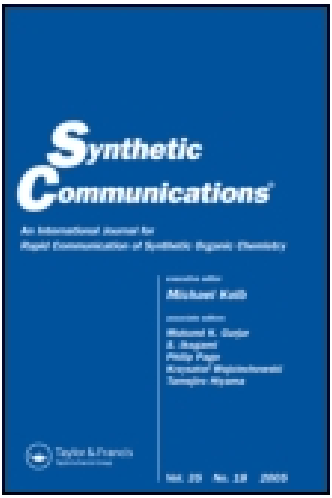

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Synthesis of Dithioacetals and Oxathioacetals with Chiral Auxiliaries

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Synthesis of Dithioacetals and Oxathioacetals with Chiral Auxiliaries

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ABSTRACT

One-pot synthesis of dithioacetals as well as an efficient method for oxathioacetal is reported. Additionally, some chiral auxiliaries were used to synthesize enantiomerically pure dithioacetals and oxathioacetals.

Key Words: Dithioacetals; Oxathioacetals; Chiral auxiliaries.

INTRODUCTION

We report herein one-pot reaction for the synthesis of dithioacetals as well as an efficient and high-yield method for the preparation of oxathioacetals.

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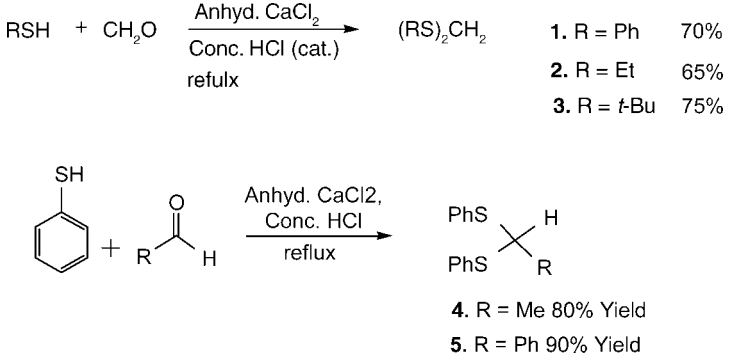
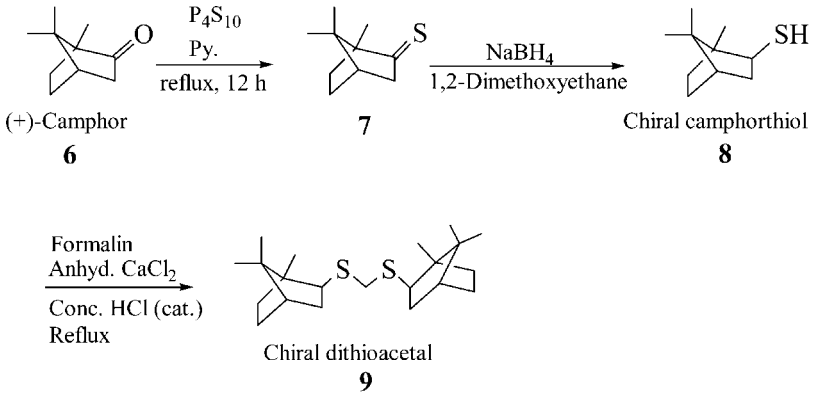
These methods are also efficiently used for the synthesis of chiral dithioacetals and oxathioacetals. Though various methods for the synthesis of dithioacetals and oxathioacetals are documented in the literature,[1] however, they often vary in protocols and yields require optimization.[2–6] The use of dithioacetals as chemical equivalent of formyl anion synthon is very common in organic synthesis. 1,3-Dithiane,[7] for example, is commercially available and can be readily metalated. Metalation of oxathioacetals is also known in the literature.[8] Thus, dithioacetals and oxathioacetals with tagged chiral auxiliaries can be used for asymmetric induction via metallation followed by alkylation.

RESULTS AND DISCUSSION

In this article, we describe a general one-pot synthesis of dithioacetals, using commercially available, inexpensive reagents and simple reaction conditions, e.g., the synthesis of *bis*(phenylthio)methane (**1**) involves refluxing a mixture of thiophenol, formalin, anhydrous calcium chloride and catalytic amount of concentrated hydrochloric acid and then allowed the reaction mixture to stand overnight at room temperature. This method is economical and fairly convenient than the one reported by Corey and Seebach.[5] This method can also be extended to synthesize C-alkyl or -aryl substituted dithioacetals. Compounds **4** and **5** were synthesized in high yields using acetaldehyde and benzaldehyde instead of formalin, respectively (Sch. 1). Chiral dithioacetal **9** was synthesized by employing the same method from chiral camphorthiol **8**, which was prepared by reducing thiocamphor **7**, obtained by reacting naturally occurring (+)-camphor **6** with phosphorous pentasulfide (Sch. 2).[9]



Scheme 1.



