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Stereoselective Azide Introduction During 1,2-Sulfur Migration in α-Hydroxyalkyldithioacetals

Carlos A. M. Afonso[a], M. Teresa Barros[a], Christopher D. Maycock[b]*

[a] Departamento de Quimica, FCT, Universidade Nova de Lisboa, 2825 Monte de Caparica, Portugal.

[b]Instituto de Tecnologia Quimica e Biologica, Universidade Nova de Lisboa, Rua da Quinta Grande 6, Apartado 127, 2780 Oeiras, Portugal.

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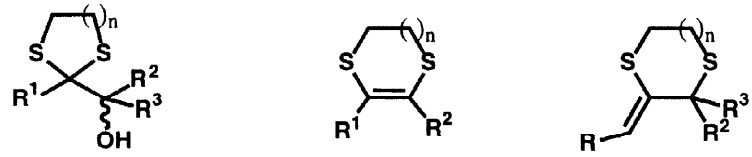
Abstract: A series α-hydroxyalkyldithiolanes were reacted with a mixture of triphenylphosphine, diethyl azodicarboxylate and hydrazoic acid to give 2-azido-1,4-dithianes stereoselectively. Reduction of the azido group to an amine resulted in racemisation.

Introduction

Several methods for the synthesis of 2,3-dihydro-1,4-dithiins **2** are documented.[1] Many of these, involve ring expansion processes of 1,3-dithiolanes. We have also reported a mild, high yielding, and general method for the preparation of mixtures of *endo* **2** and *exo* **2**, and of **3** (R^2 and $R^3 \neq H$) by ring expansion of α-hydroxyalkyldithioacetals **1** with tosyl chloride or mesyl chloride in pyridine. The *exo* double bond isomers were preferentially formed from **1**, when both R^1 and R^2 were long chain alkyl groups. The inversion of configuration at the activated carbon atom was also demonstrated.[2] As an extension of our previous work, we now wish to report similar ring expansions by 1,2 sulfur migration using the Mitsunobu reagent[3,4] as activator



1 *endo*-**2** *exo*-**2** $R^3 = H$ **3**

Scheme 1

along with our observations on azide introduction.[5] The stereoselective introduction of the azido group into heterocyclic molecules is important in organic synthesis since it can be transformed into an amino group or into further heterocyclic moieties.[6]

Results and Discussion

When alcohol **1f** was treated at room temperature with triphenylphosphine/diethyl azodicarboxylate (TPP/DEAD, 2.2 eq.) in tetrahydrofuran for 2.5 days, *endo* **2f** (20%), *exo* **2f** (40%) and recovered **1f** (30%) were obtained. This mild method appears to be a viable alternative to TsCl/pyridine reported previously[2] and during which no chloride incorporation was observed although this was one of our targets. Early attempts to insert an azido group into the product during the 1,2-sulfur migration of, for example, **1a** using TsCl/pyridine (1.5 eq.) in the

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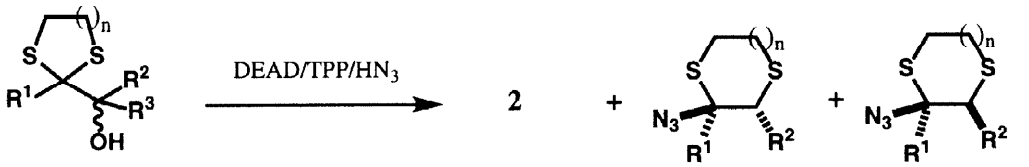
presence of sodium azide (1.5 eq.), failed and only **2a** and recovered **1a** (in a ratio of 1:1) were isolated. On the other hand, using the Mitsunobu azide modification, TPP/DEAD/HN_3, on **1a-l** the ring expanded azides **4** and **5** were obtained in moderate yields[7] along with low yields of unsaturated ring expansion products (table 1). In the case of substrate **1g** the α,β-unsaturated ester **6** was also isolated in 8% yield and resulted from competitive elimination (entry 7). The formation of compound **6** was predominant (28%) when the same azide incorporation was attempted using diphenylphosphorylazide[8] as activator and azide source (entry 8). The structure of the azide **4h** was confirmed by X-ray crystallography (figure 1). Azide **4h** has a conformation with the azide group in an axial position in accordance with the expected anomeric effect.[9] The proposed structures of the other azides were based on ^1H and ^{13}C NMR assignment in relation to **4h**.



1 $R^3 = H$ **4** *cis* **5** *trans*

Scheme 2

Table 1. Azides **4** and **5** prepared from α-hydroxyalkyldithioacetals **1**.

Entry	Substrate	n	R^1	R^2	Method	Time	Products (yield %)[a] 1	2 or 3	4+5[b]	Ratio 4:5
1	**1a**	1	Me	H	A	3 days	2	4	88	--
2	(-)**1b**[c]	2	Me	Me	A	3.5 days	25	traces	71[d]	4.6:1[e]
3	(+)**1c**[f]	1	Me	Me	A	3 days	32	1	60[g]	6.2:1[h]
4	**1d**	1	Et	Me	A	3 days	25	3	56	3.6:1[e]
5	**1e**	1	Me	Pr	A	3 days	33	4	54	6.8:1[i]
6	**1f**	1	Et	Et	A	6 days	30	traces	63	7:1[i]
7	**1g**	1	Me	CH_2CO_2Et	A	4 days	31	traces[j]	52	1.8:1[e]
8	**1g**	1	Me	CH_2CO_2Et	B	65 h	41	[k]	14	1.2:1[h]
9	**1h**	1	Ph	Me	A	3 days	22	6	62	7.1:1[h]
10	**1i**	1	Me	Ph	A	4 days	26	13	59	2.4:1[h]
11	**1j**	1	Ph	Ph	A	3 days	24	13	61	1:1.1
12	**1k**	1	-$(CH_2)_4$-		A	2 days	27	7	57	1:0
13	**1l**	2	-$(CH_2)_4$-		A	4 days	36		56	1:0
14	**6**				A	3.5 days	97%			

Method A: DEAD/TPP/HN_3(1.1 eq.), C_6H_6, RT; **Method B** DEAD/TPP/$(PhO)_2PON_3$(1.1 eq.), THF, RT. *a)* Isolated products after flash chromatography. *b)* Isolated as a mixture. *c)* Optically pure (-)-(S)-**1b** was used[2]. *d)* Optically active (+)-**4** and **5** was isolated. *e)* Ratio determined by ^1H NMR. *f)* Optically pure (+)-(S)-**1c** was prepared *g)* e.e. >99 % of (+)-**4** was determined by GLC. *h)* Ratio determined by HPLC. *i)* Ratio determined approximately by ^{13}C NMR. *j)* 8% of **6** was also isolated. *k)* 26% of **6** was also isolated. *l)* Only **4** detected by ^1H and ^{13}C NMR.

Optically pure (-)-(S)-**1b** and (+)-(S)-**1c** gave optically active azides (+)-**4c** and **5c** (entries 2 and 3). In the case of azides (+)-**4c** and **5c** an e.e. > 99% was determined by GLC.[10] As would be expected for the Mitsunobu reaction, the activated hydroxyl group was displaced by the adjacent sulfur atom with inversion of configuration to form a thiiranium ion (scheme 3), which then rearranged to the sulfonium ion. This explained the retention of optical activity which also indicates that an *endo* dithiine (alkylidene dithiane) is not an intermediate in this reaction. For further proof that the azide group was not introduced by the simple addition of hydrazoic acid to an unsaturated product, *endo* **2a** was dissolved in a benzene solution of hydrazoic acid and left during 3 days at r.t.. No azidodithianes were detected.

