# A versatile synthetic route to 1,5-dithiocins from *o*-mercapto aromatic aldehydes[1]

Ian W.J. Still, Rosanne Natividad-Preyra, and F. Dean Toste

**Abstract**: An earlier procedure for the facile preparation of benzo-fused 1,5-dithiocins **2a–2c** from *o*-mercapto-benzaldehydes has been improved and shown to be capable of extension to the preparation of several naphthalene-derived analogues. The general method also afforded several N-alkylated 1,5-dithiocins **4, 5** by replacing $NH_3$ with the appropriate primary amine. It was found that N-acylation of the 1,5-dithiocins was successful only with methyl chloroformate. Attempted N-phenylation met with limited success but was shown to be unnecessary since even the less reactive aniline readily undergoes the general reaction of primary amines. When simple α-amino acids, or their methyl esters, were employed as the primary amine in the reaction with *o*-mercaptobenzaldehyde, the formation of the N-alkylated 1,5-dithiocins **4a**, **17a**, **17b** with accompanying loss of -COOH or -COOMe was observed, in preparatively useful yields. A mechanism is proposed for this interesting transformation.

*Key words*: 1,5-dithiocins, α-amino acids, N-acylation, decarboxylation.

**Résumé** : On a amélioré une méthode proposée antérieurement pour préparer facilement des benzo-1,5-dithiocines, **2a–2c**, à partir des *o*-mercaptobenzaldéhydes et on a démontré qu'on peut l'étendre à la préparation de plusieurs dérivés du naphtalène. La méthode générale permet aussi d'obtenir plusieurs 1,5-dithiocines *N*-alkylées (**4, 5**) en remplaçant le $NH_3$ par l'amine primaire appropriée. On a observé que la *N*-acylation des 1,5-dithiocines ne se fait correctement qu'avec du chloroformiate de méthyle. Des essais en vue d'effectuer une *N*-phénylation ont conduit à des résultats mitigés; toutefois, cette limitation ne présente pas de problèmes puisque l'on peut obtenir le même produit en procédant à la réaction générale en présence d'aniline, même si celle-ci est moins réactive. Lorsqu'on utilise des acides α-aminés simples ou leurs esters méthyliques comme amine primaire dans la réaction avec l'*o*-mercaptobenzaldéhyde, on observe la formation des 1,5-dithiocines *N*-alkylées, **4a, 17a**, **17b**, avec des rendements préparativement utiles. On propose un mécanisme pour cette transformation intéressante.

*Mots clés* : 1,5-dithiocines, acides α-aminés, *N*-acylation, décarboxylation.

[Traduit par la Rédaction]

## Introduction

Molecules possessing a structurally well-defined, V-shaped molecular cleft have recently attracted considerable attention due to their application toward problems in the areas of molecular recognition, self-assembly, and supramolecular chemistry (1, 2). Molecules possessing molecular chirality in addition are of interest as potential chiral ligands and solvating agents. Chiral molecules that lock two aromatic rings in almost perpendicular planes, such as Tröger's base **1** (3) are of special interest as DNA probes owing to their different possible modes of interaction with DNA and to their chiral properties (4, 5). We felt that it would be advantageous to prepare this type of compound containing a readily functionalized group (such as a secondary amine) for which a variety of derivatives could easily be produced. The preparation of the racemic 6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocins **2a–2c**, representing easily obtained examples of such compounds, was reported earlier by us (6).

The preparation of the imino-bridged, 1,5-dithiocin ring system was reported as early as 1958 (7) and that of the dibenzo[*b*,*f*] analog **2b** by Gol'dfarb et al. (8) in 1966. These synthetic procedures, and the later serendipitous preparations of dibenzo[*b*,*f*]-1,5-dithiocins by Corrigan and West (9) and, more recently, Brieaddy and Donaldson (10), were of limited utility. Moreover, structural proof, notably the absence of NMR spectra in the earlier papers cited, was inadequate. Our previous work (6) was therefore important not only in establishing the structure of **2b** and its analogues by X-ray analysis but also in making available a general synthetic approach to such molecules.

We describe herein an improved experimental procedure for the preparation of **2a–2c** that also allows the facile preparation of N-alkyl and N-aryl analogues of these molecules. We also describe our attempts to prepare N-acyl analogues and the ready extension of our methodology to several

Received August 4, 1998.

**I.W.J. Still,[2] R. Natividad-Preyra, and F.D. Toste.** Department of Chemistry, University of Toronto at Mississauga, 3359 Mississauga Road, Mississauga, ON L5L 1C6, Canada.

[1]Taken in part from the M.Sc. thesis of R. Natividad, University of Toronto, l997.

[2]Author to whom correspondence may be addressed. Telephone: (905) 828-5354. Fax: (905) 828-5425. e-mail: istill@credit.erin.utoronto.ca

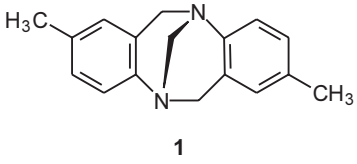
naphtho-fused analogues of **2a**. Finally, the results of our attempts to prepare chiral N-alkylated analogues of **2a** *directly* by utilizing natural α-amino acids or their methyl esters in our general approach will be discussed.

## Results and discussion

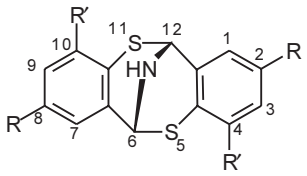
The benzo-fused 1,5-dithiocins **2a–2c** were prepared, as reported previously (6), starting from the appropriate thiol and carrying out a selective *ortho* formylation via a doubly lithiated (S,C-) intermediate. We have found that yields in the formylation could be almost doubled (to 63–81%) if *N*-formylpiperidine was used as the formylating agent, in place of DMF. We have also discovered that the subsequent cyclization step converting **3a–3c** into **2a–2c** is more conveniently achieved with $NH_4OAc$ in refluxing ethanol rather than in nitromethane, presumably by the mechanism we had previously outlined (6). The reaction was also attempted using other amonium salts (e.g., $NH_4Cl$, $NH_4SCN$) but, with the exception of $NH_4HCO_3$, only the acetate seems to offer the right balance between acid and base catalysis, which seems to be crucial.

By modifying the reaction of **3a** or **3b** and replacing the ammonium acetate with a mixture of primary amine and acetic acid (1:4) we have been able to prepare the N-alkyl analogues **4a–4c** and **5a**, **5b** in excellent yields (83–91%). Interestingly, **4a** could also be obtained in the absence of acetic acid but in a very much lower yield (27%).

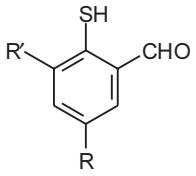
It was felt that the creation of the naphtho-fused analogues of these 1,5-dithiocins would provide molecules with more pronounced clefts and potentially more interesting solvating effects. We accordingly undertook the synthesis of the three isomeric *ortho*-mercaptonaphthaldehydes **6–8**. Compound **6** was readily obtained from 1-naphthalenethiol,[3] by our general procedure using *N*-formylpiperidine, in 43% yield. It was found in the naphthalene series that a slightly higher molar ratio of both the *n*-butyllithium and the TMEDA complexing agent gave the best results (2.5 equiv. of each, vs. 2.2 equiv. for the benzene analogues).



