(*R*)-[(2-Oxo-4-thiazolidinyl)methyl]triphenylphosphonium Iodide: A Wittig Reagent for the Synthesis of Cysteine-Derived Alkenes

Christina J. Shaffer, RuLin Fan,[1] Michael D. Lewis, James J. Kowalczyk*

Eisai Inc., 4 Corporate Drive, Andover, MA 01810-2441, USA
E-mail: jkowalczyk@alum.mit.edu

Received 27 April 2011; revised 6 September 2011

Abstract: (*R*)-[(2-Oxo-4-thiazolidinyl)methyl]triphenylphosphonium iodide (**1**), readily prepared in five steps from L-cysteine ethyl ester (39% overall on a 500 g scale), is a useful Wittig reagent for the synthesis of cysteine-derived alkenes such as those found in dipeptide isosteres and peptidomimetics. Preparation of **1** and its use in Wittig olefination reactions with aldehydes is described. The resulting thiazolidinone compounds are readily unmasked to provide the corresponding thiol, symmetrical disulfide, or *S*-trityl derivatives.

Key words: Wittig reaction, aldehydes, alkenes, peptidomimetics, thiazolidinones

In the course of preparing a series of tetrapeptide isosteres of the CA_1A_2X motif[2] (C = cysteine, A = an aliphatic amino acid, and X = methionine, serine, or glutamine) as farnesyltransferase inhibitors,[3] the need arose for a Wittig phosphonium reagent such as compound **1** (Figure 1). This paper describes the preparation of **1** and its use in Wittig olefination reactions with aldehydes and some ketones. The analogous serine-derived compound **2** has been described by Sibi and co-workers.[4] Initially we examined the use of compound **2** for the preparation of cysteine dipeptide isosteres, but extra steps (with low to modest yields) subsequent to the carbon–carbon bond forming reaction were required to convert the hydroxy into a thiol (via conversion to the mesylate, displacement with iodide, followed by trityl mercaptan, and deprotection of the trityl group). Use of compound **1** resulted in much more convergent syntheses and higher overall yields. Furthermore, in cases in which a thiazolidinone is the desired final compound, use of **1** versus **2** is much more expedient.

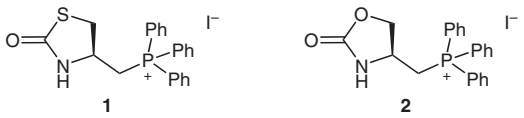
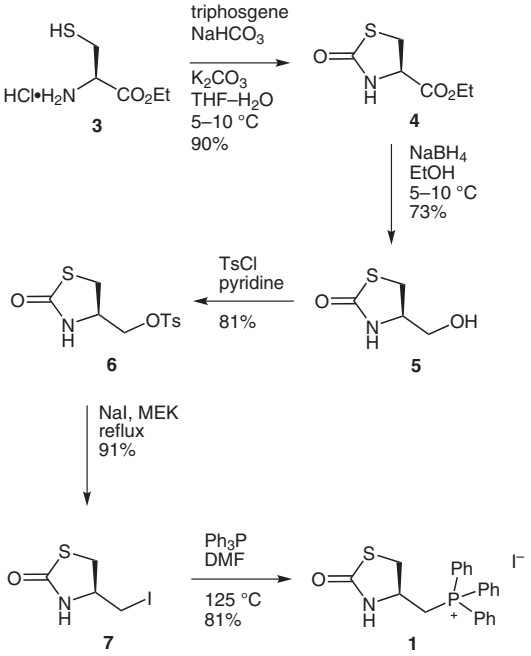


Figure 1 Wittig phosphonium reagents **1** and **2** derived from cysteine and serine, respectively

Phosphonium salt **1** is prepared from L-cysteine ethyl ester hydrochloride (**3**) in five steps in good overall yield as shown in Scheme 1. This sequence is analogous to that published for the preparation of **2**, with some important modifications. We found triphosgene[5] to be more convenient and safer to handle and to give more reproducible yields than phosgene for the thiazolidinone formation, and cysteine ethyl ester gave consistently higher yields than cysteine methyl ester.[6] Careful control of the temperature in the borohydride reduction of ester **4** (both during the reaction and the quench) gave improved yields of alcohol **5**.[7] Notably, the sequence was optimized to require no chromatography, and the final step required only a small excess of triphenylphosphine. This sequence has been used routinely to prepare **1** on a 500–1000 g scale.[8] Compound **1** is stored as a powder in a desiccator at room temperature and is routinely dried under vacuum with warming prior to use.



Scheme 1 Preparation of phosphonium reagent **1**

The Wittig reaction of **1** with benzaldehyde was optimized with regard to base, solvent, and temperature. When a suspension of **1** in THF or DME is treated with *n*-BuLi, a homogeneous orange-red solution results. In Et_2O, **1** remains undissolved even after the addition of the *n*-BuLi. The reaction is best carried out below –35 °C, but may be quenched at 0 °C. Optimal conditions were found to be 2 equivalents of *n*-BuLi in THF at ca. –46 °C (Table 1).[9]

SYNTHESIS 2011, No. 23, pp 3859–3865
Advanced online publication: 07.11.2011
DOI: 10.1055/s-0031-1289583; Art ID: M44811SS

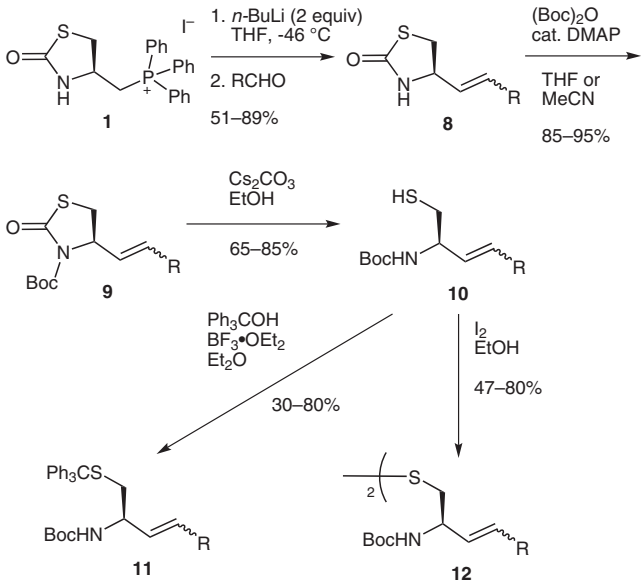
Table 1 Use of Wittig Reagent **1** in Olefination Reactions under Various Conditions

