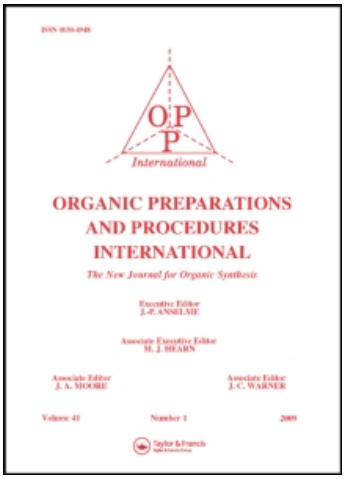

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PREPARATION OF OPTICALLY ACTIVE NEW MERCAPTO CHIRAL AUXILIARIES DERIVED FROM CAMPHOR

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PREPARATION OF OPTICALLY ACTIVE NEW MERCAPTO CHIRAL AUXILIARIES DERIVED FROM CAMPHOR

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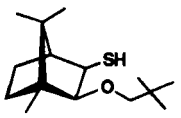
Asymmetric synthesis has gained increasing importance for the acquisition of optically active compounds in recent years.[1] Therefore, the developments of new chiral auxiliary is of a great importance in the field of asymmetric synthesis.[2] Among many successful cases, the use of sulfur-containing chiral sources, has led to remarkable results.[7] (e. g. chiral sulfide[3], sulfoxide[4,5] and sulfones[4,6]) Herein, we report three new chiral thiols **1-3** which have the potential to be good chiral auxiliaries, namely highly distinctive diastereotopic faces, and which can be efficiently prepared from camphor.[8]



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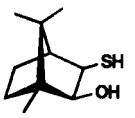

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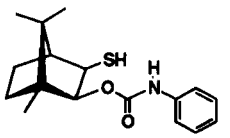
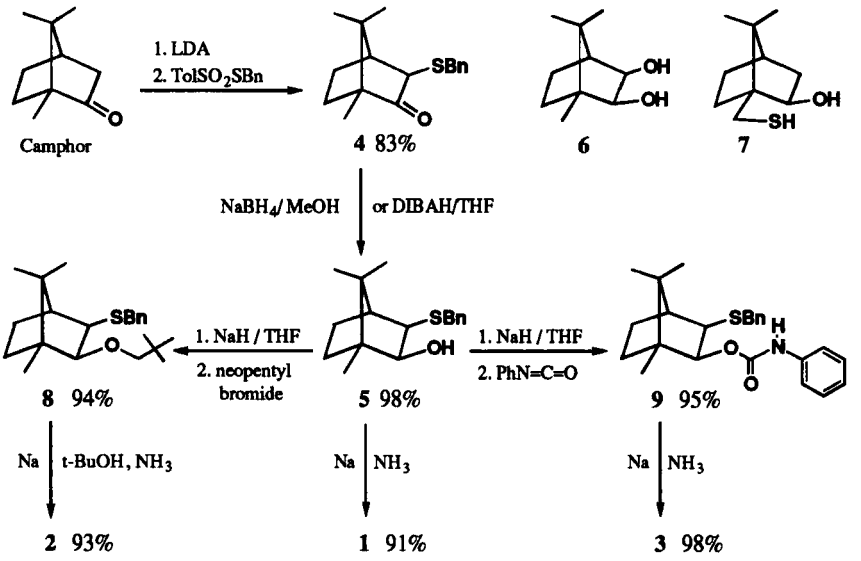


3

The synthesis begins with a modified literature procedure[9] (+)Camphor was first *exo*-sulfenylated at 3-position with LDA and benzylthiotosylate to afford 81% yield of ketone **4**, which could be stereoselectively reduced by sodium borohydride in anhydrous methanol to give *exo*-alcohol **5** in 98% yield,[10] although the reduction could also be carried out with DIBAH in excellent yield (92%),[9] the former method is much more economical for preparative scale reactions. Nevertheless, thiol **1** was obtained in 91% yield by debenzylation of alcohol **5** with sodium in liquid ammonia.[11] Compared to its diol analog **6**,[12] compound **1** bears two distinct different nucleophiles, the 3-mercapto and 2-hydroxy groups, a fast which allows selective reaction on either site. Thus, it can serve as either a mercapto or a hydroxy type chiral auxiliary. In fact, several applications of thiol **1** have been reported by us recently.[13-15]