Figure 1. A perspective view of the molecular structure of azide **4h** based on X-ray data

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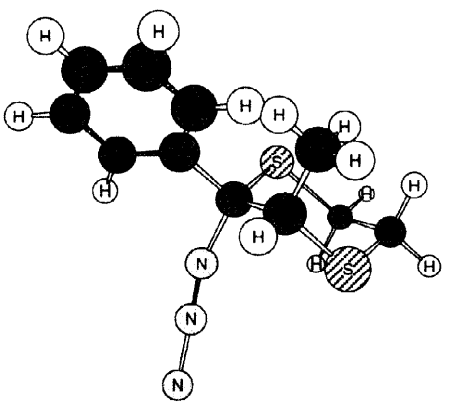
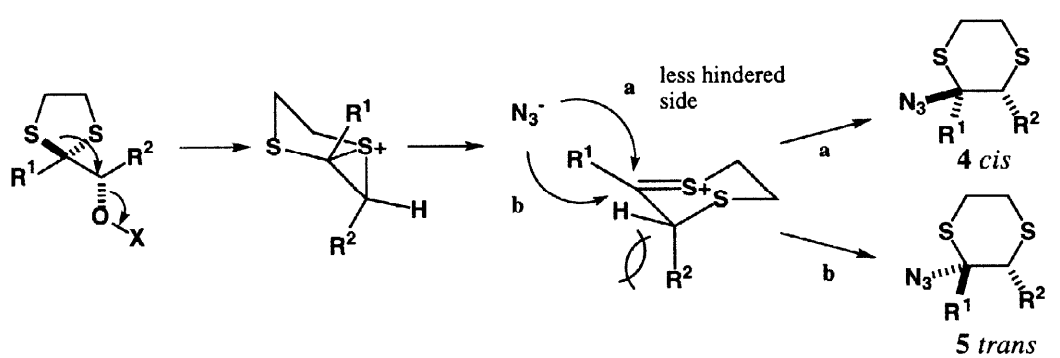


For acyclic alcohols, azide was added with poor diastereoselectivity but for the cyclic α-hydroxyalkyldithiolanes **1k** and **1l** only the *cis* **4** azide isomer was detected (entries 12 and 13). These observations also suggested that the sulfonium ion had been trapped by the azide present in a rate and product determining process (scheme 3). The preference for the formation of the azide isomer **4** must result from nucleophilic attack at the less hindered side (**a** in scheme 3) of the activated system. Interestingly, the bulky tertiary α-hydroxyalkyldithioacetal **7** was unreactive under these conditions (entry 14) and, in general, only mesyl chloride was able to activate the hydroxyl group of tertiary alcohols with any efficiency.



Scheme 3

When the Mitsunobu reactions of **1c** and **1g** were performed at ambient temperature in dichloromethane instead of benzene a decrease in the yield of azides was observed (19% and 26% respectively), and also a considerable change in the diastereomer ratio of **4**:**5**: from 6.2:1 to 2.3:1, for **1c** (table 1, entry 3 and table 2, entry 1) but only small, from 1.8:1 to 2.0:1, for **1g** (table 1, entry 7 and table 2, entry 5). Using lower

temperatures, the yield of azides increased down to around -10°C and drastically decreased at temperatures lower than this (Table 2). In the case of the diastereomer ratio **4c**:**5c** better selectivity was observed at lower temperatures as expected. On the other hand, the nearly constant ratio obtained for azides **4g**:**5g** at different temperatures suggests interference by the ester group in the key step.

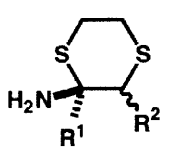
Table 2. Temperature effect on the conversion of hydroxyalkyldithiolanes **1** to azides **4** and **5** using DEAD/TPP/HN_3 (1.1 eq.), CH_2Cl_2.

Entry	Substrate	n	R^1	R^2	Temp.	Time	Isolated Products (yield, %)[a] 1	2	4,5[b]	Ratio[c] 4:5
1	**1c**	1	Me	Me	RT	3 days	40	2	41	2.3:1
2	**1c**	1	Me	Me	-10 °C	7 days	13	1	72	4.3:1
3	**1c**	1	Me	Me	-30 °C	7 days	42	traces	48	4.6:1
4	**1c**	1	Me	Me	-50 °C	7 days	65	traces	28	4.9:1
5	**1g**	1	Me	CH_2CO_2Et	RT	4 days	34		26; **6** (10 %)	2.0:1
6	**1g**	1	Me	CH_2CO_2Et	-10 °C	7 days	43		50; **6** (3 %)	2.0:1
7	**1g**	1	Me	CH_2CO_2Et	-30 °C	7 days	89		10; **6** (traces)	2.0:1
8	**1g**	1	Me	CH_2CO_2Et	-50 °C	7 days	91		3; **6** (traces)	2.3:1

a) Isolated products after flash chromatography. *b)* Isolated as a mixture. *c)* Ratio determined by HPLC.

Azide reduction

In order to achieve some functional manipulation of the prepared azides **4** and **5**, we performed the azide reduction in moderate yields using the reported reducing agents tributylphosphine[11] and 1,3-propanedithiol[12] (table 3). The reduction of optically pure azides (+)-**4c** and **5c** gave racemic *cis* and *trans* amines **8** by ^1H NMR



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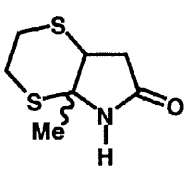

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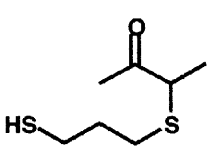

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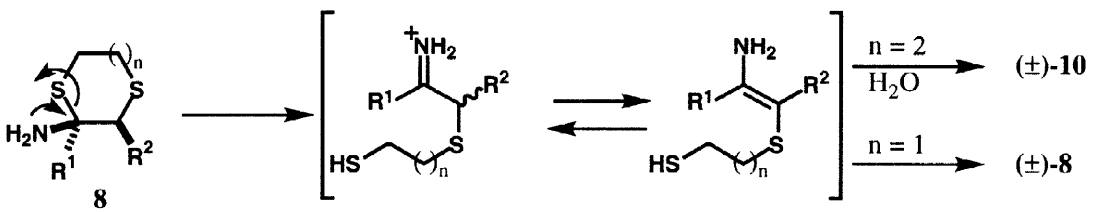
analyses of the MTPA derivatives,[13] even when their preparation was performed without amine isolation[14]. In the case of the the azides **4b** and **5b** only ketone **10** was isolated. This resulted from hydrolysis of the less stable seven membered ring amine formed. These results are explained by an amine/imine type interconversion (scheme 4) with either ring reclosure to form the dithianes or hydrolysis of the acyclic imine to form a ketone. A small quantity of the bicyclic amide **9** was also formed along with the amine **8g** when a mixture of the azide **4g** and **5g** was reduced. We expect that **9** has the *cis* ring junction and is formed from the corresponding *cis* amine.

Table 3. Reduction of the azido group of dithianes **4** and **5**.

Substrate	n	R^1	R^2	Method	Isolated Products (yield, %)[a]
(+) **4,5c**	1	Me	Me	A, 2 h	(±) **8c** (72 %)[b]
(+) **4,5c**	1	Me	Me	B, 3 d	(±) **8c** (25 %)[b]
4,5f	1	Et	Et	A, 2 h	**8f** (45 %)[c]
4h	1	Ph	Me	A, 2 h	**8h** (78 %)[d]
4,5g	1	Me	CH_2CO_2Et	B, 7 d	**8g** (67 %)[e], **9** (19 %)
4,5b	2	Me	Me	A, 22 h	**10** (59 %)

a) Isolated products after flash chromatography. *b)* Ratio of *cis:trans* of 2:1 determined by ^{1}H NMR. *c)* Mixture of *cis* and *trans* isomers. *d)* Observed only *cis* by ^{1}H NMR. *e)* Ratio of *cis:trans* of 1.1:1 determined by ^{1}H NMR.



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Scheme 4

Acknowledgements. We thank Junta Nacional de Investigação Científica e Tecnológica (grant number 827-86-115) for generous financial support.

