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Javid H. Zaidi [a] & Naseem Iqbal Gunjial [a]
[a] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan
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Asymmetric Induction through Metalation of Chiral Dithioacetals and Oxathioacetals

Javid H. Zaidi and Naseem Iqbal Gunjial
Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

Abstract: The work presented in this article consists of synthesis of chiral dithioacetals and oxathioacetals using pure chiral auxiliaries, such as, (+) camphor, (−) menthol, and L-cysteine. Metalation of these chiral dithioacetals and oxathioacetals, followed by nucleophilic addition to benzaldehyde and removal of chiral auxiliary, furnished scalemic mandelic acid with various enantiomeric purities.

Keywords: dithioacetals, metalation, oxathioacetals

INTRODUCTION

Many methods of synthesizing dithioacetals and oxathioacetals are documented in literature.[1–5] However, reaction conditions often vary in convenience and yield, and many procedures for their synthesis have resulted in optimization problems. The use of dithioacetals as a formyl anion synthon is fairly common in organic synthesis.[6] Thus dithioacetals and oxathioacetals with tagged chiral auxiliaries were used for asymmetric induction via metalation because sulfur-stabilized anions might be suitable as masked nucleophilic acylating equivalents.[7–9]

Metalation of oxathiane tagged with chiral auxiliaries has been used for diastereoslective synthesis of carbinols, which (after hydrolysis followed by oxidation) yielded enantioselectively α-hydroxy carboxylic acids.

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Address correspondence to Javid H. Zaidi, Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan. E-mail: javid_zaidi@yahoo.com

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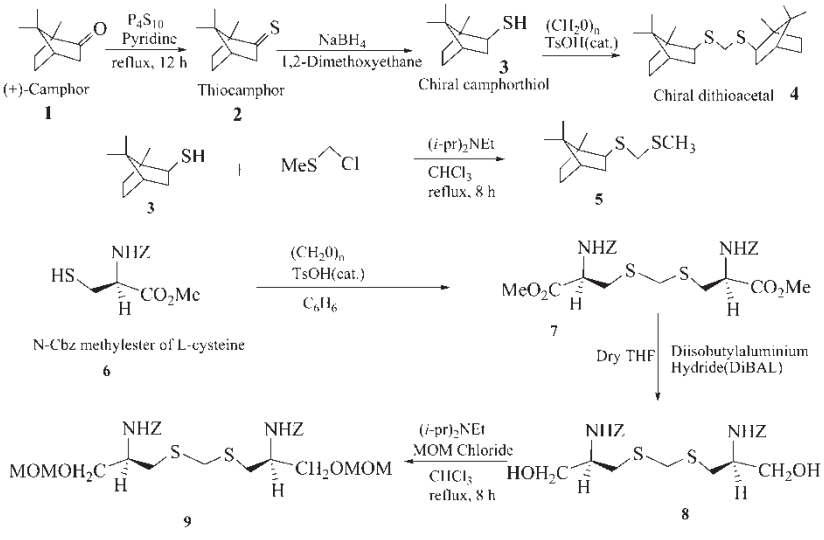
RESULTS AND DISCUSSION

Several chiral dithioacetals and oxathioacetals were synthesized using (+) camphor, (−) menthol, and L-cysteine as chiral auxiliaries. For example, camphor **1** was converted into the thiol derivative **3**, which was converted into the chiral dithioacetals **4** and **5**.[10] Similarly N-Cbz L-cysteine derivative **6** transformed into the dithioacetal derivative **7** (Scheme 1). On the other hand, thiomethylmethylation of (−) menthol afforded the oxathioacetal **11**. Moreover, (−) menthol was converted into menthoxymethyl chloride[10] and then reacted with the N-Cbz derivative of L-cystiene **6** to get the oxathioacetal **14** (Scheme 2). Because of an undesired reactivity of the carbonyl groups of ester functionalities of dithioacetal **7** and oxathioacetal **14** toward metalation, it was appropriate to convert them into the alcohols **8** and **15** and then protect them as the methoxymethyl ethers **9** and **16**[11,12] (Schemes 1 and 2).

