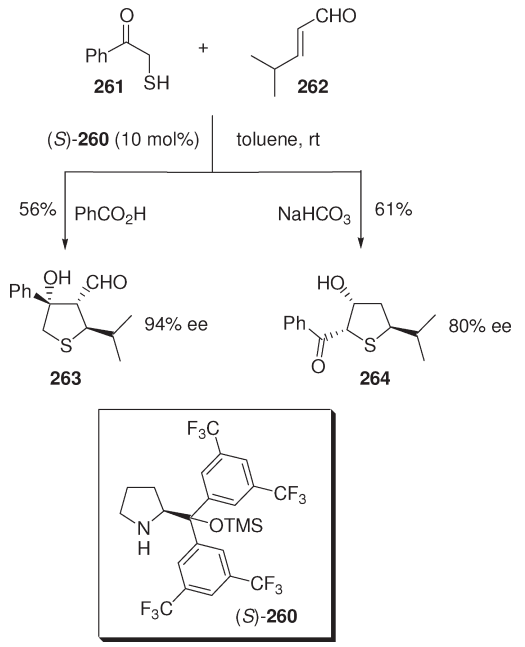
The asymmetric transition-metal-catalyzed epoxidation[105] of 1-hydroxymethyl-4-phenylsulfonylbutadiene **253** to the chiral substrate **254** was the starting step in the preparation of chiral nonracemic 2,3,4-trisubstituted tetrahydrothiophene compounds (Scheme 44).[106] Protection of **254** as the corresponding tosylate **255** and subsequent $AlCl_3$-catalyzed oxirane ring-opening by acetone produced acetal **256**. This compound was transformed into iodide **257**, which provided a 6:4 mixture of tetrahydrothiophenes **258** and **259** by reaction with thiourea and hydrolysis of the intermediate thiouronium salt.

2.3. Asymmetric Organocatalytic Processes

In recent years, extensive research efforts have been devoted in both industrial and academic settings to discover asymmetric transformations with enantioselective catalysts, and thousands of asymmetric catalytic reactions have been introduced for the synthesis of complex enantiomerically enriched molecules having multiple stereocenters. In this context, organocatalytic domino

dx.doi.org/10.1021/cr200298b |Chem. Rev. 2012, 112, 2129–2163

Scheme 45



reactions have been successfully utilized in the asymmetric synthesis of dihydro- and tetrahydrothiophene derivatives.

In 2006, Jørgensen and co-workers[107] reported a new thia-Michael/aldol domino reaction between 2-mercapto-1-phenylethanone **261** and aliphatic α,β-unsaturated aldehydes catalyzed by the L-proline derivative (*S*)-**260**. The domino process gave rise to (tetrahydrothiophen-2-yl)phenyl methanones or tetrahydrothiophene carbaldehydes depending on the use of acid or basic additives to the organocatalytic system. As an example, reaction of thiol **261** and aldehyde **262** in toluene at room temperature in the presence of catalyst (*S*)-**260** (10 mol %) and benzoic acid produced after 2 days tetrahydrothiophene carbaldehyde **263** as a single isomer in 56% yield and 94% ee (Scheme 45).

Using a basic additive instead of benzoic acid caused the concurrent formation of tetrahydrothiophene **264** in variable amounts depending on the base used. The best results were obtained by performing the organocatalyzed reaction in toluene at room temperature in the presence of $NaHCO_3$, with other bases being uneffective (NaOH) or giving low conversions (LiOH, Na_2HPO_4, Na_2CO_3, Cs_2CO_3, or Et_3N). As a matter of fact, the $NaHCO_3$-assisted domino process took place smoothly to afford a 98:2 mixture of **264** and **263**; the major isomer **264** could be isolated in 61% yield and 80% ee.

Similar results have been obtained by using different aldehydes as counterparts of thiol **261**. Accordingly, acid-catalyzed domino reactions produced tetrahydrothiophene carbaldehydes as the sole products (44−74% yield) with excellent enantioselectivities (90−96% ee), whereas base-promoted processes formed (tetrahydrothiophen-2-yl)phenyl methanones in good isolated yields (43−66%) and lower enantioselectivities (64−82% ee). A selection of optically enriched tetrahydrothiophenes **265**−**272** obtained from these processes is listed in Figure 11.

As proposed in Scheme 46 for the domino reaction involving **262**, initial activation of the aldehyde moiety by the organocatalyst provides iminium-ion intermediate **273**, which undergoes preferential thiol attack at the deshielded *Re*-face to produce (*R*)-configured enamine **274** (6:1 dr).

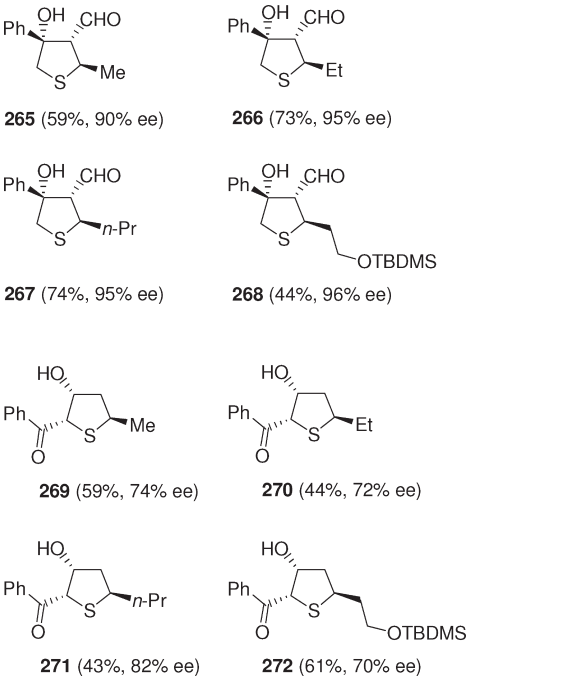
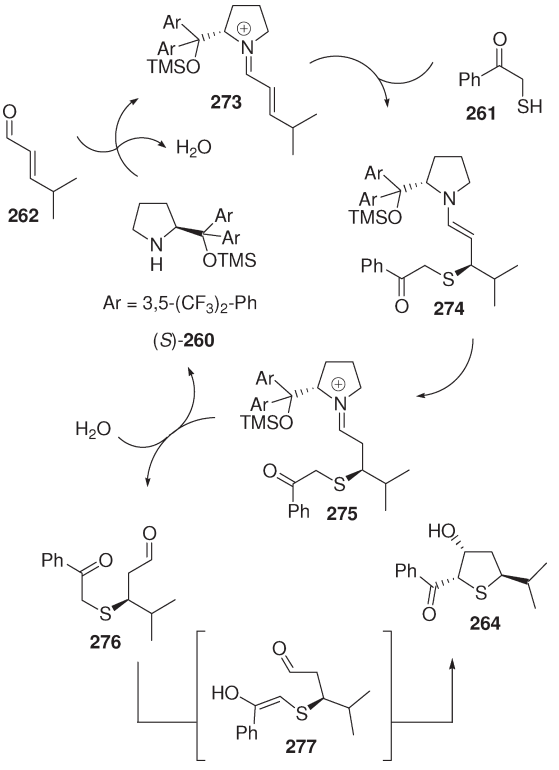


Figure 11.

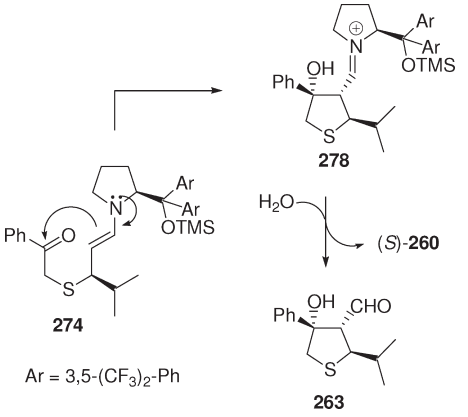
Scheme 46



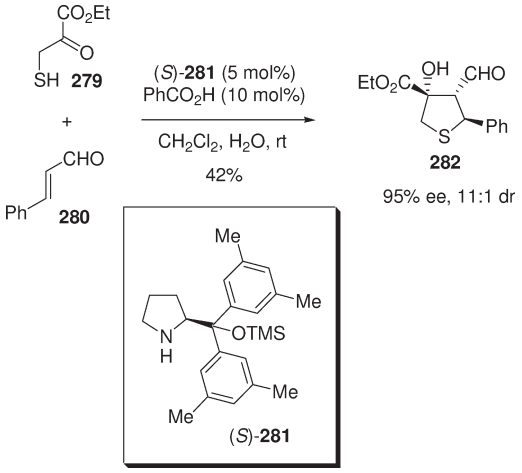
In the next step, $NaHCO_3$-promoted hydrolytic removal of the catalyst from the pyrrolidinium intermediate **275** gives rise to thioether **276**. Fast thermodynamically controlled enolization of **276** produces the (*E*)-enol **277**, which gives tetrahydrothiophene **264** through diastereospecific aldol cyclization.

dx.doi.org/10.1021/cr200298b |*Chem. Rev.* 2012, 112, 2129–2163

Scheme 47



Scheme 48



On the other hand, the use of benzoic acid as additive is likely to prevent the hydrolytic step, securing the survival of enamine **274**. The latter may participate to the diastereocontrolled intramolecular aldol-like reaction producing the tetrahydrothiophene **278** (Scheme 47). At this stage, hydrolysis of the iminium-ion moiety yields compound **263** and sets the catalyst free.

Very similar organocatalytic thia-Michael/aldol cascade reactions have been applied to the enantioselective synthesis of 4-carboxyethyl tetrahydrothiophene-3-carbaldehydes.[108] After careful investigations, the highly functionalized tetrahydrothiophene **282** could be obtained in 95% ee and 11:1 diastereomeric ratio by reaction of ethyl 3-mercapto-2-oxopropanoate **279** with *trans*-cinnamaldehyde **280** at room temperature for 1 h in the presence of chiral pyrrolidine (*S*)-**281** (5 mol %) and benzoic acid (10 mol %), in CH_2Cl_2 containing 10 equiv of water (Scheme 48).

Application of this methodology to various cinnamaldehydes provided a facile access to a range of 4-carboxyethyl tetrahydrothiophene-3-carbaldehydes in high enantioselectivities (91−97% ee) and diastereoselectivities (8:1 to >20:1 dr), as shown in Figure 12 for derivatives **283**−**286**.

Trisubstituted tetrahydrothiophene scaffolds could be smoothly obtained in a one-pot operation with high enantioselectivity through simple and elegant organocatalytic cascade thia-Michael/Michael reactions. These approaches relied on the

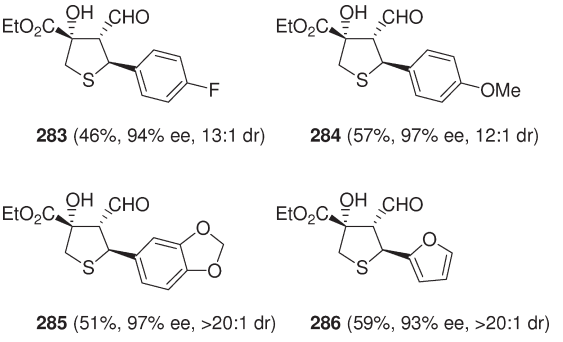
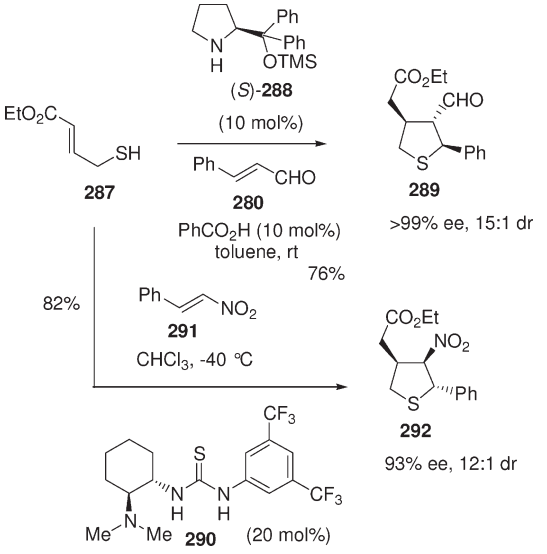


Figure 12.

Scheme 49



use of *trans*-ethyl 4-mercapto-2-butenoate **287** as the common starting substrate in chiral amine-promoted double Michael reactions with cinnamaldehydes[109] and nitroalkenes.[110]

As shown in Scheme 49, good yields (76%) and stereoselectivities (>99% ee, 15:1 dr) of the adduct **289** were achieved by reaction of **287** with *trans*-cinnamaldehyde **280** (toluene, room temperature, 3 days) in the presence of benzoic acid (10 mol %) and (*S*)-diphenylprolinol trimethylsilyl (TMS) ether **288** (10 mol %) as the basic catalyst, which is known to act through a covalent-bond (i.e., iminium-ion) activation mode.[111]

Alternatively, hydrogen-bonding donor amine−thiourea[112] **290** proved effective in catalyzing the reaction of **287** with *trans*-β-nitrostyrene **291** in $CHCl_3$ at −40 °C to produce 3-nitro tetrahydrothiophene **292** as a 12:1 diastereomeric mixture, in 82% yield and 93% ee. Two different mechanisms operate in the formation of **289** and **292**, depending on the basic catalyst involved in the domino reactions.

Thus, Michael addition of thiol **287** to the transient iminium ion **293** gives rise to enamine **294** (Scheme 50), which produces the iminium-ion intermediate **295** through intramolecular Michael reaction. The latter is eventually hydrolyzed to the tetrahydrothiophene derivative **289**.

On the other hand, a dual activation mode is likely to operate in the amine thiourea-catalyzed process, according to the model proposed by Takemoto and co-workers.[113] In this case,

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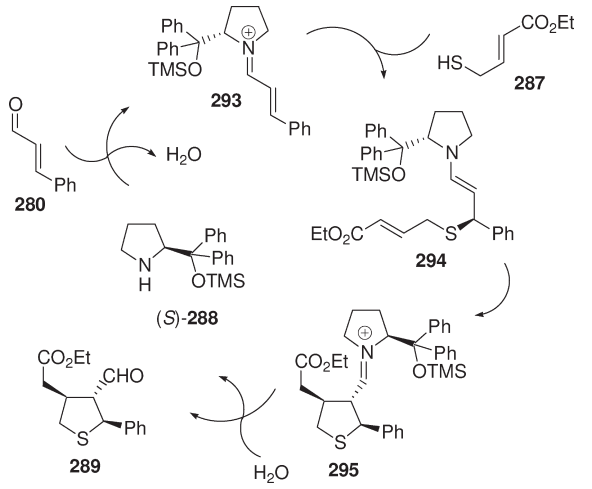
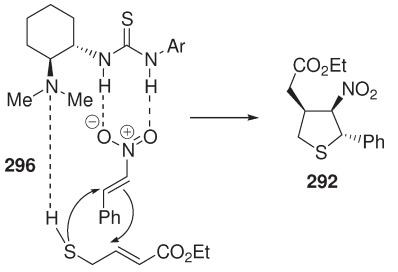
Scheme 50



Scheme 51



the carbon−sulfur bond-forming step takes place via the formation of the ternary H-bonded complex **296** arising from simultaneous interaction of the nitroolefin **291** and the mercaptobutenoate **287** with the thiourea moiety and the tertiary amine substituent of the catalyst **290**, respectively (Scheme 51).