Entry	Aldehyde or ketone	Base	Solvent	Temp (°C)	Product	Yield (%)[a]	Ratio[b] *trans*/*cis*
1	PhCHO	*n*-BuLi (1 equiv)	THF	–46	**13**	29	6:1
2	PhCHO	*n*-BuLi (2 equiv)	THF	–46	**13**	89	13:1
3	PhCHO	*n*-BuLi (3 equiv)	THF	–46	**13**	36	3:1
4	PhCHO	LiHMDS (2 equiv)	THF	–46	**13**	58	5:1
5	PhCHO	NaHMDS (2 equiv)	THF	–46	**13**	45	1:1
6	PhCHO	KHMDS (2 equiv)	THF	–46	**13**	0	–
7	PhCHO	*n*-BuLi (2 equiv)	DME	–46	**13**	74	6:1
8	PhCHO	*n*-BuLi (2 equiv)	toluene	–46	**13**	1	4:1
9	PhCHO	*n*-BuLi (2 equiv)	Et_2O	–46	**13**	N.R.	–
10	PhCHO	*n*-BuLi (2 equiv)	THF	–78	**13**	58	4:1
11	PhCHO	*n*-BuLi (2 equiv)	THF	0	**13**	0	–
12	PhCHO	*n*-BuLi (2 equiv)	THF	–78 → 0	**13**	67	>97:3[c]
13	$Ph(CH_2)_2CHO$	*n*-BuLi (2 equiv)	THF	–78	**14**	50	1:1
14	$Ph(CH_2)_2CHO$	*n*-BuLi (2 equiv)	THF	0	**14**	0	–
15	$Ph(CH_2)_2CHO$	*n*-BuLi (2 equiv)	THF	–78 → 0	**14**	62	1:1
16	$Ph(CH_2)_2CHO$	*n*-BuLi (2 equiv)	THF	–46	**14**	65	1:1
17	methyl 4-formylbenzoate	*n*-BuLi (2 equiv)	THF	–46	**15**	62	5.5:1
18	thiophene-2-carboxaldehyde	*n*-BuLi (2 equiv)	THF	–46	**20**	71	5.4:1
19	1,4-benzodioxane-6-carboxaldehyde	*n*-BuLi (2 equiv)	THF	–46	**21**	70	7:1
20	$PhCH_2CHO$	*n*-BuLi (2 equiv)	THF	–46	**22**	52	1.2:1
21	*n*-octanal	*n*-BuLi (2 equiv)	THF	–46	**23**	69	1:1
22	*n*-propanal	*n*-BuLi (2 equiv)	THF	–46	**24**	69	1.4:1
23	cyclohexane carboxaldehyde	*n*-BuLi (2 equiv)	THF	–46	**25**	72	1.3:1
24	cyclopentanone	*n*-BuLi (2 equiv)	THF	–46	**26**	5	N/A
25	cyclohexanone	*n*-BuLi (2 equiv)	THF	–46	**31**	25	N/A
26	butan-2-one	*n*-BuLi (2 equiv)	THF	–46	**32**	2	n.d.
27	$MeC(O)CH_2OSi$ (*t*-Bu)Ph_2	*n*-BuLi (2 equiv)	THF	–46	**33**	N.R.	–
28	$MeC(O)CH_2OSi$ (*t*-Bu)Ph_2	*n*-BuLi (2 equiv)	THF	–46 → 20	**34**	N.R.	–

[a] Yields are of purified, isolated material. N.R. = no reaction.
[b] Ratios were determined by ^{1}H NMR spectroscopy on the crude reaction mixtures by integration of the olefinic proton signals. N/A = Not applicable. n.d. = not determined.
[c] To the limits of detection by 500 MHz ^{1}H NMR, no *cis*-isomer was detected.

For example, in Table 1 see entries 2 and 10, or 13 and 16, to compare yields at –46 °C versus –78 °C. By comparison, the published optimal temperature for reactions with compound **2** is –78 °C.[4c] The Wittig reaction produces mostly the *trans*-alkene with aromatic aldehydes, but gives approximately one-to-one mixtures of *cis*- and *trans*-alkenes with aliphatic aldehydes. Furthermore, if the reaction with aromatic aldehydes is quenched at low temperature, the amount of *trans*-alkene is decreased, and if quenched at zero, the amount of *trans*-isomer is increased (Table 1, entries 2, 10, and 12). No such temperature dependence was observed with an aliphatic aldehyde (entry 15). In most cases the *cis*- and *trans*-alkenes are separable by chromatography on silica gel. Several ketones were examined as substrates in the reaction (entries 24–28), but only cyclohexanone gave any significant

amount of the olefin product. Hence, this reagent is most suitable for Wittig olefination reactions of aldehydes and some electrophilic ketones (Scheme 2).



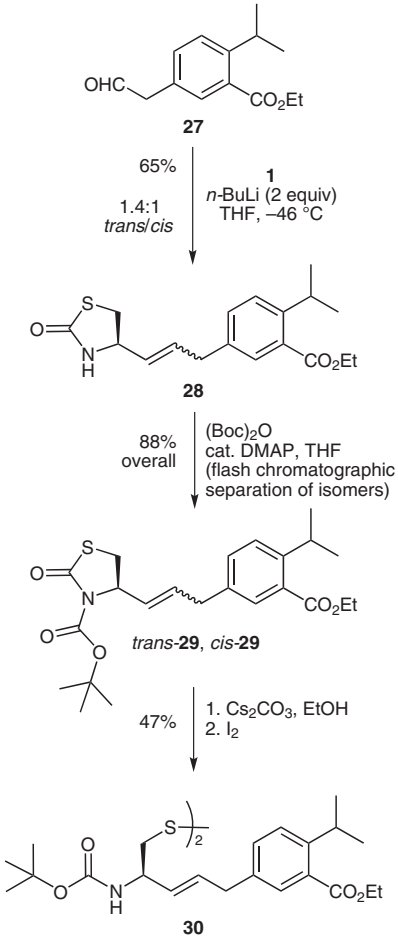
generic compound **8** corresponds to:
R = Ph (**13**), R = CH_2CH_2Ph (**14**), R = 4-$MeO_2CC_6H_4$ (**15**), R = 2-thienyl (**20**), R = 1,4-benzodioxan-6-yl (**21**), R = Bn (**22**), R = $(CH_2)_7Me$ (**23**), R = Et (**24**), R = cyclohexyl (**25**)

