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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 A₃ adenosine receptor antagonist;¹³ the 4'-thiocytidine nucleoside **9**, active against

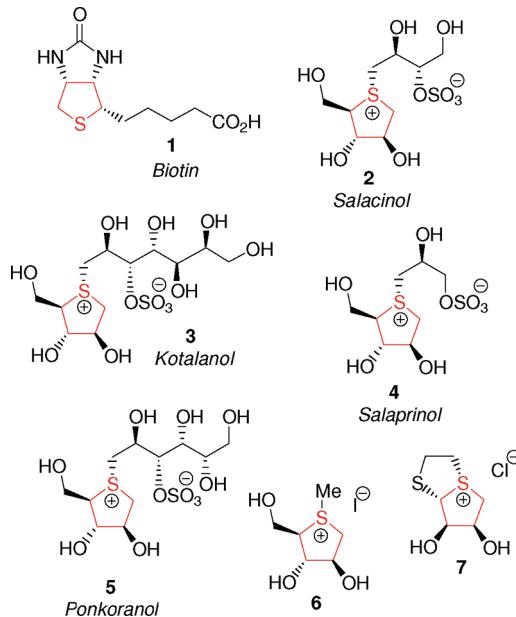


Figure 1.

HSV-1 and HSV-2;¹⁴ the cholecystokinin type-B receptor antagonist tetrolothiodin **10**;¹⁵ and (*R*)-tetrahydrothiophen-3-ol **11**,^{16–18} a pivotal intermediate to obtain the potent antibacterial Sulopenem **12**¹⁶ (Figure 2).

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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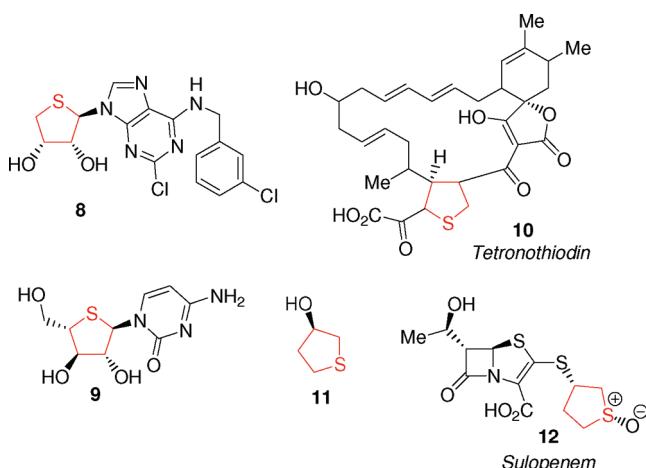


Figure 2.

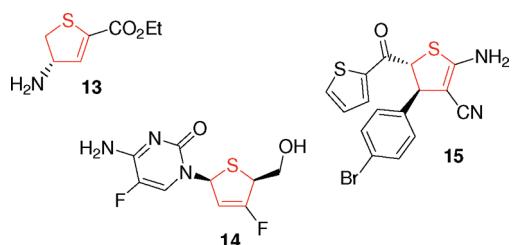


Figure 3.

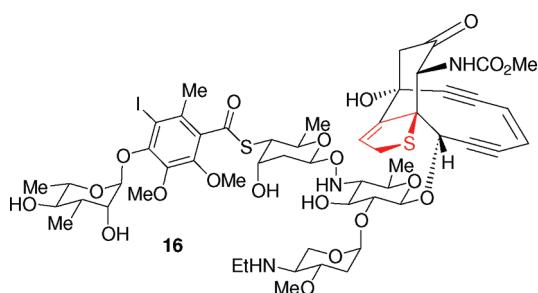


Figure 4.

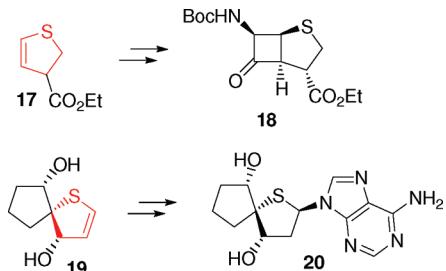


Figure 5.

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'-thiaspiracyclic 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 Clercq³¹ and Seki³² 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 enormous 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.

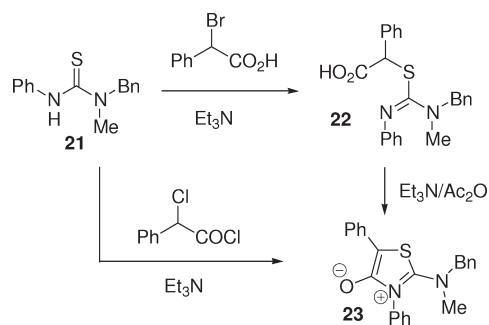
2.1. Chiral Auxiliary-Assisted Approaches

The use of chiral auxiliaries for the preparation of enantioselectively 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, menthol derivatives, and 1-phenylethylamine as auxiliaries.

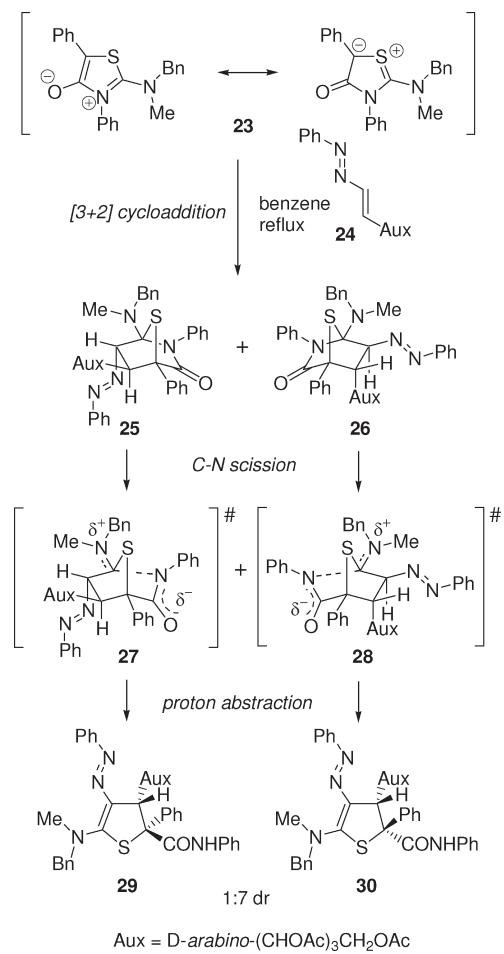
The 1,3-dipolar cycloaddition reaction between achiral sulfur-containing 1,3-dipoles and dipolarophiles with embedded carbohydrate or camphorsultam auxiliaries has emerged as a powerful tool for preparing either dihydro- or tetrahydrothiophene chiral derivatives in a stereoselective fashion. In this context, thiosomünchnones, 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 $\text{Et}_3\text{N}/\text{Ac}_2\text{O}$ system, producing thiosomünchnone **23**. The same compound also could be obtained by reaction of thiourea

Scheme 1



Scheme 2

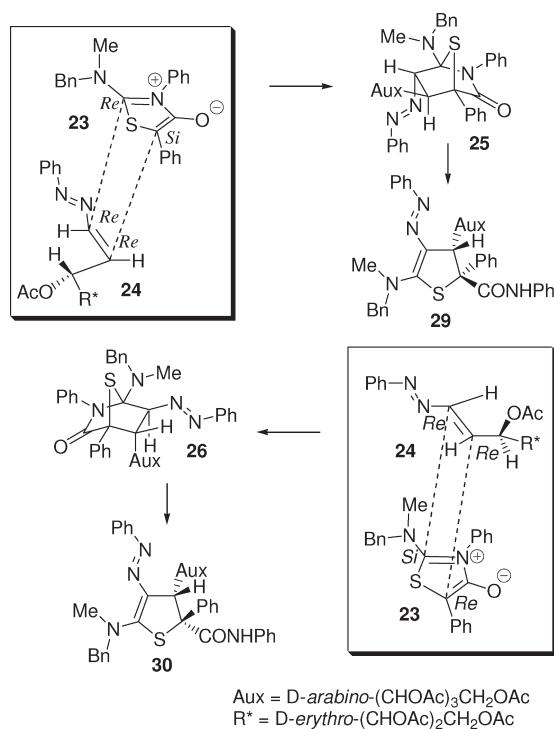


21 with α -chlorophenylacetic acid chloride in the presence of Et_3N (Scheme 1).

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**

Scheme 3



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 Höglberg⁴² 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)),

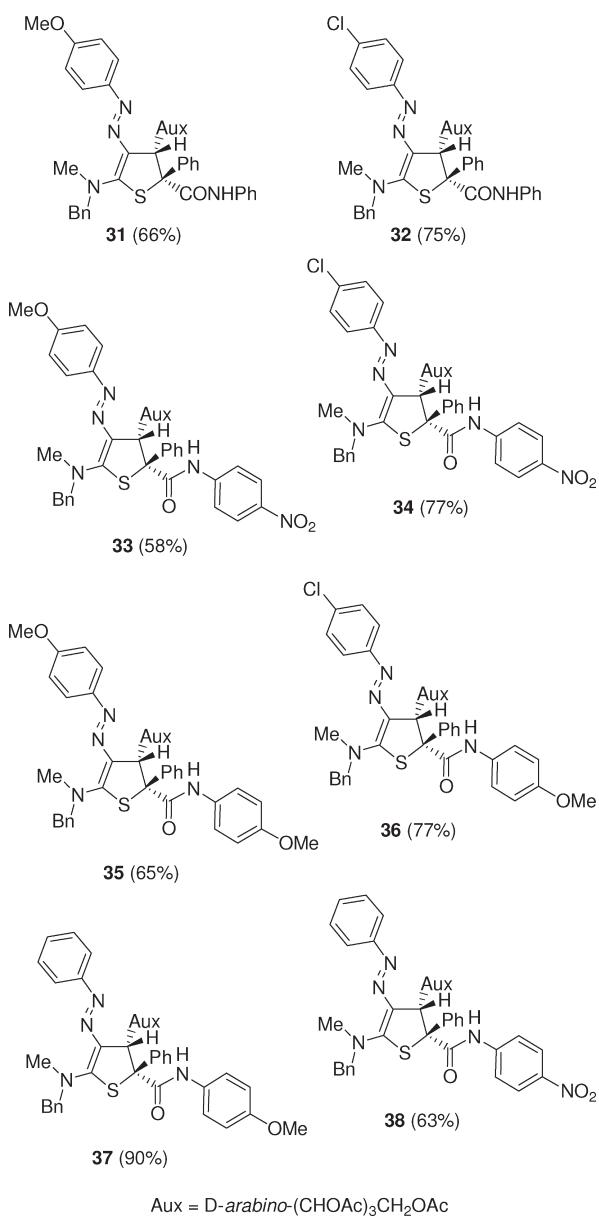


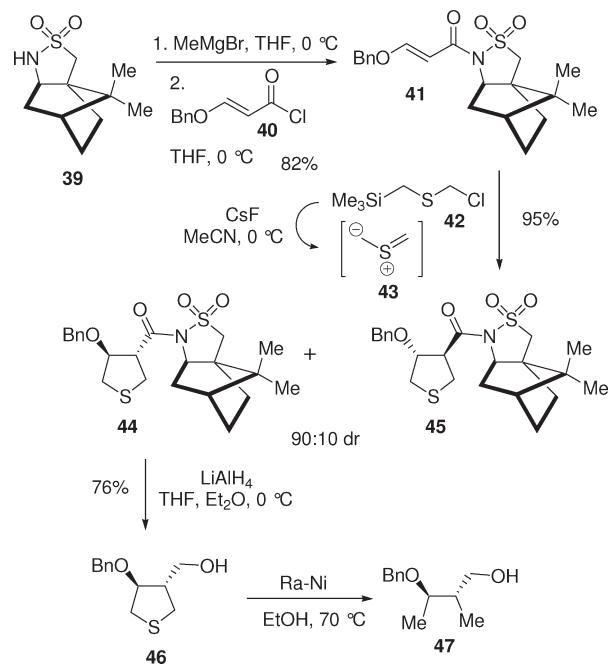
Figure 6.

which were easily separated by column chromatography. Subsequent LiAlH₄ 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 co-workers⁴⁴ to produce different 4'-thionucleosides.

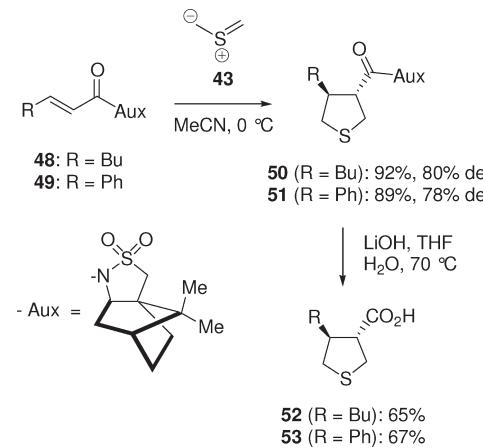
Similarly, asymmetric cycloadditions of camphorsultam amides 48 and 49 with ylide 43 under the same reaction conditions gave rise to tetrahydrothiophenes 50 and 51 in high yield and diastereoselectivity (Scheme 5). Chromatographic separation of the major diastereomer followed by removal of the chiral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

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

Scheme 4



Scheme 5

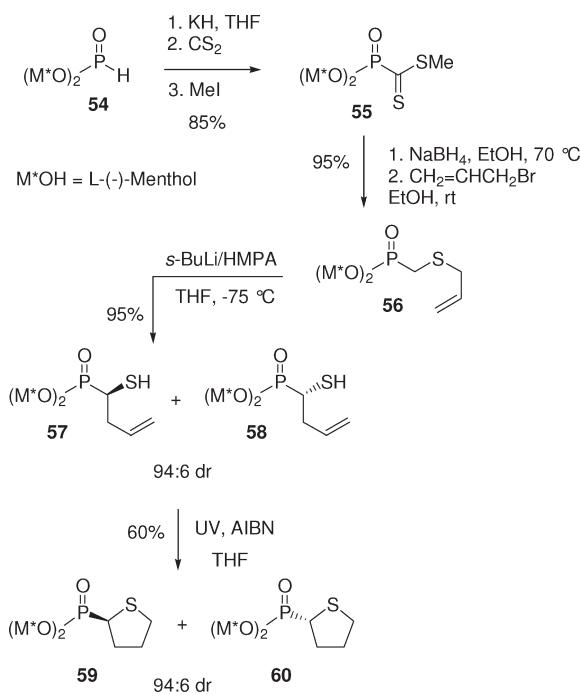


phosphonodithioformate 55, which was then reduced and treated with allyl bromide to give (allylsulfanyl)methylphosphonate 56 in 95% yield.