It should be pointed out that detailed mechanistic insights into the hydrogen-bond-mediated thia-Michael/Michael cascade reaction indicated an unprecedented interplay of stereocontrol and dynamic kinetic resolution for the observed enantioselectivity. The scope of both organocatalytic processes has been considerably expanded by varying the α,β-unsaturated aldehydes and the nitroolefins, thus opening a highly stereoselective route to a variety of 2,3,4-trisubstituted tetrahydrothiophenes. Representative compounds **297**−**308** are listed in Figure 13.

Interestingly, two quite similar organocatalytic asymmetric domino thia-Michael/aldol condensation reactions between 1,4-dithiane-2,5-diol **309** (the dimer of mercaptoacetaldehyde) and α,β-unsaturated aldehydes provided isomeric dihydrothiophene carbaldehyde derivatives.[114,115]

Thus, De Risi and co-workers[114] prepared new 4,5-dihydrothiophene-2-carbaldehydes in moderate to good yields (40−75%) and good enantioselectivities (up to 84%) by reaction of **309** with cinnamaldehydes under the catalytic action of (*S*)-diphenylprolinol TMS ether/bile acid system in CH_2Cl_2 or CH_2Cl_2/MeOH solvent mixture.

On the other hand, Xu and co-workers[115] acceded to enantiopure 2,5-dihydrothiophene-3-carbaldehydes by effecting the reaction in toluene in the presence of 4-nitrobenzoic acid.

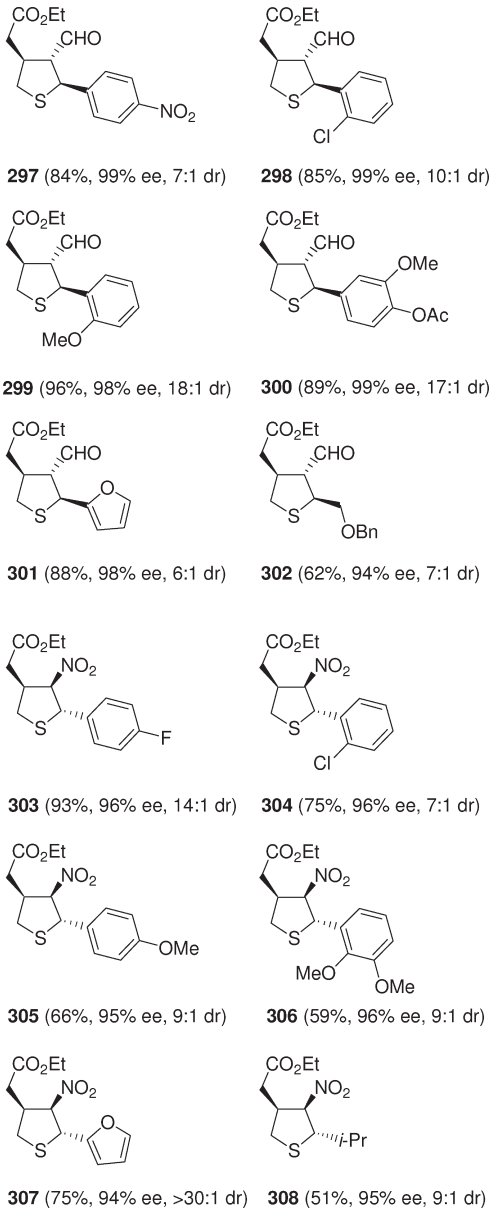


Figure 13.

Representative examples of these approaches are shown in Scheme 52.

Thus, model reaction between **309** and cinnamic aldehyde **280** in CH_2Cl_2/MeOH solvent (10:1) in the presence of (*S*)-diphenylprolinol TMS ether **288** and cholic acid **310** provided dihydrothiophene **311** in 60% yield and 84% ee. Remarkably, compound **311** was formed in lower chemical yield (40%) and enantioselectivity (62% ee) by using benzoic acid as the additive.

Instead, the same reaction has been efficiently carried out in the presence of the basic catalyst (*S*)-**288** (20 mol %) and 4-nitrobenzoic acid (10 mol %) in toluene at room temperature, giving (*R*)-configured 2,5-dihydrothiophene **312** in 78% yield and >99% ee. The dihydrothiophenes **311** and **312** may result from the common enamine intermediate **313**, which is likely to evolve by two different pahways (Scheme 53).

Thus, tautomeric equilibration of **313** should produce **314**, which generates tetrahydrothiophene **315** by 5-exo-trig cyclization (*path A*).

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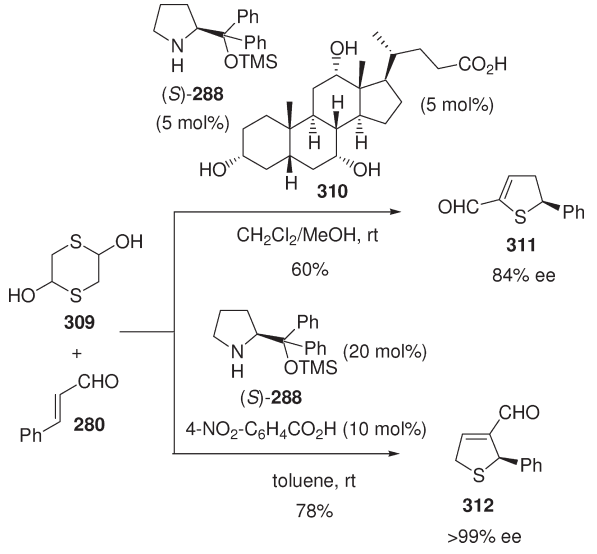
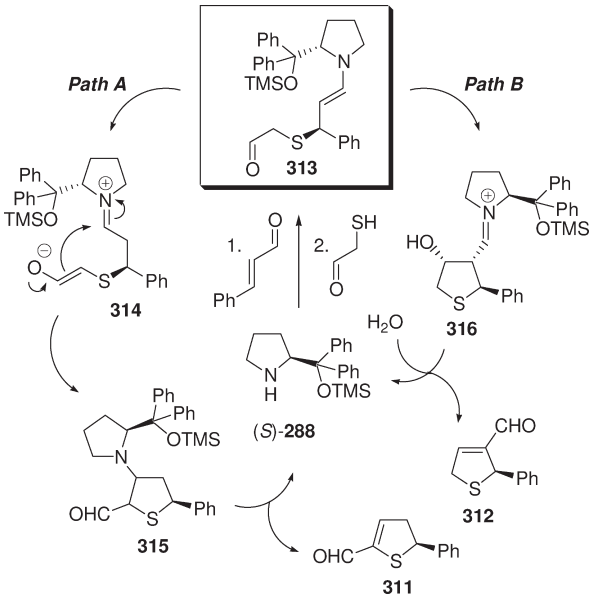
Scheme 52



Scheme 53



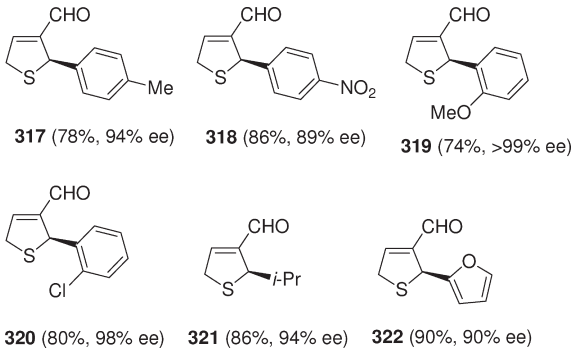
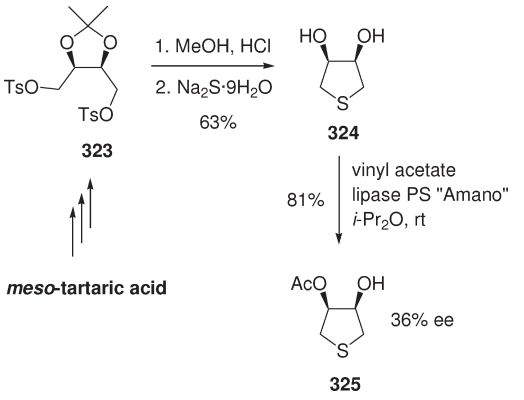
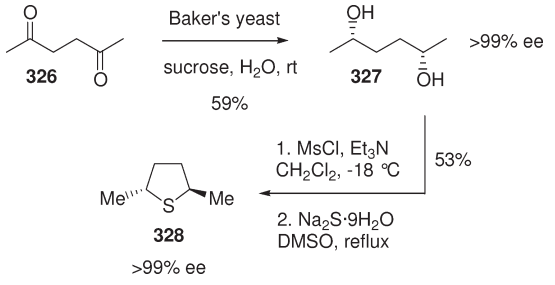


Figure 14.

Scheme 54



Scheme 55



In the last step, β-elimination of the catalyst produces dihydrothiophene **311**. Alternatively, compound **312** is plausibly formed by a mechanism similar to the one postulated by Jørgensen and co-workers[107] (Scheme 47), via intermediate **316**, a dehydration step accompanying the iminium-ion hydrolysis (*path B*). Organocatalytic domino reactions of **309** with a range of α,β-unsaturated aldehydes, including a branched aliphatic one, led Xu and coworkers to obtain analogues of **312** in good to high yields (70−90%) and excellent enantioselectivities (89−99% ee), as shown in Figure 14 for representative compounds **317**−**322**.

2.4. Desymmetrization through Bio- And Synthetic Catalysts

Enzymatic[116] and nonenzymatic[117] catalysts acting both on prochiral and *meso*-compounds have been successfully employed in the preparation of enantiopure thiolane derivatives. As shown in Scheme 54, *cis*-3,4-dihydroxythiolane **324**, easily obtained from *meso*-tartaric acid via the acetonide **323**, was desymmetrized to the monoacetate **325** by lipase-catalyzed acetylation.[118]

Baker's yeast (*Saccharomyces cerevisiae*) reduction of acetonyl acetone **326**,[119] using a higher substrate concentration in comparison to a known[120] literature protocol, provided (2*S*,5*S*)-2,5-hexanediol **327** in 59% yield with >99% ee (Scheme 55). Derivatization of **327** as the corresponding dimesylate, followed by sodium sulfide-promoted cyclization in refluxing DMSO for 15 h, furnished enantiomerically pure (2*R*,5*R*)-2,5-dimethylthiolane **328** (>99% ee) in 53% yield after distillation.

Remarkably, the enantiopure C_2-symmetric thiolane **328** proved to act as a highly efficient catalyst for asymmetric epoxidation reactions.[121] Hydroxynitrile lyases (HNLs) from *Hevea brasiliensis* (*Hb*HNL) and *Prunus amygdalus* (*Pa*HNL) were able to catalyze HCN addition to the carbonyl group of

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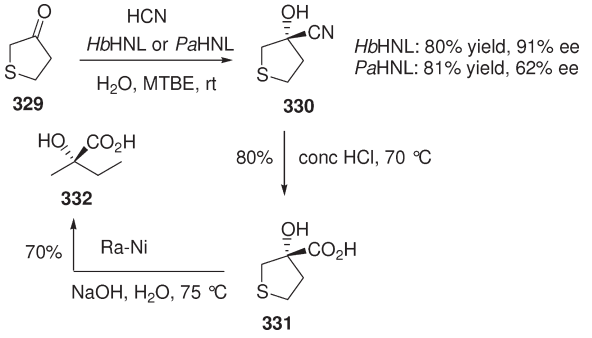
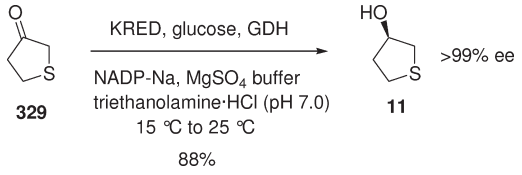
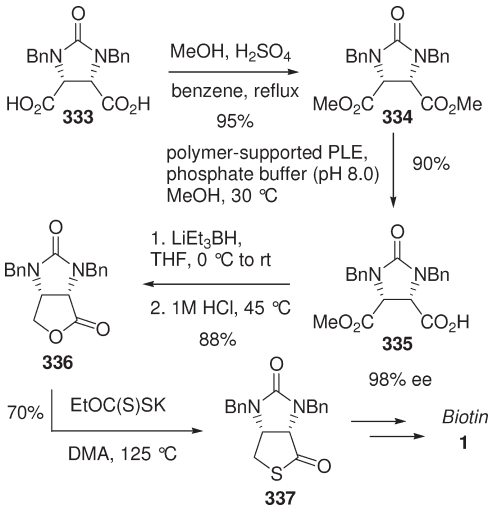
Scheme 56



Scheme 57



Scheme 58

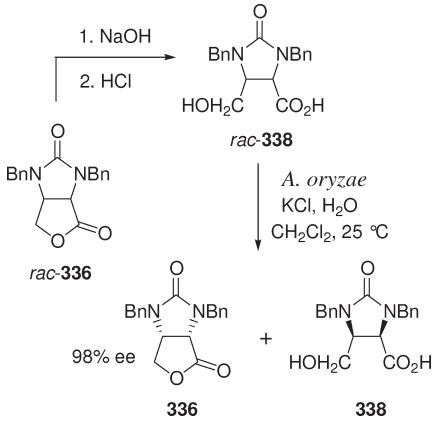


commercially available tetrahydrothiophen-3-one **329** to give the cyanohydrin **330** in 91% ee and 62% ee, respectively (Scheme 56).[122]

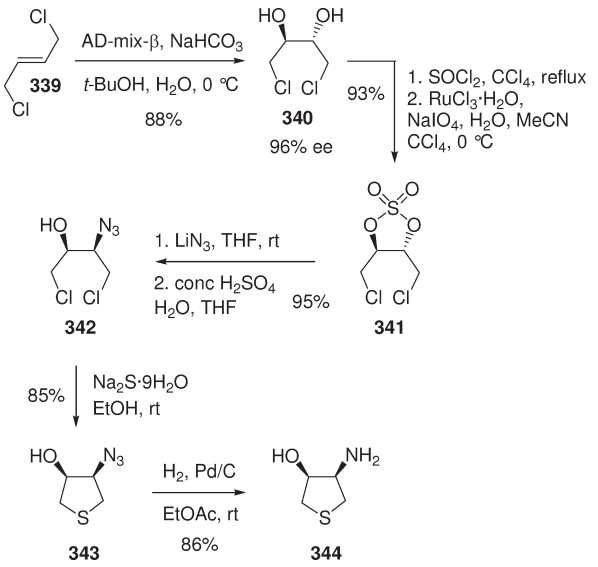
The enantiopure α-hydroxy acid **331** could be obtained from the cyanohydrin scalemic mixture through hydrolysis and fractional crystallization of the (*S*)-phenylethylamine salts. Interestingly, desulfurization of **331** with Raney nickel furnished enantiopure (*S*)-2-hydroxy-2-methylbutyric acid **332**, allowing one to consider tetrahydrothiophen-3-one **329** as a masked butanone equivalent.

