Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Domino Reactions of (Z,Z)-2,2′-Thiobis(1,3-diarylprop-2-en-1-ones) with Acetylacetone and Ethyl Acetoacetate: Stereoselective Synthesis of Highly Functionalized Dihydrofurans

Beer Mohamed Vinosha [a], Subbiah Renuga [a], Michael Gnanadeebam [a], Subbu Perumal [b] & Antonin Lycka [c]

[a] Department of Chemistry, Fatima College, Madurai, India

[b] School of Chemistry, Madurai Kamaraj University, Madurai, India

[c] Research Institute for Organic Synthesis, Pardubice-Rybitvi, Czech Republic

Version of record first published: 26 Jun 2009.

Synthetic Communications®, 39: 2776–2788, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802664236

Taylor & Francis
Taylor & Francis Group

Novel Domino Reactions of (*Z*,*Z*)-2,2′-Thiobis(1,3-diarylprop-2-en-1-ones) with Acetylacetone and Ethyl Acetoacetate: Stereoselective Synthesis of Highly Functionalized Dihydrofurans

Beer Mohamed Vinosha,[1] Subbiah Renuga,[1] Michael Gnanadeebam,[1] Subbu Perumal,[2] and Antonin Lycka[3]

[1]Department of Chemistry, Fatima College, Madurai, India
[2]School of Chemistry, Madurai Kamaraj University, Madurai, India
[3]Research Institute for Organic Synthesis, Pardubice-Rybitvi, Czech Republic

Abstract: The domino reactions of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-ones) with acetylacetone and ethyl acetoacetate in the presence of sodium ethoxide afforded the corresponding 4,5-dihydrofurans stereoselectively in moderate yields presumably via a Michael addition–enolization–displacement sequence.

Keywords: Dihydrofurans, domino reactions, stereoselective synthesis, 2,2′-thio-bis (1,3-diarylprop-2-en-1-ones)

INTRODUCTION

Recent investigations from our laboratory have shown that 2,2′-thiobis(1,3-diarylprop-2-en-1-ones) **1** and their sulfonyl counterparts are useful synthons for the construction of heterocycles such as thiazines,[1a] thianes,[1b] dithianes,[1c] and oxiranes.[2] Reaction of sulfonylbis compounds with acetylacetone/ethyl acetoacetate afforded mainly

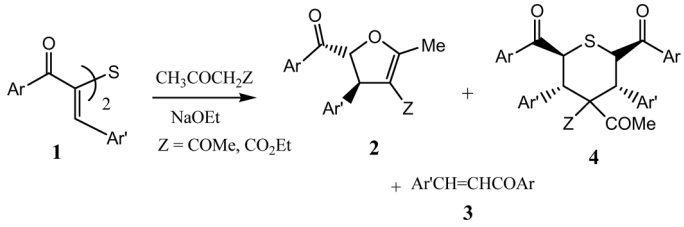
Received September 17, 2008.
Address correspondence to Subbiah Renuga, Department of Chemistry, Fatima College, Madurai 625018, India. E-mail: s.renuga@gmail.com

thianes.[3] In view of the biological importance of thianes,[4] we planned to synthesize several novel thianes from **1** in continuation of our research program to synthesize novel heterocycles employing domino reactions.[5]

However, surprisingly, the reaction of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-ones) **1** with acetylacetone/ethyl acetoacetate in the presence of sodium ethoxide furnished highly substituted dihydrofurans, and the results are described in this article. It is pertinent to note that dihydrofurans and furans constitute structural motifs in a wide range of naturally occurring substances such as alkaloids,[6] lignans,[7] and pheromones[8] and possess a multitude of biological activities,[9] viz. anticancer,[10] anti-inflammatory,[11] analgesic,[12] antifungal,[13] and antirheumatic[14] activites. They also find application as agrochemicals, as pharmaceuticals, and in the food industry,[15] besides being potential intermediates in organic synthesis.[16] Hence, there has been a sustained interest in developing new and efficient methods for the synthesis of dihydrofurans.[17a–17d]

RESULTS AND DISCUSSION

In the present study, the reaction of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-ones) **1** with acetylacetone and ethyl acetoacetate in the presence of sodium ethoxide afforded mainly dihydrofurans **2** (Scheme 1). In a typical reaction, a solution of (*Z*,*Z*)-2,2′-thiobis(1,3-diarylprop-2-en-1-one) **1**, acetylacetone/ethyl acetoacetate, and sodium ethoxide in a molar ratio of 1:2:2 in dry dimethylformamide (DMF)–ethanol (EtOH) furnished, after chromatographic separation, moderate to good yields (58–85%) of **2**. Except in one case, where the reaction of **1a** with ethyl acetoacetate (entry 8, Table 1) afforded a mixture of thiane **4** (Ar=Ar′=Ph; Z=COOEt) and dihydrofuran, all other reactions failed to furnish any characterizable product other than **2**. This reaction, when performed with equimolar amounts of **1**, acetylacetone/ethyl



1 2 4 3

Scheme 1. Synthesis of dihydrofurans.

