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Synthesis of chiral disulfides: potential reagents for enantioselective sulfurization

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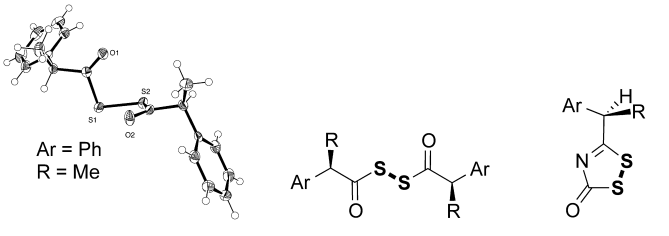
Synthesis of chiral phosphorothioates for use as antisense oligonucleotides might benefit from the use of chiral disulfides. This paper reports the synthesis of chiral analogs of phenylacetyl disulfide and of 5-methyl-3*H*-1,2,4-dithiazol-3-one from the same set of 2-arylalkanoic acids. The X-ray crystal structures of the disulfides derived from (*R*) and (*S*)-2-phenylpropanoic acid establish the stereochemistry and the helicity of these materials, and density functional theory calculations suggest that the high specific rotations can be due to preferred retention of this helicity in solution. Chiral HPLC showed that the final products were formed with enantiomeric purities from 86.1% to >99.9%.



Keywords: chiral disulfides; X-ray; chiral HPLC; phosphorothioate oligonucleotides

1. Introduction

Sulfurization of phosphorus is a key step in the synthesis of phosphorothioate oligonucleotides, reagents that can be used as DNA analogs for antisense applications (*1–4*). While elemental sulfur can be used, it was noted long ago that it is relatively slow and, when used in an automated DNA synthesizer, "led to instrument failure as a result of the insolubility of S_8 in most organic solvents" (*5*). Beaucage solved this problem in 1990 with the report of a soluble reagent, now popularly known as the Beaucage reagent (Figure 1), that rapidly delivered sulfur to the phosphorus of the phosphite triester in the phosphoramidite method of solid-phase DNA synthesis (*5, 6*). While

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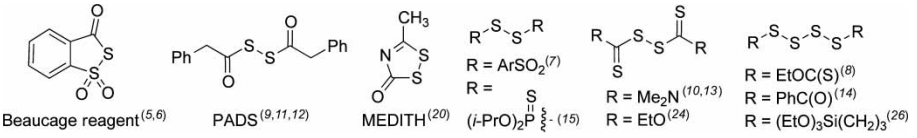


Figure 1. Examples of sulfurizing reagents.

effective, many reports have noted its poor stability in solution (necessitating its use in silylated glass (*6*)), difficult synthesis resulting in high cost, and formation of an oxidizing reagent as a byproduct, which may account for small amounts of phosphate impurity linkages (*7–10*). In order to overcome these problems, a wide variety of sulfurizing reagents, a selection of which is shown in Figure 1, has been investigated (*7–28*).

Since substitution of a terminal oxygen with a sulfur atom on the phosphate backbone of DNA results in a loss of symmetry at the phosphorothioate linkage, a mixture of diastereomeric linkages results from the sulfurization of the phosphite triester. For one reagent that has been successfully used by Isis Pharmaceuticals, phenylacetyl disulfide (PADS), it was shown that the diastereomer ratio was indistinguishable from that obtained using the Beaucage reagent (*29*, *30*). In principle, an achiral reagent could selectively give one diastereomer at early reaction, but a chiral sulfurizing reagent might do so more readily by double stereodifferentiation (*31*). A recent report by Mikolajczyk described the use of chiral disulfides for kinetic resolution of phosphines (*32*), so a similar approach involving the synthesis of chiral analogs of reagents used for phosphorothioate synthesis seemed warranted.

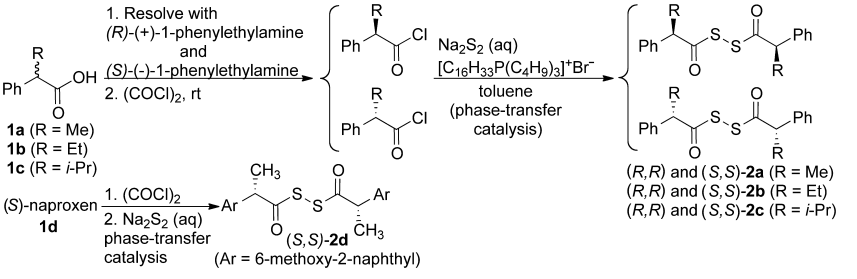
The Beaucage reagent itself does not appear to be a good choice for the synthesis of a chiral analog, but both PADS and 5-methyl-3*H*-1,2,4-dithiazol-3-one (MEDITH) (*33*),[1] another highly reactive sulfurizing reagent, presented ready opportunities for the convergent synthesis of chiral reagents; the other reagents would place centers of chirality farther from the reactive disulfide linkage. We report here (1) the synthesis of enantiomerically pure chiral analogs of PADS starting with known α-alkylated carboxylic acids, (2) X-ray diffraction results for one pair of enantiomers that unequivocally establish the absolute configurations of two disulfides and are in accord with the reported configurations of the starting carboxylic acids, (3) density functional theory (DFT) calculations that support the observed helicity about the S–S bond, (4) conversion of the enantiomerically pure chiral acids to chiral thioamides with no epimerization in cases where there is relatively little steric encumbrance, (5) conversion of the thioamides to acid-sensitive enantiomerically pure chiral analogs of MEDITH, and (6) chiral HPLC results in support of the enantiomeric purity of the new disulfides. We will report separately the results of phosphite sulfurization with these new reagents (*34*).[2]

2. Results and discussion

2.1. *Chiral analogs of PADS*

The synthesis of PADS from phenylacetyl chloride has been reported by several groups (*12*, *35–37*). Since enantiomerically pure 2-aryl carboxylic acids are well known, this seemed to be a straightforward route to the desired chiral disulfides. The method developed by Kodomari *et al.* (*35*), which gave PADS in 95% yield, was carried out by the addition of an aqueous solution of Na_2S_2 to a benzene solution of phenylacetyl chloride and hexadecyltributylphosphonium bromide as a phase-transfer catalyst. When this method was used for the synthesis of the chiral analogs of PADS using chiral carboxylic acid chlorides (*38*), crude yields of only ~60–70% were obtained. This could be improved to ~80–90% simply by the addition of the acid chloride to a vigorously

stirred mixture of aqueous Na_2S_2 and the phase-transfer catalyst in toluene (Scheme 1). A single crystallization of **2a**–**c** in methanol and of **2d** in benzene/petroleum ether gave the enantiomers in 50–63% isolated yields. The specific rotations of the disulfides are unusually high, ranging from an average of ±366 for **2a** to ±541 for **2c**.



Scheme 1. Synthesis of chiral disulfides.