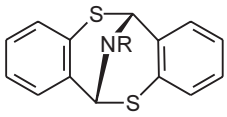

**1**



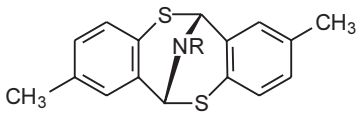

**2a** R= R′= H
**b** R= $CH_3$, R′= H
**c** R= $CH_3$, R′= S$^t$Bu



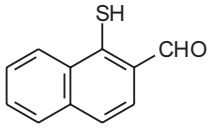

**3a** R= R′= H
**b** R= $CH_3$, R′ = H
**c** R = $CH_3$, R′= S$^t$Bu



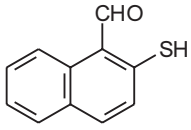

**4a** R= $CH_2CH_2C_6H_5$
**b** R= $CH_2CH(CH_3)_2$
**c** R= $C(CH_3)_3$
**d** R= $C_6H_5$



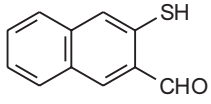

**5a** R= $CH_2CH_2C_6H_5$
**b** R= $CH_2CH(CH_3)_2$




**6**



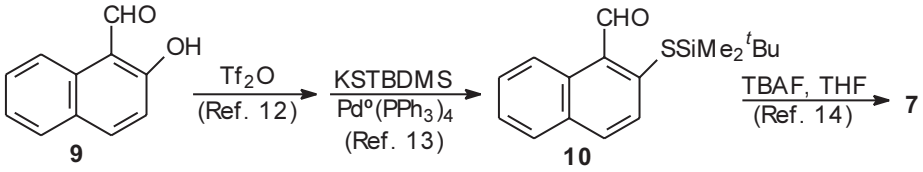

**7**




**8**

[3] 1-Naphthalenethiol is a relatively expensive reagent, which may be conveniently prepared, in 89% yield, by reduction of 1-naphthalenesulfonyl chloride with tin and concentrated HCl (see experimental section).

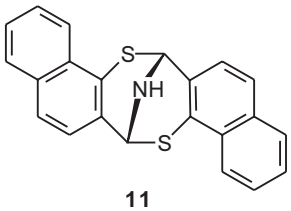
**Scheme 1.**



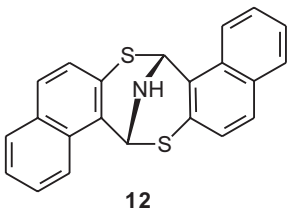

Application of our general formylation procedure to the isomeric 2-naphthalenethiol afforded the two isomeric aldehydes **7** and **8**, in isolated yields of 45% and 30%, respectively. That the major isomer was the (expected) result of 1-formylation of the naphthalene nucleus was confirmed by an unambiguous synthesis of **7** from 2-hydroxy-1-naphthaldehyde **9** in 42% overall yield, by the three-step sequence shown in Scheme 1 (11), slightly modified in Step 2 (see Experimental).

With the necessary three naphthaldehydes in hand, we were able to complete our synthesis of the three isomeric naphtho-fused 1,5-dithiocins **11**–**13**, from **6**, **7**, and **8**, respectively. The same experimental procedure was used as for the benzo-fused analogues **2a**–**2c** and excellent yields (>90%) of these crystalline solids were obtained for all three cases. Recently, Biehl et al. (15) reported the synthesis of the 1,5-dioxocin **14a** (analogous to **12**) by the reaction of **9** with ammonium acetate, accompanied by a small amount of the O-bridged derivative **14b**. The mechanism proposed by these authors for the formation of **14a** is essentially identical to that which we had earlier proposed (6), differing only in the order of the steps involved.

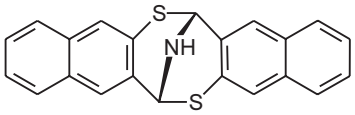
Attempts have been made to introduce an N-acyl group into these imino-bridge molecules. Using **4b** as a representative example, we sought to introduce N-benzoyl and N-propanoyl groups by reaction of **4b** with benzoyl chloride and propanoic acid–DCC, respectively, but failed to obtain the amides in preparatively useful yields. When methyl chloroformate was used, however, in refluxing acetone with $K_2CO_3$ (or, better still, $Cs_2CO_3$ (16)) as the base, we ob-



