Efficient preparation of chiral non-racemic sulfur compounds

Joannie Minville, Mélina Girardin, and Claude Spino

Abstract: *p*-Menthane-3-carboxaldehyde serves as an efficient chiral auxiliary in the preparation of chiral non-racemic *S*-alkylthiocarbamates or *S*-dithiocarbonates via the 3,3-sigmatropic rearrangement of the corresponding alkylthionocarbamates or xanthates. The transfer of chirality during rearrangement is complete, and the final products possess a chiral tertiary or quaternary carbon bearing sulfur. The rearranged products are then transformed into enantiopure cyclic or acyclic sulfur-containing products, depending on the means of clivage of the auxiliary. The synthesis of a potent MMP-13 inhibitor is presented.

Key words: 3,3-sigmatropic rearrangement, *p*-menthane-3-carboxaldehyde, *S*-alkylthiocarbamate, *S*-dithiocarbonate, alkylthionocarbamate, xanthate, ring-closing metathesis.

Résumé : Le *p*-menthane-3-carboxaldéhyde est un auxiliaire chiral efficace dans la préparation de *S*-alkylthiocarbamates ou de *S*-dithiocarbonates non chiraux par le biais d'un réarrangement sigmatropique-3,3 des alkylthionocarbamates ou des xanthates correspondants. Le transfert de chiralité durant ce réarrangement est total et les produits finaux possèdent un atome de carbone tertiaire ou quaternaire chiral portant un atome de soufre. Suivant les méthodes utilisées pour cliver l'auxiliaire, es produits réarrangés sont alors transformés en produits cycliques ou acycliques énantiopurs contenant du soufre. On rapporte la synthèse d'un puissant inhibiteur MMP-13.

Mots-clés : réarrangement sigmatropique-3,3, *p*-menthane-3-carboxaldéhyde, *S*-alkylthiocarbamate, *S*-dithiocarbonate, alkylthionocarbamate, xanthate, métathèse accompagnant une fermeture de cycle.

[Traduit par la Rédaction]

Introduction

Many natural and man-made products, containing a sulfur atom, have huge potential in medicinal chemistry (1). Figure 1 lists some examples. Montelukast **1** (singulair) is a potent antagonist of the cysteinyl leukotriene receptor and serves as a prophylactic, once-a-day, anti-asthma agent (2). Compound **3** is a potent inhibitor of phosphodiesterases (PDE4) at nanomolar concentrations (3). Natural products, containing a chiral sulfide moiety, include the fatty-acid synthetase inhibitors thiolactomycin **4** and thiotetromycin **5** (4), gliotoxin **6** (5), with antiviral, antibacterial, and immunosuppressive activities, and biotin **2** (6).

The construction of chiral C–O and C–N bonds has reached a higher level of sophistication than the making of chiral C–S bonds (7). In fact, chiral C–S bonds are often made by displacement of the corresponding chiral C–O bonds (8). When displacing a chiral allylic C–O bond, transposition may or may not occur. With Mitsunobu reactions, transposition is usually not observed (9), whereas 3,3-sigmatropic rearrangements provide products with a transposed double bond (10).

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In that regard, we viewed our chiral scaffold derived from *p*-menthane-3-carboxaldehyde **7** as ideal to implement a methodology aimed at preparing chiral sulfur-containing compounds (Scheme 1) (11). First, the bulky menthyl moiety allows rearrangements reactions to occur at low temperatures (11*b*). Thus, the 3,3-sigmatropic rearrangement of allylic thionocarbamates (12, 13), phosphonothionates (12*b*), xanthates (14), or similar precursors should proceed smoothly to give the desired chiral C–S bond, even in the case of trisubstituted double bonds. Second, the chiral auxiliary is cleavable by two completely different methods, giving rise to cyclic or acyclic products. Last, either stereochemistry of the targeted chiral C–S bond can be selected by controlling the stereochemistry of the alcohol (both are easily obtained) and (or) the geometry of the alkene and (or) the absolute configuration of **7** (both enantiomers are readily available and inexpensive). This flexibility is a great asset for synthesis.

Results and discussion

Building the thiocarbamates and xanthates

Our strategy starts with the synthesis of allylic alcohols **8**, which were prepared by one of methods A, B, or C (Scheme 2). Method A involves the preparation of vinyl iodides **17** using Schwartz' hydrozirconation or hydroboration of the substituted acetylenes **13**. After submitting vinyl iodides **17** to a metal-halogen exchange using *t*-butyllithium, the resulting vinyllithiums **18a** were stereoselectively added to (–)-*p*-menthane-3-carboxaldehyde **7** in the presence of

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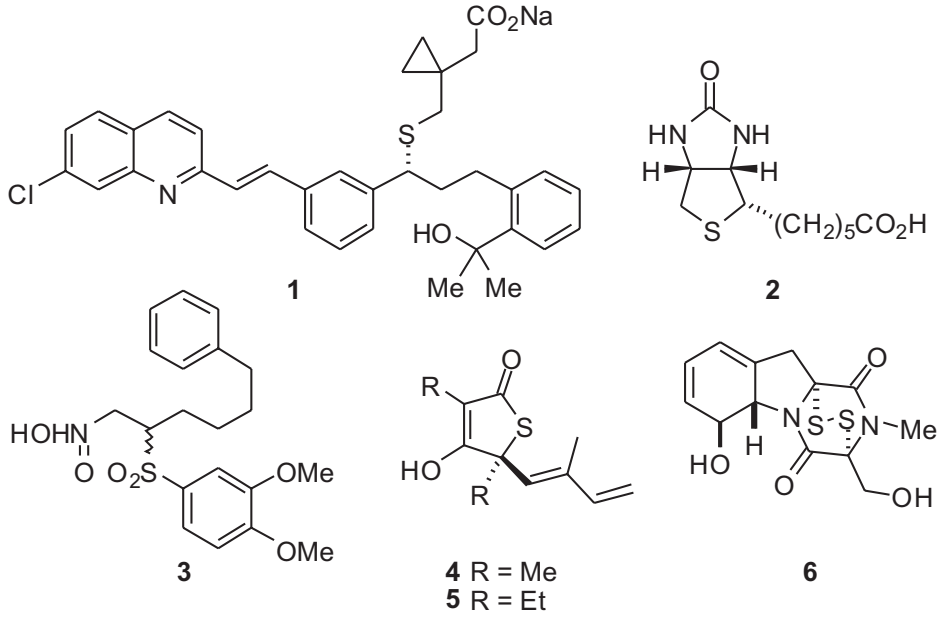
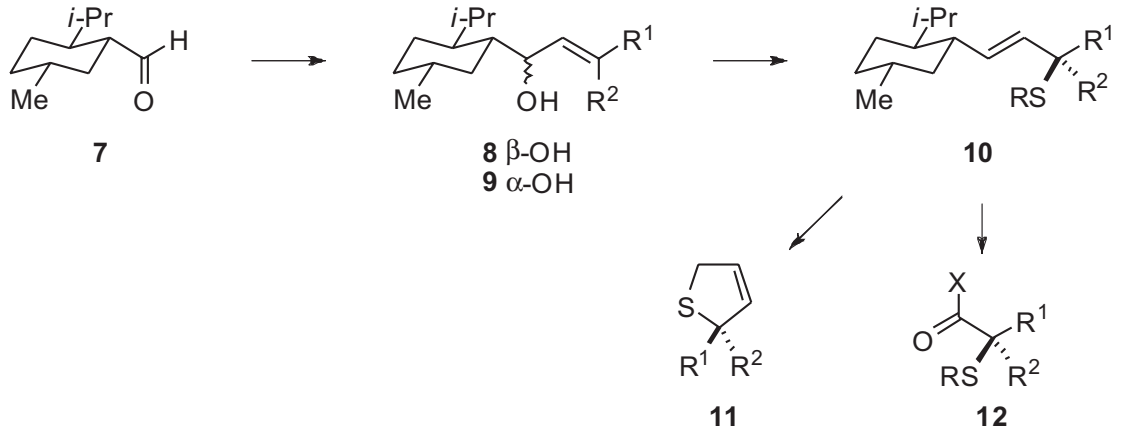
Fig. 1. Biologically active sulfur-containing natural and unnatural products.



Scheme 1. Strategy to obtain chiral sulfur compounds.



trimethylaluminium (15). The major alcohols **8a**, **c**, **d**, and **f** result from the addition of the vinyllithiums to aldehyde **7** following Felkin–Ahn's model of stereoselectivity (16). Trimethylaluminium renders this addition highly stereoselective, and the Felkin adducts **8** were isolated essentially as a single isomer (52 to 200:1; Table 1, entries 1, 3, 4, and 6). Method B uses the stereoselective addition of vinylalanes **18b**, made from the zirconium-catalyzed carboalumination (17) of alkynes **13**, to aldehyde **7**. While this method is slightly less stereoselective than method A, it is nonetheless the excess trimethylaluminium used during the carbolumination process that provides this level of stereoselection (11 to 30:1; Table 1, entries 2, 7, and 8). Evaporation of the excess trimethylaluminium prior to addition to **7** leads to lower stereoselectivities. Method C involves the addition of lithium acetylides **14** to **7**. Propargyl alcohol **15**, isolated as a 2:1 mixture of diastereomers, was then converted to the desired allylic alcohol **8** using Red-Al. All mixtures of alcohols **8** and **9** were easily separated by flash chromatography, and the sequence was continued with isomerically pure alcohols as determined by GC or HPLC.

The minor diastereomer **9** (α-OH) could be prepared in sufficient quantities first by oxidizing the major isomer **8** to the corresponding enone **19** and then by reducing the latter using Super-Hydride™ (Scheme 3). This reduction is completely diastereoselective and gives **9** as the sole diastereomer (11*a*). Having access to both alcohols **8** and **9** in large quantities allowed us to measure the diastereoselectivities of the subsequent reactions. Moreover, both enantiomers of the final chiral sulfur compounds can be prepared from a single enantiomer of the chiral auxiliary **7** via alcohols **8** or **9**, since they lead to enantiomeric products after cleavage of the chiral auxiliary, respectively.

Starting from the allylic alcohols **8** or **9**, we procured the allylic thionocarbamates as intermediates (not shown), using *N*-phenylisothiocyanate as reagent to make them. They rearranged to the *S*-allylthiocarbamates **20** or **21**, respectively, upon acidification of the reaction mixture with PPTS (Table 2). The rearrangement does not proceed (or proceeds very slowly) while the allylthionocarbamates are still under basic conditions. However, once the solution is acidified, the rearrangement takes place within a few hours at 66 °C.

Scheme 2. Preparation of alcohols **8**.