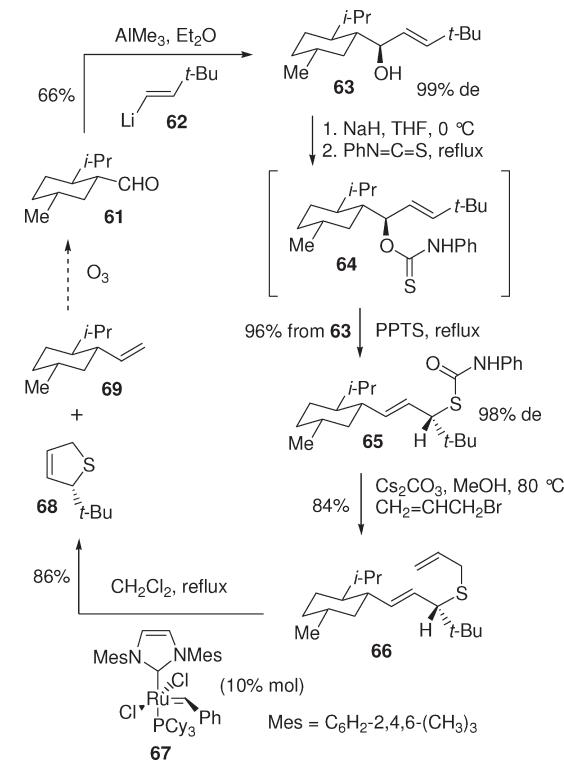
Treatment of 56 with 5 equiv of *sec*-BuLi/HMPA in tetrahydrofuran (THF) at -75 °C for 75 min followed by acidic hydrolysis and extraction with pentane gave a 94:6 mixture of the rearranged α -mercaptoprophosphonates 57 and 58 in 95% yield. UV irradiation of crude thiols 57 and 58 in the presence of 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 alkylthionocarbonate derivatives involved in [2,3]-sigmatropic rearrangements leading to S-alkylthiocarbamates, eventually converted into chiral nonracemic 2,5-dihydrothiophene compounds.⁴⁶

Scheme 6



Scheme 7



This strategy called for the synthesis of suitable allylic alcohols, incorporating the bulky methyl chiral auxiliary, as precursors of the required alkylthionocarbamates. Thus, $(-)$ -*p*-menthane-3-carboxaldehyde 61 was treated with vinylolithium 62 in the presence of trimethylaluminum to give the Felkin adduct

Scheme 8

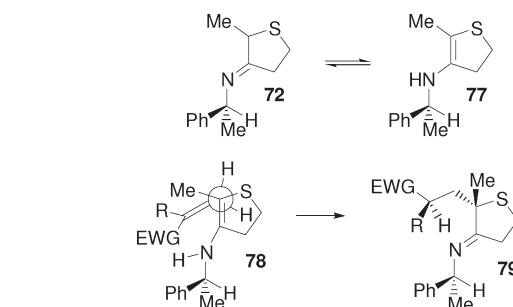
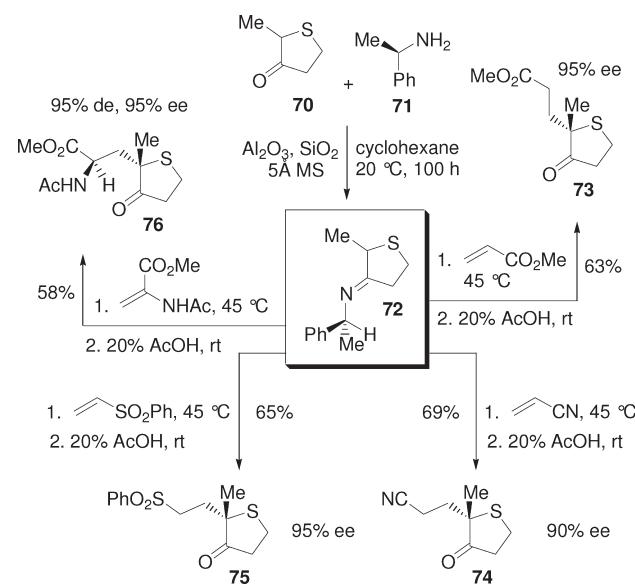


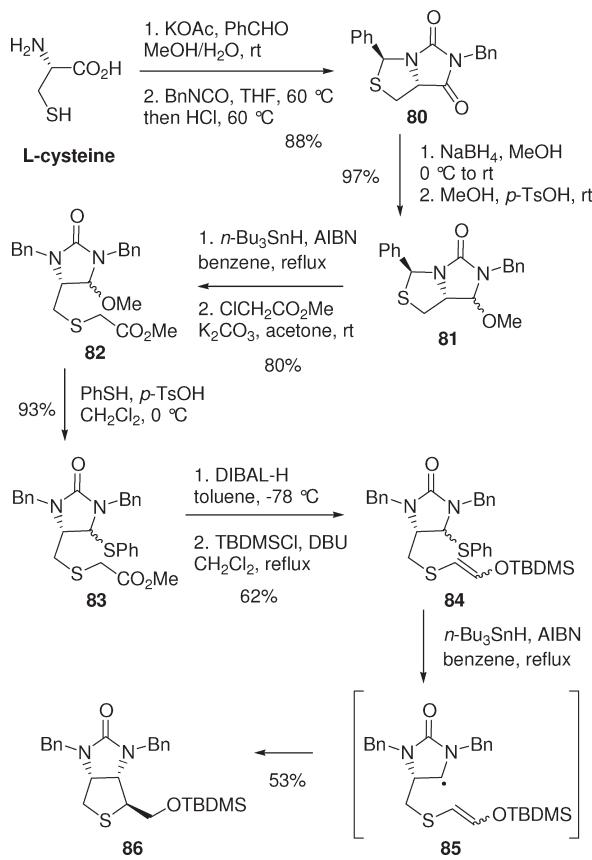
Figure 7.

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.

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).

Scheme 9



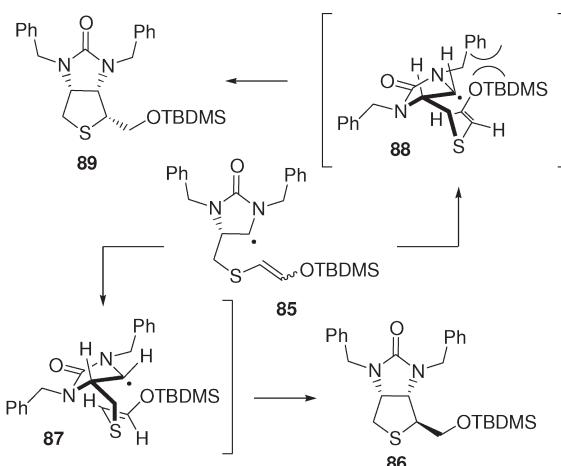
Similarly, reactions of imine 72 with acrylonitrile, phenyl vinyl sulfone, and methyl 2-acetamidoacrylate afforded the corresponding adducts 74, 75, and 76, respectively, in good yield and excellent stereoselectivity. The high-ordered, six-membered transition state 78 derived by interaction of the electrophilic 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*-Bu₃SnH/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*-Bu₃SnH 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.

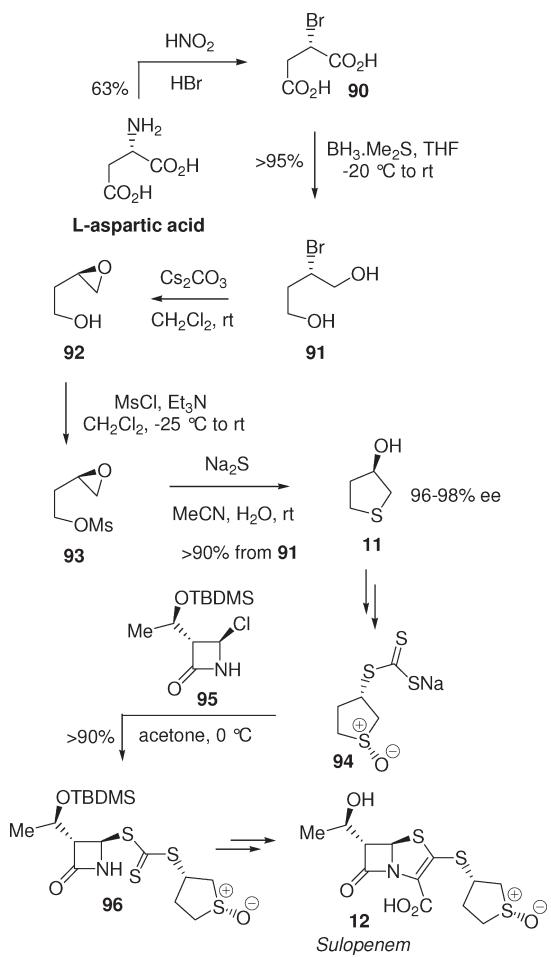
It is noteworthy that the failure to form the *cis*–*cis* isomer 89 appears to be unprecedented in cyclization of structurally related radicals.⁵² The formation of 86 could be explained by assuming that cyclization of α -amido radical 85 onto the enol ether carbon–carbon double bond proceeded via the 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.

Fizer'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.

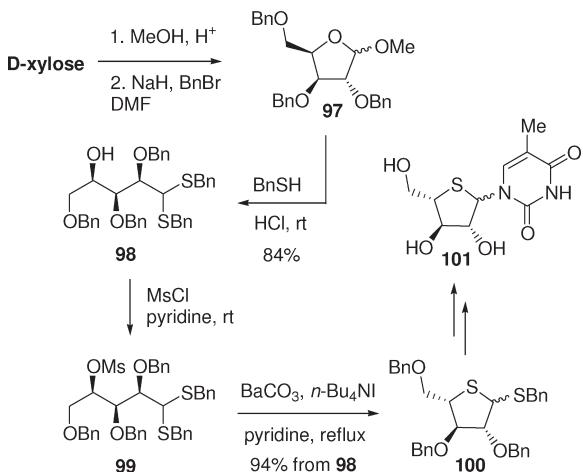
2.2.1.2. From Sugars. Natural and unnatural carbohydrates have been extensively used to obtain chiral polyhydroxylated tetrahydrothiophenes, which may act as building blocks for the synthesis of thionucleosides, either in the D- or L-series. Owing to the large collection of publications reported after 1990 on this subject, we focused our attention on the few selected approaches not previously covered in review accounts on the synthesis of 4'-thionucleosides⁵³ 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

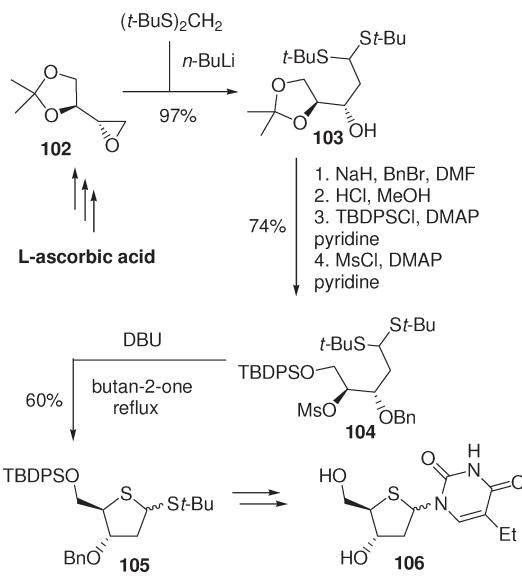


Scheme 12

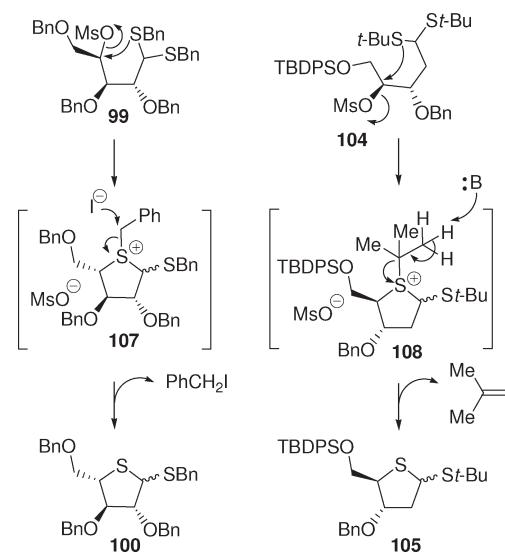


involving ring-closure of dithioacetals or thioaminals are discussed in subsection 2.2.1.2.1; subsection 2.2.1.2.2 is dedicated to thiolane ring formation through cyclization by S-centered anions; and ring-contraction reactions are collected in the final subsection 2.2.1.2.3.

Scheme 13



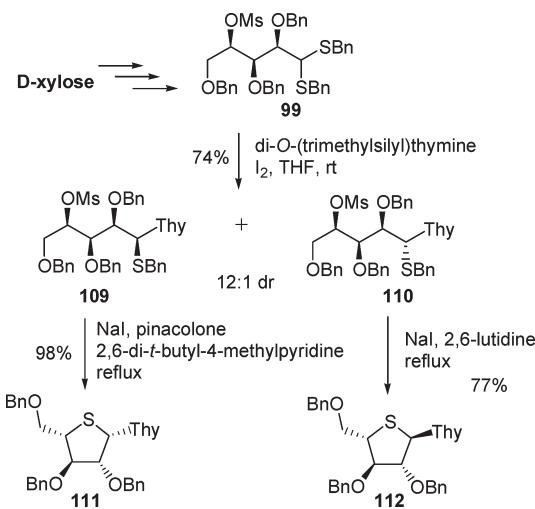
Scheme 14



2.2.1.2.1. Thiolane Ring-Closure of Dithioacetals and Thioaminals. A well-established method for building up the tetrahydrothiophene core of 4'-thiofuranoles 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 BaCO₃/n-Bu₄NI 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

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 **102** 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-workers⁶³ accomplished a facile, large-scale synthesis of the

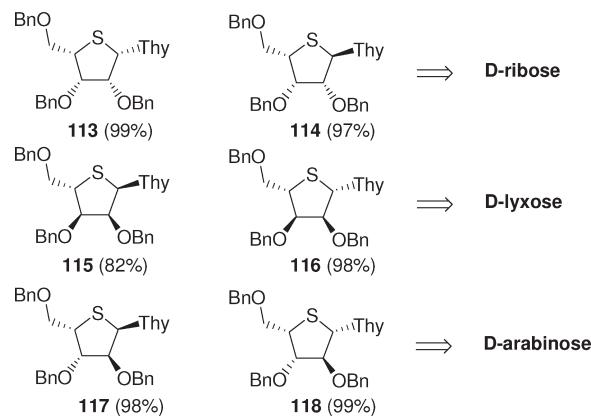
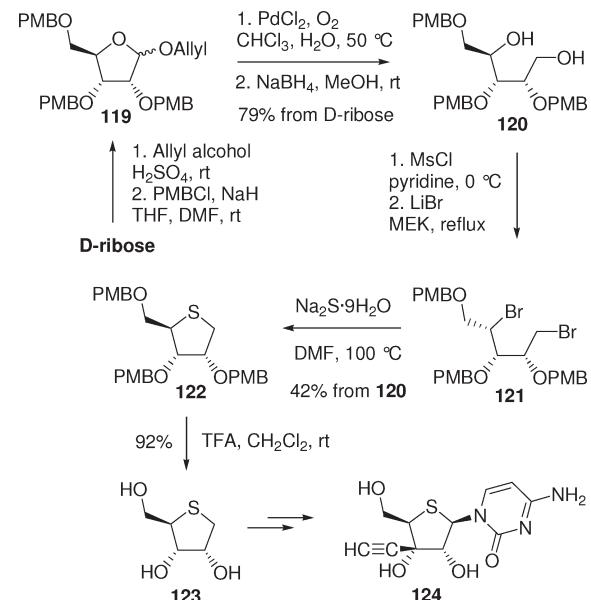


Figure 8.

Scheme 16

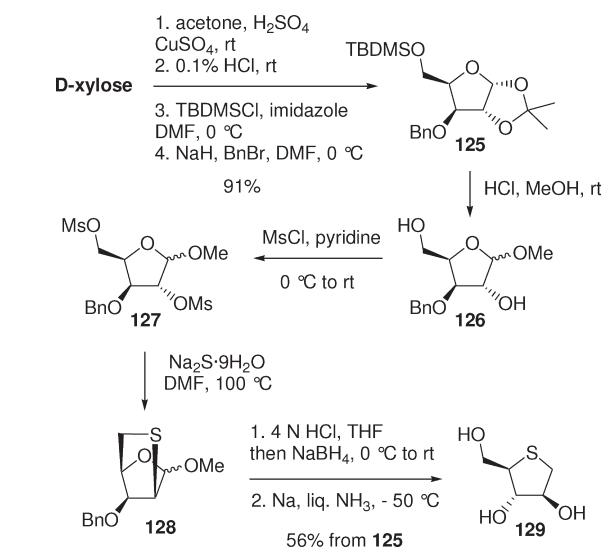


thiosugar **123** via sodium sulfide-promoted cyclization of dibromo derivative **121**, in turn obtained from D-ribose (Scheme 16).

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-xylose⁶⁵ called for the preparation of the key dimesylate intermediate **127** (Scheme 17).

