Tetrahedron 67 (2011) 41–47

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Beyond the chiral pool: a general approach to β-amino-α-keto amides

Cristian L. Harrison, Mariusz Krawiec, Raymond E. Forslund [†], William A. Nugent [*]

Chemical Development Department, Vertex Pharmaceuticals, Inc., 130 Waverly Street, Cambridge, MA 02139, United States

ARTICLE INFO

Article history:
Received 1 October 2010
Received in revised form 28 October 2010
Accepted 2 November 2010
Available online 6 November 2010

Keywords:
Sulfinylimine
Dithiolanecarboxylate
α-Ketoamide
α-Ketoester
Stereoselective synthesis

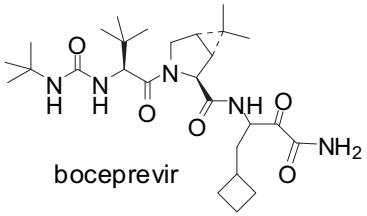
ABSTRACT

A simple route was developed for the synthesis of optically enriched β-amino-α-keto amides. The highly diastereoselective addition of alkyl dithiolanecarboxylates to optically enriched sulfinimines affords the corresponding β-amino-α-keto esters in which the ketone carbonyl group is protected as a dithiolane. Amidation of the ester functionality with a primary amine proceeds readily at room temperature. Treatment with HCl cleaves the N–S bond of the sulfinyl group to provide a free amine functionality, which can then be incorporated into a peptide. Removal of the dithiolane protecting group under oxidative conditions proceeds without epimerization as exemplified by a model dipeptide.

1. Introduction

Peptidyl α-keto amides are broadly useful in medicinal chemistry because they can serve as potent inhibitors of proteolytic enzymes such as serine and cysteine proteases. One example of a cellular target is thrombin, a serine protease that converts fibrinogen to fibrin.[1] Others include calpain, a calcium-activated cysteine protease that has been implicated in stroke, Alzheimer's disease and muscular dystrophy[2] and caspase, a cysteine protease that plays a role in apoptosis.[3] An area of considerable current interest is the use of β-amino-α-keto amide peptide isosteres as viral protease inhibitors for the treatment of hepatitis C, which has led to the drug candidates telaprevir[4] and boceprevir.[5]

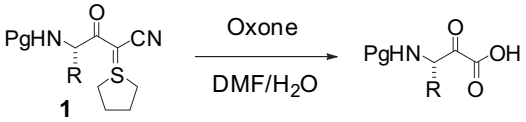
Peptidyl β-amino-α-keto amides are expected to undergo epimerization under mildly basic physiological conditions.[2] Indeed, the HCV drug candidate boceprevir is manufactured as a mixture of diastereomers[5] as shown below:



boceprevir

Nevertheless, manufacture of drugs containing this functionality pattern as a single diastereomer is potentially advantageous. Peptidyl β-amino-α-keto amides do not epimerize under the acidic conditions of the gut[2] so that administering a single compound rather than a mixture of substances should simplify the pharmacokinetics of drug uptake. Moreover, synthesis of a single diastereomer allows crystallization of the drug substance, expanding options for purification and formulation.

In general, conventional routes to β-amino-α-keto amides rely on the one-carbon homologation of an *N*-protected α-amino acid derivative. In older versions of this approach, the carbon nucleophile is cyanide[6] or an isonitrile;[7] however, using such nucleophiles the reaction is not stereoretentive. Wasserman and co-workers disclosed an improved route utilizing a (cyanomethylene)phosphorane as a nucleophile followed by ozonolysis of the resulting Wittig type intermediate.[8] This procedure affords the ketoamides in a stereoretentive fashion and has been widely embraced. In an important recent advance, Bode and co-workers[9] have demonstrated the use of a stabilized sulfur ylide to convert a protected amino acid or peptide to a homologated intermediate of type **1**. This procedure is especially attractive because such ylides are rapidly oxidized to α-keto acids with mild and easy to handle Oxone (potassium peroxymonosulfate) as shown in Eq. 1.



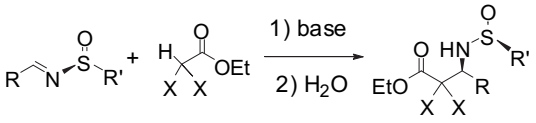
(1)

* Corresponding author. E-mail address: william_nugent@vrtx.com (W.A. Nugent).
† Present address: Ironwood Pharmaceuticals, Inc., Cambridge, MA, United States.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.018

These one-carbon homologation routes are most useful when the required α-amino acid is a readily available natural amino acid. However, a potential limitation occurs when the requisite starting material is an 'unnatural' (non-proteinaceous) amino acid. Such amino acids are themselves prepared by multi-step synthetic sequences; some are commercially available, but in general are expensive. Consequently, we sought an alternative route to optically enriched α-keto-β-amino amides that does not require an amino acid starting material.

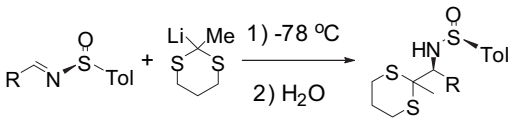
Over the last two decades, the diastereoselective addition of carbon nucleophiles to optically enriched sulfinimines has emerged as a premiere method for synthesizing chiral amines. Major contributions have come from the research groups of Davis[10] and of Ellman.[11] We wondered whether addition of the anion of a suitably protected glyoxylic acid ester to a chiral sulfinimine would provide a more general approach to β-amino-α-keto esters (Eq. 2). The literature contains a number of examples where addition of a sterically encumbered nucleophile to a sulfinimine proceeds with particularly high (often >99%) diastereoselectivity.[12]



(2)

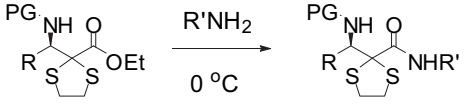
We elected to explore the use of glyoxylic acid esters protected as thioacetals as the nucleophiles in Eq. 2. This choice was influenced by three seminal papers from different research groups.

First, Davis and co-workers[13] have shown that certain dithianes can be added to *p*-tolylsulfinimines in 92–97% de (Eq. 3). We have subsequently found that replacing the methyl group of the dithiane in Eq. 3 with an electron-withdrawing carboxylate group greatly retards this transformation; nevertheless, the high diastereoselectivity observed by the Davis group was encouraging.