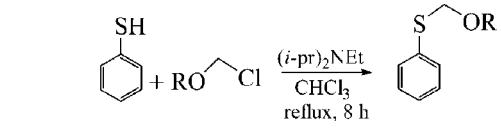
Scheme 2.

An efficient and general method has also been developed to synthesize oxathioacetals. In this method, 1 equiv. of a thiol was allowed to react with 5 equiv. of diisopropylethylamine and alkoxymethylchloride in refluxing chloroform for 8 hr under nitrogen. Alkoxymethylchloride was prepared starting from the corresponding alcohol using the previously described method.[10,11] This methodology was carried out to prepare chiral oxathioacetals as given in Sch. 3. An advantage of this methodology is that both the alcohol and the thiol components of the oxathioacetals can be varied at will using a chiral alcohol, such as (−)-menthol, and/or a thiol, such as N-protected methyl ester of L-cysteine (Sch. 4). Similarly, the chloromethyl methyl sulfide can also be used to access corresponding dithioacetals **20** and **21** as shown in Sch. 5.

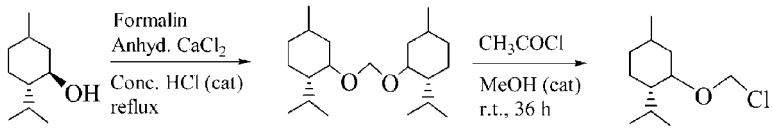
Ethyl vinyl ether can also be used for the synthesis of oxathioacetals under mild conditions. The thiol protected L-cysteine also afforded the corresponding oxathioacetal by this method in quantitative yield. ^{1}H NMR spectrum of the product indicated that it is (1 : 1) diastereoisomeric mixture, which resulted from the generation of a new chiral center. This method can also be viewed as a protection strategy of a mercaptan by an ethoxyethyl group, which can also be removed under mild conditions without any detectable racemization. The ethoxyethyl group can be a useful protecting group for L-cysteine in peptide synthesis (Sch. 6).

CONCLUSION

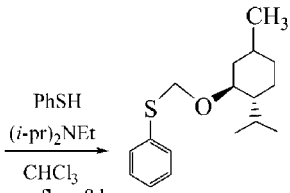
We developed a general methodology for convenient synthesis of dithioacetals as well as oxathioacetals and this strategy has been extended for the



10. R = Me 85% Yield
11. R = *n*-Bu 82% Yield



12 (–)Menthol **13** Chiral 70% **14** 90% Yield



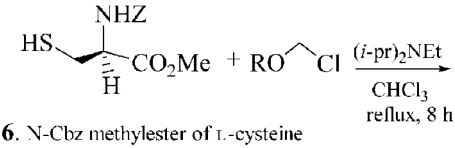
15 90%

Scheme 3.

high yield synthesis of some chiral dithioacetals and oxathioacetals. The studies related to chiral inductions proceeding from metallation protocols of these mono- and di-thioacetals as well as the use of ethyl vinyl ether appeared as a new method for the protection of thiol functionality with particular importance in L-cysteine.

EXPERIMENTAL

Chloroform and methylene chloride were dried by refluxing over P_2O_5 followed by distillation. Thin layer chromatography (TLC) was performed on precoated silica gel plates (0.25 mm, Merck). Column chromatography was performed on Merck silica gel having mesh size (0.063–0.200 mm, Merck). Melting points were reported for all crystalline products and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on GE QE 300 and 400 spectrometer (Oxford magnet). EIMS spectroscopic analysis was performed on a VG-70SE mass spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter.