Experimental Section

Reagent quality solvents were distilled prior to use. Diethyl azodicarboxylate was dried by standing over molecular sieves. Pyridine and triethylamine were dried by distillation from sodium hydroxide. Anhydrous carbon tetrachloride was prepared by distillation from phosphorus pentoxide under argon. Anhydrous dichloromethane was prepared by distillation from phosphorus pentoxide under argon. Benzene was dried by standing over sodium wire. Anhydrous tetrahydrofuran and diethyl ether were prepared by distillation from sodium/benzophenone ketyl under argon. (R)-MTPA (Sigma) was converted into the acid chloride using a literature procedure,[13] followed by Kugelrohr distillation. Column chromatography was performed using Silica gel Merck 60 H (Art. 7736) and analytical TLC using aluminum-backed silica gel Merck 60 F_{254} plates. Melting points (uncorrected) were determined on an Electrothermal Mod. IA 6304 capillary melting point apparatus. Microanalyses were carried out by LNETI using a Carlo Erba model 1106 analyser. Mass spectra (MS) and exact masses (HRMS) were obtained using a Kratos MS 25 RF and AEI/VG MS 9 mass spectrometers. Infra-red spectra (IR) were recorded on a Buck Scientific Mod. 500 infra-red spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker CXP300 spectrometer. Chemical shifts are reported as δ values relative to

tetramethylsilane (δ_H = 0 ppm), $\underline{C}DCl_3$ (δ_C = 77.0). Observed rotations at the Na-D line were measured at 25°C using a Perkin-Elmer 241 polarimeter. GLC analyses were performed using a Carlo Erba GC 6000 Vega Series 2 with a capillary chiral bore column Chiraldex-G-TA 30m x 0.25 mm from Advanced Separation Technologies. HPLC analyses were performed using Merck & Hitachi components L-600 A, L-4250, T-6300, D-6000 with Lichrocart® column 250-4, Si 60, 5 μm, at 30 °C and λ 223 nm. Literature procedures were used for the preparation of reported compounds **1a-j**[2] and **1l**.[15]

Preparation of 2-(1(S)-hydroxyethyl)-2-methyl-1,3-dithiolane (+)-1c. Fresh commercial baker's yeast (38.0 g) was suspended in a stirred solution of sucrose (40.0 g) in tap water (95 mL). The mixture was allowed to stand at 23 °C during 1 h (gas evolution). 2-Acetyl-2-methyl-1,3-dithiolane[2] (0.70 g, 4.31 mmol) was added and stirring was continued (48 h). The mixture was then saturated with NaCl and filtered through celite. The solid was washed with EtOAc (3 x 80 mL) and the aqueous filtrate was extracted with Et_2O (4 x 80 mL). The combined organic phases were dried ($MgSO_4$), evaporated and the crude product was purified by flash chromatography (eluents: petroleum ether 40/60 : EtOAc from 1:0 to 9:1) to afford recovered starting material (0.021 g, 3%) and **(+)-1c** (0.692 g, 90%) as a clear colourless oil; identical spectral data to those reported for racemic **1c**;[2] $[\alpha]_D$ = +1.5 (c 6.3, chloroform); e.e.(S) > 97% was determined by ^1H NMR analysis of its MTPA derivative[13] and its absolute configuration was determined by conversion into 3(S)-benzoyloxybutan-2-one;[16] 3,5-dinitrobenzoate derivative $[\alpha]_D$ = +59.8 (c 0.99, chloroform), m.p. 102-103 °C (petroleum ether 40/60 : EtOAc).

Preparation of 2-hydroxy-1,1-(1,2-ethanedithio)cyclohexane 1k. A mixture of 2,2-(1,2-ethanedithio)cyclohexanone[19] (0.508 g, 2.67 mmol) and sodium borohydride (0.102 g, 2.67 mmol) in ethanol (5.4 mL) was stirred at room temperature for 1 h. The mixture was evaporated, diluted with diethyl ether (40 mL) and washed sequentially with 1 M hydrochloric acid (30 mL) and saturated aqueous sodium bicarbonate (30 mL). The organic phase was dried ($MgSO_4$), evaporated to dryness and chromatographed on a silica gel column (eluent: dichloromethane) to afford **1k** (0.493 g, 96%) as a clear colourless oil; ν_{max} (film) 3440 (br, OH), 2929, 2857, 1452, 1293, 1247, 1145, 1088, 1026, 998, 884 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.30-1.66 (5H, m), 1.90 (1H, dd J 10.2, 3.8), 1.95 (1H, dd J 10.2, 4.1), 2.28 (1H, dt J 13.2, 2.0), 2.40 (1H, br, OH), 3.23-3.34 (4H, m, $S(CH_2)_2S$), 3.63 (1H, dd J 8.9, 3.7, $C\underline{H}OH$).

Preparation of 2-hydroxy-2-methyl-1,1-(1,2-ethanedithio)cyclohexane 7. Methylmagnesium iodide (13 mL of a 0.24 M solution in diethyl ether, 3.12 mmol) was added dropwise, *via* syringe, to a stirred solution of 2,2-(1,2-ethanedithio)cyclohexanone (0.543 g, 2.88 mmol) in anhydrous diethyl ether (10 mL) under argon at 0 °C (ice bath). The mixture was then refluxed for 1 h and allowed to reach ambient temperature. Saturated aqueous ammonium chloride (20 mL) was added cautiously followed by extraction with diethyl ether (3x20 mL). The combined organic phases were dried ($MgSO_4$), evaporated and the crude product was chromatographed on a silica gel column (eluent: dichloromethane) to afford **7** (0.403 g, 68%) as a clear colourless oil; ν_{max} (film) 3440 (OH), 2917, 2849, 1446, 1361, 1282, 1179, 1140, 1117, 1032, 986, 924, 862, 827, 736 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.44 (3H, s, Me), 1.60-1.77 (6H, m), 2.07 (1H, dt, J 14.0, 6.7), 2.30 (1H, dt, J 14.0, 5.4), 2.39 (1H, br, OH), 3.23-3.33 (4H, m, $-S(CH_2)_2S-$); m/z (EI^+) 204 (M^+), 186 (M^+-H_2O), 176 ($M^+-CH_2=CH_2$), 171 (M^+-H_2O-Me), 158 ($M^+-CH_2=CH_2-H_2O$),144, 131.

Preparation of 2,3-diethyl-5,6-dihydro-1,4-dithiin *endo* **2f and 2-ethyliden-3-ethyl-1,4-dithiane** *exo* **2f from 1f using TPP/DEAD.** A solution of diethyl azodicarboxylate (0.259 g, 1.49 mmol) in anhydrous tetrahydrofuran (1 mL) was added dropwise (10 min) to a stirred solution of **1f**[2] (0.130 g, 0.68

mmol) and triphenylphosphine (0.390 g, 1.49 mmol) in anhydrous tetrahydrofuran (2.5 mL) under argon at room temperature. After 2.5 days water (15 mL) was added and the mixture was extracted with diethyl ether (3x15 mL). The combined organic phases were dried ($MgSO_4$), evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:0. to 9:1) to afford in order of elution *endo* **2f** (0.024 g, 20%) as a clear colourless oil; spectral data identical to those reported;[2] *exo* **2f** (0.047 g, 40%) as a clear colourless oil; spectral data identical to those reported[2] and recovered **1f** (0.036 g, 28%).

Conversion of α-hydroxyalkyldithioacetals 1 into azides 4 and 5.

Typical Procedures: Method A using DEAD/TPP/HN_3 (1.1 eq.).