Table 1. Reaction of 2,2′-thio*bis*(1,3-diarylprop-2-en-1-ones) **1** with acetylacetone and ethyl acetoacetate

Entry	Thiobis-enones	Ar	Ar′	Z	Products (yield %)			Mp (°C)[c]
					Condition 1[a]	Condition 2[b]		
1	**1a**	C_6H_5	C_6H_5	$COCH_3$	**2a** (73)	**2a** (38)	**3a** (6)	140–142 (139–140[17a]; 114.5–115.8[17b]; 125–127[17c,17d])
2	**1b**	C_6H_5	*p*-Cl-C_6H_4	$COCH_3$	**2b** (64)	**2b** (32)	**3b** (8)	Semisolid[17b–17d]
3	**1c**	*p*-Cl-C_6H_4	C_6H_5	$COCH_3$	**2c** (61)	**2c** (29)	**3c** (5)	116–118
4	**1d**	*p*-Cl-C_6H_4	*p*-F-C_6H_4	$COCH_3$	**2d** (71)	**2d** (33)	**3d** (8)	136–138
5	**1e**	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	$COCH_3$	**2e** (75)	**2e** (35)	**3e** (10)	144–146
6	**1f**	*p*-Cl-C_6H_4	*p*-Me-C_6H_4	$COCH_3$	**2f** (71)	**2f** (34)	**3f** (9)	116–118
7	**1g**	*p*-Me-C_6H_4	C_6H_5	$COCH_3$	**2g** (74)	**2g** (34)	**3g** (7)	99–100[17a]
8	**1a**	C_6H_5	C_6H_5	COOEt	**2h** (58)	**2h** (15)	**3a** (10)	Colorless liquid[17c,17d]
					4 (32)	**4** (54)		194–196
9	**1b**	C_6H_5	*p*-Cl-C_6H_4	COOEt	**2i** (70)	**2i** (40)	**3b** (6)	Semisolid
10	**1c**	*p*-Cl-C_6H_4	C_6H_5	COOEt	**2j** (65)	**2j** (30)	**3c** (8)	Semisolid
11	**1d**	*p*-Cl-C_6H_4	*p*-F-C_6H_4	COOEt	**2k** (82)	**2k** (45)	**3d** (6)	118–120
12	**1e**	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	COOEt	**2l** (85)	**2l** (42)	**3e** (9)	134–136
13	**1f**	*p*-Cl-C_6H_4	*p*-Me-C_6H_4	COOEt	**2m** (76)	**2m** (50)	**3f** (5)	106–108

[a]The ratio of **1**–ketone–NaOEt is 1:2:2.
[b]The ratio of **1**–ketone–NaOEt is 1:1:1.
[c]Melting points of **3** agree with those reported in the literature.

acetoacetate, and sodium ethoxide, gave diminished yields of **2** along with unreacted **1** and a small amount of chalcone **3** (5–10%) (Scheme 1). The yields of dihydrofurans obtained under these conditions are given in Table 1.

The methods available in the literature for the synthesis of some of the dihydrofurans reported in this article, namely **2a, 2b, 2g**, and **2h**, suffer from either the use of hazardous arsonium compounds,[17b] formation of a mixture of stereoisomers,[17c,17d] or prolonged reaction time.[17a,][17b]

The dihydrofurans **2** were characterized using elemental analyses, infrared (IR), and ^{1}H, ^{13}C, and two-dimensional NMR spectroscopic data. The proton signals were assigned on the basis of straightforward considerations such as intensity, multiplicity, substituent-induced chemical shifts (SCS values), and H,H-correlation spectroscopy (COSY) and nuclear overhauser effect spectroscopy (NOESY) spectra. The carbon signal assignments were based on the carbon chemical shifts in conjunction with C,H-COSY correlations for proton-bearing carbons and heteronuclear multiple bond correlations (HMBC) for quaternary carbons. The signals at 193.7 and 192.0 ppm were assigned respectively to the acetyl and benzoyl carbonyls on the basis of HMBC. The *J* value of 4.8 Hz of the doublets at 5.51 and 4.56 ppm due to H-5 and H-6 respectively reveals their *trans* relationship. Compounds **2h**–**m** obtained from the reaction of **1** with ethyl acetoacetate showed similar spectroscopic features except for the fact that the signals due to the acetyl group were replaced by those of the ethoxycarbonyl group. The structures of **2** deduced from NMR spectroscopic data are in good accord with that determined from the X-ray crystallographic studies on a single crystal of **2a** (Fig. 1).[18] Compound **4** (Ar=Ar′=Ph) was characterized by elemental analysis and NMR spectroscopic data.