16. N-Cbz methylester of L-cysteine

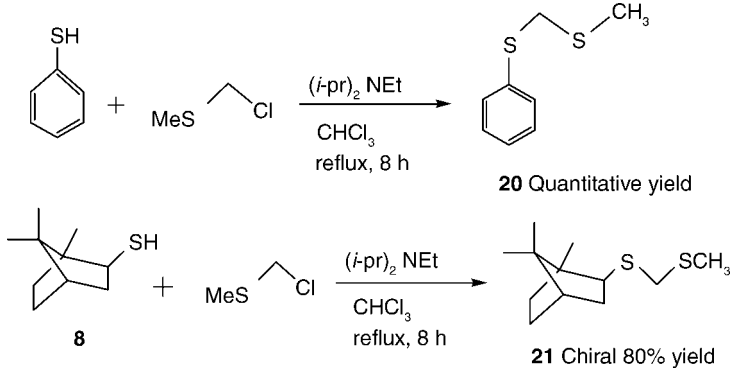
17. R = Me 75% Yield
18. R = *n*-Bu 72% Yield
19. R = menthyl 80% Yield

Scheme 4.

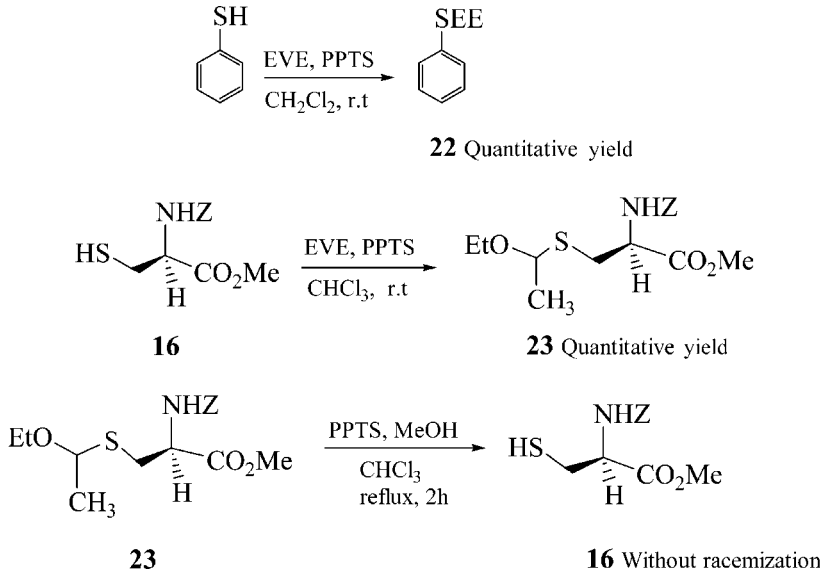
Synthesis of Dithioacetals 1, 2, and 3

Thiol 23 mL (224 mmol) was taken in a round bottom flask (100 mL), 4.4 g (40 mmol) of anhydrous $CaCl_2$, and 100 μL of conc. HCl were added, subsequently. The flask was fitted with double surface condenser and cooled to 0°C in ice bath. Formalin (37% aqueous solution) (4.3 mL) was added dropwise into the reaction flask. After complete addition of formalin the reaction mixture was refluxed vigorously for 5–10 min and was allowed to stand at room temperature over night. The reaction mixture was diluted with distilled water (ca. 20 mL) and extracted with ether (20 mL × 3). Combined organic layer was washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was column chromatographed on silica gel using 3% ethylacetate in *n*-hexane as an eluent to afford the product.

***bis*(Phenylthio)methane (1).** White solid m.p. 39°C (Lit.[5] m.p 39.5–40.5°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–7.74 (m, 10H), 4.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8 (C-1/C-1′), 129.9 (C-2, C-6/C-2′, C-6′), 129.1 (C-3, C-5/C-3′, C-5′), 124.7 (C-4/C-4′), 124.7 (CH), 34.6 (CH_2);



Scheme 5.



Scheme 6.

EIMS (m/z, %rel. abund.): 232 (M^+, 20), 123 (100); Anal. Calcd. for $C_{13}H_{12}S_2$: C, 67.20; H, 5.21. Found: C, 67.22; H, 5.26.

***bis*(Ethylthio)methane (2).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 2H), 2.65 (q, $J = 7.4$ Hz, 4H), 1.26 (t, $J = 7.4$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.7 (CH_2), 25.8 ($2CH_2$), 12.8 (CH_3); EIMS (m/z, %rel. abund.): 136.9 (M^+, 8), 121 (13), 106 (22), 74 (39), 42 (100), 32 (18); Anal. Calcd. for $C_5H_{12}S_2$: C, 44.07; H, 8.88. Found: C, 44.10; H, 8.86.