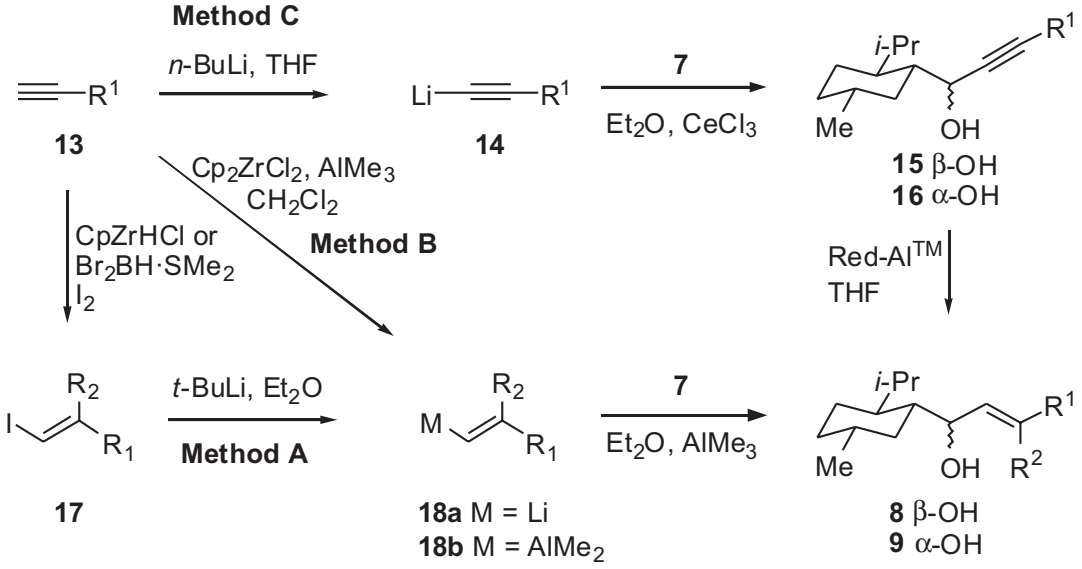
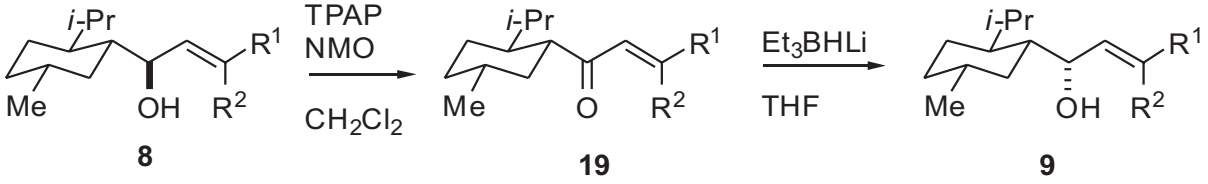


Table 1. Yields and % de of alcohols **8**.

Entry	**13**	R^1	R^2	Method	Yield (%)[a]	de (%)[b]
1	**a**	*n*-Pr	H	A	72	98
2	**b**	*n*-Pr	Me	B	87	94
3	**c**	*t*-Bu	H	A	66	>99
4	**d**	Me_3Si	H	A	46	>99
5	**e**	Ph	H	C	97	90
6	**f**	$Ph(CH_2)_4$	H	A	68	96
7	**g**	$Ph(CH_2)_4$	Me	B	82	88
8	**h**	Bn	Me	B	81	92

[a]Isolated yield.
[b]Measured by GC or HPLC on crude mixtures.

Scheme 3. Preparation of the diastereomeric alcohols **9**.

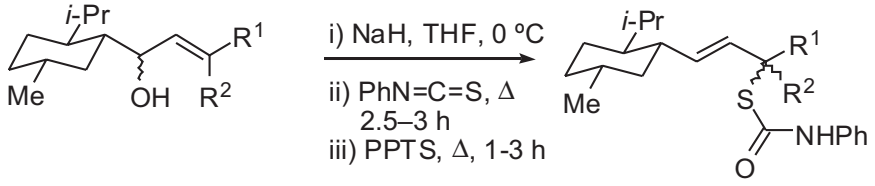


Many substrates underwent the rearrangement slowly at room temperature within several days. This sequence allowed us to prepare various *S*-allylthiocarbamates **20a**–**20h** and **21a**–**21h** in good to excellent yields with diastereomeric excesses (de) > 90%. We believe that the de of compound **21f** reported in Table 2, entry 12 is > 76%. The lower-than-expected value may be due to an impurity that co-elutes with the diastereomer of **21f**, and that we could neither identify nor remove. The structure of **20c** was confirmed by single crystal X-ray diffraction analysis, and it was consistent with a concerted rearrangement of **8c** via a chair-like transition state (TS) **20**-*E*-chair (Scheme 4).

The minor *S*-thiocarbamates in the rearrangement of the thionocarbamates derived from **8** or **9** do not come from a competing concerted transition state (18) but must instead be derived from ionic pathways competing with the concerted one. Indeed, a close look at the possible transition states (Scheme 4, only the chair-like TS are represented) (19) leads us to the conclusion that to attack the alkene face leading to the minor *S*-thiocarbamate, the thionocarbamate must maximize its $A^{1,3}$ strain, which would give a product having a *Z* double bond. There is no concerted pathway leading to **21** from **8** or to **20** from **9**. Ionic intermediates, on the other hand, would collapse to a mixture of **20** and **21** regardless of their origin.

One might wonder why we did not observe the formation of regioisomers **23** as a minor product if ionic intermediates are involved. However, it is our experience that the menthyl moiety is very efficient at preventing attack at the β position. For example, when alcohol **8g** is submitted to an acidic environment, some regioisomer **24g** was isolated as a mixture of diastereomers, but the recovered alcohol **8g** was diastereo-

Table 2. Yields and % de of thiocarbamates **20** and **21**.



8 β-OH
9 α-OH

20 β-SC(O)NHPh
21 α-SC(O)NHPh

Entry	Alcohol	R^1	R^2	Product	Yield (%)[a]	de (%)[b]
1	**8a**	*n*-Pr	H	**20a**	97	98
2	**9a**	*n*-Pr	H	**21a**	99	>99
3	**8b**	*n*-Pr	Me	**20b**	75	>99
4	**9b**	*n*-Pr	Me	**21b**	65	98
5	**8c**	*t*-Bu	H	**20c**	96	98
6	**9c**	*t*-Bu	H	**21c**	99	>99
7	**8d**	Me_3Si	H	**20d**	99	>99
8	**9d**	Me_3Si	H	**21d**	87	>99
9	**8e**	Ph	H	**20e**	81	93
10	**9e**	Ph	H	**21e**	97	90
11	**8f**	$Ph(CH_2)_4$	H	**20f**	99	97
12	**9f**	$Ph(CH_2)_4$	H	**21f**	94	76[c]
13	**8g**	$Ph(CH_2)_4$	Me	**20g**	87	98
14	**9g**	$Ph(CH_2)_4$	Me	**21g**	67	>99
15	**8h**	Bn	Me	**20h**	88	99
16	**9h**	Bn	Me	**21h**	85	>99

[a]Isolated yield.
[b]Measured by GC or HPLC on crude mixture.
[c]Presence of impurity with same retention time as diastereomer makes % de appear lower than actual value.

Scheme 4. Chair-like transition state for the rearrangement.

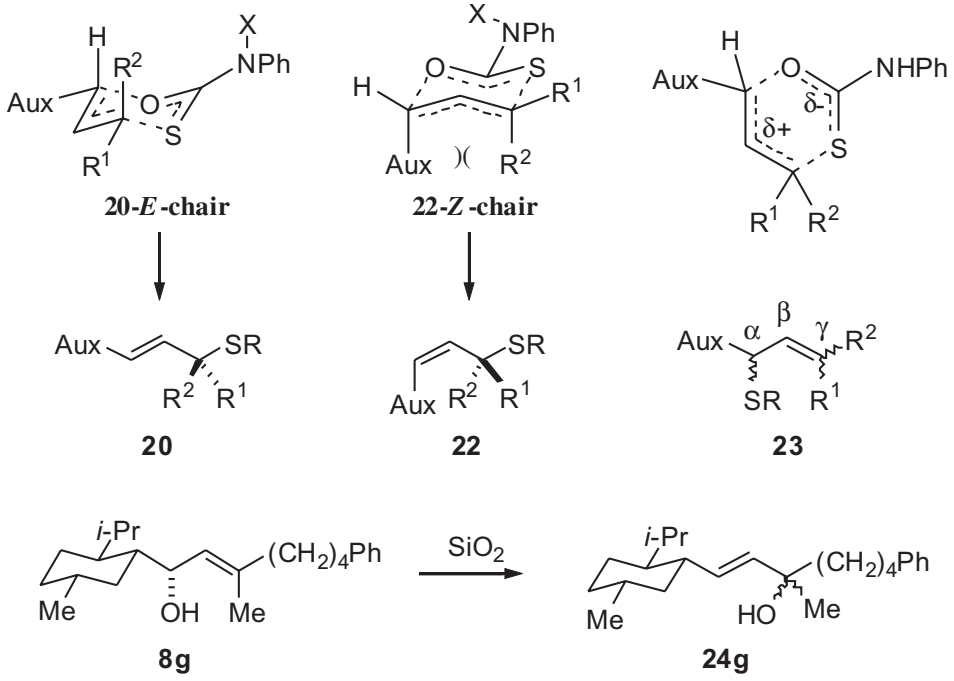
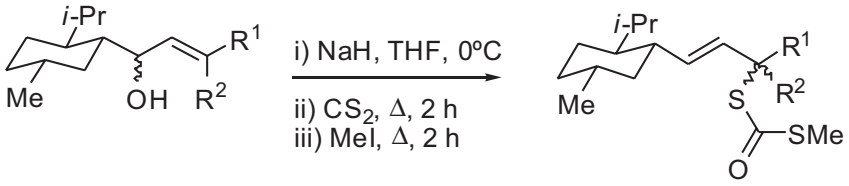


Table 3. Yields and % de of *S*-thiocarbonates **25** and **26** and *S*-thiocarbamates **27** and **28**.



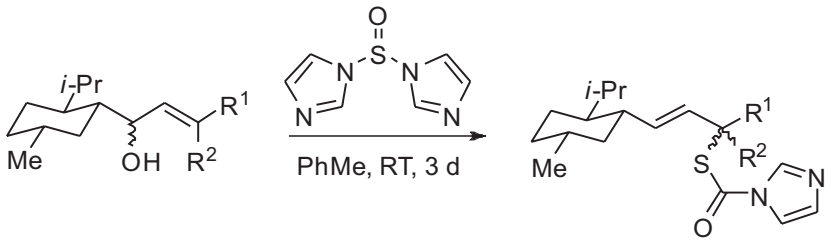
8 β-OH
9 α-OH

25 β-SC(O)SMe
26 α-SC(O)SMe

Entry	Alcohol	R^1	R^2	Product	Yield (%)[a]	de (%)[b]
1	**8b**	*n*-Pr	Me	**25b**	59	99
2	**9b**	*n*-Pr	Me	**26b**	39	98
3	**8c**	*t*-Bu	H	**25c**	99	>99
4	**9c**	*t*-Bu	H	**26c**	90	98
5	**8f**	$Ph(CH_2)_4$	H	**25f**	85	>99
6	**9f**	$Ph(CH_2)_4$	H	**26f**	85	96
7	**8c**	*t*-Bu	H	**27c**	78	97
8	**9c**	*t*-Bu	H	**28c**	42	99
9	**8e**	Ph	H	**27e**	0	—
10	**9e**	Ph	H	**28e**	0	—

[a]Isolated yield.
[b]Measured by GC or HPLC on crude mixture.

Scheme 5. Imidazole variant of the thiocarbamate rearrangement.



8 β-OH
9 α-OH

27 β-SC(O)imid
28 α-SC(O)imid

merically pure. This implies that the ionic intermediates collapsed exclusively to the regioisomer **24g**.