The formation of dihydrofurans (Scheme 2) is presumably triggered by an initial Michael addition of the enolate **5** of acetylacetone/ethyl acetoacetate to **1** to give **6**, which undergoes ring closure to the dihydrofurans via displacement of the sulfide function as depicted in **7**. The by-product viz. chalcone **3** in the reaction of **1** with acetylacetone/ethyl acetoacetate in the presence of 1 mol of base probably arises from the fragmentation of **8** to **9** (Scheme 2). The improved yield of dihydrofuran with 2 mol of base also supports the mechanism (Table 1). This mechanistic pathway is also in accordance with that reported in the literature for the formation of dihydrofurans.[17a–17c]

The predominant formation of dihydrofurans in the reaction of **1** with acetylacetone/ethyl acetoacetate in contrast to the formation of thianes by double Michael addition in the reaction of the sulfone counterpart of **1**[3] deserves mention. Probably in the case of sulfone, after the first Michael addition of acetylacetone/ethyl acetoacetate, the second

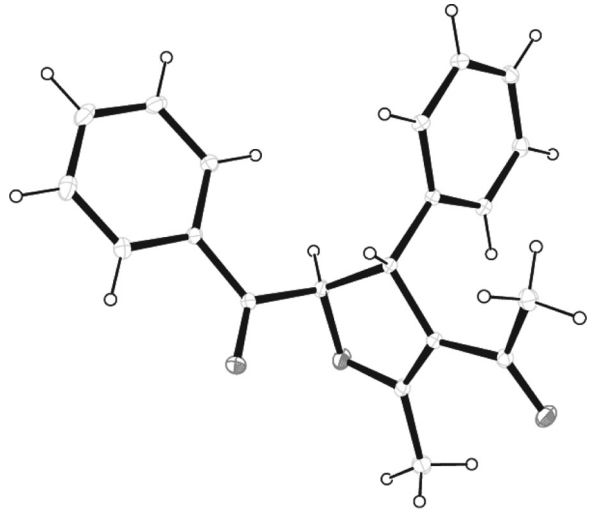
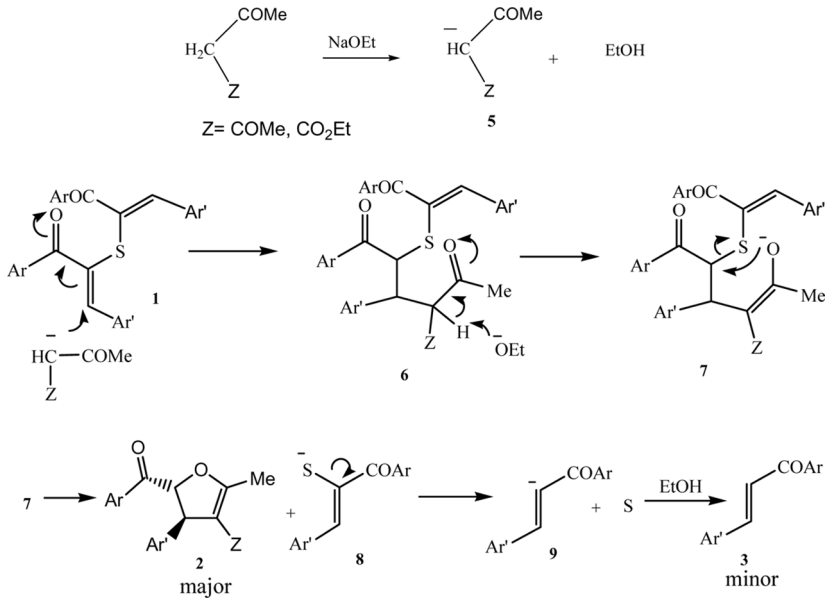


Figure 1. X-ray structure of dihydrofuran **2a**.



Scheme 2. Mechanism of formation of dihydrofurans **2** and chalcones **3** from **1**.

Michael addition leading to thianes is presumably favored over the displacement reaction leading to dihydrofurans because there are two powerful electron-withdrawing groups favoring the former reaction over the latter.

CONCLUSIONS

In conclusion, the present work describes the predominant formation of highly functionalized dihydrofurans via domino reactions of acetylacetone/ethyl acetoacetate with (*Z*,*Z*)-2,2′-thio*bis*(1,3-diarylprop-2-en-1-ones) in DMF in the presence of sodium ethoxide, in contrast to thianes obtained from the reaction of the corresponding sulfones observed in an earlier study. Investigations on the utility of the dihydrofurans as synthons in the construction of novel heterocycles currently are being explored in our group.

EXPERIMENTAL

The melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer IR-577 instrument with KBr. NMR spectra were recorded at 25°C on either a Bruker AMX 300 instrument operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C or a Bruker AMX 360 instrument operating at 360 MHz for ^{1}H and at 90 MHz for ^{13}C. Solutions in $CDCl_3$ were approximately 0.05 M, and chemical shifts were referenced internally to TMS in δ scale (ppm). Two-dimensional NMR measurements, H,H-COSY, C,H-COSY, NOESY, and HMBC, have also been performed using these instruments. Standard Bruker software was used throughout. Elemental analyses were performed on a Perkin-Elmer 2400 series II Elemental CHNS Analyser. The Michael acceptor **1** was obtained by a literature method.[19]