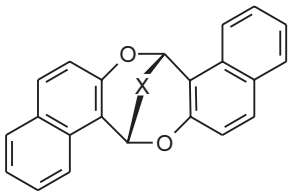

**11**



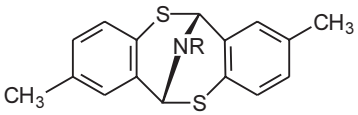

**12**



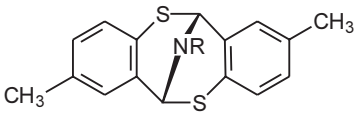

**13**



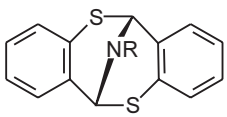

**14a** X = NH
**b** X = O




**15**
R = $CO_2Me$

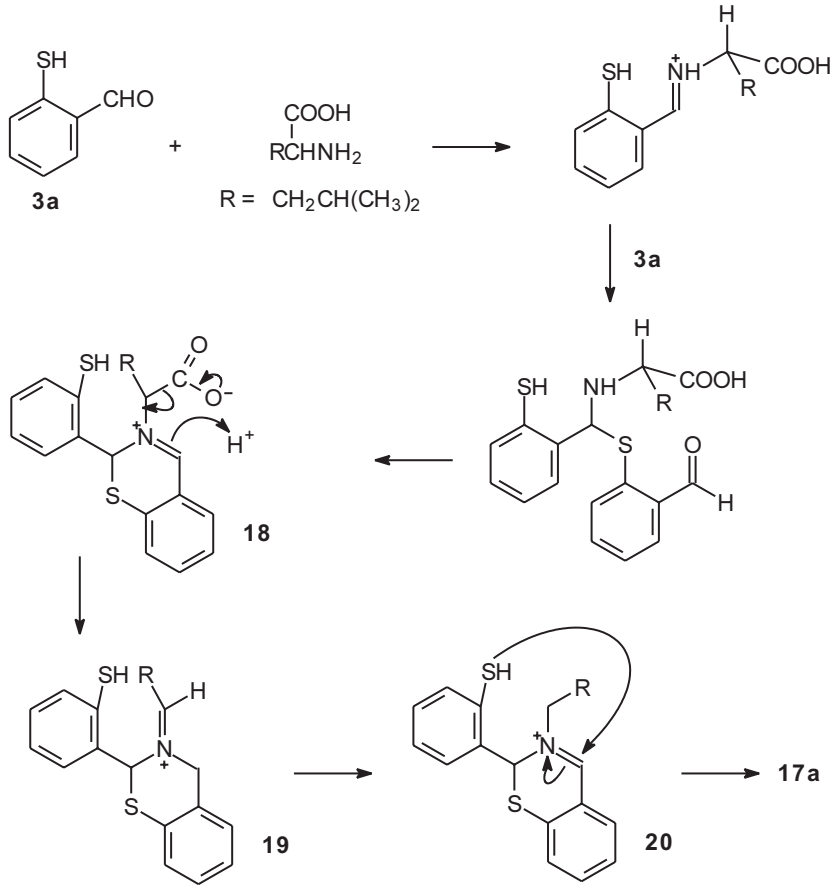



**16** R = $CH(CH_3)C_6H_5$




**17a** R = $CH_2CH_2CH(CH_3)_2$
**b** R = $CH_2CH_2OH$
**c** R = $CHCH_2CH(CH_3)_2$
$CO_2{}^tBu$

**Scheme 2.**




tained the expected carbamate **15** in over 60% yield. Unlike the starting imino analogue and its congeners, **15** shows the two methine protons, in addition to the expected downfield shift, as nonequivalent ($\delta_H$ = 6.74, 6.57), presumably due to restricted bond rotation in the N—$CO_2$Me bond.

We have also attempted to introduce an N-phenyl substituent in the 1,5-dithiocins. Using a procedure described by Barton et al. (17) we first attempted this with **2a**, using $Ph_3Bi$ as phenylating agent, with $Cu(OAc)_2$ as the catalyst. The reaction mixtures obtained in various trials were complex and in no case was more than 25% of the desired **4d** present. Accordingly, we reverted to our standard methodology, using **3a**, aniline, and a somewhat longer reflux period, and were rewarded by obtaining the crystalline **4d** in 75% yield.

One potential application of our 1,5-dithiocins was in the area of asymmetric base-catalyzed reactions. The early work of Noyori and coworkers (18) established (–)-sparteine, a readily available alkaloid, as a potential agent for enantioinduction at carbanion centres and several recent reports have made good use of this type of methodology (refs. 19 (for recent reviews) and 20). For our compounds to be useful in this type of application, it will be necessary to prepare enantiomerically pure 1,5-dithiocins. As one approach to this problem we decided to investigate the use of enantiomerically pure amines in our general method since, in principle, the diastereomeric dithiocins so obtained should be readily separable.

Our first attempt along these lines employed *R*-1-phenylethylamine as the derivatizing amine, in a reaction with **3b**. Disappointingly, however, we were unable to achieve a complete separation of the diastereomeric pair of dithiocins **16** so formed, under a variety of conditions. We next decided to use one of the readily available, inexpensive, α-amino acids to achieve our purpose. Reaction of **3a** with L-leucine under the usual conditions led, much to our surprise, to a benzo-fused dithiocin which showed no evidence for -COOH either in the IR or the proton NMR. The structure of the product has been established as **17a**, the *N*-(3′-methylbutyl) analogue of the N-alkylated series, formed here in 68% yield. When the reaction was repeated using L-leucine methyl ester the same product was obtained. Thus, formation of the N-alkylated 1,5-dithiocins in these reactions from α-amino acids *or* their methyl esters is accompanied by loss of the carboxylate moiety.

Confirmation that the structural assignment to the products of this new reaction was correct came from the reaction of **3a** with L-phenylalanine methyl ester. The product, obtained in 63% yield, was identical in all respects with **4a**, obtained independently as described above. A further example of this interesting reaction was shown by the formation of the 2′-hydroxyethyl analogue **17b** in 75% yield when **3a** was allowed to react with L-serine methyl ester under the usual conditions.

We propose that this novel reaction may proceed by a mechanism akin to the known enzymatic decarboxylation of

**Table 1.** Physical data and $^1$H NMR chemical shifts for 1,5-dithiocins **2**, **4**, **5**, **11–13**, **15**.

| | | | δ | | |
|---|---|---|---|---|---|
| Compound | Yield (%) | Melting point (°C) | $=NCH_2$ or =NH | Aromatic | =CH—S |
| **2a** | 89 | 131–133 | 2.88 | 7.28(2H), 7.04(6H) | 5.73 |
| **2b** | 91 | 205–206 | 2.83 | 7.08(2H), 6.91(4H) | 5.67 |
| **2c** | 90 | 45–47 | 4.33 | 7.15(4H) | 5.66 |
| **4a** | 84 | 147–150 | 3.01 | 7.24(2H), 7.05(6H) | 5.45 |
| **4b** | 83 | 129–131 | 2.87, 2.48 | 7.25(2H), 7.00(6H) | 5.38 |
| **4c** | 87 | 136–138 | — | 7.28(2H), 6.69(6H) | 5.87 |
| **4d** | 75 | 70–72 | — | 7.32(4H), 7.13(4H) | 6.15 |
| **5a** | 83 | 132–134 | 2.94 | 7.04(2H), 6.88(4H) | 4.92 |
| **5b** | 86 | Oil | 2.83, 2.46 | 7.05(2H), 6.89(4H) | 5.31 |
| **11** | 92 | 168–170 | Not observed | 7.95(4H), 7.78(2H) 7.75(2H), 7.53(2H), 7.44(2H) | 6.05 |
| **12** | 94 | 160–163 | Not observed | 7.83(4H), 7.62(4H) 7.48(2H), 7.02(2H) | 6.45 |
| **13** | 96 | 170–172 | Not observed | 7.76(4H), 7.62(4H) 7.38(4H) | 6.03 |
| **15** | 67 | 143–146 | — | 7.18(2H), 6.93(4H) | 6.74, 6.57 |

α-amino acids, catalyzed by pyridoxal phosphatase (21). The key intermediate in our proposed mechanism for the reaction with L-leucine (Scheme 2) is the initial iminium ion **18**, which, under the approximately neutral pH conditions employed, leads to decarboxylation and a second iminium species **19**, which undergoes a protropic rearrangement to the more stable iminium ion **20** and is trapped by thiol (thiolate), leading to the 1,5-dithiocin in the usual way. Since thiolate ions are known to be excellent nucleophiles it is quite conceivable that intramolecular demethylation could first occur in the analogous reaction with the methyl ester, leading to the same carboxylate species **18**. Indirect support for this hypothesis came from a preliminary reaction using L-leucine *tert*-butyl ester, which should be stable to thiolate ion attack. Gratifyingly, the N-alkylated dithiocin **17c**, obtained in 71% yield, showed no loss of the -COO$^t$Bu group. As expected, signals for the diastereomeric methine protons in **17c** were observable ($\delta_H$ = 5.78, 5.70) in the $^1$H NMR spectrum, indicating a 70:30 ratio of the diastereomers. Further work is under way to optimize this finding using the *tert*-butyl esters of other natural amino acids. Effective separation of the presumably scalemic diastereomers is also a prerequisite for the successful application of this approach.

Work is continuing in our attempts to prepare enantiomerically pure examples of the 1,5-dithiocins from readily accessible starting materials. We also plan to investigate the solvating and metal-complexing properties of these interesting molecules.