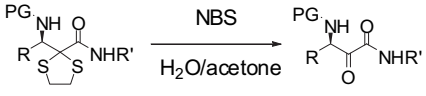
(3)

Secondly, Powers and co-workers[14] have demonstrated that α-keto esters, after protection as dithiolanes, undergo remarkably facile amidation reactions (Eq. 4). When the R′ group of the amine is sterically small, these reactions were found to proceed even at 0 °C.



(4)

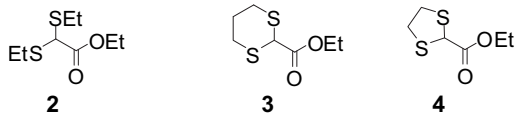
Finally, Papanikos and Meldal[15] reported that optically enriched β-amino-α-keto amides could be protected as dithiolane derivatives and subsequently deprotected without epimerization at the nitrogen-bearing β-carbon. Deprotection was accomplished in an oxidative fashion using NBS in 10% aqueous acetone (Eq. 5).



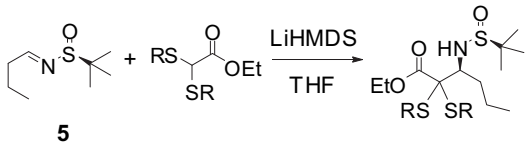
(5)

2. Results and discussion

We initially screened three commercially available thioacetal carboxylates, namely ethyl bis(ethylthio)acetate **2**, ethyl 1,3-dithiane-2-carboxylate **3**, and ethyl 1,3-dithiolane-2-carboxylate **4**.


2 **3** **4**

Screening reactions were carried using sulfinimine **5** prepared from (*S*)-*tert*-butylsulfininylamine and butyraldehyde[16] and LiHMDS as base (HMDS=hexamethyldisilazide, THF, −78 °C, 1 h). It became evident that pre-generation of the thioacetal anions (especially in the case of **4**) led to significant aldol type self-condensation of the thioacetal starting material. Consequently, a simplified protocol was adapted in which LiHMDS was added dropwise to a 1:1 mixture sulfinimine and thioacetal at −78 °C (Eq. 6).



5 (6)

Under these conditions, thioacetal **2** gave none of the desired adduct. In contrast, thioacetal **3** upon hydrolysis afforded the desired adduct in up to 50% yield. Prolonged reaction time or higher temperatures did not improve the conversion. We tentatively suggest that the reaction reaches equilibrium due to reversible addition of the relatively stable dithiane anion to the sulfinimine.

By far the best results were achieved using dithiolane **4**. After hydrolytic workup, the desired adduct could be isolated in >90% yield and the diastereomer ratio (dr) was 99:1. The stereochemistry of the predominant diastereomer was initially assigned as S,S_S by analogy to the dithiane additions of Davis[13] and this was subsequently confirmed by an X-ray crystal structure (see below). This stereochemical result is consistent with the closed transition state model proposed by Ellman.[17]

Based on these results, we explored the scope of the addition of dithiolane **4** to sulfinimines. We examined the effect of a variety of solvents and bases as well as the effect of the groups R, R′, and R″ for the general reaction shown in Eq. 7. Results are summarized in Table 1. In all cases, diastereoselectivity was excellent; for reactions utilizing *tert*-butylsulfinimines the dr was consistently at least 99:1.

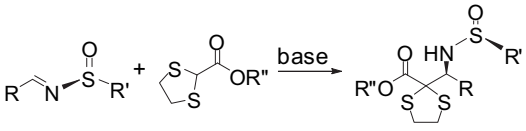
The solvent THF used in the screening studies could be replaced by other ethereal solvents such as methyl *tert*-butyl ether (MTBE) or 2-methyltetrahydrofuran (entries 2 and 8). However, the use of a less polar solvent toluene (entry 3) led to a significantly reduced conversion. A variety of alternative alkali metal bases provided the desired sulfinamide in good yield and diastereoselectivity. Effective bases included hexynyllithium, LDA (lithium diisopropylamide), and NaHMDS (entries 4–6) while KHMDS (entry 7) gave a lower conversion. (This may reflect the use of KHMDS as a commercial solution in toluene.) A particularly attractive alternative in terms of ease of handling is potassium *tert*-butoxide (entries 11–13) and this base should prove useful in larger scale applications.

As expected, substitution on the aliphatic side-chain of the sulfinimine was well tolerated. In the case of entry 10, it was noted that when the reaction was re-run at 0 °C using LiHMDS as base, a 3:2 mixture of diastereomers **9a** and **9b** was formed. These

Table 1
Effect of reaction parameters on yield for Eq. 7[a]

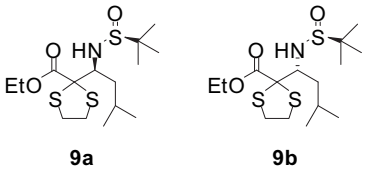
Entry	R	Product	Solvent	Base	% Yield[b]
1	*n*-Propyl	**6**	THF	LiHMDS	92
2	*n*-Propyl	**6**	MTBE		100
3	*n*-Propyl	**6**	Toluene		42[c]
4	*n*-Propyl	**6**	THF	HexynylLi	97
5	*n*-Propyl	**6**	THF	LDA	95[c]
6	*n*-Propyl	**6**	THF	NaHMDS	96
7	*n*-Propyl	**6**	THF/toluene	KHMDS	71[c]
8	Cyclopropylmethyl	**7**	2-MeTHF	LiHMDS	83
9	2-Naphthyl	**8**	THF	LiHMDS	78[d,e]
10	Isobutyl	**9a**	THF	LiHMDS	95
11	*n*-Propyl	**6**	THF	KO*t*-Bu	96[d]
12	Cyclopropylmethyl	**7**	THF	KO*t*-Bu	95[d]
13	Isobutyl	**9a**	THF	KO*t*-Bu	93[d]
14	Isobutyl[f]	**10**	THF	LiHMDS	91[d]
15	Isobutyl[g]	**11**	THF	LiHMDS	95[d]

[a] Unless otherwise indicated, R′=*tert*-butyl; R″=ethyl; see text for reaction conditions.
[b] Isolated yield after vacuum drying.
[c] Product not isolated; reported value is percent conversion of sulfinimine.
[d] Yield after flash chromatography.
[e] Sulfinimine of 15% was recovered.
[f] R′=*p*-tolyl.
[g] R″=methyl.

