Synthesis of Monoterpene Thiols

Subjects: Chemistry, Organic

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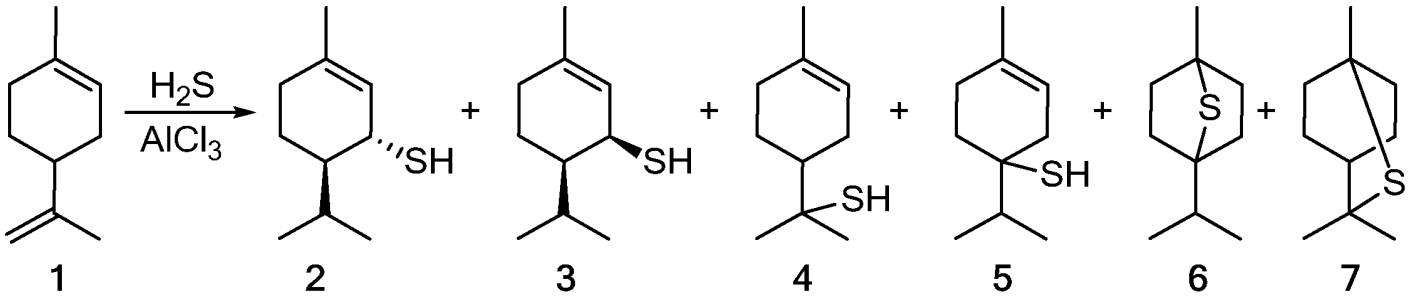
Thiols are one of the most convenient synthons in the synthesis of organosulfur compounds. The typical methods to prepare monoterpene thiols include the electrophilic addition of H_2S or dithiols to the double bond of monoterpenes; nucleophilic substitution of halides; tosylates/mesylates obtained from corresponding monoterpene alcohols; thia-Michael addition of S-nucleophiles to α,β-unsaturated ketones; nucleophilic epoxide ring opening; nucleophilic substitution of the activated methylene protons; and reduction of sulfochlorides, dithiolanes, thiiranes, and sultones.

monoterpenoids thiols asymmetric synthesis disulfides thiosulfonates

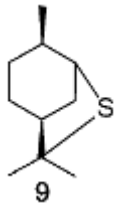
1. Synthesis from Alkenes

The synthesis of terpene thiols from limonene, α-pinene, α-, γ-terpinenes, terpinolene, and 3-carene via a reaction of them with H_2S in the presence of Lewis acids such as $AlCl_3$ or $AlBr_3$ is described in [1]. The addition of H_2S usually occurs without selectivity and is accompanied by numerous side reactions, including the rearrangement of the terpene skeleton, especially in cases with bicyclic systems. The addition of H_2S to limonene **1** catalyzed by $AlCl_3$ proceeds with no regioselectivity and gives thiols **2**–**5** in low yields, with the intramolecular cyclization of thiols **4** and **5** at the double bond affording sulfides **6** and **7** as the main products (Scheme 1) [2][3][4].

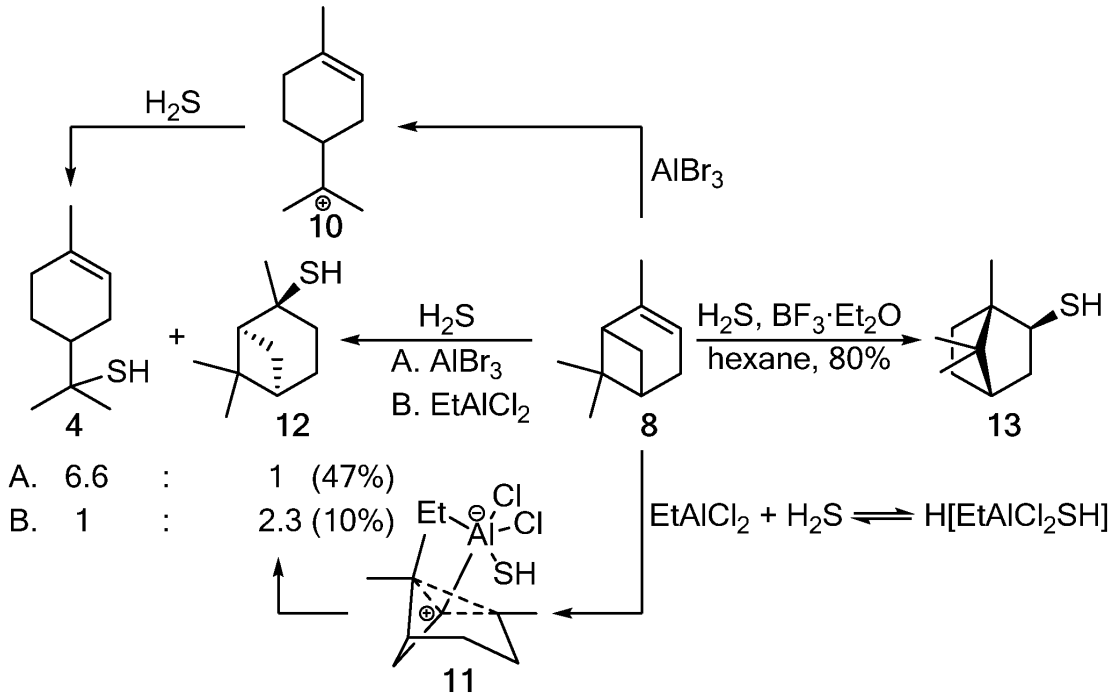


Scheme 1. The addition of H_2S to limonene **1** catalyzed by $AlCl_3$.

The interaction of α-pinene **8** with H_2S under the same conditions leads to products **2**–**7**, as well as cyclic sulfide **9** [1].

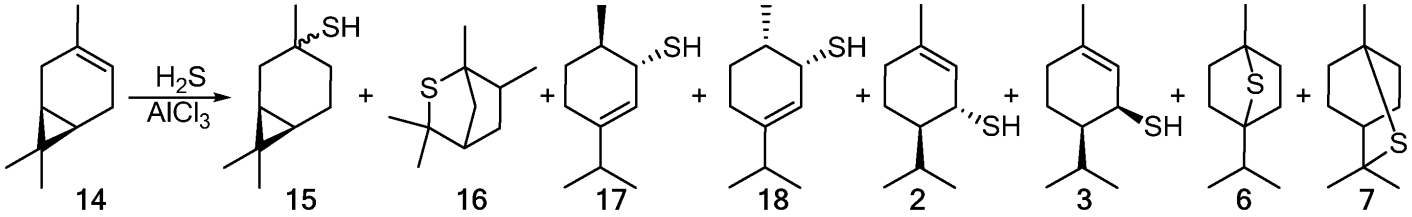


Electrophilic thiylation of α-pinene **8** with H_2S in the presence of $AlBr_3$ (A) is followed by the pinene–menthane rearrangement, providing carbocation **10**, which, when reacting with H_2S, gives thiol **4**. The softer Lewis acid $EtAlCl_2$ (B) stereoselectively catalyzes the anti-addition of H_2S via the formation of intermediate **11** and leads to *trans*-pinane-2-thiol **12** (Scheme 2) [5]. With a strong Lewis acid ($BF_3{\cdot}Et_2O$) used as a catalyst, the Wagner–Meerwein rearrangement occurs to yield isobornanethiol **13** [3][5].



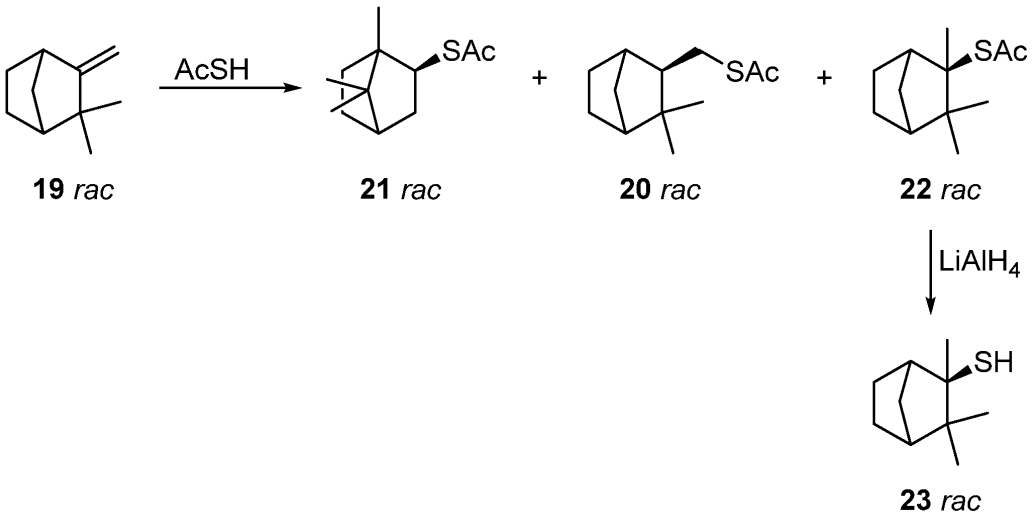
Scheme 2. The addition of H_2S to α-pinene **8**.