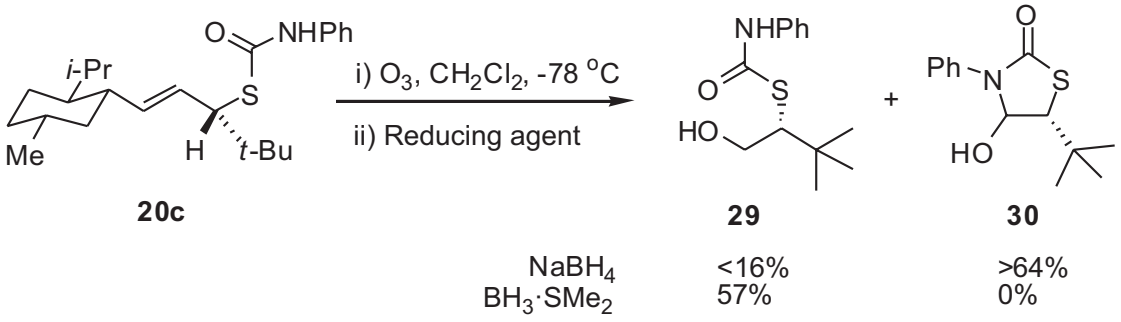
Our observation that the thionocarbamates (Scheme 4, X = H) rearrange much faster than the metallated thionocarbamates (X = Na) is in line with observations by Nakai and Zaim that electron donors (e.g., R_2N) at that position slowed the rearrangement, while an electron-withdrawing group such as Cl increased the reaction rate (18). Possibly, the proton sits exclusively on the nitrogen atom in the thionocarbamate, while the metal is perhaps on sulfur. According to Nakai and Ari-Izumi, a higher bond order for the thiocarbonyl is found in precursors that undergo fast reactions (18*a*).

Also, these authors found that substitution on the allylic fragment increased the reaction rate. Although we have not measured the actual rate constants of our reactions, we have qualitatively observed that the thionocarbamates derived from the trisubstituted allylic alcohols **8b**, g, h and **9b**, g, h rearranged substantially faster than the others. For example, the thionocarbamates derived from **8g** and **9g** rearranged in 53% and 67% yield, respectively, at room temperature in 24 h. The analogous thionocarbamates made from **8f** and **9f** did not rearrange after the same time at room temperature. Several days later, some rearrangement was observed for **8f** and **9f**, but the reaction had not reached completion. This same trend was observed for **8a** and **8c**.

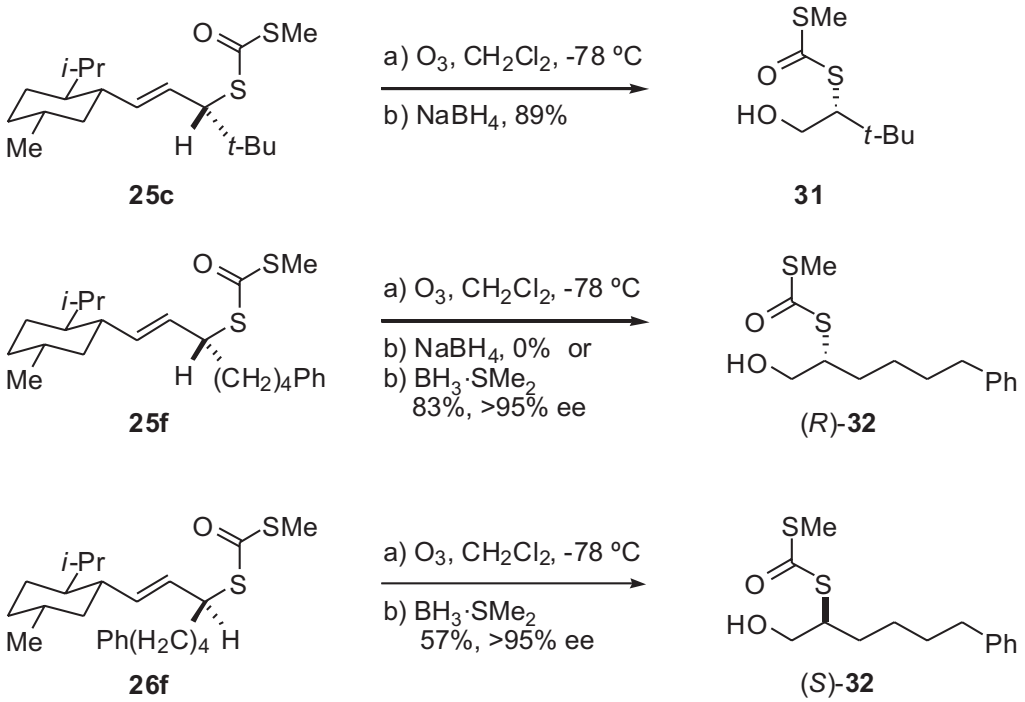
Xanthates derived from alcohols **8** or **9** rearranged to allylic dithiocarbonates **25** or **26** (Table 3, entries 1–6). The reaction conditions and times were very similar to the ones used for the thionocarbamates. Table 3 reveals that yields and diastereoselectivities are also comparable. The main difference resides in the subsequent cleavage of the chiral auxiliary (see later).

We also tested the rearrangement on the imidazole variant of thionocarbamates because they are supposed to proceed at lower temperatures, which could be an advantage for some thermally unstable substrates (Scheme 5 and Table 3, entries 7–10) (20). Indeed, we obtained a 78% yield of **27c** from **8c** after stirring for 3 days at room temperature (Table 3, entry 7). However, while the rearrangements were somewhat faster than their *N*-phenyl carbamate analogs, it proved to be less general. For example, alcohols **8e** and **9e** yielded only elimi-

Scheme 6. Oxidative cleavage of the *S*-thiocarbamate **20c**.



Scheme 7. Oxidative cleavage of *S*-thiocarbonates **25c**, **25f**, and **26f**.



nation and other decomposition products under those conditions.

The low temperature at which all of these rearrangements take place is noteworthy and likely the result of the steric volume of the menthyl fragment (steric decompression).[2] Some thionocarbamates derived from **8** or **9** undergo rearrangement at room temperature, albeit rather slowly. Usually, such compounds require heating in excess of 100 °C for the rearrangement to take place. For example, Thomas and co-workers used, in their synthesis of thiotetronic acids, a xanthate to thiocarbonate rearrangement that occurred at 145 °C during distillation (10).

Cleaving the chiral auxiliary

Oxidative cleavage

Cleavage of the auxiliary in *S*-thiocarbamate **20c** with ozone, the usual method by which we cleave this chiral auxiliary (11), resulted in the efficient conversion of the starting material. Indeed, a reductive work-up with $NaBH_4$ led to the formation of a mixture of the desired alcohol **29** and thiazolidinone **30** in 80% combined yield (Scheme 6). When $BH_3 \cdot SMe_2$ was used as the reducing agent, only alcohol **29** was formed in 57% yield. The Lemieux protocol ($OsO_4/NaIO_4$) or similar methodologies are less efficient and often lead to a mixture of products.

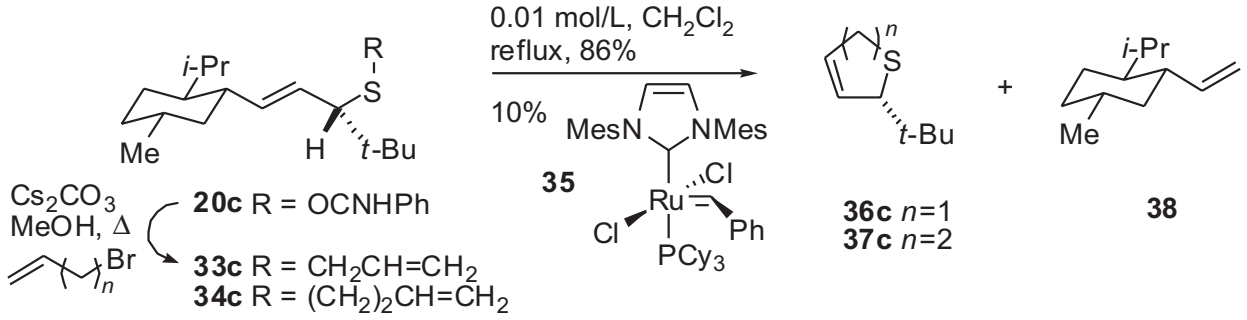
The yields of cleavage products were consistently better from *S*-thiocarbonates **25** or **26**. Here too, the use of $BH_3 \cdot SMe_2$ usually gives superior results, though sodium borohydride can give good yields of products (Scheme 7). This is the protecting group of choice for sulfur if oxidative cleavage is needed. We verified the stereochemical integrity of the alcohols **32** by making the Mosher ester derivatives on both enantiomers and found no racemization. Aldehydes can be prepared using dimethylsulfide as reducing agent but α-thioaldehydes are sensitive to racemization and must be used without purification, unless of course the α-position is dialkylated (see later).

Cleavage by ring-closing metathesis

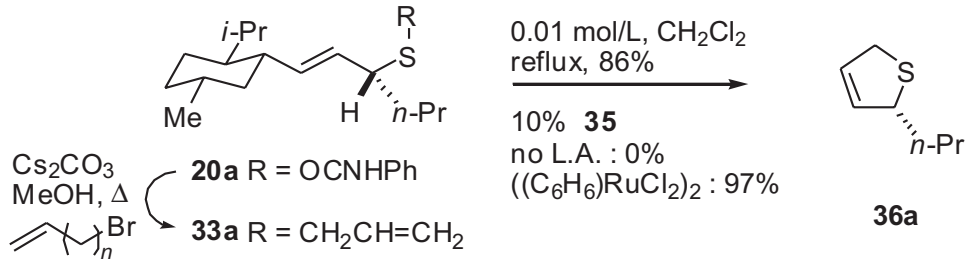
We have recently discovered that it is possible to generate

[2] We have observed the same phenomenon for the Claisen rearrangement, see ref. 11.

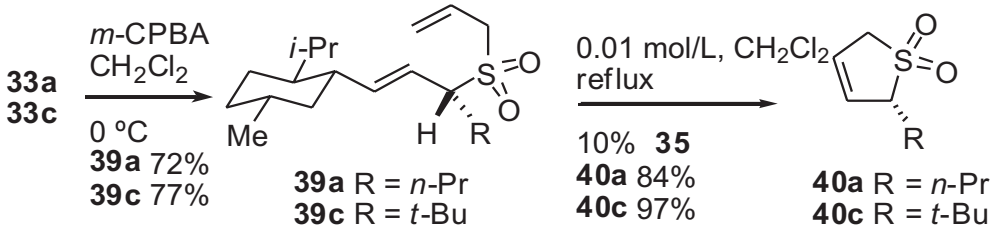
Scheme 8. RCM cleavage of allylic sulfide **33c** and **34c**.



Scheme 9. RCM cleavage of allylic sulfide **33a**.



Scheme 10. RCM cleavage of allylic sulfones **39a** and **39c**.



chiral nonracemic cycloalkenes by ring-closing metathesis (21) starting from dienes that still possess the menthyl moiety (22). To the best of our knowledge, this was the first example of a chiral auxiliary that could be cleaved by RCM. However, several heteroatoms, sulfur in particular (21, 23), may cause problems by coordinating to the metal center, and it was unclear at the onset if chiral *S*-heterocycles could be prepared by this method.

Thus, the carbamate functionality in **20c** was hydrolyzed and the resulting thiol alkylated in a one-pot procedure to give the precursor **33c** in 84% yield. To our delight, 2,5-dihydrothiophene (24) **36c** was obtained in 86% yield from **33c** using the Grubbs–Nolan catalyst **35** (25) (Scheme 8). It appeared that catalyst poisoning was not going to be a problem, or so we thought. Compound **38** is very conveniently recovered by evaporation and distillation. It can be converted back to the chiral auxiliary **7** by ozonolysis.

To our surprise, the very similar precursor **33a**, prepared in the same way from **20a**, gave no cyclic product under identical conditions (Scheme 9). Instead, some dimer (not shown) was isolated. We had to add an external Lewis acid to get the reaction to go (97% conversion by NMR).[3] A ruthenium(II) dimer was the Lewis acid that gave the best results.