Liang and co-workers[17,18] developed an eco-friendly biocatalytic process suitable for large-scale production of (*R*)-tetrahydrothiophen-3-ol **11** starting from tetrahydrothiophen-3-one **329**. Thus, engineered ketoreductase enzymes (KRED), derived from wild-type enzymes from *Lactobacillus brevis*, *Lactobacillus*

Scheme 59



Scheme 60



kefir, or *Lactobacillus minor*, in combination with glucose and a NADP-dependent glucose dehydrogenase (GDH), were able to provide (*R*)-**11** in 88% yield, >99% chemical purity, and >99% ee (Scheme 57).

The reduction was carried out at 15 °C for 16 h to reach ~90% conversion, followed by 7 h at 25 °C to reach >99% conversion. A total of ~1 MT of the chiral alcohol in 100+ kg batches has been produced using this methodology.

Remarkably, engineered ketoreductase enzymes proved superior to other biocatalysts, such as horse liver alcohol dehydrogenase[123] and fungal whole-cell systems,[124] providing the undesired (*S*)-alcohol in 33% ee and the desired (*R*)-alcohol in 81−91% ee, respectively. Immobilized pig liver esterase (PLE) on Eupergit C catalyzed the enantioselective hydrolysis of *meso*-dicarboxylic ester **334** into the (4*S*,5*R*)-hemiester **335**,[125] which was obtained in 90% yield and 98% ee after recrystallization (Scheme 58).

Chemoselective reduction of the ester group, followed by acid-catalyzed lactonization, provided enantiomerically pure lactone **336** (88% yield, 99% ee). This was eventually treated with potassium *O*-ethyl dithiocarbonate [EtOC(S)SK] in anhydrous

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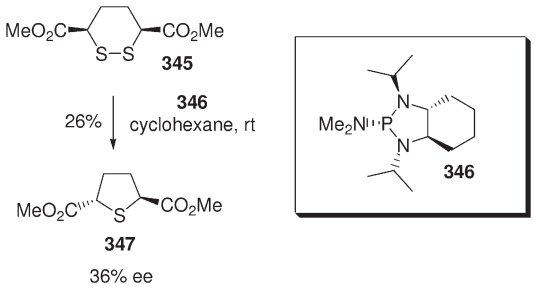
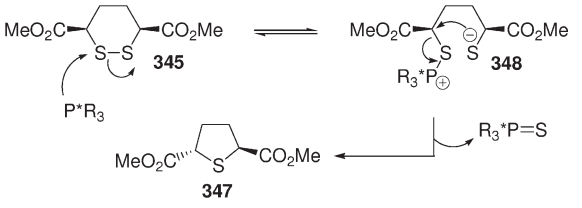
Scheme 61



Scheme 62



N,*N*-dimethylacetamide (DMA) at 125 °C for 7 h to produce the thiolactone **337**,[126] a key intermediate for the total synthesis of (+)-biotin **1**. Interestingly, enantiopure lactone **336** has been recently obtained through biocatalyzed enantioselective lactonization of *rac*-**338** (Scheme 59).[127]

Thus, saponification of *rac*-**336** provided the acid intermediate **338**, which was then incubated with dry microbial cells of *Aspergillus oryzae* (*A. oryzae*) WZ007 at 25 °C in dichloromethane containing saturated potassium chloride solution (pH 7.2). After 24 h, the reaction mixture was filtered to provide lactone **336** (≥98% ee) together with the optically active unreacted substrate **338**. Desymmetrization of prochiral compound **339**[128] gave access to optically active *cis*-4-amino tetrahydrothiophen-3-ol **344**, along the steps depicted in Scheme 60.

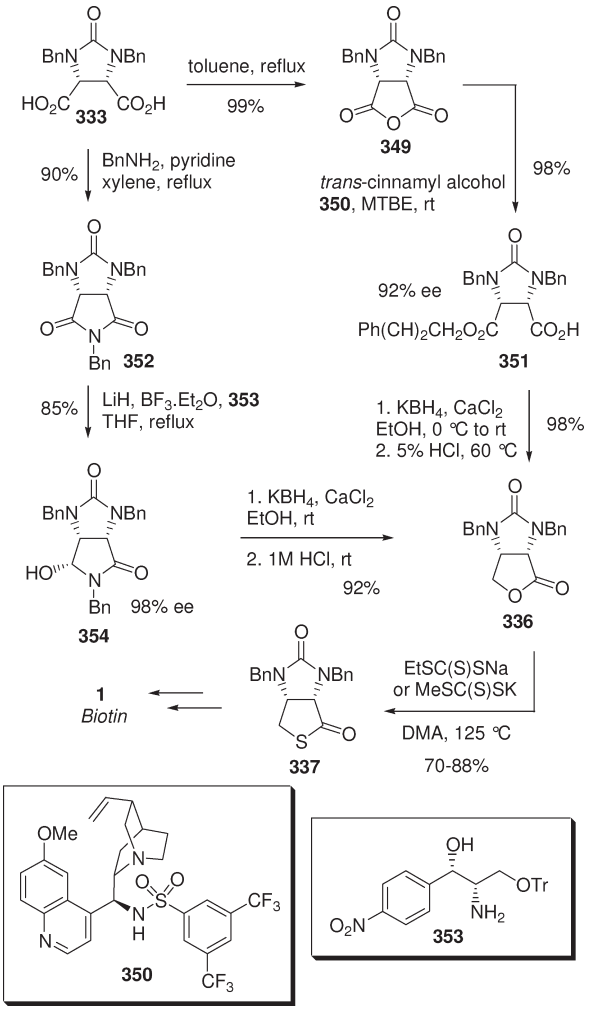
In detail, catalytic asymmetric dihydroxylation of **339** produced (2*R*,3*R*)-1,4-dichlorobutanediol **340**, subsequently converted into **341** through sequential treatment with thionyl chloride and ruthenium-catalyzed oxidation of the intermediate cyclic sulfite. Lithium azide ring-opening of the C_2-symmetric cyclic sulfate **341** produced the chlorohydrin **342**, which, treated with sodium sulfide, gave **343** in 85% yield. The latter compound was eventually reduced to **344** in 86% yield.

Chiral thiolanes with C_2-symmetry have been prepared through asymmetric desulfurization of six-membered *meso*-cyclic disulfides by using chiral aminophospines.[129] As depicted in Scheme 61, the chiral thiolane **347** was produced by treating *cis*-3,6-bis(methoxycarbonyl)-1,2-dithiane **345** with aminophosphine **346** in cyclohexane at room temperature for 96 h. The (2*S*,5*S*) absolute configuration of **347** has been established by comparison with literature data.[130]

It has been suggested[131] that the thiophane backbone construction proceeds via an initial phosphine-promoted disulfide bond cleavage giving the inner phosphonium salt **348**. This intermediate gives the thiolane **347** through thiono aminophosphine displacement by the internal sulfide nucleophile (Scheme 62).

Enantiopure thiolactone **337** has been obtained through catalytic asymmetric alcoholysis[132] of commercially available *meso*-cyclic anhydride **349**, in turn prepared by dehydration of

Scheme 63



dicarboxylic acid **333**.[133] A wide range of alcohols have been used in combination with different Lewis base catalysts, including quinine and its derivatives,[134−138] and a bifunctional amine thiourea derived from (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol.[139] As a representative example of this chemistry, reaction of **349** with *trans*-cinnamyl alcohol in the presence of sulfonamide **350** (1.1 equiv) in methyl *tert*-butyl ether (MTBE) at room temperature for 5 min afforded the hemiester **351** in 98% yield with 92% ee (Scheme 63).[137]

Reductive ring-closure of **351** gave enantiomerically pure lactone **336**, that underwent thiolactonization with sodium ethyl thioxanthogenate [EtSC(S)SNa]. This operation furnished a 70% yield of chiral thiolactone **337**,[126] eventually taken to (+)-biotin **1**.

Interestingly, compound **337** could also be obtained starting from *meso*-cyclic imide **352**, with its desymmetrization being achieved through chiral oxazaborolidine-mediated enantioselective reduction.[140−143] For example, treatment of **352** with in situ generated borane in the presence of chiral amino alcohol **353** produced hydroxylactam **354** in 85% yield and 98% ee (Scheme 63).[141] The aminal carbon reduction followed by HCl-promoted lactonization furnished **336**, which was eventually taken to the biotin precursor **337** in 88% yield by thiolactonization with

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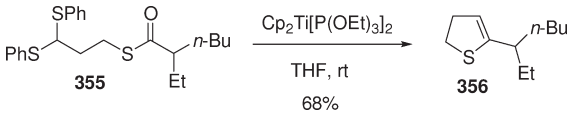
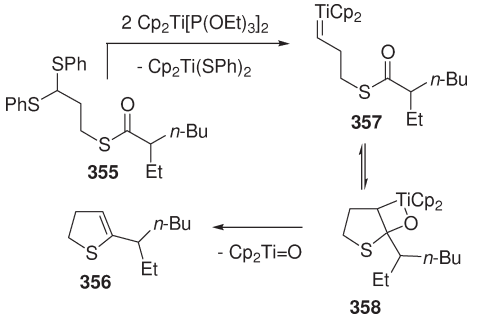
Scheme 64



Scheme 65



potassium methylthioxanthogenate [MeSC(S)SK] under the usual reaction conditions.

3. SYNTHESIS OF RACEMIC DIHYDRO- AND TETRAHYDROTHIOPHENES

Given the importance of substituted dihydro- and tetrahydrothiophene scaffolds, the development of new synthetic approaches to these interesting classes of compounds is a topical subject for organic chemists. Not surprisingly, besides the stereocontrolled routes to chiral dihydro- and tetrahydrothiophenes, a lot of papers have been devoted to the synthesis of these compounds in racemic form. In this section, a collection of papers dealing with nonconventional synthetic approaches to racemic substituted dihydro- and tetrahydrothiophene ring systems will be discussed, especially focusing on those that appeared in the literature in the past decade.

3.1. Synthesis of Racemic Dihydrothiophene Compounds

Transition metal-assisted transformations have been successfully utilized for the synthesis of a variety of substituted dihydrothiophenes. Thus, treatment of thioalkanoate **355** with the low-valent titanium species $Cp_2Ti[P(OEt)_3]_2$ (4 equiv) in THF at room temperature for 3 h gave the intramolecular olefination product **356** in 68% yield (Scheme 64).[144]

The formation of **356** is likely to proceed via titanium−carbene complex **357** and titanaoxetane intermediate **358** (Scheme 65), in analogy with the mechanism proposed for carbonyl olefination using a thioacetal-$Cp_2Ti[P(OEt)_3]_2$ system.[145] Similarly, good yields of 5-substituted-2,3-dihydrothiophenes **359**−**362** were obtained from different thioalkanoate derivatives (Figure 15).

Transition metal carbonyl-promoted cyclizations of terminal alkynes tethered to various nucleophiles have been successfully utilized for the synthesis of carbo- and heterocyclic compounds, with sulfur comparing well with oxygen, nitrogen, and carbon nucleophilic species.[146,147] Thus, irradiation of a THF solution of alkynylthiol **363** in the presence of $Cr(CO)_6$ and DBU resulted in a smooth cycloisomerization reaction producing dihydrothiophene **364** in 76% isolated yield (Scheme 66).[147]

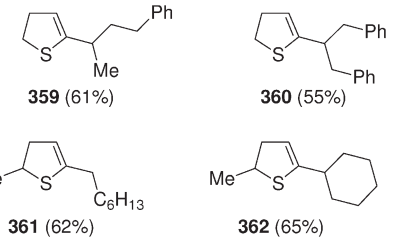
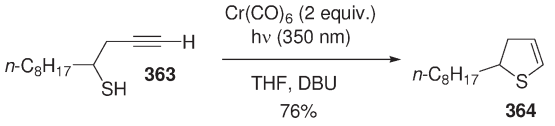
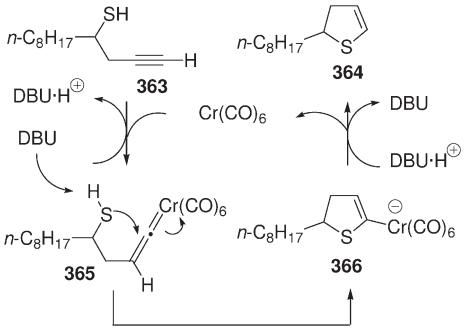


Figure 15.

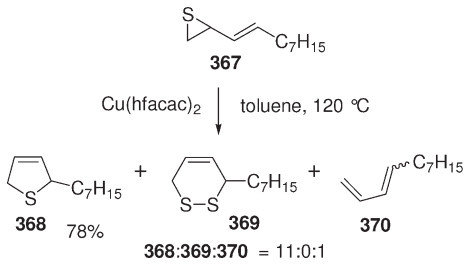
Scheme 66



Scheme 67



Scheme 68



Cycloisomerization proceeded by the initial formation of the vinylidene complex **365**, which underwent a DBU-promoted intramolecular nucleophilic addition affording the cyclic anionic intermediate **366**. Subsequent proton transfer gave rise to the dihydrothiophene **364** with concomitant regeneration of the DBU/$Cr(CO)_6$ system (Scheme 67).