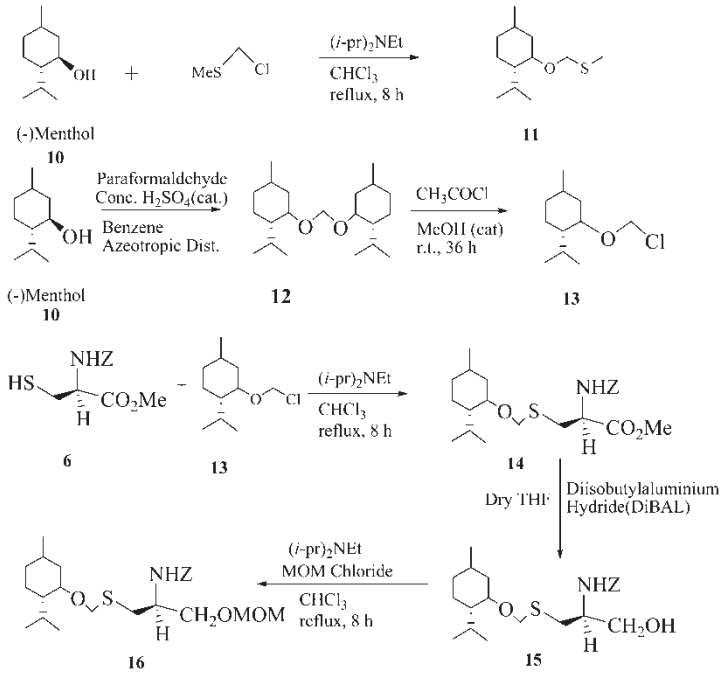
The dithioacetals **4**, **5**, and **9** and oxathioacetals **11** and **16** were metalated in dry tetrahydofuran (THF) under nitrogen at −78°C, and the resulting anions were quenched with benzaldehyde to afford the carbinols **17**–**21**. After deprotection[13] and oxidation,[14] mandelic acid was isolated and scrutinized (Scheme 3).

The optical rotations of mandelic acid samples were compared with those of commercially available (−) mandelic acid, and the enantiomeric excesses were determined.

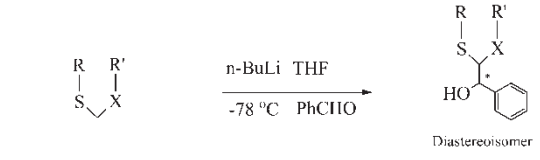
The values of enantiomeric excess (Table 1) show that asymmetric induction was appreciable. It can also be observed that in the dithioacetals and oxathioacetals, to which bulky chiral auxiliaries such as N-Cbz



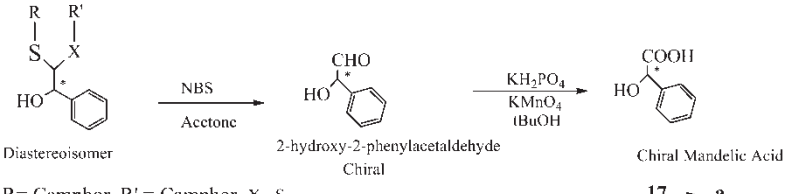
Scheme 1.



Scheme 2.



4 R= Camphor, R' = Camphor, X = S
5 R– Camphor, R' – Methyl, X – S
9 R= L-Cystiene R' = L-Cystiene, X = S
11 R= Methyl, R' = Menthol, X = O
16 R= L-Cystiene R' = Menthol, X = O
17 R= Camphor, R' = Camphor, X = S
18 R= Camphor, R' = Methyl, X = S
19 R= L-Cystiene R' = L-Cystiene, X = S
20 R= Methyl, R' = Menthol, X = O
21 R= L-Cystiene R' = Menthol, X = O



17 R= Camphor, R' = Camphor, X –S
18 R= Camphor, R' = Methyl, X =S
19 R= L-Cystiene R' = L-Cystiene, X =S
20 R= Methyl, R' = Menthol, X =O
21 R= L-Cystiene R' = Menthol, X =O

17 → **a**
18 → **b**
19 → **c**
20 → **d**
21 → **c**

Scheme 3.

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Table 1. Standard S (−) Mandelic Acid $[\alpha]_D^{25} = -2.98$ (c = 1.16 g/100 cm^3 MeOH)

Carbinol	Mandelic acid	$[\alpha]_D^{25a}$	Ee (%)
17	**a**	−2.45	82%
18	**b**	−2.35	78%
19	**c**	−2.81	94%
20	**d**	−2.21	74%
21	**e**	−2.86	95%

[a]Optical rotation of Mandelic acid from carbinols taken in MeOH with conc. c = 1.16 g/100 cm^3.

protected L-cysteine were attached, higher values of enantiomeric excess were observed.

