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PAPER

Radical-mediated reduction of the dithiocarbamate group under tin-free conditions†

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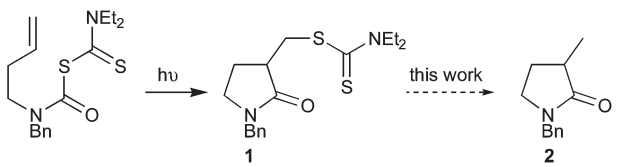
Reductive desulfurisation of dithiocarbamates is conveniently achieved using H_3PO_2–Et_3N–ACCN in refluxing dioxane. Fused and spirocyclic β-lactams, prepared through 4-*exo trig* carbamoyl radical cyclisation–dithiocarbamate group transfer reactions, are reduced without fragmentation of the strained 4-membered ring. Diethyl tetraacetyl-D-glucopyranosyl dithiocarbamate is selectively reduced with or without acyloxy group migration depending on reaction conditions and choice of reductant. Deuterium incorporation from D_3PO_2–Et_3N is observed for a system involving a nucleophilic radical intermediate, but not in the case of the electrophilic radical obtained through acyloxy group migration on a glucose derivative.

Introduction

Recent reports from our laboratory have shown carbamoyl dithiocarbamates to be practical sources of carbamoyl radicals, which undergo cyclisation reactions onto alkenes to form lactams of varying ring sizes (Scheme 1).[1,2] The dithiocarbamate group is critical to maintaining the radical chain process, and allows access to a wider variety of structures than can be prepared through chain processes based on hydrogen-atom transfer. The dithiocarbamate group also represents a useful handle for further synthetic manipulations through its incorporation in the product through formal group transfer.[3] We have previously developed conditions for both a photomediated dithiocarbamate–oxygen exchange reaction,[4] and for the elimination of dithiocarbamates to alkenes,[5] and applied these methodologies in natural product synthesis.[4,5a] In this paper we now report a protocol for the reduction of the dithiocarbamate group under tin-free radical conditions, allowing access to lactams formally the result of carbamoyl radical cyclisations based on hydrogen atom transfer, and also its application in the reduction of anomeric dithiocarbamates and xanthates.



Scheme 1 Carbamoyl radical cyclisation with dithiocarbamate group transfer and proposed desulfurisation.

Reagents previously employed for the desulfurisation of dithiocarbamates include lithium in ethylamine, RANEY® Nickel, and $LiAlH_4$–$CuCl_2$.[6,7] The presence of a radicophilic thiocarbonyl in a dithiocarbamate group suggests a potentially milder and more functional-group compatible radical-mediated reduction should be possible, analogous to the classical Barton–McCombie deoxygenation[8] of xanthates (Scheme 2, eqn (1)). Indeed, reduction of α-cyanodithiocarbamates under classical tin hydride conditions was reported by Endo (Scheme 2, eqn (2)).[9] In comparison with the Barton–McCombie deoxygenation, the byproduct of this reaction contains a carbon–sulfur rather than a carbon–oxygen double bond, although the presence of the nitrile in this system will provide an additional driving force for fragmentation of the intermediate radical to a stabilized α-cyano radical. Keen to avoid the use of toxic tin reagents,[10] we were attracted to the work of Zard[11] and Boivin,[12] who have reported methods for the reductive removal of the xanthate group (Scheme 2, eqn (3)). Their work also demonstrates that fragmentation to form C=O is not a prerequisite for an efficient radical chain process, even in the absence of an additional radical stabilizing group on R.

Results and discussion

Dithiocarbamate reduction using H_3PO_2–Et_3N–ACCN

Our studies started with the previously reported dithiocarbamate **1**, readily accessible through a 5-*exo trig* carbamoyl radical