Scheme 2 Use of reagent **1** to prepare cysteine-derived alkenes

Similar to the analogous serine-derived phosphonium salt **2**,[4c] no racemization of **1** was observed during ylide formation or Wittig reaction.[2]

After the Wittig reaction, hydrolysis of the free thiazolidinone **8** requires harsh conditions (e.g., refluxing aq KOH), but the thiazolidinone **8** is readily converted to the Boc derivative **9**, which is readily hydrolyzed at room temperature using Cs_2CO_3 in EtOH under inert atmosphere to give the corresponding free thiol **10**. The hydrolysis is complete in a few hours in EtOH, but is much slower in MeOH, requiring days at room temperature (unlike the corresponding Boc-oxazolidinones, which are cleaved by Cs_2CO_3/MeOH in a few hours). Note that for substrates containing a carboxylic ester, transesterification can be a side reaction during the thiazolidinone hydrolysis (e.g., reaction sequence **15** to **16** to **17** or **18** in the experimental section), and thus it is best to begin with ethyl esters when possible. The thiol **10** can be isolated or oxidized to the symmetrical disulfide **12** in one-pot by the addition of iodine (e.g., compound **17**), or can be protected as the trityl derivative **11** using triphenylmethanol and boron trifluoride etherate[9] (e.g., compound **19** in the experimental section) (Scheme 2). For a specific example of the sequence, see Scheme 3.

In conclusion, we have developed a thiazolidinone-based phosphonium reagent **1** which can be used in the Wittig olefination of a variety of aldehydes. This reagent complements the analogous oxazolidinone-based reagent **2** derived from serine, and offers advantages over **2** in cases



Scheme 3

in which sulfur is desired. This reagent has proven very useful for the preparation of cysteine-derived dipeptide isosteres and peptidomimetics.

Melting points are uncorrected. NMR spectra were recorded on a Varian INOVA-400 or a Varian INOVA-500 spectrometer. ^1H NMR chemical shifts were relative to internal TMS or CHD_2OD; ^{13}C NMR chemical shifts were relative to $CDCl_3$ or CD_3OD; ^{31}P NMR chemical shifts were relative to H_3PO_4 internal standard. All starting materials, reagents, and solvents were commercially available and were used as received.

Ethyl (*R*)-(–)-2-Oxo-4-thiazolidinecarboxylate (4)

A solution of L-cysteine ethyl ester hydrochloride (**3**; 504 g, 2.70 mol) in H_2O (3.6 L) was cooled to 5–15 °C, and $NaHCO_3$ (246 g, 2.93 mol) was added with efficient stirring over ca. 30 min. The solution was stirred for an additional 15 min, and K_2CO_3 (400 g, 2.89 mol) was added. The reaction solution was cooled to 5 °C (if necessary). A solution of triphosgene (402 g, 1.35 mol) in THF (anhyd, 1 L, Aldrich) was then added dropwise over 3–4 h while maintaining a reaction temperature of 5–10 °C. Stirring was continued for 1 h at which time TLC (eluent: 15% MeOH–$CHCl_3$) indicated the reaction was complete. The reaction solution was kept at 10 °C while N_2 was bubbled through to chase out excess phosgene. The THF was then removed by rotary evaporation to leave an aqueous phase and a sticky organic layer. These phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 0.7 L). The CH_2Cl_2 extracts were combined with the original organic layer, and the resulting solution was washed with brine (0.5 L). The brine washing

was back-extracted once with CH_2Cl_2 (0.5 L). All the organic phases were combined, dried (Na_2SO_4), filtered, and evaporated to give 429 g (90%) of **4** as a light yellow liquid. This liquid would sometimes solidify on standing at low temperature, and furthermore could be precipitated from EtOAc–hexane to give **4** as a white powder; mp 167–168 °C.[5]

^{1}H NMR ($CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H), 3.63 (dd, *J* = 5.2, 11.2 Hz, 1 H), 3.71 (dd, *J* = 8.1, 11.2 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 4.45 (dd, *J* = 5.3, 7.8 Hz, 1 H), 6.36 (br s, 1 H).

(*R*)-(–)-2-Oxothiazolidine-4-methanol (5)

Ester **4** (428 g, 2.44 mol) was dissolved in anhyd EtOH (5 L) at 5–10 °C. $NaBH_4$ (6.0938 g, 161.08 mmol) was added portionwise over 3–5 h to the turbid solution with stirring. Stirring was continued for 1 h, and then the solution was cooled to 0 °C. The reaction was quenched by the addition of aq HCl (4 N, 490 mL), keeping the temperature at 0 °C. Stirring was discontinued, and the mixture was allowed to stand overnight during which time a white solid precipitated. The mixture was filtered, and the solid was rinsed with EtOH (ca. 100 mL). The combined filtrates were evaporated to give a white, crystalline powder (318 g). These crystals were suspended in MeOH (180 mL) at r.t. and cooled in a refrigerator (ca. 5–10 °C) overnight. The crystals were collected by filtration, washed with cold MeOH (ca. 100 mL), and dried under vacuum at r.t. overnight to give 211 g (65%) of desired product. The combined filtrate and washings (ca. 280 mL in total) were combined with Et_2O (40 mL) and allowed to stand at r.t. overnight to afford a second crop of crystals: 26.1 g; total yield: 237.1 g of **5** (73%); mp 101–102 °C.[6]

^{1}H NMR (CD_3OD): δ = 3.28 (dd, *J* = 5.7, 11.1 Hz, 1 H), 3.61 (dd, *J* = 6.1, 11.1 Hz, 1 H), 3.52 (m, 2 H), 3.91 (m, 1 H).

MS (C.I., ammonia): *m*/*z* calcd for $C_4H_{11}N_2O_2S$ $[M + NH_4]^+$: 151; found 151 (relative abundance 100%).

(*R*)-4-(*p*-Toluenesulfonyloxymethyl)thiazolidin-2-one (6)

Alcohol **5** (236 g, 1.73 mol) was dissolved in anhyd pyridine (730 mL), and *p*-TsCl (381 g, 2.0 mol) was added portionwise with stirring while maintaining the reaction temperature below 30 °C. The resulting solution was stirred at 25–30 °C for 2 h, and then at 40–50 °C for 4 h (until completion by TLC, eluent: 15% MeOH–$CHCl_3$). The solution was allowed to cool to r.t. and was poured into rapidly stirring H_2O (10 L). The white solid precipitate was collected by filtration and was washed thoroughly with H_2O. The white powder was dried under vacuum at 40 °C for 40 h to give 414 g (81%) of **6**.