## Experimental

### General information

For all anhydrous reactions, glassware was dried in the oven overnight at 120°C prior to its use. All anhydrous reactions were run under an argon atmosphere. DMF and nitromethane were distilled from $P_2O_5$ and stored over 3Å sieves. Methanol was distilled from magnesium turnings and stored over activated 3Å sieves. Hexanes, THF, toluene, and diethyl ether were distilled from sodium – benzophenone ketyl. Triethylamine and TMEDA were distilled from calcium hydride prior to use. Alkyllithium solutions were obtained from Fluka and were titrated regularly (22). Work-up procedures involving the drying of organic extracts utilized $Na_2SO_4$. Purification was initially carried out by (flash) column chromatography, using Merck 40–60 μm silica gel or aluminum oxide and the appropriate solvent system (q.v.)

IR spectra were obtained as neat films or as KBr pellets, as indicated, and data were recorded in cm$^{-1}$. $^1$H NMR spectra were recorded at 200 MHz in $CDCl_3$, unless otherwise stated. $^{13}$C NMR and DEPT spectra were run at 100.6 MHz. High- and low-resolution mass spectra were obtained at 70 eV. Elemental analyses were performed by the Guelph Chemical Laboratories Ltd., Guelph, Ontario. Compounds for which high-resolution mass measurements are given were homogeneous by TLC analysis and gave satisfactory $^1$H and (or) $^{13}$C NMR spectra indicative of their purity. $^1$H NMR data for compounds **2a–2c**, **4a–4d**, **5a**, **5b**, **11**, **12**, **13**, and **15** have been collected in Table 1.

### 2-Mercaptobenzaldehyde 3a

To a solution of thiophenol (2.00 mL, 19.47 mmol) in 45 mL of dry hexanes under argon, TMEDA (6.43 mL, 42.83 mmol) was added via addition funnel. The clear solution was stirred for 5 min and cooled to 0°C. The 2.2 M *n*-BuLi (19.47 mL, 42.83 mmol) was added with a syringe over a period of 20 min, giving the solution a yellow colour. The mixture was stirred for an additional 0.5 h at 0°C, warmed to room temperature, and stirred for 17 h. The resulting solution turned white and became very thick in appearance. On cooling to 0°C, *N*-formylpiperidine (4.34 mL, 38.94 mmol) was slowly added, forming a red solution and an orange pastelike precipitate. The reaction mixture was stirred at 25°C for 18 h, then acidified with 1 M HCL (2 × 25 mL), extracted with $CH_2Cl_2$ (4 × 25 mL), and washed with saturated NaCl (25 mL). The solution was dried and concentrated to afford a dark orange-brown oil (2.77 g,

93%). Flash chromatography, eluting with $CH_2Cl_2$ ($R_f$ = 0.35) afforded an oil (2.42 g, 81%). IR (film), ν: 3085, 2839, 2750, 1680, 1590, 1560, 850, 750; $^1$H NMR, δ: 10.25 (s, 1H), 7.89 (dd, 1H, *J* = 7.5, 1.6 Hz), 7.80 (dd, 1H, *J* = 7.8, 1.6 Hz), 7.50 (td, 1H, *J* = 7.8, 1.6 Hz), 7.39 (td, 1H, *J* = 7.5, 1.6 Hz), 5.49 (s, 1H).

**2-Mercapto-5-methylbenzaldehyde 3b**

This aldehyde was prepared according to the same procedure. A crude orange-brown oil (1.19 g, 88%) was obtained from the solution. Flash chromatography, eluting with $CH_2Cl_2$ ($R_f$ = 0.39), afforded a yellow oil (1.01 g, 75%). IR (film), ν: 3018, 2925, 2875, 2545, 1665, 815, 780; $^1$H NMR, δ: 9.99 (s, 1H), 7.52 (d, 1H, *J* = 2.6 Hz), 7.19 (m, 2H), 5.31 (s, 1H), 2.37 (s, 3H).

**3-(*tert*-Butylthio)-2-mercapto-5-methylbenzaldehyde 3c**

To a solution of *p*-thiocresol (0.30 g, 2.40 mmol) in 30 mL of dry hexanes under argon, TMEDA (0.80 mL, 5.32 mmol) was added via addition funnel. The clear solution was stirred for 5 min and was cooled to 0°C. The 1.6 M *n*-BuLi (3.32 mL, 5.32 mmol) was added with a syringe, over a period of 20 min, giving the solution a yellow colour. The mixture was stirred for an additional 0.5 h at 0°C, warmed to room temperature, and stirred for 17 h. The resulting solution turned white and, was cooled to –10°C. Slow addition of freshly distilled *tert*-butyl disulfide (0.74 mL, 3.84 mmol) turned the mixture red in colour and stirring was continued for 16 h. The solution was washed with 1 M HCl (2 × 20 mL), saturated NaCl (20 mL), dried, and evaporated to afford a brown oil (0.38 g, 81%). Kugelrohr distillation afforded 2-(*tert*-butylthio)-4-methylbenzenethiol (0.33 g, 70%), bp 130–134°C/7 Torr (1 Torr = 133.3 Pa). IR (film), ν: 2961, 2934, 2518, 818; $^1$H NMR, δ: 7.41 (d, 1H, *J* = 1.5 Hz), 7.29 (d, 1H, *J* = 7.8 Hz), 7.04 (dd, 1H, *J* = 7.8, 1.5 Hz), 4.77 (s, 1H), 2.33 (s, 3H), 1.39 (s, 9H).

The thiol so obtained (0.20 g, 0.94 mmol) was lithiated in dry hexanes (20 mL) and TMEDA (0.33 mL, 2.17 mmol), using 2.2 M *n*-BuLi (0.98 mL, 2.17 mmol) as in the general procedure. The resulting orange mixture was treated with *N*-formylpiperidine (0.21 mL, 1.88 mmol) at 25°C. The mixture turned yellow and was stirred for 18 h. The solution was washed with 1 M HCl (2 × 15 mL), saturated NaCl (15 mL), dried, and concentrated to afford a brown oil (0.16 g, 74%). Flash chromatography, eluting with $CH_2Cl_2$ ($R_f$ = 0.45), yielded a yellow oil (0.13 g, 63%). IR (film), ν: 2960, 2925, 2893, 2480, 1684, 1672, 769; $^1$H NMR, δ: 10.05 (s, 1H), 7.63 (d, 1H, *J* = 1.6 Hz), 7.56 (d, 1H, *J* = 1.6 Hz), 6.98 (s, 1H), 2.15 (s, 3H), 1.33 (s, 9H).

**6,12-Imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 2a**

The thiosalicylaldehyde **3a** (0.90 g, 6.52 mmol) dissolved in absolute ethanol (30 mL) was treated with ammonium acetate (0.55 g, 7.17 mmol), the solution turning a yellow colour. The solution was refluxed for 3.5 h and cooled to room temperature, resulting in the formation of a white precipitate. Filtration and drying afforded a yield of (0.75 g, 89%), mp 131–133°C (lit. (6) mp 130–132°C). IR (KBr), ν: 3334, 3115, 3005, 1595, 1499, 763.

**2,8-Dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 2b**

The same procedure as that used for the preparation of **2a** was employed. A white solid was obtained directly from the reaction mixture (0.85 g, 91%), mp 205–206°C (lit. (6) mp 206–206.5°C). IR (KBr), ν: 3358, 3056, 2965, 1482, 796.