The addition of hydrogen sulfide to 3-carene **14** in the presence of $AlCl_3$ proceeds nonselectively to give the products in low yields. The detected products included a mixture of *cis*- and *trans*-thiols **15**; episulfides **16**, **6**, and **7**; and *para*-menthane thiols **17**, **18**, **2**, and **3** (Scheme 3) [1].



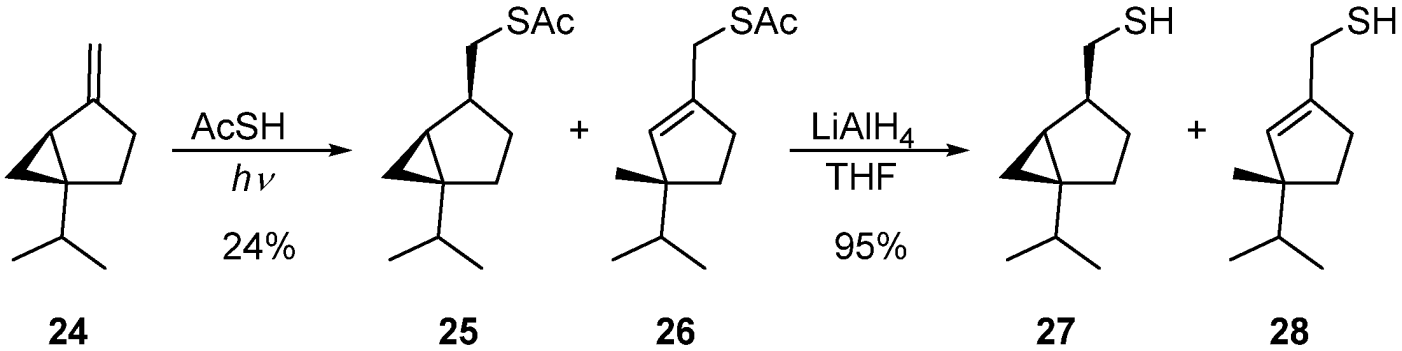
Scheme 3. The addition of H_2S to 3-carene **14** catalyzed by $AlCl_3$.

Reactions of racemic camphene **19** with thioacetic acid under various conditions were investigated in [6] (Scheme 4). It was established that, under catalyst-free conditions and with a long reaction time (12 h), the anti-Markovnikov product **20** was predominantly formed. The use of *p*-toluenesulfonic acid as a catalyst also leads to thioester **20**, but in a 15% yield. Catalysis with trifluoromethanesulfonic acid (TfOH) and $InCl_3$ at different temperatures gives different ratios of products. The optimal yield of thioacetate **21** (75%), a product of the Wagner–Meerwein rearrangement, was achieved using a catalyst TfOH at 40 °C for 20 min. The yield of a by-product, thioacetate **20**, from this procedure does not exceed 25%. The best method to obtain Markovnikov product **22** (82%) with a preserving camphane structure was catalysis via $In(OTf)_3$ at ≤0 °C. The deacylation of thioacetate **22** with $LiAlH_4$ leads to racemic camphane thiol **23** at an 86% yield.



Scheme 4. Synthesis of camphane thiol **23**.

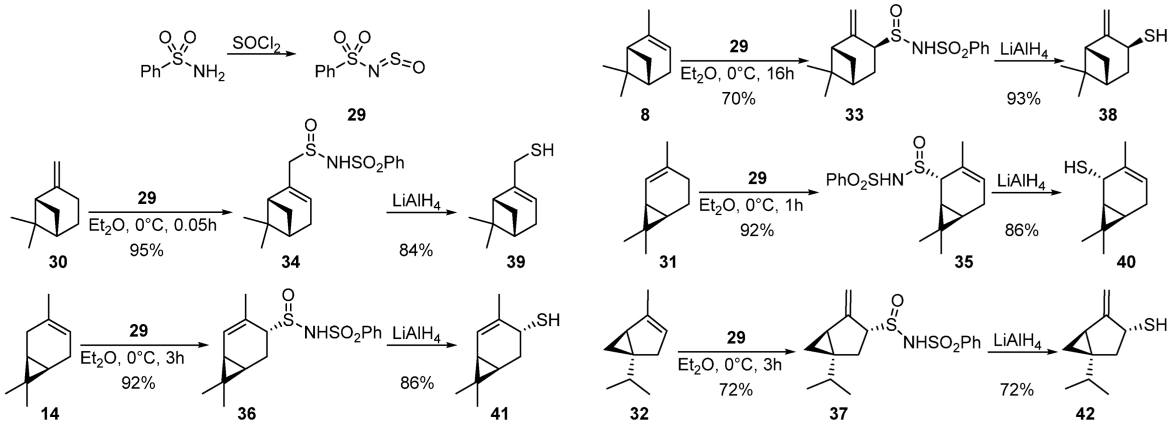
Photochemical addition of thioacetic acid to (−)-sabinene **24** gives a mixture of anti-Markovnikov bicyclic thioacetate **25** and unsaturated thioacetate **26** in an overall yield of 24% and a 3:1 ratio, respectively [7]. The unexpected formation of thioacetate **26** results from cyclopropane ring cleavage. The mixture of thioacetates **25** and **26** was treated with $LiAlH_4$ to produce thiols **27** and **28** in an overall yield of 95% (Scheme 5). The obtained thiols were isolated by preparative capillary GC.



Scheme 5. Synthesis of thiols from sabinene **24**.

2. Ene Reaction of Monoterpenes with N-sulfinylbenzenesulfonamide

An efficient method for the synthesis of monoterpene allyl thiols using *N*-sulfinylbenzenesulfonamide **29** as an enophile in ene reaction was proposed in the paper [8] (Scheme 6). The interaction of terpenes (α- and β-pinenes **8** and **30**; 2- and 3-carenes **31** and **14**; and α-thujene **32**) with *N*-sulfinylbenzenesulfonamide **29** proceeds at a double bond with the formation of adducts **33**–**37** with a migration of the double bond to an α-position. It should be noted that these reactions occur stereo- and regioselectively. The adducts **33**–**37**, when reduced with $LiAlH_4$, provide the corresponding allyl thiols, **38**–**42**.