^{1}H NMR ($CDCl_3$): δ = 3.13 (dd, *J* = 4.1, 11.3 Hz, 1 H), 3.54 (dd, *J* = 7.3, 11.3 Hz, 1 H), 4.12 (m, 2 H), 4.02 (m, 1 H), 6.04 (br s, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.1 Hz, 2 H).

Anal. Calcd for $C_{11}H_{13}NO_4S_2$: C, 45.98; H, 4.56; N, 4.87; S, 22.31. Found: C, 46.08; H, 4.54; N, 4.91; S, 22.22.

(*S*)-(–)-4-(Iodomethyl)thiazolidin-2-one (7)

Tosylate **6** (413 g, 1.44 mol), NaI (263 g, 1.75 mol), and $NaHCO_3$ (5 g, 0.059 mol) were combined in butan-2-one (ca. 5 L). The resulting solution was heated at reflux under N_2 for 8–10 h (until completion by TLC, eluent: 50% EtOAc–hexanes). The solution was cooled to r.t. and filtered. The filtrate was evaporated to give a dark yellow oil (460 g), which was dissolved in EtOAc (2 L) and the EtOAc layer was washed with sat. aq Na_2SO_3 (2 × 100 mL) and brine (2 × 100 mL). The combined aqueous phases were back-extracted with EtOAc (2 × 100 mL), and these EtOAc extracts were combined and washed with brine (50 mL). The combined EtOAc phases were dried (Na_2SO_4), filtered, and evaporated. During evaporation a white precipitate formed, and when ca. 75% of the solvent had been removed, the solid was collected by filtration to give a white powder, which was dried under vacuum (266.2 g, 76%). Further evaporation of the solvent gave a second crop of product of slightly lower purity (53 g, 15%). Overall yield of **7** as a white powder: 319.2 g (91%); mp 97.5–98 °C; $[\alpha]_D^{24}$ –11.4 (*c* = 1.47, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 3.24–3.37 (m, 3 H), 3.61 (dd, *J* = 7.5, 11.4 Hz, 1 H), 4.05–4.10 (m, 1 H), 6.51 (br s, 1 H).

^{1}H NMR (CD_3OD): δ = 3.28 (dd, *J* = 5.6, 11.5 Hz, 1 H), 3.34 (dd, *J* = 4.4, 10.3 Hz, 1 H), 3.42 (dd, *J* = 7.1, 10.5 Hz, 1 H), 3.60 (dd, *J* = 7.7, 11.5 Hz, 1 H), 3.96 (m, 1 H).

Anal. Calcd for C_4H_6INOS: C, 19.77; H, 2.49; I, 52.21; N, 5.76; S, 13.19. Found: C, 19.84; H, 2.44; I, 52.10; N, 5.68; S, 13.11.

(*R*)-(+)-4-(Triphenylphosphonylmethyl)thiazolidin-2-one Iodide (1)

Iodide **7** (318 g, 1.31 mol), Ph_3P (370 g, 1.41 mol), and DMF (320 mL) were combined and heated to 125 °C for 5–6 h. The DMF was removed under vacuum (60–80 °C) to leave a solid residue. This residue was washed with Et_2O (2 × 600 mL) to remove Ph_3P. The resulting yellow solid was pulverized with acetone (300 mL), and Et_2O (300 mL) was added, and the slurry filtered. This was repeated twice, and finally the solid was washed with ice-cold acetone (300 mL). The white powder was dried under vacuum at 40 °C to give 536 g (81%) of **1**; mp 245–246 °C; $[\alpha]_D^{24}$ +18.39 (*c* = 0.0255, MeOH).

Alternatively, crude **1** may be purified by flash chromatography on SiO_2 (eluting with MeOH–$CHCl_3$) to give a white solid. It may also be purified by dissolving in a minimum amount of MeOH and very slowly adding this solution to rapidly stirring Et_2O at r.t.; the product precipitates as a white solid.

^{1}H NMR (CD_3OD): δ = 2.97 (m, 1 H), 3.51 (ddd, *J* = 1.6, 7.2, 11.5 Hz, 1 H), 3.86–4.06 (m, 2 H), 4.34 (m, 1 H), 4.81 (br s, 1 H), 7.75–8.00 (m, 15 H).

^{13}C NMR (CD_3OD–D_2O): δ = 28.7 (d, *J* = 52.1 Hz), 37.9 (d, *J* = 7.3 Hz), 52.0 (s), 119.4 (d, *J* = 86.9 Hz), 132.5 (d, *J* = 12.7 Hz), 135.4 (d, *J* = 10.2 Hz), 137.5 (s), 178.3 (s).

^{31}P NMR (CD_3OD–D_2O): δ = 24.0 (s).

Anal. Calcd for $C_{22}H_{21}INOPS$: C, 52.29; H, 4.19; I, 25.11; N, 2.77; S, 6.34. Found: C, 52.41; H, 4.17; I, 24.99; N, 2.70; S, 6.42.

(*R*)-4-Styrylthiazolidin-2-one (13)

Compound **1** (430.1 mg, 0.8511 mmol) was dried in a flask under vacuum using a heat gun. After the flask had cooled, it was equipped with a stir bar, septum, and N_2 line, and THF (4 mL) was added via a syringe. The suspension was cooled to – 46 °C. *n*-BuLi (2.42 M, 0.70 mL, 1.694 mmol) was added, and the solution was stirred at –46 °C for 20 min (the reaction solution was homogeneous and red-orange-brown in color). Benzaldehyde (0.085 mL, 0.8362 mmol) was then added via a syringe. The color of the solution faded to yellow. Stirring was continued at –46 °C for 30 min. The reaction was quenched with sat. aq NH_4Cl (a few mL) at –46 °C. The solution became colorless and a white precipitate formed. The solution was diluted with EtOAc (30 mL) and H_2O (15 mL), and the phases were separated. The EtOAc phase was washed with pH 7.2 phosphate buffer (15 mL), H_2O (15 mL), and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil. Purification by flash chromatography (FC) on silica gel (EtOAc–hexanes) furnished the *cis*- (9.9 mg, 6%) and *trans*-isomers (142.1 mg, 83%) of **13** as oils.

cis-13

^{1}H NMR ($CDCl_3$): δ = 3.32 (dd, *J* = 8.2, 11.0 Hz, 1 H), 3.52 (dd, *J* = 7.3, 11.0 Hz, 1 H), 4.85 (q, *J* = 8.2 Hz, 1 H), 5.53 (br s, 1 H), 5.77 (dd, *J* = 9.2, 11.4 Hz, 1 H), 6.71 (d, *J* = 11.4 Hz, 1 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.31–7.40 (m, 3 H).