2-Azido-2-methyl-1,4-dithiane 4a. Diethyl azodicarboxylate (0.12 mL, 0.74 mmol) was added dropwise (5 min) to a stirred solution of **1a** (0.100 g, 0.67 mmol), triphenylphosphine (0.193 g, 0.74 mmol) in anhydrous benzene (3.5 mL) and hydrazoic acid[20] (0.6 mL of 1.3 M solution in benzene, 0.74 mmol) under argon at room temperature (water bath), and stirring was continued for 3 days. The reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:0. to 8:2) to afford in order of elution **2a** (0.004 g, 4%), as a clear colourless oil; spectral data identical to those reported;[2] **4a** (0.103 g, 88%) as white plates; m.p. 67-67.5 °C (petroleum ether 40/60 : chloroform); ν_{max} (Nujol) 2120 (N_3), 1245, 1165, 1080, 1065, 940, 925, 915, 850, 800, 770, 725 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.63 (3H, s, Me-2), 2.64 (1H, d J 14, H-3), 2.71-2.78 (2H, m), 2.87-2.95 (1H, m), 3.10 (1H, d J 14, H-3), 3.27-3.35 (1H, m); ^{13}C δ(75.47 MHz, $CDCl_3$) 27.3, 28.0, 40.2 (C-3), 64.0 (C-2); m/z (EI^+) 175 (M^+), 147 (M^+-CH_2=CH_2), 132 (M^+-HN_3), 106, 78; Anal. Calcd for $C_5H_9S_2N_3$: **C** 34.27, **H** 5.18, **N** 23.98%. Found:**C** 34.17, **H** 5.18, **N** 23.82%; and recovered **1a** (0.002 g, 2%).

(+)-2-Azido-2,3-dimethyl-1,4-dithiepanes (+)-4b and (+)-5b. **(-)-1b** (0.130 g, 0.73 mmol) was treated in a similar manner to that described earlier. After 3.5 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:0. to 8:2) to afford in order of elution **2b** (traces), by comparison with authentic sample;[2] **(+)-4b** and **(+)-5b** (0.105 g, 71%), as a clear colourless oil; b.p. 100 °C/1 mmHg (Kugelrohr); $[\alpha]_D$=+169.9 (c 0.5, chloroform); ratio **4b**:**5b** of 4.6:1 determined by ^1H NMR; ν_{max} (film) 2980, 2920, 2120 (N_3), 1445, 1410, 1375, 1250, 1115, 1070, 825 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **(+)-4b** 1.41 (3H, d J 7.4, Me-3), 1.55 (3H, s, Me-2), 1.85-1.96 (1H, m, H-6), 2.06-2.16 (1H, m, H-6), 2.69-3.30 (4H, m, H-5 and H-7), 2.89 (1H, t J 7.4, H-3) and ^1H δ partial of **(+)-5b** 1.26 (3H, d J 7.2, Me-3), 1.87 (3H, s, Me-2); ^{13}C δ(75.47 MHz, $CDCl_3$) of **(+)-4b** 17.7 (Me-3), 22.7 (C-6), 27.8, 29.7, 31.6, 51.9 (C-3), 76.0 (C-2) and ^{13}C δ partial of **(+)-5b** 25.5, 27.4, 29.1, 32.7, 57.4 (C-3); m/z (EI^+) 203 (M^+), 175, 167, 162, 160 (M^+-HN_3), 150, 123, 106; Anal. Calcd for $C_7H_{13}N_3S_2$: **C** 41.35, **H** 6.44, **N** 20.67%. Found:**C** 41.28, **H** 6.47, **N** 20.47%; and recovered **(-)-1b** (0.033g, 25%).

(+)-2-Azido-2,3-dimethyl-1,4-dithianes (+)-4c and (+)-5c. **(+)-1c** (0.500 g, 3.04 mmol) was treated in a similar manner to that described earlier. After 3 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:0. to 9:1) to afford in order of elution **2c** (0.004 g, 1%), as a clear colourless oil; by comparison with authentic sample;[2] **(+)-4c** and **(+)-5c** (0.346 g, 60%), as a clear colourless oil; b. p. 100 °C/0.9 mmHg (Kugelrohr); $[\alpha]_D$=+163.0 (c 1.4, chloroform); ratio **4c**:**5c** of 6.0:1 determined by HPLC, hexane 1mL/min; **5c** e.e. > 99% determined by GLC using a capillary chiral column (see general methods), Inj./Det. 230 °C, Oven 115 °C, helium

0.8 mL/min., retention time 15.03 and 15.67 min., **4c** retention time 20.55 min., ν_{max} (film) 2980, 2920, 2110 (N_3), 1450, 1415, 1380, 1295, 1255, 1110, 1080, 860, 835 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **(+)-4c** 1.52 (3H, d J 7.1, Me-3), 1.60 (3H, s, Me-2), 2.64-2.71 (1H, m), 2.80-2.87 (1H, m), 2.82 (1H, s if irradiated at 1.52 ppm, H-3), 2.97 (1H, ddd J 15.8, 10.4, 2.7), 3.16 (1H, ddd J 15.8, 10.4, 2.9), and ^1H δ partial of **(+)-5c** 1.20 (3H, d J 7.2, Me-2), 1.64 (3H, s, Me-2), 2.84 (1H, s if irradiated at 1.20 ppm); ^{13}C δ(75.47 MHz, $CDCl_3$) of **(+)-4c** 17.3 (Me-3), 24.2 (C-5 or C-6), 24.9 (C-5 or C-6), 29.5 (Me-2), 43.3 (C-3), 69.4 (C-2), ^{13}C δ partial of **(+)-5c** 16.4 (Me-3), 25.5 (C-5 or C-6), 29.1 (C-5 or C-6), 31.2 (Me-2), 46.8 (C-3); m/z (EI^+) 189 (M^+), 161 (M^+-CH_2=CH_2), 146 (M^+-HN_3), 120, 118, 105, 92; HRMS calcd for $C_6H_{11}N_3S_2$: 189.0394, found: 189.0401; and recovered **(+)-1c** (0.159 g, 32%).

2-Azido-2-ethyl-3-methyl-1,4-dithianes 4d and 5d. 1d (0.238 g, 1.34 mmol) was treated in a similar manner to that described earlier. After 3 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:0. to 0:1) to afford in order of elution **2d** (0.006 g, 3%), as a clear colourless oil; by comparison with authentic sample;[2] **4d** and **5d** (0.153 g, 56%), as a clear colourless oil, ratio **4d**:**5d** of 3.6:1 determined by ^1H NMR; ν_{max} (film) 2963, 2917, 2895, 2099, (N_3), 1463, 1406, 1384, 1520, 1270, 1247, 1117, 918, 861 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **4d** 1.01 (3H, t J 7.4, $CH_2\underline{Me}$), 1.59 (3H, d J 7.0, Me-3), 1.70 (1H, q J 7.4, $C\underline{H}_2Me$), 1.90 (1H, q J 7.4, $C\underline{H}_2Me$), 2.58 (1H, ddd J 7.4, 5.2, 2.3), 2.77 (1H, q J 7.0, H-3), 2.80-2.69 (1H, m), 3.05 (1H, ddd J 13.8, 11.3, 2.1), 3.24 (1H, ddd J 13.8, 11.7, 2.3); ^1H δ partial of **5d** 1.16 (3H, d J 6.7, Me-3); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4d** 17.3 ($CH_2\underline{Me}$), 23.5 (Me-3), 28.9 (C-5 and C-6), 30.2 $\underline{C}H_2Me$), 40.1 (C-3), 72.7 (C-2); ^{13}C δ partial of **5d** 28.6, 30.8, 32.2, 43.6 (C-3), 72.1 (C-2); m/z (EI^+) 203 (M^+), 175 (M^+-CH_2=CH_2), 160 (M^+-HN_3), 145 (M^+-HN_3-Me), 132, 117; and recovered **1d** (0.060 g, 25%).