3,6-Dihydrothiopyrans **37c** could not be prepared from of the corresponding precursors **34c**, after testing several solvents, catalysts, Lewis acids, and other additives (Scheme 8).

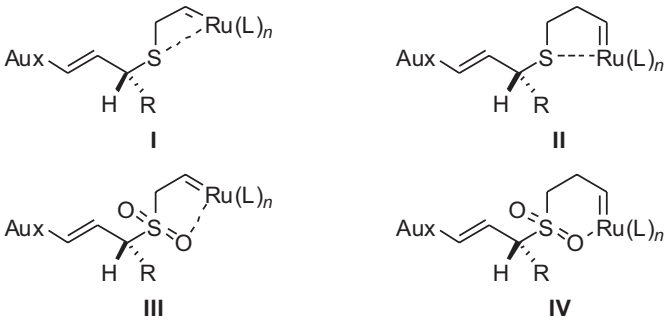
Sulfolenes **40a** and **40c** were efficiently prepared by RCM cleavage of **39a** and **39c**, respectively (Scheme 10). The low temperature used for RCM cleavage in this case was essential, since higher temperatures lead to the slow cheletropic extrusion of SO_2 in the sulfolene product to give the corresponding 1,3-dienes. Again, we were unable to prepare the analogous six-membered cyclic sulfones.

There seem to be several factors controlling the rate of RCM in our system. It is plausible that the formation of 3,6-dihydrothiopyrans **37** is prevented by the formation of a stable chelate **II** between sulfur and ruthenium (Fig. 2). The allylic sulfides do not form a stable chelate (cf. **I** in Fig. 2), and in those cases, poisoning of the catalyst probably occurs intermolecularly. In this case, bulky R groups such as *t*-Bu in **33c** or external Lewis acids are enough to allow the reaction to proceed.

We have shown previously that the formation of six-membered carbo- or *N*-heterocycles is kinetically less favored than the formation of the analogous five-membered rings (22). We suggest that under the reaction conditions and time used, the RCM reaction does not reach equilibrium and

[3] Isolated yield was low because of the high volatility of the product.

Fig. 2. Possible chelates in RCM of allylic sulfides and sulfones.



that the difference in efficiency of formation of dihydrothiophenes and dihydrothiopyrans is kinetically driven. We think that perhaps the longer C–S bond (>1.8 Å) hampers the ring-closing metathesis for six-membered ring formation and that poisoning of the catalyst is not the sole problem in this case, since a fair amount of dimer was isolated in each case.

Sulfones do form internal chelates with ruthenium, but the oxygen–ruthenium bond is weaker such that allylic sulfones (**III**, Fig. 2) undergo RCM fast enough, while homoallylic sulfones yield mostly dimer because of the slower rate of six-membered ring formation (**IV**, Fig. 2).

Synthesis of a potent MMP inhibitor

Several sulfonylhydroxamic acids are potent matrix metalloproteinase (MMP) inhibitors that have been studied in the clinic for the treatment of cancer and osteoarthritis (Fig. 3) (26). The overexpression of MMPs may result in the degradation of cartilage and may lead to medical conditions, such as osteoarthritis and rheumatoid arthritis. Compounds **41** and **43** are two highly selective inhibitors of MMP-13 in the nanomolar concentration (27) that may offer protection against cartilage degradation and potentially better treatment of osteoarthritis (28). Compounds **41** and **42** were previously prepared as racemic mixtures, but a small amount of **41** was resolved by preparative HPLC on a chiral column, and it was shown that (+)**–41** was 20 times as active as (–)**–41** (27). Their asymmetric synthesis thus becomes interesting.

We synthesized **42** as shown in Scheme 11. Alcohol **8h** was easily prepared in two steps from the commercially available propynylbenzene **43**. The ratio of β- and α-alcohols **8h** and **9h** was excellent, and their chromatographic separation was easy. Diastereomerically pure alcohol **8h** was submitted to the rearrangement conditions to give **20h** in 88% yield as essentially a single diastereomer. The *S*-thiocarbamate function could be directly coupled to iodide **45** using Tamaru's allylsulfenylation conditions to give a good yield of **46** (29). The synthesis was continued by first oxidizing the sulfur in **46**, then oxidatively cleaving the chiral auxiliary with ozone. Acid **47** could be obtained directly in one step by treating **46** with ozone, but this procedure led to lower yield of **47** and many decomposition products. Alternatively, when dimethylsulfide was used in the ozonolysis work-up, the α-sulfonylaldehyde was obtained and could be purified. Its treatment with Jones' reagent gave **47** in 53% yield for the two steps. Carrying out the two previoulsy reported steps (27) completed the synthesis of **42** for a total of eight steps and 12% overall yield from **43**.

In conclusion, we have successfully extended our *p*-menthane-3-carboxaldehyde based methodology to include the formation of chiral sulfur-bearing tertiary and quaternary carbons. This methodoly is becoming highly versatile and compares favorably to methodologies based on the classical alkylation of chiral enolates (30). Furthermore, carbo-, *N*-hetero-, and *S*-heterocyclic compounds are now directly accessible using RCM without the need for an extra step to cleave the auxiliary.

Experimental[4]

General

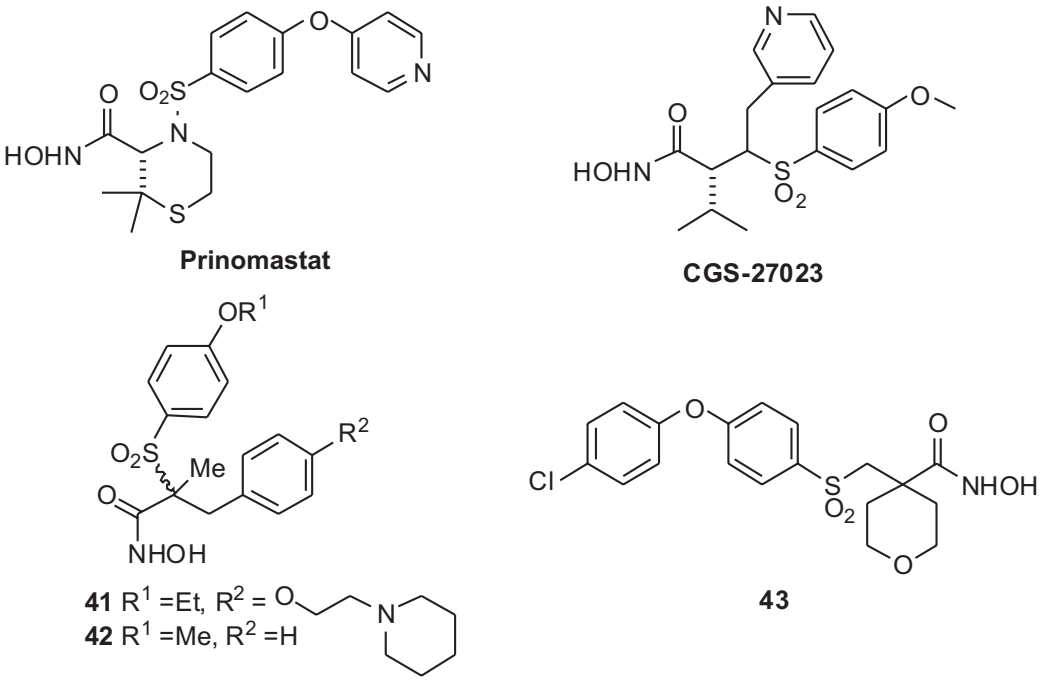
Flash chromatography was performed using Merck silica gel (230–400 Mesh ASTM) with solvents distilled prior to use. NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H NMR at 300 MHz, ^{13}C NMR at 75.5 MHz). Infrared spectra were recorded on a PerkinElmer 1600 FTIR spectrometer with a thin layer of the product on a NaCl disc. HPLC analyses were performed on a HP 1100 apparatus; GC analyses were performed on a Agilent 6890 series apparatus; GCMS analyses were performed on a HP 5890 serie II instrument (25 m length, 25μ OD, capillary Stabiliwax-DB5 column) coupled with a mass spectrometer (HP 5971). High-resolution spectrometry was performed on a ZAB-1F micromass spectrometer. Optical rotations $[\alpha]^{20}_{D}$ were measured on a PerkinElmer 343 polarimeter.

Alcohol 8f (method A)

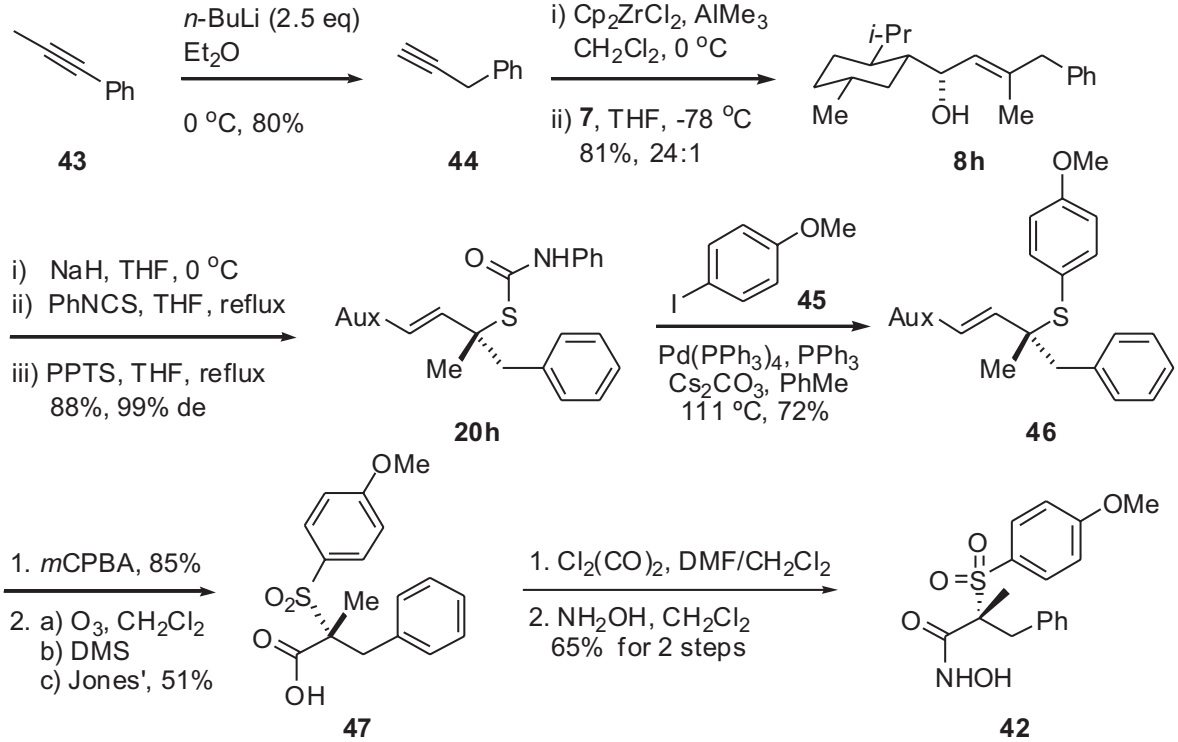
Vinyliodide **17f** (5.50 g, 19.2 mmol) was dissolved in diethyl ether (70.0 mL), and the solution was cooled to –78 °C. A solution of *t*-BuLi in pentane (38.4 mmol) was added dropwise to the mixture. The reaction mixture was stirred at –78 °C for 30 min and then at RT for 1 h. It was again cooled to –78 °C before the addition of trimethylaluminium (2.0 mol/L in hexanes, 24.0 mL, 48.0 mmol) followed by a solution of (–)-*p*-menthane-3-carboxaldehyde **7** (2.70 g, 16.0 mmol) in diethyl ether (10.0 mL). The reaction mixture was stirred at –78 °C for 2 h and then at RT overnight. The reaction was quenched with an aqueous solution of sodium bicarbonate (100 mL) at 0 °C. The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic portions were washed with brine, dried with anhyd. magnesium sulfate, and evaporated under reduced pressure. The crude product (**8f**:**9f** 52:1 by GC) was purified by flash chromatography on silica gel eluting with a mixture of hexanes/ethyl acetate (100: 0 to 95:5). A colorless oil was obtained (3.44 g, 55%).