General Procedure for the Synthesis of 4,5-Dihydrofurans 2

A solution of acetylacetone (1.0 g, 10 mmol) in absolute ethanol (20 mL) was added dropwise with stirring to a solution of sodium ethoxide prepared by dissolving sodium metal (0.24 g, 10 mmol) in absolute ethanol (8 mL). To this mixture, a solution of 2,2′-thio*bis*(1,3-diphenylprop-2-en-1-one) (2.2 g, 5 mmol) in dry dimethylformamide (50 mL) was added dropwise with stirring. After the addition was complete, the reaction mixture was kept at room temperature

for 1 h and then poured into ice water. The separated solid after chromatographic separation using ethyl acetate–petroleum ether [3:97 (v/v)] gave **2a** as a colorless solid. A similar procedure was followed for the reaction of 2,2′-thiobis(1,3-diphenylprop-2-en-1-one) with ethyl acetoacetate.

Data

trans-1-(5-Benzoyl-2-methyl-4-phenyl-4,5-dihydro-3-furanyl)-1-ethanone (**2a**)

Obtained as a colorless solid (2.2 g, 73%). Mp 140–142°C; lit. mps are 139–140[17a], 114.5–115.8[17b] and 125–127.[17c,17d] The IR and ^{1}H and ^{13}C NMR spectroscopic features of **2a** agree with those reported in the literature.[17a]

trans-1-[5-Benzoyl-4-(4-chlorophenyl)-2-methyl-4,5-dihydro-3-furanyl]-1-ethanone (**2b**)

Obtained as a semisolid.[17b–17d] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.97 (s, 3H, COMe), 2.45 (s, 3H, =CMe), 4.52 (d, 1H, $J = 4.8$ Hz, H-4), 5.62 (d, 1H, $J = 4.8$ Hz, H-5), 7.19 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 7.46 (t, 2H, $J = 7.5$ Hz), 7.61 (t, 1H, $J = 7.5$ Hz), 7.85 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.9 (=CMe), 29.4 (COMe), 51.1 (C-4), 88.9 (C-5), 115.8 (C-3), 128.7, 128.8, 128.9, 129.1, 133.1, 133.3, 134.0, 140.6 (aromatic carbons), 168.3 (C-2), 192.9 (PhCO), 193.6 (COMe). Anal. calcd. for $C_{20}H_{17}ClO_3$: C, 70.49; H, 5.03. Found: C, 70.59; H, 5.00.

trans-1-[5-(4-Chlorobenzoyl)-2-methyl-4-phenyl-4,5-dihydro-3-furanyl]-1-ethanone (**2c**)

Obtained as a colorless solid. Mp 116–118°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.94 (s, 3H, COMe), 2.46 (s, 3H, =CMe), 4.56 (d, 1H, $J = 4.8$ Hz, H-4), 5.59 (d, 1H, $J = 4.8$ Hz, H-5), 7.24–7.47 (m, 7H), 7.82 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.9 (=CMe), 29.6 (COMe), 51.7 (C-4), 89.3 (C-5), 115.8 (C-3), 127.5, 127.8, 129.1 (6), 129.1 (8), 130.5, 131.8, 140.6, 142.0 (aromatic carbons), 168.1 (C-2), 192.2 (PhCO), 194.2 (COMe). Anal. calcd. for $C_{20}H_{17}ClO_3$: C, 70.49; H, 5.03. Found: C, 70.37; H, 5.04.

trans-1-[5-(4-Chlorobenzoyl)-4-(4-fluorophenyl)-2-methyl-4,5-dihydro-3-furanyl]-1-ethanone (**2d**)

Obtained as a colorless solid. Mp 136–138°C; IR (KBr) ν 2916, 1689, 1593, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.98 (s, 3H, COMe), 2.45 (s, 3H, =CMe), 4.57 (d, 1H, $J = 4.8$ Hz, H-4), 5.54 (d, 1H, $J = 4.8$ Hz, H-5), 7.04–7.27 (m, 4H, aryl), 7.46 (d, 2H, $J = 8.4$ Hz), 7.82 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0 (=CMe), 29.6 (COMe), 50.9 (C-4), 89.3 (C-5), 116.0 (C-3), 129.1, 129.2 (0), 129.2 (4), 130.5, 131.6, 138.0, 141.0 (aromatic carbons), 168.0 (C-2), 192.2 (PhCO), 193.9 (COMe). Anal. calcd. for $C_{20}H_{16}ClFO_3$: C, 66.95; H, 4.49. Found: C, 66.74; H, 4.47.

trans-1-[5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-2-methyl-4,5-dihydro-3-furanyl]-1-ethanone (**2e**)