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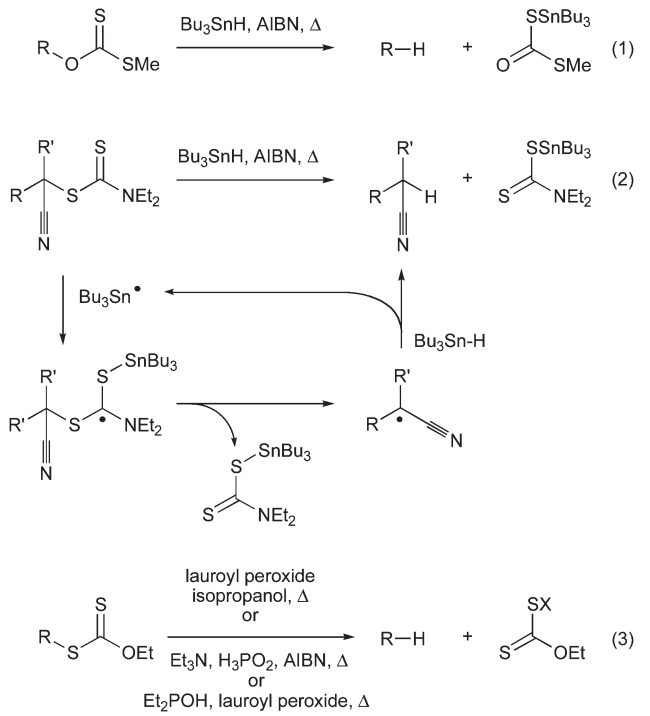
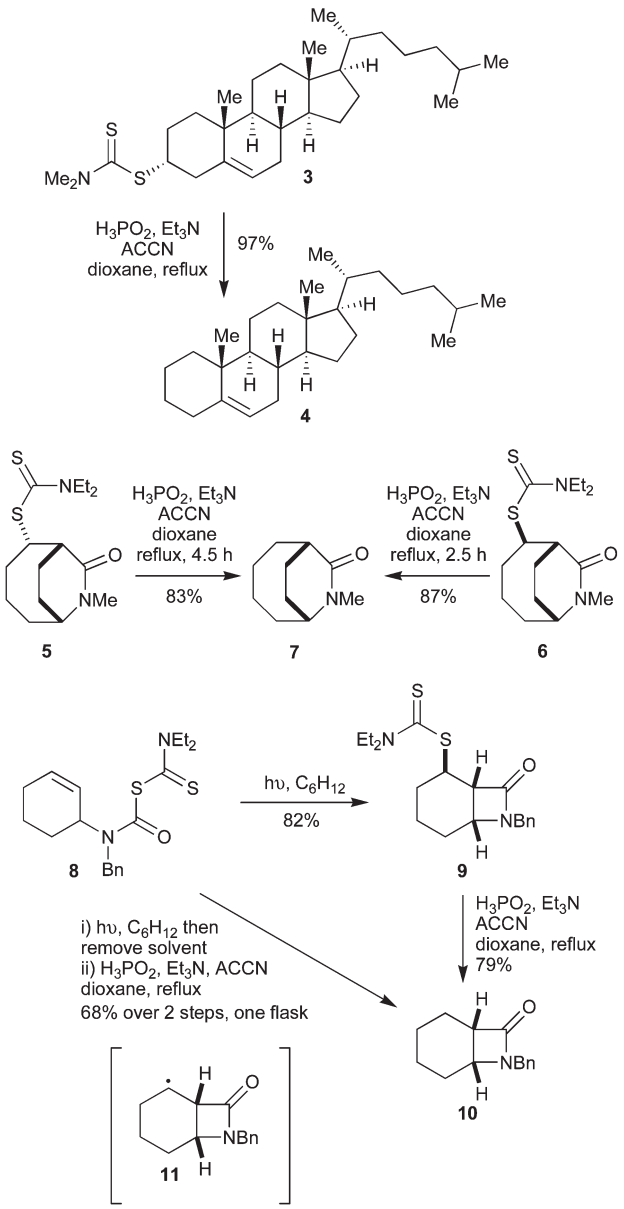


Scheme 2 Radical-mediated reduction of xanthates and dithiocarbamates.

cyclisation–dithiocarbamate group transfer reaction.[1] Gratifyingly, treatment of **1** with commercially available hypophosphorous acid (H_3PO_2, 50 wt% in H_2O, 5 equiv.) and triethylamine (5.5 equiv.) in refluxing dioxane,[12,13] initiated with substoichiometric 1,1′-azobis(cyclohexanecarbonitrile) (ACCN, or VAZO-88), gave clean conversion to the γ-lactam **2** in good yield (77%).[14] After a simple aqueous work-up no products arising from the dithiocarbamate group were observed in the crude reaction mixture, consistent with formation of a water soluble byproduct, $[Et_3NH]^+[HPO_2SC(S)NEt_2]^-$. In contrast, attempted radical-mediated reduction of **1** with dilauroyl peroxide in isopropanol[11] or with diethylphosphite[12a] gave complex reaction mixtures.

Application of the H_3PO_2–Et_3N–ACCN conditions to other dithiocarbamates showed it to be a generally high yielding process (Scheme 3). Reduction of the cholesterol-derived dithiocarbamate **3**[15] occurs in excellent yield without addition of a phosphorus-centred radical to the double bond, a potential competing reaction.[16] The diastereomeric dithiocarbamates **5** and **6**[5a] are reduced to **7** in comparable yield, albeit with different reaction times. Dithiocarbamate **9**[1] is reduced without opening of the 4-membered β-lactam ring, either through a radical or hydrolytic process.