***trans*-13**

^{1}H NMR ($CDCl_3$): δ = 3.29 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.57 (dd, *J* = 7.3, 11.0 Hz, 1 H), 4.56 (q, *J* = 7.6 Hz, 1 H), 5.62 (br s, 1 H), 6.22 (dd, *J* = 7.8, 16.0 Hz, 1 H), 6.64 (d, *J* = 15.6 Hz, 1 H), 7.28–7.40 (m, 5 H).

(*R*)-4-(4-Phenylbut-1-en-1-yl)thiazolidin-2-one (14)

Compound **1** (365.4 mg, 0.7231 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.6 mL, 1.452 mmol), and hydrocinnamaldehyde (0.095 mL, 0.7215 mmol) furnished 104.1 mg (62%) of **14** (oil) as a 1:1 *trans*/*cis* mixture after FC purification. The ratio was determined by integration of the olefinic protons at 5.63 ppm (*trans*) and 5.77 ppm (*cis*) in the ^{1}H NMR spectrum.

^{1}H NMR ($CDCl_3$): δ = 2.40 (t, *J* = 6.6 Hz, 2 H), 2.36–2.46 (m, 2 H), 2.63–2.68 (m, 1 H), 2.71 (t, *J* = 7.8 Hz, 2 H), 2.73–2.79 (m, 1 H), 2.90 (dd, *J* = 8.2, 11.0 Hz, 1 H), 3.02 (dd, *J* = 6.9, 11.0 Hz, 1 H), 3.11 (dd, *J* = 7.8, 11.0 Hz, 1 H), 3.41 (dd, *J* = 6.9, 11.0 Hz, 1 H), 4.28–4.35 (m, 2 H), 4.46 (br s, 1 H), 5.30 (br s, 1 H), 5.40–5.49 (m, 2 H), 5.63 (dt, *J* = 5.3, 16.5 Hz, 1 H), 5.77 (dt, *J* = 7.2, 14.4 Hz, 1 H), 7.14–7.33 (m, 10 H).

(*R*)-Methyl 4-[2-(2-Oxothiazolidin-4-yl)vinyl]benzoate (15)

Compound **1** (329.7 mg, 0.6524 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.54 mL, 1.31 mmol) and methyl 4-formylbenzoate (103.9 mg, 0.6329 mmol) furnished 103.9 mg (62%) of **15** after FC purification (5.5:1 mixture of *trans*/*cis* isomers); oil.

***cis*-15**

^{1}H NMR ($CDCl_3$): δ = 3.32 (dd, *J* = 7.8, 11.0 Hz, 1 H), 3.52 (dd, *J* = 6.9, 11.0 Hz, 1 H), 3.93 (s, 3 H), 4.81 (q, *J* = 8.4 Hz, 1 H), 5.63 (br s, 1 H), 5.87 (dd, *J* = 9.6, 11.4 Hz, 1 H), 6.73 (d, *J* = 11.4 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 8.05 (d, *J* = 7.8 Hz, 2 H).

***trans*-15**

^{1}H NMR ($CDCl_3$): δ = 3.30 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.61 (dd, *J* = 7.3, 11.4 Hz, 1 H), 3.92 (s, 3 H), 4.58 (q, *J* = 7.3 Hz, 1 H), 5.64 (br s, 1 H), 6.35 (dd, *J* = 7.6, 15.8 Hz, 1 H), 6.67 (d, *J* = 16.0 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 8.02 (d, *J* = 8.2 Hz, 2 H).

(*R*)-*tert*-Butyl 4-[4-(Methoxycarbonyl)styryl]-2-oxothiazolidine-3-carboxylate (16)

Compound **15** (109.8 mg, 0.4170 mmol) was dissolved in THF (2 mL) in a flask equipped with a stir bar, septum, and N_2 line. $(Boc)_2O$ (111.7 mg, 0.5118 mmol) and DMAP (5.3 mg, 0.04338 mmol) were added, and the reaction solution was stirred at r.t. for ca. 1 h. The solution was diluted with EtOAc (20 mL) and H_2O (10 mL), and the phases were separated. The EtOAc phase was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by FC (EtOAc–hexanes) furnished a *cis*/*trans* mixture of **16** (148.7 mg, 98%).

***cis*-16**

^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9 H), 3.02 (d, *J* = 11.0 Hz, 1 H), 3.66 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.94 (s, 3 H), 5.43 (t, *J* = 8.0 Hz, 1 H), 6.07 (dd, *J* = 9.4, 11.7 Hz, 1 H), 6.67 (d, *J* = 11.9 Hz, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 8.05 (d, *J* = 8.2 Hz, 2 H).

***trans*-16**

^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9 H), 3.00 (d, *J* = 11.4 Hz, 1 H), 3.72 (dd, *J* = 7.6, 11.2 Hz, 1 H), 3.92 (s, 3 H), 5.15 (t, *J* = 7.3 Hz, 1 H), 6.48 (dd, *J* = 7.3, 16.0 Hz, 1 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 8.01 (d, *J* = 8.7 Hz, 2 H).

Diethyl 4,4′-((1*E*,1′*E*,3*R*,3′*R*)-Disulfanediylbis{3-[(*tert*-butoxycarbonyl)amino]but-1-ene-4,1-diyl})dibenzoate (17)

Compound **16** (70 mg, 0.1926 mmol) was dissolved in EtOH (2.0 mL) in a flask equipped with a stir bar, septum, and N_2 line. Cs_2CO_3 (70 mg, 0.2143 mmol) was added, and the solution was stirred at r.t. overnight. I_2 (13.1 mg, 0.1032 mmol) was added, and the mixture was stirred at r.t. 10 min. The solution was diluted with EtOAc (20 mL) and H_2O (10 mL), and the phases were separated. The EtOAc phase was washed with aq 0.25 N $Na_2S_2O_3$ (10 mL) H_2O (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by FC (EtOAc–hexanes) furnished the desired disulfide **17** (39 mg, 58%), and the free thiol **18** (15 mg, 23%). (Note that the methyl ester was converted to the ethyl ester under the reaction conditions. Only *trans*-isomers were isolated.)