In order to prepare the other two hydroxy protected thiol **2** and **3**, alcohol **5** was treated with sodium hydride followed by three equivalents of neopentyl bromide in refluxing N-methyl-2-pyrrolidinone for 10 hrs to give neopentyl ether **8** in 94% yield.[16] Subsequent



debenzylation of compound **8** with sodium in liquid ammonia[17] in the presence of four equivalents of *t*-butanol yielded 93% of the desired thiol **2** (93%)[18]. On the other hand, treatment of alcohol **5** with sodium hydride followed by 1.2 equivalent of phenyl isocyanate in refluxing pyridine generated 95% yield of the carbamate **9**.[19] Finally, removal of benzyl protecting group with sodium in liquid ammonia afforded thiol **3**[20] in 98% yield. In comparison with their analogs derived from thiol **7**,[21] both thiol **2** and **3** offer better diastereotopic shielding faces due to the rigid relationship between the two *exo*-oriented 2,3-functionalities.

The three new mercapto chiral auxiliaries have been successful utilized in the asymmetric reduction of α-sulfinylketone.[13] Further application of these optically pure compounds in various synthetic reactions, such as Diels-Alder reaction[14] and diastereoselective addition to sulfenimines[15], will be reported in the near future.

EXPERIMENTAL SECTION

Melting points were determined with a Buchi 535 digital melting point apparatus and are uncorrected. Optical rotations were recorded on a Jusco polarimeter using 0.5dm cell at specific temperatures. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer with chemical shifts (δ) given in ppm from internal TMS. Infrared spectra were taken on a Hitachi 270-30 IR spectrophotometer. High resolution mass spectra were recorded on an Jeol Jms-HX110. Microanalysis were performed by NSC South Instrumental Center of ROC on a Heraeus CHN-O-Rapid and a Tacussel Coulomax instruments.

(1R,3R)-3-(Benzylthio)-1,7,7-trimethylbicyclo[2,2,1]heptan-2-one (4), {or (1R,3R)-3-(Benzylthio)camphor (4)}.- To a solution of 20.7 mL diisopropylamine (14.9 g, 147.5 mmol) in 500 mL of THF was added 1.2M n-butyllithium in hexane (122.0 mL, 146.4 mmol) at -20°. The mixture was stirred for 10 min and camphor (21.1 g, 138.7 mmol) in 150 mL of THF was

added at -78°. This cold solution was stirred for 1 hr followed by addition of a mixture of benzylthiotosylate (44.3 g, 159.2 mmol)[22] and 23.0 mL hexamethylphosphoramide (25.9 g, 144.5 mmol)[23] in 150 mL of THF at such a rate that the reaction temperature was kept below -78°, and stirring was continue for another 2.5 hrs, after completion of addition. To the resulting mixture was added 250 mL of saturated aqueous ammonium chloride in the cold followed by extraction with three 300 mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellowish solid which was recrystallized from hexane-ether mixture to give 23.2 g of exothiotosylate **4** as a white crystalline solid. The filtrate was concentrated and the residual oil was purified through 400 g of silica gel 60 by elution with 1:30 ethyl acetate-hexane to yield 8.4 g of the desired exothiotosylate **4** as a white solid (total yield 83%), mp. 72-73°. $[\alpha]_D^{20}$ = +132.6° (*c* 3.0, acetone), lit.[9] $[\alpha]_D^{25}$ = +126.6° (*c* 3.0, acetone). IR ($CHCl_3$): 2980, 1740, 1215, 1030cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.89 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.15-1.28 (m, 1H), 1.35-1.48 (m, 1H), 1.52-1.68 (m, 1H), 1.88-2.00 (m, 1H), 2.74 (s, 1H, CHS), 3.93 (d, *J* = 12.9Hz, $PhCH_2$), 4.02 (d, *J* = 12.9Hz, $PhCH_2$), 7.20-7.38 (m, 5H, ArH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 9.38, 19.83, 21.61, 28.46, 29.10, 38.45, 46.57, 50.29, 52.60, 58.07, 127.18, 128.53, 129.10, 137.91.