In 2007, Njardarson and co-workers[148] reported the first successful example of a highly selective copper-catalyzed ring-expansion of vinyl thiiranes to 2,5-dihydrothiophenes. Detailed reactivity studies showed that better results could be obtained by the use of fluorinated copper(II) acetylacetonate (acac) catalysts, which are useful to minimize competing side reactions, such as sulfur extrusion and disulfide formation. As an example, heating a toluene solution of vinyl thiirane **367** at 120 °C in the presence of

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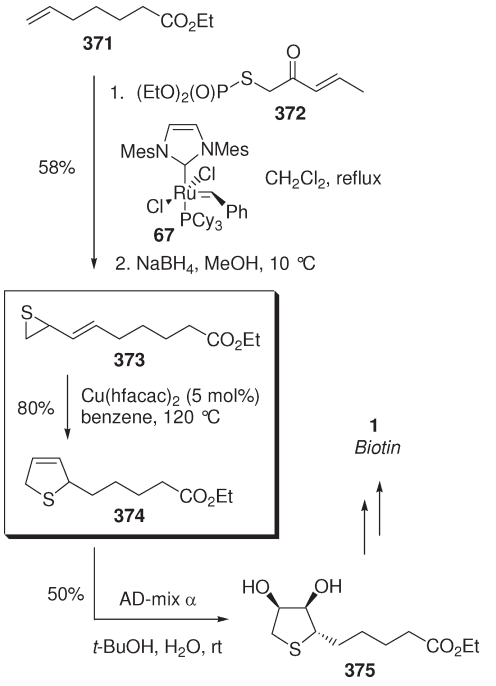
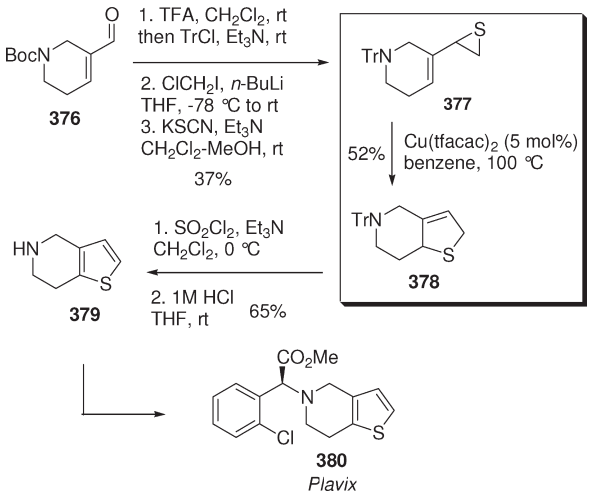
Scheme 69



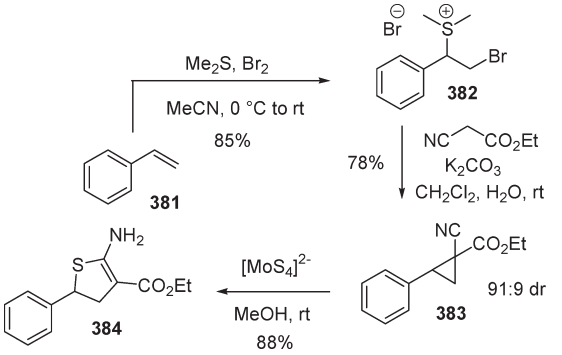
Scheme 70



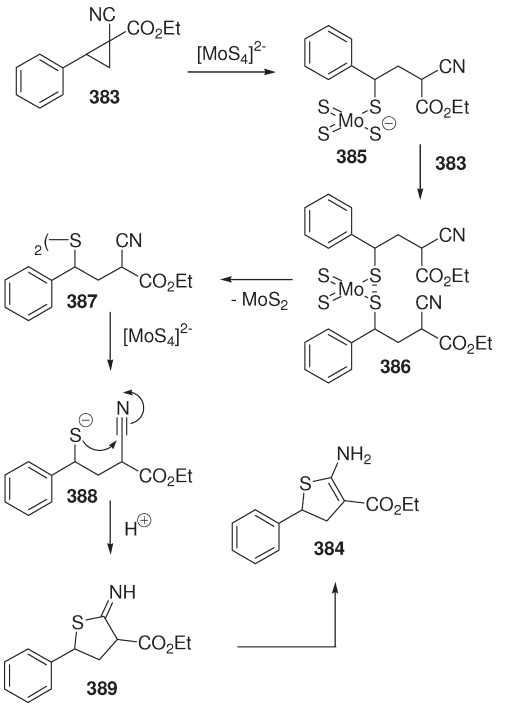
5 mol % copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] provided dihydrothiophene **368** as the major product (78% isolated yield), with other copper catalysts producing **368** along with variable amounts of disulfide **369** and diene **370** (Scheme 68).

This approach has been efficiently applied to a wide range of vinyl thiiranes with different substitution patterns, leading to excellent yields (up to 95%) of 2-substituted 2,5-dihydrothiophenes, comparing well with similar transformations employing vinyl oxiranes and vinyl aziridines as precursors of 2,5-dihydrofurans[149] and 3-pyrrolines,[150] respectively. In particular, vinyl thiiranes **373** (Scheme 69) and **377** (Scheme 70) underwent ring expansion to dihydrothiophenes **374** and **378**, key intermediates toward the synthesis of the biologically relevant compounds biotin **1** and Plavix **380**, respectively.

Scheme 71



Scheme 72



As shown in Scheme 69, vinyl thiirane **373**, readily prepared from ethyl 6-heptenoate **371** and enone thiophosphate **372** by sequential cross metathesis, $NaBH_4$ reduction, and in situ cyclization, did afford the rearranged dihydrothiophene **374** upon treatment with 5 mol % Cu(hfacac)$_2$ in benzene at 120 °C for 1.5 h. Compound **374** was eventually taken to diol **375**, an advanced intermediate in Ohrui's synthesis of biotin.[151]

On the other hand, vinyl thiirane **377**, prepared starting from the aldehyde **376** by standard chemistry, was converted into the fused dihydrothiophene **378** by action of copper(II) trifluoroacetylacetonate [Cu(tfacac)$_2$] (5 mol %) in benzene at 100 °C. Subsequent oxidation with sulfuryl chloride and deprotection of the nitrogen moiety afforded **379**, already taken to Plavix **380**[152] (Scheme 70).

Recently, it has been reported that a number of doubly activated cyclopropanes containing a cyano moiety geminal to an electron-withdrawing group underwent regioselective ring-opening reactions by action of tetrathiomolybdate anion as a

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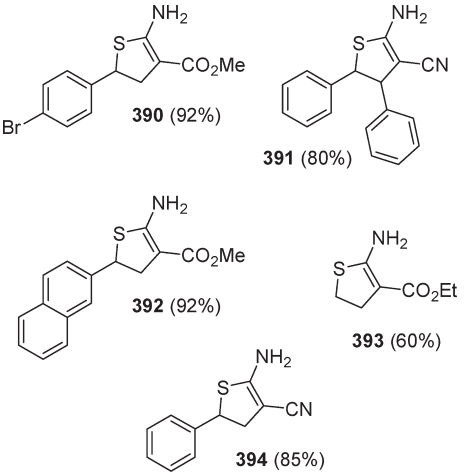


Figure 16.

sulfur-transfer reagent to provide 2-amino-4,5-dihydrothiophenes in excellent yields.[153] A representative example of this chemistry is depicted in Scheme 71. Thus, conversion of styrene to the corresponding bromosulfonium bromide **382** and subsequent treatment with ethyl cyanoacetate under basic conditions led to the formation of the cyclopropane **383** as a mixture of geometrical isomers in a 91:9 ratio (78% yield). Reaction of **383** with tetrathiomolybdate anion (1.2 equiv, MeOH, 28 °C, 1 h) gave rise to a single crystalline product, which was shown to be dihydrothiophene **384** by X-ray analysis.

Mechanistically, the formation of compound **384** could take place via a five-step pathway involving the initial nucleophilic ring-opening of cyclopropane **383** by action of tetrathiomolybdate anion to give the intermediate **385** (Scheme 72). Reaction of **385** with a second molecule of **383** produces the intermediate **386**, which undergoes an internal redox process to form the disulfide **387** by loss of MoS_2.

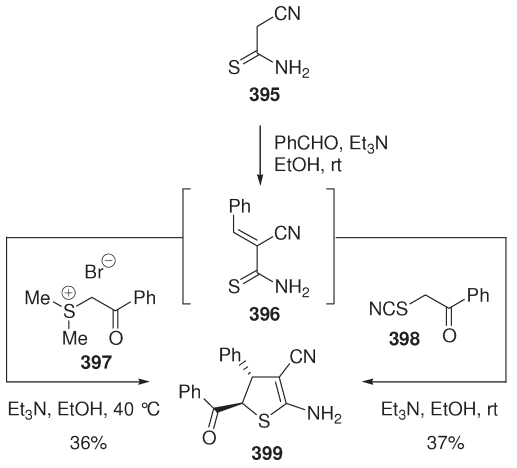
Reductive cleavage of **387** by reaction with tetrathiomolybdate followed by intramolecular cyclization of the released thiolate anion **388** produces **384** via the tautomeric dihydrothiophen-2-ylidenamine **389**. Extension of this methodology to various doubly activated cyclopropanes produced very good yields of 2-amino-4,5-dihydrothiophenes, with the most representative **390**−**394** being listed in Figure 16.

Considerable interest has been deserved since the early 1990s to the synthesis of 2-amino-4,5-dihydrothiophene derivatives. Many of these products have druglike structures and might therefore exhibit interesting biological activities.

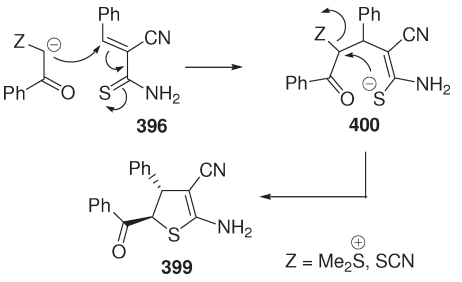
In this context, benzylidenecyanothioacetamide **396**, formed in situ by base-catalyzed condensation of benzaldehyde and α-cyanothioacetamide **395**, reacting with sulfonium bromide **397**[154] or phenacyl thiocyanate **398**[155] in the presence of Et_3N, gave rise to 4,5-*trans*-disubstituted dihydrothiophene compound **399** as the sole product, in yields of 36% and 37%, respectively (Scheme 73). These reactions are likely to proceed via the initial formation of a Michael adduct of general structure **400** from which the dihydrothiophene ring backbone is built through intramolecular nucleophilic displacement of dimethyl sulfide or thiocyanate ion (Scheme 74).

A wide range of *trans*-2-amino-4,5-dihydrothiophene-3-carbonitriles were obtained in moderate to good yields by using different arylidenecyanothioacetamides and readily available Michael donors.

Scheme 73



Scheme 74



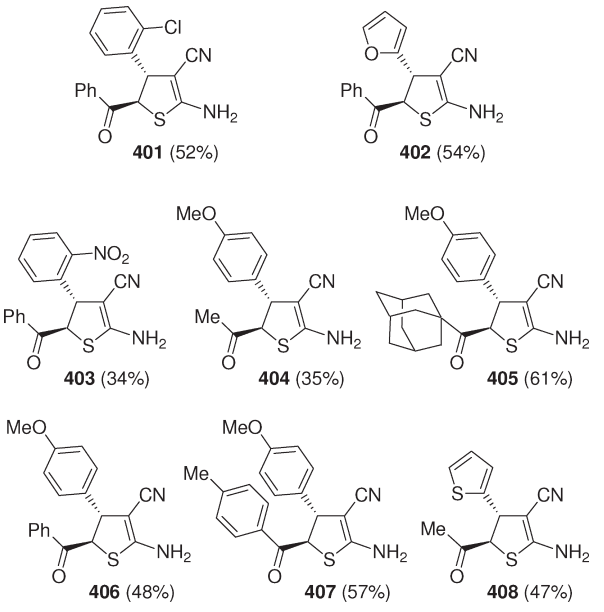


Figure 17.

The most representative examples **401**−**408** are listed in Figure 17. Interestingly, this approach worked well even with stabilized pyridinium ylides,[156,157] as recently demonstrated for the preparation of biologically active compound **15** starting from thioacetamide **409** and 2-picolinium bromide **410** (Scheme 75).[25]

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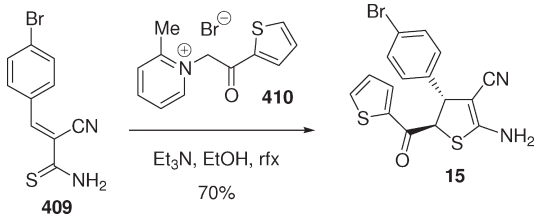
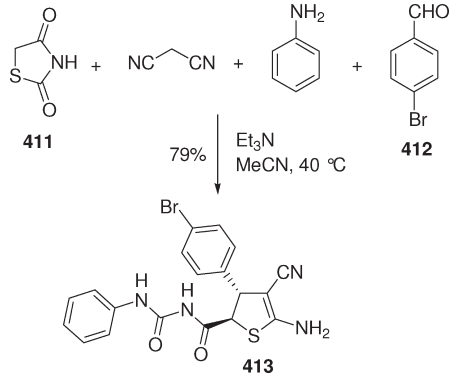
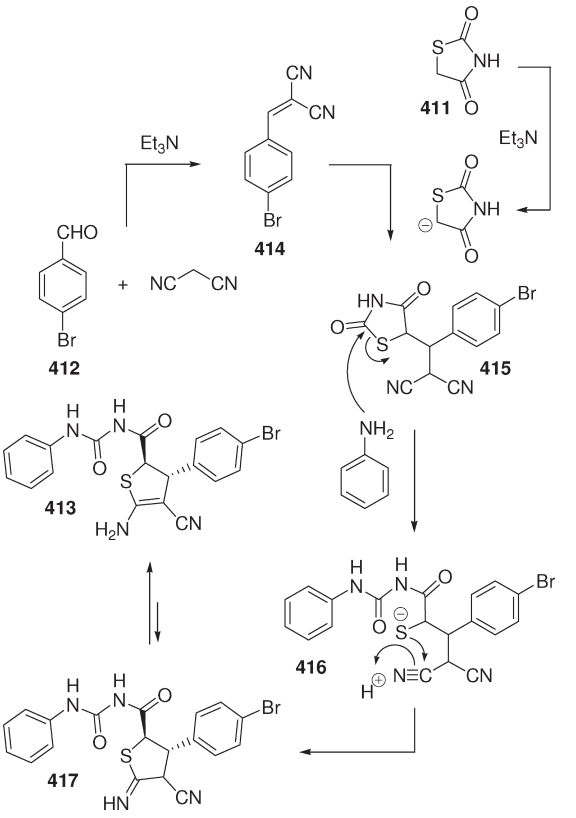
Scheme 75



Scheme 76



Scheme 77



A four-component domino reaction between 1,3-thiazolidinedione **411**, nitriles, aromatic aldehydes, and amines gave access to 2-amino-4-aryl-3-cyano-4,5-dihydrothiophenes substituted at C-5 with an ureidoformamide moiety. For instance, heating an acetonitrile solution containing equimolar amounts of **411**, *p*-bromobenzaldehyde **412**, malononitrile, and aniline in the presence of triethylamine as a base catalyst (25 mol %) for 48 h resulted in the formation of dihydrothiophene **413**, which has been obtained in 79% isolated yield (Scheme 76).[158]

The formation of **413** is likely to proceed through the mechanism outlined in Scheme 77. Thus, the arylidenemalononitrile **414**, produced by base-catalyzed Knoevenagel condensation between aldehyde **412** and malononitrile, reacted with the conjugate base of **411** leading to the intermediate adduct **415**. At this stage, aniline-promoted ring-opening of the 1,3-thiazolidinedione moiety and subsequent ring-forming reaction by thiolate addition on a cyano group gave **413** via the tautomeric imino derivative **417**.