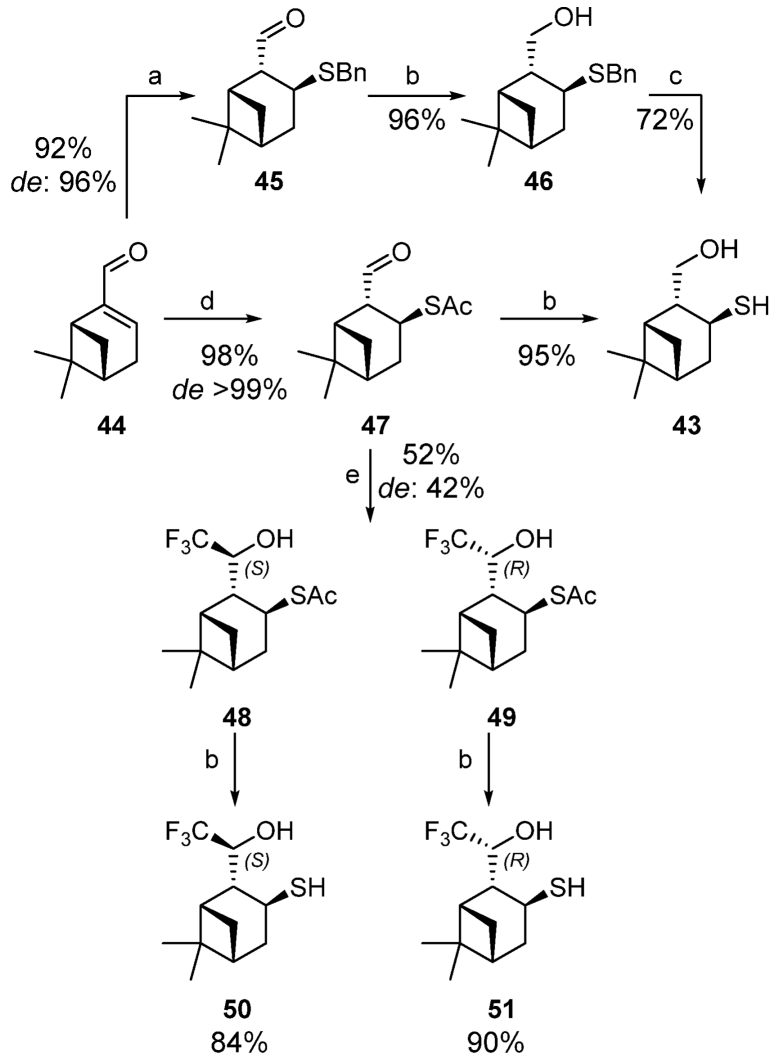


Scheme 6. Synthesis of allylic terpene thiols **38**–**42**.

3. Synthesis from α,β-Unsaturated Carbonyl Compounds

Thiols are good nucleophiles for thia-Michael addition to α,β-unsaturated carbonyl compounds [9]. However, harsh reaction conditions are required to convert the newly formed sulfide group into a synthetically more versatile SH group. Thioacids (RCOSH) are more attractive as nucleophiles for the Michael addition reaction, since the resulting thioesters can be easily transformed into corresponding thiols under mild conditions [10][11][12].

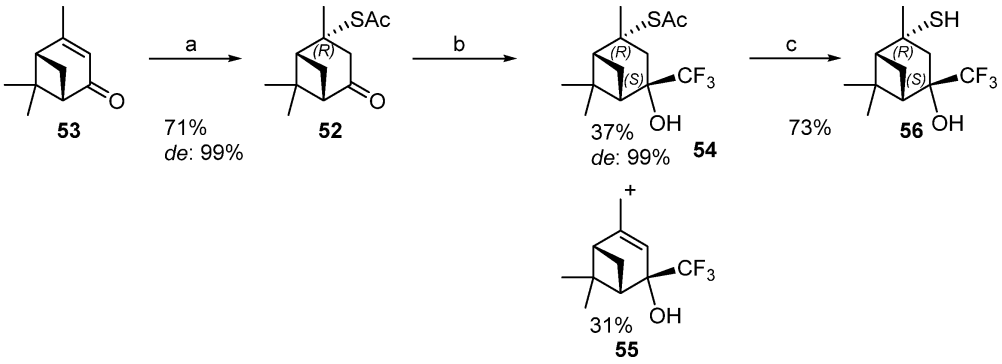
Myrtenal-based hydroxythiol **43** was synthesized by two methods with a high yield and stereoselectivity [10]. The treatment of (−)-myrtenal **44** with benzylthiol and 10% aqueous NaOH in THF at room temperature for 18 h led to sulfide **45** (yield 92%, *de* 96%). Compound **45** was reduced to the corresponding alcohol **46** (yield 96%) with $LiAlH_4$ in Et_2O, which was then hydrogenolyzed to hydroxythiol **43** under Birch reduction conditions (Scheme 7). The hydrogenolysis did not provide satisfactory results because small differences in reaction conditions altered the reaction course dramatically, sometimes producing a complex mixture of unidentified compounds. The same reaction conditions become reproducible in switching to thioacetic acid as a nucleophilic reagent, which demonstrated a high selectivity when added to (−)-myrtenal **44** to give thioacetate **47** (1,4-addition) in yield of 98% and *de* > 99%. Thioester **47** was reduced by $LiAlH_4$ to obtain hydroxythiol **43** in a 95% yield. This one-pot method allowed us to simultaneously convert thioether and aldehyde group to the corresponding thiol and primary alcohol (Scheme 7).



Scheme 7. Synthesis of pinane hydroxythiols based on myrtenal **44**.

Trifluoromethylation of 2-formylisopinocampheyl-3-thioacetate **47** by Ruppert–Prakash reagent in the presence of tetra-*n*-butylammonium fluoride (TBAF) was carried out at −30 °C for 3 days. Diastereomers **48** and **49** are formed in a 52% total yield and *de* 42% with the predominance of thioacetate **48**. Deacylation of thioacetates **48** and **49** with $LiAlH_4$ in dry Et_2O under an argon atmosphere gives the corresponding thiols **50** and **51** with 84 and 90% yields, respectively (Scheme 7) [13].

Thioacetate **52** was obtained from (1*S*)-(−)-verbenone **53** by using a procedure similar to the synthesis of 2-formylisopinocampheyl-3-thioacetate **47**. The reaction produces one of two theoretically possible diastereomers with the *R*-configuration of C-2 with a 71% yield (Scheme 8). Thioacetate **52** does not react with the Rupert–Prakash reagent under the above conditions, possibly because of the bulky TBAF use.

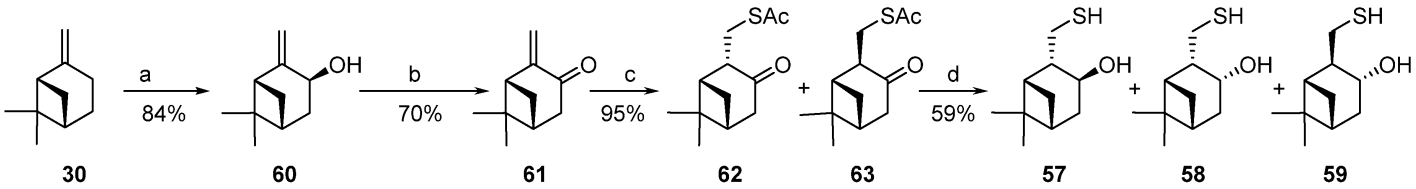


(a) CH_3COSH, Py, 8 °C, 10 h; (b) $TMSCF_3$, CsF, THF, argon, –30 °C, 72h; (c) $LiAlH_4$, Et_2O, 10 °C

Scheme 8. Synthesis of pinane hydroxythiols based on verbenone **53**.

The addition of fluorine-containing initiator CsF made it possible to obtain the only (4*S*)-diastereomer **54** in a 37% yield together with trifluoromethyl alcohol **55** (31%) that is a by-product of desulfurization (Scheme 8). Deacylation of thioacetate **54** gave hydroxythiol **56** in 73% yield [13].

The synthesis of isomeric hydroxythiols **57**–**59** was carried out on the basis of β-pinene **30** (Scheme 9) [14]. *Trans*-pinocarveol **60** was synthesized via the oxidation of β-pinene **30** with the SeO_2/TBHP system, and its further oxidation with MnO_2 led to pinocarvone **61**. An inseparable mixture of two isomeric ketothioacetates (2*S*)-**62** and (2*R*)-**63** in a 2:1 ratio in 95% yield is formed during the thia-Michael reaction of pinocarvone **61** with AcSH in the presence of catalytic amount of pyridine at −5 °C. The reduction of thioacetates with $LiAlH_4$ leads to three isomeric hydroxythiols, **57**–**59**.