EXPERIMENTAL

All the reactions were carried out in anhydrous conditions and under static pressure of nitrogen using rubber septa and three-way stopcocks. Solvents were dried and distilled by standard methods. All the reactions were monitored by thin-layer chomatography (TLC) on precoated silica-gel glass plates (layer thickness 0.25 mm, HF-254, E. Merck) and detected using ultraviolet light (λ_{max} 254 and 365 nm). Column chomatography was performed on E. Merck silica-gel (0.063–0.200 mm). IR spectra were recorded on a Schimadzu Fourier transform infrared spectrophotometer model 270. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brüker instrument at a frequency of 300 MHz and 75 MHz respectively. Tetramethylsilane (TMS) was used as internal reference. Electron impact mass spectra were performed on a VG 70 SE mass spectrometer. The optical rotation of the compounds was measured with Atago AP-100 automatic polarimeter.

Synthesis of Camphor Thiol (3)

(+) Camphor was converted into thiocamphor **2**, which, in turn, was reduced to camphor thiol **3** with sodium borohydride using a reported procedure.[10]

Thiocamphor (2). Orange red solid (13.5 g, 80%). Mp 137°C (lit.[15] 136–138°C). $[\alpha]_D^{25}$ +2.75 ($c = 1.07$ $CHCl_3$); FTIR (KBr): 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, $J = 2.1$ 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

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(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 (35), 125 (55), 113 (60), 93 (15), 85 (52), 79 (76), 69 (45). Anal. calcd. for $C_{10}H_{16}S$: C, 71.36; H, 9.58. Found: C, 71.40; H, 9.56.

Camphor thiol (3). White solid (5.6 g, 92%). Mp 220°C; $[\alpha]_D^{25} + 0.83$ ($c = 0.32$ $CHCl_3$); IR (KBr) 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 (34), 137 (56), 121 (55), 107 (68), 93 (100), 81 (10). Anal. calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.46; H, 10.68.

Synthesis of Dithioacetal (4) from Camphor Thiol

To a mixture of a solution of **3** (4.0 g, 23.5 mmol) in dry benzene (150 mL) and excess paraformaldehyde (8.0 g), p-toluenesulphonic acid (100 mg) was added as a catalyst. The reaction mixture was subjected to azeotropic distillation under static pressure of nitrogen. The reaction mixture was cooled to room temperature, and excess of benzene was removed. The residue was dissolved in ether; washed with saturated solution of $NaHCO_3$, water, and brine, and dried ($MgSO_4$). The organic layer was evaporated to give a residue, which was purified on silica-gel column chomatography using n-hexane as an eluent to give **4** (3.2 g 73%). Mp 168°C. $[\alpha]_D^{25}+0.74$ ($c = 0.25$ $CHCl_3$). IR (KBr): 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), 0.94–084 (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) 155 (34), 137 (56), 121 (55), 107 (68), 93 (100), 81 (10). Anal. calcd. for $C_{21}H_{36}S_2$: C, 71.52; H, 10.29. Found: C, 71.50; H, 10.30.

Synthesis of Dithioacetal (5) from Chloromethyl Methyl Suldide

To compound **4** (2 g, 11.9 mmol) in dry chloroform (75 mL) under nitrogen under reflux, triethylamine (8.3 mL, 60 mmol) and chloromethyl methylsulfide (10.61 mL, 60 mmol) were added. After 8 h, the reaction mixture was diluted with chloroform, washed sequentially with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica-gel using

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n-hexane as eluent to afford product **5** as colorless oil (1.8 g, 71%). $[\alpha]_D^{25} + 1.33$ ($c = 0.72$ $CHCl_3$). FTIR (NaCl): 2945, 1459, 1364, 1271, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 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 (75 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). Anal. calcd. for $C_{12}H_{22}S_2$: C, 62.55; H, 9.62. Found: C, 62.66; H; 9.57.