2.2. *X-ray structure of 2a and DFT calculations*

Single crystals of (*R*, *R*) and (*S*, *S*)-**2a** were grown by a single crystallization from hot methanol with cooling to room temperature (rt). The X-ray structure determinations confirmed both the overall structures and on the basis of Flack parameters (*39, 40*) unequivocally established the absolute stereochemistry of the α-stereocenters of the carboxylic acids, namely, (*R*)-(-)-**1a** (*41–43*) giving rise to (*R*, *R*)-(-)-**2a** and (*S*)-(+)-**1a** giving rise to (*S*, *S*)-(+)-**2a** (see Figure 2 for a representative ORTEP drawing (*44*) and the supplementary data for details; there are two independent molecules in the unit cell, differing slightly in the dihedral angles about the carbonyl to 3°–carbon bonds and the tilt of the phenyl rings).[3] The absolute configurations of the starting carboxylic acids were reported in 1956 without the use of a single-crystal X-ray diffraction structure (*41*), and other workers have reported results in agreement with this determination: each of the (+)-enantiomers

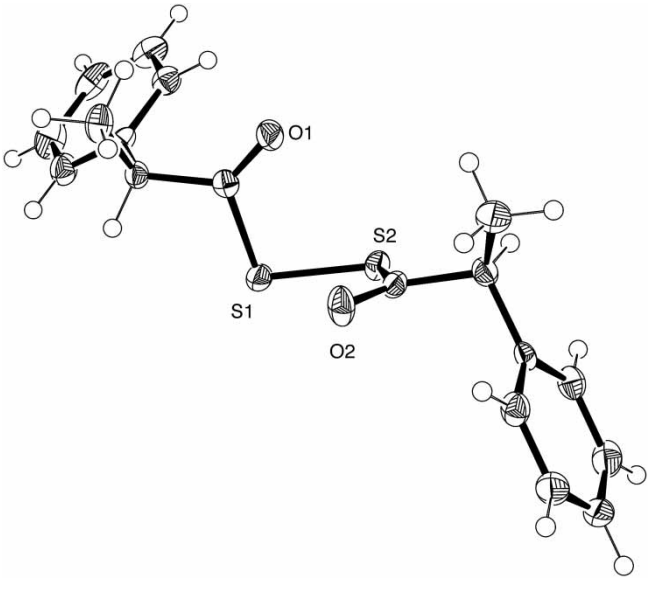


Figure 2. ORTEP drawing of Molecule 1 (see text) of (*S*,*S*)-**2a**.

of **1a**–**e** is accepted as having the *S*-configuration (*41–43, 45, 46*). A search of the Cambridge Structural Database for structures of 2-phenylpropanoic acid (**1a**) turned up several structures of diastereomeric salts and of the pure enantiomers in cocrystals, but the absolute configurations were all assumed to be correct and no attempts to crystallographically confirm the *R*- and *S*-configurations were reported (*47–50*). However, we did find one other case comparable to those of (*R*, *R*) and (*S*, *S*)-**2a** in which an ester derived from (*S*)-(+)-**1a** was subjected to a Flack analysis and the absolute configuration confirmed (*51*).

Returning now to the disulfides themselves, a search of the Cambridge Structural Database for disulfides having carbonyl groups on the disulfide linkage resulted in finding eight neutral acyclic compounds of the form RC(O)SSC(O)R′ (Table 1). Most of the R groups are aromatic (*i.e.* R = R′ = Ph (**3a**) (*52, 53*), 4-chlorophenyl (**3b**) (*54*), 2-methoxyphenyl (**3c**) (*55*), 1-indolyl (**3d**) (*56*), ferrocenyl (**3e**)) (*57*), one has R = R′ = (cyclohexyl)$_2$N (**3f**) (*58*), and two have R = F and R′ = CF_3 (**3g**), CF_2Cl (**3h**) (*59, 60*). The disulfide bond lengths fall in a fairly tight range (2.013 Å for **3d** to 2.039(2) Å for **3c**), so those for (*R*, *R*)-**2a** (2.0381(9), 2.037(1) Å) and for (*S*, *S*)-**2a** (2.0408(6), 2.0416(7) Å) are relatively long. The C–S–S–C dihedral angles range from 77.7(2)° for **3g** to 92.2(3)° for **3e**, averaging 84.2 ± 4.7°. Here, the dihedral angles for (*R*, *R*)-**2a** (−77.5(1)°, −81.2(1)°) and (*S*, *S*)-**2a** (+77.29(8)°, +81.24(8)°) fall at the acute end of the range. Finally, we note that in all cases, the CO bonds of the carbonyl groups very nearly eclipse the disulfide bond; the absolute values of the O–C–S–S dihedral angles range from 0.1(2)° (**2a**) to 10.7(6)° (**3c**). Overall, the bond lengths and dihedral angles in **2a** are comparable not just to the above dicarbonyl disulfides, but also to those in a variety of disulfides (*53, 61*), including a representative sampling of 25 neutral acyclic RC(S)SSC(S)R structures found in the Cambridge Structural Database (*62–66*) (but for R = alkoxy the C=S moieties do not eclipse the disulfide bond (*67, 68*)). As discussed by Zysman-Colman and Harpp (*69*), the near 90° dihedral angle in X–S–S–X systems arises from the fact that the bonds are mostly p in character, and so lone pair–lone pair repulsion from the electrons in non-bonding p-orbitals on the adjacent sulfur atoms is minimized, while p–σ^* overlap between the p-electrons and the S–X σ^* orbitals is maximized.

The solid-state structures of **2a** exhibit opposite helicity about the S–S bond, namely *P* (*i.e.* a "plus" sign for the C–S–S–C dihedral angle, that is, clockwise rotation of the carbonyl moieties

Table 1. Structural data (X-ray and DFT calculations) for dicarbonyl disulfides, RC(O)SSC(O)R′.

Compound	R, R′[a]	S–S (Å)	∠(CSSC) (°)	∠(SSCO$_1$) (°)	∠(SSCO$_2$) (°)	Space group/DFT[b]
3a (*52, 53*)	Ph	2.021(2)	80.8(3)	7.8(5)	−9.2(5)	$P2_1/a$[c]
3b (*54*)	4-ClC_6H_4	2.021(8)	79.1(1)	−2.9(3)	−10.3(3)	$P\bar{1}$
3c (*55*)	2-MeOC_6H_4	2.039(2)	84.7(3)	−3.5(5)	−10.7(6)	*Pbca*
3d (*56*)	1-indolyl[d]	2.013(1)	85.4	−2.0	−12.4	$P2_1/c$
3e (*57*)	(C_5H_5)Fe(C_5H_4)	2.022(2)	92.2(3)	−0.6(5)	−9.4(5)	$P2_12_12_1$
3f (*58*)	(C_6H_{12})$_2$N	2.014(1)	89.7(1)	−3.2(2)	−3.2(2)	$C2/c$
3g (*59*)	F, CF_3	2.017(2)	77.7(2)	−6.1(4)	8.0(5)	$P2_1/n$
3h (*60*)	F, CF_2Cl	2.029(1)	84.2(2)	0.8(4)	4.8(3)	$P2_1/n$
(*R*, *R*)-**2a**[e]	Ph(CH_3)CH	2.0381(9)	−77.5(1)	4.3(2)	−5.0(2)	$P12_11$
		2.037(1)	−81.2(1)	0.4(2)	6.7(2)	
(*S*, *S*)-**2a**[e]	Ph(CH_3)CH	2.0408(6)	77.29(8)	−4.4(2)	5.5(2)	$P12_11$
		2.0416(7)	81.24(8)	−0.1(2)	−6.9(2)	
(*S*, *S*)-**2a**, DFT	Ph(CH_3)CH	2.069	81.78	−3.47	−3.49	Gas phase
		2.070	−84.52	0.87	0.88	Gas phase, 0.72 kcal/mol
		2.070	90.10	−5.18	−5.81	CH_2Cl_2
		2.072	−90.04	−0.36	−0.50	CH_2Cl_2, 0.84 kcal/mol

Notes: [a]R = R′ where only one R group is given.
[b]Structures at local minima, and energies relative to the preceding structure.
[c]Data from (*52*); see text.
[d]Data from Cambridge Structural Database.
[e]Data given for two independent molecules in the unit cell.