**4,10-Bis(*tert*-butylthio)-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 2c**

The same procedure as that used for the preparation of **2a** was employed. A yellow solid was obtained from the reaction mixture (0.05 g, 90%), mp 45–47°C (lit. (6) mp 44–46°C). IR (KBr), ν: 3054, 2920, 2874, 1493, 804, 737.

***N*-(2′-Phenylethyl)-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 4a**

*Method A*

To a solution of thiosalicylaldehyde **3a** (0.04 g, 0.28 mmol) in absolute ethanol (10 mL), 0.5 mL of HOAc was added. Addition of the phenethylamine (0.02 mL, 0.15 mmol) to the above reaction vessel immediately turned the yellow solution orange in colour. The mixture was refluxed for 3.5 h, quenched with $H_2O$ (5 mL), and extracted with $CH_2Cl_2$ (2 × 10 mL). The organic layer was dried and concentrated to afford a brown oil. Flash chromatography, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.52), yielded a light yellow solid, (0.04 g, 84%), mp 147–150°C. IR (KBr), ν: 3116, 3032, 2996, 1625, 1487, 815. Exact Mass calcd. for $C_{22}H_{19}NS_2$: 361.0959; found: 361.0954. Anal. calcd. for $C_{22}H_{19}NS_2$: S 17.74; found: S 18.14.

*Method B*

A mixture of **3a** (0.14 g, 1.03 mmol), L-phenylalanine methyl ester hydrochloride (0.09 g, 0.57 mmol), and absolute ethanol (15 mL) was refluxed for 2.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow-brown oil. The oil was dissolved in $CH_2Cl_2$ (15 mL) and the organic layer washed with saturated $NaHCO_3$ (15 mL). Drying and concentration afforded a white powdery solid (0.12 g, 63%). Flash chromatography, eluting with $CH_2Cl_2$–hexanes (85:15) ($R_f$ = 0.57) gave white crystals (0.10 g, 51%), mp 149–151°C, identical in all respects with **4a** prepared above.

***N*-(Isobutyl)-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 4b**

To a solution of **3a** (0.05 g, 0.35 mmol) in absolute ethanol (8 mL), 0.5 mL of HOAc was added. Addition of isobutylamine (0.02 mL, 0.19 mmol) to the above reaction vessel immediately turned the yellow solution orange in colour. Reaction was carried out as in Method A above and, after flash chromatography, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.52), gave **4b** as a yellow solid (0.04 g, 83%), mp 129–131°C. IR (film), ν: 3053, 2456, 1515, 1489, 792, 743. Exact Mass calcd. for $C_{18}H_{19}NS_2$: 313.0958; found: 313.0956.

***N*-(*tert*-Butyl)-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 4c**

To a solution of **3a** (0.06 g, 0.40 mmol) in absolute ethanol (10 mL), 0.5 mL of HOAc and *tert*-butylamine

(0.02 mL, 0.22 mmol) were added. Reaction and work-up procedure identical with those for **4a**, **4b** afforded, on flash chromatography, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.56), **4c** as a yellow solid (0.04 g, 87%), mp 136–138°C. IR (film), ν: 3322, 3057, 2970, 2924, 1695, 1589, 1463, 819. Exact Mass calcd. for $C_{18}H_{19}NS_2$: 313.0958; found: 313.0968.

### *N*-Phenyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 4d

A mixture of **3a** (0.23 g, 1.64 mmol), aniline (0.08 g, 0.90 mmol), acetic acid (0.5 mL), and absolute ethanol (15 mL) was refluxed for 6.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a brown oil (0.24 g, 87%). Flash chromatography, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.58), resulted in a white solid (0.20 g, 75%), mp 70–72°C. IR (KBr), ν: 3075, 2961, 835; $^{13}$C NMR, δ: 147.1s, 133.3s, 130.3s, 129.5d, 128.6d, 128.0d, 127.9d, 125.0d, 123.0d, 119.5d, 61.1d. Exact Mass calcd. for $C_{20}H_{15}NS_2$: 333.0645; found: 333.0651. Anal. calcd. for $C_{20}H_{15}NS_2$: C 72.12, H 4.54, N 4.20, S 19.25; found: C 71.63, H 4.51, N 3.93, S 19.78.

### *N*-(2′-Phenylethyl)-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibe nzo[*b*,*f*]-1,5-dithiocin 5a

The same procedure was used as in the formation of **4a**. A crude yellow oil was obtained (0.06 g, 96%). Flash chromatography, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.58), yielded a beige solid (0.05 g, 83%), mp 132–134°C. Exact Mass calcd. for $C_{24}H_{23}NS_2$: 389.1272; found: 389.1263.

### *N*-Isobutyl-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 5b

The same procedure as for the formation of **4b** was used. Flash chromatography of the crude product, eluting with $CH_2Cl_2$–hexanes (4:1) ($R_f$ = 0.60), yielded a yellow oil (0.06 g, 86%) bp 150–153°C/5 Torr. Exact Mass calcd. for $C_{20}H_{23}NS_2$: 341.1272; found: 341.1270.

### 1-Naphthalenethiol

Concentrated hydrochloric acid (11.40 mL) was added to crushed ice (30 g) in a round-bottom flask, with stirring. 1-Naphthalenesulfonyl chloride (1.00 g, 4.41 mmol) was added portionwise via spatula, making sure that the solution was kept below 0°C. Tin (6.30 g, 53.04 mmol) was added to the vessel, turning the solution yellow. The mixture was refluxed for 6 h and the solution became clear. The solution was then extracted with $CH_2Cl_2$ (2 × 20 mL), washed with saturated NaCl solution, dried, and concentrated to yield a yellow oil (0.63 g, 89%), bp 138–140°C/7 Torr (lit. (23) bp 138–140°C/2 Torr).

### 1-Mercapto-2-naphthaldehyde 6

1-Naphthalenethiol (0.94 g, 5.87 mmol) was dissolved in dry hexanes (50 mL) under argon, and TMEDA (2.20 mL, 14.67 mmol) was added to the mixture. The reaction was cooled to 0°C and 1.6 M *n*-BuLi (9.17 mL, 14.67 mmol) was added dropwise. The solution initially turned cloudy white and eventually became yellow and clear. The mixture was then stirred for 0.5 h at 0°C, then warmed to room temperature before stirring for an additional 16 h. *N*-Formylpiperidine (1.11 mL, 9.98 mmol) was added via syringe and a dark red paste resulted. Vigorous stirring for 10 h formed a yellow mixture, which was then washed with 1 M HCl (2 × 25 mL) and extracted with $CH_2Cl_2$ (4 × 25 mL). Additional washing with saturated NaCl (25 mL), drying, and concentration yielded a brown oil (0.62 g, 56%). Chromatography on aluminum oxide, eluting with $CH_2Cl_2$–MeOH (95:5) ($R_f$ = 0.45), gave a yellow oil (0.47 g, 43%), bp 139–142°C/7 Torr. IR (film), ν: 3050, 2924, 2864, 1682, 1495, 825, 753; $^1$H NMR, δ: 9.82 (s, 1H), 8.33 (m, 2H), 7.95 (m, 2H), 7.66 (m, 1H), 7.31 (m, 1H), 5.31 (s, 1H). Exact Mass calcd. for $C_{11}H_8OS$: 188.0288; found: 188.0283.

