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Preparation of functionalized tertiary thiols and nitrosothiols

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Abstract—The development and preparation of five series of tertiary thiols and nitrosothiols as nitric oxide releasing molecules functionalized with acid, alcohol, or amine groups for future conjugation are reported.

1. Introduction

S-Nitrosothiols were generally considered unstable until the relatively stable trityl nitrosothiol was reported in 1931[1] and the room-temperature-stable *S*-nitroso-*N*-acetyl-DL-penicillamine (SNAP) in 1978.[2] The functional group of *S*-nitrosothiols did not receive much pharmaceutical attention until the discovery of the biological function of nitric oxide, and the role of *S*-nitrosothiols as its physiological carrier. The color of primary and secondary nitrosothiols is typically orange red and that of tertiary is green. The *S*-nitrosothiol group is made up of a sulfur–nitrogen single bond and a nitrogen–oxygen double bond according to X-ray crystallographic analysis.[2] The orientation of the N=O relative to the alkyl group attached to sulfur can be predominantly *syn* for the primary or secondary nitrosothiols and predominantly *anti* for the tertiary ones, which is predicted by theoretical calculation and confirmed by ^{15}N NMR and X-ray data.[3] The ^{15}N NMR signal of $Me_3CS^{15}NO$ appears as a singlet at 20 °C, broadens as the temperature is lowered, and separates into two peaks at −81 °C.[4] *S*-Nitrosothiols are stable under oxidative conditions like treatment with potassium ferricyanide, but decompose rapidly under reductive conditions, e.g., treatment of sodium dithionite. These results are in agreement with the calculation of the bond length of S–N bond of $MeSNO^{\bullet-}$ as the additional electron occupies the antibonding orbital of the S–N bond and elongates the bond length by 0.56 Å.[4]

Nitric oxide is an ubiquitous signaling molecule in mammalian biology and is involved in the regulation of a variety of processes.[5] A number of illnesses are associated with nitric oxide deficiency and thus could potentially be treated with nitric oxide releasing molecules.[6] One class of nitric oxide releasing molecules, which we have focused on is the nitrosothiols. The nitrosothiol functional group is capable of spontaneously releasing nitric oxide without enzymatic preactivation.[7] Due to the inherent lability of the sulfur–nitrogen bond of nitrosothiols, many compounds in this class lack sufficient stability for potential pharmaceutical applications. Thus, our goal in this study was to produce nitrosothiol molecules with appropriate stabilities as well as having at least one other functional group for attachment to therapeutic agents. Generally, tertiary nitrosothiols are more stable than secondary, primary, or aryl nitrosothiols because of the increase in steric interactions associated with the dimerization of the incipient thiyl radical that forms upon homolytic cleavage of the sulfur–nitrogen bond.[8] The stability of *S*-nitrosothiols can also be enhanced by building space protection groups around the *S*-nitrosothiol group such as bowl-shaped triarylmethyl group,[9] a dendrimer-like Bpq group[10] or a Bmt group.[11] Accordingly, our chemical design strategy was to synthesize tertiary nitrosothiols bearing an acid, an alcohol, or a primary amine group.

2. Results and discussion

Our experience with nitrosothiols suggested that, in general, shelf stability is enhanced if the compound is a crystalline solid with a melting point above 70 °C. Since adamantane is a highly symmetrical molecule and its derivatives are usually solid, preparation of adamantane based nitrosothiols was explored. 2-Adamantane thione **1** was prepared according to the literature procedure[12] (Scheme 1). Reaction of **1** with *tert*-butyl acetate and lithium diisopropylamide (LDA) provided thiol **2**. Replacing *tert*-butyl acetate with ethyl acetate also produced the corresponding product but the conversion was not clean and the yield was lower. The ester **2** was converted to acid **3** upon treatment with trifluoroacetic acid (TFA). The thiol acid **3** is a highly crystalline compound, and this reaction has been scaled up to provide 10–100 g quantities of **3** by simple trituration of the crude product with dichloromethane and filtration. The thiol group

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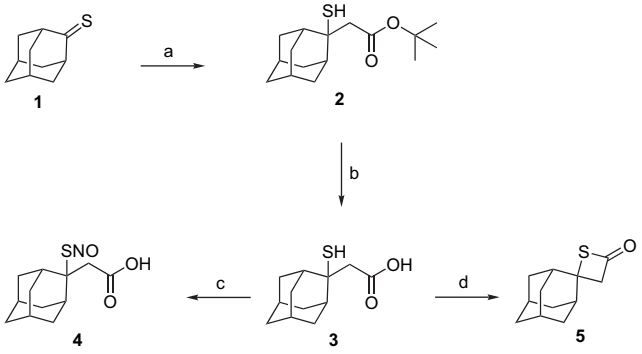
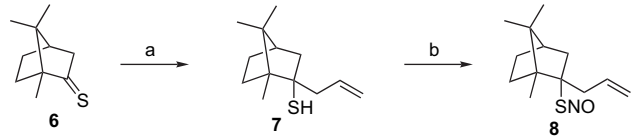
of **3** was converted to the nitrosothiol group by treatment with *tert*-butyl nitrite to afford **4**. Condensation of the acid **4** with alcohol or amine groups from compounds in various therapeutic classes has been done with 1,3-dicyclohexylcarbodiimide (DCC) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC). The thiol group of **3**, however, needs protection in order to condense the acid group of **3** with other molecules. To eliminate the need for protection and deprotection steps, the thiol acid **3** has been converted to thiolactone **5** with EDC. The thiolactone has then been reacted with amine or alcohol nucleophiles to prepare the thiol amides or esters, respectively.



a. *t*-butyl acetate, LDA, 93%; b. TFA, 66%; c. *t*-BuONO, 72%; d. EDC, 86%

Scheme 1.