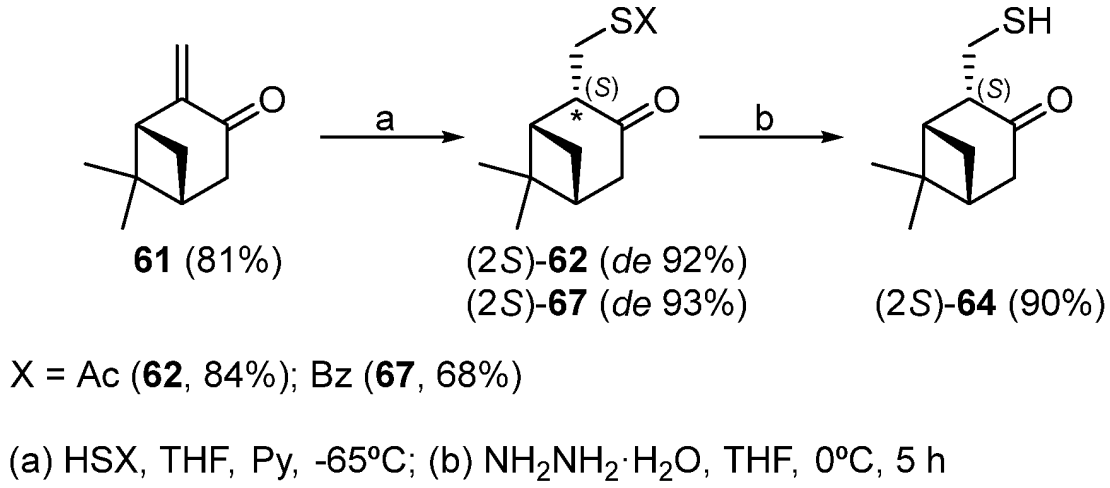


(a) SeO_2, TBHP, CH_2Cl_2, r.t.; (b) MnO_2, CH_2Cl_2, r.t.; (c) AcSH, Py, –5 ºC; (d) $LiAlH_4$, Et_2O, 5 ºC

Scheme 9. Synthesis of pinane hydroxythiols based on β-pinene **30**.

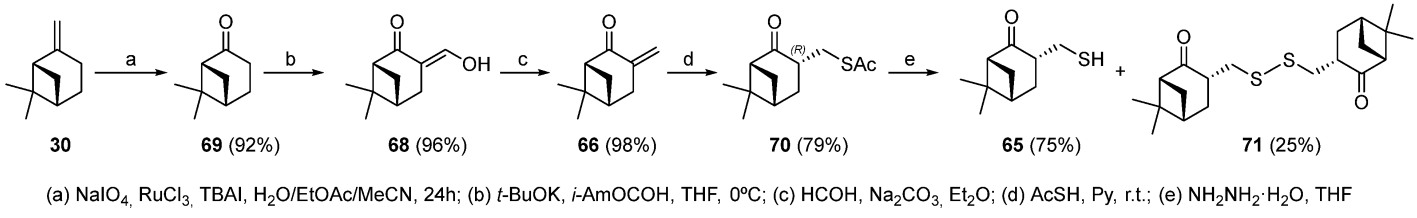
The synthesis of pinane ketothiols **64** and **65** was implemented from α,β-unsaturated pinane ketones **61** and **66** [15]. To obtain thioacetate **62** from enone **61**, the synthetical protocol proposed in [10] was used. However, the diastereoselectivity of this reaction under the described conditions did not exceed 33%, as mentioned in [14]. The *de* value of thioacetate **62** can be increased from 33 up to 92% if the reaction between pinocarvone **61** and AcSH is carried out in THF in a temperature range from −60 to −65 °C, with pyridine as a co-solvent. The same conditions are applicable for the addition of BzSH to ketone **61**, with thioacetate **67** being formed in this case with a comparable *de* of 93% (Scheme 10). Reducing thioacetate **62** via $NH_2NH_2{\cdot}H_2O$ affords thiol **64** within 4-5 h in up to a 90% yield, while deacylation of thiobenzoate **67** by the same reagent gives the thiol in only a 38-50% yield due to

incomplete conversion. Thus, at comparable maximum *de* values of thioesters **62** and **67**, the preparation of thiol **64** from compound **62** is more optimal, taking into account the higher total yield of thiol and the diacylation time.



Scheme 10. Synthesis of β-ketothiol from pinocarvone **61**.

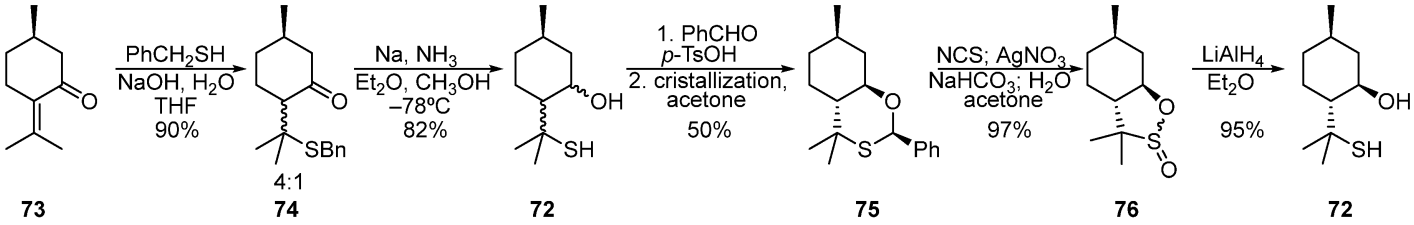
A multistep synthesis of 2-norpinanone **66** from (−)-β-pinene **30** was provided in [16] (Scheme 11). This compound was obtained via nopinone **69** and then ketoenol **68** formation. Ketoenol **68** was produced in a 96% yield from ketone **69** by its reaction with isoamyl formate and *t*-BuOK in THF at 0 °C for 6 h [15]. The following dihydroxylation of ketoalcohol **68** by formaldehyde in sodium carbonate solution afforded 2-norpinanone **66** [15]. An addition of thioacetic acid to 2-norpinanone **66** was, for the first time, implemented according to the procedure [10] and then by using pyridine as a catalyst [9] in THF at room temperature [15]. The main product of this reaction was the isomer (3*R*)-**70** (*de* 98%) (Scheme 11). Its deacylation by hydrazine hydrate ($NH_2NH_2·H_2O$) led to 2-ketothiol **65** and disulfide **71** in a 3:1 ratio, respectively. Because of the mild reducing properties of $NH_2NH_2·H_2O$ and its inability to donate protons, the diacylation proceeds chemoselectively with the preservation of the carbonyl group [17], a behavior that is not typical for $LiAlH_4$ when used [14].



Scheme 11. Synthesis of β-ketothiol based on 2-norpinanone **66**.

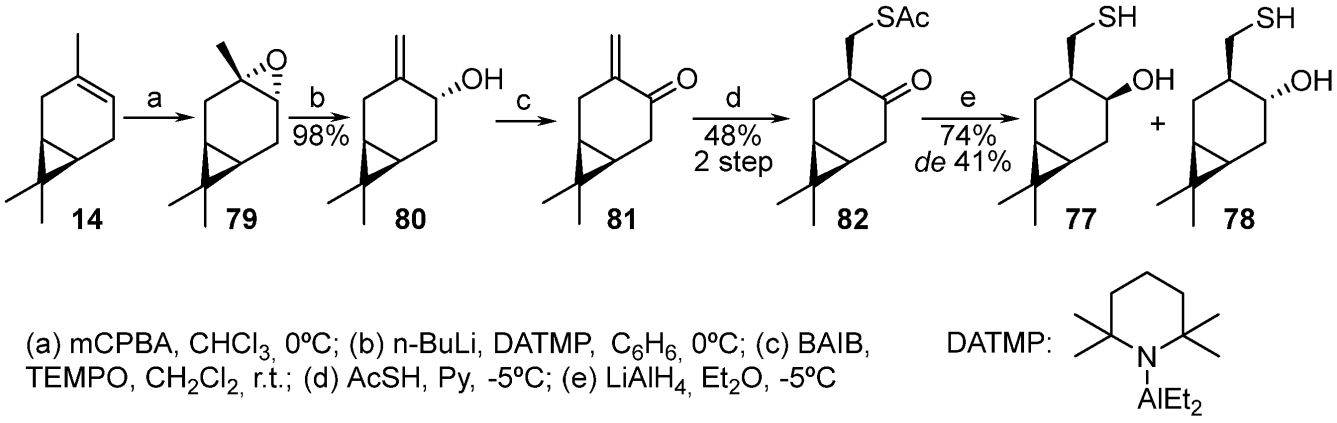
Pulegone **73** was used to synthesize *para*-menthane-derived β-hydroxythiol **72** (Scheme 12) [18][19][20][21]. The 1,4-addition of sodium benzyl thiolate to pulegone led to a diastereomeric mixture of ketosulfides **74** in a 4:1 ratio. Then, the mixture **74** was reduced under Birch conditions by Na in liquid NH_3 to give a mixture of hydroxythiols **72**. Condensation of **72** with benzaldehyde and subsequent crystallization from acetone afforded diastereomerically

pure oxathiane **75** in a 50% yield. When oxidized by $AgNO_3$ in the presence of NCS, oxathiane **75** is transformed into sultines **76**, the reduction of which with $LiAlH_4$ gives pure β-hydroxythiol **72**.