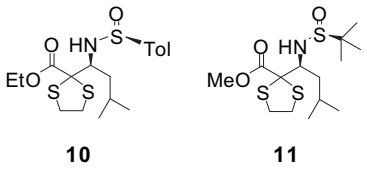


(7)

diastereomers could be separated by flash chromatography, providing a reference standard of the (R,S_S) diastereomer **9b** (In contrast, use of potassium *tert*-butoxide at 0 °C gave a complex mixture of products.).

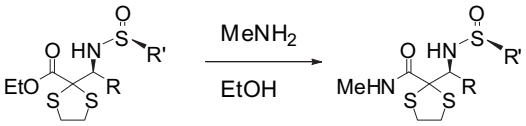

9a **9b**

Addition to an aromatic sulfinimine, namely R=2-naphthyl (entry 9), also proceeded in 99:1 dr. The conversion was somewhat lower than that for the aliphatic sulfinimines; however, the product was readily isolated as a single diastereomer by flash chromatography. Entry 14 examines the effect of replacing the *tert*-butyl group of the sulfinimine with a *p*-tolyl substituent. In this case the dr was lower (98:2); however, we anticipate that such *p*-tolylsulfinyl derivatives may have a higher tendency to exist as crystalline solids when compared to their *tert*-butyl counterparts, which could prove advantageous when working at larger scale. In this case the ethyl ester **10** was an oil but the corresponding *N*-methylamide **12d** was crystalline (see below).


10 **11**

Not surprisingly, changing the ester substituent R″ from ethyl to methyl (entry 15) had minimal impact and afforded **11** as expected. However, when the ester moiety of dithiolane **4** was replaced by a secondary amide, as exemplified by the *N*-methyl-*N*-benzyl derivative, no addition was observed. Therefore it was of interest to explore the conversion of the product esters to the corresponding amides.

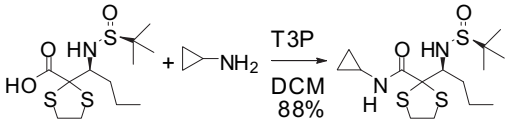
Consistent with the literature report,[14] this amidation could be carried out at room temperature in an alcoholic solvent. Commercial 33% methylamine in ethanol was conveniently employed for the examples in Eq. 8. In all cases, the reaction was complete in 16 h at room temperature.



(8)

12a, R = Pr; R' = t-Bu, 98%
12b, R = i-Bu; R' = t-Bu, 96%
12c, R = cycPrCH$_2$; R' = t-Bu, 97%
12d, R = i-Bu; R' = p-tolyl, 59%

In the case of sterically encumbered cyclopropylamine, the analogous reaction proved sluggish and an alternative approach was developed. Ester **6** was first hydrolyzed to the corresponding acid **13** using lithium hydroxide (25 °C, 4.5 h). Acid **13** was then coupled to the amine using *n*-propylphosphonic anhydride (T3P) as shown in Eq. 9. Extractive workup provided amide **14** in 84% overall yield for the two steps.



13 **14**
(9)

The amidation product **12d** proved to be a crystalline solid, which provided an opportunity to confirm the stereochemistry of the initial sulfinimine addition. As a result of the presence of three strongly diffracting sulfur atoms the structure refined remarkably well ($R1$=2.25% and $wR2$=6.22%). The resulting high resolution (0.83 Å) taken together with anomalous scattering data, confirmed that both stereocenters possess the *S* configuration. The molecular structure is shown in Fig. 1.

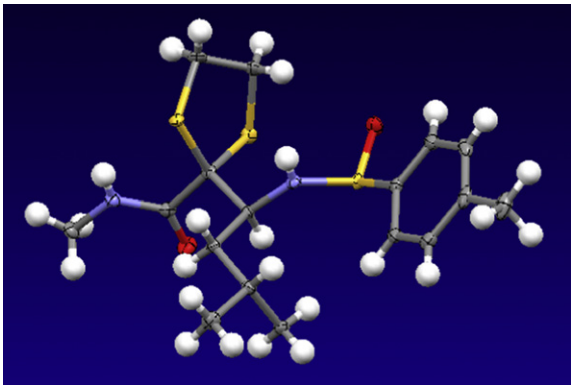
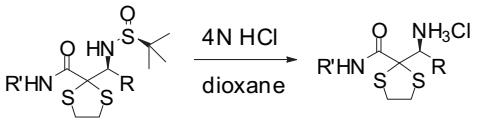


Fig. 1. Molecular structure of dithiolane amide **12d** showing S,S_S stereochemistry.

Cleavage of the S–N bond to remove the sulfinyl group in the product sulfinamides was readily accomplished by treatment with 4 N HCl in dioxane (Eq. 10). Upon addition of the resulting solution to diethyl ether, the amine hydrochloride salt precipitated and could be collected by filtration. In general, these hydrochlorides proved mildly hygroscopic. However, in the case of **15a** the product was deliquescent and changed from a white powder to a yellow gum during attempted isolation by filtration. Consequently it was not possible to obtain suitable elemental analysis for this compound. The remaining products were obtained in useful yields and purity.

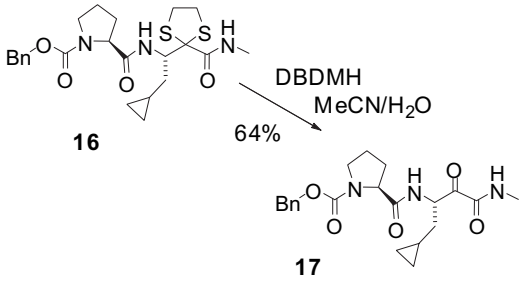


(10)

15a, R = Pr; R' = Me
15b, R = i-Bu; R' = Me, 93%
15c, R = cycPrCH$_2$; R' = Me, 88%
15d, R = Pr; R' = cycPr, 69%

It has been shown that dithiolane-protected peptidyl β-amino-α-keto amides can be deprotected with NBS without epimerization.[15] Since the earlier work involved polymer-supported peptides, we felt it was worthwhile to confirm this result in the solution phase. Dozens of reagents and protocols have been reported for removal of the dithiolane protecting group.[18] However, neighboring electron-withdrawing functionality in the dithiolanes of the present study makes them less susceptible toward oxidative cleavage. Nevertheless, NBS and DBDMH[13b] (1,3-dibromo-5,5-dimethylhydantoin) both proved to be suitable reagents for this deprotection. Although these two reagents performed comparably, an advantage of the latter is that less hydantoin side-product is formed, thereby simplifying extractive workup.