2-Azido-2-methyl-3-propyl-1,4-dithianes 4e and 5e. 1e (0.201 g, 1.04 mmol) was treated in a similar manner to that described earlier. After 3 days the reaction mixture was evaporated and the crude product was chromatographed on preparative TLC (eluent: petroleum ether 40/60 : diethyl ether 9:1) to afford in order of elution **2e** (0.008 g, 4%), as a clear colourless oil; by comparison with authentic sample;[2] **4e** and **5e** (0.122 g, 54%), as a clear colourless oil, ratio **4e**:**5e** of 6.8:1 determined approximately by ^{13}C NMR; ν_{max} (film) 2940, 2917, 2895, 2860, 2111 (N_3), 1452, 1406, 1372, 1236, 1117, 1071, 844, 822 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **4e** 0.95 (3H, t J 10.4, $CH_2\underline{Me}$), 1.23-1.47 (2H, m, $C\underline{H}_2Me$), 1.64 (3H, s, Me-2), 1.61-1.76 (2H, m, CH_2-3), 2.65-2.70 (2H, m), 2.84-2.90 (2H, m), 3.14 (1H, ddd J 6.8, 4.7, 2.2); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4e** 13.8 ($CH_2\underline{Me}$), 20.8 ($\underline{C}H_2Me$), 24.1 (C-5 or C-6), 25.6 (C-5 or C-6), 29.6 ($\underline{C}H_2$-3), 31.4 (Me-2), 49.4 (C-3), 69.3 (C-2); ^{13}C δ partial of **5e** 23.0, 28.9, 30.4, 38.8 (C-3); m/z (EI^+) 217 (M^+), 189 (M^+-CH_2=CH_2), 174 (M^+-HN_3), 145, 132, 131, 117; HRMS calcd for $C_8H_{15}N_3S_2$: 217.07074, found: 217.07528; and recovered **1e** (0.066 g, 33%).

2-Azido-2,3-diethyl-1,4-dithianes 4f and 5f. 1f (0.652 g, 3.40 mmol) was treated in a similar manner to that described earlier. After 6 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 1:0. to 8:2) to afford in order of elution **2f** (traces), by comparison with an authentic sample;[2] **4f** and **5f** (0.467 g, 63%), as a clear colourless oil; ratio **4f**:**5f** of 7:1 determined by ^{13}C NMR; ν_{max} (film) 2957, 2923, 2900, 2099 (N_3), 1458, 1406, 1247, 1111 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 0.99 (3H, t J 7.4, $CH_2\underline{Me}$), 1.10 (3H, t J 7.4, $CH_2\underline{Me}$), 1.69-1.98 (4H, m, $C\underline{H}_2Me$), 2.48 (1H, dd J 10.8, 3.0), 2.54 (1H, ddd J 13.9, 5.1, 2.2), 2.77 (1H, ddd J 13.4, 5.1, 2.6), 2.93 (1H, ddd J 13.9, 10.9, 2.6), 3.23 (1H, ddd J 13.4, 10.9, 2.2); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4f**

6.9, 12.5, 21.4, 23.7, 28.8, 30.1, 48.7 (C-3), 72.7 (C-2), ^{13}C δ partial of **5f** 51.2 (C-3), 72.1 (C-2); m/z (EI^+) 217 (M^+), 189 (M^+-CH_2=CH_2), 174 (M^+-HN_3), 159, 145, 131, 117; and recovered **1f** (0.193 g, 30%).

2-Azido-2-methyl-3-ethoxycarbonylmethyl-1,4-dithianes 4g and 5g. 1g (0.205 g, 0.87 mmol) was treated in a similar manner to that described earlier. After 4 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 9:1. to 7:3) to afford in order of elution **2g** (traces), by comparison with authentic sample;[2] **6** (0.014 g, 8%), as a clear colourless oil; ν_{max} (film) 2917, 2849, 1736 (C=O), 1270, 1179 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.27 (3H, t J 7.3, $CH_2\underline{Me}$), 1.91 (3H, s, Me), 3.14-3.21 (4H, m, -$S(CH_2)_2$S-), 4.20 (2H, q J 7.3, $C\underline{H}_2Me$), 5.95 (1H, d J 15.0, H-olefin), 7.04 (1H, d J 15.0, H-olefin); **4g** and **5g** (0.119 g, 52%), as a white solid, ratio **4g**:**5g** of 1.8:1 determined by ^1H NMR; after crystallization the ratio **4g**:**5g** was 2.8:1, m.p. 37-40 °C (ethanol); ν_{max} (film) 2980, 2912, 2116 (N_3), 1740 (C=O), 1412, 1372, 1248, 1157, 1088, 1020, 850 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **4g** 1.28 (3H, t J 7.0, $CH_2\underline{Me}$), 1.58 (3H, s, Me-2), 2.62-3.27 (7H, m, H-5, H-6, H-3, CH_2-3), 4.18 (2H, q J 7.0, $C\underline{H}_2Me$); ^1H δ partial of **5g** 1.27 (3H, t J 7.0, $CH_2\underline{Me}$), 1.67 (3H, s, Me-2), 4.17 (2H, q J 7.0, $C\underline{H}_2Me$); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4g** 14.2 ($CH_2\underline{Me}$), 24.1 (C-5 or C-6), 25.2 (C-5 or C-6), ^{13}C δ partial of **5g** 29.2, 30.4, 47.5 (C-3); m/z (EI^+) 233 (M^+-CH_2=CH_2), 218 (M^+-HN_3), 192, 172, 163, 145 131; HRMS calcd for $C_9H_{15}O_2N_3S_2$: 261.06057, found: 261.06147; and recovered **1g** (0.064 g, 31%).

2-Azido-3-methyl-2-phenyl-1,4-dithianes 4h and 5h. 1h (0.277 g, 1.22 mmol) was treated in a similar manner to that described earlier. After 3 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 1:0 to 6:4) to afford in order of elution **2h** (0.015 g, 6%), as clear colourless oil, by comparison with an authentic sample;[2] **4h** and **5h** (0.189 g, 62%), as a white plates, ratio **4h**:**5h** of 7.1:1 determined by HPLC; after recrystallization ratio **4h**:**5h** of 1:0, m.p. 89-90°C (hexane); ν_{max} (film) 3042, 2974, 2929, 2912, 2105 (N_3), 1492, 1446, 1406, 1378, 1293, 1276, 1242, 1083, 963, 929, 861, 839, 765, 697 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **4h** 1.35 (3H, d J 7.1, Me-3), 2.54 (1H, ddd J 13.9, 3.8, 2.4 H-5_{eq} or H-6_{eq}), 2.84-2.90 (1H, m, H-5_{eq} or H-6_{eq}), 2.87 (1H, q J 7.1, H-3), 3.15 (1H, dt J 13.3, 2.0, H-5_{ax} or H-6_{ax}), 3.50 (1H, dt J 13.4, 2.4, H-5_{ax} or H-6_{ax}), 7.32-7.43 (3H, m, Ar), 7.51 (2H, dd J 8.2, 1.6, Ar); ^1H δ of **5h** 0.82 (3H, d J 6.8, Me-3), 2.79-2.91 (2H, m, H-5_{eq} and H-6_{eq}), 3.28 (1H, dt J 6.6, 1.4, H-5_{ax} or H-6_{ax}), 3.38 (1H, ddd J 16.8, 4.5, 1.4, H-5_{ax} or H-6_{ax}), 3.61 (1H, q J 6.8, H-3), 7.30-7.42 (3H, m, Ar), 7.54 (2H, dd J 7.8, 1.3, Ar); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4h** 17.9 (Me-3), 21.5 (C-5 or C-6), 28.5 (C-5 or C-6), 43.1 (C-3), 76.1 (C-2), 126.0 (Ar), 128.7 (Ar), 128.8 (Ar), 140.9 (Ar C-1'); Anal. Calcd for $C_{11}H_{13}N_3S_2$: **C** 52.56, **H** 5.21%, **N** 16.72. Found:**C** 52.47, **H** 5.35%, **N** 16.63; and recovered **1h** (0.060 g, 22%).