Scheme 12. Synthesis of β-hydroxythiol based on pulegone **73**.

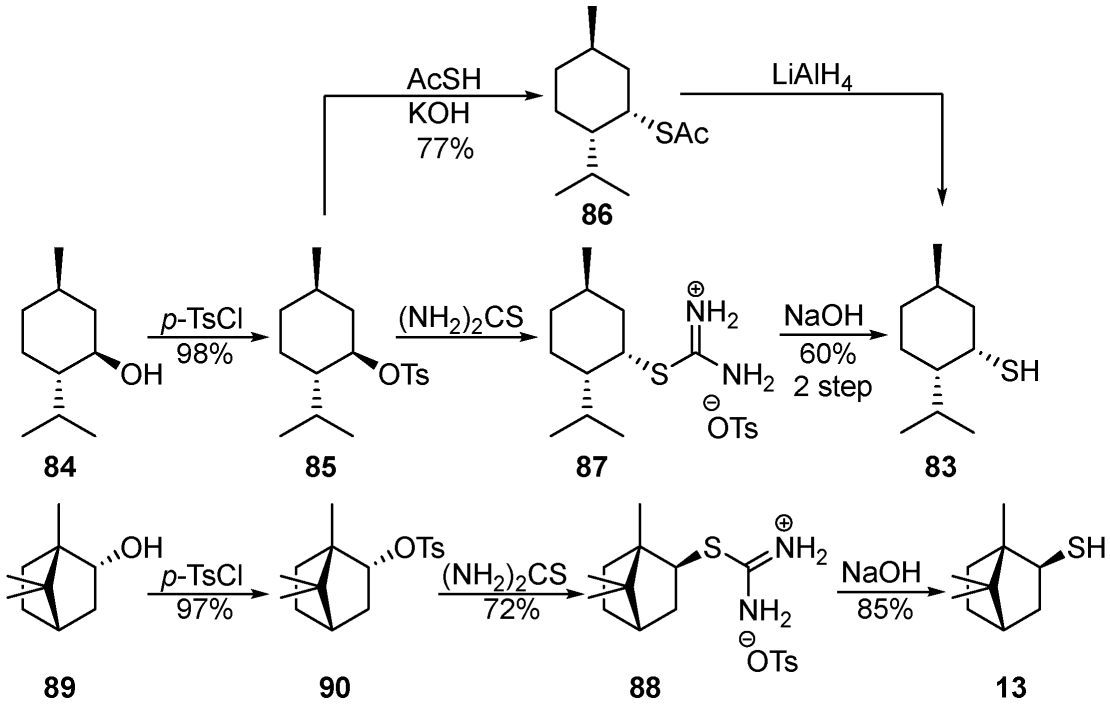
Isomeric α,β-hydroxythiols **77** and **78** were obtained from natural 3-carene **14** (Scheme 13) [22]. 3-Carene, when oxidized by *m*-CPBA, selectively forms *trans*-epoxide **79**, which is isomerized in the presence of diethylaluminum 2,2,6-tetramethylpiperidide (DATMP) to enol **80** [23]. The oxidation of alcohol **80** to enone **81** is successfully implemented by the bis(acetoxy)iodobenzene (BAIB)–2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) system. Enone **81**, being an unstable compound, cannot be isolated in its pure form. The two-step thia-Michael addition of AcSH to α,β-unsaturated ketone **81** proceeds in one pot in pyridine. As a result, only one of the two theoretically possible diastereomers, thioacetate **82**, is formed. The subsequent reduction of ketothioacetate **82** by $LiAlH_4$ leads to two diastereomeric β-hydroxythiols, **77** and **78**, in a 1:2 ratio, respectively [22].



Scheme 13. Synthesis of monoterpene hydroxythiols based on 3-carene **14**.

4. Synthesis from Alcohol via Tosylates, Halides, Isothiouronium Salts

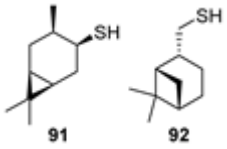
The works [24][25][26][27] cover the methods for the selective preparation of neomenthanethiol **83** using thioacetic acid (AcSH) (Scheme 14). Starting menthol **84** reacts with *p*-TsCl in pyridine to form tosylate **85**, which, when heated with AcSK, gives thioacetate **86** in a 77% yield. Substitution of the OTs (*p*-toluenesulfonate, tosylate) by the AcS-group occurs with an inversion of the chiral center via the S_N2 mechanism. The reduction of **86** by $LiAlH_4$ provides diastereomerically pure thiol **83** in a 26–40% yield (Scheme 14).



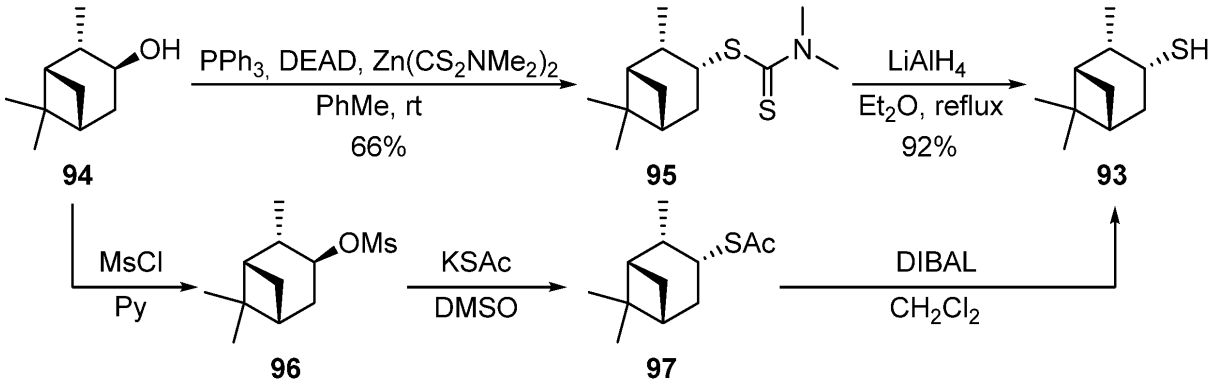
Scheme 14. Synthesis of neomenthanethiol **83** and isobornanethiol **13**.

Neomenthanethiol **83** [27][28] and isobornanethiol **13** [27][29][30][31] were also synthesized in good yields via isothiouronium salts **87** and **88**, proceeding from alcohols **84** and **89** (Scheme 14).

In addition to neomenthanethiol **83** and isobornanethiol **13**, the authors of [27] prepared 4-caranethiol **91** and *cis*-myrtanethiol **92** using the same method.

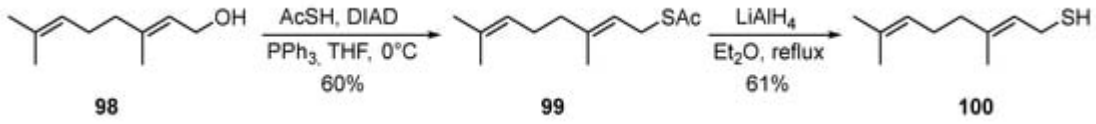


(−)-(3*R*)-Pinanthiol **93** was proposed to be obtained via the Mitsunobu-Rollin procedure from (+)-isopinocampheol **94** [32][33][34] (Scheme 15). The reaction of the alcohol **94** with zinc *N*,*N*-dimethyldithiocarbamate in the presence of triphenylphosphine and diethylazodicarboxylate (DEAD) is accompanied by an inversion of C-3 configuration and leads to dithiocarbamate **95** in a 66% yield. Dithiocarbamates baced on menthol **84** and borneol **89** were also obtained by the same original procedure [34][35]. The reduction of dithiocarbamate **95** by $LiAlH_4$ gives thiol **93** in a 92% yield. The approach to obtain thiol **93** through the corresponding mesylate **96** and thioacetate **97** was described in [36].