This approach proved to run efficiently with a wide range of aldehydes and amines regardless of their substitution patterns,[159−162] providing the *S*-heterocycles exclusively as *trans*-isomers, in good yields, as depicted in Figure 18 for representative derivatives **418**−**424**.

Remarkably, a recent work by Cai and co-workers[163] demonstrated that the domino reactions also could be carried out successfully in a "green" solvent such as poly(ethylene glycol) (PEG) 400/H_2O system, allowing for shorter reaction times and easy product isolation. Furthermore, a series of dihydrothiophene derivatives were obtained by performing the domino reactions under ultrasound irradiation[164] as well as in the presence of the natural amino acid-based functional ionic liquid Bz-His(*n*-propyl)$_2$-OMe$^+$Br$^-$.[165]

Yamamoto and co-workers[166] developed a facile and efficient method for the synthesis of 3,4-dihalo-2,5-dihydrothiophenes through electrophilic iodocyclization of *S*-4-hydroxy-2-butynyl ethanethioates, as depicted in Scheme 78 for selected examples. Thus, treatment of **425** with iodine excess in CH_2Cl_2 at room temperature for 1 h resulted in the formation of 3,4-diiododihydrothiophene **426** in 76% yield, whereas reaction of **427** with IBr electrophile provided 3-bromo-4-iodo-dihydrothiophene **428** as a single regioisomer (76% yield).

Interestingly, compound **426** has been used to prepare 2,3,4,5-tetrasubstituted thiophenes, such as **429**, featuring interesting photophysical and electrochemical properties. The formation of **426** may be accounted for by the mechanism outlined in Scheme 79. Thus, iodine-triggered formation of the iodoallene **432** followed by iodothioetherification furnished the sulfonium derivative **434** eventually taken to **426** by removal of the acetyl group. A similar mechanism was likely operating when IBr was used as the Lewis acid initiator, thus accounting for the formation of dihydrothiophene **428**.

The generality of the new synthetic approach has been demonstrated by synthesizing several functionalized dihydrothiophenes, with the iodocyclization reaction being highly tolerant of wide-ranging functionalities and substitution patterns on the starting substrates. A selection of the results obtained is shown in Figure 19 for derivatives **435**−**443**.

A straightforward route for the preparation of dihydrothiophenes has been established through cyclization of benzyl alkynyl sulfides. In this context, the rapid and efficient 5-endo-dig iodocyclization of benzyl 4-aryl-3-butynyl sulfide derivatives[167] was the key step for the preparation of 2-aryl-3-iodo-4,5-dihydrothiophenes, precursors of combretastatin A-4 analogues featuring a thiophene ring as the spacer between the two phenyl groups.

As shown in Scheme 80, conversion of 3-butynol **444** to the corresponding benzyl sulfide, followed by coupling with aryliodide

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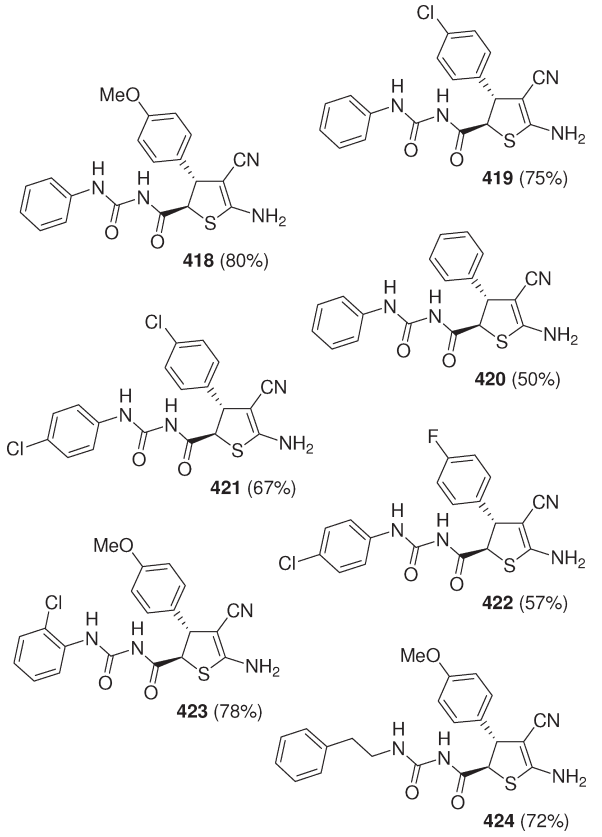
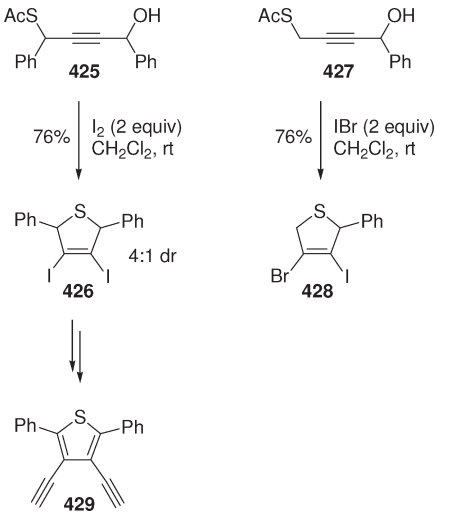


Figure 18.

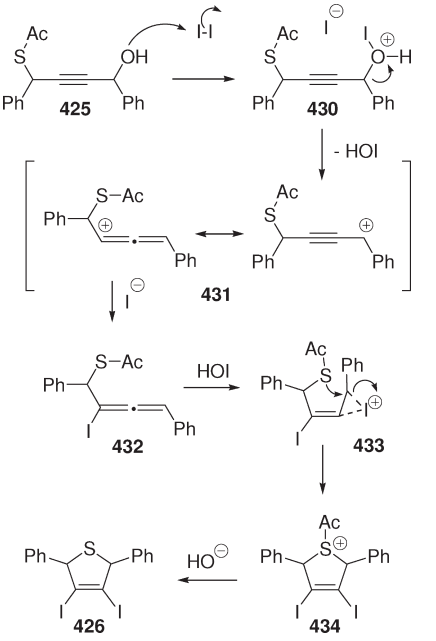
Scheme 78



445, provided the intermediate **446** in 87% overall yield. The latter, on treatment with iodine in dichloromethane, underwent quantitative transformation into dihydrothiophene **449**, which was used to prepare thiophene derivative **450**, a potent inhibitor of tubulin assembly.

Schwan and co-workers[168,169] discovered that aryl-substituted benzyl 1-alkynyl sulfides could be used to obtain 2-aryl 2,3-dihydrothiophenes in moderate to good yields through a *tert*-butoxide promoted 5-endo-trig cyclization. As an example, the reaction of the iodo derivative **451** with KO*t*-Bu (2 equiv) in

Scheme 79



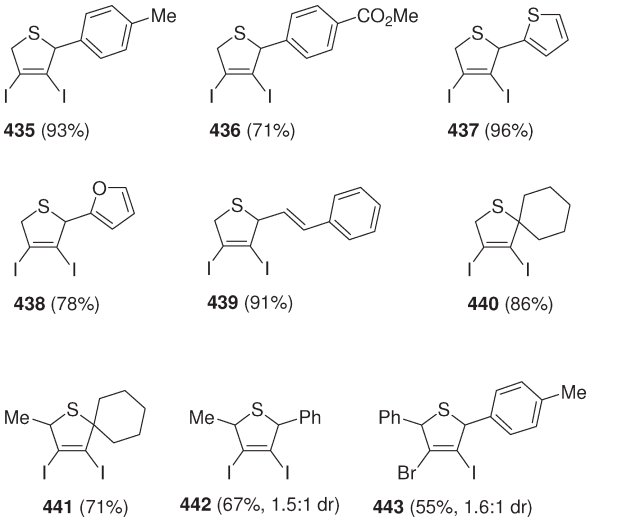


Figure 19.

acetonitrile at 0 °C for 24 h proceeded smoothly to afford a 75% yield of the dihydrothiophene compound **452** (Scheme 81).

Cyclization of several other aryl-substituted benzyl 1-alkynyl sulfides either at 0 °C or at reflux temperature provided 2-aryl 2,3-dihydrothiophenes **453**−**460** in moderate to good yields (Figure 20). Theoretical calculations on model system **461**[169] established that **452** and structurally related 2-aryl 2,3-dihydrothiophenes are formed through the mechanism depicted in Scheme 82, entailing the 5-endo-trig cyclization of allene anion **463** as the key step.

A highly stereoselective diene-transmissive Diels−Alder cycloaddition was the featured step in the preparation of dihydrothiophene scaffold **471**,[170] a useful precursor of an advanced intermediate toward the highly oxygenated triterpene quassinoids. As shown in Scheme 83, addition of alkynyllithium **467** to

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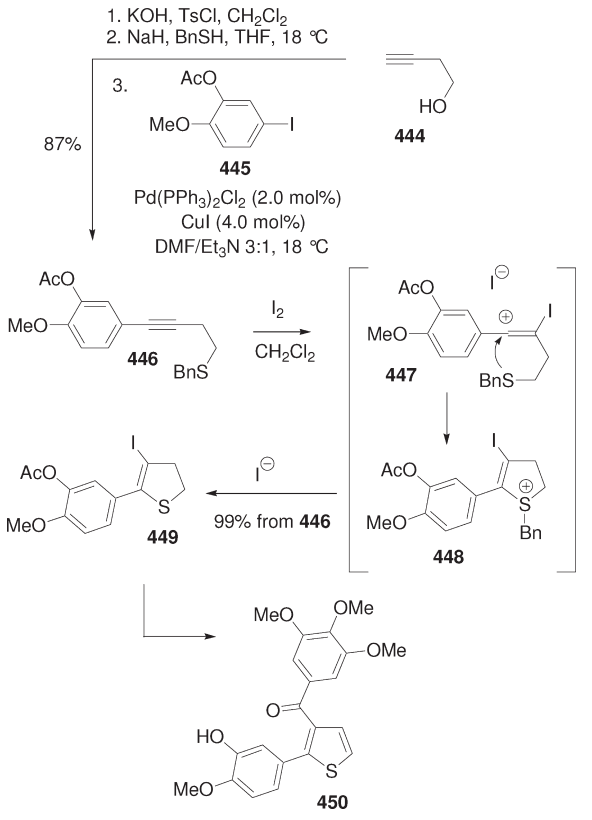
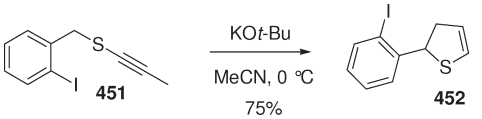
Scheme 80



Scheme 81



racemic α-chloroketone **466** furnished diastereoselectively the alkynyl oxirane **468** in 96% yield. Treatment of the latter with propenyllithium/CuCN system, followed by a thio-Mitsunobu reaction, gave the thioacetate **469** in 74% yield over two steps. An unusual deprotection with hydrazine hydrate[171] produced the nonisolated thiol **470**, which was directly coupled with methyl propiolate to provide bicyclic compound **471**, eventually taken to the advanced pentacyclic intermediate **472**.

The relative stereochemistry of **471** compares well with that of other similarly prepared compounds in the oxa-series.[172] It is likely that a reversible addition of thiol **470** to methyl propiolate generates the isomeric enethiol esters (*Z*)-**473** and (*E*)-**474**, with the latter undergoing a faster cycloaddition to produce **471** via the favored endo-transition state **475** (Scheme 84).

3.2. Synthesis of Racemic Tetrahydrothiophene Compounds

Tetrahydrothiophene compounds have been prepared using aluminacyclopentanes generated in situ through Zr-catalyzed cycloalumination reactions of olefins with organoaluminum species.[173] Thus, treatment of 1-hexene with $AlEt_3$ in the presence of catalytic amounts of Cp_2ZrCl_2 gave rise to 1-ethyl-3-butylaluminacyclopentane **477**, which was directly treated

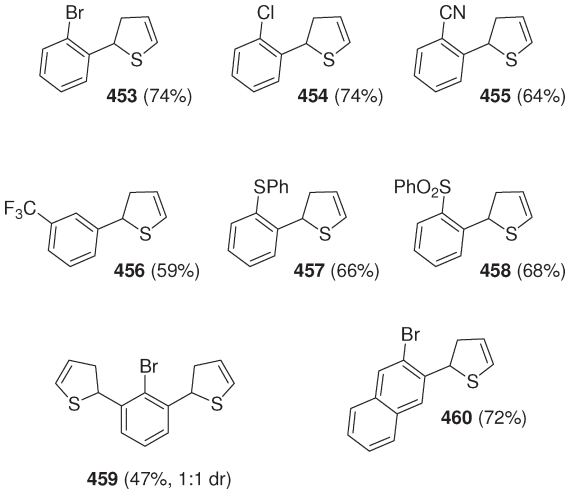
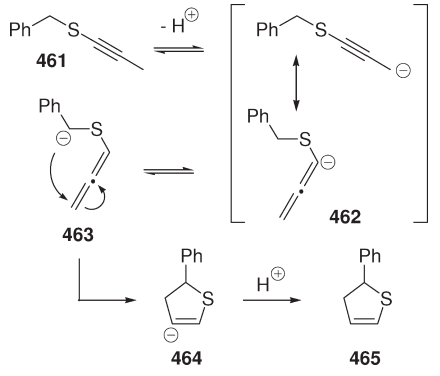


Figure 20.

Scheme 82



with thionyl chloride at −40 °C to provide 3-butyltetrahydrothiophene **481** in 85% yield via the sulfoxide intermediate **479** (Scheme 85).

This approach has been successfully applied to obtain *trans*-3,4-dialkyl-substituted tetrahydrothiophenes in very good yield. As an example, *trans*-3,4-dibenzyl tetrahydrothiophene **484** could be prepared in 80% yield from aluminacyclopentane **483**, in turn obtained from allyl benzene, $EtAlCl_2$, and Mg-metal in the presence of Cp_2ZrCl_2 catalyst (Scheme 86).

Quite surprisingly, although the synthesis of tetrahydrofuran compounds by exposure of oxetanes to electrophilic carbenes has been largely investigated,[174] less attention has been addressed to the use of thietanes as the counterparts of carbenes for preparing tetrahydrothiophenes.

This observation encouraged the Nair group[175] to investigate the chemical behavior of thietanes toward electrophilic carbene substrates generated by Rh(II)-catalyzed decomposition of diethyl diazomalonate. Initial studies in this area demonstrated that heating a benzene solution of thietane **485** (*cis*/*trans* ratio 1:2.2) in the presence of diethyldiazomalonate and $Rh_2(OAc)_4$ for 16 h, followed by chromatographic purification of the crude reaction mixture, led to diastereomeric tetrahydrothiophenes **487** (57%) and **488** (31%), along with allyl thioether **489** (9%), as depicted in Scheme 87.