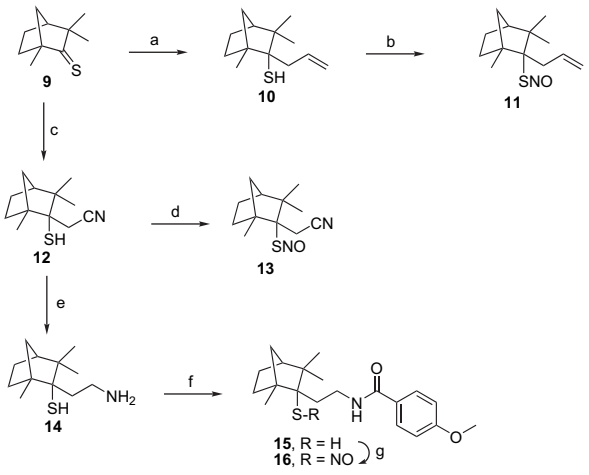
Camphor is an inexpensive high melting point solid (mp 179–181 °C) available in large quantity, and thus it was chosen as the core structure for a second series of nitrosothiols (Scheme 2). The camphor thione **6** was prepared according to the literature procedure[13] and then exposed to the lithium enolate of *tert*-butyl acetate under similar conditions as used for the preparation of **2**. In this reaction, the disappearance of the characteristic orange color of thiones appeared to indicate consumption of **6**, but upon aqueous work up the orange color returned. The recovery of **6** was confirmed by TLC and NMR. Apparently the enolizable proton of **6** was removed by the enolate, thus preventing nucleophilic addition of *tert*-butyl acetate to the thioketone. Preparation of the camphor tertiary thiol **7** was accomplished using allylmagnesium bromide. According to the literature,[14] allyl nucleophile adds to the exposed sulfur of thioketone and subsequent [2,3]-sigmatropic rearrangement produces the allyl thiol **7**. Therefore, allylmagnesium bromide could be used to alkylate a more hindered thioketone as illustrated by this and subsequent examples. The nitrosothiol **8** was then prepared from **7** and *tert*-butyl nitrite.



a. allyl magnesium bromide, 80%; b. *t*-BuONO, 70%

Scheme 2.

Since camphor thione **6** contains two alpha protons and did not react with the enolate of *tert*-butyl acetate, the use of fenchone as the core structure for the third series of



a. allyl magnesium bromide, 68%; b. *t*-BuONO, 66%;
c. *n*-BuLi, CH_3CN, 55%; d. *t*-BuONO, 76%; e. LAH, 41%;
f. 4-methoxybenzoic acid, EDC, 45%; g. *t*-BuONO, 45%

Scheme 3.

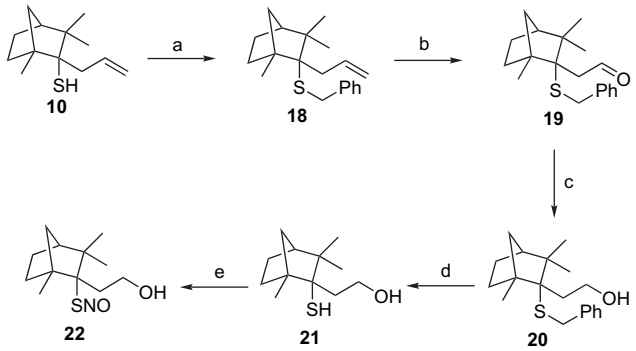
nitrosothiols was examined. Thiofenchone **9** (Scheme 3) was prepared from fenchone according to the literature procedure.[15] However, although, thiofenchone **9** has no alpha protons, it also did not react with the lithium enolate of *tert*-butyl acetate. Since the extreme steric hindrance surrounding the thioketone group of **9** was postulated to be responsible, we again chose allylmagnesium bromide as the nucleophile, which did afford thiol **10**. When the more hindered isoprenylmagnesium bromide was used, the isoprenyl nucleophile did not react with thione **9** to produce the corresponding product. However, with the sterically less encumbered thione **1**, isoprenylmagnesium bromide did react to produce the corresponding thiol **17** (Eq. 1).

(1)

Thus, the steric environment of the thioketone appears to be the primary determining factor governing the ease of nucleophilic addition. Bulky nucleophiles like the enolate of *tert*-butyl acetate or isoprenylmagnesium bromide did not react with thiofenchone **9**. Conversely, the sterically less demanding allyl and acetonitrile anions are able to readily react with the thione group in **9**. The resulting thiols **10** and **12** were readily converted to the nitrosothiols **11** and **13**, respectively, by treatment with *tert*-butyl nitrite. The nitrile group in **12** was converted to an amine **14** by reduction with lithium aluminum hydride (LAH), but attempted nitrosation of **14** with *tert*-butyl nitrite did not yield the desired product. Presuming the basic amine functionality to be the problem, the aminothiol **14** was converted to a model amide by coupling with 4-methoxybenzoic acid. The amide thiol **15** then could be readily nitrosylated to afford the nitrosothiol amide **16**.

Oxidative cleavage of the allyl group to an aldehyde was also studied (Scheme 4). The allyl thiol **10** was treated with osmium tetroxide either at ambient temperature or at 50 °C to give no reaction. Once the thiol **10** was protected

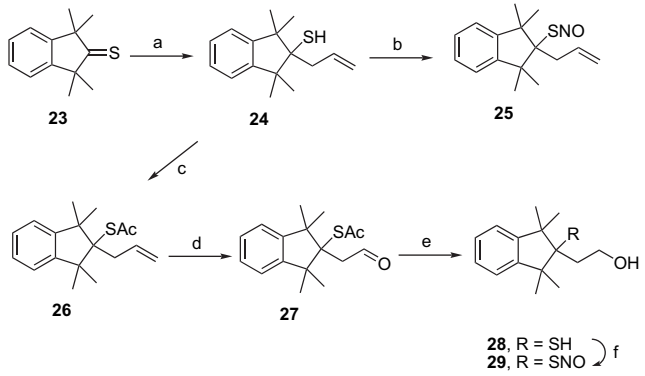
as the benzyl thioether **18**, oxidative cleavage of the allyl group to an aldehyde proceeded as expected. Compound **18** was treated with osmium tetroxide and then with periodic acid to give aldehyde **19**. Reduction of the aldehyde with sodium borohydride gave alcohol **20**. The benzyl group was removed with sodium/ammonia to give thiol alcohol **21**. Using a methanol/dichloromethane mixture as the reaction solvent, the nitrosation of **21** with *tert*-butyl nitrite proceeded smoothly to afford **22** in 90% yield. If this reaction was conducted in just dichloromethane, **22** was obtained only as a minor product with the major product being the bisnitrosylated nitrosothiol nitrite.



a. benzyl bromide, NaH, 71%; b. OsO_4; HIO_4, 51%;
c. $NaBH_4$, 88%; d. Na/NH_3, 88%; e. *t*-BuONO, 90%

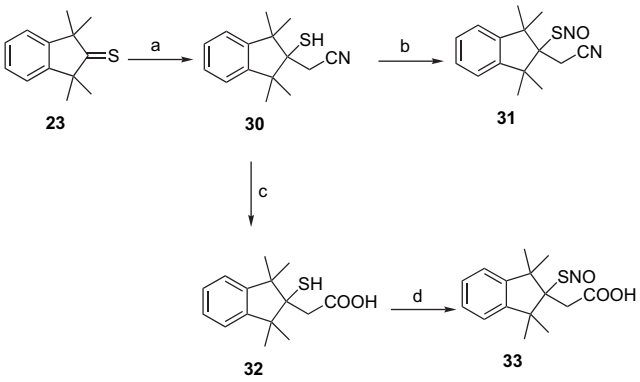
Scheme 4.