***bis*(*t*-Butylthio)methane (3).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 2H), 1.36 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.8 (C-1/C-1′), 31.38 ($6CH_3$), 27.8 (SCH_2); EIMS (m/z, %rel. abund.): 192 (M^+, 100), 103 (67); Anal. Calcd. for $C_9H_{20}S_2$: C, 56.19; H, 10.48. Found: C, 56.29; H, 10.42.

1,1-*bis*(Phenylthio)ethane (4) and *bis*(Phenylthio)phenylmethane (5)

These compounds were prepared by the same procedure as described for compounds **1**, **2**, and **3** by using acetaldehyde and benzaldehyde, respectively, instead of formalin.

Compound 4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.29 (m, 10H), 4.53 (q, $J = 6.9$ Hz, 1H), 1.61 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 132.3 (C-1/C-1′), 129.6 (C-3, C-5/C-3′, C-5′), 128.9 (C-2, 6/C-2′, C-6′), 126.7 (C-4/C-4″), 50.8 (CH), 21.6 (CH_3); EIMS (m/z, %rel. abund.): 246 (M^+, 6), 169 (54), 231 (29); Anal. Calcd. for $C_{14}H_{14}S_2$: C, 68.24; H, 5.73. Found: C, 68.20; H, 5.75.

Compound 5. Pale yellow solid m.p. 51°C (lit.[6] 52–53°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.35 (m, 6H), 7.38–7.21 (m, 9H), 5.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8 (C-1″, arom.), 132.5 (C-1/C-1′), 128.6 (C-2, C-6/C-2′, C-6′), 128.0 (C-2″/C-6″), 128.6 (CH), 128.6 (CH), 127.4 (C-C-3″/C-5″), 126.5 (C-4/C-4′), 125.4 (C-4″); EIMS (m/z, %rel. abund.): 308 (M^+, 9), 231 (69), 154 (76), 77 (100), 78 (31); Anal. Calcd. for $C_{19}H_{16}S_2$: C, 73.98; H, 5.23. Found: C, 73.90; H, 5.28.

Preparation of Chiral Thiocamphor (7)

(+)-Camphor **(6)** (15.2 g, 99.8 mmol) was dissolved in dried and distilled pyridine (100 mL) and the solution was set to gentle reflux with stirring. Phosphorouspentasulfide (12 g, 27 mmol) was added in portions to the above solution. The reddish orange suspension was left refluxing with stirring for 12 hr. Pyridine (80 mL) was then removed by distillation. Cold residue was diluted with petroleum ether (40–60°C) (150 mL) and was washed with 2 N hydrochloric acid (50 mL × 3), distilled water, brine, and dried ($MgSO_4$). Solvent was evaporated under reduced pressure to afford orange-red solid (13.5 g, 80% yield) which was pure enough (TLC analysis) and was used in the next step without purification. Small quantity of this product was passed through a silica gel column using *n*-hexane as an eluent for spectral analysis and measurement of optical rotation.

Compound 7. M.p. 137°C (Aldrich Catalog Handbook of Chemicals, 1994; 136–138°C); $[\alpha]_D^{25} = -2.3$ ($c = 0.1$ $CHCl_3$). IR ($CHCl_3$): υ 2960, 1450, 1410, 1390, 1360, 1300, 1260, 1210, 1130, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81–2.74 (m, 1H), 2.40 (d, $J = 21$ Hz, 1H), 2.16 (t, $J = 4.4$ Hz, 1H), 2.05–1.94 (m, 1H), 1.79–1.71 (m, 1H), 1.41–1.22 (m, 2H), 1.09 (s, 3H), 1.03 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 267.0 (C-2), 69.3 (C-1), 55.5 (C-3), 48.9 (C-4), 145.1 (C-5), 33.9 (C-6), 26.2 (C-5), 21.7 (C-8), 19.8 (C-9), 13.1 (C-10); EIMS (m/z, %rel. abund.): 168 (M^+, 100), 153, 125, 113, 93, 85, 79, 69; HRMS for $C_{10}H_{16}S$ (after recrystallization): 168.1864, found: 168.1802; Anal. Calcd. for $C_{10}H_{16}S$: C, 71.36; H, 9.58. Found: C, 71.40; H, 9.56.