The protected dipeptide **16** was conveniently prepared by treating dithiolane amide **15c** with Cbz-proline using HOBT/EDCl as coupling reagent (HOBT=1-hydroxybenzotriazole, EDCl=*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride). Hydrolytic workup provided **16** as a white foam, which retained some solvent. The protected dipeptide was then treated with 4 equiv of 1,3-dibromo-5,5-dimethylhydantoin in 10% aqueous acetonitrile (Eq. 11). Aqueous workup and vacuum drying provided the deprotected dipeptide **17** as a white waxy solid in 64% overall yield for two steps.

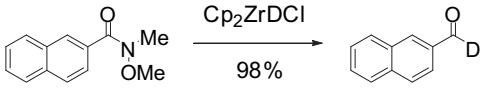


16 **17**

(11)

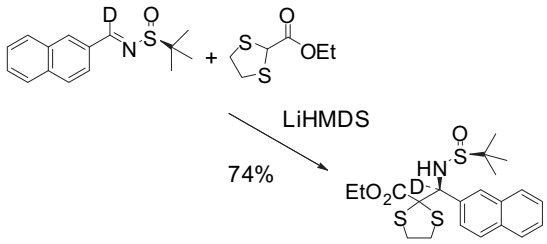
Consistent with the report of Papanikos and Meldal,[15] dipeptide **17** was homogeneous on several HPLC columns. Given the presence of two stereogenic centers in **17**, this indicates that deprotection proceeds without epimerization at the nitrogen-bearing β-carbon atom. Also in accord with the earlier studies, the ^{1}H and ^{13}C NMR spectra of both the protected dipeptide **16** and deprotected **17** showed two sets of resonances (approximately 60:40 ratio at 25 °C). These were shown[15] by variable temperature NMR to arise from the presence of two amide conformers.

Finally, we note that our protocol is particularly well-suited for the preparation of deuterium-labeled β-amino-α-keto amides bearing deuterium at the β position. For example, deuterium-labeled 2-naphthylcarboxaldehyde was conveniently prepared from the Weinreb amide using chemistry developed by Georg and co-workers[19] (Eq. 12).



(12)

The aldehyde was converted to the *tert*-butylsulfinimine in the usual manner.[16] Addition of ethyl dithiolanecarboxylate proceeded as in the case of the protio analogue **8** and afforded **18** in >98% isotopic purity (Eq. 13).



18

(13)

3. Conclusion

Taken together, the two-step dithiolane addition/amidation sequence provides a straightforward approach to the synthesis of protected β-amino-α-keto amides and affords these compounds in high yield and purity. A particular advantage of this approach is that it does not derive its chirality from an α-amino acid, providing a broad scope and equally ready access to the (*R*)- and (*S*)-enantiomers. The products can be elaborated into peptide structures and deprotected under oxidative conditions without epimerization.

4. Experimental

4.1. General

Commercial anhydrous tetrahydrofuran was used as received. The starting *tert*-butylsulfinimines used in this study are known compounds, which were prepared following Ellman's protocol[16] (copper sulfate-promoted condensation) and purified by flash chromatography in 5:1 hexanes/ethyl acetate. The tolyl sulfinimine starting material used in the preparation of **10** was prepared according to the literature procedure.[20] All other materials were reagent grade chemicals used as received. Flash chromatography was carried out on 60 Å silica gel following the procedure of Still and co-workers.[21] Glassware used in the sulfinimine additions was not flame dried but was flushed with dry nitrogen for 30 min prior to use. ^{1}H and ^{13}C NMR were obtained on a Bruker Avance 400 or Avance 500 NMR spectrometer. Coupling constants *J* are given in hertz.

4.2. Synthesis

4.2.1. Addition of alkyl dithiolanecarboxylates to sulfinimines

*4.2.1.1. Ethyl (S,S$_S$)-2-[1-tert-butylsulfinylamino]butyl-1,3-dithiolanecarboxylate, **6**.* A flask was charged with a solution of ethyl 1,3-

dithiolanecarboxylate (713 mg, 4.00 mmol) and [*N*(*E*),*S*(*S*)]-2-methyl-*N*-(butylidene)-2-propanesulfinamide (701 mg, 4.00 mmol) in tetrahydrofuran (10 mL) under a nitrogen atmosphere. The solution was cooled to −78 °C whereupon a 1.0 M solution of potassium *tert*-butoxide in THF (5.00 mL, 5.00 mmol) was added dropwise. The mixture was stirred an additional 1 h at −78 °C and was then added to half-saturated aqueous ammonium chloride (100 mL) and the product was extracted into ethyl acetate (50 mL then 25 mL). The organic phase was dried over magnesium sulfate, the solvent was distilled at reduced pressure, and the residue was dried in high vacuum to afford **6** as a colorless liquid. HPLC analysis and NMR indicate the product is >99% a single diastereomer. The crude product is >97% AUC by HPLC and should be suitable for most synthetic applications. Nevertheless the product was purified by flash chromatography in 4:1 ethyl acetate/hexanes (R_f=0.31) to afford analytically pure **6** (1.36 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J*=7, 3H), 1.19 (s, 9H), 1.23 (t, *J*=7, 3H), 1.23–1.58 (m, 4H), 3.22–3.42 (m, 4H), 3.70 (m, 1H), 3.81 (m, 1H), 4.19 (q, *J*=7, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 13.9, 20.0, 22.1, 37.8, 39.95, 39.98, 56.9, 61.7, 62.3, 76.24, 171.00. Anal. Calcd for $C_{14}H_{27}NO_3S_3$: C, 47.56; H, 7.70; N, 3.96. Found: C, 47.71; H, 7.58; N, 7.64.

4.2.1.2. Ethyl (S,S$_S$)-2-[(1-tert-butylsulfinylamino)-2-cyclopropylethyl]-1,3-dithiolane-2-carboxylate, ***7***. Colorless oil (95%). R_f=0.33 in 4:1 ethyl acetate/hexanes. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.05 (d, *J*=12.7, 1H), 4.14–4.07 (m, 2H), 3.82 (t, *J*=7.2, 1H), 3.44–3.36 (m, 3H), 3.30–3.19 (m, 2H), 1.21–1.16 (m, 3H), 1.11 (s, 9H), 0.98–0.94 (m, 2H), 0.48–0.36 (m, 1H), 0.35–0.30 (m, 1H), 0.11–0.08 (m, 1H), −0.036 to −0.09 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): 168.6, 74.5, 60.8, 60.0, 54.3, 48.6, 36.5, 36.3, 20.8, 12.0, 7.2, 3.9, 2.5. Anal. Calcd for $C_{15}H_{27}NO_3S_3$: C, 49.28; H, 7.44; N, 3.83. Found: C, 49.41; H, 7.35; N, 3.72.