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-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

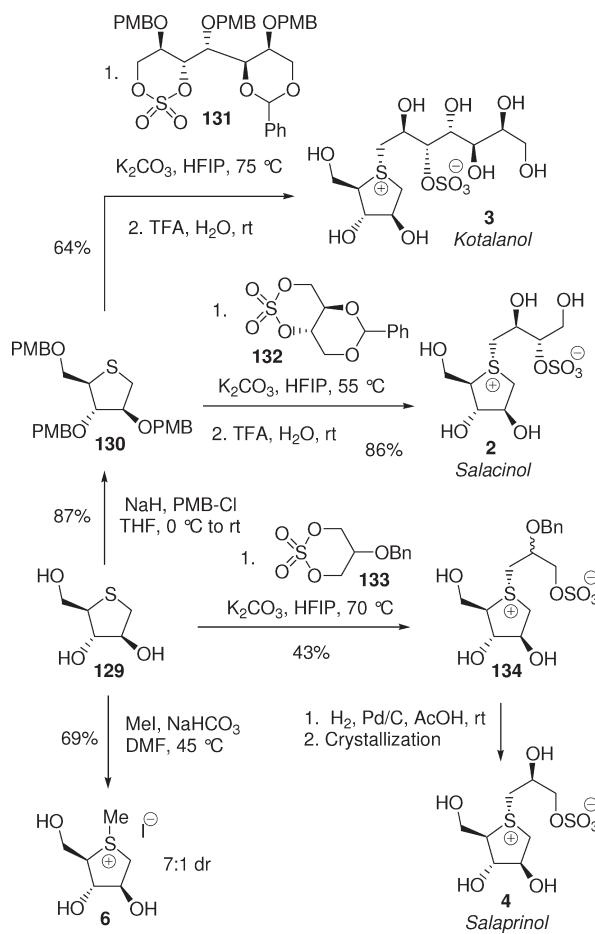
The 4'-thionucleoside **9** has been prepared starting from D-xylose, conveniently transformed in two steps into the fully protected intermediate **97** (Scheme 19).¹⁴ Acid hydrolysis of the acetal group, followed by $LiBH_4$ reduction produced the diol **135**, which was then taken to the per-benzylated 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

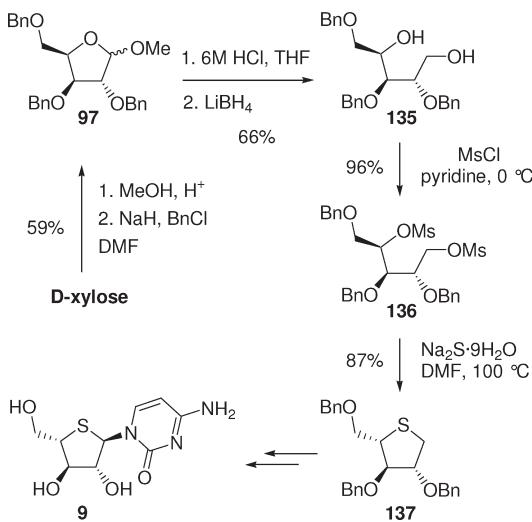
The synthesis of thiosugar **141**,¹³ precursor of D-4'-thioadenosine derivatives endowed with antagonist activity on human A₃ adenosine receptor, was easily accomplished through cyclization of dimesylate **140**, in turn prepared from D-mannose (Scheme 21).

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

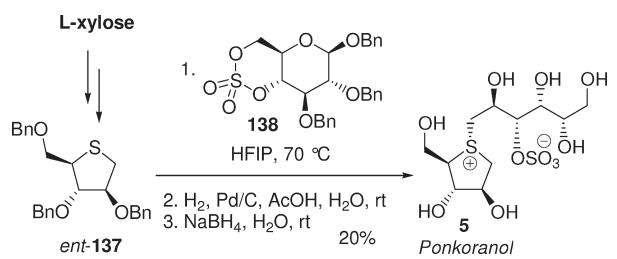


Scheme 19

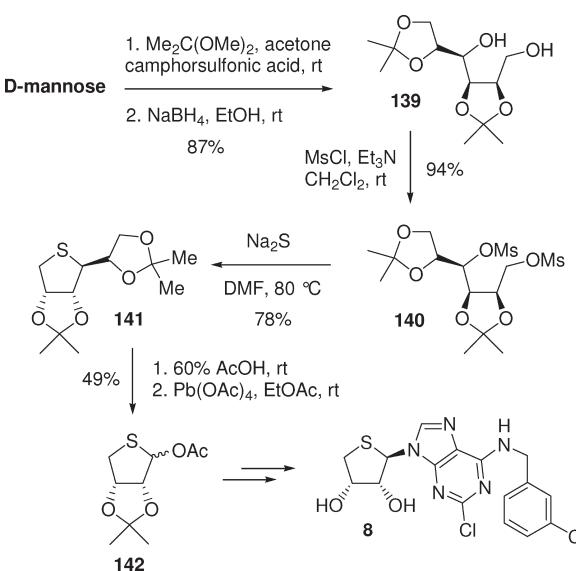


sulfide. Selective hydrolysis of the 5,6-acetonide residue and oxidative cleavage of the resulting diol unexpectedly gave access to acetate **142**, indicating that oxidative cleavage of diol, oxidation of the resulting aldehyde to the acid, and oxidative decarboxylation of the acid occurred simultaneously.⁷⁰

Scheme 20



Scheme 21



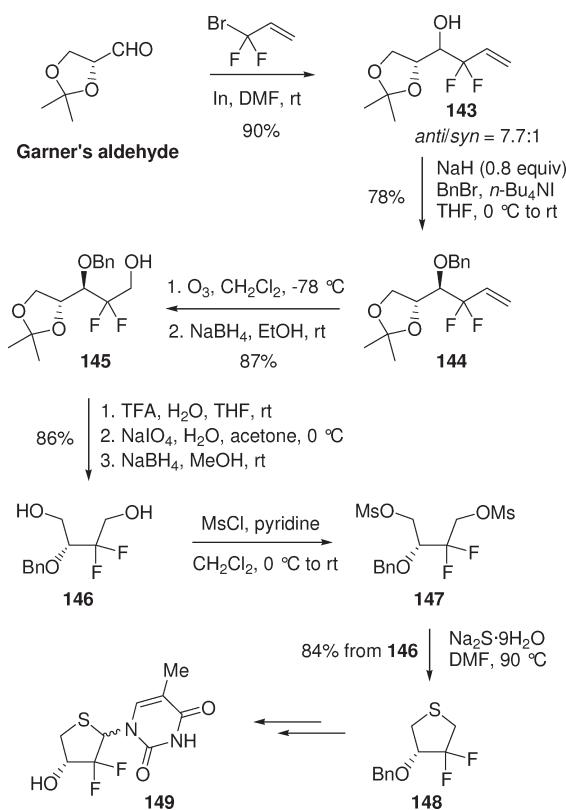
Compound 142 was eventually used to prepare a series of N^6 -substituted D-4'-thionucleosides, including 8. The cyclization of a dimesylate intermediate was the key step for the preparation of *gem*-difluorinated thionucleosides starting from 1-(R)- or 1-(S)-glyceraldehyde acetonide.^{71–75}

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 $n\text{-Bu}_4\text{NI}$ 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, dibenzylidethioacetal 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 dibenzylidethioacetals with L-arabino, D-lyxo, D-galacto, and D-glucu 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-workers¹² 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.

Scheme 23

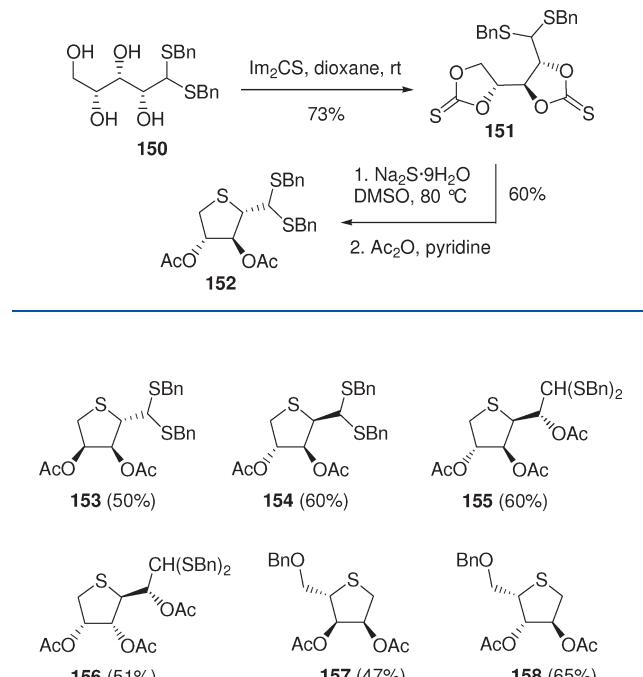
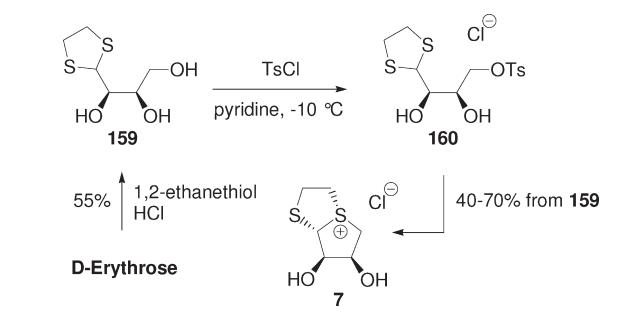


Figure 9.

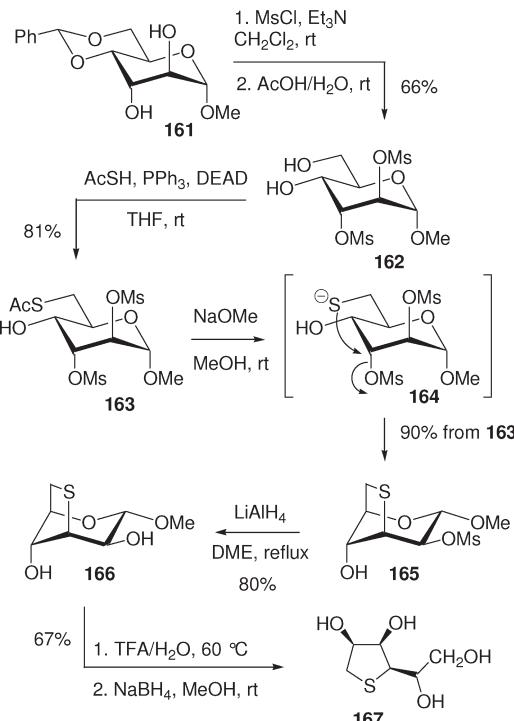
Scheme 24



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)

Scheme 25



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.

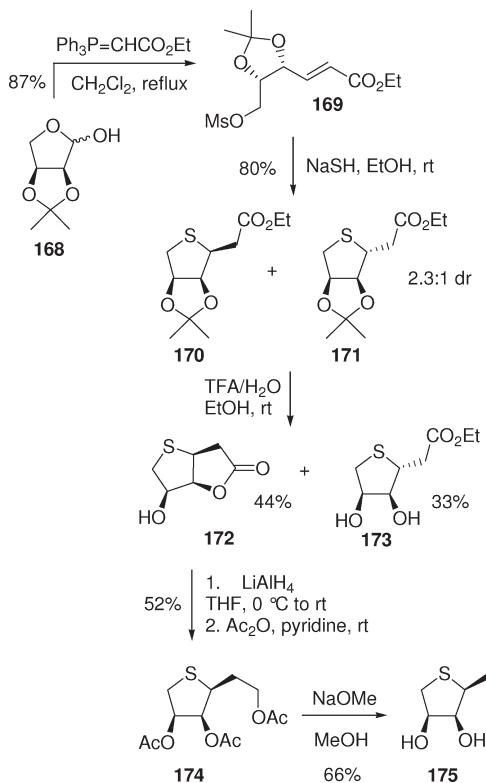
These results compare well with those obtained in related studies dealing with the synthesis of homochiral hydroxylated pyrrolidines via reaction of 169 with ammonia.⁸⁴ However, due to a facile interconversion of tetrahydrothiophenes 170 and 171 via a retro-Michael-Michael reaction, the thiophane synthesis 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.

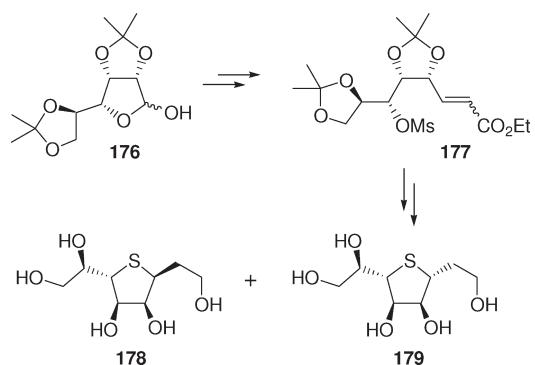
Oxidation of 183 with singlet oxygen in a 1:1 MeOH/CH₂Cl₂ mixture containing diisopropylethylamine afforded a 1.6:1 diastereomeric mixture of 4-hydroxybutenolide 184 in 71% yield. Sequential reduction and acid-catalyzed lactonization gave a very good yield of enantiomerically pure butenolide 185, which, when treated with methanolic potassium carbonate, afforded the lactone 187 via an intramolecular thia-Michael reaction. Subsequent LiAlH₄ 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 Me₃SiI with

Scheme 26



Scheme 27

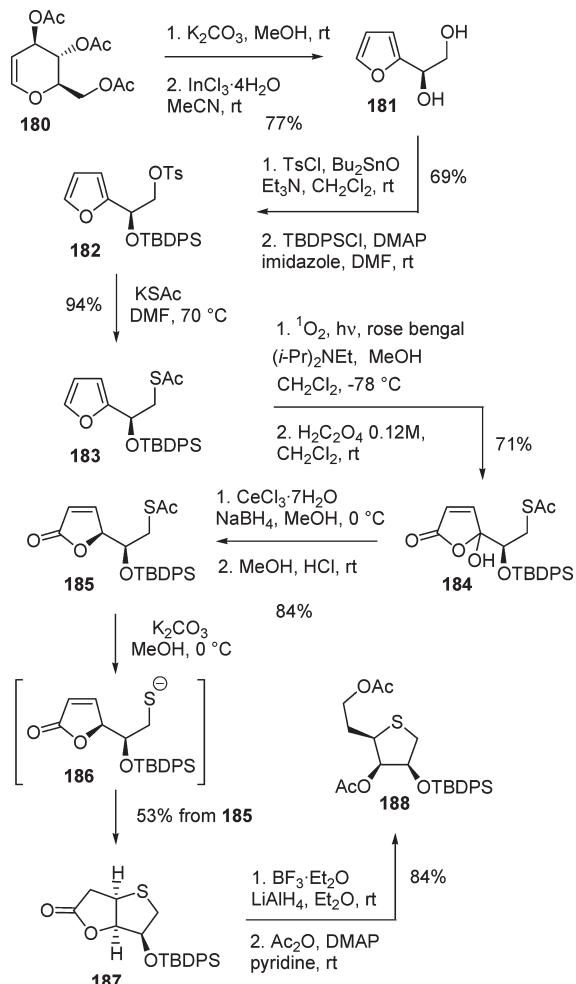


(4*R*,*S**R*)-dihydroxythiepane **190**⁸⁶ in turn obtained from D-mannitol-derived dibromo derivative **189**,⁸⁷ produced the oxonium intermediate **191** (Scheme 29).