2-Azido-2-methyl-3-phenyl-1,4-dithianes 4i and 5i. 1i (0.128 g, 0.56 mmol) was treated in a similar manner to that described earlier. After 4 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:0 to 9:1) to afford in order of elution **2i** (0.015 g, 13%), as clear colourless oil, by comparison with authentic sample;[2] **4i** and **5i** (0.084 g, 59%), as clear colourless oil; ratio **4i**:**5i** of 2.4:1 determined by HPLC; ν_{max} (film) 3081, 3056, 3025, 2950, 2900, 2100 (N_3), 1494, 1447, 1406, 1369, 1244, 1150, 1075, 869, 759, 700 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of **4i** 1.74 (3H, s, Me-2), 2.99-3.26 (4H, m, H-5 and H-6), 4.20 (1H, s, H-3), 7.28-7.34 (3H, m, Ar), 7.47 (2H, dd J 5.9, 3, Ar); ^1H δ of **5i** 1.40 (3H, s, Me-2), 2.78 (1H, dd J 12.4, 3.7), 2.92 (1H, dd J 13.0, 3.7), 3.27 (1H, m), 3.49 (1H, t J 12.4), 4.34 (1H, s, H-3), 7.28-7.39 (3H, m, Ar), 7.47 (2H, dd 5.9, 3 Ar); ^{13}C δ(75.47 MHz, $CDCl_3$) of **4i** 22.5 (Me-2), 29.5, 30.5, 54.3 (C-3), 68.5 (C-2), 128.3, 128.9,

138.4 (C-1'); ^{13}C δ partial of **5i** 25.9 (Me-2), 28.9, 32.7, 57.3 (C-3), 128.1, 129.1; m/z (EI+) 251 (M^+), 223 (M^+-CH_2=CH_2), 208 (M^+-HN_3), 193 (M^+-HN_3-Me), 180, 153, 147, 121; and recovered **1i** (0.033 g, 26%).

2-Azido-2,3-diphenyl-1,4-dithianes 4j and 5j. 1j (0.150 g, 0.52 mmol) was treated in a similar manner to that described earlier. After 3 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 9:1 to 7:3) to afford in order of elution **2j** (0.019 g, 13%), as white solid, by comparison with authentic sample;[2] **4j** (0.047 g, 29%), as a white unstable solid, ν_{max} (film) 3048, 3020, 2951, 2906, 2111 (N_3), 1492, 1446, 1406, 1265, 1248, 1077, 1032, 736, 697 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 2.91 (1H, dd J 12.4, 4.0), 3.01 (1H, dd J 17.2, 4.0), 3.41 (1H, t J 12.2), 3.58 (1H, t J 13.3), 4.55 (1H, s, H-3), 6.84-7.18 (10H, m, Ar); **5j** (0.052 g, 32%), as white needles, m.p. 96-97 °C (hexane); ν_{max} (film) 3048, 3020, 2951, 2906, 2105 (N_3), 1492, 1452, 1242, 1088, 1043, 702 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 2.84 (1H, t J 3.5), 3.18 (1H, dt J 12.5, 5.0), 3.38 (1H, dt J 12.5, 3.5), 3.65 (1H, dt J 12.5, 3.5), 3.92 (1H, s, H-3), 7.07-7.31 (10H, m, Ar); ^{13}C δ(75.47 MHz, $CDCl_3$) 24.4 (C-5 or C-6), 28.3 (C-5 or C-6), 51.7 (C-3), 75.3 (C-2), 126.5, 127.2, 127.7, 128.2, 128.4, 128.9, 139.8 (C-1'); m/z (EI+) 313 (M^+), 287, 273, 270, 242; Anal. Calcd for $C_{16}H_{15}N_3S_2$: **C** 61.31, **H** 4.82, **N** 13.41%. Found:**C** 61.33, **H** 4.74, **N** 13.21%; and recovered **1j** (0.037 g, 24%).

1,4-Dithiane 4k. 1k (0.095 g, 0.50 mmol) was treated in a similar manner to that described earlier. After 2 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:0 to 0:1) to afford in order of elution *endo* **2k** (0.006 g, 7%), as a clear colourless oil; ν_{max} (film) 2906, 2832, 2809, 1600, 1429, 1424, 1406, 1316, 1276, 1123, 1100, 998, 782 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.70 (4H, t J 5.6, $C\underline{H}_2CH_2C$=C), 2.09 (4H, t J 5.6, $CH_2C\underline{H}_2C$=C), 3.17 (4H, s, CH_2S); m/z (EI+) 172 (M^+), 157, 144 (M^+-CH_2=CH_2), 106, 101; **4k** (0.061 g, 57%), as a white plates; m.p. 54-54.5 °C (methanol); ν_{max} (film) 2923, 2849, 2094 (N_3), 1446, 1242, 1015, 867 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.49-2.5 (9H, m), 2.71-2.76 (1H, m, H-5_{eq} or H-6_{eq}), 2.83-2.97 (1H, m, H-5_{eq} or H-6_{eq}), 3.04 (1H, ddd J 14.6, 12.2, 2.6, H-5_{ax} or H-6_{ax}), 3.34 (1H, ddd J 14.6, 13.2, 2.6, H-5_{ax} or H-6_{ax}); ^{13}C δ(75.47 MHz, $CDCl_3$) 22.7, 22.8, 26.1, 28.3, 30.6, 39.3, 45.0 (CH), 69.9 (CN_3); m/z (EI+) 215 (M^+), 187 (M^+-CH_2=CH_2), 172 (M^+-HN_3), 157 (M^+-HN_3-Me), 144 (M^+-HN_3-CH_2=CH_2), 131, 128; Anal. Calcd for $C_8H_{13}N_3S_2$: **C** 44.62, **H** 6.09%, **N** 19.51. Found:**C** 45.06, **H** 6.02, **N** 19.01%; and recovered **1k** (0.026 g, 27%).

1,4-Dithiane 4l. 1l (0.155 g, 0.76 mmol) was treated in a similar manner to that described earlier. After 4 days the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:0 to 0:1) to afford, in order of elution **4l** (0.097 g, 56%), as a clear colourless oil; ν_{max} (film) 2917, 2849 (N_3), 1452, 1236, 1026, 867, 850 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) 1.40-2.28 (10H, m), 2.64 (1H, dd J 14.9, 5.7), 2.81-2.71 (2H, m), 3.05 (1H, ddd J 14.6, 8.5, 6.2), 3.24-3.40 (1H, m); ^{13}C δ(75.47 MHz, $CDCl_3$) 22.7, 24.5, 27.1, 30.2, 31.7, 36.9, 53.0 (CH), 78.1 (CN_3);

m/z (EI+) 229 (M^+), 201 (M^+-CH_2=CH_2), 186 (M^+-HN_3), 158, 126, 119, 112; HRMS calcd for $C_9H_{15}N_3S_2$: 229.07074, found: 229.07037; and recovered **1l** (0.055 g, 36%).

Method B using DEAD/TPP/$(PhO)_2PON_3$ (1.1 eq).
2-azide-2-methyl-3-ethoxycarbonylmethyl-1,4-dithianes 4g and 5g. Diethyl azodicarboxylate (0.067 mL, 0.43 mmol) was added dropwise (5 min) to a stirred solution of **1g** (0.092 g, 0.39 mmol), triphenylphosphine (0.112 g, 0.43 mmol) in anhydrous tetrahydrofuran (1.9 mL) and diphenylphosphorylazide (0.092 mL, 0.43 mmol) under argon at room temperature (water bath), and stirring was continued for 65 h. The reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 9:1. to 7:3) to afford in order of elution **2g** (traces), by comparison with an authentic sample;[2] **6** (0.022 g, 26%), as a clear colourless oil; spectroscopically identical to **4g** and **5g** (0.014 g, 14%), as a white solid, ratio **4g**:**5g** of 1.2:1 determined by HPLC; and recovered **1g** (0.038 g, 41%).