The above chemistry was applied to the preparation of other nitric oxide releasing molecules as described below (Schemes 5–7). 1,1,3,3-Tetramethylindane-2-thione **23** was prepared according to the literature procedure[15,16] and reacted with allylmagnesium bromide to give thiol **24** (Scheme 5). Thiol **24** was converted to nitrosothiol **25** using *tert*-butyl nitrite. Alternatively the thiol group of **24** was protected with an acetyl group, instead of a benzyl group, to save one-step in the deprotection, to afford **26**. Compound **26** was treated with osmium tetroxide and then periodic acid to give **27**. The conversion of the aldehyde to an alcohol and the removal of the acetyl group were completed in one reaction with LAH to produce thiol alcohol **28**, which was then converted to nitrosothiol **29** with *tert*-butyl nitrite using methanol/dichloromethane as the reaction solvent.



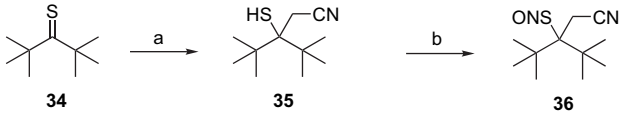
a. allyl magnesium bromide, 83%; b. *t*-BuONO, 51%;
c. Ac_2O, 77%; d. OsO_4; HIO_4, 25%; e. LAH, 58%; f. *t*-BuONO, 88%

Scheme 5.



a. CH_3CN, *n*-BuLi, 69%; b. *t*-BuONO, 45%; c. Conc. HCl, HOAc, 66%;
d. *t*-BuONO, 57%

Scheme 6.



a. CH_3CN, *n*-BuLi, 84%; b. *t*-BuONO, 92%;

Scheme 7.

To evaluate a different approach for the preparation of acid functionalized tertiary thiols and nitrosothiols, the indanethione **23** was reacted with acetonitrile and *n*-butyl lithium to give thiol nitrile **30** (Scheme 6). The nitrile group was hydrolyzed with concentrated hydrochloric acid in acetic acid to give thiol acid **32**. Both thiols **30** and **32** were converted to nitrosothiols **31** and **33**, respectively, with *tert*-butyl nitrite in dichloromethane.

One more series of nitric oxide releasing molecules were explored as shown in Scheme 7. Di-*tert*-butyl thione **34**[17] was reacted with acetonitrile and *n*-butyl lithium to give thiol nitrile **35**. Nitrosation with *tert*-butyl nitrite afforded nitrosothiol **36**.

3. Conclusions

The success of the addition of nucleophiles to thioketones is determined by the overall steric interaction between these two molecules. The carbanion of *tert*-butyl acetate reacts with 2-adamantane thione **1** but not with the more sterically hindered thiofenchone **9**. The linear allylmagnesium bromide reacts with thiofenchone **9**, but the bulkier isoprenylmagnesium bromide did not. With the less sterically hindered 2-adamantane thione **1**, isoprenylmagnesium bromide reacts successfully. In the design of tertiary thiols, the steric interaction between nucleophiles and thioketones must be considered.

Many *S*-nitrosothiols have been prepared under biphasic conditions using nitrous acid, but we enjoyed the convenience of using *tert*-butyl nitrite as the nitrosation agent in dry organic solvents. Alcohol solvents are usually not recommended for the nitrosation reaction using *tert*-butyl

nitrite because of the transfer of NO group to the alcohol solvent. We did find an advantage of using methanol as a co-solvent to suppress the over nitrosation in the preparation of nitrosothiol alcohol **22** and **29**.

In this study, nitric oxide releasing nitrosothiols functionalized with an acid, an alcohol, or an amine group for future conjugation were prepared. These functional groups along with the intermediate aldehydes and 1,2-diols prepared from the allyl double bond offer a broad choice of potential chemical linkages that one might envision utilizing between these nitric oxide releasing molecules and the therapeutic agents of interest.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (Merck, 230–400 mesh). ^{1}H and ^{13}C NMR were recorded on a Brucker AMX-300 instrument. Chemical shifts are referenced to TMS and reported in parts per million. Low-resolution mass spectra were recorded on a Perkin–Elmer API-150EX spectrometer with atmospheric pressure turbo ion spray. Elemental analyses were done at Robertson Microlit Laboratories, Madison, NJ. The consumption of thiols in the preparation of nitrosothiol was usually monitored by TLC staining with Phosphomolybdic acid (PMA). Thiol compounds are usually very sensitive to PMA and gave a blue spot instantly at room temperature and the nitrosothiols usually required heating before giving a blue spot.

4.1.1. *tert*-Butyl (2-mercaptoadamantan-2-yl)acetate (2). To butyl acetate (25 mL, 21.6 g, 186 mmol) in THF (400 mL) at −78 °C was added lithium diisopropylamide monotetrahydrofuran (1.5 M solution in cyclohexane, 100 mL, 150 mmol). The solution was stirred at −78 °C for 40 min and 2-adamantane thione **1**[12] (21.9 g, 131.6 mmol) in THF (400 mL) was added. The reaction mixture was stirred at room temperature for 2 h, and then diluted with dichloromethane and HCl (2 N, 75 mL). The organic phase was removed, washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (ethyl acetate/hexane 1:19) to give **2** (34.7 g, 93%). Mp 56–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 2H), 2.47 (m, 2H), 2.38 (s, 1H), 2.11 (m, 2H), 1.98 (s, 2H), 1.96 (m, 2H), 1.96–1.84 (m, 6H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 80.7, 54.0, 47.2, 38.9, 38.1, 33.9, 33.23, 28.1, 27.4, 26.8. LRMS (APIMS) *m*/*z* 283 (MH^+). Anal. Calcd for $C_{16}H_{26}O_2S$: C, 68.04; H, 9.28. Found: C, 68.14; H, 9.30.