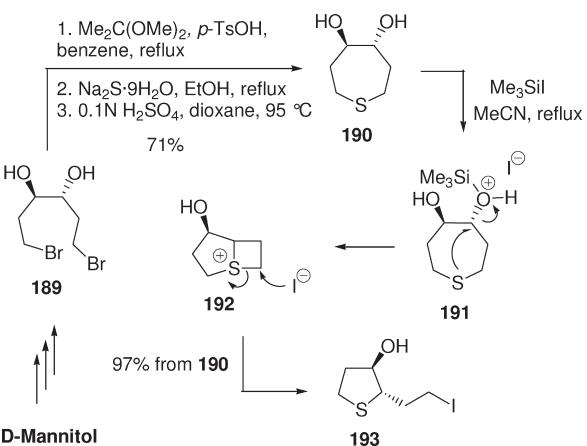
The bicyclic sulfonium salt **192** was ultimately formed through transannular nucleophilic substitution via displacement of the hydroxyl group coordinated with the silicon reagent. Subsequent iodide attack at the α -position of the 4-membered ring moiety gave a 97% yield of the optically pure tetrahydrothiophene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

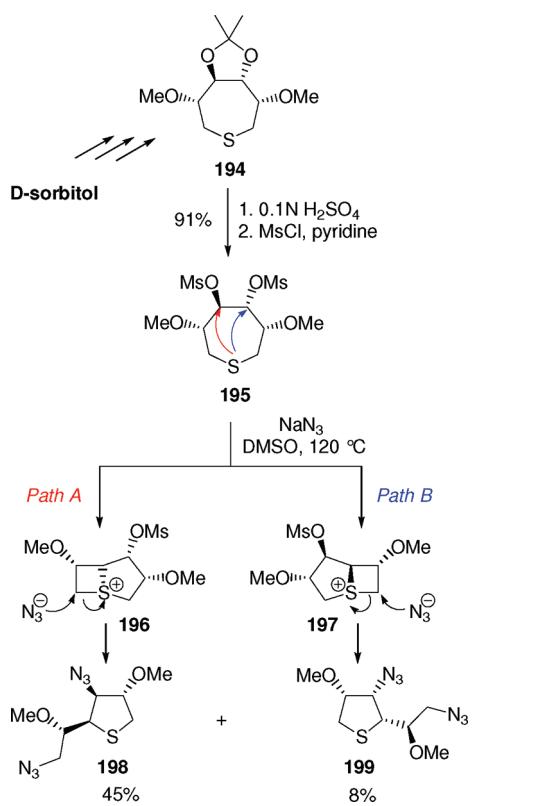


Scheme 29

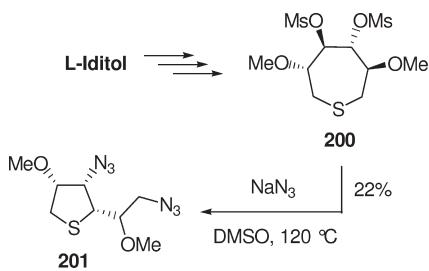


azide to yield chromatographically separable tetrahydrothiophenes **198** and **199**. This result has been explained by assuming that nucleophilic transannular substitution produced the diastereomeric bicyclic sulfonium salt intermediates **196** (*path A*) and **197** (*path B*), precursors of thiolane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

Scheme 30



Scheme 31

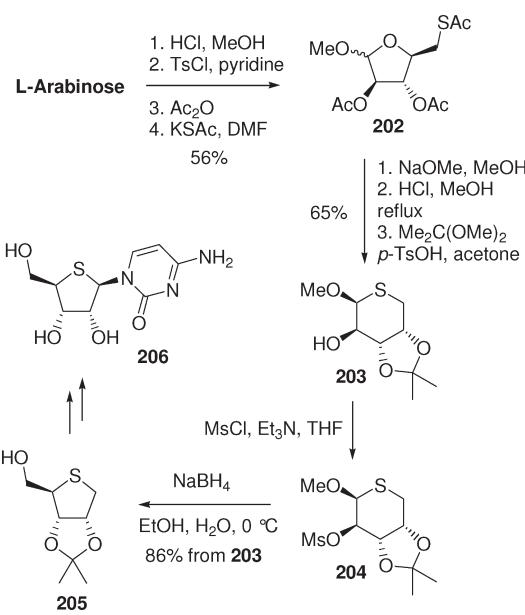


On the other hand, the tetrahydrothiophene 201 has been obtained as the sole product when using the C_2 -symmetric dimesylthiepane 200, prepared from L-iditol⁹⁰ as the starting material (Scheme 31). The chiral polyhydroxylated tetrahydrothiophene 205 has been prepared from the L-arabinose-derived tetrahydrothiopyran compound 204 via a reductive ring-contraction reaction (Scheme 32).⁹¹

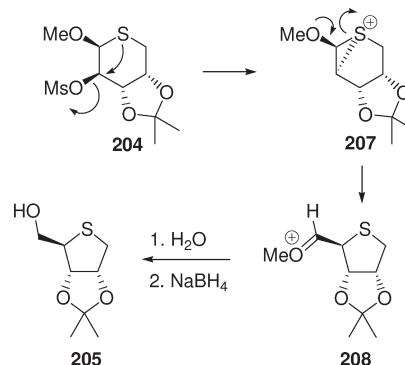
Thus, the 5-thioacetate 202 was submitted to sequential deacetylation, acid-catalyzed recyclization, and acetonide protection to produce the isopropylidene derivative 203. The latter was taken to the corresponding mesylate 204, which was directly treated with NaBH_4 in aqueous EtOH to give protected 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).⁹²

2.2.1.3. From α -Hydroxy Acid Esters. Optically pure α -hydroxy acid esters, namely, (*S*)-dimethyl malate⁹² and (*S*)-ethyl

Scheme 32



Scheme 33



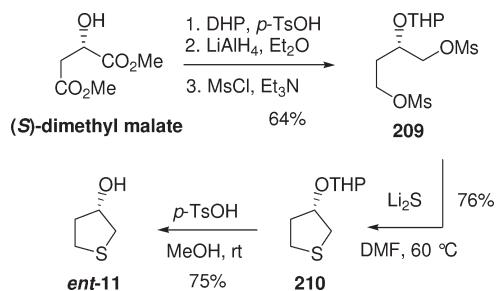
lactate,⁹³ have been successfully used as synthetic precursors of chiral tetrahydrothiophene compounds. Thus, (*S*)-tetrahydrothiophen-3-ol *ent*-11 has been prepared in five steps starting from (*S*)-dimethyl malate in $\sim 37\%$ overall yield (Scheme 34).⁹²

In detail, protection of the hydroxyl group of (*S*)-dimethylmalate as the corresponding tetrahydropyranyl (THP) ether followed by ester groups reduction and mesylation of the resulting diol provided the bimesylate 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.

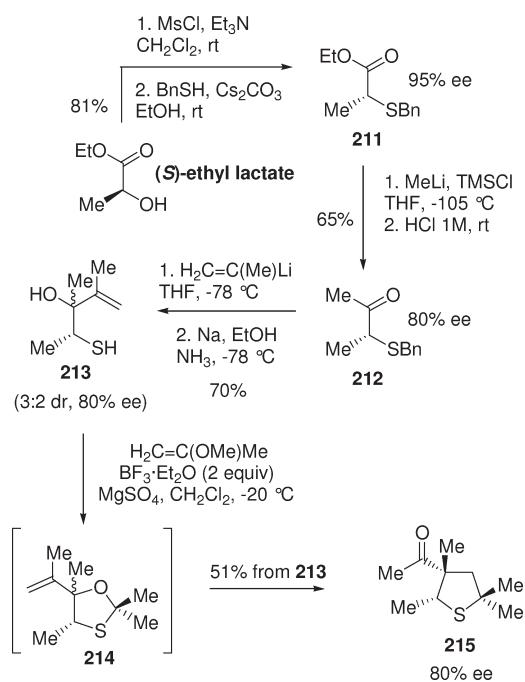
Similarly, (*R*)-tetrahydrothiophen-3-ol 11 was prepared starting from optically pure (*R*)-dimethyl malate. A new tetrahydrothiophene synthesis featuring an unusual carbon–carbon bond-forming reaction to form the cyclic thioether nucleus has been achieved by acid-promoted rearrangement of 5-alkenyl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

Scheme 34



Scheme 35

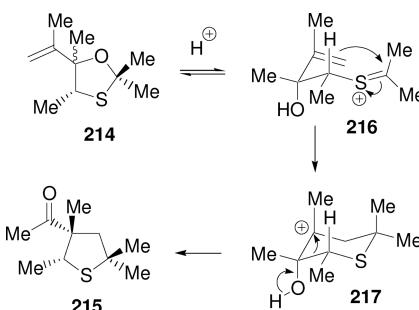


group of (S)-ethyl lactate and subsequent displacement with benzyl sulfide anion of the derived mesylate derivative provided the enantiomerically pure α -thioester 211 (81% yield, 95% ee), which was taken to the methyl ketone 212 by careful treatment with excess methylolithium in the presence of trimethylsilyl 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 $\text{BF}_3\cdot\text{Et}_2\text{O}$ 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.

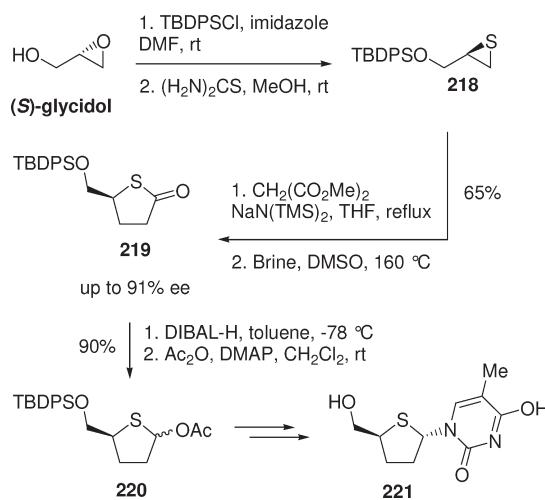
The formation of 215 is likely to require ring-opening of oxathiolane 214 as the starting move. The produced thionium ion 216 may evolve to the tetrahydrothiopyranyl carbonium ion 217, which successively takes part in a pinacol rearrangement (Scheme 36). As a result, the conversion of 214 to 215 would 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

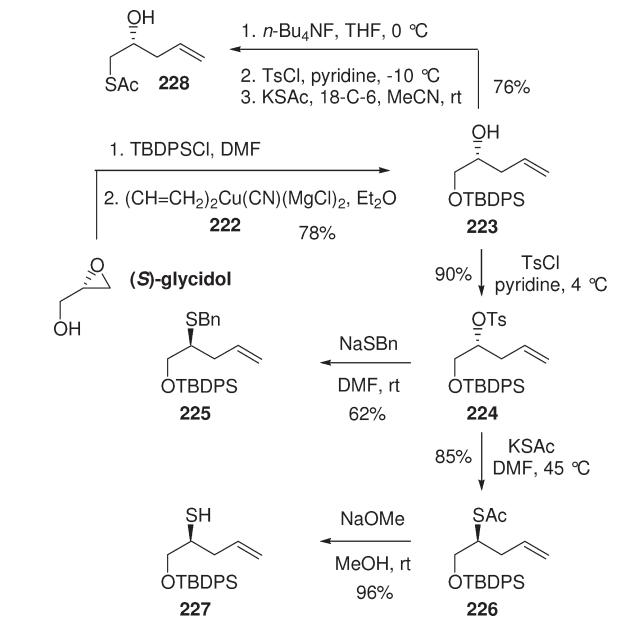


enantiomerically pure thiolactones, useful precursors of uracil and cytosine 4'-thionucleosides.⁹⁵ As shown in Scheme 37, (S)-glycidol was converted into the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether and treated with thiourea to give the (R)-thiirane 218. Its reaction with dimethyl malonate 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.

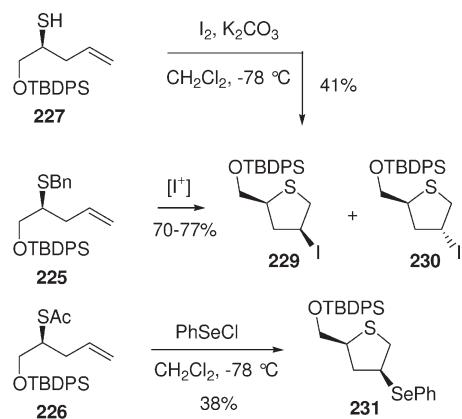
Similarly, (R)-glycidol was converted into the (R)-enantiomer of 219, eventually taken to thiofuranose analogues in the L-series. Differently protected unsaturated sulfanyl alcohol derivatives have been exploited as precursors of chiral tetrahydrothiophene compounds via electrophile-promoted thioetherification.⁹⁶

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 $\text{S}_{\text{N}}2$ 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

Scheme 38



Scheme 39

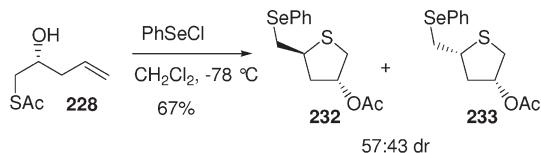


potassium thioacetate provided 1-sulfanyl-4-penten-2-ol **228**, with an overall yield of 76%.

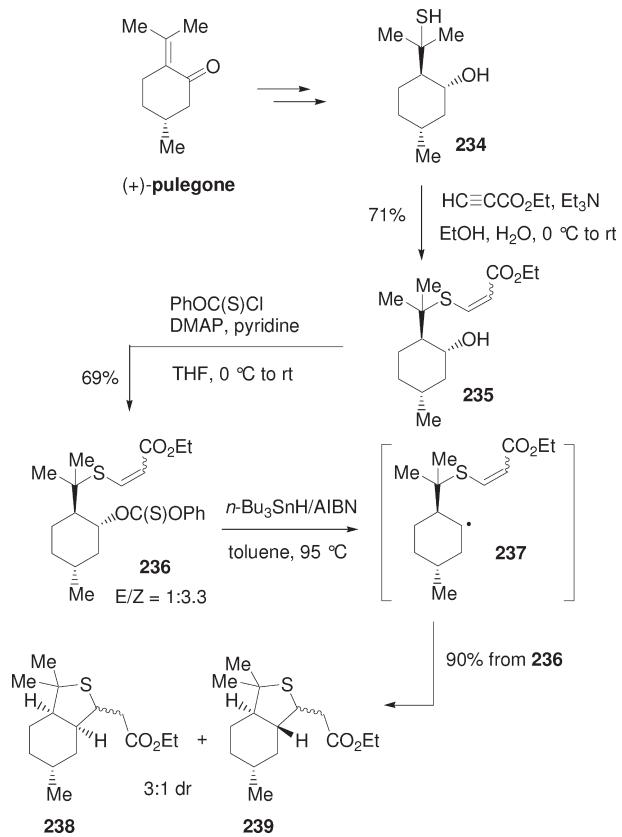
Treatment of unsaturated sulfanyl alcohols **225**–**228** with iodine and selenium electrophiles provided chiral tetrahydrothiophene derivatives via chemoselective cyclothioetherification reactions, which proceeded by endo- or exo-mode depending on the position of the sulfur atom, its protecting group, 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 $-78^\circ C$ 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 $-78^\circ C$ 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-workers⁹⁷ 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 -Bu₃SnH/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).

Scheme 42

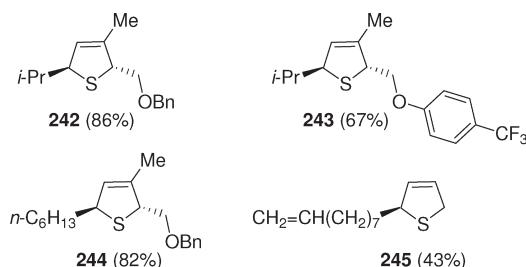
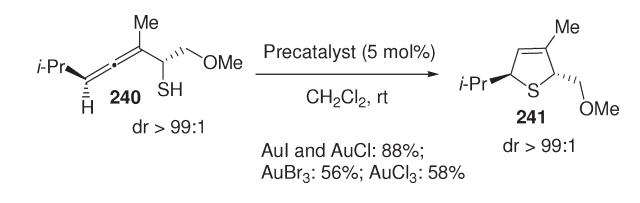
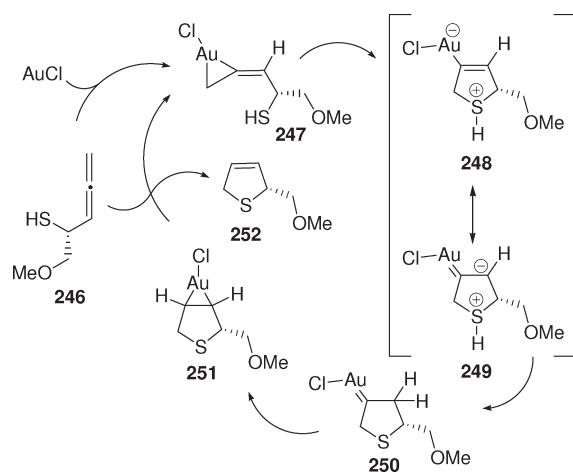


Figure 10.