The two steps required to transform **8** to **10** can be conveniently combined without purification of the intermediate dithiocarbamate **9**. At the end of the photomediated cyclisation, the solvent is simply removed and the crude reaction mixture dissolved in dioxane and submitted to the reduction conditions. In this manner, a 68% overall yield of **10** was achieved, comparable to the 65% expected from the individual transformations, but requiring only one purification. A switch of solvents from



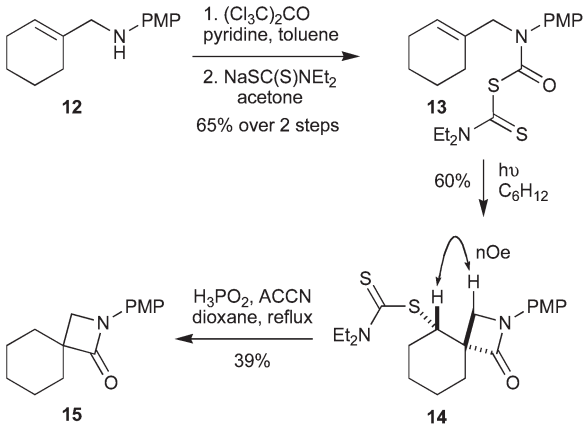
Scheme 3 Reduction of dithiocarbamates using Et_3N–H_3PO_2–ACCN.

cyclohexane to dioxane is necessary: it was neither possible to cleanly cyclise **8** to **9** in dioxane (59% and 34% yields by *hν* or ACCN initiation respectively), nor reduce **9** with H_3PO_2–Et_3N–ACCN in cyclohexane rather than dioxane as solvent. Similarly treatment of **8** with H_3PO_2–Et_3N–ACCN in dioxane gave only approximately 5% of **10** as part of a complex reaction mixture.

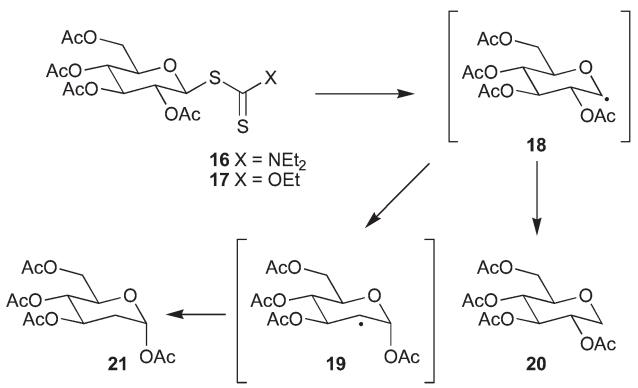
Spirocyclic β-lactam synthesis

Radicals adjacent to 4-membered ring systems are prone to ring-opening, driven by release of ring strain.[17] However, as has been previously noted,[18,19] this reaction pathway has not been observed for radicals adjacent to the β-lactam ring such as **11**, which is an intermediate both in the 4-*exo trig* carbamoyl radical cyclisation of **8** and the reduction of **9**. It therefore appeared feasible that a 4-*exo trig* carbamoyl radical cyclisation could be

used to prepare spirocyclic β-lactams, a class of compound shown to display a range of interesting biological activities and transformations.[20] In order to investigate this novel approach, the known amine **12**, prepared in one step by reductive amination of commercially available 1-cyclohexene-1-carboxaldehyde with *para*-methoxyaniline,[21] was converted to the carbamoyl radical precursor **13** under our previously reported conditions (Scheme 4).[1] Irradiation of **13** with a 500 W halogen lamp gave a spirocyclic dithiocarbamate **14** as a single diastereomer, the stereochemistry of which was determined by nOe analysis, which showed the proton adjacent to sulfur to be on the same side of the cyclohexyl ring as the methylene group of the β-lactam. Reduction of **14** successfully gave the spirocyclic β-lactam **15**, in reduced yield compared to reduction of **9**.



Scheme 4 Spirocyclic β-lactam synthesis.



Scheme 5 Reduction of anomeric dithiocarbamates and xanthates.

Unfortunately it was not possible to isolate any other compounds from the reaction mixture in sufficient purity to permit identification of alternative reaction pathways.

Reduction of anomeric dithiocarbamates and xanthates

The reduction of anomeric sugar derivatives bearing acetyloxy or related groups at C-2 is of long-standing interest both mechanistically and in selective carbohydrate synthesis. Anomeric radicals such as **18** can undergo hydrogen abstraction to give **20**, or rearrange, through acyloxy group migration,[22] to **19** prior to reduction to give the 2-deoxysugar **21** (Scheme 5). Application of our standard conditions to the known dithiocarbamate **16**[23] and xanthate **17**[24] gave approximately 1 : 1 mixtures of **20** and **21** in comparable yields and reaction times (Table 1, entries 1 and 5).

The ratio of **20** : **21** can be controlled through concentration effects. Increased dilution gave solely the rearranged product **21**, the rate of intermolecular H-abstraction being slower at the lower concentration, allowing the intramolecular rearrangement to compete effectively (Table 1, entry 2). Conversely, at higher concentration, the radical **18** undergoes H-abstraction more rapidly, giving a higher proportion of **20** compared to **21** in the isolated mixture (entry 3). At still higher concentrations the reaction becomes impractical due to solubility issues, but partial success was achieved through doubling the concentration of Et_3N and H_3PO_2, which led solely to the non-rearranged reduction product **20**, albeit in lower isolated yield (entry 4).