The observed outcomes may be accounted for by the initial formation of sulfonium ylide **486**, which collapses to the

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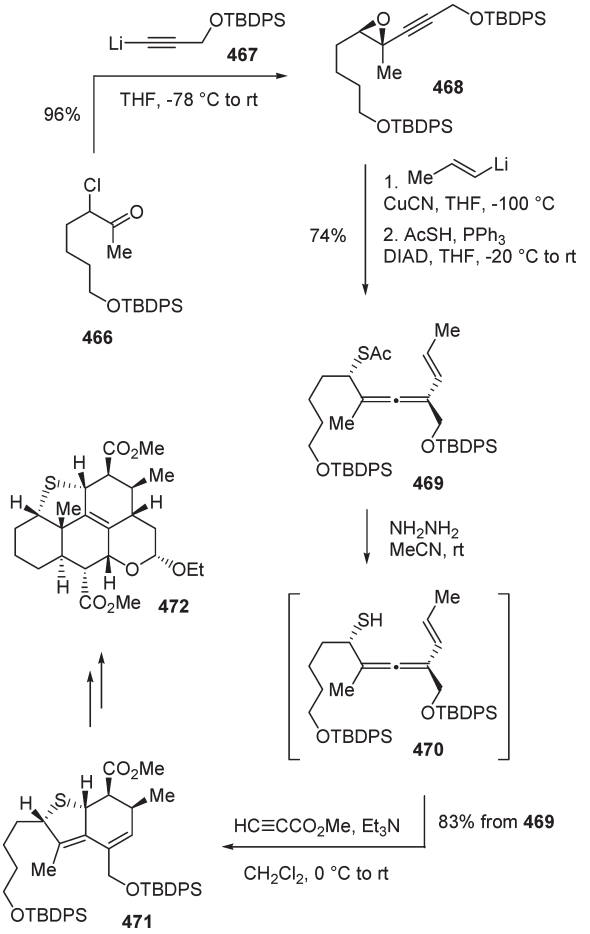
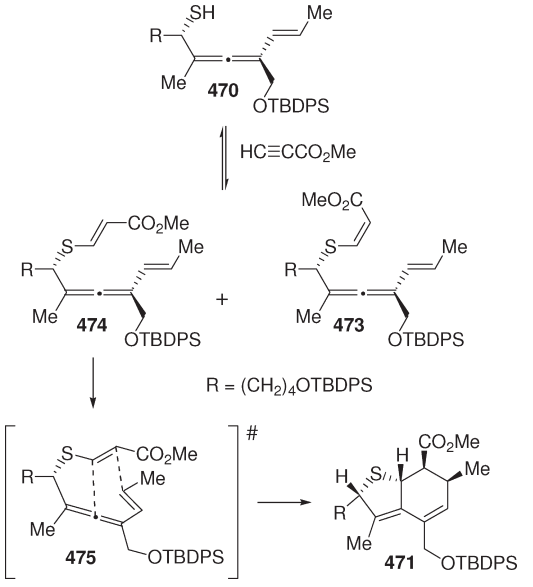
Scheme 83

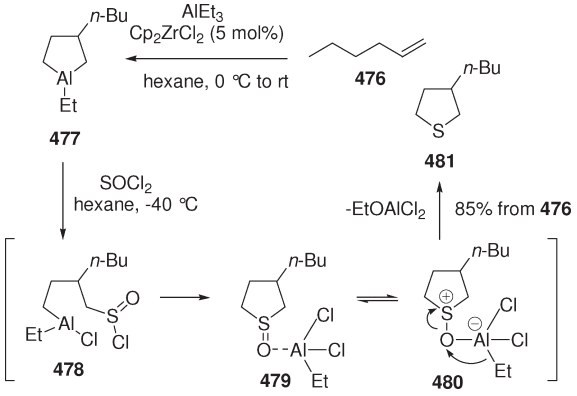


Scheme 84

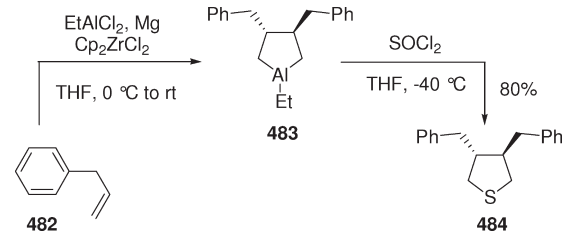


tetrahydrothiophene compounds by Stevens rearrangement.[176] Conversely, a β-elimination process is likely to be implicated in

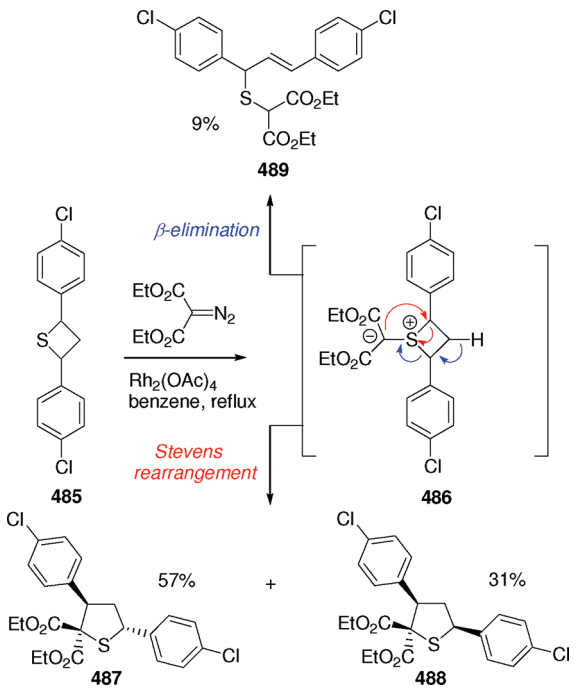
Scheme 85



Scheme 86



Scheme 87



the production of the open-chain derivative **489**. Successful results were also observed with 2-aryl-substituted and 2-alkyl-substituted thiethanes, with the expected tetrahydrothiophene scaffolds being obtained in appreciable yields, as shown in Figure 21 for compounds **490** and **491**.

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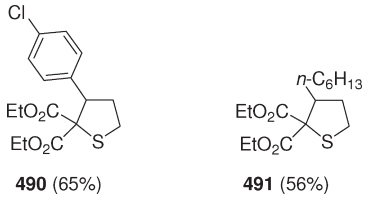
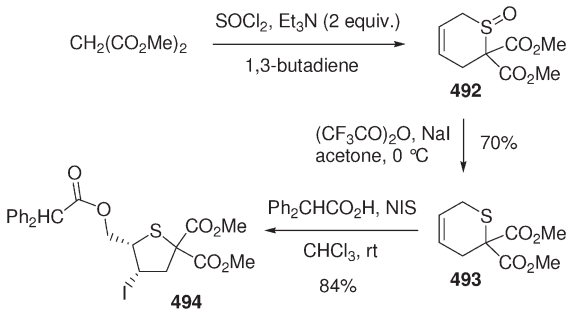


Figure 21.

Scheme 88



Lucassen and Zwanenburg[177] discovered an interesting stereocontrolled ring-contraction of 3,6-dihydro-2*H*-thiopyrans to 4,5-*cis*-substituted thiolanes. For example, 3,6-dihydro-2*H*-thiopyran **493**, in turn prepared by reaction of dimethyl malonate with thionyl chloride in the presence of triethylamine and 1,3-butadiene followed by reduction of the intermediate sulfoxide **492**, produced iodothiolane **494** upon treatment with *N*-iodosuccinimide and excess diphenylacetic acid in chloroform for 16 h at room temperature (Scheme 88). The formation of symmetrically 2,2-substituted thiolane **494** may be rationalized according to the mechanism shown in Scheme 89.

Thus, carbon−carbon double-bond oxidation by *N*-iodosuccinimide produced the bicyclic iodonium ion **495**, which rearranged to thiiranium ion **496**. Subsequent ring-opening by the carboxylate nucleophile produced the five-membered ring product **494**. Successful results also could be achieved by the use of various carboxylic acids, such as acetic acid, trichloroacetic acid, formic acid, and propiolic acid.

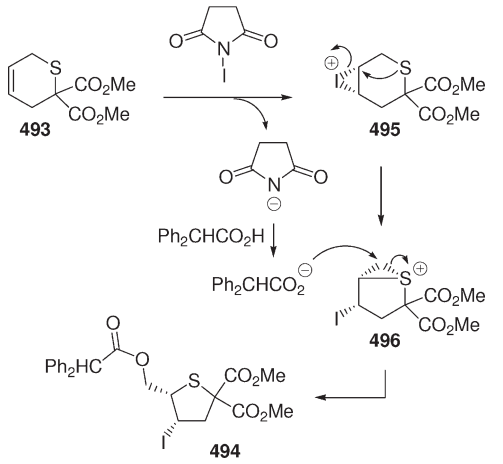
Interestingly, application of this method to dihydrothiopyrans derived from methyl phenylacetate, ethyl cyanoacetate, and diethyl cyanomethane phosphonate paved the way to the preparation of unsymmetrically 2,2-substituted thiolanes **497**−**502** as 1:1 mixtures of isomers in good to excellent yields (Figure 22).

A tandem annulation strategy featuring the use of both carbon−sulfur and carbon−carbon bond ring-forming reactions was deployed to the synthesis of polysubstituted thiophanes. Thus, a one-pot, base-catalyzed thia-Michael/cyclization sequence between ethyl 2-mercaptoacetate **503** and *trans*-cinnamaldehyde **280** provided the four diastereomeric racemates **504**−**507** (Scheme 90).[178]

The 3,4-disubstituted tetrahydrothiophene **509** has been obtained by tandem thia-Michael/Henry reaction between 2-nitroethyl acetate **508**, used as a stable precursor for nitroethylene, and 1,4-dithiane-2,5-diol **309**, as the masked form of mercaptoacetaldehyde (Scheme 91).[179]

Similarly, tetrahydrothiophene derivative **510** was obtained when **508** was employed as the counterpart of ethyl 4-mercapto-2-butenoate **287** in a tandem thia-Michael/Michael sequence.

Scheme 89



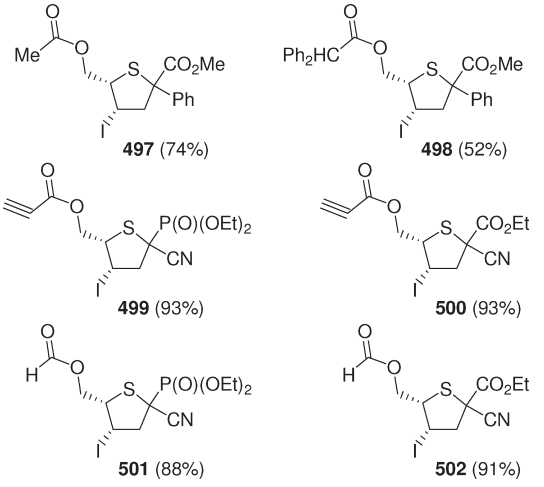


Figure 22.

The methodology based on tandem Michael−Henry and Michael−Michael reactions also has been applied successfully to the preparation of tetrahydrothiophenes **511**−**514**, depicted in Figure 23.

Recently, the tandem thia-Michael/Henry annulation strategy has been conveniently applied to the synthesis of cyclic nitroaldolization adducts via reaction between **309** and nitroalkenes in the presence of 20% triethylamine,[180] with the original reference[179] being rather surprisingly quoted only in the Supporting Information. The compounds obtained have been eventually converted into 3-nitro-2-substituted thiophenes by microwave irradiation on acidic alumina in the presence of chloranil.

Intramolecular Pauson−Khand reaction of substituted allyl propargyl sulfides has proven to be an effective tool for obtaining bicyclic ring systems featuring a tetrahydrothiophene nucleus fused with a cyclopentenone unit.[181] A recent application of this approach led to the "ketone biotin" **520** (Scheme 92).[182] Thus, the readily available propargyl alcohol **516**, on reaction with $Co_2(CO)_8$ followed by treatment with allyl mercaptan in the presence of $BF_3 \cdot Et_2O$, produced the intermediate **517**. The latter was not isolated but directly submitted to the pivotal Pauson−Khand cyclization in refluxing toluene to provide a

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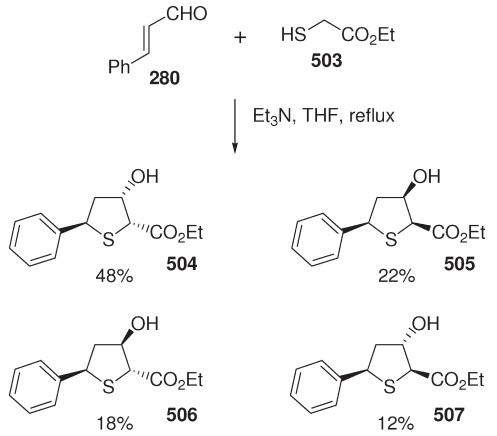
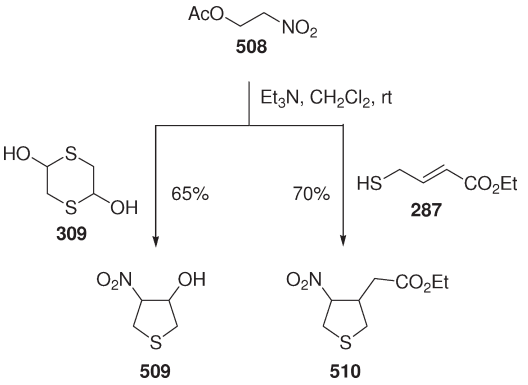
Scheme 90



Scheme 91



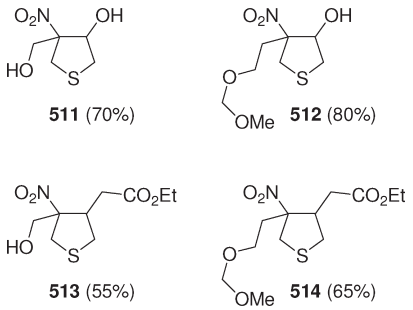
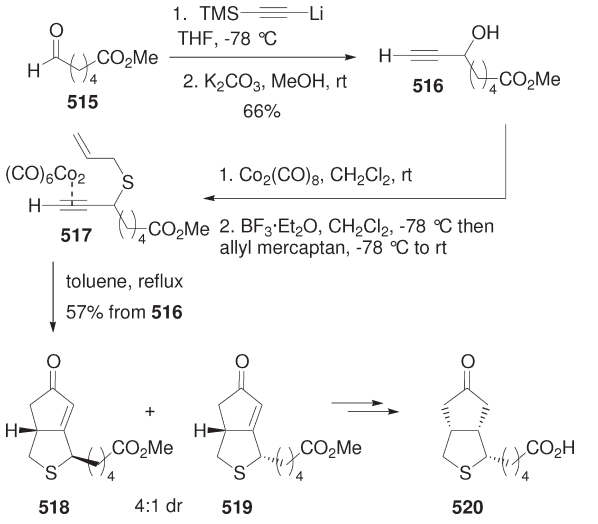
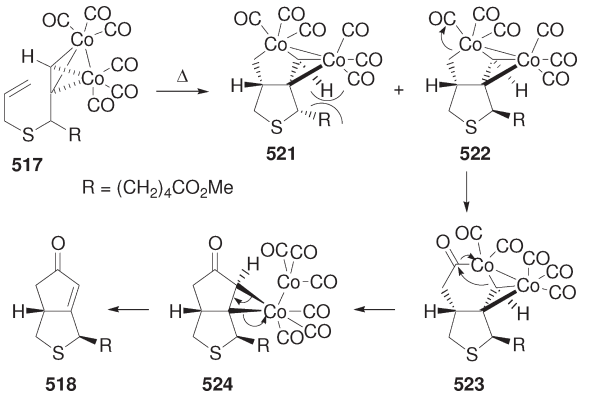


Figure 23.