Obtained as a colorless solid. Mp 144–146°C; ^1H NMR (360 MHz, $CDCl_3$) δ: 1.97 (s, 3H, -COMe), 2.43 (s, 3H, =CMe), 4.56 (d, 1H, $J = 4.8$ Hz, H-4), 5.51 (d, 1H, $J = 4.8$ Hz, H-5), 7.18 (d, 2H, $J = 8.3$ Hz), 7.33 (d, 2H, $J = 8.3$ Hz), 7.45 (d, 2H, $J = 7.2$ Hz), 7.80 (d, 2H, $J = 7.2$ Hz); ; ^{13}C NMR (90 MHz, $CDCl_3$) δ: 14.9 (=CMe), 29.5 (COMe), 51.0 (C-4), 89.1 (C-5), 115.9 (C-3), 128.9, 129.2, 129.3, 130.5, 131.8, 133.6, 140.6, 140.8 (aromatic carbons), 168.0 (C-2), 192.0 (PhCO), 193.7 (COMe). Anal. calcd. for $C_{20}H_{16}Cl_2O_3$: C, 64.02; H, 4.30. Found: C, 64.10; H, 4.28.

trans-1-[5-(4-Chlorobenzoyl)-2-methyl-4-(4-methylphenyl)-4,5-dihydro-3-furanyl]-1-ethanone (**2f**)

Obtained as a colorless solid. Mp 116–118°C; IR (KBr) ν 2910, 1688, 1590, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 3H, COMe), 2.36 (s, 3H, *p*-tolyl-Me), 2.45 (s, 3H, =CMe), 4.49 (d, 1H, $J = 4.8$ Hz, H-4), 5.57 (d, 1H, $J = 4.8$ Hz, H-5), 7.12–7.20 (m, 4H), 7.45 (d, 2H, $J = 8.1$ Hz), 7.81 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.7 (=CMe), 20.9 (*p*-tolyl-Me), 29.4 (COMe), 51.3 (C-4), 89.3 (C-5), 115.5 (C-3), 127.2, 128.9, 129.6, 130.3, 131.5, 137.3, 138.8, 140.4 (aromatic carbons), 167.9 (C-2), 192.1 (PhCO), 194.1 (COMe). Anal. calcd. for $C_{21}H_{19}ClO_3$: C, 71.08; H, 5.40. Found: C, 71.23; H, 5.43.

trans-1-[2-Methyl-5-(4-methylbenzoyl)-4-phenyl-4,5-dihydro-3-furanyl]-1-ethanone (**2g**)

Obtained as a colorless solid. Mp 99–100°C[17a]; IR (KBr) ν 2920, 1695, 1616, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 3H, COMe),

2.43 (s, 3H), 2.47 (s, 3H), 4.51 (d, 1H, $J = 4.5$ Hz, H-4), 5.64 (d, 1H, $J = 4.5$ Hz, H-5), 7.24–7.40 (m, 7H, aryl), 7.77 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0 (=CMe), 21.8 (*p*-tolyl-Me), 29.6 (COMe), 52.0 (C-4), 89.4 (C-5), 115.8 (C-3), 127.6, 127.7, 129.1, 129.2, 129.5, 131.8, 142.2, 145.2 (aromatic carbons), 168.5 (C-2), 192.9 (PhCO), 194.3 (COMe). Anal. calcd. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.84; H, 6.27.

trans-5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (**2 h**) and 4-Acetyl-2,6-dibenzoyl-4-ethoxycarbonyl-3,5-diphenylthiane (**4**)

The mixture of products **2h** and **4** was separated by column chromatography using ethyl acetate–petroleum ether [2:98 (v/v)]. Compound **2h** was obtained as a colorless liquid (1.9 g, 58%). The IR and ^{1}H and ^{13}C NMR spectroscopic features of **2h** agree with those reported in the literature.[17c,17d]

Compound **4** was obtained as a colorless solid. Mp 194–196°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, 3H, $J = 7.2$ Hz, OCH_2CH_3), 1.34 (s, 3H, $COCH_3$), 4.14 (q, 2H, $J = 7.2$ Hz, OCH_2CH_3), 4.44 (d, 2H, $J = 11.4$ Hz, H-3,5), 6.28 (d, 2H, $J = 11.4$ Hz, H-2,6), 7.04–7.14 (m, 10H), 7.41 (m, 4H), 7.52 (t, 2H, $J = 7.5$ Hz), 7.91 (d, 4H, $J = 7.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.4 (OCH_2CH_3), 33.9 (COMe), 45.8 (C-3,5), 51.9 (C-2,6), 61.2 (OCH_2CH_3), 69.8 (C-4), 127.5, 128.3, 128.4, 128.6, 129.1 133.4, 136.1, 138.5 (aromatic carbons), 171.8, 194.9, 206.3. Anal. calcd. for $C_{36}H_{32}O_5S$: C, 74.98; H, 5.59. Found: C, 74.81; H, 5.61.

trans-5-Benzoyl-4-(4-chlorophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylic Acid Ethyl Ester (**2i**)