Zard has previously demonstrated that anomeric xanthate **17** is reduced cleanly to **21** using lauroyl peroxide as radical initiator and cyclohexane as solvent and hydrogen source.[25] The intermediate radical **19** is sufficiently electrophilic to abstract a hydrogen from cyclohexane, the process benefiting from charge transfer in the transition state leading to **21** and the nucleophilic cyclohexyl radical. The initial radical **18**, in contrast, is nucleophilic, and H-abstraction is therefore unfavourable. We have compared the reduction of xanthate **17** with dithiocarbamate **16** under the Zard conditions, and found the latter also to be an effective substrate, giving **21** in comparable yield and a slightly reduced reaction time (Table 1, entries 6 and 7).

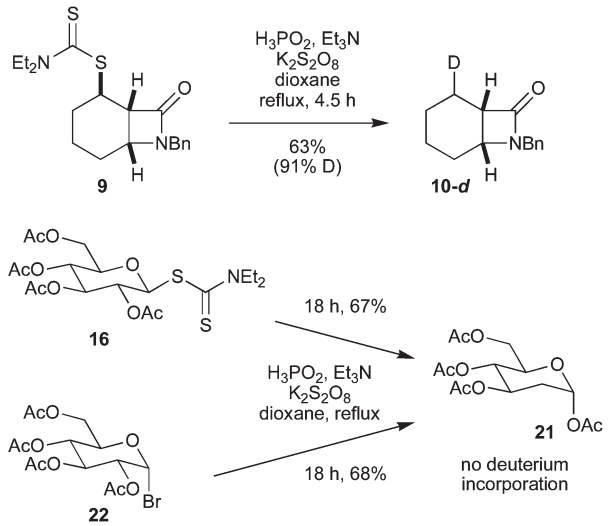
Deuterium incorporation

Oshima has reported the use of D_3PO_2 as a source of deuterium in radical-mediated reduction of alkyl and aryl iodides.[26] We have found that certain dithiocarbamates can also be reduced

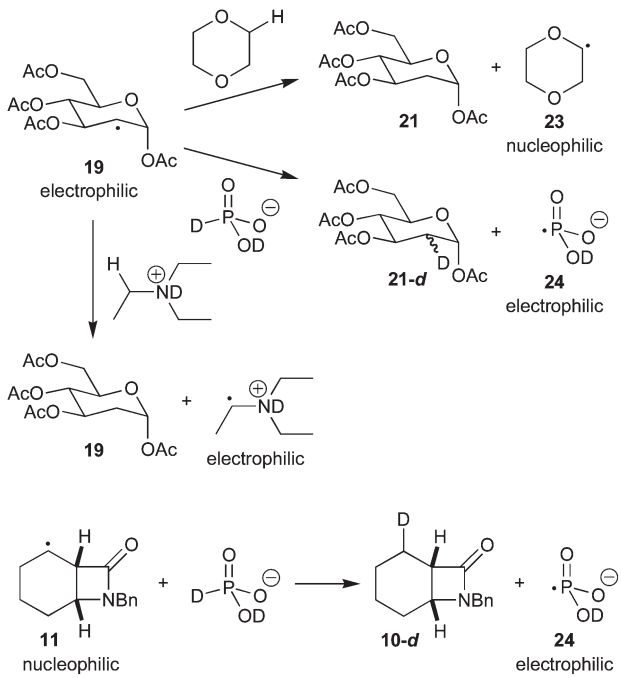
Table 1 Reduction of anomeric dithiocarbamate **16** and xanthate **17**

Entry	Substrate	Reagents (equivalents), solvent (substrate concentration)	Time/h	Ratio[a] **20** : **21**	Isolated yield (%)
1	**16**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.1 M)	18	1 : 1	85
2	**16**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.01 M)	18	0 : 1	86
3	**16**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.5 M)	18	3 : 1	71
4	**16**	H_3PO_2 (10), Et_3N (11), ACCN (0.3), dioxane (0.5 M)	18	1 : 0	44
5	**17**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.1 M)	18	1 : 1	79
6	**16**	Dilauroyl peroxide (0.4), cyclohexane (0.1), reflux	4	0 : 1	88
7	**17**	Dilauroyl peroxide (0.4), cyclohexane (0.1), reflux	6	0 : 1	86[b]

[a] Determined by integration in ^1H NMR of crude reaction mixture. [b] Literature yield 65% (ref. 25*a*).



Scheme 6 Deuterium incorporation studies.



Scheme 7 Polar effects in H/D-atom abstraction.

with good levels of deuterium incorporation using commercially available D_3PO_2 in D_2O (Scheme 6). Consistent with the observations of Oshima, better yields and higher levels of deuterium incorporation were obtained using potassium peroxodisulfate as radical initiator, compared with ACCN (for **10-*d***, 32% yield and 82% deuterium incorporation *vs.* 63% yield, 91% deuterium incorporation using $K_2S_2O_8$).