4.2.1.3. Ethyl 2-(S,S$_S$)-[(tert-butylsulfinylamino)-(2-naphthyl) methyl]-1,3-dithiolane-2-carboyxlate, ***8***. Colorless oil (78%). R_f=0.35 in 2:1 ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.12 (t, *J*=7.3, 3H), 3.14–3.27 (m, 4H), 4.04 (m, 2H), 4.52 (d, *J*=5.4, 1H), 5.19 (d, *J*=5.4, 1H), 7.36–7.41 (m, 2H), 7.49 (m, 1H), 7.68–7.74 (m, 3H), 7.79 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.5, 40.1, 40.4, 56.3, 62.8, 63.7, 77.0, 126.17, 126.24, 126.4, 127.6, 127.8, 128.2, 128.9, 132.8, 133.5, 135.0, 170.2. Anal. Calcd for $C_{21}H_{27}NO_3S_3$: C, 57.63; H, 6.22; N, 3.20. Found: C, 57.71; H, 6.18; N, 3.35.

4.2.1.4. Ethyl (S,S$_S$)-2-[1-tert-butylsulfinylylamino]-3-methylbutyl-1,3-dithiolanecarboxylate, ***9a***. Pale yellow oil (93%). R_f=0.37 in 4:1 ethyl acetate/hexanes. ^{1}H NMR (C_6D_6): δ 0.72 (d, *J*=7, 3H), 0.79 (d, *J*=7, 3H), 0.89 (t, *J*=7, 3H), 0.98 (s, 9H), 1.28 (m, 1H), 1.50 (m, 1H), 1.81 (m, 1H), 3.80–3.94 (m, 3H), 3.15 (m, 1H), 3.75 (m, 1H), 3.92 (q, *J*=7, 2H), 4.07 (m, 1H). ^{13}C NMR (C_6D_6): δ 12.0, 19.1, 20.7, 22.0, 23.2, 38.3, 38.4, 43.3, 54.7, 58.9, 60.3, 75.3, 169.2. Anal. Calcd for $C_{15}H_{29}NO_3S_3$: C, 49.01; H, 7.95; N, 3.81. Found: C, 49.15; H, 7.97; N, 3.69.

4.2.1.5. Ethyl (S,S$_S$)-2-[4-methylphenylsulfinylamino]-3-methylbutyl-1,3-dithiolanecarboxylate, ***10***. Pale yellow oil (91%). HPLC analysis indicated that the product consisted of two diastereomers in a 98:2 ratio. For the major diastereomer, R_f=0.31 in 1:1 ethyl acetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (d, *J*=6.5, 3H), 0.85 (d, *J*=6.5, 3H), 1.17 (td, *J*=7.1, 1.9, 3H), 1.41 (m, 1H), 1.79 (m, 1H), 2.14–2.25 (m, 1H), 2.27 (s, 3H), 3.15–3.34 (m, 4H), 3.93–4.04 (m, 1H), 4.11 (q, *J*=7.1, 2H), 4.36 (d, *J*=9.7, 1H), 7.16 (d, *J*=8.1, 2H), 7.49 (d, *J*=8.1, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 20.9, 21.3, 23.8, 24.9, 39.99, 40.02, 44.7, 60.9, 62.5, 76.1, 125.3, 129.3, 141.2, 144.0, 171.0. Anal. Calcd for $C_{18}H_{27}NO_3S_3$: C, 53.83; H, 6.78; N, 3.49. Found: C, 53.93; H, 6.71; N, 3.57.

4.2.1.6. Methyl (S,S$_S$)-2-[1-tert-butylsulfinylylamino]-3-methylbutyl-1,3-dithiolanecarboxylate, ***11***. Colorless oil (95%). R_f=0.34 in 4:1 ethyl acetate/hexanes. ^{1}H NMR (C_6D_6): δ 0.73 (d, *J*=6.5, 3H), 0.77 (d, *J*=6.5, 3H), 0.98 (s, 9H), 1.26 (m, 1H), 1.51 (m, 1H), 1.80 (m, 1H), 2.82–3.92 (m, 3H), 3.10–3.16 (m, 1H), 3.36 (s, 3H), 3.77 (d, *J*=9.6, 1H), 4.03 (td, *J*=10.0, 1.8, 1H). ^{13}C NMR (C_6D_6): δ 21.0, 22.8, 24.0, 25.2, 40.4, 40.2, 45.0, 52.9, 56.6, 61.0, 77.1, 171.7. Anal. Calcd for $C_{14}H_{27}NO_3S_3$: C, 47.56; H, 7.70; N, 3.96. Found: C, 47.77; H, 7.56; N, 3.94.

4.2.1.7. Ethyl (R,S$_S$)-2-[1-tert-butylsulfinylylamino]-3-methylbutyl-1,3-dithiolanecarboxylate, ***9b***. A solution of ethyl 1,3-dithiolanecarboxylate (360 mg, 2.02 mmol) and [*N*(*E*),*S*(*S*)]-2-methyl-*N*-(3-methylbutylidene)-2-propanesulfinamide (380 mg, 2.01 mmol) in THF (8.0 mL) was cooled to 0 °C. A 1.0 M solution of lithium bis (trimethylsilyl)amide in THF (2.5 mL, 2.5 mmol) was added dropwise and stirring was continued for 15 min at 0 °C. The solution was added to 50 mL of half-saturated aqueous ammonium chloride and the product was extracted into ethyl acetate (2×25 mL). The organic extracts were dried over sodium sulfate and the solvent was distilled at reduced pressure to afford 0.89 g of a pale yellow liquid, which contained two principal components by NMR. Flash chromatography in 4:1 ethyl acetate/hexanes allowed the separation of **9b** (150 mg, R_f=0.55) from its lower R_f diastereomer **9a** (190 mg, R_f=0.37). Compound **9b** was a pale yellow solid. ^{1}H NMR (400 MHz, C_6D_6): δ 0.89 (d, *J*=6.7, 3H), 0.94 (t, *J*=7.1, 3H), 1.05 (*J*=6.3, 3H), 1.11 (s, 9H), 1.61–1.70 (m, 1H), 1.79–1.88 (m, 1H), 2.45 (m, 1H), 2.72–2.83 (m, 2H), 2.91–3.01 (m, 2H), 3.84–4.00 (m, 3H), 4.13 (t, *J*=9.2, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 13.8, 21.4, 22.9, 24.10, 24.12, 39.8, 40.1, 45.0, 56.6, 62.0, 63.0, 76.9, 171.5. Anal. Calcd for $C_{15}H_{29}NO_3S_3$: C, 49.01; H, 7.95; N, 3.81. Found: C, 49.27; H, 8.01; N, 3.91.