^{1}H NMR ($CDCl_3$): δ = 1.39 (t, *J* = 7.1 Hz, 6 H), 1.47 (s, 18 H), 3.00–3.91 (m, 4 H), 4.36 (q, *J* = 7.2 Hz, 4 H), 4.66 (br s, 1 H), 5.04 (br s, 1 H), 6.28 (dd, *J* = 5.7, 15.8 Hz, 2 H), 6.58 (d, *J* = 15.6 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 4 H), 7.97 (d, *J* = 8.2 Hz, 4 H).

18

^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 6.9 Hz, 3 H), 1.47 (s, 9 H), 2.72–2.90 (m, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.58–5.01 (br d, 1 H), 6.22 (dd, *J* = 6.0, 16.0 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.99 (d, *J* = 8.2 Hz, 2 H).

(*R*,*E*)-Ethyl 4-{3-[(*tert*-Butoxycarbonyl)amino]-4-mercaptobut-1-en-1-yl}benzoate (18)

Compound **16** (145 mg, 0.3990 mmol) was dissolved in EtOH (2.0 mL) in a flask equipped with a stir bar, septum, and N_2 line, and Cs_2CO_3 (141.4 mg, 0.4347 mmol) was added. The solution was stirred at r.t. overnight. The reaction solution was diluted with EtOAc (20 mL) and 0.1 N HCl (10 mL), and the phases were separated. The EtOAc phase was washed with H_2O (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to furnish crude **18**, which could be further purified by FC, if desired (see preparation of **17**).

(*R*,*E*)-Ethyl 4-{3-[(*tert*-Butoxycarbonyl)amino]-4-(tritylthio)but-1-en-1-yl}benzoate (19)

The crude compound **18** (134.6 mg, 0.3990 mmol) was dissolved in Et_2O (4 mL), and Ph_3COH (195.1 mg, 0.7494 mmol) was added. The solution was cooled to 0 °C, $Et_2O{\cdot}BF_3$ (0.074 mL, 0.8029 mmol) was added, and the resulting solution was stirred at 0 °C for ca. 1.25 h. The solution was diluted with EtOAc (20 mL) and sat. aq $NaHCO_3$ (10 mL), and the phases were separated. The EtOAc phase was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by FC (EtOAc–hexanes) furnished **19** (71 mg, 32%), disulfide **17** (50 mg, 23%), and the ethyl ester of **15** (9.6 mg, 4.2%) (a contaminant in crude **18**).

^{1}H NMR ($CDCl_3$): δ = 1.39 (t, *J* = 7.1 Hz, 3 H), 1.44 (s, 9 H), 2.41–2.52 (m, 2 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 4.39–4.69 (br d, 1 H), 6.08 (dd, *J* = 5.9, 15.6 Hz, 1 H), 6.41 (d, *J* = 15.6 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 7.42–7.20 (m, 15 H), 7.96 (d, *J* = 8.2 Hz, 2 H).

(*R*)-4-[2-(Thiophen-2-yl)vinyl]thiazolidin-2-one (20)

Compound **1** (405.8 mg, 0.8030 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.65 mL, 1.573 mmol), and thiophene-2-carboxaldehyde (0.073 mL, 0.7883 mmol) furnished 117.9 mg (71%) of **20** as a 5.4:1 *trans*/*cis* mixture after FC purification.

^{1}H NMR ($CDCl_3$): δ = 3.29 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.56 (dd, *J* = 7.3, 11.0 Hz, 1H), 3.65 (dd, *J* = 6.9, 11.0 Hz, 1 H), 4.50 (q, *J* = 7.5 Hz, 1 H), 5.16 (q, *J* = 7.9 Hz, 1 H), 5.50 (br s, 1 H), 5.67 (dd, *J* = 9.2, 11.4 Hz, 1 H), 6.04 (dd, *J* = 7.8, 15.6 Hz, 1 H), 6.70 (d, *J* = 11.4 Hz, 1 H), 6.76 (d, *J* = 15.6 Hz, 1 H), 6.99 (dd, *J* = 3.7, 5.0 Hz, 1 H), 7.01 (d, *J* = 2.7 Hz, 1 H), 7.06 (dd, *J* = 3.7, 5.0 Hz, 1 H), 7.22 (d, *J* = 5.0 Hz, 1 H), 7.35 (d, *J* = 5.0 Hz, 1 H).

(*R*)-4-[2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)vinyl]thiazolidin-2-one (21)
Compound **1** (325.6 mg, 0.6443 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.53 mL, 1.283 mmol), and 1,4-benzodioxan-6-carboxaldehyde (104.3 mg, 0.6354 mmol) furnished 116.3 mg (70%) of **21** as a 7:1 *trans*/*cis* mixture after FC purification.

***trans*-21**
^{1}H NMR ($CDCl_3$): δ = 3.26 (dd, *J* = 7.8, 11.0 Hz, 1 H), 3.53 (dd, *J* = 7.3, 11.0 Hz, 1 H), 4.26 (m, 4 H), 4.52 (q, *J* = 7.6 Hz, 1 H), 5.54 (br s, 1 H), 6.05 (dd, *J* = 7.8, 15.6 Hz, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.86 (d, *J* = 1.8 Hz, 1 H), 6.90 (d, *J* = 1.8 Hz, 1 H).

***cis*-21**
^{1}H NMR ($CDCl_3$): δ = 3.28 (dd, *J* = 8.2, 11.0 Hz, 1 H), 3.51 (dd, *J* = 8.2, 11.0 Hz, 1 H), 4.26 (m, 4 H), 4.89 (q, *J* = 8.2 Hz, 1 H), 5.50 (br s, 1 H), 5.66 (dd, *J* = 9.4, 11.2 Hz, 1 H), 6.56 (d, *J* = 11.4 Hz, 1 H), 6.65 (d, *J* = 2.3 Hz, 1 H), 6.67 (d, *J* = 2.3 Hz, 1 H), 6.69 (d, *J* = 1.8 Hz, 1 H).

(*R*)-4-(3-Phenylprop-1-en-1-yl)thiazolidin-2-one (22)
Compound **1** (394.7 mg, 0.7810 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.65 mL, 1.573 mmol), and phenylacetaldehyde (0.085 mL, 0.7605 mmol) furnished 86.7 mg (52%) of **22** as a 1.2:1 *trans*/*cis* mixture after FC purification; oil.