Reduction of azides: Typical Procedures.
Using Bu_3P:

Preparation of 2-amino-2,3-dimethyl-1,4-dithiane (±) 7c. Freshly distilled tributylphosphine (0.15 mL, 0.59 mmol) was added dropwise (5 min) to a stirred solution of **(+) 4c** and **5c** (0.102 g, 0.54 mmol) in anhydrous dichloromethane (5.4 mL) under argon at room temperature, and stirring was continued for 2 h. The reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 6:0. to 1:1) to afford (±) **8c** (0.063g, 72%), as clear colourless oil; ratio *cis:trans* of 2:1 determined by ^1H NMR; racemic, by ^1H NMR analyses of the MTPA derivative;[13] ν_{max} (film) 3360, 3292, 2963, 2923, 2900, 1611, 1446, 1412, 1372, 1287, 1248, 1179, 1094, 1077, 804 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of major isomer 1.21 (3H, d, J 7.0, Me-3), 1.51 (3H, s, Me-2), 2.28 (2H, br, NH_2), 2.73-3.2 (4H, m, H-5 and H-6), 3.44 (1H, q J 7.0, H-3); ^1H δ partial of minor isomer; 1.43 (3H, s, Me-2), 1.58 (3H, d J 7.0, Me-3), 2.86 (3H, q J 7.0, H-3); m/z (EI+) 163 (M^+), 105, 95, 83, 72, 71, 60; **3,5-dinitrobenzoate derivative**; white plates, m.p. 149-151 °C (hexane : dichloromethane), ^1H δ(300 MHz, $CDCl_3$) of major isomer 1.32 (3H, d J=7.1, Me-3), 1.98 (3H, s, Me-2), 2.70-2.82 (2H, m), 2.96-3.13 (2H, m), 3.57 (1H, q J 7.1, H-3), 7.78 (1H, br, N-H), 8.99-9.01 (2H, m, Ar), 9.19 (1H, t J 2.2, Ar); ^1H δ partial of minor isomer; 1.80 (3H, d J 6.8, Me-3), 1.87 (3H, s, Me-2); Anal. Calcd for $C_{13}H_{15}N_3O_5S_2$: **C** 43.69, **H** 4.23%. Found:**C** 43.71, **H** 4.26.

Preparation of 2-amino-2,3-diethyl-1,4-dithiane 8f. A mixture of 4f and 5f (0.166 g, 0.76 mmol) was treated with tributylphosphine in a similar manner to that described earlier. After 2 h the reaction mixture was evaporated and the crude product was chromatographed on preparative TLC (eluent: dichloromethane) to afford **8f** (0.066 g, 45%), as a clear colourless oil; ν_{max} (film) 3360, 2957, 2923, 2895, 2866, 1458, 1406, 1372, 1282, 1105, 833, 804 cm^{-1}; ^1H δ(300 MHz, $CDCl_3$) of major isomer 1.00 (3H, t J 7.3, $CH_2\underline{Me}$), 1.09 (3H, t J 7.4, $CH_2\underline{Me}$), 1.58-1.92 (4H, m, $C\underline{H}_2Me$), 2.43 (2H, br, NH_2), 2.66-2.97 (3H, m), 3.10-3.27 (2H, m); m/z (EI+) 191 (M^+), 174, 163 (M^+-CH_2=CH_2), 147, 145; **3,5-dinitrobenzoate derivative**; white plates, m.p. 186-188 °C(hexane : dichloromethane), ^1H δ(300 MHz, $CDCl_3$) of major isomer 0.89 (3H, t J 7.3, $CH_2\underline{Me}$), 1.19 (3H, t J 7.2, $CH_2\underline{Me}$), 1.86 (2H, q J 7.3, $C\underline{H}_2Me$), 2.13-2.24 (1H, m), 2.42-2.47 (1H, m), 2.66-2.77 (2H, m), 2.96-3.06 (3H, m), 7.90 (1H, br, NH), 9.01-9.06 (2H, m, Ar), 9.19 (1H, t J 2.0, Ar); Anal. Calcd for $C_{15}H_{19}N_3O_5S_2$: **C** 46.74, **H** 4.97%. Found:**C** 46.04, **H** 4.85%.

Preparation of 2-amino-3-methyl-2-phenyl-1,4-dithiane 8h. **4h** (0.037 g, 0.15 mmol) was treated with tributylphosphine in a similar manner to that described earlier. After 2 h the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 2:8. to 0:1) to afford **8h** (0.026 g, 78%), as white plates, only *cis* by ^{1}H NMR, m.p. 61-62.5 °C (hexane); ν_{max} (film) 3366, 3303, 3054, 3019, 2974, 2923, 2900, 1605, 1492, 1446, 1412, 1378, 1520, 1276, 1202, 1077, 861, 839, 753, 691 cm^{-1}; ^{1}H δ(300 MHz, $CDCl_3$) 0.82 (3H, d J 7.0, Me-3), 2.66 (2H, br, NH_2), 2.77-2.89 (2H, m), 3.21-3.36 (2H, m), 3.86 (1H, q J 7.0, H-3), 7.27 (1H, t J 7.3, Ar), 7.36 (2H, t J 7.3, Ar), 7.72 (2H, d J 7.3, Ar); m/z (EI$^+$) 225 (M^+), 186, 156, 133, 132, 104; HRMS calcd for $C_{11}H_{15}NS_2$: 225.064459, found: 225.06347

Preparation of ketone 10. A mixture of **4b** and **5b** (0.037 g, 0.18 mmol) was treated with tributylphosphine in a similar manner to that described above. After 22 h the reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : diethyl ether from 8:2. to 1:1) to afford **10** (0.019 g, 59%), as a clear colourless oil; ν_{max} (film) 2968, 2929, 2866, 1719, 1452, 1378, 1361, 1316, 1259, 1230, 1213, 1162, 1066 cm^{-1}; ^{1}H δ(300 MHz, $CDCl_3$) 1.35 (1H, t J 7.2, SH), 1.39 (3H, d J 7.0, CHMe), 1.84 (2H, qui J 7.2, CH_2CH_2S), 2.28 (3H, s, MeCO), 2.56 (2H, q J 7.2, CH_2SH), 2.61 (2H, t J 7.2, SCH_2), 3.35 (1H, q J 7.0 CHMe), m/z (EI$^+$) 178 (M^+), 160 (M^+-H_2O), 135, 133, 122.

Using 1,3-propanedithiol:

Preparation of 2-amino-2,3-dimethyl-1,4-dithiane (±) 8c. Anhydrous triethylamine (0.062 mL, 3 eq) and 1,3-propanedithiol (0.045 mL, 3 eq) was added to a stirred solution of a mixture of (+) **4c** and **5c** (0.028 g, 0.15 mmol) in anhydrous methanol (0.7 mL) under argon at room temperature, and stirring was continued for 3 days. The reaction mixture was evaporated and the crude product was chromatographed as described earlier to afford in order of elution, recovered (+) **3c**,**4c** (0.011 g, 39%) and (±) **8c** (0.006g, 25%), as a clear colourless oil; ratio *cis:trans* of 2:1 determined by ^{1}H NMR ; racemic, by ^{1}H NMR analyses of the MTPA derivative.

Preparation of 2-amino-2-methyl-3-ethoxycarbonylmethyl-1,4-dithiane 8g and pyrrolidinone 9. Anhydrous triethylamine (0.117 mL, 3 eq) and 1,3-propanedithiol (0.084 mL, 3 eq) was added to a stirred solution of **4g** and **5g** (0.073 g, 0.28 mmol) in anhydrous methanol (1.4 mL) under argon at room temperature, and stirring was continued for 7 days. The reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: dichloromethane : diethyl ether from 1:0. to 8:2) to afford in order of elution **8g** (0.044 g, 67%), as clear colourless oil; ratio *cis:trans* of 1.1:1 determined by ^{1}H NMR; ν_{max} (film) 3445 (NH), 3315 (NH), 2974, 2900, 1734 (CO), 1418, 1372, 1358, 1270, 1242, 1157, 1094, 1037, 822 cm^{-1}; ^{1}H δ(300 MHz, $CDCl_3$) of *cis* 1.27 (3H, t J 7.1, CH_2Me), 1.52 (3H, s, Me-2), 2.30 (2H, br, NH_2), 2.75-3.15 (6H, m), 3.25 (1H, dd J 10.5, 3.3, H-3), 4.17 (2H, q J 7.1, CH_2Me), and ^{1}H δ of *trans* 1.27 (3H, t J 7.1, CH_2Me), 1.45 (3H, s, Me-2), 2.30 (2H, br, NH_2), 2.61 (1H, dd J 12.6, 6.3, H-3), 2.75-3.15 (6H, m), 4.15 (2H, q J 7.1, CH_2Me) and **9** (0.010g, 19%), as white plates; m.p. 133-134 °C (petroleum ether 40/60 : dichloromethane); ν_{max} (film) 3190 (br, NH), 2974, 2946, 2906, 1696 (CO), 1416, 1386, 1344, 1287, 1265, 1191, 1151, 1077, 924 cm^{-1}; ^{1}H δ(300 MHz, $CDCl_3$) 1.84 (3H, s, Me), 2.54 (1H, dd J 15.9, 6.4), 2.59 (1H, dt J 10.5, 4.1), 2.78 (1H, dt 11.4, 4.1), 2.91-3.01 (3H, m), 3.07 (1H, dd J 11.4, 6.9), 7.10 (1H, br, NH); m/z (EI$^+$) 189 (M^+), 159, 129, 97, 69; HRMS calcd for $C_7H_{11}NOS_2$: 189.02820, found: 189.02617.