4.2.2. Amidation reactions

4.2.2.1. (S,S$_S$)-2-[1-(tert-Butylsulfinylamino)butyl]-N-methyl-1,3-dithiolane-2-carboxamide, ***12a***. A heavy-walled glass tube was charged with ethyl (*S*,*S*$_S$)-2-[1-(*tert*-butylsulfinylamino)butyl]-1,3-dithiolane-2-carboxylate (0.50 g, 1.4 mmol) and a chilled 8.0 M solution of methylamine in ethanol (5 mL, 40 mmol). The mixture was allowed to warm to room temperature and was allowed to stand for 16 h. Distillation of the solvent at reduced pressure afforded **12a** (0.47 g, 98%) as a viscous amber-colored oil. ^{1}H NMR (500 MHz, CD_3OD): δ 0.89 (t, *J*=7, 3H), 1.22 (s, 9H), 1.34 (m, 1H), 1.50 (m, 1H), 1.59 (m, 1H), 2.75 (s, 3H), 3.19 (m, 2H), 3.40 (m, 2H), 3.91 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 14.2, 21.3, 24.7, 27.4, 37.8, 41.0, 41.2, 58.4, 64.7, 78.7, 174.2. Anal. Calcd for $C_{13}H_{26}N_2O_2S_3$: C, 46.12; H, 7.74; N, 8.27. Found: C, 45.99; H, 7.83; N, 8.39.

4.2.2.2. (S,S$_S$)-2-[1-(tert-Butylsulfinylamino)-3-methylbutyl]-N-methyl-1,3-dithiolane-2-carboxamide, ***12b***. Straw-colored liquid (96%). ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, *J*=6.5, 6H), 1.23 (s+m, 10H total), 1.55 (m, 1H), 1.84 (m, 1H), 3.29 (m, 2H), 3.40 (m, 2H), 4.02 (d, *J*=10.6, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 21.4, 23.4, 24.4, 25.9, 27.4, 40.9, 41.2, 44.8, 58.4, 68.1, 78.8, 174.2. Anal. Calcd for $C_{14}H_{28}N_2O_2S_3$: C, 47.71; H, 8.01; N, 7.95. Found: C, 47.68; H, 7.90; N, 7.86.

4.2.2.3. (S,S$_S$)-2-[1-(tert-Butylsulfinylamino)-2-cyclopropylethyl]-N-methyl-1,3-dithiolane-2-carboxamide, ***12c***. Amber glass (97%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.38 (s, 1H), 4.06–4.00 (m, 2H), 3.97–3.88 (m, 1H), 3.45–3.40 (m, 1H), 3.34–2.95 (m, 2H), 2.77 (s, 3H), 1.60–1.54 (m, 1H), 1.15 (s, 9H), 1.05–0.99 (m, 1H), 0.83–0.74 (m, 1H), 0.46–0.40 (m, 1H), 0.35–0.30 (m, 1H), 0.06 to −0.03 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.0, 77.2, 63.2, 56.0, 40.1, 39.9, 26.8, 22.5, 9.1, 5.9, 4.1. Anal. Calcd for $C_{14}H_{26}N_2O_2S_3$: C, 47.97; H, 7.48; N, 7.99. Found: C, 47.73; H, 7.62; N, 7.99.

4.2.2.4. (S,S$_S$)-2-[1-(4-Methylphenylsulfinylamino)-3-methylbutyl]-N-methyl-1,3-dithiolane-2-carboxamide, ***12d****.* White crystals (59%), mp 147–154 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83 (d, J=6.5, 3H), 0.84 (d, J=6.5, 3H), 1.12 (m, 1H), 1.50 (m, 1H), 1.82 (m, 1H), 2.36 (s, 3H), 2.61 (s, 3H), 3.16–3.39 (m, 4H), 4.01 (dd, J=10.6, 1.9, 1H), 7.33 (d, J=8.1, 2H), 7.52 (d, J=8.1, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.76, 20.87, 23.64, 23.71, 26.6, 42.5, 60.4, 77.5, 125.2, 129.1, 140.1, 144.0, 170.8. Anal. Calcd for $C_{17}H_{26}N_2O_2S_3$: C, 52.82; H, 6.78; N, 7.25. Found: C, 52.70; H, 6.80; N, 7.47.

4.2.2.5. (S,S$_S$)-2-[1-(tert-Butylsulfinylamino)butyl]-N-cyclopropyl-1,3-dithiolanecarboxamide, ***14****.* A flask was charged with dithiolane ester **6** (1.41 g, 4.00 mmol), methanol (9.6 mL), and water (1.6 mL). Lithium hydroxide (0.19 g, 7.93 mmol) was added and the mixture was stirred for 4.5 h at room temperature, after which it was added to water (25 mL) and was acidified with 1 N HCl (9.0 mL, 9.0 mmol). The product was extracted into dichloromethane (2×20 mL) and was dried over sodium sulfate. Removal of the solvent at reduced pressure afforded (S,S$_S$)-2-[1-*tert*-butylsulfinylamino]butyl-1,3-dithiolanecarboxylic acid **13** (1.14 g, 88%) as a crisp off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, J=7.0, 3H), 1.12–1.35 (m, 2H), 1.19 (s, 9H), 1.51 (m, 2H), 3.32–3.63 (m, 4H), 3.74 (m, 1H), 4.59 (d, J=9.8, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6, 20.5, 22.9, 38.1, 40.12, 40.14, 57.7, 63.5, 75.5, 173.7. A flask was charged with a portion of this material (0.94 g, 2.9 mmol), triethylamine (2.4 mL, 17 mmol), and dichloromethane (9.4 mL). The mixture was cooled to 0 °C and a 50% w/w solution of propylphosphonic anhydride in ethyl acetate (2.76 g, 4.3 mmol) was added. After 1 h at 0 °C, cyclopropylamine (300 μL, 4.3 mmol) was added and the mixture was allowed to warm to room temperature overnight. The mixture was added to 50 mL of water and the product was extracted into dichloromethane (25 mL) and dried over sodium sulfate. Distillation of solvent at reduced pressure afforded **14** (1.00 g, 95%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.48 (m, 2H), 0.74 (d, J=7.0, 2H), 0.81 (t, J=6.5, 3H), 1.05–1.55 (m, 4H), 1.16 (s, 9H), 2.67 (m, 1H), 3.12–3.46 (m, 4H), 3.87 (td, J=9.6, 2.3, 1H), 4.05 (d, J=9.5, 1H), 7.43 (d, J=2.7, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 6.4, 6.6, 13.6, 20.0, 22.7, 22.9, 37.4, 39.85, 39.91, 56.9, 63.5, 77.0, 172.4. Anal. Calcd for $C_{15}H_{28}N_2O_2S_3$: C, 49.41; H, 7.74; N, 7.68. Found: C, 49.25; H, 7.99; N, 7.79.