from front to back on looking down the S–S bond, or alternatively $S_{S\text{-}S}$) for (S, S)-**2a** and *M* (*i.e.* for "minus", or $R_{S\text{-}S}$) for (R, R)-**2a** (*70*). The major difference between **2a** and the compounds **3a**–**h** is that only **2a** is non-racemic, and so only for **2a** are the signs of the dihedral angles important. That is, for **3a**–**h**, either both the *P* and *M* forms must be present in the crystal, or if the compound crystallizes in a chiral space group, we presume both enantiomorphs of the crystals were present. In fact, the latter must be the case for **3e**, which crystallizes in the chiral space group $P2_12_12_1$, and by chance two structures have been reported. While the authors did not comment on this, one is *P* (*57*) and the other is *M* (*71*), and data for the structure with the smaller *R*-factor value is given in Table 1. In addition, one structure, that of **3a**, was refined in a centrosymmetric space group ($P2_1/c$), yet was described as having "right-handed chirality" which would imply a single enantiomer; the published packing diagram in fact showed identical chiral molecules, which would not be possible in $P2_1/c$ (*53*). The structure of **3a** (refined in $P2_1/a$) had been reported previously with essentially the same molecular structure (*52*), but no packing diagram was published. While the data are in line with the other structures, the values must be viewed with caution.

While it seems most unlikely that (R, R) and (S, S)-**2a** are atropisomers – that is, that they do not interconvert with respect to rotation about the S–S bond – the high specific rotations noted for each of the disulfides could be due to a preferred helicity in solution driven by the stereogenic centers. DFT calculations (*72*) were carried out to assess the relative energies of *P*-(S, S)-**2a** and *M*-(S, S)-**2a**. The (*S*,*S*)-isomer was first optimized (6-31+G(d), B3LYP) starting from the X-ray coordinates of Molecule 1, to give a structure that was little changed (S–S 2.069 Å, ∠(C–S–S–C) + 81.8°; Table 1). Rotation about the S–S bond followed by reoptimization (6-31+G(d), B3LYP) gave a local minimum with virtually the same S–S bond length (2.070 Å) and a C–S–S–C dihedral angle of −84.5°. The energies of the optimized structures were calculated at the 6-311+G(2d,p) level again using the B3LYP functional, and the energy of this *M* conformation of (S, S)-**2a** was calculated to be 0.72 kcal/mol higher than that of *P*-(S, S)-**2a**. The optimizations were then repeated, using solvation (polarizable continuum model (PCM) model) in methylene chloride, since that solvent was used to measure the optical rotations, and the two minima were located but with modest changes in the dihedral angles (approximately ±90°; Table 1), and there was a small predicted increase (to 0.84 kcal/mol) in the change in energy upon rotation (Figure 3). While the two structures look different with respect to the orientations of the phenyl rings, in fact there is only a small change in the S–C–C–C(Ph) dihedral angles, and hence in the conformation about the carbonyl to 3°–carbon bond. The *P* minimum was difficult to find because the potential

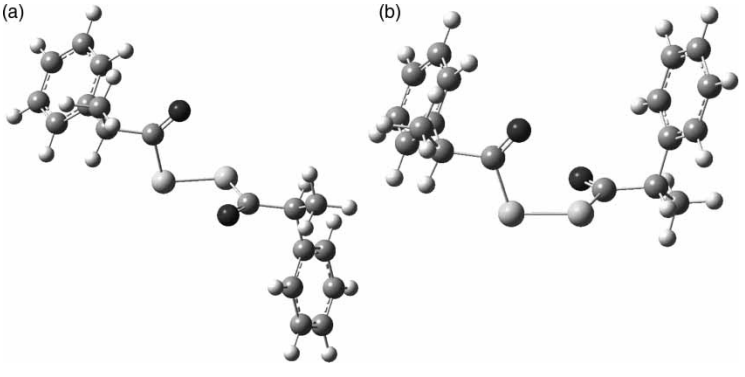


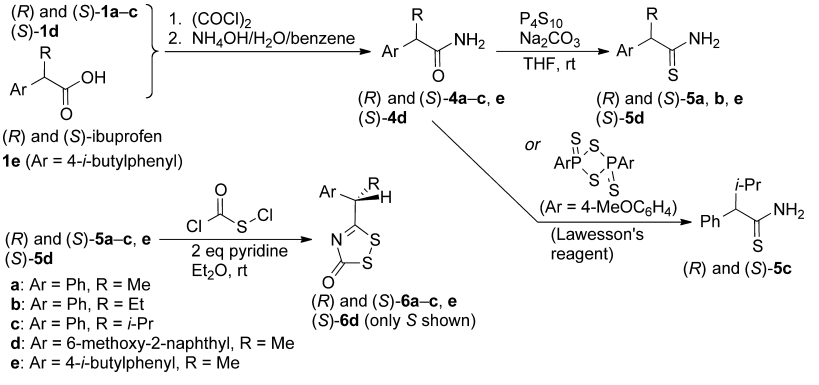
Figure 3. Calculated structures (optimized using DFT, 6-31+G(d), B3LYP) of *P*–(*S*,*S*)-**2a** (a) and *M*–(*S*,*S*)-**2a** (b) with solvation by CH_2Cl_2 (PCM). In both (a) and (b), the carbonyl on the left and the two sulfur atoms are approximately in one plane; in (a) the carbonyl on the right is in front of the C(=O)SS plane, while in (b) it is behind. In (a) ∠(S–C–C–C(Ph)) = −88.9, −89.9°, and in (b) −97.8, −98.2°; in the X-ray structure of (*S*,*S*)-**2a**, ∠(S–C–C–C(Ph)) = −88.7(1), −103.2(1)° in Molecule 1, and −80.2(1), −92.2(1)° in Molecule 2.

energy surface appeared to be quite flat, with another minimum at ∠(C–S–S–C) = 83.47°, which was 0.18 kcal/mol higher in energy than the 90.10° minimum, but the calculation kept optimizing to an apparent local energy maximum found at ∠(C–S–S–C) ≈ 87.7°, which was energetically 0.01 kcal/mol higher. Nevertheless, both in the gas phase and in solution, the ∼0.8 kcal/mol energy difference between the rotamers is in agreement with the observed solid state structure. However, it confirms the supposition that these are not likely to be true atropisomers, but the difference could certainly give a preference in solution and account for the high optical rotations of the disulfides. Interestingly, the one related enantiomerically pure disulfide, which has a thiocarbonyl RC(S)SSC(S)R core (R = (*R*)-2-[*N*-(1-phenylethyl)amino]-1-cyclopentene), has an even larger optical rotation ($[\alpha]_D^{20} - 2102$) (*73*); here too the X-ray structure was reported, but it appears that the more crowded atropisomer was observed in the solid state.

2.3. *Synthesis of chiral analogs of MEDITH*

Chiral sulfurizing reagents based on the MEDITH structure (Figure 1) are attractive for a number of reasons. First, MEDITH and a related ethoxy (in place of the methyl)-substituted analog are particularly reactive (*19*, *20*). In our hands, for instance, the phosphorus of a chiral *N*-sulfonylvaline-derived oxazaphospholidinone (*74*) was sulfurized by MEDITH while the Beaucage reagent did not react (*75*). Second, the structure of MEDITH is arguably the most different from those of the acyclic di and tetrasulfides shown in Figure 1 and therefore chiral analogs provide the greatest opportunities for different results from the PADS analogs. Third, the starting materials for the synthesis of the MEDITH analogs are the same as the chiral carboxylic acids **1a**–**d** used for the PADS analogs.