Deuterium incorporation was not observed when these conditions were applied to the glucosyldithiocarbamate **16** nor to the glucosylbromide **22** under conditions previously determined to result in complete acyloxy group migration prior to reduction (*vide supra*). The lack of deuterium incorporation points to a significant role of polar effects[27] in the reactions of the common intermediate radical **19**, which is electrophilic in nature due to the flanking electron-withdrawing acetate groups (Scheme 7). Of the possible traps for **19**, only hydrogen abstraction from dioxane (or excess triethylamine, not shown) offers a polarity-matched reaction pathway, resulting in the nucleophilic α-oxo radical **23**. Deuterium abstraction from the phosphonium salt is now disfavoured due to both the increased strength of the P–D bond compared to the P–H bond in Et_3N–H_3PO_2, and also because of the electrophilic nature of the resulting phosphorus-centred radical **24**. In contrast, polar effects favour deuterium abstraction in the case of the nucleophilic alkyl radical **11** derived from **9**, giving rise to the observed high level of deuterium incorporation.

Conclusions

In conclusion, we have shown that the combination of H_3PO_2–Et_3N–ACCN in refluxing dioxane represents an efficient, tin-free methodology for the reductive removal of the dithiocarbamate group, the overall process also benefiting from formation of a water-soluble byproduct. In combination with the advantages of the dithiocarbamate group transfer reaction in terms of substrate scope, this methodology expands the range of lactams that can be prepared through carbamoyl radical cyclisation reactions.

Experimental

Unless otherwise stated, all reactions were run under argon atmosphere using degassed solvents, and commercially available reagents were used as supplied. ^{1}H NMR are referenced to residual $CHCl_3$ at 7.26 ppm, and ^{13}C to $CDCl_3$ at 77.16 ppm.

General procedure for reduction of dithiocarbamates using H_3PO_2–Et_3N–ACCN

A solution of dithiocarbamate (1 equiv.), triethylamine (5.5 equiv.) and hypophosphorous acid (50 wt% in water, 5.0 equiv.) in dioxane (0.08 M dithiocarbamate in dioxane) was heated to reflux for 20 min under an argon atmosphere. ACCN (0.15 equiv.) was added to the solution, and the resultant reaction mixture was heated to reflux. An additional portion of ACCN (0.15 equiv.) was added if required, typically after 4 h of reflux. Upon completion (by t.l.c. analysis) the reaction mixture was cooled to room temperature. EtOAc and H_2O were added, and the aqueous layer extracted a further two times with EtOAc (approximately equal volumes of H_2O and EtOAc as dioxane were used). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography.

1-Benzyl-3-methylpyrrolidin-2-one (2). According to the general procedure, a solution of dithiocarbamate **1**[1] (0.25 g, 0.74 mmol) in dioxane (9.3 mL) was treated with Et_3N (0.56 mL, 4.07 mmol) and aq. H_3PO_2 (0.38 mL, 3.72 mmol), then ACCN (0.027 g, 0.11 mmol). After 4 h at reflux, a further portion of ACCN (0.027 g, 0.11 mmol) was added, and heating continued for a further 14 h. Work-up followed by column

chromatography (1 : 1 hexane–EtOAc) afforded the title compound as a yellow oil (0.108 g, 77%), whose analytical data were consistent with that reported in the literature.[28]

Cholest-5-ene (4). According to the general procedure, a solution of dithiocarbamate **3**[15] (0.4 g, 0.84 mmol) in dioxane (10 mL) was treated with Et_3N (0.64 mL, 4.62 mmol) and aq. H_3PO_2 (0.44 mL, 4.2 mmol), then ACCN (0.03 g, 0.12 mmol). The reaction was complete after 5 h. Work-up followed by column chromatography (60–80 petroleum ether) afforded the title compound as a white solid (0.30 g, 97%), whose analytical data were consistent with that reported in the literature.[29]

(±)-(1*R,6*R**)-7-Methyl-8-oxo-7-azabicyclo[4.2.2]decane (7)**

*Starting from dithiocarbamate **5**.* According to the general procedure, a solution of dithiocarbamate **5**[5a] (0.05 g, 0.16 mmol) in dioxane (2 mL) was treated with Et_3N (0.12 mL, 0.88 mmol), aq. H_3PO_2 (0.08 mL, 0.80 mmol), and ACCN (0.006 g, 0.024 mmol). After 2 h at reflux, a further portion of ACCN (0.027 g, 0.11 mmol) was added, and heating continued for a further 2.5 h. Work-up followed by column chromatography (EtOAc followed by 9 : 1 CH_2Cl_2–MeOH) afforded the title compound as a white solid (0.022 g, 83%). m.p. 82–84 °C; ν_{max} (neat)/cm^{-1}: 2925, 1634 (C═O), 1451, 1369; δ_H (300 MHz; $CDCl_3$); 1.37–1.84 (8H, m, 4 × CH_2), 1.98–2.25 (4H, m, 2 × CH_2), 2.75–2.84 (1H, m, CH), 2.96 (3H, s, NCH_3), 3.62–3.71 (1H, m, CH); δ_C (100 MHz; $CDCl_3$) 23.6 (CH_2), 23.9 (CH_2), 24.9 (CH_2), 25.2 (CH_2), 29.9 (CH_2), 34.1 (CH_3), 34.8 (CH_2), 35.9 (CH_2), 39.6 (CH), 57.0 (CH), 175.5 (C═O); *m*/*z* (EI) 167.1 ([M]$^+$, 71%), 139.1 (26%), 124.1 (36%), 96.1 (100%); HRMS (EI) calculated for $C_{10}H_{17}NO$ [M]$^+$ 167.1310, found 167.1318.