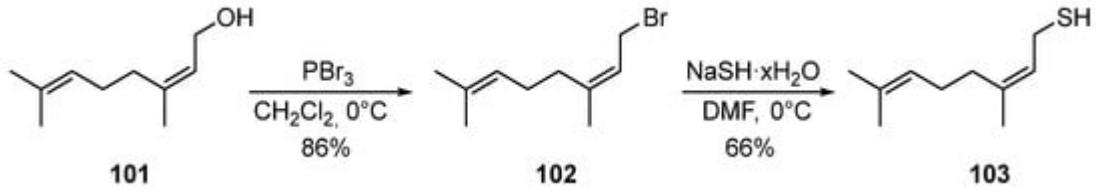
Scheme 15. Synthesis of (1*S*,2*S*,3*R*,5*R*)-3-pinanethiol **93**.

Geraniol **98** reacts with thioacetic acid under Mitsunobu-type conditions [37] to form thioacetate **99** in a good yield, which, when treated with $LiAlH_4$, is converted into the corresponding thiol **100** in a 61% yield (Scheme 16) [38].



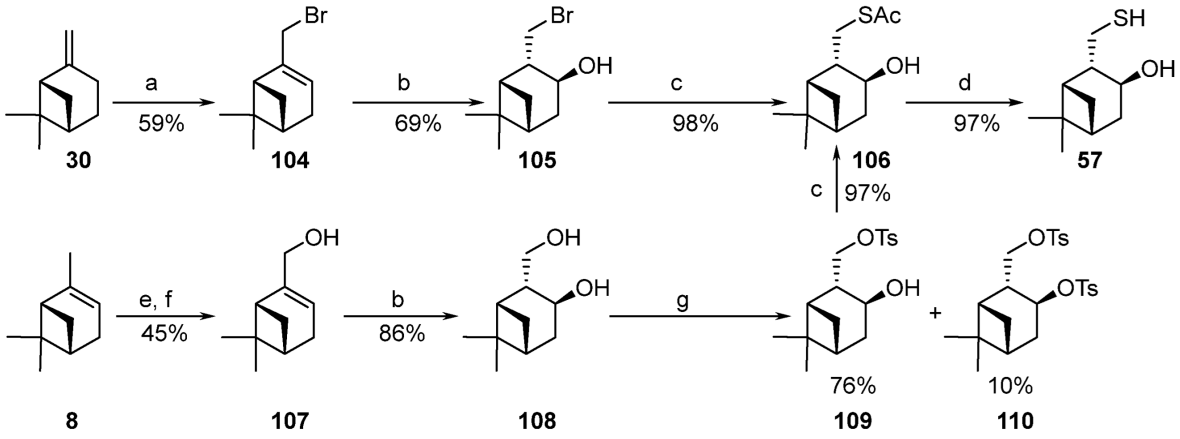
Scheme 16. Synthesis of thiogeraniol **100**.

The ability of nerol **101** to be converted into bromide **102** under the action of PBr_3, and then into thiol **103** by using NaSH via two successive nucleophilic substitutions with yields of 86 and 66%, respectively, was described in [39] (Scheme 17).



Scheme 17. Synthesis of thionerol **103**.

Diastereomerically pure hydroxythiol **57** can also be obtained via two alternative routes [14]. The first one involves the bromination of β-pinene **30** by NBS (*N*-bromosuccinimide) to form myrtenyl bromide **104**, which undergoes hydroboration–oxidation and is selectively transformed to bromoalcohol **105.** The nucleophilic replacement of bromide by thioacetate AcS^- leads to compound **106**, which can also be synthesized starting from α-pinene **8** (Scheme 18). The second route is associated with the oxidation of α-pinene **8** to myrtenal, followed by its reduction to myrtenol **107**, which is converted into diol **108** by the same hydroboration–oxidation procedure. The further reaction of tosyl chloride with diol **108** leads to both monotosylate **109** (76%) and ditosylate **110** (10%). The nucleophilic substitution of the *para*-toluenesulfonate group in **109** by AcS^- also results in thioacetate **106**. When reduced, thioacetate **106** affords hydroxythiol **57** (Scheme 18) [14].

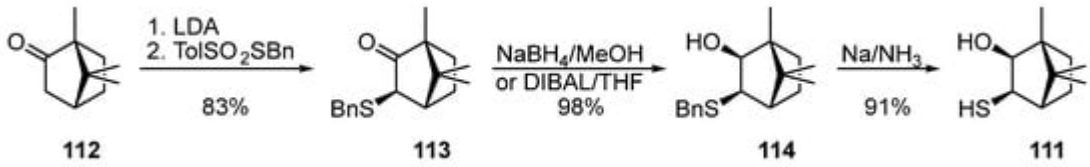


(a) NBS, CCl_4, 0ºC; (b) BH_3, Et_2O, OH^-/H_2O_2, 0ºC; (c) AcSK, DMF, r.t.; (d) $LiAlH_4$, Et_2O, 5ºC; (e) SeO_2, TBHP, CH_2Cl_2, r.t.; (f) $NaBH_4$, EtOH; (g) TsCl, Py, r.t.

Scheme 18. Synthesis of 10-hydroxyisopinocampheylthiol **57** from α- and β-pinene.

5. Nucleophilic Substitution of the Activated Methylene Proton

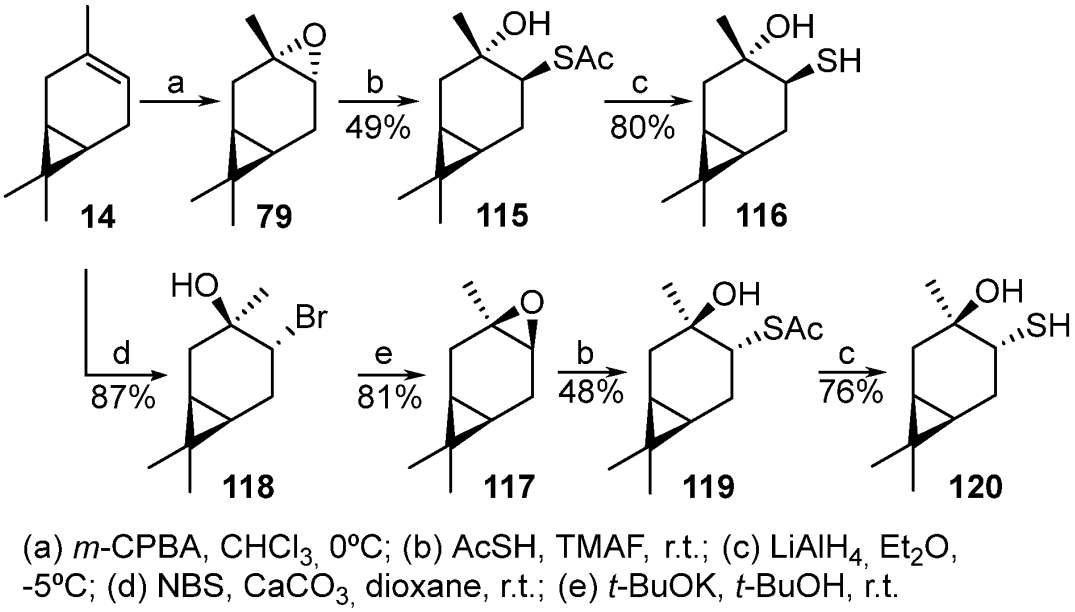
The synthesis of bornane α-hydroxythiol **111** was described in [40][41] (Scheme 19). The nucleophilic substitution of a proton of the activated methylene group in camphor **112** by benzyl *p*-toluenesulfonate promoted by LDA leads to the formation of ketosulfide **113**, which, being reduced by $NaBH_4$ in methanol or dibutylaluminum hydride (DIBAL) in THF, gives hydroxysulfide **114**, which is capable of being transformed into hydroxythiol **111** by the Birch reduction.



Scheme 19. Synthesis of bornane α-hydroxythiol **111** from camphor **112**.