Scheme 92



Scheme 93



metallocycle **522** would be preferentially formed as it minimizes the steric interactions between the valeric side chain and the acetylenic proton, whereas **521** has a severe 1,3-pseudodiaxial interaction in the sterically congested concave face.

The metallocycle **522** undergoes CO insertion to give the acyl−Co complex **523**, which collapses to compound **518** by migration of a carbon−cobalt bond to the adjacent carbonyl group followed by reductive elimination of the dicobalt carbonyl residue. A similar mechanistic pathway may be accounted for by the formation of the minor isomer **519** from cobalt−metallocycle **521**.

4. CONCLUSIVE REMARKS

Dihydro- and tetrahydrothiophenes represent an attractive class of compounds both from a synthetic as well as a biological point of view and have attracted the attention of many chemists, pharmacologists, and biologists in the last few decades. The high synthetic usefulness and the wide distribution in nature gave to dihydro- and tetrahydrothiophenes a privileged role in organic chemistry. Despite the number of approaches to these compounds, there are still many challenges in the area, focused, in particular, in structurally diverse and enantiopure materials, with the catalytic enantioselective

4:1 diastereomeric mixture of **518** and **519** in 57% yield, with the minor diastereomer being the precursor of the target compound **520**.

The unfavorable stereoselective outcome of the cyclization reaction can be tentatively explained on the basis of the mechanistic hypothesis proposed by Magnus and co-workers[183] for the synthesis of substituted bicyclo[3.3.0]octenones through intramolecular Pauson−Khand cyclization of suitable enynes. As shown in Scheme 93, complex **517** can produce *cis*-fused cobalt−metallocycles **521** and **522** via ligand exchange between a carbon monoxide residue and the olefin group, followed by alkene insertion into a carbon−cobalt bond. It is likely that the

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carbon−sulfur bond formation being the more promising approach to fulfill the above requirements.

This review clearly demonstrates that the rich chemistry of dihydro- and tetrahydrothiophenes has witnessed a great advance in the last few decades, with new applications and synthetic routes for these products being developed. Certainly, future research in this area will provide new routes and applications for these fascinating molecules.

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BIOGRAPHIES

Born in Ferrara, Simonetta Benetti (back, right) received her Degree in Chemistry in 1971 from the University of Ferrara. Since 1982 she has occupied the position of Associated Professor of Organic Chemistry at the "Dipartimento di Chimica" of the same university. Since 1971 she has carried out research on the synthesis of natural organic substances and their structural analogues of particular pharmaceutical interest and has studied new synthetic methods of general applicability.

Carmela De Risi (front, left) was born in Ferrara. She graduated in Chemistry at the University of Ferrara in 1992 and became "Dottore in Ricerca" in Organic Chemistry in 1996. In 1999 she was appointed as Researcher of Organic Chemistry at the "Dipartimento di Scienze Farmaceutiche" of the University of Ferrara. Her main research interests include the synthesis of biologically active natural and non-natural organic compounds, the chemistry of heterocycles, and the development of general synthetic methodologies.

Gian Piero Pollini (back, left) was born in Genoa. He graduated in chemistry from Pavia University in 1962 under the guidance of Prof. Giorgio Traverso. He began his research and teaching career in the University of Perugia as assistant professor (1964−1967), then (1968) he moved to the University of Ferrara where he was Professor of Organic Chemistry in the Faculty of Pharmacy from 1981 to 2010. He was Chairman of the "Dipartimento di Scienze Farmaceutiche" (1983−1990) and Dean of the Faculty of Pharmacy (1994−2000). At present he is Senior Scientist and Director of IUSS-1391 in the same university. His research interests include the development of new methods and reagents and their application to the synthesis of natural and non-natural targets with interesting biological and chemical properties.

Born in Fenil del Turco, Vinicio Zanirato (front, right) graduated in "Chimica e Tecnologia Farmaceutiche" at the University of Ferrara in 1982 and became "Dottore in Ricerca" in Pharmaceutical Sciences in 1987. In 1990 he was appointed as Researcher at the "Dipartimento di Scienze Farmaceutiche" of the University of Ferrara. In 1998 he was promoted to the position of Associate Professor at the University of Siena, and in January 2003 he came back to the University of Ferrara where he was appointed as an Associate Professor of Organic Chemistry at the Faculty of Pharmacy. His research interests include natural product synthesis and new reaction methodologies.

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REFERENCES

(1) Damani, L. A. In *Sulfur-containing drugs and related organic compounds: Chemistry, biochemistry, and toxicology*; Ellis Horwood Ltd.: Chichester, U.K., 1989; Vol. 1, Part B.

(2) Zempleni, J.; Wijeratne, S. S.; Hassan, Y. I. *Biofactors* **2009**, *35*, 36.

(3) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1997**, *38*, 8367.

(4) Yuasa, H.; Takada, J.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1137.

(5) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547.

(6) Matsuda, H.; Morikawa, T.; Yoshikawa, M. *Pure Appl. Chem.* **2002**, *74*, 1301.

(7) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339.

(8) Yoshikawa, M.; Xu, F. M.; Nakamura, S.; Wang, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Heterocycles* **2008**, *75*, 1397.

(9) Tanabe, G.; Sakano, M.; Minematsu, T.; Matsuda, H.; Yoshikawa, M.; Muraoka, O. *Tetrahedron* **2008**, *64*, 10080.

(10) Some recent examples: (a) Tanabe, G.; Yoshikai, K.; Hatanaka, T.; Yamamoto, M.; Shao, Y.; Minematsu, T.; Muraoka, O.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2007**, *15*, 3926. (b) Nasi, R.; Patrick, B. O.; Sim, L.; Rose, D. R.; Pinto, B. M. *J. Org. Chem.* **2008**, *73*, 6172. (c) Tanabe, G.; Xie, W.; Ogawa, A.; Cao, C.; Minematsu, T.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2195. (d) Eskandari, R.; Jones, K.; Rose, D. R.; Pinto, B. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5686. (e) Mohan, S.; Jayakanthan, K.; Nasi, R.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Org. Lett.* **2010**, *12*, 1088. (f) Eskandari, R.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Org. Lett.* **2010**, *12*, 1632.

(11) Yuasa, H.; Takada, J.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1137.

(12) Siriwardena, A. H.; Chiaroni, A.; Riche, C.; El-Daher, S.; Winchester, B.; Grierson, D. S. *J. Chem. Soc., Chem. Commun.* **1992**, 1531.

(13) Jeong, L. S.; Choe, S. A.; Gunaga, P.; Kim, H. O.; Lee, H. W.; Lee, S. K.; Tosh, D. K.; Patel, A.; Palaniappan, K. K.; Gao, Z.-G.; Jacobson, K. A.; Moon, H. R. *J. Med. Chem.* **2007**, *50*, 3159.

(14) Satoh, H.; Yoshimura, Y.; Sakata, S.; Miura, S.; Machida, H.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 989.

(15) Ohtsuka, T.; Kotaki, H.; Nakayama, N.; Itezono, Y.; Shimma, N.; Kudoh, T.; Kuwahara, T.; Arisawa, M.; Yokose, K. *J. Antibiot.* **1993**, *46*, 11.

(16) Volkmann, R. A.; Kelbaugh, P. R.; Nason, D. M.; Jasys, V. J. *J. Org. Chem.* **1992**, *57*, 4352.

(17) (a) Liang, J.; Jenne, S. J.; Mundorff, E.; Voladri, R.; Lalonde, J.; Huisman, G. WO patent 2009/029554 A2, 2009. (b) Liang, J.; Jenne, S. J.;

Mundorff, E.; Voladri, R.; Lalonde, J.; Huisman, G. U.S. patent 2009/0093031 A1, 2009. (c) Liang, J.; Jenne, S. J.; Mundorff, E.; Voladri, R.; Lalonde, J.; Huisman, G. U.S. patent 7,977,078 B2, 2011. (d) Liang, J.; Jenne, S. J.; Mundorff, E.; Voladri, R.; Lalonde, J.; Huisman, G. U.S. patent 2011/0217754 A1, 2011.

(18) Liang, J.; Mundorff, E.; Voladri, R.; Jenne, S.; Gilson, L.; Conway, A.; Krebber, A.; Wong, J.; Huisman, G.; Truesdell, S.; Lalonde, J. *Org. Process Res. Dev.* **2010**, *14*, 188.

(19) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976.

(20) Davoust, M.; Brière, J.-F.; Jaffrès, P.-A.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 4166.

(21) Ye, L. W.; Sun, X.-L.; Li, C.-Y.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 1335.

(22) Noh, J.; Jeong, Y.; Ito, E.; Hara, M. *J. Phys. Chem. C* **2007**, *111*, 2691.

(23) Qiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 6206.

(24) Zhu, W.; Chong, Y.; Choo, H.; Mathews, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 1631.

(25) Darwish, E. S. *Molecules* **2008**, *13*, 1066.

(26) Chatterjee, M.; Mah, S. C.; Tullius, T. D.; Townsend, C. A. *J. Am. Chem. Soc.* **1995**, *117*, 8074.

(27) Martyres, D. H.; Baldwin, J. E.; Adlington, R. M.; Lee, V.; Probert, M. R.; Watkin, D. J. *Tetrahedron* **2001**, *57*, 4999.

(28) Dong, S.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1580.

(29) (a) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609. (b) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133.

(30) (a) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (b) Pellissier, E. *Tetrahedron* **2006**, *62*, 5559. (c) Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129. (d) Wojaczyńska, E.; Wojaczyński, J. *Chem. Rev.* **2010**, *110*, 4303.

(31) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.

(32) Seki, M. *Med. Res. Rev.* **2006**, *26*, 434.

(33) *Asymmetric synthesis—The essentials*; Christmann, M., Brase, S., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 2007.

(34) Potts, K. T. Mesoionic Ring Systems. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, p 1.

(35) Ávalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Diánez, M. J.; Estrada, M. D.; Jiménez, J. L.; López-Castro, A.; Palacios, J. C.; Garrido, S. P. *J. Chem. Soc., Chem. Commun.* **1995**, 2213.

(36) Ávalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738.

(37) Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Acc. Chem. Res.* **2005**, *38*, 460.

(38) Areces, P.; Ávalos, M.; Babiano, R.; Cintas, P.; González, L.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Eur. J. Org. Chem.* **2001**, 2135.

(39) Ávalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C.; Raithby, P. R. *J. Org. Chem.* **2000**, *65*, 5089.

(40) Ávalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2261.

(41) Ávalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139.

(42) Karlsson, S.; Högberg, H.-E. *Org. Lett.* **1999**, *1*, 1667.

(43) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1613.

(44) Corsaro, A.; Pistarà, V.; Chiacchio, M. A.; Vittorino, E.; Romeo, R. *Tetrahedron Lett.* **2007**, *48*, 4915.

(45) Marchand, P.; Gulea, M.; Masson, S.; Saquet, M.; Collignon, N. *Org. Lett.* **2000**, *2*, 3757.

(46) Minville, J.; Girardin, M.; Spino, C. *Can. J. Chem.* **2007**, *85*, 603.

(47) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

(48) For an application of Grubbs−Nolan catalyst in metathesis reactions of sulfur-containing compounds, see: Spagnol, G.; Heck, M.-P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767.

(49) Desmaële, D.; Delarue-Cochin, S.; Cavé, C.; d'Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421.

(50) Tran Huu Dau, M. E.; Riche, C.; Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1059.

(51) Chavan, S. P.; Chittiboyina, A. G.; Ramakrishna, G.; Tejwani, R. B.; Ravindranathan, T.; Kamat, S. K.; Rai, B.; Sivadasan, L.; Balakrishnan, K.; Ramalingam, S.; Deshpande, V. H. *Tetrahedron* **2005**, *61*, 9273.

(52) Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

(53) (a) Yokoyama, M. *Synthesis* **2000**, *12*, 1637. (b) Gunaga, P.; Moon, H. R.; Choi, W. J.; Shin, D. H.; Park, J. G.; Jeong, L. S. *Curr. Med. Chem.* **2004**, *11*, 2585. (c) Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337.

(54) For some examples, see: (a) Branalt, J.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 1783. (b) Mann, J.; Tench, A. J.; Weymouth-Wilson, A. C.; Shaw-Ponter, S.; Young, R. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 677. (c) Ponter-Shaw, S.; Rider, P.; Young, R. J. *Tetrahedron Lett.* **1996**, *37*, 1871. (d) Birk, C.; Voss, J.; Wirsching, J. *Carbohydr. Res.* **1997**, *304*, 239. (e) Jeong, L. S.; Moon, H. R.; Choi, Y. J.; Chun, M. W.; Kim, H. O. *J. Org. Chem.* **1998**, *63*, 4821. (f) Secrist, J. A., III; Tiwari, K. N.; Shortnacy-Fowler, A. T.; Messini, L.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1998**, *41*, 3865.

(55) Wirsching, J.; Voss, J. *Eur. J. Org. Chem.* **1999**, 691.

(56) Miller, J. A.; Pugh, A. W.; Ullah, G. M.; Gutteridge, C. *Tetrahedron Lett.* **2000**, *41*, 10099.

(57) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.

(58) Trost, B. M.; Nubling, C. *Carbohydr. Res.* **1990**, *202*, 1.

(59) Yamagata, K.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3355.

(60) Rahim, S. G.; Trivedi, N.; Bogunovic-Batchelor, M. V.; Hardy, G. W.; Mills, G.; Selway, J. W. T.; Snowden, W.; Littler, E.; Coe, P. L.; Basnak, I.; Whale, R. F.; Walker, R. T. *J. Med. Chem.* **1996**, *39*, 789.

(61) (a) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carbohydr. Res.* **1991**, *216*, 237. (b) Birk, C.; Voss, J.; Wirsching, J. *Carbohydr. Res.* **1997**, *304*, 239.

(62) Chapdelaine, D.; Cardinal-David, B.; Prévost, M.; Gagnon, M.; Thumin, I.; Guindon, Y. *J. Am. Chem. Soc.* **2009**, *131*, 17242.