### 2-Mercapto-1-naphthaldehyde 7 and 3-mercapto-2-naphthaldehyde 8

2-Naphthalenethiol (2.00 g, 12.48 mmol) was ground and dissolved in dry hexanes (80 mL), under argon, and TMEDA (4.69 mL, 31.20 mmol) was added to the mixture. The mixture was cooled to 0°C and 1.6 M *n*-BuLi (19.50 mL, 31.20 mmol) was added dropwise. The solution initially turned a cloudy white colour and eventully became yellow and clear. The mixture was then stirred for 0.5 h at 0°C and warmed to room temperature before stirring for an additional 16 h. *N*-Formylpiperidine (2.78 mL, 24.96 mmol) was added via syringe and a dark red paste resulted. Vigorous stirring for 10 h formed a yellow mixture, which was washed with 1 M HCl (2 × 30 mL) and extracted with $CH_2Cl_2$ (4 × 30 mL). Washing with saturated NaCl (30 mL), drying, and concentration afforded a brown oil (1.76 g, 75%). Chromatography on aluminum oxide, eluting with $CH_2Cl_2$–MeOH (95:5) ($R_f$ = 0.64), resulted in compound **7** (0.70 g, 45%), mp 122–124°C. IR (film), ν: 2957, 2924, 2851, 2725, 2555, 1722,774; $^1$H NMR, δ: 11.03 (s, 1H), 8.66 (d, 1H, *J* = 7.5 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 7.63 (m, 1H), 7.48 (m, 1H), 7.34 (d, 1H, *J* = 7.5 Hz), 7.31 (d, 1H, *J* = 7.7 Hz), 4.85 (s, 1H). Exact Mass calcd. for $C_{11}H_8OS$: 188.0288; found: 188.0285.

An earlier fraction obtained on eluting with $CH_2Cl_2$ –MeOH (95:5) ($R_f$ = 0.33) resulted in **8** (0.47 g, 30%), mp 134–136°C. IR (film), ν: 2970, 2930, 2850, 2578, 1708, 1525, 734; $^1$H NMR, δ: 10.15 (s, 1H), 8.26 (s, 1H), 7.89 (d, 1H, *J* = 3.9 Hz), 7.73 (m, 1H), 7.68 (m, 1H), 7.52 (d, 1H, *J* = 7.6 Hz), 7.45 (dd, 1H, *J* = 7.6, 3.8 Hz), 5.48 (s, 1H). Exact Mass calcd. for $C_{11}H_8OS$: 188.0288; found: 188.0281.

### Synthesis of 7 by an alternative route, from 2-hydroxy-1-naphthaldehyde 9

*A. 2-(*tert*-Butyldimethylsilylthio)-1-naphthaldehyde **10***

To a solution of 2-hydroxy-1-naphthaldehyde (1.00 g, 5.81 mmol), in 16 mL of pyridine at 0°C, triflic anhydride (1.09 mL, 6.45 mmol) was slowly added. Evolution of a white gas occurred and the resulting mixture was stirred at 0°C for an additional 5 min. The mixture was then warmed to room temperature and stirred for 24 h. Water (15 mL) was added to the solution, which was extracted with diethyl ether (2 × 15 mL), washed with $H_2O$ (15 mL), 10% aqueous HCl, and then with saturated NaCl (15 mL). The organic layer was dried and concentrated to obtain a brown, foamy solid (1.32 g, 75%). Recrystallization from $CH_2Cl_2$–hexanes af-

forded a beige solid (1.15 g, 65%). IR (KBr), ν: 3160, 2834, 2755, 1702, 1587, 856, 784; $^1$H NMR, δ: 10.81 (s, 1H), 8.45 (d, 1H, *J* = 6.3 Hz), 8.25–7.17 (m, 5H).

Dry THF (25 mL) was saturated with $H_2S$ gas, and the reaction vessel was then cooled to –78°C. The 1.6 M *n*-BuLi (8.00 mL, 13.00 mmol) was added dropwise to the above solution, which was allowed to warm to 0°C, with stirring for 0.5 h. The mixture was then recooled to –78°C and TBDMS-Cl (1.68 g, 11.11 mmol) was added portionwise with a spatula. The yellow mixture was warmed to room temperature and was partitioned between pentane (50 mL) and $H_2O$ (25 mL). The organic layer was extracted and washed with $H_2O$ (20 mL), dried, and concentrated to afford TBDMS-SH as a clear oil (83%). IR (film), ν: 2737, 2560; $^1$H NMR, δ: 0.97 (s, 9H),0.29 (s, 6H), 0.11 (s, 1H).

Potassium hydride (0.31 g, 7.69 mmol), was initially washed with dry pentane (3 × 20 mL) and was placed in a flask with 10 mL of pentane. The silanethiol above (1.13 g, 7.63 mmol) was added slowly to the reaction mixture at 0°C and stirring was continued for 2 h. Solvent was removed and a white solid was obtained (0.98 g, 69%). The salt was recrystallized from toluene to yield white crystals of TBDMS-SK (0.87 g, 61%).

A solution of this salt (0.12 g, 0.66 mmol) in dry THF (15 mL) was added to tetrakis(triphenylphosphine)palladium (0) (0.06 g, 0.05 mmol) and the triflate obtained above (0.20 g, 0.66 mmol) in toluene (20 mL). The brown solution was refluxed for 5 h, after which it was partitioned between $H_2O$ (25 mL) and ethyl acetate (25 mL). The organic layer was washed with $H_2O$ (2 × 15 mL), dried, and concentrated to afford a brown oil (0.14 g, 73%). Flash chromatography, eluting with $CH_2Cl_2$ ($R_f$ = 0.44), afforded **10** as a yellow oil (0.10 g, 52%). IR (film), ν: 2990, 2946, 2856, 2725, 1722, 1597, 1517; $^1$H NMR, δ: 10.85 (s, 1H), 8.35 (d, 1H, *J* = 8.2 Hz), 7.98 (d, 1H, *J* = 7.1 Hz), 7.78 (dd, 1H, *J* = 8.1, 4.0 Hz), 7.60 (m, 1H), 7.41 (m, 1H), 7.17 (dd, 1H, *J* = 7.0, 3.9 Hz), 1.05 (s, 9H), 0.48 (s, 6H).

*B. Deprotection of **10** to give **7***

To a solution of the protected thiol **10** (0.53 g, 0.18 mmol) in THF (10 mL) at 0°C, tetrabutylammonium fluoride (0.20 mL, 0.19 mmol) was added dropwise. The mixture was stirred for 3 h, eventually turning a deep yellow colour. The reaction mixture was washed with saturated $NH_4Cl$ (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL), dried, and concentrated to afford a brown oil (0.30 g, 90%). Flash chromatography, eluting with $CH_2Cl_2$ ($R_f$ = 0.48), resulted in a yellow solid (76% yield), mp 124–126°C. This product was identical (mixture mp, IR, $^1$H NMR) with the *2-mercapto-1-naphthaldehyde* **7** prepared as described above.