6. Epoxide and Thiiran Ring Opening

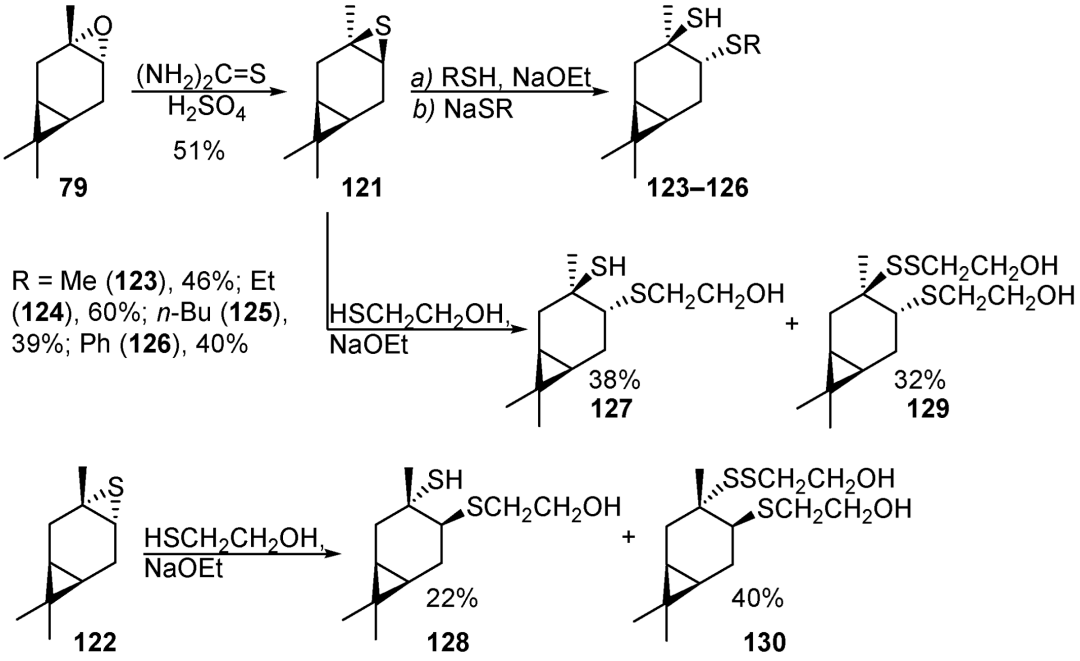
The nucleophilic ring opening of epoxide **79** with AcSH catalyzed by tetramethylammonium fluoride (TMAF) yields hydroxythioacetate **115**, which is readily deacylated by $LiAlH_4$ to form the corresponding α-hydroxythiol **116** (Scheme 20).



Scheme 20. Synthesis of monoterpene hydroxythiols **116** and **120** based on 3-carene **14**.

Cis-epoxide **117** was obtained according to the known method [42] through bromohydrin **118** in 70% total yield. The interaction of epoxide **117** with AcSH in the presence of TMAF leads to thioacetate **119**, the deacylation of which gives α-hydroxythiol **120** (Scheme 20) [22].

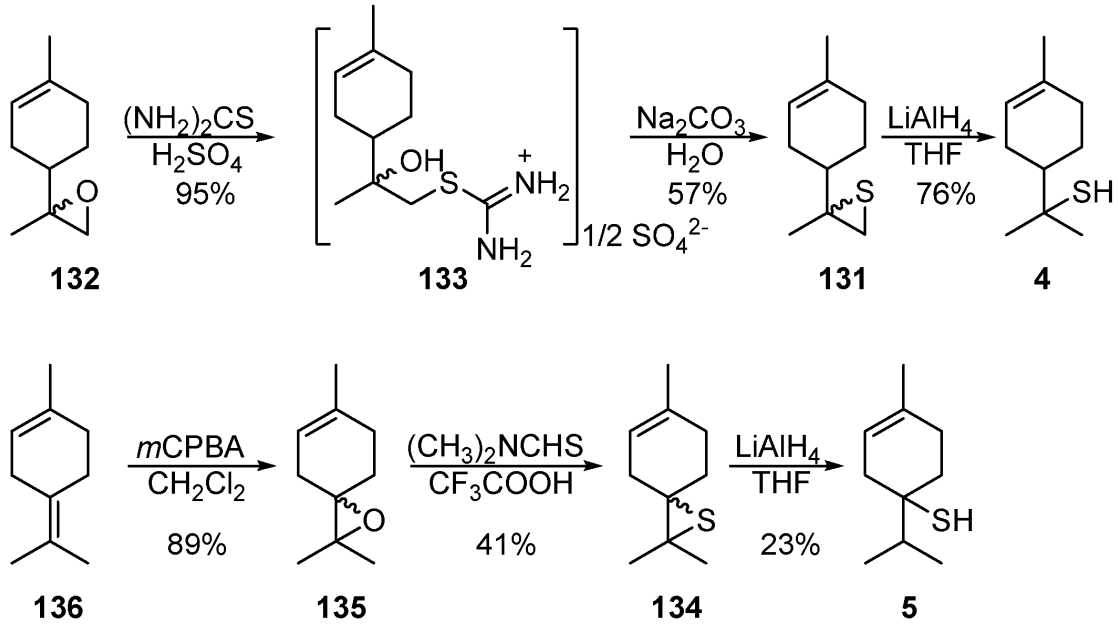
The nucleophilic sulfenylation of carane thiiranes, *cis*-**121** and *trans*-**122**, by mono- (MeSH, EtSH, *n*-BuSH, PhSH) and bifunctional ($HSCH_2CH_2OH$) thiols, promoting with sodium ethoxide and thiolates, affords mercaptosulfides **123–128** with only moderate yields. By-product disulfides **129** and **130** are additionally formed during the reaction of thiiranes **121** and **122** with 2-mercaptoethanol (Scheme 21) [43].



Scheme 21. Sulfenylation of carane thiiranes **121** and **122**.

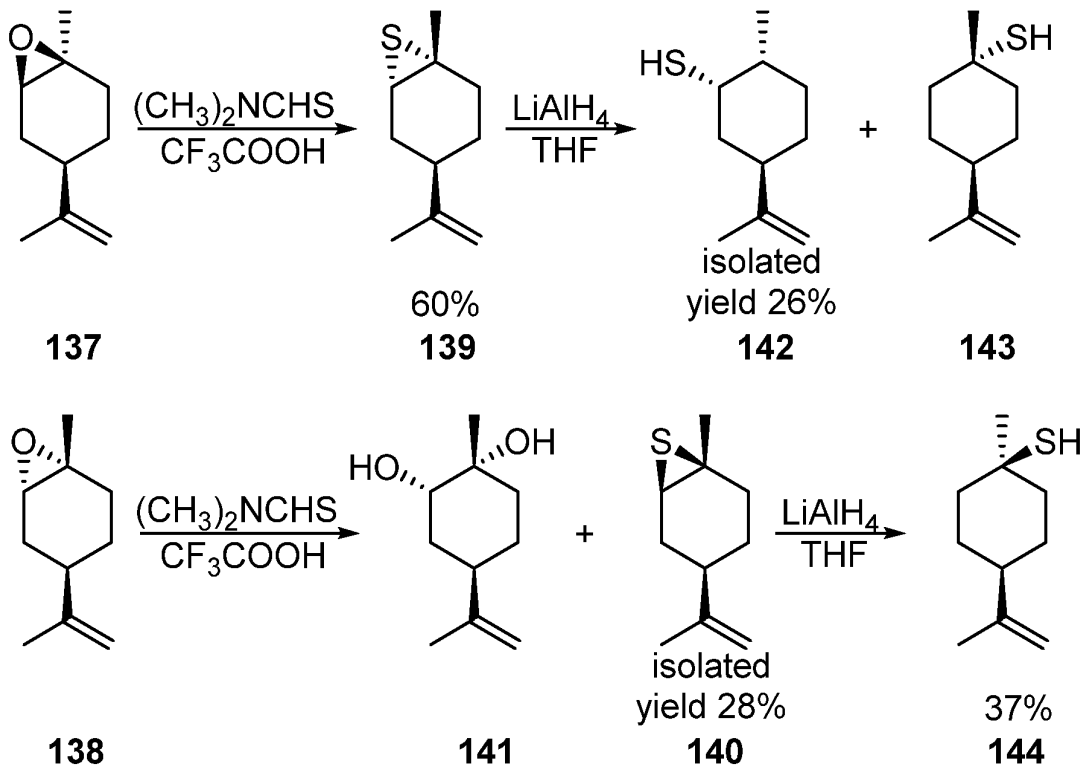
7. Reduction of Thiiranes, Thiolanes, Sulfonyl Chlorides, and Sultones

Monoterpene thiols can be obtained via the reduction of thiiranes. A method for the directed synthesis of racemic thiol **4** from thiirane **131** through oxirane **132** and isothiouronium salt **133** was described in [4]. The sequential reflux of epoxide **132** with thiourea and Na_2CO_3 leads to the corresponding thiirane **131**, the reduction of which by $LiAlH_4$ gives thiol **4** in a moderate yield. A similar protocol for obtaining racemic thiol **5** was reported in [44]; however, thiiran **134** in this study was synthesized from oxirane **135** using the *N*,*N*-dimethylthioformamide (DMTF)–TFA system as a reagent (Scheme 22).