Scheme 43

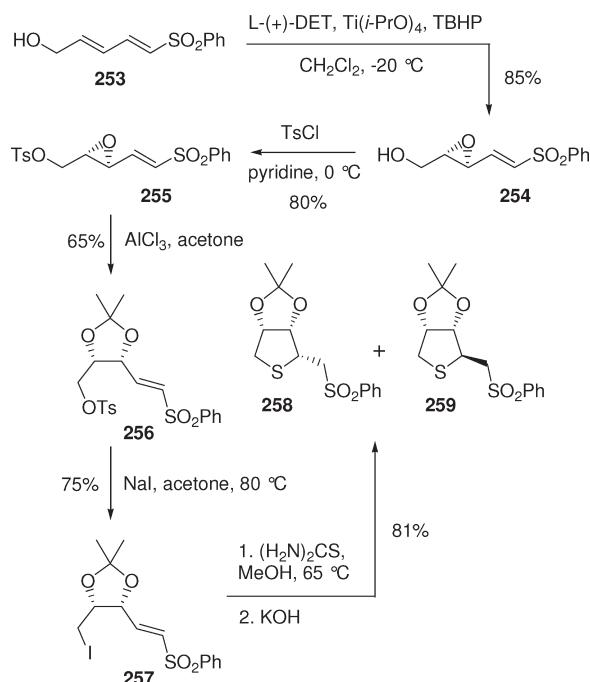


2.2.2. From Alternative Enantiopure Sources. Gold catalysis has been developed in recent years as an innovative strategy to construct a wide range of carbo- and heterocycles.⁹⁹ Thus, Krause and co-workers^{100,101} opened a new elegant way to five- and six-membered heterocycles through gold-catalyzed 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 CH₂Cl₂ 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 AuBr₃ and AuCl₃ 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 CH₂Cl₂ 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 epoxidation¹⁰⁵ 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 AlCl₃-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

Scheme 45

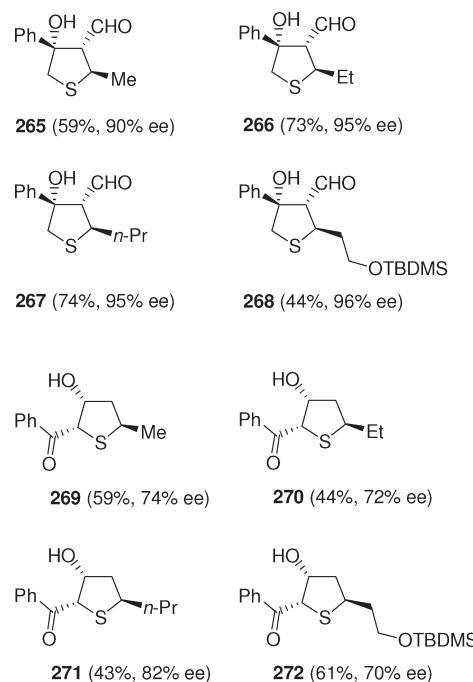
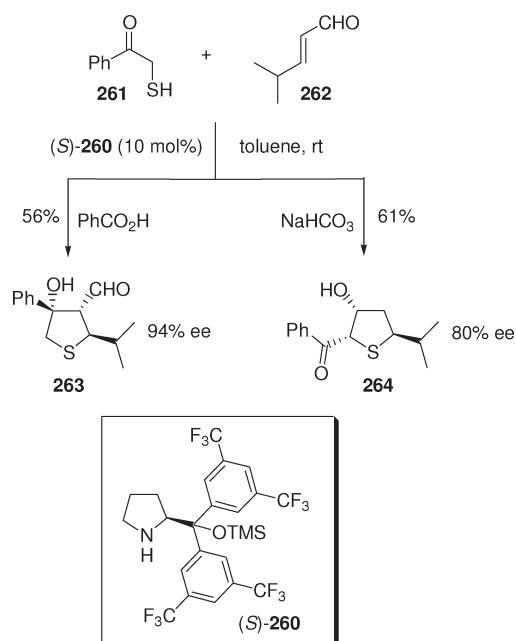


Figure 11.

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

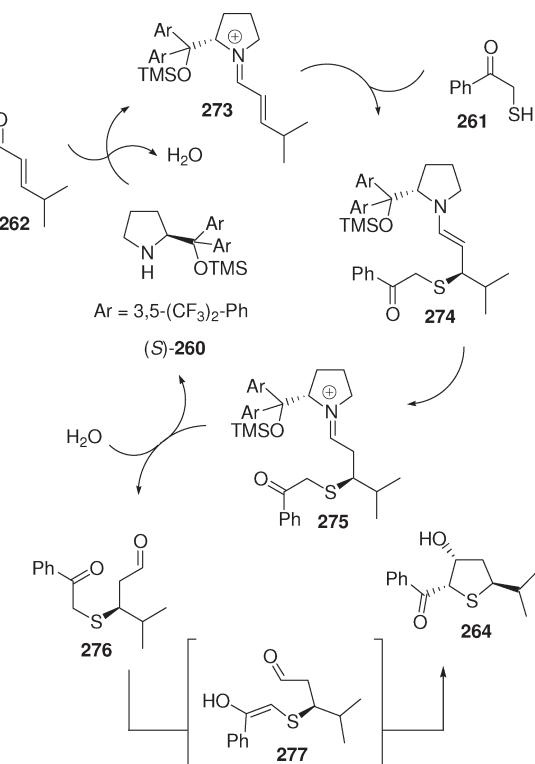
In 2006, Jørgensen and co-workers¹⁰⁷ reported a new thia-Michael/aldol domino reaction between 2-mercaptop-1-phenylethanone **261** and aliphatic α,β -unsaturated aldehydes catalyzed by the L-proline derivative **(S)-260**. The domino process gave rise to (tetrahydrothiophen-2-yl)phenyl methanones or 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 ineffective (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.

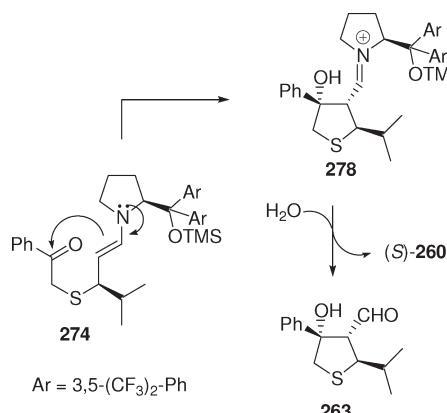
As proposed in Scheme 46 for the domino reaction involving **262**, initial activation of the aldehyde moiety by the organocatalyst provides iminium-ion intermediate **273**, which undergoes preferential thiol attack at the deshielded *Re*-face to produce (*R*)-configured enamine **274** (6:1 dr).

Scheme 46

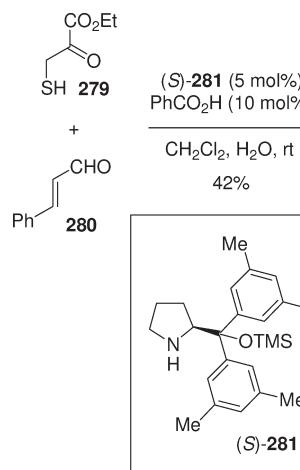


In the next step, NaHCO_3 -promoted hydrolytic removal of the catalyst from the pyrrolidinium intermediate **275** gives rise to thioether **276**. Fast thermodynamically controlled enolization of **276** produces the (*E*)-enol **277**, which gives tetrahydrothiophene **264** through diastereospecific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

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-mercaptopropanoate 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 CH₂Cl₂ 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

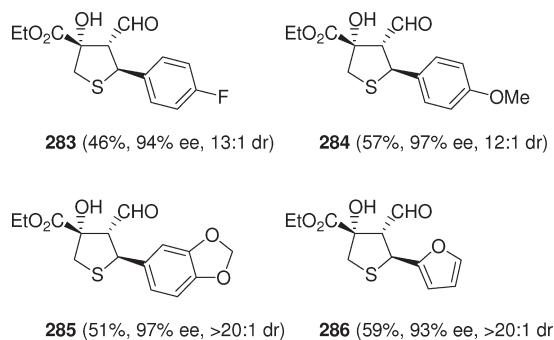
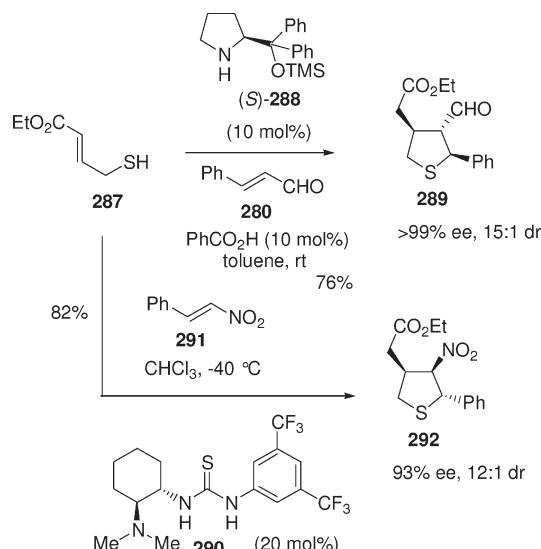


Figure 12.

Scheme 49



use of *trans*-ethyl 4-mercaptopropanoate 287 as the common starting substrate in chiral amine-promoted double Michael reactions with cinnamaldehydes¹⁰⁹ and nitroalkenes.¹¹⁰

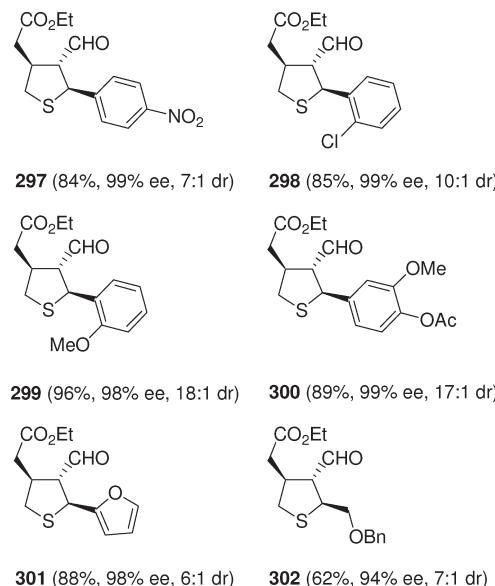
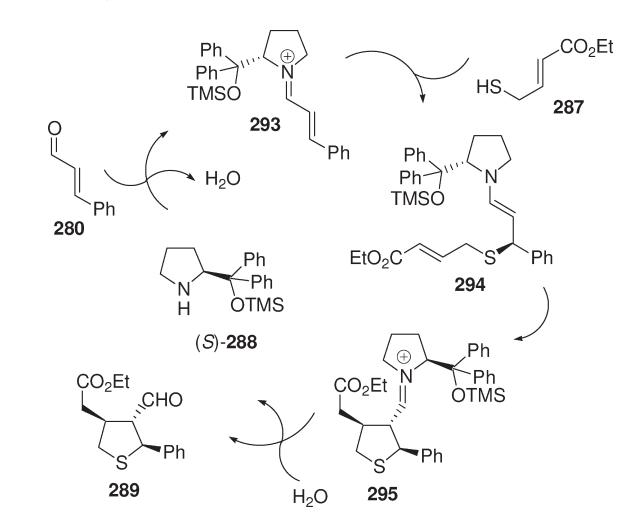
As shown in Scheme 49, good yields (76%) and stereoselectivities (>99% ee, 15:1 dr) of the adduct 289 were achieved by reaction of 287 with *trans*-cinnamaldehyde 280 (toluene, room temperature, 3 days) in the presence of benzoic acid (10 mol %) and (S)-diphenylprolinol trimethylsilyl (TMS) ether 288 (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–thiourea¹¹² 290 proved effective in catalyzing the reaction of 287 with *trans*- β -nitrostyrene 291 in CHCl₃ 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.

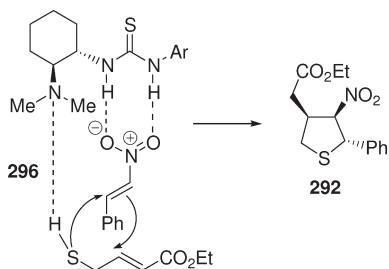
Thus, Michael addition of thiol 287 to the transient iminium ion 293 gives rise to enamine 294 (Scheme 50), which produces the iminium-ion intermediate 295 through intramolecular Michael reaction. The latter is eventually hydrolyzed to the tetrahydrothiophene derivative 289.

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,

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-workers¹¹⁴ 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ solvent mixture.

On the other hand, Xu and co-workers¹¹⁵ acceded to enantiopure 2,5-dihydrothiophene-3-carbaldehydes by effecting the reaction in toluene in the presence of 4-nitrobenzoic acid.

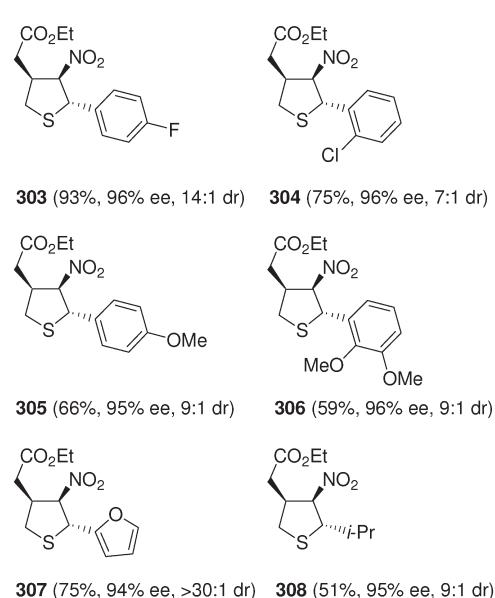


Figure 13.

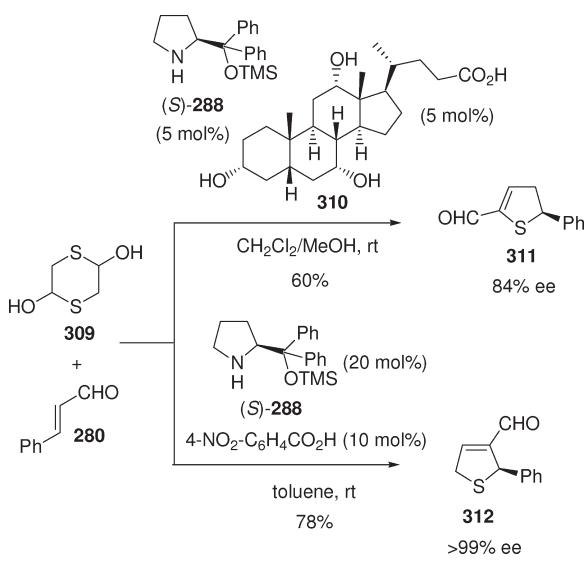
Representative examples of these approaches are shown in Scheme 52.

Thus, model reaction between 309 and cinnamic aldehyde 280 in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 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.