4.1.2. (2-Mercaptoadamantan-2-yl)acetic acid (3). Trifluoroacetic acid (15 mL) was added to **2** (10.76 g, 38.10 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 40 min and concentrated to dryness. The resultant solid was treated with dichloromethane (40 mL) and concentrated to dryness three times. The resultant solid was triturated with dichloromethane (20 mL). The solid was collected by filtration and washed with a minimum amount of dichloromethane to give **3** (5.6447 g, 66%). Mp 178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.5 (br s, 1H), 3.04 (s, 2H), 2.49 (m, 2H), 2.25 (s, 1H), 2.1–2.0 (m, 4H), 1.9 (m, 2H), 1.7–1.6 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 53.4, 46.3, 38.9, 37.8, 33.8, 33.2, 27.4, 26.8. LRMS (APIMS, −ve scan) *m*/*z* 225 ($M-H^-$). Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.40; H, 7.90.

4.1.3. [2-(Nitrosothio)adamantane-2-yl]acetic acid (4). Compound **3** (773.1 mg, 3.416 mmol) was dissolved in hot methylene chloride (40 mL). The methylene chloride solution was cooled to room temperature and *tert*-butyl nitrite (420 μL, 370 mg, 3.59 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and then concentrated. This crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to give **4** (628.2 mg, 2.46 mmol, 72%). Mp 72–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.8 (br, 1H), 3.77 (s, 2H), 2.78 (s, 2H), 2.4 (m, 2H), 2.1–1.7 (m, 10H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 66.7, 42.4, 38.3, 35.1, 33.4, 32.5, 26.71, 26.66. APIMS (IS, NH_4OAc) *m*/*e* 254 ($M-H^-$).

4.1.4. 4*H*-Spiro[thiethane-2,2′-tricyclo[3.3.1.1^{3,7}]decan]-4-one (5). A mixture of **3** (516 mg, 2.28 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (445 mg, 2.32 mmol) in dichloromethane (10 mL) was stirred at room temperature for 1 h, diluted with dichloromethane, and washed with 0.1 M HCl and brine. The organic phase was dried over magnesium sulfate, filtered, evaporated, and chromatographed (ethyl acetate/hexane 1:3, then 1:1) to give **5** (0.41 g, 86%). Mp 77–78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 2H), 2.20 (m, 2H), 1.95–1.78 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 63.4, 54.9, 39.9, 36.5, 35.6, 33.7, 26.6, 25.8. LRMS (APIMS) *m*/*z* 209 ($M+H^+$), 226 (MNH_4^+).

4.1.5. 2-Allyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-thiol (7). A solution of (1*R*)-(−)-thiocamphor **6**[13] (0.5 g, 2.97 mmol) in ether (10 mL) cooled to 0 °C was treated with allylmagnesium bromide (1 M in ether, 4.5 mL, 4.5 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Excess cold 2 N HCl was added carefully, and the solution was extracted with ether. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (neat hexane) to give **7** (0.5 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05–5.91 (m, 1H), 5.17–5.10 (m, 2H), 2.54–2.46 (m, 2H), 2.30–2.18 (m, 1H), 2.10 (s, 1H), 1.75–1.68 (m, 3H), 1.58–1.46 (m, 3H), 1.16 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 117.9, 55.4, 52.7, 50.7, 49.7, 47.9, 45.7, 31.3, 27.1, 22.1, 21.4, 14.3.

4.1.6. 2-Allyl-1,7,7-trimethyl-2-(nitrosothio)bicyclo[2.2.1]-heptane (8). A solution of **7** (100 mg, 0.48 mmol) in hexane (5 mL) was treated dropwise with *tert*-butyl nitrite (113 μL, 0.95 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated, and the residue was chromatographed (neat hexane) to give **8** (80 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1H), 5.06–4.99 (m, 2H), 3.26–3.18 (m, 2H), 2.64 (m, 1H), 2.15–2.02 (m, 2H), 1.96–1.82 (m, 2H), 1.75–1.62

(m, 1H), 1.47–1.37 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 117.7, 68.8, 54.7, 50.8, 46.5, 45.8, 45.5, 31.6, 27.1, 21.5, 21.3, 13.5.

4.1.7. 2-Allyl-1,3,3-trimethylbicyclo[2.2.1]heptane-2-thiol (10). (1*R*)-(−)-Fenchone was converted to hydrazone with hydrazine in acetic acid, and the resultant hydrazone was converted to the thioketone **9** with sulfur monochloride and triethylamine according to the literature procedure.[16] A solution of **9** (10.9 g, 65 mmol) in ether (150 mL) was treated with allylmagnesium bromide (1 M in ether, 100 mL, 100 mmol) dropwise at room temperature. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h, cooled in an ice bath, and quenched carefully with 1 N HCl. The organic phase was washed with water, brine, and dried over sodium sulfate. After filtration and evaporation, the residue was purified by column chromatography (neat hexane) to give **10** (9.3 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13–6.04 (m, 1H), 5.10–5.03 (m, 2H), 2.72–2.62 (m, 1H), 2.40–2.30 (m, 1H), 2.27–2.15 (m, 1H), 1.90–1.80 (m, 1H), 1.79–1.67 (m, 2H), 1.47–1.31 (m, 1H), 1.20 (s, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.22–1.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 116.9, 63.5, 54.1, 50.8, 45.2, 44.6, 40.6, 35.0, 28.3, 27.2, 24.8, 18.2.

4.1.8. 2-Allyl-1,3,3-trimethyl-2-(nitrosothio)bicyclo[2.2.1]-heptane (11). A solution of **10** (80 mg, 0.38 mmol) in hexane (2 mL) was added to a solution of *tert*-butyl nitrite (68 μL, 0.57 mmol) in hexane (2 mL). The reaction mixture was stirred at room temperature in the dark for 30 min, and then additional *tert*-butyl nitrite (20 μL) was added. The reaction mixture was stirred for an additional 1 h at room temperature in the dark. The solvent was evaporated, and the residue was purified by column chromatography (neat hexane) to give **11** (60 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90–5.81 (m, 1H), 4.93–4.84 (m, 2H), 3.43–3.25 (m, 2H), 2.14 (d, J=10.5 Hz, 1H), 1.82–1.61 (m, 3H), 1.60–1.50 (m, 1H), 1.40 (s, 3H), 1.24 (s, 3H), 1.38–1.20 (m, 2H), 0.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 117.7, 68.8, 54.7, 50.8, 46.5, 45.8, 45.5, 31.6, 27.1, 21.5, 21.3, 13.5.