**8,16-Imino-8*H*,16*H*-dinaphtho [2,1-*b*,*f*]-1,5-dithiocin 12**

A mixture of the naphthaldehyde **7** (0.04 g, 0.20 mmol) and ammonium acetate (0.02 g, 0.20 mmol) in absolute ethanol (15 mL) was refluxed for 3.5 h. The solution was cooled and the ethanol was removed. The yellow solid was recrystallized from methanol to give **12** (0.03 g, 94%), mp 160–163°C. IR (KBr), ν: 3356, 2952, 1583, 835, 806. Exact Mass calcd. for $C_{22}H_{15}NS_2$: 357.0646; found: 357.0647.

**8,16-Imino-8*H*,16*H*-dinaphtho [1,2-*b*,*f*]-1,5-dithiocin 11**

The same procedure outlined for compound **12** was used for the formation of **11**. Yellow crystals were obtained (0.03 g, 92%) mp 168–170°C. IR (KBr), ν: 3033, 2953, 2846, 1529, 818. Exact Mass calcd. for $C_{22}H_{15}NS_2$: 357.0646; found 357.0643.

**8,16-Imino-8*H*,16*H*-dinaphtho [2,3-*b*,*f*]-1,5-dithiocin 13**

The same procedure was used for the formation of **13**. Yellow crystals were obtained, recrystallized from methanol (0.04 g, 96%), mp 170–172°C. IR (KBr), ν: 3197, 2953, 1590, 1495, 1492, 805. Exact Mass calcd. for $C_{22}H_{15}NS_2$: 357.0646; found: 357.0640.

**8,16-Imino-8*H*,16*H*-dinaphtho[2,1-*b*,*f*]-1,5-dioxocin 14a**

A mixture of 2-hydroxy-1-naphthaldehyde (1.72 g, 10.00 mmol) and ammonium acetate in 15 mL of ethanol was refluxed for 4.5 h, then cooled to room temperature. The ethanol was partially evaporated and the yellow solid was recrystallized to yield **14a** (1.55 g, 95%), mp 241–243°C (lit. (15) mp 240–242°C). IR (KBr), ν: 3332, 1616, 955; $^1$H NMR, δ: 8.18 (d, 2H, *J* = 6.0 Hz), 7.72 (t, 4H, *J* = 5.8 Hz), 7.59 (d, 2H, *J* = 6.0 Hz), 7.36 (d, 2H, *J* = 5.8 Hz), 7.05 (d, 2H, *J* = 5.8 Hz), 6.63 (d, 2H, *J* = 2.5 Hz), 3.00 (br s, 1H); $^{13}$C NMR, δ: 150.3s, 131.5s, 131.0d, 128.9s, 128.4d, 127.2d, 123.7d, 121.9d, 118.3d, 112.4s, 75.6d. Exact Mass calcd. for $C_{22}H_{15}NO_2$: 325.1101; found: 325.1093.

***N*-(Methoxycarbonyl)-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 15**

The amine **2b** (0.20 g, 0.70 mmol) was dissolved in acetone (15 mL), then cesium carbonate (1.37 g, 4.20 mmol) was added to the solution, which was stirred for 5 min. Slow addition of methyl chloroformate (0.22 mL, 2.80 mmol) with a syringe resulted in a red-coloured solution. The mixture was refluxed for 16 h under argon. Removal of the $Cs_2CO_3$ by gravity filtration and evaporation of the acetone solution yielded an orange oil. A solution of 4% NaOMe in methanol was added to the oil and stirring was continued for 2 h. A white precipitate was obtained (0.16 g, 67%), which was filtered off and recrystallized from $CH_2Cl_2$–hexanes, mp 143–146°C. IR (KBr), ν: 3347, 2975, 2846, 1698, 1503, 731. Exact Mass calcd. for $C_{18}H_{17}NO_2S_2$: 343.0700; found: 343.0702.

***N*-(1′-Phenylethyl)-2,8-dimethyl-6,12-imino-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin 16**

To thiosalicylaldehyde **3b** (0.11 g, 0.69 mmol) dissolved in 20 mL of absolute ethanol and 1 mL of acetic acid, the *R*-(+)-1-phenylethylamine (0.05 mL, 0.38 mmol) was added dropwise. The solution turned an orange colour and was then refluxed for 4.5 h. The mixture was washed with $H_2O$ (10 mL), extracted with $CH_2Cl_2$ (3 × 15 mL), dried, and concentrated to yield a brown oil (0.12 g, 86%). Flash chromatography, eluting with ethyl acetate – hexanes (1:1) ($R_f$ = 0.57), gave a foamy beige solid (0.10 g, 77%), mp 81–83°C. IR (KBr), ν: 3367, 2949, 1485; $^1$H NMR, δ: 7.39 (m, 4H), 6.92 (m, 7H), 5.53, 5.48 (2s, 2H), 4.17, 3.90 (2q, 1H, *J* = 7.8 Hz), 2.25 (s, 6H), 1.61, 1.55 (2d, 3H, *J* = 7.8 Hz); $^{13}$C NMR, δ: 143.2s, 134.3s, 133.1s, 129.8d, 129.2d, 127.6d, 127.5d, 127.4s, 127.2d, 126.5d, 60.0d, 59.3d, 22.5q, 20.9q.

Exact Mass calcd. for $C_{24}H_{23}NS_2$: 389.1272; found: 389.1264.

**_N_-(3′-Methylbutyl)-6,12-imino-6_H_,12_H_-dibenzo[_b_,_f_]-1,5-dithiocin 17a**

A mixture of thiosalicylaldehyde **3a** (0.12 g, 0.85 mmol), L-leucine (0.06 g, 0.47 mmol), and absolute ethanol (30 mL) was refluxed for 4.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow oil (0.09 g, 68%). Flash chromatography, eluting with $CH_2Cl_2$ – hexanes (85:15) ($R_f$ = 0.52), gave a yellow oil (0.08 g, 60%). IR (film), ν: 3057, 2945, 2853, 830, 742; $^1$H NMR, δ: 7.28 (m, 2H), 7.0 (m, 6H), 5.41 (s, 2H), 2.98 (m, 1H), 1.62 (m, 4H), 0.91 (d, 6H, $J$ = 7.5 Hz). Exact Mass calcd. for $C_{19}H_{21}NS_2$: 327.1115; found: 327.1112.

**_N_-(2′-Hydroxyethyl)-6,12-imino-6_H_,12_H_-dibenzo[_b_,_f_]-1,5-dithiocin 17b**

A mixture of **3a** (0.14 g, 1.03 mmol), L-serine methyl ester hydrochloride (0.09 g, 0.57 mmol), and absolute ethanol (15 mL) was refluxed for 4.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow-brown oil. This was dissolved in $CH_2Cl_2$ (15 mL) and the organic layer was washed with saturated $NaHCO_3$ (15 mL), dried, and concentrated to afford a yellow oil (0.14 g, 88%). Flash chromatography, eluting with $CH_2Cl_2$–hexanes (85:15) ($R_f$ = 0.57), gave white needle crystals (0.11 g, 75%), mp 165–167°C. IR (film), ν: 3395, 2993, 1626, 1505, 806; $^1$H NMR, δ: 7.82 (dd, 4H, $J$ = 7.8, 7.6 Hz), 7.32 (dt, 4H, $J$ = 7.8, 7.7 Hz), 6.21 (s, 2H), 4.35 (m, 2H), 3.50 (m, 3H).