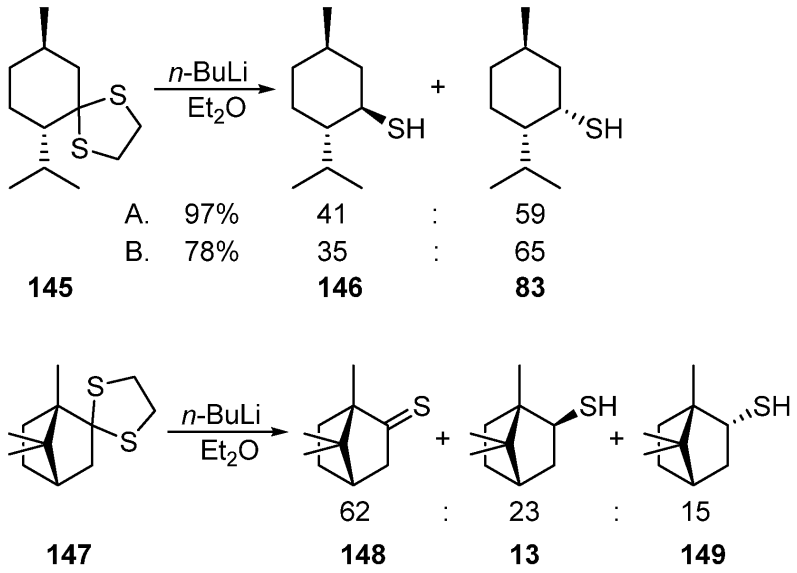
Scheme 22. Scheme for the synthesis of racemic 1-*p*-menthene-8-thiol **4** and 1-*p*-menthene-4-thiol **5**.

Trans-limonene-1,2-epoxide **137** and *cis*-1,2-limonene-1,2-epoxide **138** were transformed by the DMTF-TFA system into *cis*-**139** and *trans*-1,2-epithio-*p*-ment-8-ene **140**, respectively (Scheme 23) [45]. The yield of thiirane **140** is lower than that of thiirane **139**, since the reaction is accompanied by the formation of the by-product diol **141**, which is yielded during the acid hydrolysis of epoxide **138**. The reductive cleavage of the thiirane ring of **139** proceeds readily to give thiols **142** and **143**, of which only thiol **142** was isolated in its pure form. Thiirane **140** was proposed to reduce to thiol **144** at only a 37% yield.



Scheme 23. Synthesis and reduction of *para*-menthane thiiranes **139** and **140**.

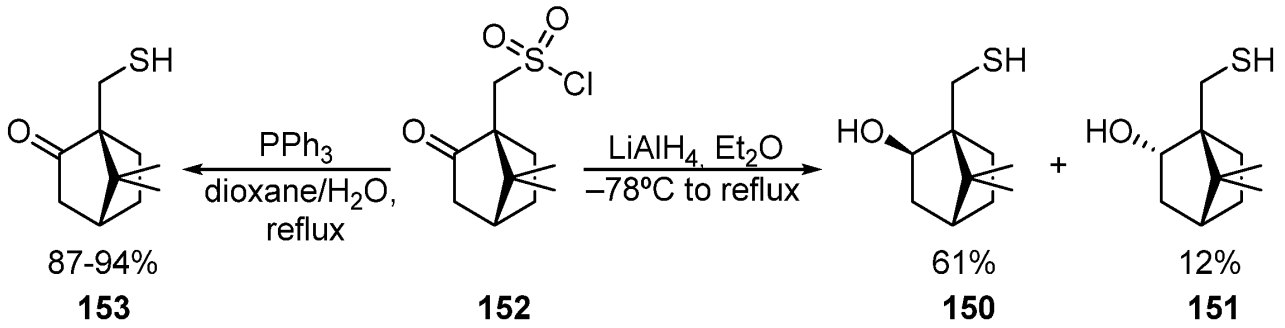
Thioketals can also be used as the starting compounds for the synthesis of monoterpene thiols. Thus, the reductive cleavage of menthone dithiolane **145** using *n*-BuLi leads to the diastereomeric mixture of menthanethiol **146** and neomenthanethiol **83** (Scheme 24) (A) [46], (B) [47].



Scheme 24. Reductive cleavage of menthone dithiolane **145** and camphor dithiolane **147**.

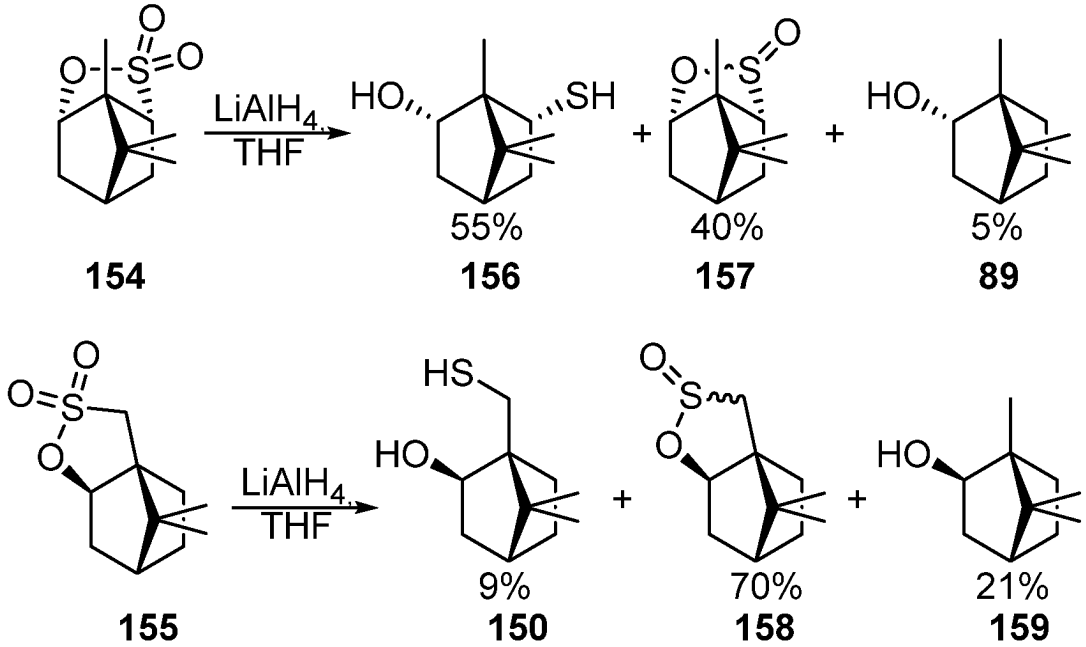
The reductive cleavage of camphor dithiolane **147** induced by *n*-BuLi produces thiocamphor **148** (62%) as the major product; the mixture of *exo*-**13** and *endo*-**149** thiols accounts for only 38% (Scheme 24) [48].

Some methods to obtain bornane β-hydroxythiols **150** and **151** by reducing camphor-10-sulfonyl chloride **152** are described in [49][50][51]. As a result of this transformation, two diastereomeric hydroxythiols, **150** and **151**, are formed (Scheme 25). Camphor-10-sulfonyl chloride **152** can also be selectively converted into ketothiol **153** by using PPh_3 as a reducing agent [52][53].



Scheme 25. Synthesis of 10-thioisoborneol **150**, 10-thioborneol **151**, and 10-thiocamphor **153**.

The authors of [54][55] carried out the reduction of bornane sultones **154** and **155** by $LiAlH_4$ in THF to form the corresponding mixture of hydroxythiols **156** and **150**, sultines **157** and **158**, borneol **89**, and isoborneol **159** (Scheme 26).



Scheme 26. Reduction of monoterpene sultones **154** and **155**.

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