*Starting from dithiocarbamate **6**.* According to the general procedure, a solution of dithiocarbamate **6**[5a] (0.05 g, 0.16 mmol) in dioxane (2 mL) was treated with Et_3N (0.12 mL, 0.88 mmol) and aq. H_3PO_2 (0.08 mL, 0.80 mmol), then ACCN (0.006 g, 0.024 mmol). The reaction was complete after 2.5 h. Work-up followed by column chromatography (EtOAc followed by 9 : 1 CH_2Cl_2–MeOH) afforded the title compound as a white solid (0.023 g, 87%).

(±)-(1*S,6*R**)-7-Benzyl-7-azabicyclo[4.2.0]octan-8-one (10)**

*Starting from dithiocarbamate **9**.* According to the general procedure, a solution of dithiocarbamate **9**[1] (0.15 g, 0.4 mmol) in dioxane (5 mL) was treated with Et_3N (0.31 mL, 2.2 mmol) and aq. H_3PO_2 (0.21 mL, 2.0 mmol), then ACCN (0.015 g, 0.06 mmol). After 4 h at reflux, a further portion of ACCN (0.015 g, 0.06 mmol) was added, and heating continued for a further 14 h. Work-up followed by column chromatography (1 : 2 hexane–EtOAc) afforded the title compound as a yellow oil (0.068 g, 79%). ν_{max} (neat)/cm^{-1}: 2935 (br), 1734 (C═O), 1400; δ_H (300 MHz; $CDCl_3$) 1.26–1.91 (8H, m, 4 × CH_2), 3.20 (1H, q, *J* = 5.3 Hz CHCO), 3.65 (1H q, *J* = 4.0 Hz, NCH), 4.10 (1H, d, *J* = 15.0 Hz, NC*H*$_2$Ph), 4.60 (1H, d, *J* = 15.0 Hz, NC*H*$_2$Ph), 7.26–7.37 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 16.8 (CH_2), 18.9 (CH_2), 19.7 (CH_2), 22.9 (CH_2), 44.4 (CH_2), 47.0 (CH), 50.1 (CH), 127.6 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 136.2 (C), 170.9 (C═O); *m*/*z* (EI) 215.1 ([M]$^+$, 75%), 134.1 (28%), 124.1 (36%), 91.1 (100%), 82.1 (62%), 67.1 (63%); HRMS (EI) calculated for $C_{14}H_{17}NO$ [M]$^+$ 215.1310, found 215.1318.

*Starting from carbamoyldithiocarbamate **8**.* A solution of carbamoyl dithiocarbamate **8**[1] (0.5 g, 1.38 mmol) in cyclohexane (14 mL) was degassed and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 5 h the solvent was removed under reduced pressure. The crude material was dissolved in dioxane (17 mL) and treated with triethylamine (1.05 mL, 7.59 mmol) and aq. H_3PO_2 (0.71 mL, 6.9 mmol). After 20 min at reflux ACCN (0.05 g, 0.2 mmol) was added. After a further 4 h at reflux, another portion of ACCN (0.05 g, 0.2 mmol) was added, and heating continued for a further 14 h. The work up was completed according to the general procedure. The crude product was purified by column chromatography (1 : 2 hexane–EtOAc) to afford the title compound as a yellow oil (0.201 g, 68%).

Diethylthiocarbamic acid-[4-methoxyphenyl(cyclohex-2-enyl)-carbamic acid]-thioanhydride (13). A solution of triphosgene (0.50 g, 1.70 mmol) in toluene (43 mL) was treated with pyridine (0.45 mL, 5.50 mmol), and subsequently with a solution of (4-methoxyphenyl)cyclohex-1-enylmethylamine (**12**)[21] (1.0 g, 4.6 mmol) in toluene (7 mL). The reaction was stirred at room temperature for 18 h, quenched with saturated Na_2CO_3 (30 mL) and extracted with Et_2O (3 × 25 mL). The combined extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the carbamoyl chloride (1.24 g, 97%) as a yellow oil, of sufficient purity to be used directly in the next step without any further purification. δ_H (300 MHz; $CDCl_3$); 1.51–1.70 (4H, m, 2 × CH_2), 1.91–2.08 (4H, m, 2 × CH_2), 3.83 (3H, s, $ArOCH_3$), 4.19 (2H, s, CH_2N), 5.41–5.43 (1H, m, CH═C), 6.89–6.97 (2H, m, 2 × ArH), 7.17–7.23 (2H, m, 2 × ArH).