4.1.9. (2-Mercapto-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-acetonitrile (12). A solution of *n*-butyl lithium (2.5 M in hexane, 29.7 mL, 74.3 mmol) was cooled to −78 °C and then treated with a solution of acetonitrile (3.9 mL, 74.3 mmol) in THF (98 mL). The solution was stirred at −78 °C for 1 h and then treated with a solution of **9**[15] (5 g, 29.7 mmol) in THF (50 mL). The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature over 1 h. Water (50 mL) was added carefully and then THF was removed by evaporation. The residue was diluted with more water and extracted with ether. The combined organic phase was washed with water, brine, and dried over sodium sulfate. The residue after filtration and evaporation was purified by column chromatography (ethyl acetate/hexane 1:9) to give **12** (3.41 g, 55%). Mp 170–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (d, J=16.6 Hz, 1H), 2.67 (d, J=16.6 Hz, 1H), 2.25–2.13 (m, 1H), 1.78–1.67 (m, 3H), 1.67 (s, 1H), 1.50–1.37 (m, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 1.30–1.19 (m, 2H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 119.9, 60.5, 53.7, 50.1, 45.1, 40.6, 34.3, 30.9, 26.8, 26.3, 24.8, 17.8. LRMS (APIMS) m/z 227 (MNH_4^+).

4.1.10. [1,3,3-Trimethyl-2-(nitrosothio)bicyclo[2.2.1]-hept-2-yl]acetonitrile (13). To a solution of **12** (70 mg, 0.33 mmol) in dichloromethane (5 mL) was added *tert*-butyl nitrite (130 μL, 1 mmol). The reaction mixture was stirred at room temperature in the dark for 2 h. Additional *tert*-butyl nitrite (40 μL, 0.31 mmol) was added and the solution was stirred for an additional 30 min in the dark. The solvent was evaporated, and the residue was purified by column chromatography on a preparative plate (ethyl acetate/hexane 1:4) to give **13** (60 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (d, J=17.0 Hz, 1H), 3.57 (d, J=17.0 Hz, 1H), 2.20–2.10 (m, 1H), 1.95 (br s, 1H), 1.75–1.53 (m, 3H), 1.50 (s, 3H), 1.29 (s, 3H), 1.40–1.21 (m, 2H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.8, 70.1, 55.0, 50.2, 48.0, 41.6, 33.6, 27.2, 25.8, 25.5, 25.0, 18.6. LRMS (APIMS) m/z 256 (MNH_4^+).

4.1.11. 2-(2-Aminoethyl)-1,3,3-trimethylbicyclo[2.2.1]-heptane-2-thiol (14). To a solution of **12** (2.9 g, 13.7 mmol) in THF (20 mL) was added a solution of LAH (1 M in THF, 21 mL, 21 mmol). The reaction mixture was refluxed for 1.5 h. The solution was cooled to 0 °C and sodium sulfate decahydrate was added to decompose excess reducing agent. The solid was removed by filtration and washed with dichloromethane/methanol (100 mL, 4:1). The combined filtrate was dried over sodium sulfate, filtered, and evaporated. The residue was purified by column chromatography (hexane/ether 1:19), and the solid was recrystallized from ether/hexane (1:1) to give **14** (1.2 g, 41%). Mp 42–43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06–2.95 (m, 1H), 2.92–2.82 (m, 1H), 2.35–2.22 (m, 1H), 2.02–1.91 (m, 1H), 1.80–1.70 (m, 1H), 1.69–1.57 (m, 3H), 1.48–1.30 (m, 4H), 1.10 (s, 6H), 1.20–1.02 (m, 2H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.0, 54.4, 50.7, 44.8, 43.7, 41.2, 40.5, 34.6, 28.0, 26.4, 24.7, 18.2. LRMS (APIMS) m/z 214 (MH^+).

4.1.12. *N*-[2-(2-Mercapto-1,3,3-trimethylbicyclo[2.2.1]-hept-2-yl)ethyl]-4-methoxybenzamide (15). A solution of 4-dimethylaminopyridine (5 mg, 47 μmol), compound **14** (0.1 g, 0.47 mmol), and 4-methoxybenzoic acid (78 mg, 0.52 mmol) in DMF (1 mL) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.52 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with water, brine, and then dried over sodium sulfate. The residue, after filtration and evaporation, was purified by column chromatography (ethyl acetate/hexane 1:2) to give **15** (73 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=8.8 Hz, 2H), 6.98 (d, J=8.8 Hz, 2H), 6.55 (t, J=6.3 Hz, 1H), 3.83 (s, 3H), 3.85–3.72 (m, 1H), 3.62–3.51 (m, 1H), 2.38–2.14 (m, 2H), 1.80–1.60 (m, 4H), 1.46–1.31 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 1.20–1.10 (m, 3H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 162.0, 128.6, 127.0, 113.6, 64.3, 55.5, 54.5, 50.8, 44.8, 41.3, 40.6, 39.5, 34.8, 28.2, 26.3, 24.7, 18.2.

4.1.13. 4-Methoxy-*N*-{2-[1,3,3-trimethyl-2-(nitrosothio)-bicyclo[2.2.1]hept-2-yl]ethyl}benzamide (16). To a solution of *tert*-butyl nitrite (89 μL, 68 mg, 0.66 mmol) in dichloromethane (2 mL) was added dropwise a solution of **15** (66 mg, 0.19 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature in the dark

for 40 min. The solvent was evaporated and the residue was chromatographed (ethyl acetate/hexane 1:2) to give **16** (32 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 6.00 (br s, 1H), 3.85 (s, 3H), 3.57–3.35 (m, 2H), 2.99–2.76 (m, 2H), 2.15 (d, 1H), 1.88–1.62 (m, 4H), 1.62–1.45 (m, 1H), 1.45 (s, 3H), 1.31 (s, 3H), 1.4–1.15 (m, 1H), 0.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 162.1, 128.5, 126.6, 113.7, 74.3, 55.7, 55.3, 50.7, 48.5, 42.1, 39.2, 36.1, 34.0, 28.2, 25.1, 25.0, 19.4. LRMS (APIMS) m/z 377 (MH^+).