Conversion of 8g to 9. Acetic acid (0.011 mL, 0.19 mmol) was added to a stirred solution of **8g** (0.044 g, 0.19 mmol) in anhydrous benzene (2 mL) under argon at room temperature and the stirring was continued for 3 days. The reaction mixture was evaporated and the crude product was chromatographed on a silica gel column (eluents: dichloromethane : diethyl ether from 1:0. to 8:2) to afford **9** (0.034 g, 96%), as a white solid.

References and Notes

1. Karmas, G. *J. Org. Chem.*, **1967**, *32*, 3147; Rubinstein, H.; Wuerthele, M. *J. Org. Chem.*, **1969**, *34*, 2762; Massingill, J.; Reinecke, M.; Hodgkins, J. *J. Org. Chem.*, **1970**, *35*, 823; Asinger, F.; Saus, A.; Offermanns, H.; Scherberich, P. *Liebigs Ann. Chem.*, **1971**, *753*, 151; Yoshino, H.; Kawazoe, Y.; Taguchi, T. *Synthesis*, **1974**, 713; Chen, C. *Tetrahedron Lett.*, **1976**, *25*; Ueda, N. N.; Shimizu, H.; Kataoka, T.; Hori, M. *Tetrahedron Lett.*, **1984**, *25*, 757; Russell, G.; Law, W.; Zaleta, M. *J. Am. Chem. Soc.*, **1985**, *107*, 4175; Caputo, R.; Ferreri, C.; Palumbo, G. *Tetrahedron*, **1986**, *42*, 2369; Williams, J.; Tran, P. *Synthesis*, **1988**, 705; Yamanaka, H.; Tsunai, T.; Kuwabara, M.; Fukunishi, K.; Nomura, M. *Synthesis*, **1990**, 211. Saigo, K.; Hashimoto, Y.; Fang, L.; Hasegawa, M. *Heterocycles* **1989**, *29*, 2079. For pioneering work on 1,2-sulfur migration in acyclic systems see for example: Blatcher, B.; Warren, S. *J. Chem. Soc. Perkin Trans. I*, **1979**, 1074. Blatcher, B.; Warren, S. *J. Chem. Soc. Perkin Trans. I*, **1985**, 1055.
2. Afonso, C. A. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Synthesis* **1991**, 575.
3. Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1967**, *40*, 935. Related reviews: Mitsunobu, O. *Synthesis*, **1981**, 1. Castro, B. R. *Org. Reactions* **1983**, *29*, 1. Hughes, D. L. *Org. Reactions* **1992**, *42*, 335; *Org. Prep. Proc. Int.* **1996**, *28*, 127.
4. For a study on the mechanism of *Mitsunobu* azide modification see also: Afonso, C. M.; Barros, M. T.; Godinho, L. S.; Maycock, C. D. *Tetrahedron* **1994**, *50*, 9671.
5. For related transformations using other nucleophiles see: Tarnchompoo, B.; Thebtaranonth, Y. *Tetrahedron Lett.*, **1984**, *25*, 5567; Cardani, S.; Gennari, C.; Scolastico, C.; Villa, R. *Tetrahedron* **1989**, *45*, 7397; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, 55, 6116; Waddell, S. T.; Blizzard, T. A.; Doss, G. A. *Heterocycles* **1993**, *36*, 1213.
6. Larock, R. C. *Compreensive Organic Transformations: A Guide to Functional Group Preparations*; VCH Publishers, Inc. 1989. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
7. Shorter reaction times resulted in only slightly less azide formation. For example, **1b** when treated with DEAD/TPP/HN_3 (1.1 eq) during 1 h afforded a mixture of **4b** and **5b** in 57% yield.
8. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977; Yoshida, J.-I.; Maekawa, T.; Morita, Y.; Isoe S. *J. Org. Chem.* **1992**, *57*, 1321; Irako, N.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1992**, *48*, 7251.
9. For a review see: Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.
10. We were unable to determine the enantiomeric excess of azide mixture (+)-**4b** and (+)-**5b** due to complete decomposition under GLC analysis conditions.
11. The azides **4c** and **5c** were unreactive to Ph_3P/CH_2Cl_2, reflux, 17 h, which is probably due to the azido group being severley sterically hindered. Some reported examples of azide reduction using Ph_3P: a) Eguchi, S.; Takeuchi, H. *J. Chem. Soc. Chem. Commun.* **1989**, 602; Molina, P.; Arques, A.; Vinader, M. V. *J. Org. Chem.* **1990**, *55*, 4724 and references cited therein; Murahashi, S.-I.; Tanigawa, Y.;

Imada, Y.; Taniguchi, Y. *Tetrahedro Lett.* **1986**, *27*, 227 and references cited therein; b) For reviews see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353; Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297; Johnson, A. W.; Kaska, W. C.; Starzewski, K. A. O.; Dixon, D. A. *Ylides and Imines of Phosphorus*; John Wiley & Sons, Inc; **1993**; pp. 435. Some reported examples of azide reduction using *n*-Bu_3P: Afonso, C. A. M. *Tetrahedron Lett.* **1995**, *36*, 8857; *Synthetic Comm.* **1998**, *28*, 261 and references cited therein.

12 Bayley, H.; Standring, D. N.; Knowles, J. R.; *Tetrahedron Lett.* **1978**, 3633.

13 Dale, J. A.; Dull, D. L.; Mosher, H. S.*J. Org. Chem.* **1969**, *34*, 2543.

14 After reaction of **(+)-4c** and **(+)-5c** in the presence of Bu_3P, CH_2Cl_2, RT, 2 h; the crude mixture was dissolved in pyridine (1.1 eq.), and (+)-MTPACl (1.1 eq.), RT, 1 h to give after usual purification a 1:1 mixture of Mosher's amide derivatives.

15 Trost, B. M.; Hiroi, K.; Jungheim, L. N. *J. Org. Chem.* **1980**, *45*, 1839.

16 3(S)-Benzoyloxybutan-2-one was prepared in 94% by prior hydroxyl protection (benzoyl chloride (1.5 eq.)/pyridine (3 eq.), benzene, rt, 24 h) and further deprotection of the carbonyl group using literature procedure[17] ($HgO/BF_3O(Et)_2$); m.p.37.5-38 °C (petroleum ether 40/60), $[\alpha]_D$ = +32.7 ± 0.2 (c 1.61, chloroform), reported[18] for 3(R)-benzoyloxybutan-2-one $[\alpha]_D$ = -35.7 (c 1.0, CH_2Cl_2).

17 Fuchs, P. L.; Vedejs, E. *J. Org. Chem.* **1971**, *36*, 366.

18 Barros, M. T.; Leitão, A. J.; Maycock, C. D. *Tetrahedron Lett.* **1995**, *36*, 6537.

19 Woodward, R. B.; Pachter, I. J.; Scheinbaum M. L. *J. Org. Chem.* **1971**, *36*, 1137.

20 Fieser, L. F.; Fieser M. *Reagents for Organic Synthesis,* vol 1, pag. 446, 1967, John Wiley and Sons INC.