Preparation of Chiral Camphorthiol (8)

Thiocamphor crude (6 g, 35.7 mmol) was dissolved in 1,2-dimethoxyethane (25 mL) and stirred at room temperature. Sodium borohydride

(340 mg, 8.93 mmol) was added to above solution and stirred at room temperature over night. The reaction mixture was quenched with distilled water along with a few drops of 0.1 N solution of hydrochloric acid. The reaction mixture was extracted with ether (50 mL × 2). Combined organic layer was washed with distilled water, brine, and dried over $MgSO_4$. Solvents were evaporated under reduced pressure and the residue was chromatographed on silica gel column using *n*-hexane as an eluent to afford white crystalline solid (5.6 g, 92% yield).

Compound 8. M.p. 220°C, $[\alpha]_D^{25} = +5.9$ ($c = 0.6$ $CHCl_3$); IR ($CHCl_3$): υ 2950, 2890, 2720, 2590, 1500, 1390, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 2.94–2.84 (m, 1H), 2.02–1.94 (m, 2H), 1.73–1.60 (m, 3H), 1.28–1.11 (m, 2H), 1.02 (s, 3H), 0.89 (s, 3H), 0.805 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.8 (C), 46.3 (C), 42.9 (CH), 44.2 (CH), 35.2 (CH_2), 31.6 (CH_2), 27.5 (CH_2), 20.8 (CH_3), 18.7 (CH_3), 13.7 (CH_3); EIMS (*m*/*z*, %rel. abund.): 170 (M^+, 15%), 155, 137, 121, 107, 93 (100), 81; exact mass calcd. for $C_{10}H_{18}S$: 170.2022, found: 170.1997; Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.46; H, 10.68.

Chiral *bis*(Thiocamphor)methane (9)

This compound was prepared by using the method described for the preparation of compounds **1**, **2**, and **3** to afford compound **9** as white crystalline solid.

Compound 9. M.p. 168°C; IR ($CHCl_3$): υ 2945, 1640, 1260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.15 (s, 2H), 2.94–2.89 (m, 2H), 1.93–1.82 (m, 3H), 1.70–1.63 (m, 5H), 1.27–1.13 (m, 4H), 0.98 (s, 6H), 0.95 (s, 6H), 0.94–0.84 (m, 2H), 0.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2 (C-1/C-1′), 49.4 (C-2/C-2′), 45.3 (C-7/C-7′), 42.9 (C-4/4′), 35.5 (C-3/3′), 33.6 (CH_2), 33.0 (C-7/7′), 28.0 (C-8/8′), 23.4 ($2CH_3$), 21.1 ($2CH_3$), 13.6 ($2CH_3$); EIMS (*m*/*z*, %rel. abund.): 352 (M^+, 15); Anal. Calcd. for $C_{21}H_{36}S_2$: C, 71.52; H, 10.29. Found: C, 71.50; H, 10.30.

Synthesis of Oxathioacetals

Thiol (1 mmol) was dissolved in dried and distilled chloroform (10 mL) under static nitrogen atmosphere. It was set to gentle reflux with stirring. Diisopropylethylamine (5 mmol) and alkoxymethylchloride (5 mmol) are added into the refluxing solution subsequently. The reaction mixture was allowed to reflux for 8 hr. Reaction mixture was cooled, diluted with chloroform (ca. 10 mL) and was washed with distilled water, brine, and dried

($MgSO_4$). Solvent was removed under reduced pressure and residue was purified on a silica gel column.

Methoxymethylphenylsulfide (10). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.44 (m, 2H), 7.31–7.17 (m, 3H), 4.95 (s, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1 (C-3/C-5), 134.2 (C-1), 129.0 (C-4), 123.3 (C-2/C-6), 75.6 (CH_2), 56.0 (CH_3); EIMS (m/z, %rel. abund.): 154 (M^+, 42), 123 (59), 109 (19), 77 (100), 51 (14). Anal. Calcd. for $C_8H_{10}OS$: C, 71.52; H, 10.29. Found: C, 71.49; H, 10.28.

***n*-Butoxymethylphenylsulphide (11).** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.47 (m, 2H), 7.32–7.18 (m, 3H), 5.0 (s, 2H), 3.62 (t, $J = 6.5$ Hz, 2H), 1.62–1.55 (m, 2H), 1.43–1.35 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (C-3/C-5), 137.0 (C-1), 129.1 (C-4), 123.2 (C-2/C-6), 75.4 (SCH_2), 72.0 (OC-1′), 29.2 (C-2′), 18.1 (C-3′), 12.9 (C-4′); EIMS (m/z, %rel. abund.): 196 (M^+, 29), 181 (22), 139 (53), 123 (62), 77 (100), 62 (49); Anal. Calcd. for $C_{11}H_{16}OS$: C, 67.30; H, 8.22. Found: C, 67.31; H, 8.21.