4.1.14. 2-(1,1-Dimethylprop-2-en-1-yl)adamantane-2-thiol (17). A solution of **1** (80 mg, 0.48 mmol) in THF (5 mL) was added 3,3-dimethylallylmagnesium bromide (0.12 M in THF, 12 mL, 1.44 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 15 min and the orange color disappeared gradually. Hydrogen chloride solution (1 M) was added. The organic phase was washed with water and brine, and then dried with magnesium sulfate. The THF solution was concentrated, and the residue was purified by chromatography (neat hexane) to give **17** (80 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J=17.5 and 10.8 Hz, 1H), 5.03–4.93 (m, 2H), 2.75–2.71 (m, 2H), 2.56–2.52 (m, 2H), 2.18 (m, 2H), 2.02 (s, 2H), 1.86 (m, 2H), 1.72–1.55 (m, 8H), 1.35 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 109.6, 65.9, 46.6, 40.5, 37.5, 36.3, 34.5, 27.4, 27.2, 26.9.

4.1.15. 2-Allyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl benzyl sulfide (18). A solution of **10** (10.1 g, 48.1 mmol) in THF (250 mL) was treated in one portion with sodium hydride (1.34 g of 95%, 53 mmol). After 10 min, benzyl bromide (5.8 mL, 48 mmol) was added slowly and the reaction mixture was stirred at room temperature for 3 h. Water (100 mL) was added and then THF was removed by evaporation. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine and dried over magnesium sulfate. After filtration and concentration, the residue was purified by column chromatography twice (first chromatography: hexane; second chromatography: hexane followed by dichloromethane) to give **18** (10.2 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 6.49–6.31 (m, 1H), 5.19–5.08 (m, 2H), 3.70 (d, J=10.5 Hz, 1H), 3.58 (d, J=10.5 Hz, 1H), 2.79–2.62 (m, 2H), 2.51–2.40 (m, 1H), 1.91–1.73 (m, 2H), 1.60–1.38 (m, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.15–1.30 (m, 1H).

4.1.16. [2-(Benzylthio)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]acetaldehyde (19). A solution of **18** (10.2 g, 34 mmol) in a mixture of acetone (370 mL) and water (40 mL) was treated with *N*-methylmorpholine oxide (50% in water, 35 mL, 170 mmol) followed by osmium tetroxide (4% in water, 10.3 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 42 h. Then acetone was removed by evaporation, and the residue was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in a mixture of THF (79 mL) and ether (210 mL) and cooled to 0 °C. To this was added slowly a solution of periodic acid in a mixture of THF (30 mL) and ether (90 mL). The solution was stirred at 0 °C for 1 h and at room temperature for 30 min, filtered through Celite, and concentrated. After filtration and concentration, the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to give **19** (5.3 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (t, J=2.4 Hz, 1H), 7.31–7.19 (m, 5H), 3.69 (d, J=10.6 Hz, 1H), 3.62 (d, J=10.6 Hz, 1H), 2.85 (d, J=2.5 Hz, 2H), 2.46–2.34 (m, 1H), 1.86–1.73 (m, 2H), 1.67 (m, 1H), 1.42–1.57 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 1.20–1.30 (m, 1H), 1.12 (s, 3H). LRMS (APIMS) m/z 303 (MH^+).

4.1.17. 2-[2-(Benzylthio)-1,3,3-trimethylbicyclo[2.2.1]-hept-2-yl]ethanol (20). A suspension of **19** (5.3 g, 17.4 mmol) in methanol (70 mL) was treated with sodium borohydride (0.67 g, 17.4 mmol) in one portion. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed by evaporation. The residue was suspended in ethyl acetate, washed with water, brine, and dried over sodium sulfate. After filtration and concentration, the residue was purified by column chromatography (ethyl acetate/hexane 1:4 then 1:3) to give **20** (4.43 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 4.06–3.95 (m, 1H), 3.91–3.80 (m, 1H), 3.75 (d, J=2.4 Hz, 2H), 2.56–2.43 (m, 1H), 2.32–2.22 (m, 1H), 2.19–2.00 (m, 2H), 1.83–1.72 (m, 2H), 1.53–1.36 (m, 2H), 1.20 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 1.30–1.10 (m, 2H). LRMS (APIMS) m/z 305 (MH^+).

4.1.18. 2-(2-Mercapto-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)ethanol (21). A solution of **20** (4.4 g, 14.5 mmol) in ether (5 mL) was treated with liquid ammonia followed by the addition of sodium (approx 1 g) until a permanent blue color was obtained. The final reaction mixture was stirred for 45 min, and then ammonium chloride was added to disperse the blue color. Then ammonia was allowed to evaporate. The residue was partitioned between ether and water. The organic phase was washed with water, brine, and dried over sodium sulfate. The residue after filtration and evaporation was purified by column chromatography (ethyl acetate/hexane 1:4) to give **21** (2.8 g, 88%). Mp 55–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93–3.80 (m, 2H), 2.39–2.16 (m, 2H), 1.95 (br s, 1H), 1.82–1.50 (m, 4H), 1.34–1.47 (m, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 1.00–1.23 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.01, 62.2, 54.4, 50.6, 44.8, 43.7, 40.6, 34.4, 28.2, 26.2, 24.6, 18.1. LRMS (APIMS) m/z 232 (MNH_4^+).

4.1.19. 2-[1,3,3-Trimethyl-2-(nitrosothio)bicyclo[2.2.1]-hept-2-yl]ethanol (22). A solution of **21** (0.5 g, 2.33 mmol) in a mixture of methanol (5 mL) and dichloromethane (5 mL) was cooled over ice and then treated slowly with *tert*-butyl nitrite (1 mL, 7.5 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 30 min. The solvent was evaporated and the residue was purified by column chromatography (ethyl acetate/hexane 1:4) to give **22** (0.51 g, 90%). Mp 83–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71–3.50 (m, 2H), 3.14–2.91 (m, 1H), 1.86–1.74 (m, 1H), 2.19–2.09 (m, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 1.83–1.20 (m, 7H), 0.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.3, 61.8, 55.6, 50.6, 48.3, 42.0, 38.8, 33.8, 28.1, 25.1, 25.0, 19.3. LRMS (APIMS) m/z 261 (MNH_4^+).