The chiral carboxylic acids shown in Scheme 2 were converted to the acid chlorides (*38*) and then treated with concentrated NH_4OH (*42*) to give the chiral amides (**4a**–**e**), for which literature data are available, albeit from alternate synthetic routes that generally did not give both enantiomers (*45*, *46*, *76*, *77*). The conversions of the chiral amides to the thioamides were initially attempted with Lawesson's reagent (*78*), but only racemic products were isolated. The problem was traced to racemization of the thioamides on silica gel (*79*), even on silica gel treated with 1% Et_3N. Since the use of Lawesson's reagent required purification by column chromatography, other methods were tried, including P_4S_{10} alone (*80*), P_4S_{10} on basic alumina (*80*), and P_4S_{10}/Na_2CO_3 (*81*). The P_4S_{10}/Na_2CO_3 procedure gave the highest yields and it did not require column chromatography, the purification of the products instead being carried out by an aqueous work-up followed by crystallization. The α-methyl- and ethyl-substituted chiral amides **4a**, **b**, **d**, and **e** were converted in this way to the new thioamides **5a**, **b**, **d**, and **e** in 85–95% yield. Only the *i*-Pr-substituted **4c**



Scheme 2. Synthesis of MEDITH analogs.

failed to react with P_4S_{10}/Na_2CO_3, even after stirring for longer times or at reflux. It is reasonable to suppose that the "adamantane-like" structure of P_4S_{10} gives too much steric hindrance with the relatively bulky isopropyl group. In this case for the conversion to the thioamide, Lawesson's reagent was used followed by chromatography on neutral alumina (rather than silica) treated with 1% Et_3N, and modest 43–48% yields of the enantiomers of **5c** were obtained following crystallization. Not surprisingly, however, as will be seen below, the enantiomeric purities of **5c** were lower than those of the other thioamides.

The synthesis of MEDITH or analogs with different substituents at the 5-position has been reported previously (*82–86*), and we chose Barany's procedure (*85*) since it was used to prepare material for phosphite triester sulfurization (*20*). This method gave only a ∼10% yield when applied to the synthesis of (*S*)-**6d**, so optimization of the reaction was attempted using achiral 2-phenylethanethioamide. It immediately became apparent that Barany's procedure using thioacetamide essentially fails for the 2-phenyl-substituted analog – only traces of the product were detected by NMR following the initial reaction, which gave a dark gum. Switching solvent from dimethoxyethane to methylene chloride or acetonitrile gave the same result. Racemic 2-phenylpropanethioamide was tried next, both at rt and at −35°C (the literature conditions were <10°C), with both normal and inverse addition of reactants, but again only traces of the product formed.

During the course of these experiments, we observed that a mixture of triethylamine and chlorocarbonylsulfenyl chloride in dimethoxyethane appeared to react and gave a dark solution, so an rt reaction of 2-phenylpropanethioamide and chlorocarbonylsulfenyl chloride was run in the absence of the base. To our surprise, the reaction was complete within 5 min, as judged by ^{1}H NMR and TLC. When this method was used starting with (*S*)-**5d**, the product **6d** was in fact isolated in ∼95% yield, but it was found to be racemic. Evidently, the two equivalents of HCl produced must be sequestered to prevent racemization, but a milder base than triethylamine was required to prevent reaction with the chlorocarbonylsulfenyl chloride. Pyridine was found to be effective, and ether was used as the solvent to facilitate removal of the pyridinium chloride salt; in this way, optically active material was formed in ∼95% crude yield. Compounds (*S*)-**6d** and both enantiomers of **6a** were isolated in 92% and 60% yields, respectively, following crystallization, while both enantiomers of each of **6b**, **c**, and **e** were obtained as viscous oils that did not solidify, in 85–92% yield.

The acid sensitivity of the MEDITH analogs toward racemization was not anticipated and would not be observable directly in the parent compound. We presume that the enol tautomer is relatively stable and that this accounts for the observed racemization, although even without enol formation, related epimerization in acid has been observed at a stereocenter attached to the C=N moiety of a five-membered oxazole heterocycle (*87*). We briefly examined the reaction of MEDITH itself in $CDCl_3$ with D_2O/HCl, but in fact no deuterium incorporation took place under these conditions and we have not pursued this further.

2.4. *Enantiomeric purity of disulfides*

The starting materials for the new disulfides described here, the chiral carboxylic acids **1a**–**e**, have all been reported, along with their enantiomeric purities and a variety of optical rotations for some of the individual acids. Determination of the optical purity of the starting acids on the basis of optical rotation was therefore somewhat uncertain; our values and literature values may be found in the supplementary data, along with data for the diastereomeric salts and amides. Regardless of the starting material purity, chiral HPLC is necessary for determining the enantiomeric purity of the disulfide products, and as will be seen below in at least some cases, high enantiomeric purity can be achieved.

For disulfides **2a**–**d**, it is necessary to separate the meso and racemic mixture by chiral HPLC. In all cases, it was necessary to prepare this mixture by the synthesis of the disulfides from the racemic acid. For naproxen-derived **2d** where the racemic acid was not the starting material, the mixture was prepared by racemization of **1d** with DBU at 120°C (*88*). We found that these mixtures could be separated on the new Chiral Technologies bonded CHIRALPAK® IB column, but the separation for **2a**–**c** was remarkably sensitive to minor changes in the percentage of 2-propanol in hexane (0.25% at 25°C gave excellent results); for **2d**, the mixture was separated by eluting with 8% acetone in hexanes. In two cases, we have detected 0.09% and 0.03% of the wrong enantiomer or the meso isomer as impurities, so we conservatively estimate a detection limit of $>0.1\%$; these values are uncorrected for any potential differences in the absorbance of the meso diastereomers. The enantiomeric purities of the PADS analogs ranged from 98.99% for (*S*, *S*)-**2c** to $>99.9\%$ for (*S*, *S*)-**2a** and (*S*, *S*)-**2b**. Each of the PADS analogs is a solid, and can benefit from purification by removal of the "wrong" enantiomer of the chiral acid chlorides in the disulfide reaction by removal of any of the meso diastereomer that forms.

Both the new chiral thioamides **5a**–**e** and the MEDITH analogs **6a**–**e** were similarly analyzed by chiral HPLC. The racemic mixtures were prepared by simply mixing the enantiomers for all but the naproxen-derived compounds **5d** and **6d**; for **5d**, the racemic mixture was prepared by stirring a mixture of (*S*)-**5d** and silica gel in CH_2Cl_2 for 1 h, and for **6d**, the racemic mixture was prepared by reaction of (*S*)-**5d** and ClSC(O)Cl in the absence of pyridine. The enantiomeric purities of the thioamides ranged from 88.9% and 85.8% for (*R*) and (*S*)-**5c** to $>99.9\%$ for (*R*) and (*S*)-**5b**; enantiomer separations were easily achieved for **5a**–**c** and **e** on CHIRALPAK® IB eluting with 10% acetone in hexanes at 20°C. However, for **5d**, we were unable to find any conditions for separation of the enantiomers on any of CHIRALPAK® IA, B, or C. For the final MEDITH analogs, the enantiomeric purities ranged from 88.5% and 86.1% for (*R*) and (*S*)-**6c** to 99.1% and 99.4% for (*R*) and (*S*)-**6a**. Separation of these enantiomers was much more difficult and was achieved on CHIRALPAK® IA or B eluting with 0.25–1% methanol or ethanol in hexanes at temperatures from 12°C to 25°C except for **6d**, which was carried out with 8% acetone in hexanes at 20°C on CHIRALPAK® IC. While we were concerned that racemization might be occurring on-column during the HPLC runs, no change in enantiomer ratios was detected when we decreased the column contact time by eluting at higher flow rates.