Preparation of Acetal of (−)-Menthol (13).

(−)-Menthol **(12)** (39.32 g, 25 mmol) was placed in a round bottom flask and anhydrous $CaCl_2$ (5.6 g, 50 mmol), concentrated hydrochloric acid (140 μL) were added subsequently. The reaction flask fitted with a reflux condenser, was cooled in an ice bath. Formalin (37 % aqueous solution, 10 mL) was added dropwise into the flask. After complete addition of formalin the reaction mixture was vigorously refluxed for 5–10 min and was allowed to stand at room temperature for 8 hr. The reaction mixture was diluted with water (50 mL) and was extracted with ether (50 mL × 3). Combined organic layer was washed with water, brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure and residue was chromatographed on a silica gel column using 3% ethylacetate in *n*-hexane as an eluent to afford white crystalline product **13**.

Compound 13. M.p. 58°C $[\alpha]_D^{25} = -6.4$ ($c = 0.2$ $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (s, 2H), 3.25–3.16 (m, 2H), 2.18–2.06 (m, 4H), 1.61–0.75 (m, 14H), 0.852 (d, $J = 7$ Hz, 6H), 0.841 (d, $J = 7$ Hz, 6H), 0.706 (d, $J = 7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.29 (OCH_2), 79.1 (C-1/C-1′), 48.6 (C-2/C-2′), 42.4 (C-6/C-6′), 34.4 (C-4/C-4′), 31.6 (2C), 25.3 (C-5/C-5′), 23.1 (CH_3), 21.2 ($2CH_3$), 16.1 ($2CH_3$); EIMS (m/z, %rel. abund.): 324 (M^+, 31), 309 (13), 294 (18), 266 (7), 238 (22), 186 (56), 170 (19), 156 (100), 140 (68); Anal. Calcd. for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.60; H, 12.54.

Preparation of Menthoxymethylchloride (14).

Compound **13** (16.2 g, 50 mmol) and anhydrous methanol (200 μL) were stirred at room temperature under static nitrogen atmosphere. Freshly distilled acetyl chloride (3.5 mL, 0.048 mol) was then added dropwise with a syringe. The reaction mixture was allowed to stir at room temperature for 36 hr. After 36 hr the compound **14** was ready to be used without any workup.

Menthoxymethyl Phenylsulfide (15), Alkoxymethylthioacetals of N-Protected Methyl Ester of L-Cysteine 17, 18, and 19

These compounds were synthesized by the method described for the preparation of compounds **10** and **11**.

Menthoxymethyl Phenylsulfide (15). Colorless oil; $[\alpha]_D^{25} = -9.2$ ($c = 1.2$ $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, $J = 8$ Hz, 2H), 7.31–7.28 (m, 2H), 7.24–7.19 (m, 1H), 5.16 (d, $J = 11.7$ Hz, 1H), 6.02 (d, $J = 11.7$ Hz, 1H), 3.49–3.41 (m, 1H), 2.15–2.06 (m, 3H), 1.67–1.58 (m, 3H), 0.997–0.947 (m, 3H), 0.906 (d, $J = 6.5$ Hz, 3H), 0.834 (d, $J = 7$ Hz, 3H), 0.688 (d, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.1 (C-3/C-5), 129.2 (C-1), 128.7 (C-4), 126.1 (C-2/C-6), 72.7 (OCH_2), 68.3 (C), 48.2 (C), 39.9 (C), 34.4 (CH_2), 31.4 (CH_2), 25.1 (C), 23.0 (CH_2), 22.3 (CH_3), 21.1 (CH_3), 15.8 (CH_3); EIMS (m/z, %rel. abund.): 278 (M^+, 26), 264 (35), 222 (34), 140 (8), 124 (6), 110 (72), 77 (100), 64 (41), 51 (14); $C_{17}H_{26}OS$: 278 (M^+, 26), 264 (35), 222 (34), 140 (18), 124 (6), 110 (72), 77 (100), 64 (41), 51 (14); Anal. Calcd. for $C_{17}H_{26}OS$: C, 73.33; H, 9.41. Found: C, 73.20; H, 9.54.