4.1.20. 2-Allyl-1,1,3,3-tetramethylindane-2-thiol (24). 2-Indanone was tetramethylated with methyl iodide and

potassium hydroxide in DMSO, and the resultant 1,1,3,3,-tetramethyl-2-indaneone was treated with hydrazine in acetic acid and then with sulfur monochloride and triethylamine to give **23** following literature procedures.[15,16] A solution of **23** (10 g, 50 mmol) in ether (100 mL) was cooled over ice. To this was added a solution of allylmagnesium bromide (147 mL of 1 M solution in ether, 147 mmol) dropwise. The resultant solution was stirred over ice for 30 min, quenched carefully with excess 2 N HCl. The organic phase was dried over sodium sulfate and filtered. After evaporation, the residue was purified by column chromatography (ether/hexane 1:19) to give **24** (10 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.21 (m, 2H), 7.16–7.12 (m, 2H), 6.2–6.0 (m, 1H), 5.24–5.15 (m, 2H), 2.67–2.65 (m, 2H), 1.55 (s, 1H), 1.50 (s, 6H), 1.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 135.4, 127.2, 122.2, 118.1, 68.4, 50.5, 40.9, 29.1, 28.6. Anal. Calcd for $C_{16}H_{22}S$: C, 78.00; H, 9.00. Found: C, 77.86; H, 8.97.

4.1.21. 2-Allyl-1,1,3,3-tetramethyl-2-(nitrosothio)indane (25). To a solution of *tert*-butyl nitrite (405 μL, 314 mg, 3 mmol) in dichloromethane (2 mL) was added dropwise a solution of **24** (250 mg, 1 mmol) in dichloromethane (2 mL). The resultant solution was stirred at room temperature in the dark for 45 min. The volatiles were evaporated and the residue was chromatographed (ether/hexane 1:99) to give **25** (150 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.28–7.22 (m, 2H), 6.09–5.95 (m, 1H), 5.31–5.17 (m, 2H), 3.78 (d, J=6.7 Hz, 2H), 1.76 (s, 6H), 1.49 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 135.1, 127.6, 122.2, 118.0, 80.7, 51.6, 37.1, 29.2, 28.3. Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.65; H, 7.69; N, 4.82.

4.1.22. *S*-(2-Allyl-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-inden-2-yl)ethanethioate (26). A solution of **24** (9 g, 36.6 mmol) in pyridine (189 mL, 185 g, 2.3 mol) was cooled over ice and treated dropwise with acetic anhydride (110 mL, 119 g, 1.17 mol) and 4-dimethylaminopyridine (0.5 g). The crude reaction mixture was stirred at room temperature for 12 h. The volatile material was evaporated and the residue was chromatographed (ether/hexane 1:19) to give **26** (8.1 g, 77%). Mp 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.24 (m, 2H), 7.11–7.06 (m, 2H), 6.02–5.85 (m, 1H), 5.17–5.00 (m, 2H), 3.19 (d, J=6.6 Hz, 2H), 2.23 (s, 3H), 1.51 (s, 6H), 1.43 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 149.2, 136.5, 127.7, 122.4, 117.0, 51.7, 34.8, 31.8, 29.3, 28.4. Anal. Calcd for $C_{18}H_{24}OS$: C, 74.95; H, 8.39. Found: C, 74.76; H, 8.38.

4.1.23. *S*-[1,1,3,3-Tetramethyl-2-(2-oxoethyl)-2,3-dihydro-1*H*-inden-2-yl]ethanethioate (27). A mixture of *N*-methylmorpholine *N*-oxide (50% in water, 31 mL, 131 mmol) and **26** (8 g, 26 mmol) in water (100 mL) was treated with acetone to give a homogeneous solution (approx 350 mL). Osmium tetroxide (8 mL of 4% aqueous solution, 1.31 mmol) was introduced and the resulting solution was stirred at room temperature overnight. The volume was reduced by evaporation and the residue was diluted with more water and then extracted with ethyl acetate followed by dichloromethane. The combined organic phases were dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in 240 mL of 3:1 ether/THF and cooled over ice under nitrogen. Periodic acid (9 g, 39 mmol) was added in portions over 20 min. The reaction mixture was stirred over ice for 1 h and at room temperature for 40 min. The solid was removed by filtration through Celite, and the filtrate was washed with water, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane 1:19) to give **27** (2 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J=2.5 Hz, 1H), 7.25–7.19 (m, 2H), 7.11–7.06 (m, 2H), 3.32 (d, J=2.5 Hz, 2H), 2.31 (s, 3H), 1.46 (s, 6H), 1.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 196.1, 147.5, 127.7, 122.2, 71.6, 51.4, 45.0, 31.4, 29.3, 27.6. Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64. Found: C, 70.02; H, 7.69. LRMS (APIMS) m/z 291 (MH^+).

4.1.24. 2-(2-Mercapto-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-inden-2-yl)ethanol (28). A solution of **27** (2.07 g, 7.12 mmol) in THF (80 mL) was cooled over ice and a solution of LAH (1 M in THF, 14.2 mL, 14.2 mmol) was added dropwise. The ice bath was removed and the resultant solution was stirred at room temperature for 45 min. Sodium sulfate decahydrate was added to decompose excess reducing agent. The reaction mixture was filtered and the solid was washed with dichloromethane/methanol 4:1. The filtrate was dried over sodium sulfate and filtered. After evaporation the residue was chromatographed (ethyl acetate/hexane 1:4) to give **28** (1.04 g, 58%). Mp 85–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.15–7.10 (m, 2H), 4.01 (br s, 2H), 2.20–2.15 (m, 2H), 1.87 (br s, 1H), 1.50 (s, 6H), 1.38 (s, 6H), 1.32 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 127.2, 122.2, 67.9, 60.4, 50.5, 39.0, 29.3, 28.3. LRMS (APIMS) m/z 268 (MNH_4^+).