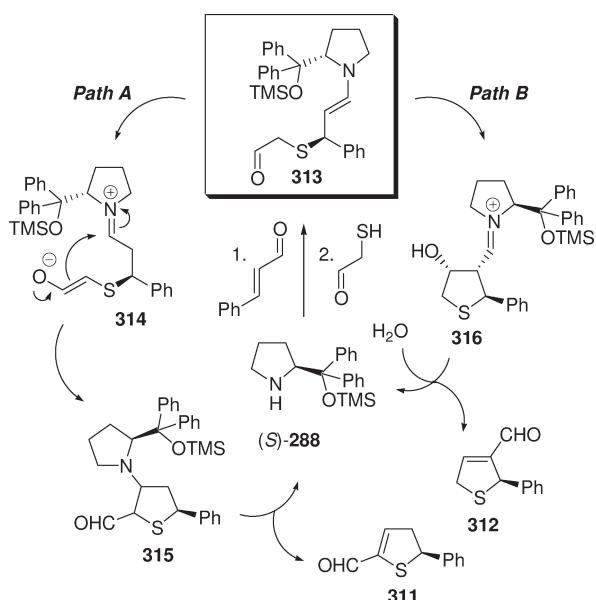
Instead, the same reaction has been efficiently carried out in the presence of the basic catalyst (S)-288 (20 mol %) and 4-nitrobenzoic acid (10 mol %) in toluene at room temperature, giving (*R*)-configured 2,5-dihydrothiophene 312 in 78% yield and >99% ee. The dihydrothiophenes 311 and 312 may result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

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

Scheme 52



Scheme 53



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-workers¹⁰⁷ (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 co-workers 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

Enzymatic¹¹⁶ and nonenzymatic¹¹⁷ catalysts acting both on prochiral and *meso*-compounds have been successfully employed in the preparation of enantiopure thiolane derivatives. As shown in

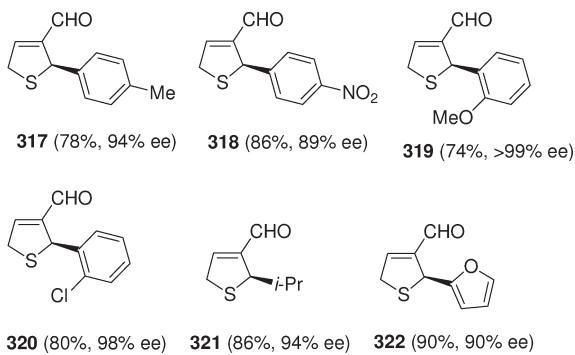
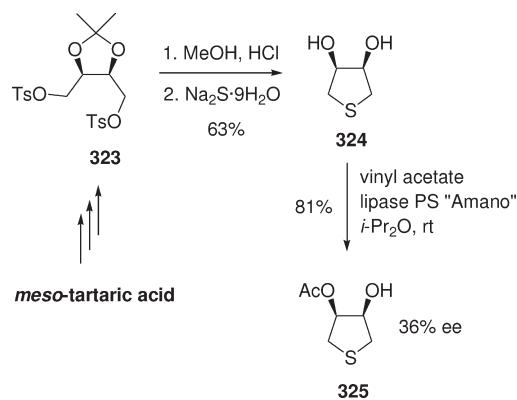
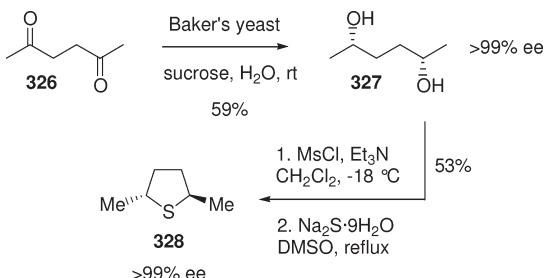


Figure 14.

Scheme 54



Scheme 55

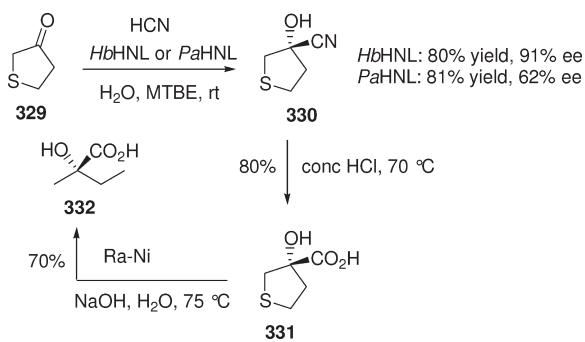


Scheme 54, *cis*-3,4-dihydroxythiolane 324, easily obtained from *meso*-tartaric acid via the acetonide 323, was desymmetrized to the monoacetate 325 by lipase-catalyzed acetylation.¹¹⁸

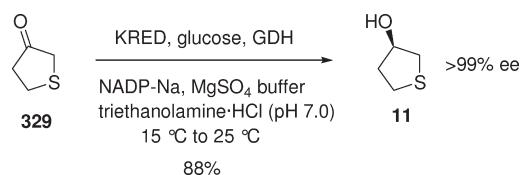
Baker's yeast (*Saccharomyces cerevisiae*) reduction of acetonyl acetone 326,¹¹⁹ using a higher substrate concentration in comparison to a known¹²⁰ literature protocol, provided (2*S*,5*S*)-2,5-hexanediol 327 in 59% yield with >99% ee (Scheme 55). Derivatization of 327 as the corresponding dimesylate, 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* (*HbHNL*) and *Prunus amygdalus* (*PaHNL*) were able to catalyze HCN addition to the carbonyl group of

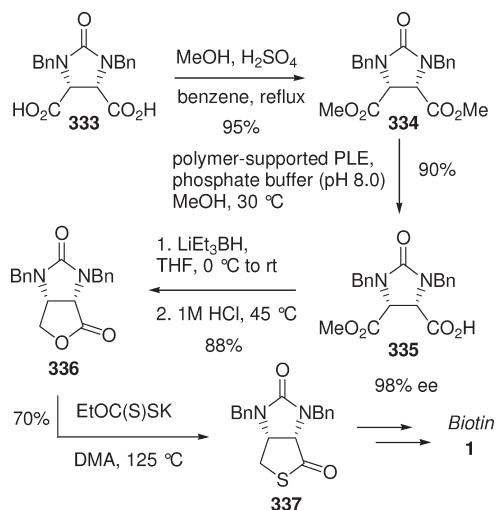
Scheme 56



Scheme 57



Scheme 58

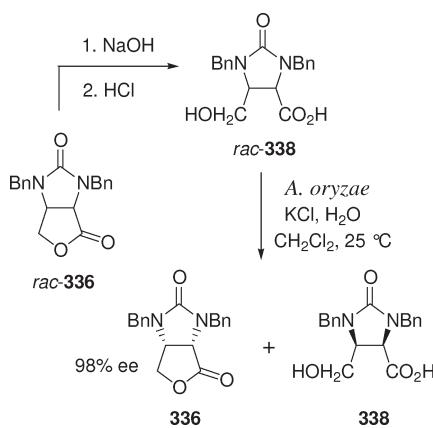


commercially available tetrahydrothiophen-3-one **329** to give the cyanohydrin **330** in 91% ee and 62% ee, respectively (Scheme 56).¹²²

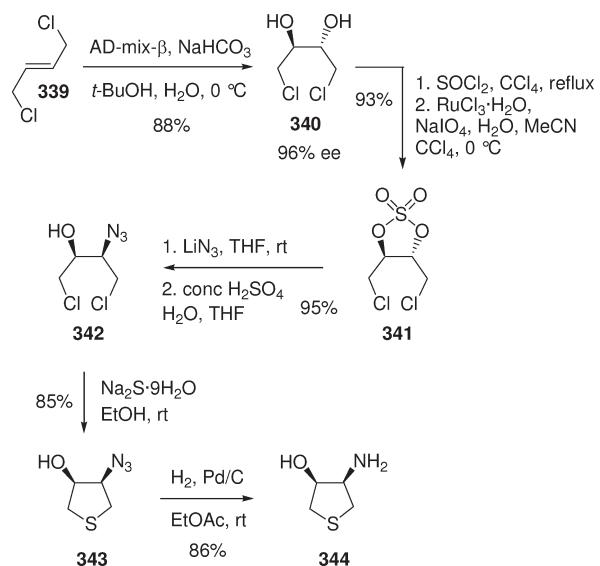
The enantiopure α -hydroxy acid **331** could be obtained from the cyanohydrin scalemic mixture through hydrolysis and fractional crystallization of the (*S*)-phenylethylamine salts. Interestingly, desulfurization of **331** with Raney nickel furnished enantiopure (*S*)-2-hydroxy-2-methylbutyric acid **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



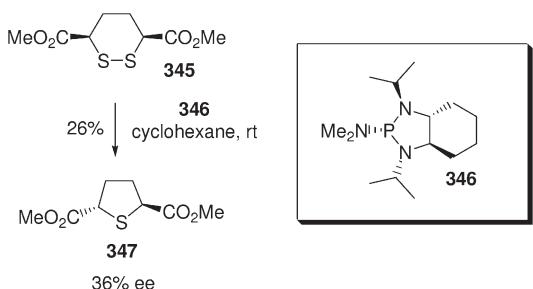
kefir, or *Lactobacillus minor*, in combination with glucose and a NADP-dependent glucose dehydrogenase (GDH), were able to provide (*R*)-**11** in 88% yield, >99% chemical purity, and >99% ee (Scheme 57).

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.

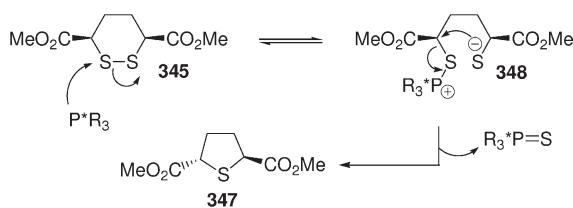
Remarkably, engineered ketoreductase enzymes proved superior to other biocatalysts, such as horse liver alcohol dehydrogenase¹²³ and fungal whole-cell systems,¹²⁴ providing the undesired (*S*)-alcohol in 33% ee and the desired (*R*)-alcohol in 81–91% ee, respectively. Immobilized pig liver esterase (PLE) on Eupergit C catalyzed the enantioselective hydrolysis of *meso*-dicarboxylic ester **334** into the (*4S,5R*)-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

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 ($\geq 98\%$ ee) together with the optically active unreacted substrate 338. Desymmetrization of prochiral compound 339¹²⁸ gave access to optically active *cis*-4-amino tetrahydrothiophen-3-ol 344, along the steps depicted in Scheme 60.

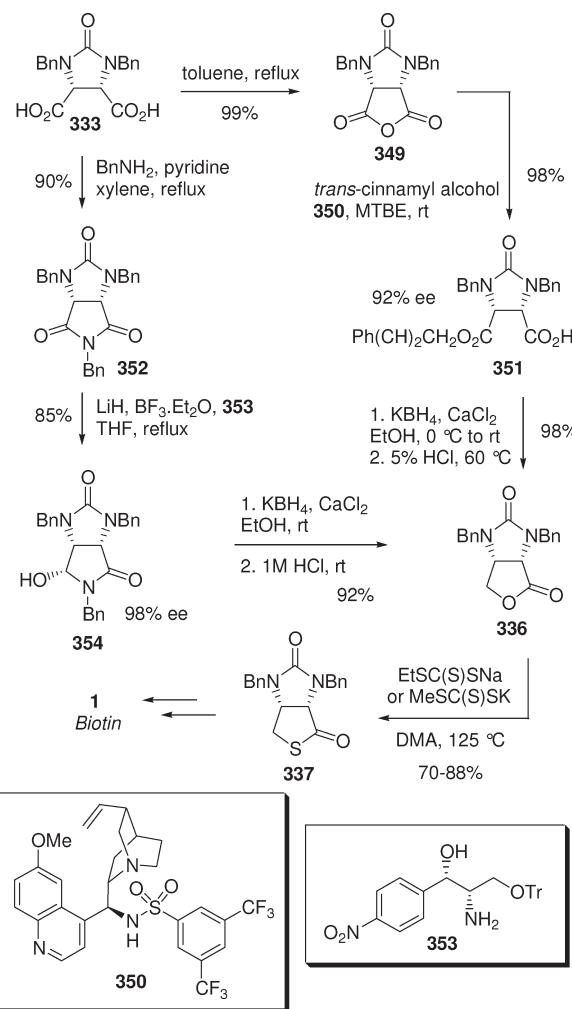
In detail, catalytic asymmetric dihydroxylation of 339 produced (2*R*,3*R*)-1,4-dichlorobutanediol 340, subsequently converted into 341 through sequential treatment with thionyl chloride and ruthenium-catalyzed oxidation of the intermediate cyclic sulfite. Lithium azide ring-opening of the *C*₂-symmetric 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 aminophosphines.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 suggested¹³¹ 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 alcoholysis¹³² of commercially available *meso*-cyclic anhydride 349, in turn prepared by dehydration of

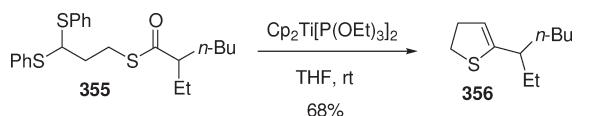
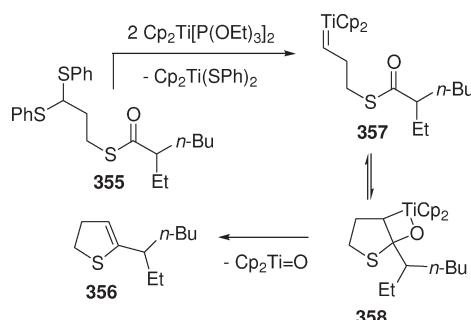
Scheme 63



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

Scheme 64**Scheme 65**

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

3. SYNTHESIS OF RACEMIC DIHYDRO- AND TETRAHYDROTHIOPHENES

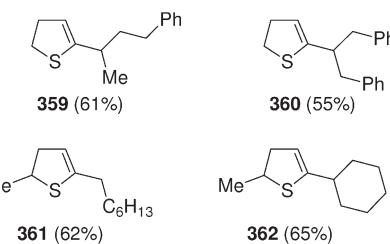
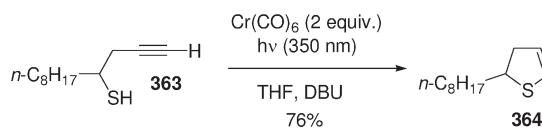
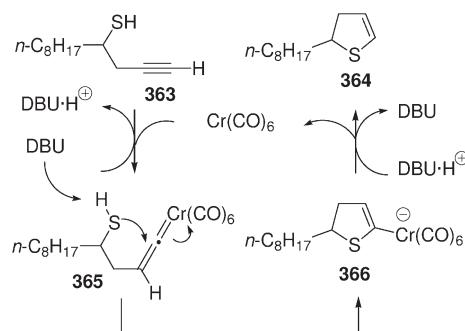
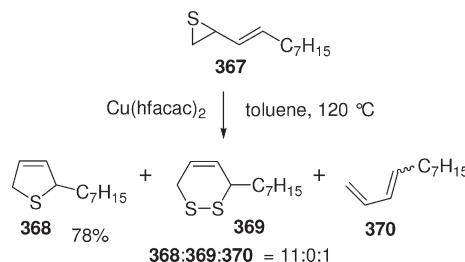
Given the importance of substituted dihydro- and tetrahydrothiophene scaffolds, the development of new synthetic approaches to these interesting classes of compounds is a topical subject for organic chemists. Not surprisingly, besides the stereocontrolled routes to chiral dihydro- and tetrahydrothiophenes, 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 $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ (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 titanoxetane intermediate **358** (Scheme 65), in analogy with the mechanism proposed for carbonyl olefination using a thioacetal- $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ system.¹⁴⁵ Similarly, good yields of 5-substituted-2,3-dihydrothiophenes **359**–**362** were obtained from different thioalkanoate derivatives (Figure 15).