(63) Minakawa, N.; Kato, Y.; Uetake, K.; Kaga, D.; Matsuda, A. *Tetrahedron* **2003**, *59*, 1699.

(64) Minakawa, N.; Kaga, D.; Kato, Y.; Endo, K.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2182.

(65) Muraoka, O.; Yoshikai, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2006**, *14*, 500.

(66) Ghavami, A.; Sadalapure, K. S.; Johnston, B. D.; Lobera, M.; Snider, B. B.; Pinto, B. M. *Synlett* **2003**, 1259.

(67) For an account on synthetic approaches to salacinol, see: Mohan, S.; Pinto, B. M. *Carbohydr. Res.* **2007**, *342*, 1551.

(68) Jayakanthan, K.; Mohan, S.; Pinto, B. M. *J. Am. Chem. Soc.* **2009**, *131*, 5621.

(69) Johnston, B. D.; Jensen, H. H.; Pinto, B. M. *J. Org. Chem.* **2006**, *71*, 1111.

(70) Gunaga, P.; Kim, H. O.; Lee, H. W.; Tosh, D. K.; Ryu, J.-S.; Choi, S.; Jeong, L. S. *Org. Lett.* **2006**, *8*, 4267.

(71) Zhang, X.; Xia, H.; Dong, X.; Jin, J.; Meng, W.-D.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 9026.

(72) Wu, Y.-Y.; Zhang, X.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 3941.

(73) Yue, X.; Wu, Y.-Y.; Qing, F.-L. *Tetrahedron* **2007**, *63*, 1560.

(74) Zheng, F.; Zhang, X.; Qing, F.-L. *Chem. Commun.* **2009**, 1505.

(75) Zheng, F.; Fu, L.; Wang, R.; Qing, F.-L. *Org. Biomol. Chem.* **2010**, *8*, 163.

(76) Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2002**, *43*, 815.

(77) Danquigny, A.; Benazza, M.; Protois, S.; Demailly, G. *Tetrahedron Lett.* **2004**, *45*, 4365.

(78) Danquigny, A.; Meziane, M. A. A.; Demailly, G.; Benazza, M. *Tetrahedron* **2005**, *61*, 6772.
(79) Izquierdo, I.; Plaza, M.-T.; Asenjo, R.; Rodríguez, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1117.
(80) Izquierdo, I.; Plaza, M.-T.; Ramírez, A.; Aragón, F. *J. Heterocycl. Chem.* **1996**, *33*, 1239.
(81) Izquierdo, I.; Plaza, M.-T.; Aragón, F. *Tetrahedron: Asymmetry* **1996**, *7*, 2567.
(82) Izquierdo, I.; Plaza, M.-T.; Asenjo, R.; Ramírez, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1417.
(83) Riedner, J.; Robina, I.; Fernández-Bolaños, J. G.; Gómez-Bujedo, S.; Fuentes, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3391.
(84) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827.
(85) Besada, P.; Pérez, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 6941.
(86) Cerè, V.; Peri, F.; Pollicino, S. *J. Org. Chem.* **1997**, *62*, 8572.
(87) Cope, A. C.; Shen, T. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5916.
(88) Fuzier, M.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1995**, *36*, 6443.
(89) Arcelli, A.; Cerè, V.; Peri, F.; Pollicino, S.; Sabatino, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1389.
(90) Kuszmann, J.; Sohar, P. *Carbohydr. Res.* **1977**, *56*, 105.
(91) Yoshimura, Y.; Kuze, T.; Ueno, M.; Komiya, F.; Haraguchi, K.; Tanaka, H.; Kano, F.; Yamada, K.; Asami, K.; Kaneko, N.; Takahata, H. *Tetrahedron Lett.* **2006**, *47*, 591.
(92) Ghosh, A. K.; Thompson, W. J.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 924.
(93) Molina Ponce, A.; Overman, L. E. *J. Am. Chem. Soc.* **2000**, *122*, 8672.
(94) (a) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329. (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.
(95) Young, R. J.; Shaw-Ponter, S.; Thomson, J. B.; Miller, J. A.; Cumming, J. G.; Pugh, A. W.; Rider, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2599.
(96) Jana, G.; Viso, A.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2003**, 209.
(97) Bilokin, Y. V.; Melman, A.; Niddam, V.; Benhamú, B.; Bachi, M. D. *Tetrahedron* **2000**, *56*, 3425.
(98) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943.
(99) (a) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (b) Rudolph, M.; Hashmi, S. K. *Chem. Commun.* **2011**, *47*, 6536.
(100) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897.
(101) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063.
(102) Yao, Q. *Org. Lett.* **2002**, *4*, 427.
(103) (a) Negishi, Y.; Tsukuda, T. *J. Am. Chem. Soc.* **2003**, *125*, 4046. (b) Jadzinsky, P. D.; Calero, G.; Ackerson, C. J.; Bushnell, D. A.; Kornberg, R. D. *Science* **2007**, *318*, 430.
(104) Ando, K. *J. Org. Chem.* **2010**, *75*, 8516.
(105) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.
(106) Díez, D.; Templo Benéitez, M. T.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Molecules* **2004**, *9*, 323.
(107) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986.
(108) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2009**, *50*, 2946.
(109) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833.
(110) Yu, C.; Zhang, Y.; Song, A.; Ji, Y.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 770.
(111) For recent reviews on chiral prolinol silyl ethers promoted reactions, see: (a) Palomo, C.; Mielgo, A. *Chem. Asian J.* **2008**, *3*, 922. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.
(112) For recent reviews on ureas and thioureas as hydrogen-bonding donors, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.
(113) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
(114) Baricordi, N.; Benetti, S.; De Risi, C.; Fogagnolo, M.; Pollini, G. P.; Zanirato, V. *Lett. Org. Chem.* **2009**, *6*, 593.
(115) Tang, J.; Xu, D. Q.; Xia, A. B.; Wang, Y. F.; Jiang, J. R.; Luo, S. P.; Xu, Z. Y. *Adv. Synth. Catal.* **2010**, *352*, 2121.
(116) For reviews on enzymatic desymmetrization, see: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110.
(117) For a review on nonenzymatic desymmetrization, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.
(118) Kielbasiński, P.; Albrycht, M.; Mikolajczyk, M.; Wieczorek, M. W.; Majzner, W. R.; Filipczak, A.; Ciolkiewicz, P. *Heteroat. Chem.* **2005**, *16*, 93.
(119) Otten, S.; Fröhlich, R.; Haufe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 189.
(120) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765.
(121) For some examples, see: (a) Julienne, K.; Metzner, P.; Henryon, V.; Greiner, A. *J. Org. Chem.* **1998**, *63*, 4532. (b) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731. (c) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620.
(122) Fechter, M. H.; Gruber, K.; Avi, M.; Skranc, W.; Schuster, C.; Pöchlauer, P.; Klepp, K. O.; Griengl, H. *Chem.—Eur. J.* **2007**, *13*, 3369.
(123) Jones, J. B.; Schwartz, H. M. *Can. J. Chem.* **1981**, *59*, 1574.
(124) Nagai, H.; Konuki, K.; Ito, M.; Sameshima, T. U.S. Patent 2008/0050787 A1, 2008.
(125) Chen, F.-E.; Chen, X.-X.; Dai, H.-F.; Kuang, Y.-Y.; Xie, B.; Zhao, J.-F. *Adv. Synth. Catal.* **2005**, *347*, 549.
(126) (a) Seki, M.; Shimizu, T.; Inubushi, K. *Synthesis* **2002**, 361. (b) Seki, M.; Kimura, M.; Hatsuda, M.; Yoshida, S.-i.; Shimizu, T. *Tetrahedron Lett.* **2003**, *44*, 8905. (c) Mori, Y.; Kimura, M.; Seki, M. *Synthesis* **2003**, 2311. (d) Seki, M.; Hatsuda, M.; Yoshida, S.-i. *Tetrahedron Lett.* **2004**, *45*, 6579. (e) Seki, M.; Hatsuda, M.; Mori, Y.; Yoshida, S.-i.; Yamada, S.-i.; Shimizu, T. *Chem.—Eur. J.* **2004**, *10*, 6102.
(127) Zheng, J.-Y.; Wang, Z.; Zhu, Q.; Zhang, Y.-J.; Yan, H.-D. *J. Mol. Catal. B: Enzym.* **2009**, *56*, 20.
(128) Kim, B. M.; Bae, S. J.; Seomoon, G. *Tetrahedron Lett.* **1998**, *39*, 6921.
(129) Miyake, Y.; Takada, H.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1595.
(130) Achiwa, K.; Morimoto, Y.; Terao, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2266.
(131) (a) Harpp, D. N.; Gleason, J. G.; Snyder, J. P. *J. Am. Chem. Soc.* **1968**, *90*, 4181. (b) Harpp, D. N.; Gleason, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 2437.
(132) For a recent review on asymmetric alcoholysis, see: Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.
(133) Hanbauer, M. H. F.; Winkler, B.; Stanek, M.; Schoppel, G.; Wehrli, C. WO patent 2008/071696 A1, 2008.
(134) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737.
(135) Huang, J.; Xiong, F.; Chen, F.-E. *Tetrahedron: Asymmetry* **2008**, *19*, 1436.
(136) Dai, H.-F.; Chen, W.-X.; Zhao, L.; Xiong, F.; Sheng, H.; Chen, F.-E. *Adv. Synth. Catal.* **2008**, *350*, 1635.
(137) Xiong, F.; Chen, X.-X.; Chen, F.-E. *Tetrahedron: Asymmetry* **2010**, *21*, 665.
(138) Chen, X.-X.; Xiong, F.; Fu, H.; Liu, Z.-Q.; Chen, F.-E. *Chem. Pharm. Bull.* **2011**, *59*, 488.
(139) Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2009**, *351*, 547.
(140) Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Lett.* **1999**, *40*, 8873.
(141) Chen, F.-E.; Dai, H.-F.; Kuang, Y.-Y.; Jia, H.-Q. *Tetrahedron: Asymmetry* **2003**, *14*, 3667.

(142) Chen, F.-E.; Yuan, J.-L.; Dai, H.-F.; Kuang, Y.-Y.; Chu, Y. *Synthesis* **2003**, 2155.
(143) Chen, F.-E.; Jia, H.-Q.; Chen, X.-X.; Dai, H.-F.; Xie, B.; Kuang, Y.-Y.; Zhao, J.-F. *Chem. Pharm. Bull.* **2005**, *53*, 743.
(144) Rahim, Md. A.; Fujiwara, T.; Takeda, T. *Synlett* **1999**, 1029.
(145) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.
(146) McDonald, F. E. *Chem.—Eur. J.* **1999**, *5*, 3103.
(147) McDonald, F. E.; Burova, S. A.; Huffman, L. G., Jr. *Synthesis* **2000**, 970.
(148) Rogers, E.; Araki, H.; Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2007**, *129*, 2768.
(149) Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054.
(150) Brichacek, M.; Lee, D. E.; Njardarson, J. T. *Org. Lett.* **2008**, *10*, 5023.
(151) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, *16*, 2765.
(152) Bouisset, M.; Radisson, J. U.S. Patent 5,036,156, 1991.
(153) Gopinath, P.; Chandrasekaran, S. *J. Org. Chem.* **2011**, *76*, 700.
(154) Samet, A. V.; Shestopalov, A. M.; Nesterov, V. N.; Semenov, V. V. *Synthesis* **1997**, 623.
(155) Dotsenko, V. V.; Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 1431.
(156) Shestopalov, A. M.; Bogomolova, O. P.; Litvinov, V. P. *Synthesis* **1991**, 277.
(157) Dawood, K. M. *Synth. Commun.* **2001**, *31*, 1647.
(158) Sun, J.; Xia, E.-Y.; Zhang, L.-L.; Yan, C.-G. *Eur. J. Org. Chem.* **2009**, 5247.
(159) Sun, J.; Zhang, L.-L.; Xia, E.-Y.; Yan, C.-G. *J. Org. Chem.* **2009**, *74*, 3398.
(160) Sun, J.; Xia, E.-Y.; Zhang, L.-L.; Yan, C.-G. *Sci. China Chem.* **2010**, *53*, 863.
(161) Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. *Synthesis* **2010**, 3987.
(162) Sun, J.; Xia, E.-Y.; Yao, R.; Yan, C.-G. *Mol. Divers.* **2011**, *15*, 115.
(163) Lu, G.-p.; Zeng, L.-Y.; Cai, C. *Green Chem.* **2011**, *13*, 998.
(164) Shi, D.-Q.; Zou, Y.; Hu, Y.; Wu, H. *J. Heterocycl. Chem.* **2011**, *48*, 896.
(165) Kumar, A.; Gupta, G.; Srivastava, S. *Green Chem.* **2011**, *13*, 2459.
(166) Yang, F.; Jin, T.; Bao, M.; Yamamoto, Y. *Tetrahedron Lett.* **2011**, *52*, 936.
(167) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341.
(168) McConachie, L. K.; Schwan, A. L. *Tetrahedron Lett.* **2000**, *41*, 5637.
(169) Motto, J. M.; Castillo, Á.; Greer, A.; Montemayer, L. K.; Sheepwash, E. E.; Schwan, A. L. *Tetrahedron* **2011**, *67*, 1002.
(170) Dion, A.; Dubé, P.; Spino, C. *Org. Lett.* **2005**, *7*, 5601.
(171) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.
(172) Spino, C.; Hill, B.; Dubé, P.; Gingras, S. *Can. J. Chem.* **2003**, *81*, 81.
(173) Dzhemilev, U. M.; Ibragimov, A. G.; Gilyazev, R. R.; Khafizova, L. O. *Tetrahedron* **2004**, *60*, 1281.
(174) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
(175) Nair, V.; Nair, S. M.; Mathai, S.; Liebscher, J.; Ziemer, B.; Narsimulu, K. *Tetrahedron Lett.* **2004**, *45*, 5759.
(176) Pine, S. H. *Org. React.* **1970**, 18.
(177) Lucassen, A. C. B.; Zwanenburg, B. *Eur. J. Org. Chem.* **2004**, 74.
(178) Juárez, E.; García, A.; Hommer, H.; Salas, M.; Gordillo, B. *Heteroat. Chem.* **2006**, *17*, 289.
(179) Barco, A.; Baricordi, N.; Benetti, S.; De Risi, C.; Pollini, G. P. *Tetrahedron Lett.* **2006**, *47*, 8087.
(180) O'Connor, C. J.; Roydhouse, M. D.; Przybyl, A. M.; Wall, M. D.; Southern, J. M. *J. Org. Chem.* **2010**, *75*, 2534.
(181) (a) Stumpf, A.; Jeong, N.; Sunghee, H. *Synlett* **1997**, 205. (b) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3346.
(182) McNeill, E.; Chen, I.; Ting, A. Y. *Org. Lett.* **2006**, *8*, 4593.
(183) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861.