4.1.25. 2-[1,1,3,3-Tetramethyl-2-(nitrosothio)-2,3-dihydro-1*H*-inden-2-yl]ethanol (29). An ice cooled solution of **28** (1.04 g, 4.15 mmol) in a mixture of dichloromethane/methanol (20 mL, 1:1) was treated dropwise with *tert*-butyl nitrite (2.5 mL, 19 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 30 min. The residue after evaporation was purified by column chromatography (ethyl acetate/hexane 1:4) to give **29** (1.05 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.21 (m, 2H), 7.15–7.10 (m, 2H), 3.86 (t, J=7.5 Hz, 2H), 3.18–3.13 (m, 2H), 1.63 (s, 6H), 1.51 (s, 1H), 1.30 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 127.6, 122.2, 80.2, 60.0, 51.3, 35.5, 29.3, 28.1. Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.45; H, 7.67; N, 4.67. LRMS (APIMS) m/z 297 (MNH_4^+).

4.1.26. (2-Mercapto-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-inden-2-yl)acetonitrile (30). A solution of *n*-butyl lithium (2.5 M in hexane, 29.4 mL, 73.4 mmol) was cooled to −78 °C, and to it was added dropwise a solution of acetonitrile (3.8 mL, 73.4 mmol) in THF (98 mL). The suspension was stirred at −78 °C for 1 h. A solution of **23**[15,16] (6 g, 29.4 mmol) in THF (49 mL) was added in one portion. The resulting solution was stirred at −78 °C for 1 h, quenched with water, and then THF was evaporated. The residue was treated with ethyl acetate and then with water, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water and then brine, dried over sodium sulfate, filtered, and evaporated.

The residue was purified by column chromatography twice (ethyl acetate/hexane 1:9 each time) to give **30** (5 g, 69%). Mp 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.19–7.14 (m, 2H), 2.83 (m, 2H), 1.85 (s, 1H), 1.55 (s, 6H), 1.44 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 127.8, 122.3, 118.1, 64.0, 50.0, 29.2, 28.1, 27.3. Anal. Calcd for $C_{15}H_{19}NS$: C, 73.42; H, 7.80; N, 5.71. Found: C, 73.18; H, 7.75; N, 5.62. LRMS (APIMS) *m/z* 263 (MNH_4^+).

4.1.27. [1,1,3,3-Tetramethyl-2-(nitrosothio)-2,3-dihydro-1*H*-inden-2-yl]acetonitrile (31). To a solution of *tert*-butyl nitrite (325 μL, 251 mg, 2.4 mmol) in dichloromethane (3 mL) was added **30** (200 mg, 0.82 mmol) dropwise as a solution in dichloromethane (2 mL). The resultant solution was stirred in the dark for 40 min. The solvent was evaporated, and the residue was chromatographed (ethyl acetate/hexane 1:9). The fractions containing the product were pooled and concentrated, and hexane added. After standing overnight at 4 °C, the solid was filtered to give **31** (0.1 g, 45%). Mp 67–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2H), 7.28–7.21 (m, 2H), 3.86 (s, 2H), 1.72 (s, 6H), 1.43 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 128.4, 122.4, 117.6, 73.8, 51.6, 30.1, 27.1, 24.5. LRMS (APIMS) *m/z* 292 (MNH_4^+).

4.1.28. (2-Mercapto-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-inden-2-yl)acetic acid (32). A solution of **30** (0.5 g, 2.1 mmol) in concentrated HCl (10 mL) and acetic acid (10 mL) was refluxed for 52 h. The crude reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate. The organic phase was washed with water twice and then extracted with saturated sodium bicarbonate. The basic aqueous phase was acidified to pH 2 with concentrated HCl. The resulting solution was then extracted with dichloromethane, and the combined organic phase was dried over sodium sulfate, filtered, and concentrated to give **32** (240 mg). The ethyl acetate phase after basification also contained some product. This ethyl acetate solution was dried with sodium sulfate, filtered, and concentrated and chromatographed (ethyl acetate/hexane 1:1) to give more **32** (120 mg, 360 mg total, 66%). Mp 159–161 °C. ^{1}H NMR ($CDCl_3$) δ 7.28–7.24 (m, 2H), 7.19–7.15 (m, 2H), 2.97 (s, 2H), 2.06 (s, 1H), 1.58 (s, 6H), 1.42 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 177.9, 148.1, 127.4, 122.5, 65.0, 50.9, 41.6, 29.5, 27.5. LRMS (APIMS) *m/z* 282 (MNH_4^+).

4.1.29. [1,1,3,3-Tetramethyl-2-(nitrosothio)-2,3-dihydro-1*H*-inden-2-yl]acetic acid (33). To a solution of *tert*-butyl nitrite (169 μL, 130 mg, 1.27 mmol) in dichloromethane (4 mL) was added **32** (112 mg, 0.42 mmol) in one portion as a solid. The solution was stirred for 45 min in the dark, and the solvent was evaporated. The solid was dissolved in a minimum amount of hot ether, and three volumes of hot hexane were added. The solution was allowed to stand at 4 °C overnight and the solid was collected by filtration to give **33** (75 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.20 (m, 2H), 7.15–7.10 (m, 2H), 3.89 (s, 2H), 1.63 (s, 6H), 1.61 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 127.7, 122.4, 52.0, 37.1, 29.6, 27.7. Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.19; H, 6.70; N, 4.50. LRMS (APIMS) *m/z* 294 (MH^+), 311 (MNH_4^+), 292 ($M-H^-$).

4.1.30. 3-Butyl-3-mercapto-4,4-dimethylpentanenitrile (35). A solution of *n*-butyl lithium (2.5 M in hexane, 25.3 mL, 63.2 mmol) was cooled to −78 °C, and to it was added a solution of acetonitrile (3.3 mL, 63.2 mmol) in THF (98 mL). The reaction mixture was stirred at −78 °C for 1 h, and then a solution of **34**, which was prepared following literature procedure,[17] was added in one portion. The reaction mixture was stirred at room temperature for 1 h and quenched carefully with 2 N HCl, and then THF was removed by evaporation. The residue was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine and dried over sodium sulfate. After filtration and concentration, the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to give **35** (3.5 g, 84%). Mp 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 2H), 1.66 (s, 1H), 1.29 (s, 18H). LRMS (APIMS) *m/z* 217 (MNH_4^+).

4.1.31. 3-Butyl-4,4-dimethyl-3-(nitrosothio)pentanenitrile (36). A solution of **35** (200 mg, 1 mmol) in dichloromethane (5 mL) was treated with *tert*-butyl nitrite (160 μL, 123 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to give **36** (210 mg, 92%). Mp 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 2H), 1.36 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.5, 73.1, 43.1, 30.3, 24.3. LRMS (APIMS) *m/z* 246 (MNH_4^+).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.019.

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