Anal. Calcd for $C_{17}H_{22}OS$: C, 74.41; H, 8.08; S, 11.68. Found: C, 74.35; H, 8.12; S, 11.62

(1R,2S,3R)-3-(Benzylthio)-1,7,7-trimethylbicyclo[2,2,1]heptan-2-ol (5), {or (1R,2S,3R)-3-(Benzylthio)camphanol (5)}.- To a solution of ketone **4** (2.10 g, 7.66 mmol) in 120mL of anhydrous methanol was added 1.20 g (31.70 mmol) of sodium borohydride in one portion at -30°. The reaction was allowed to stirred at -25° for 24 hours then diluted with 100 mL of diethyl ether. The resulting mixture was poured into 100 mL of water and extracted with three portions of 200 mL of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil which was chromatographed through 80 g of silica gel 60 by elution with 1:30 ethyl acetate-hexane to give 2.08 g (98%) of alcohol **5** as a colorless oil. $[\alpha]_D^{20}$ = -8.91° (*c* 2.18, acetone), lit.[9] $[\alpha]_D^{25}$ = -8.90° (*c* 3.0, acetone): IR ($CHCl_3$): 3430 (br), 2960, 1235, 1070; ^{1}H NMR (300MHz, $CDCl_3$): δ 0.75 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.00-1.08 (m, 1H), 1.38-1.50 (m, 1H), 1.65-2.00 (m 2H), 2.67 (d, *J* = 4.2Hz, 1H, OH), 2.93 (d, *J* = 7.8Hz, 1H, CHS), 3.47 (dd, *J* = 7.8, 4.2Hz, 1H, C<u>H</u>OH), 3.69 (s, 2H, $PhCH_2$), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 11.62, 21.31, 21.35, 29.02, 33.14, 39.15, 46.70, 49.62, 53.02, 56.85, 78.74, 127.27, 128.69, 128.80, 138.19.

Anal. Calcd for $C_{17}H_{24}OS$: C, 73.86; H, 8.75; S, 11.60, Found: C, 73.95; H, 8.82; S, 11.55

(1R,2S,3R)-3-(Mercapto)-1,7,7-trimethylbicyclo[2,2,1]heptan-2-ol (1), {or (1R,2S,3R)-3-(Mercapto)camphanol (1)}.- A solution of compound **5** (4.20 g, 15.2 mmol) in 50 mL of THF was added slowly to a well stirred solution of sodium (1.75 g, 76.1 mmol) in 100 mL of liquid ammonia at -78° (bath temperature). The resulted blue solution was stirred for 10 min then 50 mL of methanol was added followed by 100 mL of aqueous saturated ammonium

chloride. The reaction mixture was allowed to reach the ambient temperature, the aqueous layer was seperated and extracted with three 200 mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellowish oil. The crude product was purified through 120 g of silica gel 60 by elution with 1:20 ethyl acetate-hexane to give 2.57 g (91%) of the desired thiol **1** as a crystalline solid, mp. 131-132°. $[\alpha]_D^{20}$ = +5.09° (*c* 1.18, $CHCl_3$): IR ($CHCl_3$): 3465 (br), 3032, 1198, 1070; ^{1}H NMR (300MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.00-1.15 (m, 1H), 1.40-1.55 (m, 1H), 1.70 (d, *J* = 9.6Hz, 1H, SH), 1.70-1.84 (m, 2H), 2.55 (br s, 1H, OH), 3.26 (dd, *J* = 9.6, 7.2Hz, 1H, CHS), 3.56 (d, *J* = 7.2Hz, 1H, C<u>H</u>OH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 11.72, 21.37, 21.60, 29.00, 33.27, 47.21, 48.42, 49.67, 54.25, 79.40.