Methoxymethylthioacetal of N-Protected Methyl Ester of L-Cysteine (17). Colorless oil; $[\alpha]_D^{25} = +1.34$ ($c = 0.752$ $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 6.15 (bd, $J = 8$ Hz, 1H), 5.11 (s, 2H), 4.65–4.51 (m, 3H), 3.74 (s, 3H), 3.31 (s, 3H), 3.14 (dd, $J = 14.4$, $J = 5.3$ Hz, 1H), 3.0 (dd, $J = 14.4$, $J = 5.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (CO), 166.2 (CONH), 132.6 (C-1, arom.), 130.8 (C-4), 128.9 (C-2/C-6), 127.0 (C-3/C-5), 58.5 (OCH_3), 57.0 (CH), 50.8 (CH_3), 32.6 (CH_2S); EIMS (m/z, %rel. abund.): 269 (M^+, 34), 238 (17), 206 (48), 77 (56), 77 (100); Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.40; H, 5.67; N, 5.26.

***n*-Butoxymethlythioacetal of N-Protected Methyl Ester of L-Cysteine (18).** Colorless oil; $[\alpha]_D^{25} = +1.3$ ($c = 1.0$ $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 5H), 6.35 (bd, $J = 8.5$ Hz, 1H), 5.1 (s, 2H), 4.67–4.53 (m, 3H), 3.73 (s, 3H), 3.67–3.55 (m, 1H), 3.38–3.31 (m, 1H), 3.2 (dd, $J = 14.4$, $J = 5.3$ Hz, 1H), 2.95 (dd, $J = 14.4$, $J = 5.3$ Hz, 1H), 1.60–1.56

(m, 2H), 1.41–1.23 (m, 2H), 0.84 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (CO), 166.7 (CONH), 132.8 (C-1, arom.), 130.9 (C-4, arom.), 129.0 (C-3/C-5), 127.1 (C-2/C-6), 72.7 (OCH_2), 56.3 (CH), 50.6 (OCH_3), 34.4 (CH_2S), 31.6 (CH_2), 20.4 (CH_2), 14.1 (CH_3). EIMS (m/z, %rel. abund.): 311 (M^+, 9), 280 (46), 254 (13), 252 (23), 238 (22), 206 (32); Anal. Calcd. for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.33; H, 7.67; N, 3.68.

Menthoxymethylthioacetal of N-Protected Methyl Ester of L-Cysteine (19). White crystalline solid, m.p. 107°C; $[\alpha]_D^{25} = -2.4$ ($c = 0.6$ $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.24 (m, 5H), 6.13 (bd, $J = 8.1$ Hz, 1H), 5.1 (s, 2H), 4.68–4.60 (m, 3H), 3.73 (s, 3H), 3.33–3.24 (m, 1H), 3.13 (dd, $J = 14$, $J = 5.5$ Hz, 1H), 3.0 (dd, $J = 14$, $J = 5.5$ Hz, 1H), 2.14–2.04 (m, 2H), 1.64–1.55 (m, 2H), 1.25–0.817 (m, 5H), 0.88 (d, $J = 7.1$ Hz, 6H), 0.74 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (CO), 167.0 (CONH), 132.8 (C-1, arom.), 130.6 (C-4, arom.), 129.0 (C-2/C-6), 126.9 (C-3/C-5), 75.9 [C-1″, 56.8 (CH), 50.4 (OCH_3), 48.2 (CH, C-2′), 36.0 (CH_2), 34.7 (CH, C-5), 34.0 (CH_2S), 33.8 (CH_2), 28.0 ($CH(CH_3)_2$)], 26.7 (CH_2), 20.6 (CH_3), 18.0 (CH_3), 17.0 (CH_3); EIMS (m/z, %rel. abund.): 393 (M^+, 23), 334 (27), 316 (48), 288 (68), 267 (29), 77 (100); Anal. Calcd. for $C_{21}H_{31}NO_4S$: C, 64.09; H, 7.94; N, 3.56. Found C, 64.15; H, 7.88; N, 3.49.