[4] Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5199. For more information on obtaining material, refer to cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Fig. 3. Biologically active sulfonylhydroxamic acids.



Scheme 11. Synthesis of MMP-13 inhibitor **42**.



Compound 8f

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30–7.25 (m, 2H), 7.19–7.15 (m, 3H), 5.66–5.49 (m, 2H), 4.41–4.31 (m, 1H), 2.61 (t, 2H, *J* = 7.5 Hz), 2.15–2.06 (m, 3H), 1.70–1.58 (m, 5H), 1.44 (dt, 2H, *J* = 14.9, 7.5 Hz), 1.35–1.21 (m, 4H), 1.06–0.78 (m, 2H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.87 (d, 3H, *J* = 6.6 Hz), 0.76 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 142.7 (s), 132.5 (d), 130.4 (d), 128.4 (d), 128.2 (d), 125.7 (d), 71.3 (d), 44.8 (d), 43.0 (d), 35.8 (q), 35.1 (t), 33.8 (q), 32.8 (d), 32.2 (t), 31.0 (t), 28.9 (t), 26.3 (d), 24.3 (q), 22.8 (t), 21.6 (t), 15.5 (t). IR (neat) ν (cm^{-1}): 3395, 2927, 2857, 1454, 966, 698. LRMS (*m*/*z*, relative in-

tensity) 328 (M^+, 18), 285 (4), 171 (95), 83 (100). HRMS calcd. for $C_{23}H_{36}O$: 328.2766, found: 328.2769. $[\alpha]^{20}_D$ –9.2 (c = 1.39, $CHCl_3$).

Compound 9f

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36–7.31 (m, 2H), 7.26–7.21 (m, 3H), 5.75–5.66 (m, 1H), 5.61–5.53 (m, 1H), 4.45–4.41 (m, 1H), 2.69 (t, 2H, J = 7.7 Hz), 2.23–2.13 (m, 3H), 2.08–1.99 (m, 2H), 1.81–1.62 (m, 3H), 1.56–1.32 (m, 2H), 1.13–0.70 (m, 6H), 1.01 (d, 3H, J = 6.6 Hz), 0.94 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 142.6 (s), 132.7 (d), 129.3 (d), 128.4 (d), 128.3 (d), 125.7 (d), 72.1 (d), 44.7 (d), 44.0 (d), 35.9 (q), 35.3 (t), 34.0 (q), 32.6 (d), 32.4 (t), 31.0 (t), 29.1 (t), 26.1 (d), 24.3 (q), 23.0 (t), 21.6 (t), 15.3 (t). IR (neat) ν (cm^{-1}): 3342, 2929, 2856, 1453, 971, 698. LRMS (*m*/*z*, relative intensity) 328 (M^+, 20), 267 (12), 171 (100), 91 (90). HRMS calcd. for $C_{23}H_{36}O$: 328.2766, found: 328.2762. $[\alpha]^{20}_D$ –20.5 (c = 1.71, $CHCl_3$). 98% de (GC).

Alcohol 8g (method B)

A flask containing a solution of *bis*(cyclopentadienyl)zirconium dichloride (129 mg, 0.44 mmol) in 6.3 mL of dichloromethane was put under vacuum and then filled with argon (3×). Trimethylaluminium (545 μL, 5.69 mmol) was added using a sass equipped with a syringe under an argon atmosphere. The solution was stirred 10 min at RT and then 5 min at 0 °C before the dropwise addition of hex-5-ynylbenzene (300 mg, 1.90 mmol). The mixture was stirred at RT overnight. A solution of (–)-*p*-menthane-3-carboxaldehyde **7** (246 mg, 1.46 mmol) in 4.9 mL of tetrahydrofuran was added dropwise to the reaction mixture at –78 °C. The reaction was warmed to RT and stirred overnight. A saturated aqueous solution of potassium carbonate was added dropwise until gas evolution stopped. The white precipitate was dissolved in a 1 N aq. solution of HCl. Then a 5 N aq. solution of HCl was added until the two layers were clear. The two phases were separated, and the aqueous layer was extracted three times with dichloromethane (50 mL). The organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude compound was determined to be a mixture of the two diastereomers **8g** and **9g** in a ratio of 94:6 (88% de). The crude product was purified by flash chromatography on silica gel (100% hexanes to 5% EtOAc in hexanes). Two colorless oils were isolated (major diastereomer **8g**, 132 mg, 75%, >99% de by HPLC.; minor diastereomer **9g**, 12 mg, 7%, >99% de).

Compound 8g

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30–7.25 (m, 2H), 7.19–7.15 (m, 3H), 5.34 (d, 1H, J = 7.7 Hz), 4.67 (d, 1H, J = 8.3 Hz), 2.62 (t, 2H, J = 7.7 Hz), 2.23–2.14 (m, 1H), 2.04 (t, 2H, J = 7.4 Hz), 1.71–1.42 (m, 7H), 1.63 (s, 3H), 1.35–1.24 (m, 3H), 1.14 (br s, 1H), 1.04–0.79 (m, 2H), 0.94 (d, 3H, J = 7.1 Hz), 0.88 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 142.7 (s), 136.5 (s), 128.4 (d), 128.2 (d), 127.2(d), 125.7 (d), 67.6 (d), 44.9 (d), 43.2 (d), 39.5 (t), 35.8 (t), 35.2 (t), 34.1 (t), 32.8 (d), 31.0 (t), 27.2 (t), 26.3 (d), 24.3 (t), 22.9 (q), 21.7 (q), 16.5 (q), 15.6 (q). IR (neat) ν (cm^{-1}): 3362, 2927, 2857, 1453, 1001, 698. LRMS (*m*/*z*, relative intensity) 342 (M^+, 8), 324 (M^+ - H_2O, 4), 203 (81), 185 (49), 91 (100). HRMS calcd. for $C_{24}H_{38}O$: 342.2922, found: 342.2924. $[\alpha]^{20}_D$ –25.9 (c = 1.01, $CHCl_3$).

Compound 9g

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36–7.25 (m, 2H), 7.19–7.16 (m, 3H), 5.32 (d, 1H, J = 9.4 Hz), 4.59 (dd, 1H, J = 9.4, 3.9 Hz), 2.62 (t, 2H, J = 7.7 Hz), 2.06 (t, 2H, J = 7.1 Hz), 1.94 (dd, 1H, J = 12.7, 2.8 Hz), 1.84–1.77 (m, 1H), 1.69 (s, 3H), 1.72–1.18 (m, 8H), 1.07–0.70 (m, 10H), 0.90 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 142.5 (s), 140.5 (s), 128.4 (d), 128.2 (d), 125.6(d), 123.4 (d), 67.8 (d), 44.5 (d), 44.1 (d), 39.7 (t), 35.7 (t), 35.2 (t), 34.0 (t), 32.6 (d), 30.8 (t), 27.3 (t), 26.4 (d), 24.1 (t), 22.8 (q), 21.5 (q), 16.4 (q), 15.3 (q). IR (neat) ν (cm^{-1}): 3355, 2931, 2858, 1453, 1020, 698. LRMS (*m*/*z*, relative intensity) 342 (M^+, 14), 324 ($M^+ - H_2O$, 4), 203 (100), 185 (75), 91 (79). HRMS calcd. for $C_{24}H_{38}O$: 342.2922, found: 342.2924. $[\alpha]^{20}_D$ –27.3 (c = 0.70, $CHCl_3$).

General procedure for the preparation of *S*-allylthiocarbamates

To a solution of the allylic alcohol **8** or **9** (0.198 mmol) in THF (2 mL) at 0 °C was added NaH 60% *w*/*w* in oil (15 mg, 0.372 mmol), and the mixture was stirred for 1 h at this temperature before the addition of phenylisothiocyanate (47 μL, 0.396 mmol). The reaction was heated to reflux and stirred for 3 h. It was then cooled down to RT before the addition of pyridinium *p*-toluenesulfonate (124 mg, 0.495 mmol) in THF (3.3 mL). The reaction was then heated to reflux for 2–3 h. Then, the reaction was stopped by the addition of water (5 mL) and Et_2O (5 mL). The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried with anhyd. $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% hexanes to 5% EtOAc in hexanes) to afford the desired product.

S-allylthiocarbamate 20c

Prepared following the general procedure for the synthesis of *S*-allylthiocarbamates. Reaction time after the addition of pyridinium *p*-toluenesulfonate: 2 h. Compound **20c** was isolated as a white solid (74 mg, 96%, 98% de by GC), mp 102–103 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41 (d, 2H, J = 8.3 Hz), 7.30 (t, 2H, J = 8.0 Hz), 7.11–7.07 (m, 2H), 5.50–5.47 (m, 2H), 3.97–3.94 (m, 1H), 1.91–1.78 (m, 2H), 1.70 (dm, 1H, J = 12.1 Hz), 1.62–1.53 (m, 2H), 1.36–1.21 (m, 1H), 1.01 (s, 9H), 0.98–0.78 (m, 4H), 0.85 (d, 3H, J = 7.2 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.70 (d, 3H, J = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 165.1 (s), 138.1 (d), 137.9 (s), 129.0 (d), 127.0 (d), 124.1 (d), 119.5 (d), 59.9 (d), 47.0 (s), 44.9 (d), 42.9 (t), 35.1 (t), 34.4 (d), 32.5 (d), 28.2 (d), 27.9 (q), 23.9 (t), 22.5 (q), 21.4 (q), 15.1 (q). IR ($CHCl_3$) ν (cm^{-1}): 3395–3210 (br), 2958, 2922, 2869, 1659, 1440, 1143, 750. LRMS (*m*/*z*, relative intensity) 387 (M^+, 5), 330 ($(M - C_4H_9)^+$, 3), 177 (64), 97 (100). HRMS calcd. for $C_{24}H_{37}ONS$: 387.2596, found: 387.2591. $[\alpha]_D^{20}$ –118.7 (c = 1.31, $CHCl_3$).

S-allylthiocarbamate 20g

Prepared following the general procedure for the synthesis of *S*-allylthiocarbamates. Reaction time after the addition of pyridinium *p*-toluenesulfonate: 3 h. Compound **21g** was isolated as a colorless oil (83 mg, 87%, 80% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (d, 2H, *J* = 7.7 Hz), 7.32–7.24 (m, 4H), 7.18–7.03 (m, 5H), 5.66 (d, 1H, *J* = 15.6 Hz), 5.39 (dd, 1H, *J* = 15.6, 9.1 Hz), 2.61 (t, 2H, *J* = 7.7 Hz), 2.07–1.94 (m, 2H), 1.93–1.55 (m, 6H), 1.62 (s, 3H), 1.45–1.32 (m, 3H), 1.04–0.71 (m, 5H), 0.85 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 6.1 Hz), 0.67 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 165.0 (s), 142.5 (s) 137.7 (s), 135.7 (d), 133.2 (d), 129.0 (d), 128.2 (d), 125.7 (d), 124.2 (d), 119.6 (d), 55.3 (s), 47.1 (d), 45.0 (d), 43.2 (t), 40.6 (t), 35.9 (t), 35.1 (t), 32.4 (d), 31.6 (t), 28.2 (d), 24.5 (q), 24.0 (t), 22.5 (q), 21.4 (q), 15.2 (q). IR (neat) ν (cm^{-1}): 3456, 2925, 2865, 1660, 1436, 1139, 750. LRMS (*m*/*z*, relative intensity) 477 (M^+, 4), 325 (60), 137 (60), 119 (100). HRMS calcd. for $C_{31}H_{43}ONS$: 477.3065, found: 477.3056. $[\alpha]^{20}_D$ –37.0 (*c* = 1.30, $CHCl_3$).