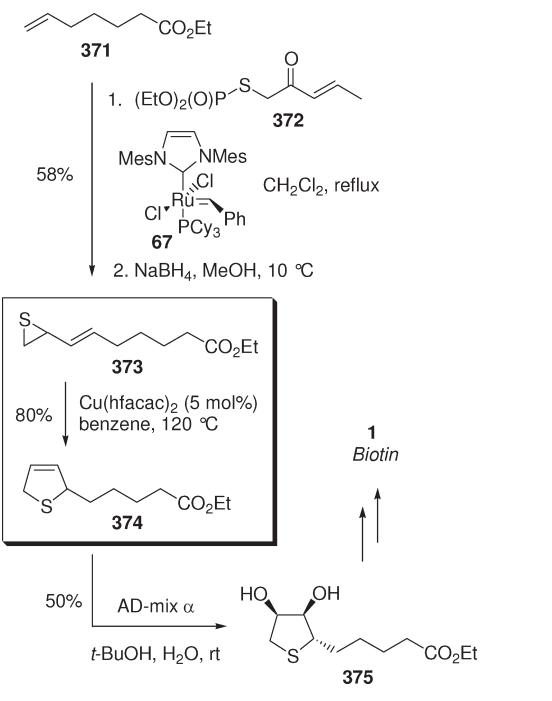
Transition metal carbonyl-promoted cyclizations of terminal alkynes tethered to various nucleophiles have been successfully utilized for the synthesis of carbo- and heterocyclic compounds, with sulfur comparing well with oxygen, nitrogen, and carbon nucleophilic species.^{146,147} Thus, irradiation of a THF solution of alkynylthiol **363** in the presence of $\text{Cr}(\text{CO})_6$ 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**

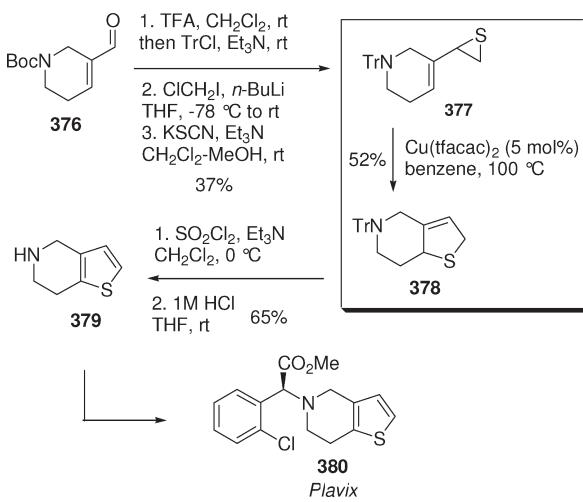
Cycloisomerization proceeded by the initial formation of the vinylidene complex **365**, which underwent a DBU-promoted intramolecular nucleophilic addition affording the cyclic anionic intermediate **366**. Subsequent proton transfer gave rise to the dihydrothiophene **364** with concomitant regeneration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

In 2007, Njardarson and co-workers¹⁴⁸ 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) acetylacetone (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

Scheme 69



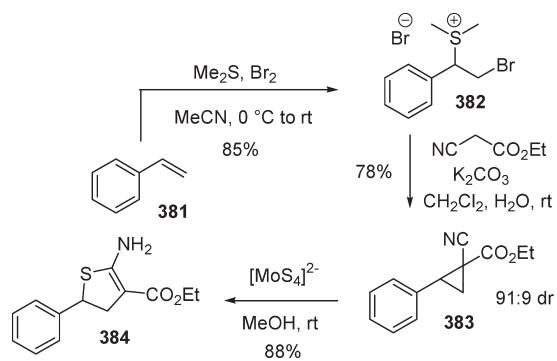
Scheme 70



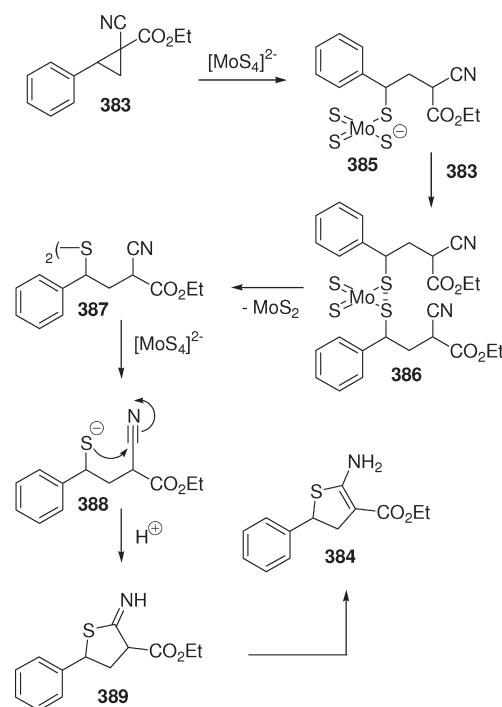
5 mol % copper(II) hexafluoroacetylacetone [$Cu(hfacac)_2$] provided dihydrothiophene 368 as the major product (78% isolated yield), with other copper catalysts producing 368 along with variable amounts of disulfide 369 and diene 370 (Scheme 68).

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-dihydrofurans¹⁴⁹ 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 Ohru'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) trifluoroacetylacetone [$Cu(tfacac)_2$] (5 mol %) in benzene at 100 °C. Subsequent oxidation with sulfonyl chloride and deprotection of the nitrogen moiety afforded 379, already taken to Plavix 380 (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

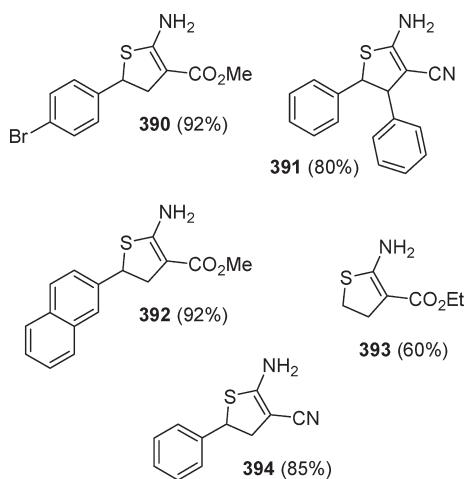


Figure 16.

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 MoS₂.

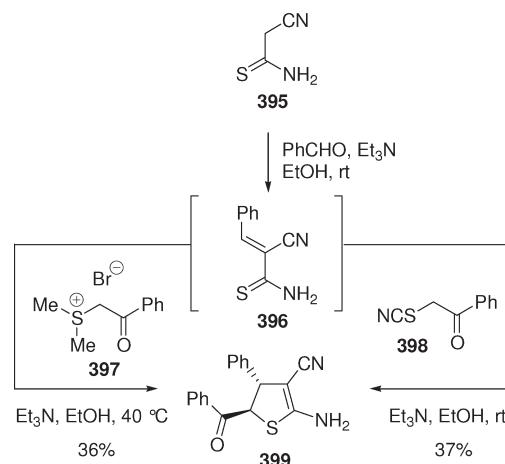
Reductive cleavage of **387** by reaction with tetrathiomolybdate followed by intramolecular cyclization of the released thiolate anion **388** produces **384** via the tautomeric dihydrothiophen-2-ylideneamine **389**. Extension of this methodology to various doubly activated cyclopropanes produced 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 phenyl thiocyanate **398**¹⁵⁵ in the presence of Et₃N, 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

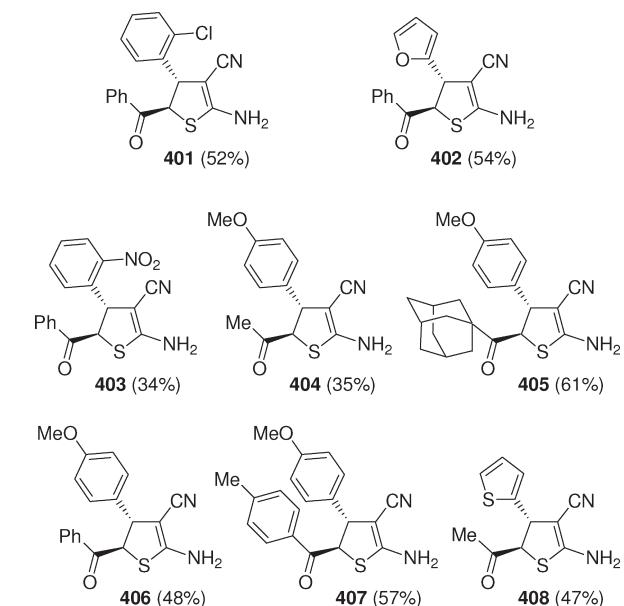
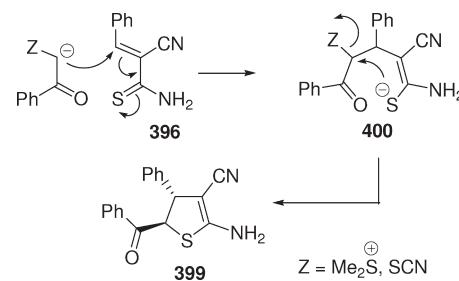
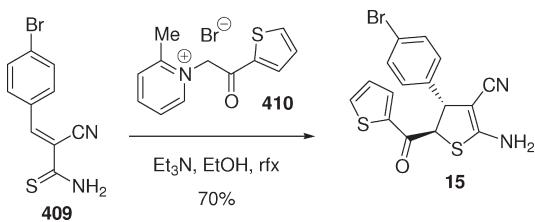


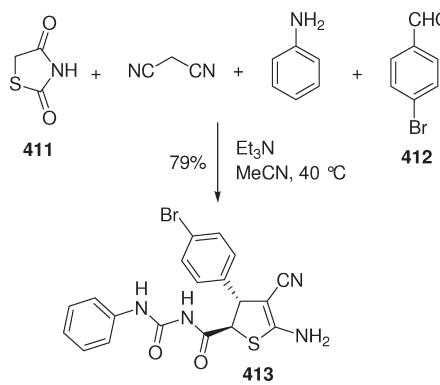
Figure 17.

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

Scheme 75



Scheme 76



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

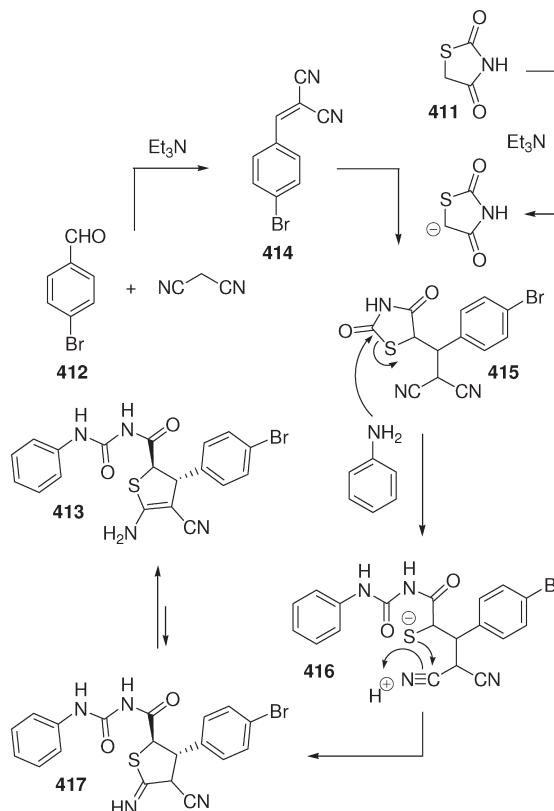
The formation of **413** is likely to proceed through the mechanism outlined in Scheme 77. Thus, the arylidene malononitrile **414**, produced by base-catalyzed Knoevenagel condensation between aldehyde **412** and malononitrile, reacted with the conjugate base of **411** leading to the intermediate 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-workers¹⁶³ demonstrated that the domino reactions also could be carried out successfully in a “green” solvent such as poly(ethylene glycol) (PEG) 400/H₂O 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 irradiation¹⁶⁴ 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-workers¹⁶⁶ 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

Scheme 77



ethanethioates, as depicted in Scheme 78 for selected examples. Thus, treatment of **425** with iodine excess in CH₂Cl₂ 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 regiosomer (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 derivatives¹⁶⁷ 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 aryl iodide

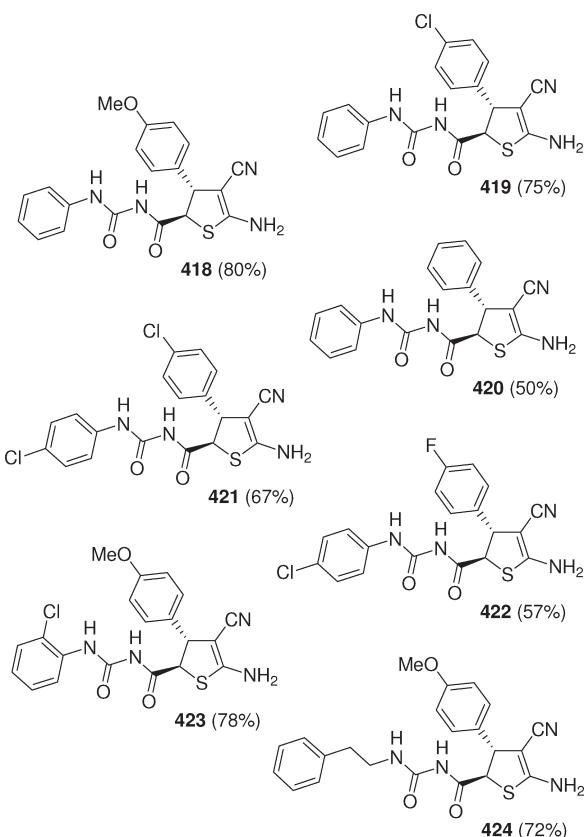
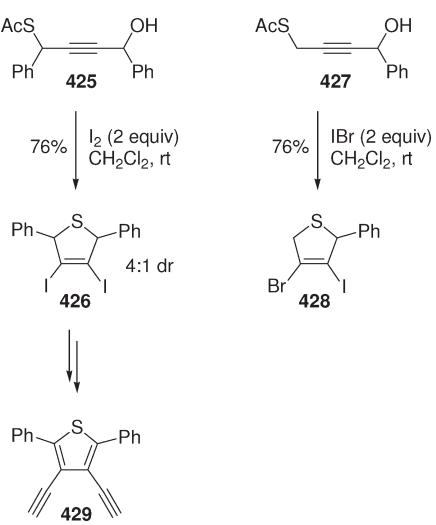


Figure 18.

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 $KO\text{t-Bu}$ (2 equiv) in

Scheme 79

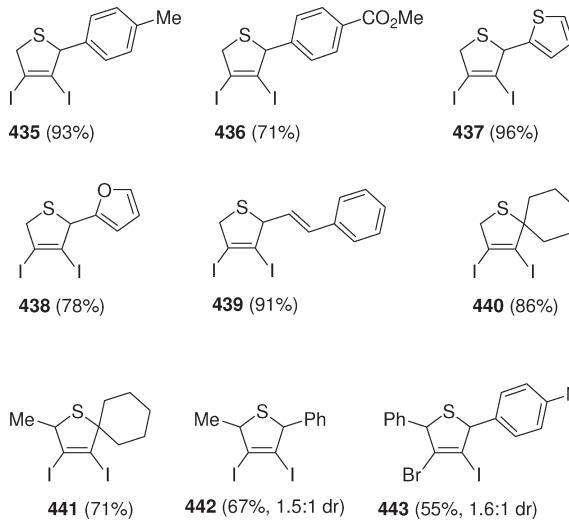
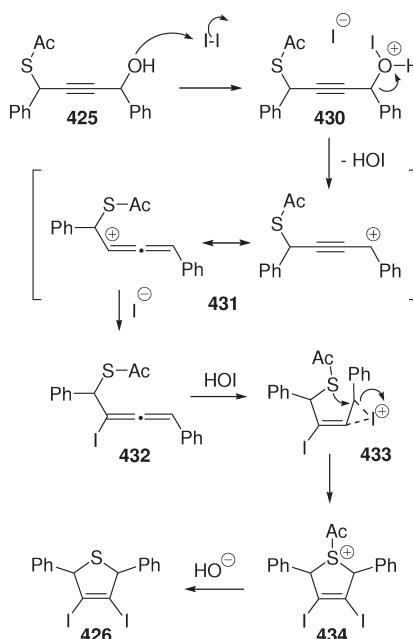


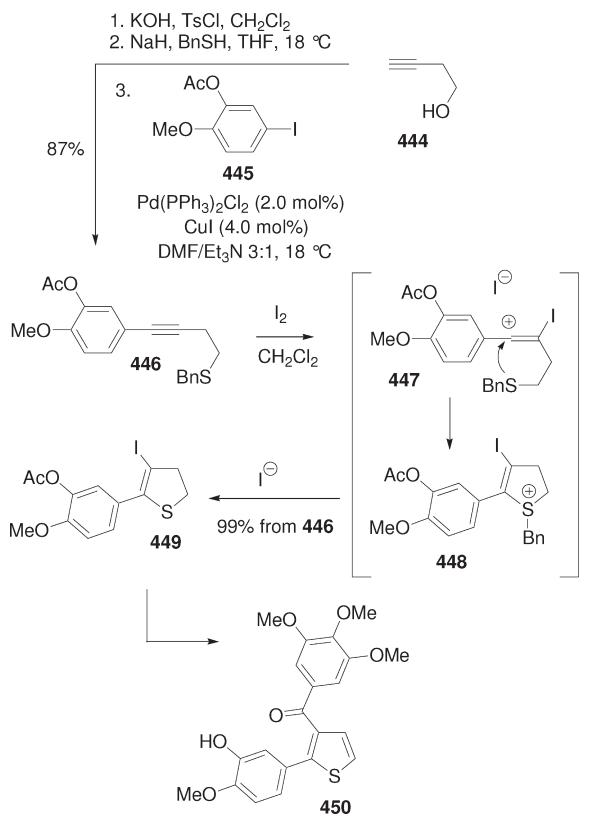
Figure 19.