**_N_-(1′-_tert_-Butyloxycarbonyl-3′-methylbutyl)-6,12-imino-6_H_,12_H_-dibenzo[_b_,_f_]-1,5-dithiocin 17c**

A mixture of **3a** (0.22 g, 1.60 mmol), L-leucine *tert*-butyl ester (0.19 g, 0.88 mmol), and absolute ethanol (15 mL) was refluxed for 4.5 h. Work-up as for **17b**, followed by flash chromatography, eluting with $CH_2Cl_2$–hexanes (85:15) ($R_f$ = 0.67), gave a yellow solid (0.24 g, 71%), mp 154–156°C. $^1$H NMR, δ: 7.33 (m, 4H), 7.01 (m, 4H), 5.78, 5.70 (2s, 2H), 3.65 (t, 1H, $J$ = 9.1 Hz), 1.82 (m, 1H), 1.64 (m, 2H), 1.20 (s, 9H), 0.90 (d, 6H, $J$ = 9.4 Hz). Exact Mass calcd. for $C_{24}H_{29}NO_2S_2$: 427.1639; found: 427.1644.

## Acknowledgements

Support of this work by a Natural Sciences and Engineering Research Council of Canada research grant is gratefully acknowledged. One of us (F.D.T.) acknowledges the award of an Ontario Graduate Scholarship.

## References

1. (*a*) M. Harmata, C.L. Barnes, S.R. Karra, and S. Elahmad. J. Am. Chem. Soc. **116**, 8392 (1994); (*b*) S. Paliwal, S. Geib, and C.S. Wilcox. J. Am. Chem. Soc. **116**, 4497 (1994); (*c*) D. St. C. Black, D.C. Craig, N. Kumar, and D.B. McConnell. Tetrahedron Lett. **37**, 241 (1996); (*d*) K. Mitra and K.S. Gates. Tetrahedron Lett. **36**, 1391 (1995); (*e*) B.G. Bag and U. Maitra. Synth. Commun. **25**, 1849 (1995).
2. J. Rebek, Jr. Acc. Chem. Res. **23**, 399 (1990).
3. (*a*) J. Tröger. J. Prakt. Chem. **36**, 225 (1887); (*b*) M.A. Spielman. J. Am. Chem. Soc. **57**, 583 (1935); (*c*) V. Prelog and P. Wieland. Helv. Chim. Acta, **27**, 1127 (1944).
4. H. Salez, A. Wardani, M. Demeunynck, A. Tatibouet, and J. Lhomme. Tetrahedron Lett. **36**, 1271 (1995).
5. S.H. Wilen, J.Z. Qi, and P.G. Williard. J. Org. Chem. **56**, 485 (1991).
6. F.D. Toste, A.J. Lough, and I.W.J. Still. Tetrahedron Lett. **36**, 6619 (1995).
7. (*a*) F. Asinger and M. Theil. Angew. Chem. **70**, 667 (1958); (*b*) M. Theil, F. Asinger, and G. Trümpler. Liebigs Ann. Chem. **619**, 137 (1958).
8. Y.L. Gol'dfarb, A.E. Skorova, and M.K. Kirmalova. Izv. Akad. Nauk SSSR, Ser. Khim. 1421 (1966); 1426 (1966).
9. M.F. Corrigan and B.O. West. Aust. J. Chem. **29**, 1413 (1976).
10. L.E. Brieaddy and K.H. Donaldson. J. Heterocycl. Chem. **32**, 1683 (1995).
11. J.C. Arnould, M. Didelot, C. Cadilhac, and M.J. Pasquet. Tetrahedron Lett. **37**, 4523 (1996).
12. P.J. Stang, M. Hanack, and L.R. Subramanian. Synthesis, 85 (1982).
13. (*a*) E.I. Miranda, M.J. Diaz, I. Rosado, and J.A. Soderquist. Tetrahedron Lett. **35**, 3221 (1994); (*b*) A.M. Rane, E.I. Miranda, and J.A. Soderquist. Tetrahedron Lett. **35**, 3225 (1994).
14. T.D. Nelson and R.D. Crouch. Synthesis, 1031 (1996).
15. E.R. Biehl, H.M. Refat, A.A. Fadda, and Y. Lu. Heterocycles, **43**, 977 (1996).
16. (*a*) E.J. Corey, M.G. Bock, A.P. Kozikowski, A.V. Rao, D. Floyd, and B. Lipshutz. Tetrahedron Lett. 1051 (1978); (*b*) K.J. Butcher. Synlett, 825 (1994).
17. (*a*) D.H.R. Barton, J.-P. Finet, and J. Khamsi. Tetrahedron Lett. **28**, 887 (1987); (*b*) D.H.R. Barton, N. Ozbalik, and M. Ramesh. Tetrahedron Lett. **29**, 857 (1988).
18. H. Nozaki, T. Aratani, T. Toraya, and R. Noyori. Tetrahedron, **27**, 905 (1971).
19. (*a*) P. Beak, A. Basu, D.J. Gallagher, Y.S. Park, and S. Thayumanaran. Acc. Chem. Res. **29**, 552 (1996); (*b*) D. Hoppe. Angew. Chem. Int. Ed. Engl. **36**, 2282 (1997).
20. (*a*) M. Oestreich, R. Fröhlich, and D. Hoppe. Tetrahedron Lett. **39**, 1745 (1998); (*b*) K.M.B. Gross, Y.M. Jun, and P. Beak. J. Org. Chem. **62**, 7679 (1997); (*c*) S. Norsikian, I. Marek, and J.-F. Normant. Tetrahedron Lett. **38**, 7523 (1997); (*d*) K. Nishimura, M. Ono, Y. Nagaoka, and K. Tomioka. J. Am. Chem. Soc. **119**, 12974 (1997); (*e*) N. Voyer, J. Roby, S. Chénard, and C. Barberis. Tetrahedron Lett. **38**, 6505 (1997); (*f*) D.E. Ward and W.-L. Lu. J. Am. Chem. Soc. **120**, 1098 (1998).
21. E.E. Snell and S.J. di Mari. Enzymes, **2**, 335 (1976).
22. M. Casey, J. Leonard, and B. Lygo. Advanced practical organic chemistry. Chapman and Hall, New York. 1990. p. 230.
23. The Merck Index. 12th ed. Whitehouse, N.J. 1996. p. 1095.

## List of abbreviations

TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TBAF: tetra-*n*-butylammonium fluoride
TBDMS: *tert*-butyldimethylsilyl
Tf: trifluoromethanesulfonyl
Triflate: trifluoromethanesulfonate
DCC: dicyclohexylcarbodiimide