S-allylthiocarbamate 20h

Prepared following the general procedure for the synthesis of *S*-allylthiocarbamates. Reaction time after the addition of pyridinium *p*-toluenesulfonate: 3 h. Compound **21h** was isolated as a colorless oil (77 mg, 88%, 99% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 7.2 Hz), 7.35–7.22 (m, 4H), 7.15–7.09 (m, 2H), 5.82 (d, 1H, *J* = 15.4 Hz), 5.32 (dd, 1H, *J* = 15.4, 9.4 Hz), 3.35 (ABq, 2H), 2.01–1.90 (m, 1H), 1.76–1.57 (m, 4H), 1.61 (s, 3H), 1.46–1.30 (m, 1H), 1.08–0.78 (m, 4H), 0.86 (d, 3H, *J* = 6.6 Hz), 0.83 (d, 3H, *J* = 7.1 Hz), 0.74 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 165.1 (s) 137.7 (s), 137.1 (s), 136.2 (d), 132.4 (d), 131.0 (d), 129.1 (d), 127.7 (d), 126.5 (d), 124.3 (d), 119.7 (d), 55.6 (s), 47.0 (d), 46.6 (t), 44.9 (d), 43.3 (t), 35.1 (t), 32.4 (d), 28.0 (d), 24.3 (q), 24.0 (t), 22.5 (q), 21.4 (q), 15.5 (q). IR (neat) ν (cm^{-1}): 3310, 3029, 2922, 1666, 1514, 1438, 1139. LRMS (*m*/*z*, relative intensity) 435 (M^+, 1), 344 (8), 283 (23), 145 (85), 84 (100). HRMS calcd. for $C_{28}H_{37}ONS$: 435.2596, found: 435.2593. $[\alpha]^{20}_D$ –49.2 (*c* = 1.03, $CHCl_3$).

S-allylthiocarbamate 21c

Prepared following the general procedure for the synthesis of *S*-allylthiocarbamates. Reaction time after the addition of pyridinium *p*-toluenesulfonate: 2 h. Compound **21c** was isolated as a colorless oil (77 mg, >99%, >99% de by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (d, 2H, *J* = 7.7 Hz), 7.30 (t, 2H, *J* = 7.7 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 7.04 (s, 1H), 5.47–5.44 (m, 2H), 3.94–3.91 (m, 1H), 1.87–1.78 (m, 2H), 1.69 (d, 1H, *J* = 12.1 Hz), 1.61–1.54 (m, 2H), 1.38–1.26 (m, 1H), 1.01 (s, 9H), 0.98–0.80 (m, 4H), 0.86 (d, 3H, *J* = 6.6 Hz), 0.71 (d, 3H, *J* = 7.2 Hz), 0.62 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 164.9 (s), 138.0 (s), 138.0 (d), 129.0 (d), 126.9 (d), 124.1 (d), 119.4 (d), 60.2 (d), 47.2 (s), 44.8 (d), 43.1 (t), 35.1 (t), 34.2 (d), 32.5 (d), 28.0 (d), 27.8 (q), 24.0 (t), 22.6 (q), 21.2 (q), 15.1 (q). IR (neat) ν (cm^{-1}): 3298, 2954, 2914, 2869, 1659, 1499, 1439, 1147, 749. LRMS (*m*/*z*, relative intensity) 387 (M^+, 12), 330 ($(M - C_4H_9)^+$, 8), 177 (71), 97 (100). HRMS calcd. for $C_{24}H_{37}ONS$: 387.2596, found: 387.2591. $[\alpha]^{20}_D$ –165.1 (*c* = 1.03, $CHCl_3$).

S-allylthiocarbamate 21g

Prepared following the general procedure for the synthesis of *S*-allylthiocarbamates. Reaction time after the addition of pyridinium *p*-toluenesulfonate: 3 h. Compound **21g** was isolated as a colorless oil (64 mg, 67%, 98% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (d, 2H, *J* = 7.7 Hz), 7.32–7.24 (m, 4H), 7.18–7.14 (m, 3H), 7.08 (t, 1H, *J* = 7.7 Hz), 6.98 (br s, 1H), 5.62 (d, 1H, *J* = 15.7 Hz), 5.39 (dd, 1H, *J* = 15.7, 9.4 Hz), 2.61 (t, 2H, *J* = 7.7 Hz), 2.04–1.79 (m, 3H), 1.73–1.45 (m, 6H), 1.64 (s, 3H), 1.43–1.25 (m, 3H), 1.04–0.78 (m, 4H), 0.85 (d, 3H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 7.2 Hz), 0.64 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 164.9 (s), 142.5 (s) 137.6 (s), 135.7 (d), 133.2 (d), 129.0 (d), 128.4 (d), 128.2 (d), 125.6 (d), 124.1 (d), 119.4 (d), 53.6 (s), 47.2 (d), 44.8 (d), 43.2 (t), 40.7 (t), 35.7 (t), 35.1 (t), 32.4 (d), 31.6 (t), 28.0 (d), 24.5 (q), 24.3 (t), 24.0 (t), 22.5 (q), 21.4 (q), 15.2 (q). IR (neat) ν (cm^{-1}): 3302, 2947, 2928, 2869, 1660, 1513, 1435, 1137, 749. LRMS (*m*/*z*, relative intensity) 477 (M^+, 1), 357 (1), 325 (95), 119 (100). HRMS calcd. for $C_{31}H_{43}ONS$: 477.3065, found: 477.3056. $[\alpha]^{20}_D$ –175.6 (*c* = 0.52, $CHCl_3$).

General procedure for the preparation of thiocarbonates

To a solution of the allylic alcohol **8** or **9** (0.099 mmol) in THF (1 mL) at 0 °C was added NaH 60% *w*/*w* in oil (7 mg, 0.198 mmol), and the mixture was stirred for 1 h at this temperature before the addition of carbon disulfide (24 μL, 0.396 mmol). The reaction was heated to reflux and stirred for 2 h. It was then cooled down to RT before the addition of methyl iodide (25 μL, 0.396 mmol) and was again heated to reflux for 45 min. Then, the reaction was stopped by the addition of water (5 mL) and Et_2O (5 mL). The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried with anhyd. $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% hexanes to 2% EtOAc in hexanes) to afford the desired product.

Thiocarbonate 25b

Prepared following the general procedure for the synthesis of thiocarbonates. Compound **25b** was isolated as a colorless oil (90 mg, 59%, >99% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.56 (d, 2H, *J* = 16.0 Hz), 5.34 (dd, 1H, *J* = 15.7, 9.1 Hz), 2.33 (s, 3H), 1.94–1.68 (m, 6H), 1.62–1.52 (m, 2H), 1.58 (s, 3H), 1.38–1.23 (m, 2H), 1.01–0.76 (m, 7H), 0.86 (d, 6H, *J* = 6.6 Hz), 0.67 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 188.7 (s), 135.7 (d), 132.4 (d), 58.0 (s), 47.1 (d), 44.9 (d), 43.1 (t), 35.1 (t), 32.4 (d), 30.9 (t), 28.2 (d), 24.5 (q), 24.0 (t), 22.5 (q), 21.4 (q), 18.0 (t), 15.2 (q), 14.4 (q), 12.8 (q). IR (neat) ν (cm^{-1}): 2955, 2927, 2871, 1641. LRMS (*m*/*z*, relative intensity) 343 (MH^+, 4), 250 (8), 235 (100). HRMS calcd. for $C_{19}H_{35}OS_2$ (MH^+): 343.2129, found: 343.2135. $[\alpha]^{20}_D$ –46.9 (*c* = 0.73, $CHCl_3$).

Thiocarbonate 25c

Prepared following the general procedure for the synthesis of thiocarbonates. Compound **25c** was isolated as a colorless oil (135 mg, 99%, >99% de by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.43–5.40 (m, 2H), 4.04–4.06 (m, 1H), 2.40 (s, 3H), 1.87–1.75 (m, 2H), 1.74–1.68 (m, 1H), 1.62–1.50 (m, 3H), 1.36–1.25 (m, 1H), 0.99–0.77 (m, 3H), 0.95 (s, 9H), 0.85 (d, 3H, J = 7.2 Hz), 0.84 (d, 3H, J = 6.6 Hz), 0.68 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 188.8 (s), 138.7 (d), 126.1 (d), 59.8 (d), 47.0 (d), 44.9 (d), 42.8 (t), 35.1 (t), 34.4 (s), 32.4 (d), 28.3 (d), 27.7 (q), 23.9 (t), 22.5 (q), 21.4 (q), 15.0 (q), 13.1 (q). IR (neat) ν (cm^{-1}): 2956, 2927, 2869, 2360, 2340, 1646, 1366, 861. LRMS (*m/z*, relative intensity) 342 (M^+, 6), 267 (23), 235 (84), 177 (82), 97 (100). HRMS calcd. for $C_{19}H_{34}OS_2$: 342.2051, found: 342.2044. $[\alpha]^{20}_D$ +85.3 (c = 0.83, $CHCl_3$).

Thiocarbonate 26b

Prepared following the general procedure for the synthesis of thiocarbonates. Compound **26b** was isolated (60 mg, 39%, >96% de by HPLC) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.55 (d, 2H, J = 15.4 Hz), 5.35 (dd, 1H, J = 15.4, 9.4 Hz), 2.32 (s, 3H), 1.98–1.72 (m, 6H), 1.70–1.50 (m, 2H), 1.60 (s, 3H), 1.43–1.24 (m, 2H), 1.01–0.66 (m, 7H), 0.86 (d, 6H, J = 6.6 Hz), 0.66 (d, 3H, J = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 188.6 (s), 135.7 (d), 132.5 (d), 58.0 (s), 47.2 (d), 44.8 (d), 43.3 (t), 35.1 (t), 32.4 (d), 30.9 (t), 28.0 (d), 24.3 (q), 24.0 (t), 22.5 (q), 21.4 (q), 18.0 (t), 15.2 (q), 14.3 (q), 12.7 (q). IR (neat) ν (cm^{-1}): 2955, 2927, 2871, 1642. LRMS (*m/z*, relative intensity) 343 (MH^+, 3), 250 (5), 235 (100). HRMS calcd. for $C_{19}H_{35}OS_2$ (MH^+): 343.2129, found: 343.2135. $[\alpha]^{20}_D$ –22.9 (c = 0.74, $CHCl_3$).

Thiocarbonate 26c

Prepared following the general procedure for the synthesis of thiocarbonates. Compound **26c** was isolated as a colorless oil (122 mg, 90%, 98% de by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.41–5.38 (m, 2H), 4.05 (dd, 1H, J = 5.5, 3.3 Hz), 2.38 (s, 3H), 1.95–1.75 (m, 2H), 1.73–1.60 (m, 1H), 1.58–1.51 (m, 3H), 1.36–1.28 (m, 1H), 0.99–0.78 (m, 9H), 0.96 (s, 9H), 0.65 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 188.7 (s), 138.7 (d), 126.0 (d), 60.0 (d), 47.2 (d), 44.7 (d), 43.0 (t), 35.1 (t), 34.2 (s), 32.4 (d), 27.8 (d), 27.8 (q), 24.0 (t), 22.5 (q), 21.4 (q), 15.3 (q), 13.0 (q). IR (neat) ν (cm^{-1}): 2955, 2927, 2869, 1647. LRMS (*m/z*, relative intensity) 342 (M^+, 5), 235 (38), 177 (35), 97 (100). HRMS calcd. for $C_{19}H_{34}OS_2$: 342.2051, found: 342.2044. $[\alpha]^{20}_D$ –157.3 (c = 0.49, $CHCl_3$).