In order to evaluate the enantioselectivities of the disulfide-forming syntheses, enantiomeric purity data are collected in Table 2. Values for each compound were determined either by comparison of observed specific rotation to literature values (for **1** and **4**) or by HPLC as described above (for **2**, **5**, and **6**). The comparison of the PADS analogs to the precursor chiral carboxylic acids shows that each of the disulfides has equal or greater enantiomeric purity, so not only is there no evidence of epimerization, but as expected, the enantiomeric purity can be enhanced by removal of the meso (and racemate) by crystallization, as particularly seems to be the case for (*R*)-**1a** conversion to (*R*, *R*)-**2a**. The conversions of the acids to the amides consistently gave similar enantiomeric purities (average deviation $\pm 0.5\%$) except for **1e** to **4e**, but given the higher enantiomeric purities for **5e** and **6e**, it is more likely that the specific rotations are in error. The HPLC values for the thioamides are, with two exceptions, remarkably similar to the $[\alpha]_D$ values for the acids (average deviation $\pm 1.4\%$); the exceptions are for the α-isopropyl cases where the thioamide syntheses necessitated the use of Lawesson's reagent, which gave a significant drop in enantiomeric purity on going from the amides (**4c**) to the thioamides (**5c**). The P_4S_{10}/Na_2CO_3 method, in contrast, clearly proceeded with high retention of enantiopurity, as seen for the overall conversion of **1a**, **b**, and **e** to **4a**, **b**, and **e**. Last, the conversions of the thioamides to the MEDITH analogs proceeded with comparable (or better) enantiomeric purity for **5a**, **c**, **e** to **6a**, **c**, and **e**; for **5a** to **6a**, the purity improved, suggesting that like the PADS case, crystallization must serve to remove some racemate. On the other hand, there was a drop in purity on going from the α-2-phenylbutane case **5b** to **6b**, and a smaller but still noticeable drop for the naproxen case **4d** to

Table 2. Enantiomeric purity[a] of chiral precursors and disulfides.

Compound	Acid (**1**)[b]	PADS (**2**)[c]	Amide (**4**)[b]	Thioamide (**5**)[c]	MEDITH (**6**)[c]
(*R*)-**a**	91.7	99.4	92.8	91.3	99.1
(*S*)-**a**	99.9	>99.9	98.9	98.2	99.4
(*R*)-**b**	97.2	99.4	95.8	>99.9	91.3
(*S*)-**b**	>99.9	>99.9	>99.9	>99.9	91.2
(*R*)-**c**	97.9	99.9	97.3	88.9	88.5
(*S*)-**c**	98.7	99.0	98.4	85.8	86.1
(*S*)-**d**	99.4	99.4	100		94.9
(*R*)-**e**	97.6		89.7	98.7	96.3
(*S*)-**e**	95.8		88.2	93.5	96.5

Notes: [a]Enantiomeric purity = [major configuration]/[(*R*) + (*S*) + meso] × 100.
[b]Evaluated from observed $[\alpha]_D$ by comparison to literature values; see supplementary data for data used. Literature data were averaged if more than one value was available, (*R*) and (*S*) values were combined where available and included in the average, and corrected for HPLC %ee when available. In cases where our observed $[\alpha]_D$ was higher than the literature value, it was taken as 100% enantiomeric purity and $[\alpha]_D$ for the opposite configuration was compared with this new 100% value.
[c]Evaluated from chiral HPLC data; see supplementary data for HPLC conditions and chromatograms.

6d. In the naproxen case, we were unable to resolve the thioamide enantiomers, so we can only guess that the loss occurred at this stage, rather than the acid to amide stage. In any case, there is no explanation for these modest differences. For instance, while **6b** is an oil and so presents no opportunity for crystallization-enhanced purity, **6e** is also an oil and formed in high enantiomeric purity; **6d** on the other hand is a solid, just like **6a**, which gave the highest enantiomeric purity.

3. Conclusion

Conversion of α-alkyl-substituted phenyl acetic acids to diacyl disulfides is readily carried out to give the desired compounds in >99.0% enantiomeric purity. The absolute configurations of the methyl-substituted compounds (*R*) and (*S*)-**2a** were unequivocally established by single-crystal X-ray diffraction. The high specific rotations ($[\alpha]_D \approx 360$–540) suggest that the helicity about the S–S bond observed in the solid state may be preferentially retained in solution. Conversion of the same set of chiral carboxylic acids to thioamides without racemization could best be carried out by avoidance of both acidic conditions and chromatography; specific rotation and HPLC data showed this could be accomplished using P_4S_{10} under basic conditions but not with Lawesson's reagent. Conversion of the thioamides to the MEDITH analogs was carried out in much higher yield than previously described, by using pyridine rather than triethylamine to sequester the HCl generated during the reaction. The heterocycles, which were formed in up to ~99% enantiomeric purity, were quite sensitive toward acid-induced racemization, and so while six of the cases proceeded with comparable enantiomeric purity upon conversion of the thioamides, three gave up to 9% lower enantiomeric purities. Work on the results of reactions of these new chiral disulfides with dinucleoside phosphite triesters will be reported separately (*34*).

4. Experimental section

4.1. *Carboxylic acids, acid chlorides, and amides*

Resolutions of racemic **1a** (*41*), **1b** (*41*), **1c** (*42*), and **1e** (*88*) were carried out as described in the referenced papers, except that for **1e** the starting point was the racemate rather than the partially enriched material. Racemic **1b** was synthesized using the method described for **1c** (*42*), and **1c** was prepared using the literature procedure (*42*). Racemic **1e** was obtained by ether extraction from commercial ibuprofen tablets, and (*S*)-**1d** was isolated from commercial sodium naproxen

tablets by ether extraction from an aqueous acidic solution of the powdered material. In all cases, the procedure used for **1e** (*88*) was employed to regenerate the acid from the diastereomeric α-methylbenzylamine salts (*i.e.* via hydrolysis with 0.5 M H_2SO_4). Enantiomeric purities were evaluated by comparison with literature values of specific rotations for the salts (*42*, *88*, *89*) used for the resolutions and for the final acids (*42*, *45*, *46*, *77*, *88*, *90*). A few cautions need to be included here: there is a typo for the rotation of the salt of (*S*)-**1a** (*88*) (it should be +19.0, not −19.0); the rotations for the salts of **1a** and **b** given by Mosher in his Table 1 are completely in error (*42*) (the values given are in fact Pettersson's values for the acids (*41*)), and while not published (to our knowledge), the specific rotation of the salts of **1e** are ∼0, so the resolution procedure described in the literature (*88*) is accurate but does not mention the reason one must monitor the progress of the successive crystallizations by hydrolysis of a small fraction of the salt – it is necessary to measure the specific rotation of the enantio-enriched **1e** since the rotation of the crystallized salt remains ∼0 throughout the successful resolution procedure. Further details (including optical rotations) may be found in the supplementary data.

The acids were converted to the acid chlorides by reaction with neat oxalyl chloride (*38*) rather than thionyl chloride (*42*) because the usual thionyl chloride procedure failed with naproxen (**1d**), while oxalyl chloride gave complete (and much cleaner) reaction in 30 min. The other carboxylic acids required 2 h for complete conversion. Following removal of the excess oxalyl chloride and volatiles on a vacuum line, the acid chlorides were used without further isolation in the next step (*38*). Conversions to the amides **4a**–**e** were carried out as previously described for **1c** (*42*), and specific rotations have all been reported (*45*, *76*, *77*); however, work-up details differed significantly from that described (*42*) and may be found with the compound data in the supplementary data.