Synthesis of Dithioacetal of N-Cbz-Protected Methyl Ester of L-Cystiene (9)

The dithioacetal **7** was prepared according to the same procedure as described for **4**. Colorless oil (4.5 g, 72%). $[\alpha]_D^{25}$ +1.80 (c = 0.70 $CHCl_3$). FTIR (NaCl cm^{-1}): 3400, 1750, 1711. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.38 (m, 10H), 5.2 (s, 2H), 4.65–4.83 (m, 2H), 3.78 (s, 6H), 3.66 (s, 2H), 3.21–3.38 (m, 4H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.6 (CO), 153.78 (CONH), 136.02 (Ar), 128.6–128.57 (Ar), 67.80 (CH_2O), 61.98 (CHNH), 52.81 (OCH_3), 48.04 (SCH_2S), 33.24 (SCH_2). EIMS (m/z, % rel. abund.): 550 (M^+, 5), 178 (10), 147 (4), 146 (50), 91 (100), 77 (7), 65 (29), 51 (8). Anal. calcd. for $C_{25}H_{30}N_2O_8S_2$: C, 54.5; H, 5.4; N, 5.09. Found: C, 53.50; H, 5.30; N, 5.02.

The dithioacetal **7** (4.0 g, 7.2 mmol) was dissolved in dry THF (100 mL) under nitrogen and cooled to 0°C. The solution of diisobutylaluminium hydride (DIBAL) in n-hexane (56 mL, 56.64 mmol) was added dropwise. The reaction mixture was heated under reflux for 3 h, quenched with saturated solution of NaF, and repeatedly extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the crude product was purified on a silica-gel column with 10% ethyl acetate in petroleum ether to afford a colorless oil (2.5 g, 70%). $[\alpha]_D^{25}$ +2.54($c = 0.99$ $CHCl_3$). FTIR (NaCl cm^{-1}): 3437, 3400, 1699. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.38 (m, 10H), 5.16 (s, 4H), 4.64–4.67 (m, 2H), 4.32–4.35 (d, $J = 4.9$ Hz, 4H), 3.71–3.78 (m, 4H), 2.98–3.17 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 154.9 (CO), 135.99 (Ar), 128.63–128.10 (Ar), 67.78 (CH_2O), 63.56 (CH_2OH), 62.28 (CHNH), 48.05 (SCH_2S), 32.61 (SCH_2). EIMS (m/z, % rel. abund.): 494 (M^+, 3), 222 (3), 178 (4), 145 (5), 91 (100), 77 (7), 65 (28). Anal. calcd. for $C_{23}H_{30}N_2O_6S_2$: C, 55.8; H, 6.07; N, 5.6. Found: C, 55.1; H, 6.30; N, 4.9.

The alcoholic group of **8** was protected with methoxymethyl chloride[12] to afford compound **9** as a colorless oil (1.76 g, 75%). $[\alpha]_D^{25}$ +4.25 ($c = 2.23$ $CHCl_3$) FTIR (NaCl cm^{-1}): 1750. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63–7.47

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(m, 10H), 5.37 (d, $J = 6$ Hz, 4H), 5.24 (s, 4H), 4.71–4.67 (m, 2H), 4.29–4.22 (m, $J = 3$ Hz, 4H), 3.48 (s 2H), 3.38 (s, 3H) 2.98–3.17 (m, 4H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1 (CO), 137.62 (Ar), 128.80–128.27 (Ar), 97.34 (OCH_2O), 68.78 (CH_2O), 62.16 (CH_2O), 60.28 (CHNH), 55.23 (OCH_3), 49.05 (SCH_2S), 32.91 (SCH_2). EIMS (m/z, % rel. abund.): 582 (M^+, 6), 405 (5), 390 (8), 355 (4), 303 (6), 221 (6), 147 (15), 111 (10), 77 (15), 69 (72), 57 (100), 55 (63). Anal. calcd. for $C_{27}H_{38}N_2O_8S_2$: C, 55.6; H, 6.5; N, 4.8. Found: C, 55.50; H, 6.15; N, 4.5.