4.2.3. Removal of sulfinyl group

4.2.3.1. (S)-2-[1-Amino-3-methylbutyl]-N-methyl-1,3-dithiolane-2-carboxamide hydrochloride, ***15b****.* A 4.0 M solution of hydrogen chloride in dioxane (21 mL, 84 mmol) was added to a flask containing (S,S$_S$)-2-[(1-*tert*-butylsulfinylamino)-3-methylbutyl]-*N*-methyl-1,3-dithiolane-2-carboxamide (2.43 g, 6.89 mmol). The mixture was stirred for 1 h, was filtered to remove a trace of cloudiness, and was added dropwise to diethyl ether (100 mL) with stirring. The precipitate was collected by filtration and dried in high vacuum to afford **15b** (1.59 g, 93%) as a yellowish solid. ^{1}H NMR (500 MHz, CD_3OD): δ 0.94 (d, J=5.1, 3H), 0.96 (d, J=5.1, 3H), 1.26 (m, 1H), 1.60 (m, 1H), 1.79 (m, 1H), 2.79 (s, 3H), 3.40–3.58 (m, 4H), 3.97 (dd, J=9.9, 2.0, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 21.4, 24.0, 26.0, 27.6, 41.1, 41.7, 42.1, 56.6, 75.3, 172.1. Anal. Calcd for $C_{10}H_{21}ClN_2OS_2$: C, 42.16; H, 7.43; N, 9.83. Found: C, 42.34; H, 7.37; N, 9.67.

4.2.3.2. (S)-2-[1-Amino-2-cyclopropylethyl]-N-methyl-1,3-dithiolane-2-carboxamide hydrochloride, ***15c****.* Light yellow solid (88%), mp: 75–76 °C. $[\alpha]_D^{24}$ −6.85 (*c* 2.22, H_2O). ^{1}H NMR (500 MHz, CD_3OD): δ 3.82–3.77 (m, 1H), 3.35–3.21 (m, 4H), 3.31–3.10 (m, 1H), 2.57 (s, 3H), 1.51–1.44 (m, 1H), 1.17–1.11 (m, 1H), 0.67–0.60 (m, 1H), 0.43–0.31 (m, 2H), 0.03 to −0.11 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 171.2, 74.4, 59.4, 41.8, 41.1, 37.8, 27.5, 8.7, 6.4, 4.8. Anal. Calcd for $C_{10}H_{19}ClN_2OS_2$: C, 42.46; H, 6.77; N, 9.90. Found: C, 42.57; H, 6.70; N, 9.75.

4.2.3.3. (S)-2-[1-Aminobutyl]-N-cyclopropyl-1,3-dithiolane-2-carboxamide hydrochloride, ***15d****.* Pale yellow solid (69%). ^{1}H NMR (500 MHz, CD_3OD): δ 0.61 (m, 2H), 0.76 (m, 2H), 0.93 (t, 3H, J=7), 1.34–1.73 (m, 4H), 2.68 (m, 1H), 3.36–3.63 (m, 4H), 3.91 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 6.7, 6.9, 14.2, 20.7, 24.6, 35.3, 41.2, 42.0, 58.2, 74.8, 173.2. Anal. Calcd for $C_{11}H_{21}ClN_2OS_2$: C, 44.50; H, 7.13; N, 9.44. Found: C, 44.58; H, 6.92; N, 9.64.

4.3. Applications

4.3.1. Preparation of dipeptide ***17***

1-Hydroxybenzotriazole (2.25 g, 14.7 mmol), *N*-methylmorpholine (2.97 g, 29.4 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (3.94 g, 20.6 mmol), and dithiolane amide **15c** (5.08 g, 90% purity, 16.2 mmol) were added in that order to a cooled (0–5 °C) solution of CBz-proline (3.70 g, 14.7 mmol) in dichloromethane (37 mL). The mixture was stirred overnight (18 h) and then quenched with water (37 mL). After phase separation, the organic phase was washed with $NaHCO_3$ (5% w/w solution, 36 mL) and HCl (1 M solution, 36 mL) and then concentrated by rotary evaporation. The mixture was dried under high vacuum, furnishing dithiolane-protected dipeptide **16** as a white foam, which retained 15% of ethyl acetate by NMR. This material was used in the subsequent step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.00–8.05 (m, 1H), 7.50–765 (m, 1H), 7.24–7.39 (m, 5H), 5.04–5.10 (m, 1.5H, part of a mixture of two rotamers), 4.89 (d, 0.5H, J=20, part of a mixture of two rotamers), 4.65–4.74 (m, 1H), 4.35–4.45 (m, 1H), 3.35–3.50 (m, 2H), 3.15–3.32 (m, 4H), 2.60–2.64 (m, 3H), 2.02–2.18 (m, 1H), 1.76–1.96 (m, 3H), 1.34–1.43 (m, 1H), 1.00–1.07 (m, 0.5H, part of a mixture of two rotamers), 0.86–0.93 (m, 0.5H, part of a mixture of two rotamers), 0.61–0.68 (m, 0.5H, part of a mixture of two rotamers), 0.40–0.47 (m, 0.5H, part of a mixture of two rotamers), 0.33–0.40 (m, 0.5H, part of a mixture of two rotamers), 0.22–0.28 (m, 0.5H, part of a mixture of two rotamers), 0.02–0.11 (m, 1.5H, part of a mixture of two rotamers), −0.12–−0.02 (m, 1.5H, part of a mixture of two rotamers). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.7, 171.4, 170.7, 154.2, 153.9, 137.1, 128.3, 128.1, 127.7, 127.4, 126.8, 76.1, 65.8, 65.6, 59.9, 59.2, 54.7, 54.5, 47.1, 46.5, 38.3, 38.2, 31.3, 29.8, 26.9, 23.9, 22.9, 8.4, 4.8, 4.7, 4.1, 4.0. HRMS: 478.1825, calcd for $C_{23}H_{32}O_4N_3S_2+H^+$: 477.1829. Water (2.00 mL) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 2.34 g, 8.20 mmol) were added in that order to a solution of **16** (1.00 g, 2.05 mmol) in acetonitrile (20 mL), generating an orange solution. The mixture is stirred for 1 h, at which point the reaction was determined to be complete by HPLC. Isopropyl acetate (35 mL) was added to the solution. The mixture was washed with a solution of $Na_2S_2O_3$ (4.32 g, 17.4 mmol) in water (20 mL), after which the organic phase was colorless. The organic phase was washed with $NaHCO_3$ (5% w/w solution, 2×50 mL), and was analyzed by HPLC to ensure complete removal of hydantoin by-products. The mixture was concentrated by rotary evaporation and the resulting oil was dried under high vacuum to yield dipeptide **17** (533 mg, 64% for two steps) as a white waxy solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.59–8.61 (m, 1H), 8.35–8.39 (m, 1H), 7.28–7.37 (m, 5H), 5.00–5.06 (m, 3H), 4.33 (dd, 0.6H, J=8.0, 2.5, part of a mixture of two rotamers), 4.28 (dd, 0.4H, J=8.0, 2.5, part of a mixture of two rotamers), 3.33–3.45 (m, 2H), 2.64 (d, J=5.0, 3H), 2.09–2.19 (m, 1H), 1.75–1.86 (m, 3H), 1.68 (ddd, 0.4H, J=14.0, 8.0, 6.0, part of a mixture of two rotamers), 1.60 (ddd, 0.6H, J=14.0, 8.0, 6.0, part of a mixture of two rotamers), 1.37–1.49 (m, 1H), 0.77–0.85 (m, 0.4H, part of a mixture of two rotamers), 0.65–0.73 (m, 0.5H, part of a mixture of two rotamers), 0.21–0.44 (m, 2H), −0.05 to 0.09 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.9, 172.2, 171.9, 161.2, 161.1, 153.9, 153.7, 137.0, 136.9, 128.4, 128.1, 127.7, 127.5, 127.4, 126.9, 65.8, 59.2, 58.7, 54.5, 54.5, 47.1, 46.4,