4.2. *Synthesis of PADS analogs: (S,S)-di-2-phenylpropanoyl disulfide ((S,S)-2a)*

The following procedure is representative of the method used for **2a**–**d**. An aqueous solution of sodium disulfide was prepared by heating a mixture of sulfur (0.050 g, 1.6 mmol) and sodium sulfide nonahydrate (0.375 g, 1.56 mmol) in water (1.5 ml) at 90°C for 15 min with stirring. After cooling the aqueous solution, hexadecyltributylphosphonium bromide (0.071 g, 0.14 mmol) and 4 ml of toluene were added. With vigorous stirring at rt, a solution of (*S*)-2-phenylpropanoyl chloride (0.350 g, 2.08 mmol) dissolved in 1 ml of toluene was added dropwise over 2–3 min. After 20 min of stirring, the reaction solution was transferred to a separatory funnel with an additional 5 ml of toluene. The aqueous layer was separated and the organic layer washed with 5 ml of H_2O, and then dried with $MgSO_4$. The solvent was removed on a rotary evaporator and the crude product was passed through a pad of silica gel eluting with CH_2Cl_2. The UV-active material moving with the solvent front was collected and the solvent evaporated to afford the product as a pale white solid (0.31 g, 90% yield). The compound was crystallized from hot methanol to give white crystals of **2a** (0.18 g, 53% yield). mp 57–58°C; $[\alpha]_D^{26}$ + 370.2 (*c* 0.55, CH_2Cl_2); HPLC >99.9% (*S*, *S*), <0.1% (*R*, *R*), <0.1% meso; IR (KBr, cm^{-1}): 1735, 1720; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 4.06 (q, $^3J_{HH}$ = 7.1 Hz, 1H), 1.58 (d, $^3J_{HH}$ = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 195.2, 138.4, 129.0, 128.3, 128.0, 53.6, 18.6 ppm; HRMS (ESI): Calcd. for $C_{18}H_{22}NO_2S_2$ $[M + NH_4]^+$: 348.1092, found 348.1090.

4.3. *Synthesis of thioamides*

4.3.1. *(S)-2-Phenylpropanethioamide ((S)-**5a**)*

The following procedure is representative of the method used for **5a**, **b**, **d**, and **e**. Under a nitrogen atmosphere, a mixture of P_4S_{10} (0.647 g, 1.46 mmol) and Na_2CO_3 (0.156 g, 1.47 mmol) in 70 ml

of dry THF was stirred at rt for 1.5 h. To the resulting clear yellow solution was added a solution of (*S*)-**4a** (0.320 g, 2.14 mmol) dissolved in 10 ml of THF. The reaction solution was stirred at rt for ∼24 h and then the solvent was removed on a rotary evaporator to give a gum. The gum was then dissolved in 50 ml of CH_2Cl_2 and washed in a separatory funnel with 10 ml of 5% $NaHCO_3$ and then with 20 ml of brine. The organic layer was removed, dried with anhydrous $MgSO_4$, and the solvent was again removed on a rotary evaporator to give a gum. The gum was taken up in 6 ml of benzene and then 30 ml of petroleum ether (30–60°) was added to give a turbid solution which was cooled in a freezer at −18°C to give (*S*)-**5a** as a white solid (0.33 g, 93% yield). mp 76–78°C; $[\alpha]_D^{27}$ + 80.0 (*c* 0.59, C_6H_6); HPLC 98.2% (*S*), 1.8% (*R*); IR (KBr, cm^{-1}): 3489, 3419, 3371, 3276, 3158, 1620, 1594; ^{1}H NMR (400 MHz, CD_3CN): δ 7.94 (br s, 1H), 7.70 (br s, 1H), 7.42–7.24 (m, 5H), 4.04 (q, $^3J_{HH}$ = 8.0 Hz, 1H), 1.54 (d, $^3J_{HH}$ = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN): 213.7, 143.5, 129.5, 128.4, 128.1, 53.2, 21.7 ppm; HRMS (ESI): Calcd. for $C_9H_{12}NS$ $[M + H]^+$: 166.0690, found 166.0684.

4.3.2. *(R)-3-Methyl-2-phenylbutanethioamide ((R)-**5c**)*

Under a nitrogen atmosphere, a solution of (*R*)-**4c** (0.507 g, 2.86 mmol) in 10 ml of THF was added to a solution of Lawesson's reagent (see Scheme 2; 1.16 g, 2.87 mmol) in 30 ml of THF. The reaction mixture was stirred at rt for ∼24 h and then the solvent was evaporated on a vacuum line. The resulting gum was dissolved in 50 ml of EtOAc and washed in a separatory funnel with 10 ml of 5% $NaHCO_3$. The organic layer was removed, dried with anhydrous $MgSO_4$, and the solvent was removed on a rotary evaporator to give a gum. The gum was dissolved in 3:1:0.01 EtOAc/hexanes/Et_3N and passed through a pad of neutral alumina (Brockmann I) pre-washed with the same solvent mixture. All the UV-active material moving with the solvent front was collected and crystallized from 1:9 benzene/petroleum ether to afford (*R*)-**5c** as a white solid (0.26 g, 48%). mp 99–101°C; $[\alpha]_D^{30}$ − 84.0 (*c* 0.62, C_6H_6); HPLC 88.9% (*R*), 11.1% (*S*); IR (KBr, cm^{-1}): 3497, 3445, 3380, 3279, 3164, 1622, 1595; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.87 (br s, 2H,), 7.48–7.23 (m, 5H), 3.38 (d, $^3J_{HH}$ = 11.0 Hz, 1H), 2.62–2.49 (m, 1H), 1.03 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 0.695 (d, $^3J_{HH}$ = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 212.7, 141.6, 129.5, 129.2, 128.1, 68.2, 33.4, 21.5, 20.7 ppm; HRMS (ESI): Calcd. for $C_{11}H_{16}NS$ $[M+H]^+$: 194.1003, found 194.0996.

4.4. *Synthesis of MEDITH analogs: (S)-5-(1-(6-methoxynapthalen-2-yl)ethyl)-3H-1,2,4-dithiazol-3-one ((S)-6d)*

In a nitrogen-filled glove box, a solution of thioamide (*S*)-**5d** (0.1019 g, 0.4153 mmol) and pyridine (0.0748 g, 0.946 mmol) in 10 ml of ether was added at rt to a solution of chlorocarbonylsulfenyl chloride (0.0695 g, 0.531 mmol) in 4 ml of ether. After stirring for ∼2 min, TLC (3:1 hexane/EtOAc) indicated the complete conversion of **5d** to **6d**. The pyridinium chloride was filtered out and the solvent was removed using a vacuum pump to give a gum. The gum was dissolved in ∼2 ml of ether and hexane was added until the solution became turbid (∼6 ml). The resulting turbid solution was placed in the glove box freezer (−32°C) overnight to give **6d** as a white solid after filtration and rinsing with hexane (0.12 g, 92% yield). mp 84–86°C; $[\alpha]_D^{28}$ + 54.0 (*c* 0.50, C_6H_6); HPLC 94.9% (*S*), 5.1% (*R*); IR (KBr, cm^{-1}): 1713, 1536; ^{1}H NMR (400 MHz, CD_3CN): δ 7.17–7.87 (m, 6H), 4.57 (q, $^3J_{HH}$ = 7.1 Hz, 1H), 3.90 (s, 3H), 1.83 (d, $^3J_{HH}$ = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 201.2, 188.3, 159.3, 135.63, 135.55, 130.5, 129.7, 128.6, 128.5, 127.7, 120.4, 106.8, 56.1, 48.0, 20.9 ppm; HRMS (ESI): Calcd. for $C_{15}H_{14}NO_2S_2$ $[M+H]^+$: 304.0466, found 304.0466.