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Synthesis of Oxathioacetal (11) with Chloromethyl Methyl Suldide

The oxathioacetal **11** was synthesized by the same procedure as for **5** and obtained as white crystalline solid (3.4 g, 70%). Mp 47°C: $[\alpha]_D^{25} + 4.74$ ($c = 1.85$ $CDCl_3$), FTIR (KBr cm^{-1}): 2959. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.82 (s, 2H), 3.31–3.23 (m, 1H), 2.19 (s, 3H), 2.21–2.24 (m, 1H) 2.14–2.16 (m, 1H), 1.61–1.67 (m, 2H), 1.30–1.44 (m, 4H), 0.94 (d, $J = 6.5$ Hz 6H), 0.834 (d, $J = 7$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3 (OCH_2), 79.1 (OCH), 48.6 (CH), 42.4 (CH), 34.3 (CH_2), 31.4 (CH_2), 25.3 (CH), 23.1 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 14.12 (CH_3). EIMS (m/z, % rel. abund.): 216 (M^+, 11), 185 (3), 138 (44), 83 (100), 69 (42), 57 (40), 55 (65). Anal. calcd. for $C_{12}H_{24}SO$: C, 66.6; H, 11.1. Found: C, 65.8; H, 10.57.

Synthesis of Acetal of (−) Menthol (12)

Compound **12** was prepared using a reported procedure[10] as a white crystalline solid (5.2 g, 80%). Mp 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.

Synthesis of Menthoxymethyl Chloride (13)

Freshly distilled acetyl chloride (0.88 mL, 12.06 mmol) was added dropwise to a mixture of **12** (3.5 g, 10.8 mmol) and 2–3 drops of dry methanol at room temperature under nitrogen. The reaction mixture was allowed to stand at room temperature for 36 h. Compound **13** was ready to use without purification.

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Synthesis of Oxathioacetal of N-cbz-Protected Methyl Ester of L-Cysteine with Menthol (16)

The oxathioacetal **14** was synthesized by reacting N-Cbz L-cysteine **6** with **13**. [10] White crystalline solid (4.5 g, 70%). Mp 107°C. $[\alpha]_D^{25}$ −2.38 ($c = 0.58$ $CHCl_3$); FTIR (KBr cm^{-1}): 3355, 1751, and 1690. ^1H 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, $J = 14$ Hz and 5.5 Hz, 1H), 3.0 (dd, $J = 14$ Hz and 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 (75 MHz, $CDCl_3$): δ 169.1 (CO), 167.0 (CONH), 132.8 (C-1, Ar), 130.6 (C-4, Ar), 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 $C_{21}H_{33}NO_5S$: C, 61.3; H, 8.02; N, 3.4. Found C, 61.15; H, 7.88; N, 3.3.

The compound **15** was synthesized by reduction and protection as described for synthesis of compound **9.** Yellow oil (2.3 g, 74%). $[\alpha]_D^{25}$ −2.79 (c = 1.30 $CHCl_3$,) FTIR (NaCl cm^{-1}): 3331, 1724. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.34 (m, 5H), 5.54 (bd, 2H) 5.13 (s, 2H), 4.71–4.70 (d, 2H), 4.66–4.62 (m, 1H), 3.76 (dd, 2H), 3.59 (dd, 2H), 3.36 (s, 3H), 2.92–2.87 (m, 1H), 2.1–2.19 (m, 1H), 1.65–1.59 (m, 2H), 1.41–1.27 (m, 5H), 0.89 (d, $J = 7.2$ Hz, 6H), 0.79 (d, $J = 6.9$ Hz, 3H). EIMS (m/z, % rel. abund.): 453 (M^+, 9), 253 (4), 238 (3), 139 (5), 108 (8), 91 (100), 83 (36), 69 (13), 57 (15), 55 (25). Anal. calcd. for $C_{22}H_{37}NO_5S$: C, 61.8; H, 8.6; N, 3.2. Found: C, 61.50; H, 8.15; N, 3.1.

General Procedure for Metalation of Dithioacetals

A solution of dithioacetal (2 mmol) in anhydrous THF (20 mL) was cooled to −78°C under nitrogen and treated with a solution of n-butyllithium (2.5 M solution in hexane) (2.4 mmol). After stirring for 2 h at −78°C the reaction mixture was warmed to −25°C and quenched with benzaldehyde (4 mmol) dropwise. After 8 h, it was diluted with water (50 mL) and extracted with ethyl acetate. The organic layers were washed sequentially with water and brine and dried ($MgSO_4$). The product was purified on a silica-gel column using ethyl acetate–hexane mixtures as eluent to afford pure carbinols.