34.8, 31.1, 29.9, 25.4, 24.6, 23.7, 22.9, 7.9, 4.9, 4.2, 4.1. HRMS: 402.2021, calcd for $C_{21}H_{27}N_3O_5+H^+$: 402.2024.

4.3.2. Ethyl 2-(S,S_S)-[(tert-butylsulfinylamino)-2-deuterio-(2-naphthyl)methyl]-1,3-dithiolane-2-carboxylate, ***18****.* A flask was charged with ethyl 1,3-dithiolane-2-carboxylate (0.23 g, 1.3 mmol) and [*N*(*E*),*S*(*S*)]-*N*-[deuterio-(2-naphthyl)methylene]-2-methylpropane-2-sulfinamide (0.33 g, 1.3 mmol) in tetrahydrofuran (5.0 mL) under a nitrogen atmosphere. The solution was cooled to −78 °C whereupon a 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (1.5 mL, 1.5 mmol) was added dropwise. The mixture was stirred for 2 h at −78 °C and was then added to half-saturated aqueous ammonium chloride (30 mL) and the product was extracted into ethyl acetate (2×15 mL). After drying over sodium sulfate, the solvent was removed at reduced pressure. The crude product was purified by flash chromatography, eluting with 4:1 ethyl acetate/hexanes. Distillation of solvent afforded **18** (0.41 g, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.12 (t, J=7.3, 3H), 3.14–3.27 (m, 4H), 4.04 (m, 2H), 4.52 (s, 1H), 7.36–7.41 (m, 2H), 7.49 (m, 1H), 7.68–7.74 (m, 3H), 7.79 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.5, 40.1, 40.4, 56.3, 62.8, 63.3 (1:1:1 triplet, J [^{2}H–^{13}C]=20.7), 77.0, 126.17, 126.24, 126.4, 127.6, 127.8, 128.2, 128.9, 132.8, 133.5, 135.0, 170.2.

4.4. X-ray crystal structure of dithiolane amide 12d

A suitable crystal was grown by slow evaporation of an ether/heptane solution. Crystallographic data (excluding structure factors) for structure **12d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 790869. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).

References and notes

1. St. Charles, R.; Matthews, J. H.; Zhang, E. L.; Tulinsky, A. *J. Med. Chem.* **1999**, *42*, 1376.
2. Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R., III; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37*, 2918.
3. Villa, P.; Kaufmann, S. H.; Earnshaw, W. C. *Trends Biochem. Sci.* **1997**, *22*, 388.
4. Lin, C.; Kwong, A. D.; Perni, R. B. *Infect. Disord. Drug Targets* **2006**, *6*, 3.
5. Njorage, F. G.; Chen, K. X.; Shih, N.-Y. *Acc. Chem. Res.* **2008**, *41*, 50.
6. Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.* **1977**, *20*, 510.
7. Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E. *Tetrahedron Lett.* **2002**, *43*, 4067.
8. (a) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364; (b) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972.
9. Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 4253.
10. (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003; (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
11. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
12. (a) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215; (b) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403; (c) Chen, Q.; Li, J.; Yuan, C. *Synthesis* **2008**, 2986.
13. (a) Davis, F. A.; Ramachandar, T.; Liu, H. *Org. Lett.* **2004**, *6*, 3393; (b) Davis, F. A.; Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett.* **2006**, *47*, 2743.
14. Li, Z.; Patil, G. S.; Golubski, Z. E.; Hori, H.; Tehrani, K.; Foreman, J. E.; Eveleth, D. D.; Bartus, R. T.; Powers, J. C. *J. Med. Chem.* **1993**, *36*, 3472.
15. Papanikos, A.; Meldal, M. *J. Comb. Chem.* **2004**, *6*, 181.
16. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
17. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
18. For reviews, see: (a) Burghardt, T. E. *J. Sulfur Chem.* **2005**, *26*, 411; (b) Banerjee, A. K.; Laya, M. S. *Russ. Chem. Rev.* **2000**, *69*, 947.
19. Spletstoser, J. T.; White, J. M.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 2787.
20. Kamimura, A.; Okawa, H.; Morisaki, Y.; Ishikawa, S.; Uno, H. *J. Org. Chem.* **2007**, *72*, 3569.
21. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.