Sodium diethyldithiocarbamate trihydrate (7.09 g, 31.4 mmol) was added to a solution of carbamoyl chloride (2.2 g, 7.87 mmol) in acetone (79 mL) at room temperature. The solution was stirred at room temperature for 18 h, quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (4 : 1 petroleum ether–EtOAc) gave the title compound as a yellow oil (2.05 g, 67%). ν_{max} neat cm^{-1}: 2929, 1669 (C═O), 1508, 1418, 1237, 1194; δ_H (300 MHz; $CDCl_3$) (mixture of rotamers) 1.28–1.39 (6H, t, *J* = 7.1 Hz, 2 × CH_3), 1.48–1.68 (4H, m, 2 × CH_2), 1.89–2.07 (4H, m, 2 × CH_2), 3.72–3.89 (2H, m, NC*H*$_2$CH$_3$), 3.84 (3H, s, $ArOCH_3$), 3.99–4.10 (2H, m, NC*H*$_2$CH$_3$), 4.19 (2H, s, C*H*$_2$NH), 5.37–5.41 (1H, m, CH═C), 6.88–6.98 (2H, m, 2 × ArH), 7.12–7.20 (2H, m, 2 × ArH); δ_C (100 MHz; $CDCl_3$) (mixture of rotamers) 11.2 (CH_3), 13.6 (CH_3), 22.3 (CH_2), 22.8 (CH_2), 25.3 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 48.8 (CH_2), 50.4 (CH_2), 55.6 (CH_3), 58.0 (CH_2), 113.6 (CH), 114.6 (CH), 125.0 (CH), 127.0 (CH), 128.3 (CH), 132.5 (C), 134.5 (C), 137.9 (C), 157.1 (C═O), 185.6 (C═S); *m*/*z* (EI) 393 ([M]$^+$ 22%), 331 (100%), 244 (33%), 218 (25%); HRMS (EI) calculated for $C_{20}H_{29}N_2O_2S_2$ [M]$^+$ 393.1670, found 393.1652.

(±)-(4*R,5*S**)-2-(4-Methoxyphenyl)-1-oxo-2-azaspiro[3.5]nonan-5-yl diethylcarbamodithioate (14).** A solution of carbamoyl dithiocarbamate **13** (0.32 g, 0.83 mmol) in cyclohexane (8.3 mL) was degassed for 15 min and irradiated with a 500 W

halogen lamp that generated enough heat to bring the solvent to reflux. After 8 h the solvent was removed under reduced pressure and the crude product purified by column chromatography (3 : 1 petroleum ether–EtOAc) to give the title compound as a white solid (0.19 g, 60%). m.p. 147–148 °C; ν_{max} (neat)/cm^{-1}: 2929, 1671 (C═O), 1509, 1415, 1243; δ_H (300 MHz; $CDCl_3$); 1.27 (6H, t, J = 7.1 Hz, 2 × CH_3), 1.48–2.11 (7H, m, CH_2), 2.36–2.48 (1H, m, CH_2), 3.31 (1H, d, J = 5.8 Hz, NCH_2C), 3.64 (1H, d, J = 5.8 Hz, NCH_2C), 3.70–3.77 (2H, m, NCH_2CH_3), 3.80 (3H, s, $ArOCH_3$) 3.98–4.05 (2H, m, NCH_2CH_3), 4.76–4.80 (1H, m, SCH), 6.88 (2H, d, J = 12.6 Hz, ArH), 7.31 (2H, d, J = 12.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 11.7 (CH_3), 12.6 (CH_3), 22.7 (CH_2), 23.5 (CH_2), 30.8 (CH_2), 31.9 (CH_2), 46.9 (CH_2), 49.8 (CH_2), 50.5 (CH_2), 53.0 (CH), 55.6 (CH_3), 58.7 (C), 114.1 (CH), 114.4 (CH), 117.6 (2 × CH), 132.2 (C), 156.0 (C), 167.7 (C═O), 193.7 (C═S); m/z (ESI) 415 ([M + Na]$^+$, 100%); HRMS (EI) calculated for $C_{21}H_{28}N_2O_2S_2Na$ [M]$^+$ 415.1490, found 415.1490.

2-(4-Methoxyphenyl)-2-azaspiro[3.5]nonan-1-one (15). According to the general procedure, a solution of dithiocarbamate **14** (0.29 g, 0.74 mmol) in dioxane (9.25 mL) was treated with Et_3N (0.56 mL, 4.07 mmol) and aq. H_3PO_2 (0.38 mL, 3.70 mmol), then ACCN (0.027 g, 0.11 mmol). The reaction was complete after 6 h. Work-up followed by column chromatography (3 : 1 petroleum ether–EtOAc) afforded the title compound as a white solid (0.069 g, 39%). m.p. 119–122 °C; ν_{max} (neat)/cm^{-1}: 2928, 1733 (C═O), 1511, 1392, 1243; δ_H (300 MHz; $CDCl_3$) 1.28–1.44 (2H, m, CH_2), 1.56–1.71 (2H, m, CH_2), 1.73–1.97 (6H, m, 3 × CH_2), 3.40 (2H, s, NCH_2), 3.81 (3H, s, $ArOCH_3$), 6.89 (2H, d, J = 12.6 Hz, ArH), 7.31 (2H, d, J = 12.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 23.5 (2 × CH_2), 25.3 (CH_2), 31.2 (2 × CH_2), 51.9 (NCH_2), 55.4 (C), 55.6 (OCH_3), 114.5 (2 × ArCH), 117.5 (2 × ArCH), 132.7 (ArC–N), 156.0 (ArC–O), 170.6 (C═O); m/z (EI) 245 ([M$^+$] 52%), 149 (100%), 135 (22%); HRMS (EI) calculated for $C_{15}H_{19}NO_2$ [M$^+$] 245.1416, found 245.1417.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol (20)