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.47; H, 9.74; S, 17.21. Found: C, 64.42; H, 9.74; S, 17.23

(1R,2S,3R)-3-(Benzylthio)-2-neopentoxy-1,7,7-trimethylbicyclo[2,2,1]heptane (8).- To a solution of oil-free sodium hydride (2.70 g, 112.5 mmol) in 20 mL of N-methylpyrrolidinone was added alcohol **5** (9.50 g, 34.4 mmol) in 20 mL of N-methylpyrrolidinone at ambient terperature. The mixture was heated to 130° then neat neopentyl bromide (15.50 g, 102.6 mmol) was slowly added, and stirring was continued for another 10 hours. The resulting mixture was poured into 20 mL of aqueous saturated ammonium chloride, and washed with 2N aqueous hydrochloric acid (3 x 30 mL). The washes were extracted with three 30 mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. The crude product was chromatographed through 300 g of silica gel 60 by elution with 1:30 ethyl acetate-hexane to give 11.13 g (94%) of neopentyl ether **8** as a colorless oil. $[\alpha]_D^{20}$ = -91.53° (*c* 3.03, acetone): IR ($CHCl_3$): 2960, 1206, 1106; ^{1}H NMR (300MHz, $CDCl_3$): δ 0.76 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.80-1.00 (m, 1H), 0.92 (s, 9H, CH_3), 1.19 (s, 3H, CH_3), 1.38-1.48 (m, 1H), 1.62-1.73 (m, 1H), 1.74 (d, *J* = 3.9Hz, 1H, CH), 2.81 (d, *J* = 7.8Hz, 1H, SCH), 2.91 (d, *J* = 7.8Hz, 1H, OCH_2), 3.17 (d, *J* = 7.8Hz, 1H, OCH), 3.38 (d, *J* = 7.8Hz, 1H, OCH_2), 3.67 (d, *J* = 13.2Hz, 1H, SCH_2), 3.72 (d, *J* = 13.2Hz, 1H, SCH_2), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 12.02, 21.19, 21.48, 26.98, 28.41, 32.78, 33.48, 37.37, 47.11, 50.48, 51.03, 55.11, 83.72, 89.07, 126.64, 128.28, 128.96, 139.38.

Anal. Calcd for $C_{22}H_{34}OS$: C, 76.24; H, 9.89; S, 9.25. Found: C, 76.12; H, 9.97; S, 9.18

(1R,2S,3R)-3-Mercapto-2-neopentoxy-1,7,7-trimethylbicyclo[2,2,1]heptane (2).- A mixture of compound **8** (6.00 g, 17.4 mmol) and t-butanol (4.85 g, 6.5 mmol) in 60 mL of THF was added slowly to a well stirred solution of sodium (2.50 g, 108.7 mmol) in 60 mL of liquid ammonia at -84° bath temperature. The blue solution was stirred for 30 min then added 30 mL of methanol followed by 100 mL of saturated aqueous ammonium chloride. The reaction pot was allowed to reach the ambient temperature, and the resulting mixture was extracted with three 300 mL portions of hexane. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified through

200 g of silica gel 60 by elution with 1:20 ethyl acetate-hexane to give 4.13 g (93%) of the desired thiol **2** as a colorless oil. $[\alpha]_D^{20}$ = -70.35° (*c* 1.98, $CHCl_3$): IR ($CHCl_3$): 3028, 2960, 1230, 1106, 1000; ^1H NMR (300MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.80-1.00 (m, 1H), 0.95 (s, 9H, CH_3), 1.04 (d, *J* = 8.4Hz, 1H, SH), 1.20 (s, 3H, CH_3), 1.40-1.53 (m, 1H), 1.63-1.76 (m, 1H), 1.71 (d, *J* = 2.4Hz, 1H, CH), 1.85 (dt, *J* = 7.8, 5.1Hz, 1H, CH_2), 2.97 (d, *J* = 7.8Hz, 1H, OCH_2), 3.17-3.23 (m, 2H, SCH and OCH), 3.46 (d, *J* = 7.8Hz, 1H, OCH_2); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 12.19, 21.44, 21.62, 27.02, 28.69, 32.83, 33.50, 47.29, 47.88, 50.61, 55.35, 83.84, 88.73.