Obtained as a semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.01 (t, 3H, $J = 7.2$ Hz, $COOCH_2Me$), 2.41 (d, 3H, $J = 1.2$ Hz, =CMe), 3.98 (m, 2H, $COOCH_2Me$), 4.37 (dd, 1H, $J = 1.2$ & 4.8 Hz, H-4), 5.67 (d, 1H, $J = 4.8$ Hz, H-5), 7.16 (d, 2H, $J = 8.4$ Hz), 7.30 (d, 2H, $J = 8.4$ Hz), 7.42 (t, 2H, $J = 7.5$ Hz), 7.55 (t, 1H, $J = 7.5$ Hz), 7.81 (d, 2H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 ($COOCH_2CH_3$), 14.0 (=CMe), 50.9 (C-4), 59.5 ($COOCH_2CH_3$), 88.8 (C-5), 106.4 (C-3), 128.6 (6), 128.7 (1), 128.8, 129.1, 133.1, 133.3, 133.9, 140.9 (aromatic carbons), 164.5 ($COOCH_2CH_3$), 168.4 (C-2), 193.0 (PhCO). Anal. calcd. for $C_{21}H_{19}ClO_4$: C, 68.02; H, 5.16; Found: C, 68.12; H, 5.13.

trans-5-(4-Chlorobenzoyl)-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic Acid Ethyl Ester (**2j**)

Obtained as a semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (t, 3H, $J = 6.6$ Hz, $COOCH_2\underline{Me}$), 2.42 (s, 3H, =CMe), 3.94 (m, 2H, $COO\underline{CH_2}Me$), 4.37 (distorted dd, 1H, H-4), 5.66 (d, 1H, $J = 4.8$ Hz, H-5), 7.09–7.55 (m, 7H), 7.78 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 ($COOCH_2\underline{CH_3}$), 14.0 (=C$\underline{Me}$), 51.5 (C-4), 59.5 ($COO\underline{CH_2}CH_3$), 89.1 (C-5), 106.8 (C-3), 127.4, 127.8, 129.0, 129.4, 130.5, 131.6, 140.4, 142.2 (aromatic carbons), 164.7 ($\underline{COO}CH_2CH_3$), 168.1 (C-2), 192.3 (Ph$\underline{CO}$). Anal. calcd. for $C_{21}H_{19}ClO_4$: C, 68.02; H, 5.16. Found: C, 67.94; H, 5.19.

trans-5-(4-Chlorobenzoyl)-4-(4-fluorophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylic Acid Ethyl Ester (**2k**)

Obtained as a colorless solid. Mp 118–120°C; IR (KBr) ν 2983, 1693, 1654, 1208 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, 3H, $J = 7.2$ Hz, $COOCH_2\underline{Me}$), 2.41 (d, 3H, $J = 1.2$ Hz, =CMe), 3.91–4.04 (m, 2H, $COO\underline{CH_2}Me$), 4.43 (dd, 1H, $J = 1.2$ & 4.8 Hz, H-4), 5.61 (d, 1H, $J = 4.8$ Hz, H-5), 7.00–7.06 (m, 2H), 7.20–7.24 (m, 2H), 7.43 (d, 2H, $J = 6.9$ Hz), 7.80 (d, 2H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 ($COOCH_2\underline{CH_3}$), 14.0 (=C$\underline{Me}$), 50.7 (C-4), 59.6 ($COO\underline{CH_2}CH_3$), 89.0 (C-5), 106.8 (C-3), 115.5, 115.8, 128.9 (6), 129.0 (7), 129.1 (3), 130.3, 131.7, 138.0 (7), 138.1 (2), 140.5 (aromatic carbons), 164.6 ($\underline{COO}CH_2CH_3$), 168.1 (C-2), 192.2 (Ar$\underline{CO}$). Anal. calcd. for $C_{21}H_{18}ClFO_4$: C, 64.87; H, 4.67. Found: C, 64.99; H, 4.65.

trans-5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylic Acid Ethyl Ester (**2l**)

Obtained as a colorless solid. Mp 134–136°C; IR (KBr) ν 2981, 1693, 1654, 1205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, 3H, $J = 7.2$ Hz, Hz, $COOCH_2\underline{Me}$), 2.41 (s, 3H, =CMe), 3.98 (m, 2H, $COO\underline{CH_2}Me$), 4.43 (d, 1H, $J = 4.2$ Hz, H-4), 5.60 (d, 1H, $J = 4.8$ Hz, H-5), 7.19 (d, 2H, $J = 8.1$ Hz) 7.32 (d, 2H, $J = 8.1$ Hz) 7.43 (d, 2H, $J = 8.4$ Hz) 7.78 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 ($COOCH_2\underline{CH_3}$), 14.0 (=C$\underline{Me}$), 50.8 (C-4), 59.6 ($COO\underline{CH_2}CH_3$), 88.8 (C-5), 106.6 (C-3), 128.8, 128.9, 129.1, 130.3, 131.6, 133.1, 140.5, 140.8 (aromatic carbons), 164.5 ($\underline{COO}CH_2CH_3$), 168.2 (C-2), 192.0 (Ar$\underline{CO}$). Anal. calcd. for $C_{21}H_{18}Cl_2O_4$: C, 62.24; H, 4.48. Found: C, 62.31; H, 4.45.

trans-5-(4-Chlorobenzoyl)-2-methyl-4-(4-methylphenyl)-4, 5-dihydrofuran-3-carboxylic Acid Ethyl Ester (**2m**)