Carbinol (17). Yellow oil (0.84 g, 65%). $[\alpha]_D^{25}$ + 0.85 ($c = 0.45$ $CHCl_3$). FTIR (NaCl): 3429, 2945, 1459, 1364, 1271, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 4.70 (d, $J = 4.5$ Hz, 1H), 4.68 (d, $J = 4.7$ Hz, 1H), 4.10 (d, $J = 4.1$ Hz, 1H), 4.06 (d, $J = 3.7$ Hz, 1H), 2.99–2.86 (m, 2H), 2.64–2.59 (m, 4H), 1.45–1.42 (m, 4H), 1.36–1.31

(m, 2H), 1.28–1.27 (m, 4H), 0.93 (s, 6H), 0.91 (s, 6H), 0.88 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.88 (Ar′), 127–128 (Ar), 65.35 (CHOH), 36.53 (CH), 34.53 (C), 33.84 (CH), 33.95 (CH), 30.32 (CH_2), 29.72 (CH_2), 29.29, (CH_2), 28.65 (CH_3), 25.93 (CH_3). Anal. calcd. for $C_{28}H_{41}OS_2$: C, 73.3, H, 9.1. Found: C, 72.50; H, 9.30.

Carbinol (18). Yellow viscous oil (0.52 g, 69%). $[\alpha]_D^{25} + 1.95$ ($c = 0.76$ $CHCl_3$). IR (NaCl): 3407, 2927, 1451, 1380, 1260, 1081, 1028 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.26 (m, 5H), 4.79 (d, $J = 4.4$ Hz, 1H), 4.75 (d, $J = 4.1$ Hz, 1H), 3.86 (d, $J = 3.5$ Hz, 1H), 3.84 (d, $J = 3.9$ Hz, 1H), 2.67–2.90 (m, 1H), 2.10 (s, 3H), 2.02 (d, $J = 3$ Hz, 2H), 1.36–1.21 (m, 2H), 0.98 (s, 3H), 0.95 (s, 3H), 0.87–0.84 (m, 2H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.38, 127–128, 68.39, 37.73, 35.63, 33.94, 33.65, 31.32, 30.10, 30.2, 26.42, 24.23, 18.3. Anal. calcd. for $C_{19}H_{27}OS_2$: C, 67.8; H, 8.3. Found: C, 67.50; H, 8.1.

Carbinol (19.) Yellow oil (0.34 g, 58%).$[\alpha]_D^{25} + 3.14$ ($c = 1.22$ $CHCl_3$), FTIR (NaCl cm^{-1}): 3402, 3345. ^{1}H NMR ($CDCl_3$, 75 MHz): δ 7.45–7.27 (m, 15H), 5.51 (d, $J = 4.5$ Hz, 4H), 5.16 (s, 4H), 4.89 (d, $J = 7.3$ Hz, 1H), 4.87 (d, $J = 7.9$ Hz, 1H), 4.71 (d, $J = 3.9$ Hz, 1H) 4.70 (d, $J = 3.4$ Hz, 1H), 4.64–4.55 (m, 2H), 4.33–4.28 (d, $J = 6.6$ Hz, 4H), 3.49 (s, 3H), 3.05–3.18 (m, 4H), ^{13}C NMR ($CDCl_3$. 75 MHz): δ 158.2 (CO), 142.1 (Ar), 128.8–128.2 (Ar), 98.3 (OCH_2O), 78.7 (CHOH) 68.7 (CH_2O), 64.3 (CH_2O), 59.8 (CHNH), 57.6 (SCHS), 55.2 (OCH_3), 32.8 (SCH_2). Anal. calcd. for $C_{34}H_{44}N_2O_9S_2$: C, 59.3; H, 6.3; N, 4.06. Found: C, 59.50; H, 6.15; N, 4.5.

General Procedure for Metalation of Oxathioacetals

Oxathioacetal (2.31 mmol) solution in (15 mL) dry THF was treated with n-butyllithium (2.5 M solution in hexane, 2.4 mmol) at −78°C under nitrogen, allowed to warm to 0°C, and then immediately recooled to −78°C. Benzaldehyde (6.46 mmol) was then added dropwise. After 2 h of stirring at −78°C, the reaction mixture was allowed to stand overnight at −25°C. It was diluted with a saturated solution of NH_4Cl (20 mL), extracted with ethyl acetate, washed with water and brine, and dried ($MgSO_4$). The product was purified on a silica-gel column by eluting with 8% ethyl acetate in n-hexane.