Anal. Calcd for $C_{15}H_{28}OS$: C, 70.25; H, 11.00; S, 12.50. Found: C, 70.42; H, 11.07; S, 12.58

(1R,2S,3R)-3-(Benzylthio)-2-(N-phenylcarbamoyl)oxo-1,7,7-trimethylbicyclo[2,2,1]heptane (9).- To a solution of alcohol **5** (1.22 g, 4.42 mmol) in 2 mL of pyridine was added phenyl isocyanate (0.50g, 4.19 mmol) at ambient terperature. The resulting mixture was heated to reflux for 1 hour, cooled to at ambient terperature, and then added 20 mL of water, and washed with 2N aqueous hydrochloric acid (3 X 30 mL). The washes were extracted with three 30 mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a golden oil. The crude product was purified through 60g of silica gel 60 by elution with 1:10 ethyl acetate-hexane to give 1.66 g (95%) of carbamate **9** as a pale yellow viscous oil, mp. 96-97°. $[\alpha]_D^{25}$ = -49.53° (*c* 1.18, acetone): IR ($CHCl_3$): 3440, 2956, 1732, 1600, 1520, 1204, 1090; ^1H NMR (300MHz, $CDCl_3$): δ 0.79 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.80-1.25 (m, 2H), 1.49-1.75 (m, 2H), 1.79 (d, *J* = 4.2Hz, 1H, CH), 2.95 (d, *J* = 7.5Hz, 1H, CHS), 3.73 (s, 2H, $PhCH_2$), 4.86 (d, *J* = 7.5Hz, 1H, CHOC), 6.68 (br s, 1H, NH), 7.07 (t, *J* = 8.1Hz, 1H, ArH), 7.10-7.38 (m, 7H, ArH), 7.44 (d, *J* = 8.1Hz, 2H, ArH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 11.56, 20.90, 21.28, 28.55, 33.27, 39.13, 47.51, 49.39, 53.09, 54.59, 82.08, 118.80, 123.36, 126.87, 128.37, 128.99, 138.09, 138.27, 153.39.

Exact Mass Calcd for $C_{24}H_{29}NO_2S$: 395.1920. Found: 395.1922.

Anal. Calcd for $C_{24}H_{29}NO_2S$: C, 72.87; H, 7.39; N, 3.54; S, 8.11

Found: C, 72.98; H, 7.44; N, 3.68; S, 8.08

(1R,2S,3R)-3-(Mercapto)-2-(N-phenylcarbamoyl)oxo-1,7,7-trimethylbicyclo[2,2,1]heptane (3).- Compound **9** (3.50 g, 8.9 mmol) in anhydrous ether was debenzylated with sodium (1.35 g, 58.8 mmol) in liquid ammonia in a similar manner as compound **5**. The crude product was purified through 80 g of silica gel 60 by elution with 1:20 ethyl acetate-hexane to give 2.66 g (98%) of the desired thiol **3** as a crystalline solid, mp.106-107°. $[\alpha]_D^{25}$ = +86.88° (*c* 1.08, $CHCl_3$), IR ($CHCl_3$): 3440, 2948, 1734, 1600, 1524, 1428, 1206, 1066; ^1H NMR (300MHz, $CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.15-1.30 (m, 2H), 1.50-1.62 (m, 1H), 1.70-1.84 (m, 2H), 1.88 (d, *J* = 8.1Hz, 1H, SH), 3.36 (dd, *J* = 8.1, 7.5Hz, 1H, CHS), 4.77 (d, *J* = 7.5Hz, 1H, CHO), 6.70 (br s, 1H, NH), 7.06 (t, *J* = 7.8Hz, 1H, ArH), 7.31 (t, *J* = 7.8Hz, 2H, ArH), 7.42 (d, *J* = 7.8Hz, 2H, ArH); ^{13}C NMR (75.4MHz, $CDCl_3$): δ 11.72,

21.15, 21.40, 28.63, 33.31, 46.26, 47.80, 49.46, 54.43, 82.34, 118.91, 123.49, 128.99, 137.92, 153.307.

Exact Mass Calcd for $C_{17}H_{23}NO_2S$: 305.1450. Found: 305.1449.

Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59; S, 10.50

Found: C, 66.57; H, 7.68; N, 4.58; S; 10.64

Acknowledgement.- We thank The National Science Council of Republic of China for financial support under Grant No. NSC82-0208-M005-019, and to Professor Guy Solladie for very helpful discussions.

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23. **CAUTION: HMPA is reported to be a potential carcinogen!**

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