Obtained as a colorless solid. Mp 106–108°C; IR (KBr) ν 2979, 1693, 1653, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (t, 3H, $J = 7.2$ Hz, $COOCH_2\underline{Me}$), 2.36 (s, 3H, *p*-tolyl-Me), 2.43 (s, 3H, =CMe), 3.97 (m, 2H, -$COO\underline{CH_2}CH_3$), 4.36 (dd, 1H, $J = 1.2$ & 4.8 Hz, H-4), 5.65 (d, 1H, $J = 4.8$ Hz, H-5), 7.12–7.27 (m, 4H), 7.43 (d, 2H, $J = 8.7$ Hz), 7.79 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0 (-$COOCH_2\underline{CH_3}$), 14.0(5) (=C$\underline{Me}$), 21.1 (*p*-tolyl-$\underline{Me}$), 51.3 (C-4), 59.6 (-$COO\underline{CH_2}CH_3$), 89.2 (C-5), 107.0 (C-3), 127.3, 129.1, 129.4, 130.3, 131.7, 137.0, 139.3, 140.4 (aromatic carbons), 164.8 ($\underline{CO}OCH_2CH_3$), 168.0 (C-2), 192.4 (Ar$\underline{CO}$). Anal. calcd. for $C_{22}H_{21}ClO_4$: C, 68.66; H, 5.50. Found: C, 68.54; H, 5.51.

ACKNOWLEDGMENTS

S. R. and M. G. thank the University Grants Commission for the financial support under Major Research Project F. 31-96/2005 (SR). S. R. and M. G. also thank the secretary and the principal, Fatima College, Madurai, for providing facilities.

REFERENCES

1. (a) Gnanadeepam, M.; Selvaraj, S.; Perumal, S.; Hewlins, M. J. E.; Lycka, A. 2,6-Diaroyl-3,5-diaryl-4-methyltetrahydro-1,4-thiazine-1,1-dioxides–A synthetic and stereochemical study. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *155*, 167–173; (b) Selvaraj, S.; Renuga, S.; Gnanadeepam, M.; Perumal, S.; Sivakolunthu, S. Synthesis and stereochemical studies of some 4,4-diethoxycarbonyl-2,6-diaroyl-3,5-diarylthiane-1,1-dioxides. *Indian J. Chem.* **1999**, *38B*, 376–377; (c) Gnanadeepam, M.; Renuga, S.; Selvaraj, S.; Perumal, S.; Hewlins, M. J. E. Synthesis and NMR spectral studies of 2e,6e-diaroyl-3e,5e-diaryl-1,4-dithiane-1,1-dioxides. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *134/135*, 171–176.
2. Renuga, S.; Selvaraj, S.; Perumal, S.; Hewlins, M. J. E. Diastereoselective synthesis of 2,2′-thio*bis*- and 2,2′-sulfonyl*bis*-(2-aroyl-3-aryloxiranes). *Tetrahedron* **1999**, *55*, 9309–9316.
3. (a) Renuga, S.; Selvaraj, S.; Perumal, S.; Lycka, A.; Gnanadeebam, M. Diastereoselective synthesis and ^1H and ^{13}C NMR study of 4-acetyl-2,6-diaroyl-3,5-diaryl-4-ethoxycarbonylthiane-1,1-dioxides. *Magn. Reson. Chem.* **2001**, *39*, 651–653; (b) Renuga, S.; Perumal, S.; Gnanadeepam, M. Department of Chemistry, Fatima College, Madurai. Unpublished results.