^{1}H NMR ($CDCl_3$): δ = 3.24–3.17 (m, 2 H), 3.47–3.39 (m, 6 H), 4.36 (q, *J* = 7.5 Hz, 1 H), 4.84 (q, *J* = 6.6 Hz, 1 H), 5.40–5.38 (br s, 2 H), 5.56 (dd, *J* = 7.8, 15.1 Hz, 1 H), 5.63 (dd, *J* = 9.2, 10.5 Hz, 1 H), 5.86 (dd, *J* = 5.9, 13.7 Hz, 1 H), 5.93 (dt, *J* = 8.4, 16.7 Hz, 1 H), 7.42–7.15 (m, 10 H).

(*R*)-4-(Non-1-en-1-yl)thiazolidin-2-one (23)
Compound **1** (380.0 mg, 0.7520 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.62 mL, 1.500 mmol), and octanal (0.114 mL, 0.7299 mmol) furnished 114.4 mg (69%) of **23** as a 1:1 *trans*/*cis* mixture after FC purification; oil.

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 3.4 Hz, 6 H), 1.34 (m, 20 H), 2.09 (m, 4 H), 3.17 (dd, *J* = 7.8, 11.0 Hz, 1 H), 3.18 (dd, *J* = 8.9, 10.8 Hz, 1 H), 3.39 (dd, *J* = 6.9, 11.0 Hz, 1 H), 3.44 (dd, *J* = 7.3, 11.0 Hz, 1 H), 4.33 (q, *J* = 7.6 Hz, 1 H), 4.72 (q, *J* = 8.2 Hz, 1 H), 5.42–5.30 (br s, 2 H), 5.47 (m, 2 H), 5.64 (dt, *J* = 5.4, 16.2 Hz, 1 H), 5.75 (dt, *J* = 7.2, 14.4 Hz, 1 H).

(*R*)-4-(But-1-en-1-yl)thiazolidin-2-one (24)
Compound **1** (541.9 mg, 1.072 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.88 mL, 2.129 mmol), and propanal (0.075 mL, 1.039 mmol) furnished 112.2 mg (69%) of **24** as a 1.4:1 *trans*/*cis* mixture after FC purification; oil.

^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.01 (t, *J* = 7.6 Hz, 3 H), 2.11 (m, 4 H), 3.18 (dd, *J* = 8.5, 10.8 Hz, 2 H), 3.39 (dd, *J* = 6.9, 11.0 Hz, 1 H), 3.44 (dd, *J* = 7.3, 11.0 Hz, 1 H), 4.34 (q, *J* = 7.6 Hz, 1 H), 4.73 (q, *J* = 8.4 Hz, 1 H), 5.44 (t, *J* = 9.8 Hz, 1 H), 5.49 (t, *J* = 7.6 Hz, 1 H), 5.5 (br s, 2 H), 5.64 (dt, *J* = 5.3, 15.1 Hz, 1 H), 5.81 (dt, *J* = 6.3, 15.3 Hz, 1 H).

(*R*)-4-(2-Cyclohexylvinyl)thiazolidin-2-one (25)
Compound **1** (409.8 mg, 0.8109 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.67 mL, 1.621 mmol), and cyclohexanecarboxaldehyde (0.084 mL, 0.6964 mmol) furnished 105.2 mg (72%) of **25** as a 1.3:1 *trans*/*cis* mixture after FC purification.

^{1}H NMR ($CDCl_3$): δ = 1.14 (m, 6 H), 1.28 (m, 4 H), 1.56 (m, 3 H), 1.68 (m, 7 H), 1.98 (m, 1 H), 2.64 (m, 1 H), 3.18 (dd, *J* = 8.9, 19.5 Hz, 2 H), 3.37 (dd, *J* = 6.9, 11.0 Hz, 1 H), 3.44 (dd, *J* = 6.9 Hz, 11.0 Hz, 1 H), 4.32 (q, *J* = 7.6 Hz, 1 H), 4.74 (q, *J* = 8.4 Hz, 1 H), 5.35 (t, *J* = 10.1 Hz, 1 H), 5.41 (br s, 2 H), 5.43 (dd, *J* = 7.8, 15.1 Hz, 1 H), 5.49 (t, *J* = 10.3 Hz, 1 H), 5.70 (dd, *J* = 6.9, 15.6 Hz, 1 H).

(*R*)-4-(Cyclohexylidenemethyl)thiazolidin-2-one (26)
Compound **1** (437.4 mg, 0.8655 mmol), THF (4 mL), *n*-BuLi (2.42 M, 0.7 mL, 1.694 mmol), and cyclohexanone (0.088 mL, 0.8491 mmol) furnished 41 mg (25%) of **26** after FC purification.

^{1}H NMR ($CDCl_3$): δ = 1.55 (m, 6 H), 2.15 (m, 4 H), 3.15 (dd, *J* = 8.9, 10.8 Hz, 1 H), 3.35 (dd, *J* = 6.9, 11.0 Hz, 1 H), 4.69 (q, *J* = 8.2 Hz, 1 H), 5.18 (d, *J* = 9.2 Hz, 1 H), 5.59 (br s, 1 H).

(*R*)-Ethyl 2-Isopropyl-5-[3-(2-oxothiazolidin-4-yl)allyl]benzoate (28)
Compound **1** (52.62 g, 104.1 mmol), THF (500 mL), *n*-BuLi (2.5 M, 93.6 mL, 1.694 mmol), and compound **27**[10] (24.18 g, 103.2 mmol) furnished 22.5 g (65%) of **28** as a pale yellow oil after FC purification (EtOAc–hexanes).

***trans*-28**
^{1}H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 3.19 (dd, *J* = 7.3, 10.7 Hz, 1 H), 3.37 (d, *J* = 6.9 Hz, 2 H), 3.47 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.63 (sept, *J* = 6.9 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 5.53 (br s, 1 H), 5.56 (m, 1 H), 5.89 (m, 1 H), 7.24 (dd, *J* = 2.1, 8.0 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 1.8 Hz, 1 H).

***cis*-28**
^{1}H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 6.6 Hz, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 3.23 (dd, *J* = 8.7, 11.0 Hz, 1 H), 3.42 (d, *J* = 7.3 Hz, 2 H), 3.46 (m, 1 H), 3.64 (sept, *J* = 6.9 Hz, 1 H), 4.36 (q, *J* = 6.9 Hz, 2 H), 4.82 (q, *J* = 2.1 Hz, 1 H), 5.45 (br s, 1 H), 5.65 (m, 1 H), 5.83 (m, 1 H), 7.23 (dd, *J* = 2.1, 8.0 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 1.8 Hz, 1 H).