Carbinol (20). colorless oil (0.51 g, 69%). $[\alpha]_D^{25} - 4.75$ ($c = 0.67$ $CHCl_3$); FTIR (NaCl cm^{-1}): 3386, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 − 7.27 (m, 5H), 4.82 (d, 1H, $J = 4.3$ Hz), 4.79 (d, 1H, $J = 3.9$ Hz), 4.69 (d, 1H, $J = 3.7$ Hz), 4.65 (d, 1H, $J = 3.5$ Hz), 3.31 − 3.23 (m, 1H), 2.19 (s, 3H), 2.21 − 2.24 (m, 1H), 2.14 − 2.16 (m, 1H), 1.61 − 1.67 (m, 2H), 1.30 − 1.44 (m, 4H), 0.94 (d, $J = 6.5$ Hz 6H), 0.834 (d, $J = 7$ Hz, 3H). ^{13}C

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NMR (75 MHz, $CDCl_3$): δ 135.4 (Ar), 126–129 (Ar), 95.9 (OCHS), 81.5 (CHO), 76.7 (CHOH), 47.2 (CH), 41.9 (CH), 32.3 (CH_2), 31.9 (CH_2), 27.3 (CH), 23.9 (CH_2), 21.6 (CH_3), 20.2 (CH_3), 16.1 (CH_3). Anal. calcd. for $C_{19}H_{30}O_2S$: C, 70.8; H, 9.3. Found: C, 69.50; H, 9.1.

Carbinol (21). Colorless oil (0.38 g, 62%) $[\alpha]_D^{25} - 0.43$(c = 0.22 $CHCl_3$). FTIR (NaCl cm^{-1}): 3442, 3329, 1719. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.21 (m, 10H), 5.66 (bd, 2H), 5.12 (s, 2H), 4.88 (d, 1H, 6.5 Hz), 4.85 (d, 1H, 6.8 Hz), 4.72 (d, 1H, 4.2 Hz), 4.70 (d, 1H, 3.9 Hz), 4.64–4.61 (m, 1H), 3.86 (dd, 2H), 3.75 (dd, 2H), 3.35 (s, 3H), 2.90–2.82 (m, 1H), 2.19–2.02 (m, 1H), 1.69–1.58 (m, 2H), 1.39–1.31 (m, 5H), 0.91 (d, $J = 6.9$ Hz, 6H), 0.85 (d, $J = 7.2$ Hz, 3H). Anal. calcd. for $C_{29}H_{42}NO_6S$: C, 65.4; H, 7.8; N, 2.6. Found: C, 65.3; H, 7.1; N, 2.5.

General Procedure for Synthesis of Samples of Mandelic Acids from Carbinols (17–21)

Solution of carbinol (1.0 mmol) in acetone (10 mL) was added to N-bromosuccinimide (8 mmol) in 90–97% aqueous acetone (25 mL) at 25°C. The reaction mixture quickly turned red (bromine) but soon faded to a yellow orange color, was stirred for 5–10 min, and was then shaken with a mixture of saturated aqueous sodium sulphite and 1:1 dichloromethane. The organic phase was sequentially washed with 1.0 M aqueous sodium bicarbonate, water, and brine and dried ($MgSO_4$).

The α-hydroxy aldehyde (1 mmol) thus obtained was oxidized to mandelic acid by dissolving it in t-butylalcohol (10 mL) and treatment with 5% aqueous solution of KH_2PO_4 (3.4 mL) and 1M aqueous solution of $KMnO_4$ (5 mL). After 45 min, the reaction was quenched with a saturated aqueous solution of Na_2SO_3. The pH of the solution was brought to 5 by adding 4N HCl solution dropwise. The product was extracted with ethyl acetate. The product was washed with de-ionized water and brine and dried ($MgSO_4$) to yield enantiomerically enriched mandelic acid as a white crystalline solid.

Samples of synthesized mandelic acids (a, b, c, d, e). Mp 127–129°C (lit.[15] 131°C). IR (NaCl cm^{-1}): 3420–2635 (O-H), 1714 (C═O). ^1H NMR (300 MHz, $CDCl_3$): δ 10.9 (s, 1H) 7.35–7.25 (m, 5H) 5.01 (s, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9 (COOH), 127-135 (Ar), 85.9 (CHOH). The $[\alpha]_D^{25}$ values of various samples of mandelic acids are reported in Table 1.

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