4. (a) Matsuda, H.; Ohara, K.; Morii, Y.; Hashimoto, M.; Miyairi, K.; Okuno, T. α-Selective glycosylation with 5-thioglucopyranosyl donors: Synthesis of an isomaltotetraoside mimic composed of 5-thioglucopyranose units. *Bioorg. Med. Chem. Lett.* **2003**, 1063; (b) Bozo, E.; Boros, S.; Kuszmann, J. Conversion of 2,6-anhydro-D-altrose and -mannose derivatives with 4-substituted phenyl thiols to prepare compounds with potential antithrombotic activity. *Carbohydr. Res.* **2001**, *332*, 325–333; (c) Bozo, E.; Boros, S.; Kuszmann, J. Synthesis of 4-substituted phenyl 3,6-anhydro-1,3-dithio-D-glucofuranosides and -pyranosides as well as 2,6-anhydro-1,2-dithio-α-D-altrofuranosides possessing antithrombotic activity. *Carbohydr. Res.* **2000**, *329*, 525–538.
5. (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Berlin, 2006; (b) Mondal, S.; Malik, C. K.; Ghosh, S. A novel asymmetric approach to a densely functionalized lactarane ring system through a domino ring opening–ring closing metathesis of a norbornene derivative. *Tetrahedron Lett.* **2008**, *49*, 5649–5651.
6. (a) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. A novel total synthesis of (+)-himbacine, a potent antagonist of the muscarinic receptor of M_2 subtype. *Tetrahedron Lett.* **1999**, *40*, 3399–3402; (b) Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. Total synthesis of (±)-didehydrostemofoline (asparagamine A) and (±)-isodidehydrostemofoline. *J. Am. Chem. Soc.* **2003**, *125*, 15284–15285.
7. Rao, C. B. S. *Chemistry of Lignans*; Andhra University Press: Waltair, 1978.
8. (a) de March, P.; Figueredo, M.; Font, J.; Raya, J. Highly efficient, enantioselective synthesis of (+)-grandisol from a C_2-symmetric bis(α,β-butenolide). *Org. Lett.* **2000**, *2*, 163–165; (b) Harcken, C.; Bruckner, R. Synthesis of optically active butenolides and γ-lactones by the Sharpless asymmetric dihydroxylation of β,γ-unsaturated carboxylic esters. *Angew. Chem., Int. Ed.* **1997**, *36*, 2750–2752.
9. (a) Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep.* **1992**, *9*, 217–241; (b) Merritt, A. T.; Ley, S. V. Clerodane diterpenoids. *Nat. Prod. Rep.* **1992**, *9*, 243–287; (c) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Synthesis and biological evaluation of a novel series of furans: Ligands selective for estrogen receptor α. *J. Med. Chem.* **2001**, *44*, 3838–3848.
10. (a) Navarro, E.; Alonso, S. J.; Trujillo, J.; Jorge, E.; Perez, C. General behavior, toxicity, and cytotoxic activity of elenoside, a lignan from *Justicia hyssopifolia. J. Nat. Prod.* **2001**, *64*, 134–135; (b) Joseph, H.; Gleye, J.; Moulis, C.; Mensah, L. J.; Roussakis, C.; Gratas, C. Justicidin B, a cytotoxic principle from *Justicia pectoralis. J. Nat. Prod.* **1988**, *51*, 599–600.
11. Cho, J. Y.; Baik, K. U.; Yoo, E. S.; Yoshikawa, K.; Park, M. H. In vitro antiinflammatory effects of neolignan woorenosides from the rhizomes of *Coptis japonica. J. Nat. Prod.* **2000**, *63*, 1205–1209.
12. Borsato, M. L. C.; Grael, C. F. F.; Souza, G. E. P.; Lopes, N. P. Analgesic activity of the lignans from *Lychnophora ericoides. Phytochemistry* **2000**, *55*, 809–813.

13. Kemp, M. S.; Burden, R. S. Phytoalexins and stress metabolites in the sapwood of trees. *Phytochemistry* **1986**, *25*, 1261–1269.
14. da Silva Filho, A. A.; Albuquerque, S.; Silva, M. L. A.; Eberlin, M. N.; Tomazela, D. M.; Bastos, J. K. Tetrahydrofuran lignans from *Nectandra megapotamica* with trypanocidal activity. *J. Nat. Prod.* **2004**, *67*, 42–45.
15. Hislop, J.-A.; Hunt, M. B.; Fielder, S.; Rowan, D. D. Synthesis of deuterated γ-lactones for use in stable isotope dilution assays. *J. Agric. Food Chem.* **2004**, *52*, 7075–7083.
16. (a) Garzino, F.; Méou, A.; Brun, P. Asymmetric radical synthesis of 2,5-diaryl-2,3-dihydrofurans—Application to the preparation of (+)-phyltetralin. *Eur. J. Org. Chem.* **2003**, 1410–1414; (b) Lipshutz, B. H. Five-membered heteroaromatic rings as intermediates in organic synthesis. *Chem. Rev.* **1986**, *86*, 795–819.
17. (a) Chuang, C.-P.; Tsai, A.-I. Pyridinium ylides in the synthesis of 2,3-dihydrofurans. *Synthesis* **2006**, 675–679; (b) Cao, W.; Chen, G.; Chen, J.; Chen, R. Simple approach to the high stereoselective synthesis of *trans*-2,3-dihydrofuran derivatives. *Synth. Commun.* **2005**, *35*, 527–533; (c) Yang, Z.; Fan, M.; Mu, R.; Liu, W.; Liang, Y. A facile synthesis of highly functionalized dihydrofurans based on 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reaction of halides with enones. *Tetrahedron* **2005**, *61*, 9140–9146; (d) Yang, Z.; Fan, M.; Liu, W.; Liang, Y. A novel facile synthetic route to highly substituted 2,3-dihydrofurans via ammonium ylides. *Synthesis* **2005**, 2188–2192.
18. Nandhini, M. S.; Krishnakumar, R. V.; Mostad, A.; Renuga, S.; Selvaraj, S. Perumal S.: Natarajan, S. *trans*-3-Acetyl-5-benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran at 150 K. *Acta Cryst.* **2003**, *E59*, o1321–o1323.
19. Gnanadeebam, M.; Renuga, S.; Selvaraj, S.; Perumal, S.; Dhanabalan, A.; Hewlins, M. J. E. Diastereoselective synthesis of 2,2′-thiobis- and 2,2′-sulfonylbis-(1,3-diarylprop-2-en-1-ones)-an oxidative configurational switch. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 203–214.