General procedure for the preparation of *S*-allylimidazoyl thiocarbonates

To a solution of the allylic alcohol (0.099 mmol) in acetonitrile (0.5 mL) was added thiocarbonyldiimidazole (53 mg, 0.297 mmol), and the mixture was stirred for 3 days at RT. Then, the reaction was stopped by the addition of water (5 mL) and Et_2O (5 mL). The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried with anhyd. $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% hexanes to 5% EtOAc in hexanes) to afford the desired product.

Imidazoyl thiocarbonate 27c

Prepared following the general procedure for the synthesis of imidazoyl thiocarbonates. Compound **27c** was isolated as a colorless oil (28 mg, 78% yield, 97% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H), 7.45 (s, 1H), 7.06 (s, 1H), 5.58–5.41 (m, 2H), 4.10 (d, 1H, J = 9.3 Hz), 1.91–1.66 (m, 3H), 1.60–1.45 (m, 2H), 1.34–1.23 (m, 2H), 1.02 (s, 9H), 1.01–0.62 (m, 3H), 0.84 (d, 3H, J = 7.2 Hz), 0.81 (d, 3H, J = 6.6 Hz), 0.68 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 165.3 (s), 140.0 (d), 135.4 (d), 130.6 (d), 125.3 (d), 115.9 (d), 60.9 (d), 47.0 (d), 44.9 (d), 42.7 (t), 35.0 (t), 34.5 (s), 32.4 (d), 28.3 (d), 27.8 (q), 23.9 (t), 22.5 (q), 21.4 (q), 15.0 (q). IR (neat) ν (cm^{-1}): 3125, 2954, 2924, 1762, 1693. LRMS (*m/z*, relative intensity) 362 (M^+, 3), 306 (39), 107 (100). HRMS calcd. for $C_{21}H_{34}ON_2S$: 362.2392, found: 362.2386. $[\alpha]^{20}_D$ –47.3 (c = 0.64, $CHCl_3$).

Imidazoyl thiocarbonate 28c

Prepared following the general procedure for the synthesis of imidazoyl thiocarbonates. Compound **27c** was isolated as a colorless oil (17 mg, 42% yield, 99% de by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.48 (s, 1H), 7.08 (s, 1H), 5.58–5.41 (m, 2H), 4.10 (d, 1H, J = 9.3 Hz), 1.93–1.81 (m, 1H), 1.72–1.52 (m, 4H), 1.39–1.22 (m, 2H), 1.04 (s, 9H), 0.98–0.65 (m, 3H), 0.86 (d, 3H, J = 6.6 Hz), 0.76 (d, 3H, J = 7.2 Hz), 0.57 (d, 3H, J = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 165.4 (s), 139.8 (d), 135.6 (d), 130.6 (d), 125.2 (d), 116.1 (d), 61.1 (d), 47.2 (d), 44.7 (d), 42.9 (t), 35.1 (t), 34.4 (s), 32.4 (d), 28.0 (d), 27.8 (q), 24.0 (t), 22.5 (q), 21.2 (q), 15.1 (q). IR (neat) ν (cm^{-1}): 2955, 2927, 2869, 1695, 1467. LRMS (*m/z*, relative intensity) 362 (M^+, 10), 306 (62), 95 (100). HRMS calcd. for $C_{21}H_{34}ON_2S$: 362.2392, found: 362.2386. $[\alpha]^{20}_D$ –98.8 (c = 1.42, $CHCl_3$).

Alcohol 31

Thiocarbonate **25c** (50 mg, 0.146 mmol) was solubilized in 4.9 mL of dichloromethane and Sudan III (1 mg) was added. The mixture was cooled down to –78 °C. Ozone was bubbled through the solution until the indicator color passed from red to pale pink or from red to violet. Then, dry nitrogen was bubbled through the solution for 5 min before sodium borohydride (55 mg, 1.459 mmol) was added. The mixture was stirred at –78 °C for 30 min and was slowly warmed to RT overnight. Then, the reaction was stopped by the addition of water (5 mL) and dichloromethane (5 mL). The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried with anhyd. $MgSO_4$, and concentrated under reduced pressure without heating. The crude product was purified by flash chromatography on silica gel (100% hexanes to 10% EtOAc in hexanes) to afford the desired product. Menthyl alcohol was also recovered in 80% yield. Compound **31** was isolated as a colorless oil (27 mg, 89%, 93% ee by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.00 (dd, 1H, J = 11.3, 3.6 Hz), 3.72 (dd, 1H, J = 8.8, 3.9 Hz), 3.62 (dd, 1H, J = 11.6, 8.8 Hz), 2.44 (s, 3H), 1.90–1.50 (br s, 1H), 1.02 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 190.3 (s), 62.6 (t), 60.3 (d), 34.4 (s), 28.1 (q), 13.3 (q). IR (neat) ν (cm^{-1}): 3430,

2962, 2931, 1646. LRMS (*m/z*, relative intensity) 266 (M + NH_4^+, 7), 209 (MH^+, 1), 195 (24), 178 (100). HRMS calcd. for $C_8H_{16}O_2S_2$: 209.0670, found: 209.0667. $[\alpha]^{20}_D$ +9.5 (*c* 0.86, $CHCl_3$).

Alcohol (R)-32

The substrate (68 mg, 0.239 mmol) was solubilized in 2.4 mL of dichloromethane. The mixture was cooled down to –78 °C. Ozone was bubbled through the solution until TLC showed completion. Nitrogen was then bubbled through the solution for 5 min before a borane-methylsulfide solution (2 mol/L in THF, 0.48 mL, 0.955 mmol) was slowly added. The mixture was stirred at –78 °C for 30 min and was slowly warmed to RT overnight. Then, the reaction was stopped by the addition of water (5 mL) and dichloromethane (5 mL). The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried with anhyd. $MgSO_4$, and concentrated under reduced pressure without heating. The crude product was purified by flash chromatography on silica gel (100% hexanes to 20% EtOAc in hexanes) to afford 56 mg of the desired product (83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.28 (m, 2H), 7.20–7.16 (m, 3H), 3.79–3.66 (m, 3H), 2.62 (t, 2H, *J* = 7.7 Hz), 2.43 (s, 3H), 1.97 (s, 1H), 1.84–1.72 (m, 1H), 1.70–1.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 190.2 (s), 142.3 (s), 128.3 (d), 125.7 (d), 65.4 (t), 48.9 (d), 35.7 (t), 31.1 (t), 30.5 (t), 26.6 (t), 13.3 (q) IR (neat) ν (cm^{-1}): 3600–3200 (br), 3025, 2931, 2857, 1644, 869. LRMS (*m/z*, relative intensity) 285 (MH^+, 15), 159 (70), 117 (75), 91 (100). HRMS calcd. for $C_{14}H_{21}O_2S_2$ (MH^+): 285.0983, found: 285.0980. $[\alpha]^{20}_D$ +4.5 (*c* = 2.37, $CHCl_3$).

General procedure for the preparation of RCM precursors

The thiocarbamate (0.064 mmol) and the bromide (0.322 mmol) were solubilized in 1 mL of methanol, and cesium carbonate (0.322 mmol) was added. The mixture was stirred and heated overnight at 80 °C in a sealed tube. Water (5 mL) and diethyl ether (5 mL) were added to the reaction mixture. The two layers were separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhyd. $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% hexanes to 4% EtOAc in hexanes).

Sulfide 33c

Prepared following the general procedure for the synthesis of RCM precursors. Compound **33c** was isolated as a colorless oil (54 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.76 (dddd, 1H, *J* = 15.9, 10.6, 8.4, 5.7 Hz), 5.31 (dd, 1H, *J* = 15.9, 10.6 Hz), 5.12–5.04 (m, 3H), 3.07 (dd, 1H, *J* = 13.9, 5.7 Hz), 2.99 (dd, 1H, *J* = 13.9, 8.4 Hz), 2.83 (d, 1H, *J* = 9.9 Hz), 2.03–1.56 (m, 4H), 1.43–1.32 (m, 1H), 1.25–0.67 (m, 11H), 0.97 (s, 9H), 0.71 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 137.6 (d), 135.2, (d), 127.5 (d), 116.5 (t), 58.8 (d), 47.2 (d), 45.2 (d), 44.2 (t), 35.1 (t), 33.8 (t), 33.2 (s), 32.6 (d), 28.2 (q), 28.1 (d), 23.8 (t), 22.6 (q), 21.4 (q), 15.0 (q). IR (neat) ν (cm^{-1}): 2955, 2920, 2871, 1641, 1458, 1366, 971, 912. LRMS (*m/z*, relative intensity) 308 (M^+, 6), 267 ((M – C_3H_5)$^+$, 24), 257 ((M – C_4H_9)$^+$, 100), 177 (78), 97 (88). HRMS calcd. for $C_{20}H_{36}S$: 308.2538, found: 308.2543. $[\alpha]^{20}_D$ +9.6 (*c* = 1.31, $CHCl_3$).

Sulfide 34c

Prepared following the general procedure for the synthesis of RCM precursors. Compound **34c** was isolated as a colorless oil (54 mg, 75% yield.) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.82 (ddt, 1H, *J* = 16.8, 10.3, 6.6 Hz), 5.31 (dd, 1H, *J* = 15.1, 10.3 Hz), 5.15–5.07 (m, 2H), 5.02–4.99 (m, 1H), 2.88 (d, 1H, *J* = 10.3 Hz), 2.48–2.38 (m, 2H), 2.36–2.21 (m, 2H), 1.98–1.80 (m, 2H), 1.74–1.70 (m, 1H), 1.65–1.56 (m, 3H), 1.40–1.25 (m, 1H), 0.98–0.77 (m, 3H), 0.97 (s, 9H), 0.87 (d, 3H, *J* = 7.2 Hz), 0.86 (d, 3H, *J* = 6.6 Hz), 0.71 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 137.3 (d), 137.1, (d), 127.6 (d), 115.5 (t), 60.1 (d), 47.2 (d), 45.0 (d), 44.0 (s), 35.1 (t), 34.0 (t), 33.8 (q), 32.5 (d), 29.8 (t), 28.2 (d), 28.0 (q), 23.9 (t), 22.5 (q), 21.4 (t), 15.0 (q). LRMS (*m/z*, relative intensity) 322 (M^+, 25), 265 (95), 205 (69), 177 (72), 127 (100). HRMS calcd. for $C_{21}H_{38}S$: 322.2694, found: 322.2705. $[\alpha]^{20}_D$ –12.3 (*c* = 0.86, $CHCl_3$).