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

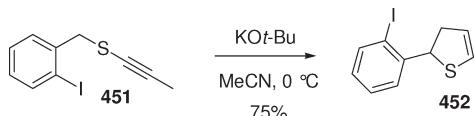
Cyclization of several other aryl-substituted benzyl 1-alkynyl sulfides either at 0 °C or at reflux temperature provided 2-aryl 2,3-dihydrothiophenes 453–460 in moderate to good yields (Figure 20). Theoretical calculations on model system 461¹⁶⁹ established that 452 and structurally related 2-aryl 2,3-dihydrothiophenes 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 quassinooids. As shown in Scheme 83, addition of alkynyllithium 467 to

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 hydrate¹⁷¹ produced the nonisolated thiol 470, which was directly coupled with methyl propionate 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 propionate 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

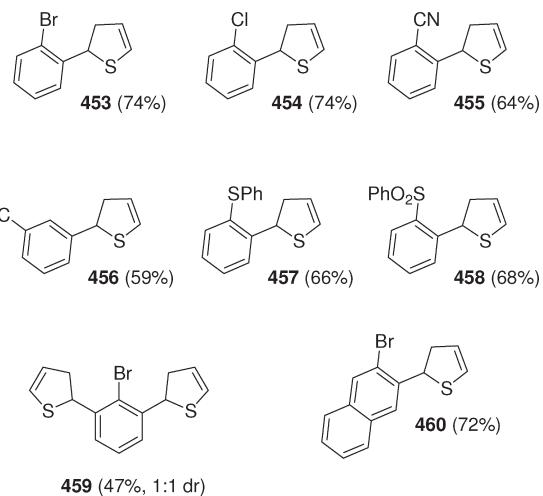
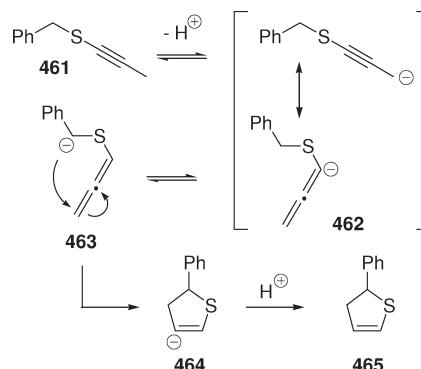


Figure 20.

Scheme 82



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

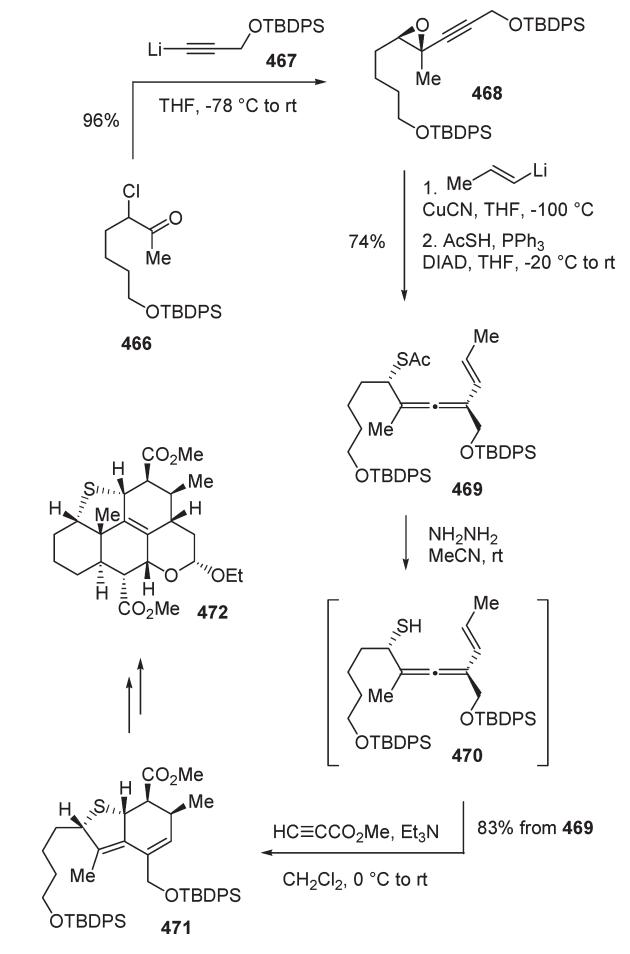
This approach has been successfully applied to obtain *trans*-3,4-dialkyl-substituted tetrahydrothiophenes in very good yield. As an example, *trans*-3,4-dibenzyl tetrahydrothiophene 484 could be prepared in 80% yield from aluminacyclopentane 483, in turn obtained from allyl benzene, EtAlCl_2 , and Mg-metal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

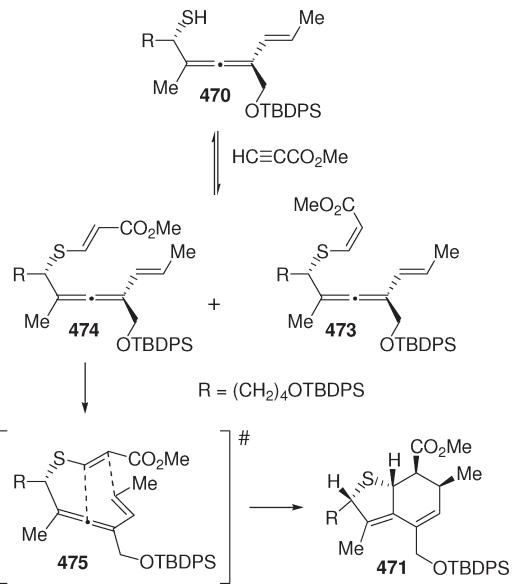
This observation encouraged the Nair group¹⁷⁵ to investigate the chemical behavior of thietanes toward electrophilic carbene substrates generated by Rh(II)-catalyzed decomposition of diethyl diazomalonate. Initial studies in this area demonstrated that heating a benzene solution of thietane 485 (*cis/trans* ratio 1:2.2) in the presence of diethyldiazomalonate and $\text{Rh}_2(\text{OAc})_4$ 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

Scheme 83

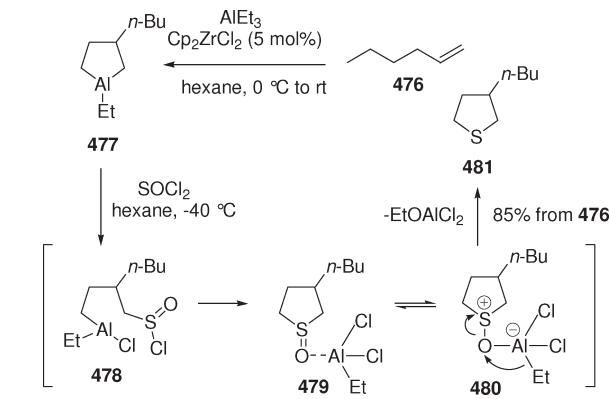


Scheme 84

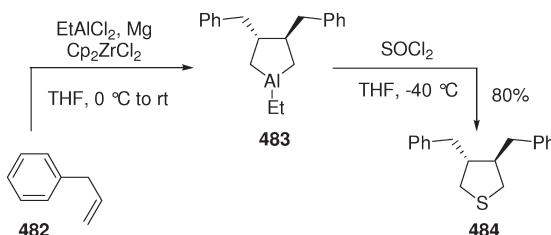


tetrahydrothiophene compounds by Stevens rearrangement.¹⁷⁶ Conversely, a β -elimination process is likely to be implicated in

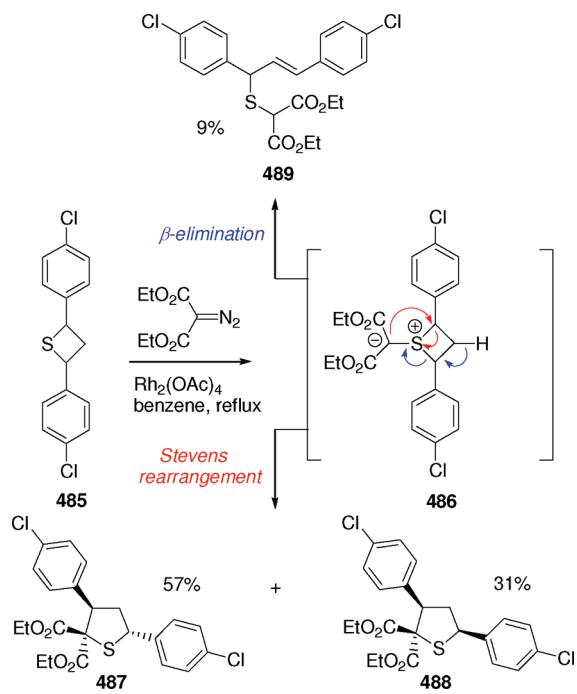
Scheme 85



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**.

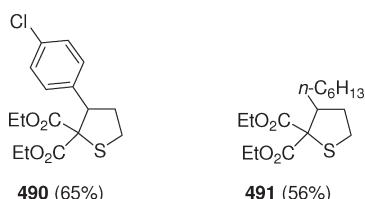
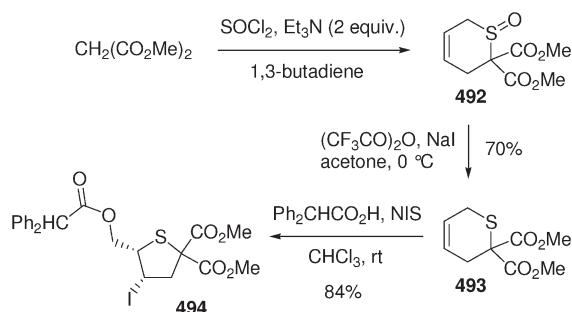


Figure 21.

Scheme 88



Lucassen and Zwanenburg¹⁷⁷ 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 propionic 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-mercaptopropanoate 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-mercaptop-2-butenoate 287 in a tandem thia-Michael/Michael sequence.

Scheme 89

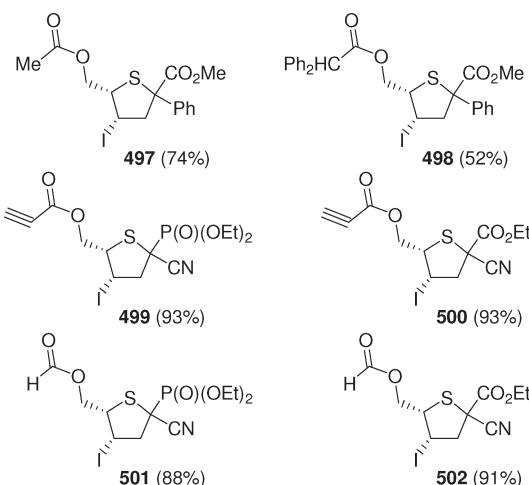
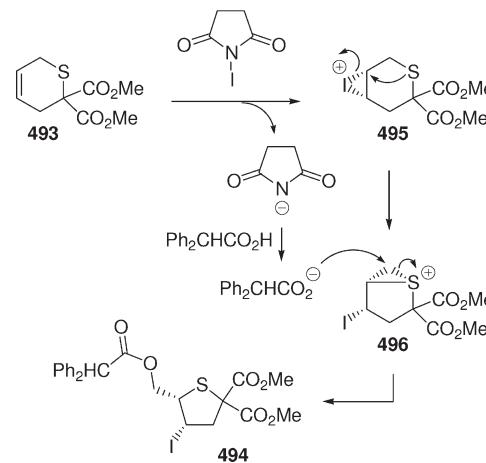


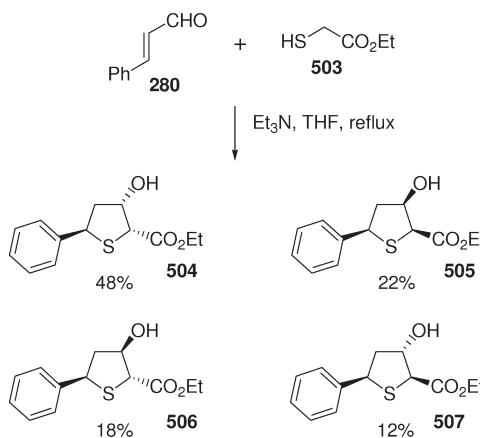
Figure 22.

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 reference¹⁷⁹ 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 $\text{Co}_2(\text{CO})_8$ followed by treatment with allyl mercaptan in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, produced the intermediate 517. The latter was not isolated but directly submitted to the pivotal Pauson–Khand cyclization in refluxing toluene to provide a

Scheme 90



Scheme 91

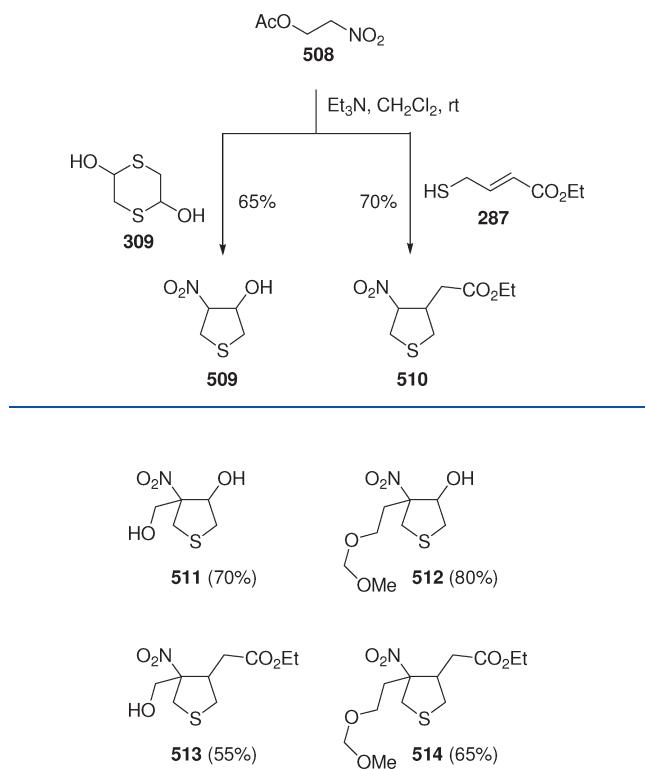
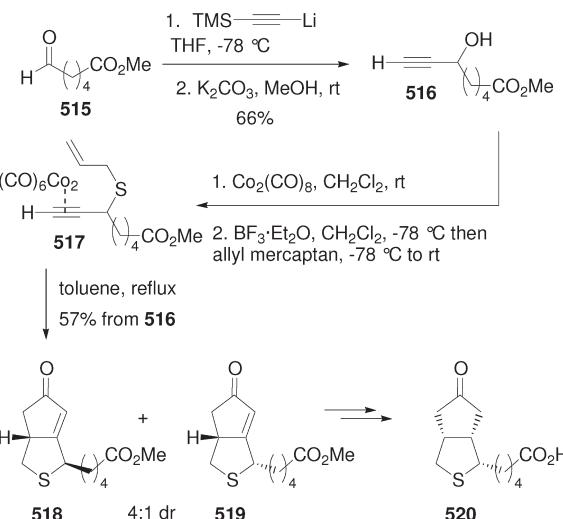


Figure 23.

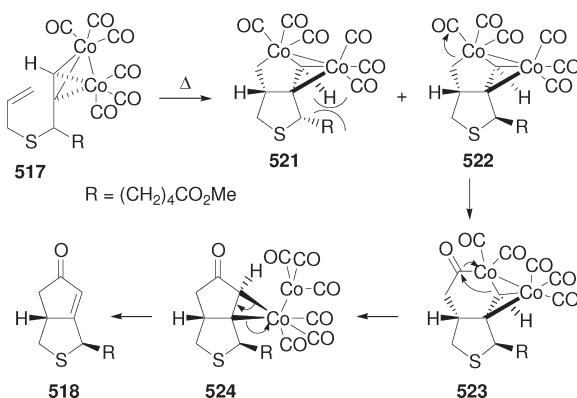
4:1 diastereomeric mixture of **518** and **519** in 57% yield, with the minor diastereomer being the precursor of the target compound **520**.

The unfavorable stereoselective outcome of the cyclization reaction can be tentatively explained on the basis of the mechanistic hypothesis proposed by Magnus and co-workers¹⁸³ 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

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-pseudodioxial 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

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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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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