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Supplementary data

Experimental procedures for the synthesis of **1b**, resolution of **1e**, synthesis of **4a** and **d** and data for **4a**–**e**; tables of observed and literature specific rotations of **1**, the salts used for resolutions, and **4**; experimental data, spectra, and HPLC chromatograms for new compounds; coordinates from DFT calculations; details of the structure determination. Supplementary data associated with this article can be found in the online version.

Notes

1. The usual name quoted in the literature, 3-methyl-1,2,4-dithiazolin-5-one, appears to us to be in error; the parent ring system is fully unsaturated (hence the "ol" ring termination) and the position of the unsaturation is indicated by giving the *H* the lowest available number.
2. The highest de's for phosphite triester sulfurization with the disulfides reported here for R_{PS} and S_{PS} phosphorothioates were 14.7% and 7.9%, respectively.
3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 779771 and 779772. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or Email: deposit@ccdc.cam.ac.uk).

References

(1) Matsukura, M.; Shinozuka, K.; Zon, G.; Mitsuya, H.; Reitz, M.; Cohen, J.S.; Broder, S. *Proc. Natl Acad. Sci. USA* **1987,** *84,* 7706–7710.
(2) Stein, C.A.; Cheng, Y.-C. *Science* **1993,** *261,* 1004–1012.
(3) Dias, N.; Stein, C.A. *Mol. Cancer Ther.* **2002,** *1,* 347–355.
(4) Rayburn, E.R.; Zhang, R. *Drug Discovery Today* **2008,** *13,* 513–521.
(5) Iyer, R.P.; Egan, W.; Regan, J.B.; Beaucage, S.L. *J. Am. Chem. Soc.* **1990,** *112,* 1253–1254.
(6) Iyer, R.P.; Phillips, L.R.; Egan, W.; Regan, J.B.; Beaucage, S.L. *J. Org. Chem.* **1990,** *55,* 4693–4699.
(7) Efimov, V.A.; Kalinkina, A.L.; Chakhmakhcheva, O.G.; Hill, T.S.; Jayaraman, K. *Nucleic Acids Res.* **1995,** *23,* 4029–4033.
(8) Zhang, Z.; Nichols, A.; Alsbeti, M.; Tang, J.X.; Tang, J.Y. *Tetrahedron Lett.* **1998,** *39,* 2467–2470.
(9) Cheruvallath, Z.S.; Carty, R.L.; Moore, M.N.; Capaldi, D.C.; Krotz, A.H.; Wheeler, P.D.; Turney, B.J.; Craig, S.R.; Gaus, H.J.; Scozzari, A.N.; Cole, D.L.; Ravikumar, V.T. *Org. Process Res. Dev.* **2000,** *4,* 199–204.
(10) Song, Q.; Wang, Z.; Sanghvi, Y.S. *Nucleosides, Nucleotides Nucleic Acids* **2003,** *22,* 629–633.
(11) Kamer, P.C.J.; Roelen, H.C.P.F.; van den Elst, H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989,** *30,* 6757–6760.
(12) Roelen, H.C.P.F.; Kamer, P.C.J.; van den Elst, H.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1991,** *110,* 325–331.
(13) Vu, H.; Hirschbein, B.L. *Tetrahedron Lett.* **1991,** *32,* 3005–3008.
(14) Rao, M.V.; Reese, C.B.; Zhengyun, Z. *Tetrahedron Lett.* **1992,** *33,* 4839–4842.
(15) Stec, W.J.; Uznanski, B.; Wilk, A.; Hirschbein, B.L.; Fearon, K.L.; Bergot, B.J. *Tetrahedron Lett.* **1993,** *34,* 5317–5320.
(16) Rao, M.V.; Macfarlane, K. *Tetrahedron Lett.* **1994,** *35,* 6741–6744.
(17) Xu, Q.; Musier-Forsyth, K.; Hammer, R.P.; Barany, G. *Nucleic Acids Res.* **1996,** *24,* 1602–1607.
(18) Arterburn, J.B.; Perry, M.C. *Tetrahedron Lett.* **1997,** *38,* 7701–7704.
(19) Zhang, Z.; Nichols, A.; Tang, J.X.; Alsbeti, M.; Tang, J.Y. *Nucleosides Nucleotides* **1997,** *16,* 1585–1588.
(20) Zhang, Z.; Nichols, A.; Tang, J.X.; Han, Y.; Tang, J.Y. *Tetrahedron Lett.* **1999,** *40,* 2095–2098.
(21) Tang, J.-Y.; Han, Y.; Tang, J.X.; Zhang, Z. *Org. Process Res. Dev.* **2000,** *4,* 194–198.
(22) Ju, J.; McKenna, C.E. *Bioorg. Med. Chem. Lett.* **2002,** *12,* 1643–1645.
(23) Zhang, Z.; Han, Y.; Tang, J.X.; Tang, J. *Tetrahedron Lett.* **2002,** *43,* 4347–4349.
(24) Cheruvallath, Z.S.; Kumar, R.K.; Rentel, C.; Cole, D.L.; Ravikumar, V.T. *Nucleosides, Nucleotides Nucleic Acids* **2003,** *22,* 461–468.
(25) Krotz, A.H.; Gorman, D.; Mataruse, P.; Foster, C.; Godbout, J.D.; Coffin, C.C.; Scozzari, A.N. *Org. Process Res. Dev.* **2004,** *8,* 852–858.
(26) Hyodo, M.; Sato, Y.; Yamashita, S.; Hattori, A.; Kambe, E.; Kataoka, M.; Hayakawa, Y. *Tetrahedron* **2005,** *61,* 965–970.