(S)-2-tert-Butyl-2,5-dihydrothiophene 36c

A solution of sulfide **33c** (92 mg, 0.30 mmol) in dichloromethane (30 mL, 0.01 mol/L), was brought to reflux and then degassed by passing a stream of argon for 15 min while refluxing. The Grubbs–Nolan catalyst **35** (25 mg, 10 mol%) was quickly added while the solution was still under reflux. The resulting pale pink solution was refluxed for 18 h. It was cooled to room temperature, and volatiles were removed under reduced pressure without heating. Analysis of the crude reaction mixture showed complete conversion to **36c** and auxiliary by-product **38**. The crude product was purified by flash chromatography on silica gel (100% pentane) to afford the desired product **36c** (36 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.86 (tt, 1H, *J* = 6.6, 2.2 Hz), 5.77 (tt, 1H, *J* = 6.6, 2.2 Hz), 4.12 (br s, 1H), 3.64 (br s, 2H), 0.94 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 130.9 (d), 128.9 (d), 68.0 (d), 38.4 (t), 35.5 (s), 27.1 (q). IR (neat) ν (cm^{-1}): 2956, 2868, 1712, 1691, 1463. LRMS (*m/z*, relative intensity) 142 (M^+, 20), 85 (100), 77 (10). HRMS calcd. for $C_8H_{14}S$: 142.0816, found: 142.0814. $[\alpha]^{20}_D$ –43.1 (*c* = 1.23, $CHCl_3$).

Sulfone 39c

The allylic sulfide **33c** (192 mg, 0.622 mmol) was solubilized in 3 mL of dichloromethane, and *m*-chloroperbenzoic acid (215 mg, 1.24 mmol) was added to the solution. The mixture was stirred for 10 min at RT and was then cooled to 0 °C before the addition 5 mL of a saturated aqueous solution of $NaHCO_3$ and 5 mL of dichloromethane. The two layers were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5% to 10% EtOAc in hexanes). The desired product was isolated as a white solid (163 mg, 77%), mp 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.88 (dddd, 1H, *J* = 16.0, 10.3, 9.0, 6.1 Hz), 5.60 (dd, 1H, *J* = 15.1, 10.3 Hz), 5.49–5.31 (m, 3H), 3.85 (dd, 1H, *J* = 13.8, 9.0 Hz), 3.41 (dd, 1H, *J* = 13.8, 6.1 Hz), 3.32 (d, 1H, *J* =

10.5 Hz), 2.11–2.00 (m, 1H), 1.76–1.59 (m, 4H), 1.43–1.17 (m, 1H), 1.14 (s, 9H), 1.05–0.78 (m, 4H), 0.86 (d, 3H, J = 6.1 Hz), 0.85 (d, 3H, J = 7.7 Hz), 0.69 (d, 3H, J = 6.6 Hz). IR (CHCl3) ν (cm^{-1}): 3028, 2957, 1310, 1126. LRMS (*m/z*, relative intensity) 358 (MNH_4^+, 30), 235 (100), 97 (70). HRMS calcd. for $C_{20}H_{40}NO_2S$ (MNH_4^+): 358.2780, found: 358.2784. $[\alpha]^{20}_D$ –73.5 (c = 0.73, $CHCl_3$).

Sulfolene 40c

A solution of **39c** (50 mg, 0.15 mmol) in dichloromethane (147 mL, 0.001 mol/L) was brought to reflux and then degassed by passing a stream of argon for 15 min while refluxing. The Grubbs–Nolan catalyst **35** (12 mg, 10 mol%) was quickly added while the solution was still under reflux. The resulting pale pink solution was refluxed for 18 h. It was cooled to room temperature, and volatiles were removed under reduced pressure without heating. Analysis of the crude reaction mixture showed complete conversion to **40c** and auxiliary by-product **38**. The crude product was purified by flash chromatography on silica gel (100% hexanes to 30% EtOAc in hexanes) to afford the desired product **40c** (21 mg, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.17–6.06 (m, 2H), 3.75–3.56 (m, 2H), 3.55–3.53 (m, 1H), 1.18 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 129.1 (d), 124.0 (d), 74.4 (d), 56.4 (t), 34.5 (s), 27.1 (q). IR (neat) ν (cm^{-1}): 2963, 2868, 1298, 1245, 1109. LRMS (*m/z*, relative intensity) 192 (MNH_4^+, 40), 175 (MH^+, 5), 110 (100), 96 (95). HRMS calcd. for $C_8H_{15}SO_2$ (MH^+): 175.0793, found: 175.0790. $[\alpha]^{20}_D$ –15.2 (c = 1.96, $CHCl_3$).

Sulfonylhydroxamic acid 42

Carboxylic acid **47** (45 mg, 0.135 mmol) was dissolved in dichloromethane (20 mL), and one drop of *N,N*-dimethylformamide was added. The mixture was cooled to 0 °C, and oxalyl chloride (151 μL, 1.73 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. The solution was concentrated under reduced pressure, and the residue was taken up in dichloromethane (2 mL).

In a separate flask, the hydrochloride salt of hydroxylamine (435 mg, 6.26 mmol) was dissolved in a 5:1 mixture of tetrahydrofuran and water (6.2 mL), and it was cooled to 0 °C. Triethylamine (1.1 mL, 7.9 mmol) was added dropwise, and the reaction mixture was stirred 1 h at 0 °C.

The acyl chloride solution previously prepared was added to the hydroxylamine solution at 0 °C. The resulting mixture was stirred 2 h, then water (10 mL) and chloroform (10 mL) were added. The two phases were separated, and the aqueous phase was extracted with chloroform (3 × 10 mL). The combined organic phases were washed with brine, dried over anhyd. magnesium sulfate, and concentrated under reduced pressure. Flash chromatography on silica gel, eluting with ethyl acetate, gave a white solid (31 mg, 65%), mp 48–51 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.72 (br s, 1H), 7.77 (d, 2H, J = 8.5 Hz), 7.23–7.22 (m, 3H), 7.13–7.11 (m, 2H), 7.02 (d, 2H, J = 8.5 Hz), 3.88 (s, 3H), 3.58 (d, 1H, J = 13.8 Hz), 3.10 (d, 1H, J = 13.8 Hz), 1.65 (br s, 1H), 1.35 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 164.8 (s), 164.5 (s), 133.5 (s), 132.4 (d), 130.3 (d), 128.6 (d), 127.6 (d), 125.7 (s), 114.5 (d), 71.6 (s), 55.7 (q), 38.7 (t), 16.1 (q). IR (CHCl3) ν (cm^{-1}): 3650–3500 (br), 3500–3175 (br), 3028, 2934, 2845, 1656, 1595, 1141. LRMS (*m/z*, relative intensity) 349 (M^+, 3), 285 (20), 155 (100). HRMS calcd. for $C_{17}H_{19}NO_5S$ (M^+): 349.0984, found: 349.0990. $[\alpha]^{20}_D$ –12.9 (c = 1.80, $CHCl_3$).

Arylsulfide 46

Thiocarbamate **20h** (94 mg, 0.22 mmol) and the aryl iodide **45** (66 mg, 0.28 mmol) were dissolved in toluene (1.0 mL). Cesium carbonate (91 mg, 0.28 mmol) and triphenylphosphine (17 mg, 0.065 mmol) were added, and argon was bubbled through the solution for 5 min prior to the addition of $Pd(PPh_3)_4$ (25 mg, 0.022 mmol). The reaction mixture was stirred and heated to reflux temperature overnight. The mixture was filtered through Celite®, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% hexanes to 10% EtOAc in hexanes). A colorless oil was isolated (66 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (d, 2H, J = 8.5 Hz), 7.24–7.11 (m, 5H), 6.81 (d, 2H, J = 8.5 Hz), 5.56 (d, 1H, J = 15.5 Hz), 4.62 (dd, 1H, J = 15.5, 9.1 Hz), 3.80 (s, 3H), 3.03 (d, 1H, J = 12.9 Hz), 2.87 (d, 1H, J = 12.9 Hz), 1.92–1.81 (m, 1H), 1.67 (br d, 1H, J = 12.1 Hz), 1.54–1.21 (m, 4H), 1.18 (s, 3H), 1.07–0.51 (m, 4H), 0.84 (d, 3H, J = 6.6 Hz), 0.72 (d, 3H, J = 6.6 Hz), 0.68 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 160.2 (s), 139.2 (d), 137.4 (s), 134.9 (d), 133.7 (d), 130.6 (d), 127.5 (d), 126.2 (d), 122.9 (s), 113.7 (d), 55.2 (q), 54.1 (s), 48.0 (t), 47.0 (d), 44.7 (d), 43.0 (t), 35.0 (t), 32.4 (d), 27.7 (d), 23.9 (t), 23.6 (q), 22.5 (q), 21.4 (q), 15.5 (q). IR (neat) ν (cm^{-1}): 2953, 2923, 1588, 1493, 1246. LRMS (*m/z*, relative intensity) 422 (M^+, 1), 283 (18), 145 (100). HRMS calcd. for $C_{28}H_{38}OS$: 422.2643, found: 422.2637. $[\alpha]^{20}_D$ –42.2 (c = 1.45, $CHCl_3$).

Carboxylic acid 47

Arylsulfide **46** was treated as per the preparation of sulfone **39c**. A white solid was obtained after chromatography (834 mg, 85%), mp 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (d, 2H, J = 8.8 Hz), 7.26–7.18 (m, 3H), 7.11–7.08 (m, 2H), 6.95 (d, 2H, J = 8.8 Hz), 5.73 (d, 1H, J = 15.8 Hz), 4.81 (dd, 1H, J = 15.8, 9.3 Hz), 3.86 (s, 3H), 3.34 (d, 1H, J = 12.9 Hz), 3.23 (d, 1H, J = 12.9 Hz), 2.02–1.90 (m, 1H), 1.67 (br d, 1H, J = 12.6 Hz), 1.55–1.19 (m, 4H), 1.16 (s, 3H), 0.84 (d, 3H, J = 6.6 Hz), 0.80–0.47 (m, 4H), 0.68 (d, 3H, J = 6.0 Hz), 0.66 (d, 3H, J = 6.0 Hz). IR ($CHCl_3$) ν (cm^{-1}): 2922, 1595, 1497, 1458, 1289. LRMS (*m/z*, relative intensity) 455 (MH^+, 1), 437 (8), 283 (100), 145 (85). HRMS calcd. for $C_{28}H_{39}O_3S$ (MH^+): 455.2620, found: 455.2622. $[\alpha]^{20}_D$ –75.9 (c = 0.69, $CHCl_3$).

The resulting sulfone (35 mg, 0.079 mmol) was solubilized in dichloromethane (1.0 mL). The mixture was cooled down to –50 °C, then ozone was bubbled through the solution for 4 h. Nitrogen was then bubbled through the solution for 10 min before Jones' reagent was added dropwise until the orange color persisted. The reaction mixture was stirred for 60 min at RT. Then, 2-propanol was added dropwise until the solution became blue-green. The mixture was concentrated under reduced pressure, and the resulting solids were dissolved in a minimum amount of water (1 mL). Dichloromethane (1 mL) was added, and the two phases were separated. The aqueous layer was extracted

with dichloromethane (3 × 1 mL). The combined organic fractions were washed with brine, dried over anhyd. magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10% methanol in dichloromethane). A colorless oil was isolated (13 mg, 51%). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.89–7.85 (m, 2H), 7.19 (br s, 5H), 7.11 (d, 2H, J = 9.3 Hz), 3.90 (s, 3H), 3.72 (d, 1H, J = 12.6 Hz), 2.86 (d, 1H, J = 12.7 Hz), 1.24 (s, 3H). IR (neat) ν (cm^{-1}): 3700–3100 (br), 2925, 2851, 1709, 1595, 1265, 1141. LRMS (*m/z*, relative intensity) 335 (MH^+, 5), 317 (10), 163 (70), 91 (100). HRMS calcd. for $C_{17}H_{19}O_5S$ (MH^+): 335.0953, found: 335.0946. $[\alpha]^{20}_D$ –17.7 (*c* = 0.56, $CHCl_3$).

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