*From dithiocarbamate **16**, Table 1, entry 4.* According to the general procedure, dithiocarbamate **16**[23] (0.25 g, 0.52 mmol) was treated with aq. H_3PO_2 (0.54 mL, 5.20 mmol), Et_3N (0.79 mL, 5.72 mmol) and ACCN (0.019 g, 0.08 mmol) in dioxane (1 mL). After 4 h at reflux, a further portion of ACCN (0.019 g, 0.08 mmol) was added, and heating continued for a further 14 h. Work-up followed by column chromatography (9 : 1 hexane–EtOAc) gave the title compound as a white solid (0.037 g, 44%), whose analytical data were consistent with that reported in the literature.[30]

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-α-D-arabino-hexopyranose (21)

(a) Using H_3PO_2–Et_3N–ACCN, Table 1 entry 2. According to the general procedure, dithiocarbamate **16**[23] (0.50 g, 1.04 mmol) was treated with aq. H_3PO_2 (0.54 mL, 5.20 mmol), Et_3N (0.79 mL, 5.72 mmol) and ACCN (0.038 g, 0.16 mmol) in dioxane (104 mL). After 4 h at reflux, a further portion of ACCN (0.038 g, 0.16 mmol) was added, and heating continued for a further 14 h. Work-up followed by column chromatography (9 : 1 hexane–EtOAc) gave the title compound as a white solid (0.29 g, 85%), whose analytical data were consistent with that reported in the literature.[31]

(b) Using dilauroyl peroxide/cyclohexane,[25a] Table 1 entry 9. A solution of dithiocarbamate **16**[23] (0.48 g, 1.00 mmol) in cyclohexane (10 mL) was heated to reflux under argon for 15 min. Dilauroyl peroxide (0.08 g, 0.2 mmol) was added, and reflux continued for 1 h, after which time a further portion of dilauroyl peroxide (0.08 g, 0.2 mmol) was added. After 4 h at reflux, the solvent was removed under reduced pressure. Purification by column chromatography (hexane–EtOAc 9 : 1) gave the title compound as a white solid (0.30 g, 88%), whose analytical data were consistent with that reported in the literature.[31]

(±)-(1*S,6*R**)-2-Deuterio-7-benzyl-7-azabicyclo[4.2.0]octan-8-one (10-*d*, 91% D).** Dithiocarbamate **9**[1] (0.05 g, 0.14 mmol) was dissolved in dioxane (2 mL) and treated with triethylamine (0.1 mL, 0.8 mmol) and D_3PO_2 (50 wt% in D_2O, 0.07 mL, 0.69 mmol). After 20 min at reflux $K_2S_2O_8$ (0.006 g, 0.02 mmol) was added. After a further 4 h at reflux, another portion of $K_2S_2O_8$ (0.006 g, 0.02 mmol) was added, and heating continued for a further 14 h. The reaction mixture was cooled to room temperature, EtOAc (2 mL) and H_2O (2 mL) were added, and the aqueous layer extracted a further two times with EtOAc (2 × 2 mL). The combined organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (1 : 2 hexane–EtOAc) to afford the title compound as a clear oil (63%, 0.019 g). ν_{max} (neat)/cm^{-1}: 2935 (br), 1734 (C═O), 1400; δ_H (300 MHz; $CDCl_3$) 1.15–2.18 (8H, m, 4 × CH_2), 3.15–3.23 (1H, m, CHCO), 3.65 (1H q, J = 4.0 Hz, NCH), 4.10 (1H, d, J = 15.2 Hz, NCH_2), 4.60 (1H, d, J = 15.2 Hz, NCH_2), 7.26–7.37 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) 16.8 (CH_2), 18.8 (CH_2), 19.3 (CHD, t, J = 19.4 Hz), 19.5, 22.8 (CH_2), 44.4 (NCH_2), 46.9 (CH), 50.1 (CH), 127.6 (ArCH), 128.3 (2 × ArCH), 128.7 (2 × ArCH), 136.2 (ArC), 170.9 (C═O); m/z (EI) 216.1 ([M]$^+$, 71%), 125.1 (7%), 91.1 (100%), 82.1 (95%); HRMS (EI) calculated for $C_{14}H_{16}NOD$ [M]$^+$ 216.1373, found 216.1376. 91% D by MS analysis.

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