(27) Krotz, A.H.; Hang, A.; Gorman, D.; Scozzari, A.N. *Nucleosides, Nucleotides Nucleic Acids* **2005,** *24,* 1293–1299.
(28) Guzaev, A.P. *Tetrahedron Lett.* **2011,** *52,* 434–437.
(29) Wyrzykiewicz, T.K.; Cole, D.L. *Bioorg. Chem.* **1995,** *23,* 33–41.
(30) Cheruvallath, Z.S.; Sasmor, H.; Cole, D.L.; Ravikumar, V.T. *Nucleosides, Nucleotides Nucleic Acids* **2000,** *19,* 533–543.
(31) Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds;* Wiley-Interscience: New York, 1994; p 965.
(32) Perlikowska, W.; Gouygou, M.; Mikolajczyk, M.; Daran, J.-C. *Tetrahedron: Asymmetry* **2004,** *15,* 3519–3529.
(33) Powell, W.H. *Pure Appl. Chem.* **1983,** *55,* 409–416.
(34) Mukhlall, J.A.; Hersh, W.H. *Nucleosides, Nucleotides & Nucleic Acids* **2011,** submitted for publication.
(35) Kodomari, M.; Fukuda, M.; Yoshitomi, S. *Synthesis* **1981,** 637–638.
(36) Tamami, B.; Kiasat, A.R. *Synth. Commun.* **1998,** *28,* 1275–1280.
(37) Jia, X.-S.; Liu, X.-T.; Li, Q.; Huang, Q.; Kong, L.-L. *J. Chem. Res.* **2006,** 547–548.
(38) Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* **1990,** *20,* 2033–2040.
(39) Flack, H.D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983,** *39,* 876–881.
(40) Flack, H.D.; Bernardinelli, G. *Chirality* **2008,** *20,* 681–690.
(41) Pettersson, K. *Ark. Kemi* **1956,** *10,* 283–296.
(42) Aaron, C.; Dull, D.L.; Schmiegel, J.L.; Jaeger, D.; Ohashi, Y.; Mosher, H.S. *J. Org. Chem.* **1967,** *32,* 2797–2803.
(43) Clark, D.R.; Mosher, H.S. *J. Org. Chem.* **1970,** *35,* 1114–1118.
(44) Farrugia, L.J. *J. Appl. Crystallogr.* **1997,** *30,* 565.
(45) Wang, M.-X.; Lu, G.; Ji, G.-J.; Huang, Z.-T.; Meth-Cohn, O.; Colby, J. *Tetrahedron: Asymmetry* **2000,** *11,* 1123–1135.
(46) Wu, Z.-L.; Li, Z.-Y. *Tetrahedron: Asymmetry* **2001,** *12,* 3305–3312.
(47) Kinbara, K.; Kobayashi, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1998,** 1767–1775.
(48) Kinbara, K.; Kobayashi, Y.; Saigo, K. *Perkin 2* **2000,** 111–119.
(49) Koshima, H.; Nakagawa, T.; Matsuura, T. *Tetrahedron Lett.* **1997,** *38,* 6063–6066.
(50) Lemmerer, A.; Bathori, N.B.; Bourne, S.A. *Acta Crystallogr., Sect. B: Struct. Sci.* **2008,** *64,* 780–790.
(51) Volonterio, A.; Bravo, P.; Capelli, S.; Meille, S.V.; Zanda, M. *Tetrahedron Lett.* **1997,** *38,* 1847–1850.
(52) Rout, G.C.; Seshasayee, M.; Subrahmanyan, T.; Aravamudan, G. *Acta Crystallogr., Sect. C: Cryst Struct. Commun.* **1983,** *39,* 1387–1389.
(53) Paul, C.; Srikrishnan, T. *J. Chem. Crystallogr.* **2004,** *34,* 211–217.
(54) Niyomura, O.; Kitoh, Y.; Nagayama, K.-I.; Kato, S. *Sulfur Lett.* **1999,** *22,* 195–207.
(55) Niyomura, O.; Kato, S.; Inagaki, S. *J. Am. Chem. Soc.* **2000,** *122,* 2132–2133.
(56) Bereman, R.D.; Baird, D.M.; Bordner, J.; Dorfman, J.R. *Polyhedron* **1983,** *2,* 25–30.
(57) Beyer, L.; Richter, R.; Seidelmann, O. *J. Prakt. Chem.* **1999,** *341,* 704–726.
(58) Li, F.; Yin, H.D.; Hong, M.; Zhai, J.; Wang, D.Q. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2006,** *E*62, o1417–o1418.
(59) Erben, M.F.; Della Vedova, C.O.; Willner, H.; Trautner, F.; Oberhammer, H.; Boese, R. *Inorg. Chem.* **2005,** *44,* 7070–7077.
(60) Erben, M.F.; Della Vedova, C.O.; Willner, H.; Boese, R. *Eur. J. Inorg. Chem.* **2006,** 4418–4425.
(61) Higashi, L.S.; Lundeen, M.; Seff, K. *J. Am. Chem. Soc.* **1978,** *100,* 8101–8106.
(62) Williams, G.A.; Statham, J.R.; White, A.H. *Aust. J. Chem.* **1983,** *36,* 1371–1377.
(63) Wang, Y.; Liao, J.H. *Acta Crystallogr., Sect. B: Struct. Sci.* **1989,** *45,* 65–69.
(64) Adams, R.D.; Huang, M. *Eur. J. Inorg. Chem.* **1998,** *1998,* 1025–1028.
(65) Weber, W.G.; McLeary, J.B.; Sanderson, R.D. *Tetrahedron Lett.* **2006,** *47,* 4771–4774.
(66) Keter, F.K.; Nell, M.J.; Guzei, I.A.; Omondi, B.; Darkwa, J. *J. Chem. Res.* **2009,** 322–325.
(67) Watanabe, Y. *Acta Crystallogr., Sect. B: Struct. Sci.* **1971,** *27,* 644–649.
(68) Jamir, L.; Yella, R.; Patel, B.K. *J. Sulfur Chem.* **2009,** *30,* 128–134.
(69) Zysman-Colman, E.; Harpp, D.N. *J. Sulfur Chem.* **2004,** *25,* 291–316.
(70) Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds;* Wiley-Interscience: New York, 1994; pp 1120–1121.
(71) Imrie, C.; Cook, L.; Levendis, D.C. *J. Organomet. Chem.* **2001,** *637–639,* 266–275.
(72) Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A., Jr.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J.A. *Gaussian 03W, Revision D.01;* Gaussian, Inc.: Wallingford, CT, 2004.
(73) Cea-Olivares, R.; García-Montalvo, V.; Hernández-Ortega, S.; Rodríguez-Narváez, C.; García y García, P.; López-Cardoso, M.; de March, P.; González, L.; Elias, L.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **1999,** *10,* 3337–3340.

(74) Hersh, W.H.; Xu, P.; Simpson, C.K.; Grob, J.; Bickford, B.; Hamdani, M.S.; Wood, T.; Rheingold, A.L. *J. Org. Chem.* **2004,** *69*, 2153–2163.
(75) Hersh, W.H., unpublished results.
(76) Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* **1994,** *72*, 142–145.
(77) Allegretti, M.; Bertini, R.; Cesta, M.C.; Bizzarri, C.; Di Bitondo, R.; Di Cioccio, V.; Galliera, E.; Berdini, V.; Topai, A.; Zampella, G.; Russo, V.; Di Bello, N.; Nano, G.; Nicolini, L.; Locati, M.; Fantucci, P.; Florio, S.; Colotta, F. *J. Med. Chem.* **2005,** *48*, 4312–4331.
(78) Yde, B.; Yousif, N.M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984,** *40*, 2047–2052.
(79) Bishop, J.E.; Dagam, S.A.; Rapoport, H. *J. Org. Chem.* **1989,** *54*, 1876–1883.
(80) Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* **2006,** *47*, 2315–2317.
(81) Shalaby, M.A.; Grote, C.W.; Rapoport, H. *J. Org. Chem.* **1996,** *61*, 9045–9048.
(82) Zumach, G.; Kühle, E. *Angew. Chem., Int. Ed. Engl.* **1970,** *9*, 54–63.
(83) Goerdeler, J.; Nandi, K. *Chem. Ber.* **1975,** *108*, 3066–3070.
(84) Goerdeler, J.; Nandi, K. *Chem. Ber.* **1981,** *114*, 549–563.
(85) Chen, L.; Thompson, T.R.; Hammer, R.P.; Barany, G. *J. Org. Chem.* **1996,** *61*, 6639–6645.
(86) Roy, S.K.; Tang, J.-Y. Sulfurizing reagent: 3-aryl-1,2,4-dithiazoline-5-ones. US Patent 6,500,944 B2, December 31, 2002.
(87) Davulcu, A.H.; McLeod, D.D.; Li, J.; Katipally, K.; Littke, A.; Doubleday, W.; Xu, Z.; McConlogue, C.W.; Lai, C.J.; Gleeson, M.; Schwinden, M.; Parsons, R.L., Jr. *J. Org. Chem.* **2009,** *74*, 4068–4079.
(88) Ebbers, E.J.; Ariaans, G.J.A.; Bruggink, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **1999,** *10*, 3701–3718.
(89) Zalkow, L.H.; Glinski, J.A.; Gelbaum, L.T.; Moore, D.; Melder, D.; Powis, G. *J. Med. Chem.* **1988,** *31*, 1520–1526.
(90) Tsuchihashi, G. *Tetrahedron Lett.* **1982,** *23*, 5427–5430.