***tert*-Butyl (*R*)-4-{3-[3-(Ethoxycarbonyl)-4-isopropylphenyl]prop-1-en-1-yl}-2-oxothiazolidine-3-carboxylate (29)**
Compound **28** (9.7345 g, 29.22 mmol) was dissolved in THF (185 mL), and $(Boc)_2O$ (11.54 g, 52.88 mmol) and DMAP (513.6 mg, 4.204 mmol) were added. The solution was stirred at r.t. for 2 h. The solution was diluted with EtOAc (800 mL), washed with H_2O (2 × 400 mL) and brine (400 mL). The EtOAc layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. Purification by FC (EtOAc–hexanes) furnished a *cis*/*trans* mixture of **29** (11.1329 g, 88%) as a yellow oil (ca. 1.4:1 *trans*/*cis*).

***trans*-29**
^{1}H NMR ($CDCl_3$): δ = 1.24 (dd, *J* = 2.3, 6.9 Hz, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.40 (s, 9 H), 2.91 (dd, *J* = 0.9, 11.0 Hz, 1 H), 3.38 (d, *J* = 6.9 Hz, 2 H), 3.61 (dd, *J* = 6.6, 13.5 Hz, 1 H), 3.64 (sept, *J* = 6.9 Hz, 1 H), 4.36 (q, *J* = 7.3 Hz, 2 H), 4.93 (t, *J* = 7.3 Hz, 1 H), 5.75 (m, 1 H), 5.87 (m, 1 H), 7.25 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 1.8 Hz, 1 H).

***cis*-29**
^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.9 Hz, 6 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 1.50 (s, 9 H), 2.85 (dd, *J* = 2.3, 11.0 Hz, 1 H), 3.53 (d, *J* = 7.3 Hz, 2 H), 3.60 (dd, *J* = 7.3, 11.0 Hz, 1 H), 3.62 (sept, *J* = 6.9 Hz, 1 H), 4.35 (q, *J* = 7.3 Hz, 2 H), 5.53 (m, 1 H), 5.78 (m, 1 H), 5.86 (m, 1 H), 7.27 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 7.50 (d, *J* = 1.8 Hz, 1 H).

Diethyl 5,5′-((2*E*,2′*E*,4*R*,4′*R*)-Disulfanediylbis{4-[(*tert*-butoxycarbonyl)amino]pent-2-ene-5,1-diyl})bis(2-isopropylbenzoate) (30)
Compound *trans*-**29** (8.238 g, 19.00 mmol) was dissolved in absolute EtOH (250 mL). Cs_2CO_3 (6.5120 g, 20.02 mmol) was added, and the suspension was stirred at r.t. overnight. I_2 (1.31 g, 10.32

mmol) was added to the homogeneous solution. The mixture was stirred at r.t. until the I_2 dissolved (30 min). The solution was diluted with EtOAc (1000 mL), and the EtOAc layer was washed with H_2O (2×500 mL) and brine (500 mL), dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. Purification by FC (EtOAc–hexanes) furnished 3.6497 g (47%) of **30**.

^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.9 Hz, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.42 (s, 9 H), 2.8–3.0 (m, 2 H), 3.36 (d, *J* = 6.9 Hz, 2 H), 3.63 (sept, *J* = 6.9 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.43–4.92 (br d, 1 H), 5.52 (m, 1 H), 5.77 (m, 1 H), 7.25 (d, *J* = 6.9 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 1.8 Hz, 1 H).

Acknowledgment

We thank Amy E. Christuk for contributions to the preparation of compound **1**.

References

(1) Current address: School of Pharmacy, JiangSu University, Zhenjiang City, Jiang Su Province, ZP 212003, P. R. of China.

(2) (a) Garcia, A. M.; Kowalczyk, J. J.; Lewis, M. D. US Patent 6486202 B1 20021126, **2002**; *Chem. Abstr.* **2003**, *138*, 4818. (b) Lewis, M. D.; Kowalczyk, J. J.; Christuk, A. E.; Fan, R.; Harrington, E. M.; Sheng, X. C.; Yang, H.; Garcia, A. M.; Hishinuma, I.; Nagasu, T.; Yoshimatsu, K. US Patent 5840918, **1998**; *Chem. Abstr.* **1995**, *124*, 146855. (c) Lewis, M. D.; Garcia, A. M.; Kowalczyk, J. J.; Yang, H.; Schwartz, C. E. PCT Int. Appl. WO 9838162, **1998**; *Chem. Abstr.* **1998**, *129*, 231021. (d) Yang, H.; Sheng, X. C.; Harrington, E. M.; Ackermann, K.; Garcia, A. M.; Lewis, M. D. *J. Org. Chem.* **1999**, *64*, 242. (e) Harrington, E. M.; Kowalczyk, J. J.; Pinnow, S. L.; Ackermann, K.; Garcia, A. M.; Lewis, M. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2775.

(3) (a) Barbacid, M. *Ann. Rev. Biochem.* **1987**, *56*, 779. (b) Khosravi-Far, R.; Der, C. J. *Cancer Metastasis Rev.* **1994**, *13*, 67. (c) Sebti, S. M.; Hamilton, A. D. *Drug Discovery Today* **1998**, *3*, 26. (d) Williams, T. M.; Dinsmore, C. J. *Adv. Med. Chem.* **1999**, *4*, 273.

(4) (a) Sibi, M. P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407. (b) Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1675. (c) Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509. (d) Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434.

(5) Falb, E.; Nudelman, A.; Hassner, A. *Synth. Commun.* **1993**, *23*, 2839.

(6) Ethyl (*R*)-(–)-2-oxo-4-thiazolidinecarboxylate (**4**) has recently become available commercially from Aldrich Chemical Co.

(7) The enantiomer of **5**, prepared from D-cysteine methyl ester, has been reported (mp 103.5–104.5 °C): Kubodera, N.; Nagano, H.; Takagi, M.; Matsunaga, I. *Heterocycles* **1982**, *18*, 259.

(8) Similarly, the enantiomer of **1** was prepared from D-cysteine ethyl ester according to Scheme 1.

(9) Hiskey, R. G.; Tucker, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 4794.

(10) Compound **27** was prepared in 4 steps from 4-isopropylbenzaldehyde (bromination; halogen–metal exchange using *t*-BuLi and quench with ethyl chloroformate; Wittig reaction with (methoxymethyl)triphenylphosphonium chloride + *t*-BuOK; enol ether hydrolysis with aq HI in MeCN). See ref. 2a. Compound **27** may also be prepared in 6 steps from 5-formylsalicylic acid via Stille coupling using tributyl(prop-1-en-2-yl)stannane and a hydrogenation.