Preparation of Dithioacetals: Reaction of Thiols with Chloromethyl Methylsulfide

The thiol (1 mmol) was dissolved in anhydrous chloroform (10 mL) and was stirred under static nitrogen atmosphere. Diisopropylethylamine (5 mmol) was added to the above solution and was set to gentle reflux. Chloromethyl methylsulfide (5 mmol) was slowly added into the reaction mixture and was refluxed for 8 hr. Reaction was allowed to cool to room temperature and was diluted with chloroform (10 mL). Organic layer was washed with distilled water, brine, and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography.

Thiomethylthiophenylmethane (20). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.40 (m, 5H), 4.1 (s, 2H), 2.16, (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2 (C-3/C-5), 130.4 (C-2/C-6), 139.6 (C-3/C-5), 124.6 (C-4), 40.0 (CH_2), 18.1 (CH_3); EIMS (m/z, %rel. abund.): 170 (M^+, 29), 155 (51), 123 (79), 109 (81), 77 (100), 64 (31), 51 (16); Anal. Calcd. for $C_8H_{10}S_2$: C, 56.42; H, 5.92. Found: C, 56.50; H, 5.88.

Thiomethylthiocamphormethane (21). Colorless oil; ^{1}H NMR ($CDCl_3$); δ 3.60 (s, 2H), 2.94–2.84 (m, 1H), 2.15 (s, 3H), 1.95–1.57 (m, 3H), 1.26–1.12

(m, 2H), 0.98 (s, 3H), 0.95 (s, 3H), 0.90–0.88 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.7 (C-2), 49.6 (C-1), 45.3 (C-7), 44.0 (C-5), 36.9 (SCH_2), 35.0 (C-6), 33.0 (C-3), 26.6 (C-4), 21.4 (CH_3), 19.4 (CH_3), 14.2 (SCH_3), 12.6 (CH_3); EIMS (m/z, %rel. abund.): 230 (M^+, 16), 216 (43), 184 (58), 170 (66), 138 (100), 123 (12), 93 (44), 79 (24), 65 (8); exact mass calcd. for $C_{12}H_{22}S_2$ 230.274, found 230.264; Anal. Calcd. for $C_{12}H_{22}S_2$: C, 62.55; H, 9.62. Found: C, 62.66; H, 9.57.

Preparation of Ethoxyethylthioacetals

Thiol (1 mmol) was stirred in methylene chloride (20 mL), to this solution few crystals of pyridinium *p*-toluenesulfonate (PPTS) were added. Ethyl vinyl ether (1.5 mmol) was added slowly into the reaction flask and was stirred at room temperature for 1 hr. Reaction was quenched with saturated aqueous solution of sodium bicarbonate. Organic layer was separated, washed with distilled water, brine, and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was chromatographed to afford the pure compound.

Ethoxyethylthiobenzene (22). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H), 7.25–7.23 (m, 3H), 4.8 (q, $J = 6.5$ Hz, 1H), 4.01–3.93 (m, 1H), 3.50–3.42 (m, 2H), 1.48 (d, $J = 6.5$ Hz, 3H) 1.2 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1 (C-1, arom.), 128.8 (C-3/C-5′), 127.3 (C-2/C-6), 125.6 (C-4), 69.4 (CH_2O), 65.3 (OCH_2), 34.0 (SCH_2), 14.2 (CH_3); EIMS (m/z, %rel. abund.): 182 (M^+, 7), 137 (49), 78 (13), 77 (100), 51 (31); Anal. Calcd. for $C_{10}H_{14}O_4S$: C, 65.89; H, 7.74. Found: C, 65.93; H, 7.70.

Ethoxyethylthioacetal of N-Protected Methyl Ester of L-Cysteine (23). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 6.34, 6.05 (brd, $J = 8$ Hz, 1H), 5.1 (s, 2H), 4.66–4.54 (m, 2H), 3.76–3.30 (m, 5H), 3.11–2.9 (m, 2H), 1.5 and 1.46 (d, $J = 6.4$ Hz, 3H), 1.2–1.13 (m, 3H); integration of –NH proton at δ 6.34 and 6.05 and methyl protons at δ 1.5 and 1.46 showed that it was about 1 : 1 mixture of diastreoisomers.

Deprotection of Ethoxyethyl Group in Compound (23)

Ethoxyethylthioacetal of N-protected methyl ester of L-cysteine **(23)** (100 mg) was dissolved in methanol (10 mL) and few crystals of PPTS were added to this solution and was refluxed gently for 2 hr. After workup and purification by silica gel column chromatography N-protected methyl ester of L-cysteine was obtained and no detectable change in its optical rotation was observed.

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