Studies Related to Maytansinoids

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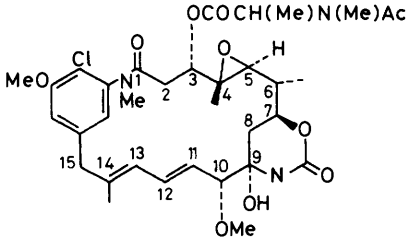
(3*R*, 4*R*, 5*R*)-3-Benzoyloxy-4,5-dihydroxycylohexanone ethylene dithioacetal (10), a compound elaborated from D-(−)-quinic acid, was cleaved at the *cis*-diol position by the use of triphenylbismuth carbonate. The resulting dialdehyde (11) was converted, in several steps *via* the diol (12), into (2*R*)-1-benzoyloxy-2-carbamoyloxy-7,9-dioxadecan-4-one ethylene dithioacetal (19). Removal of the ethylene dithioacetal group using phenylseleninic anhydride afforded the acyclic (2*R*)-benzoyloxy-2-carbamoyloxy-7,9-dioxadecan-4-one (21). The enantiomer of the diol (12) was also prepared from D-(−)-quinic acid, as was the target ethylene dithioacetal (28).

THE maytansinoids are a group of natural products isolated originally by Kupchan *et al.*[1] in low yield from the plant family *Maytenus serrata*. Recently,[2] they have also been obtained from the fermentation broth of a *Nocardia* sp. They are related by their ansa macrolide structure and differ only slightly in their functionality. The parent compound maytansine (1) has been the focus of a number of medical [3] and chemical research groups.[4,5]



(1)

The former because of its potent antitumour activity; in clinical trials it has been used successfully in the treatment of acute lymphoblastic leukemia and malignant lymphoma.[3] The latter because maytansine possesses unique structural features and presents an interesting synthetic challenge. Many research groups have contributed to the synthesis of various fragments of the molecule, the most notable contributions being those of Corey *et al.*[6] and Meyers *et al.*[7]

All the syntheses of maytansinoids so far reported have, as is normal with such a large molecule, been convergent with the molecule being divided into three portions: (*a*) the aromatic fragment with the diene moiety attached and the amino-group suitably protected (western and southern portions); (*b*) the β-hydroxy-ketone portion which finally becomes the carbinol-amide (eastern portion); (*c*) the linking or northern portion of the molecule. In the two total syntheses of maytansinol recently published,[6,7] Corey used the more obvious amide linkage to complete the macrolide ring whereas Meyers used an anionic C–C bond forming reaction to achieve the same end. These two strategies for ring closure, in such a large ring system, were crucial to success.

Our approach was to prepare three distinct portions which, when assembled † would afford a maytansinoid which was modified *inter alia* at C-6 (6-nor) and at C-10 (10-demethoxy). The simplification of the molecule was reasonable since structure–activity studies [8] have not implicated the C-6 methyl- or the C-10 methoxy-groups in the biological activity of the maytansinoids. It has been shown, by minor structural modifications to the natural products, that the C-3 ester group and the carbinol-amide unit are essential for antileukemic activity. Certain analogues of the carbinol-amide fragment also show biological activity.[9]

Here we report the synthesis of the chiral epoxide [10] (28), which comprises the C_6—C_{11} portion of the proposed maytansinoid, and several carbamoyloxy-ketones (as models) for use in cyclization reactions. Other useful intermediates are also described which demonstrate the utility of D-(−)-quinic acid (2) as a chiral, naturally occurring starting material for synthesis.

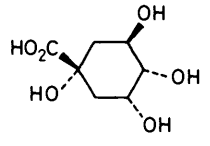
The ketone (3) [11] may be obtained from D-(−)-quinic acid (2) in high yield and provides the β-hydroxy-ketone function. The hydroxy-group in this molecule could be carbamoylated using the method described later, but the product (4) was prone to β-elimination, as are the tosylate [12] (5) and the acetate (6), to give the α,β-unsaturated ketone (8), even under mildly basic conditions. The benzoate (7), however, was more stable and could be prepared in high yield using pyridine and benzoyl chloride. Hence the former approach was not pursued further.

It was obvious from these studies that in order for the molecule described herein to survive a sequence of reactions it would be necessary to protect the carbonyl function.

Acetalization of the ketone (3) using ethane-1,2-diol and acid resulted only in aromatization of the ring. Therefore, trimethylsilyl methyl sulphide, a reagent known to dithioketalize carbonyl compounds under mild conditions,[13] was considered. This reagent gave, on reaction with the β-ketol (3), the dithioacetal (9) with the hydroxy-group trimethylsilylated. The need for desilylation would have been inconvenient in the later stages and so attempts were made to use the benzoate (7). Ethane-1,2-dithiol and either zinc iodide or boron

† This approach was developed in collaboration with Dr. P. Potier, Dr. and Mrs. (Dr.) Khuong-Huu, and their collaborators. We thank all these colleagues for very helpful discussions.

trifluoride etherate as acid catalyst gave good yields of the corresponding acetal (10), formed by the desired reaction with simultaneous deprotection of the diol. This latter feature was beneficial because the next step involved cleavage of the vicinal diol. It is interesting to note that trimethylsilyl methyl sulphide did not remove the cyclohexylidene group under the conditions used.



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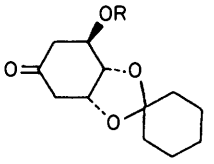
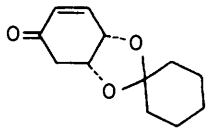


(3) R = H
(4) R = $CONH_2$
(5) R = p-$MeC_6H_4SO_2$
(6) R = Ac
(7) R = Bz



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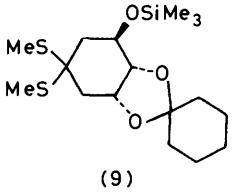

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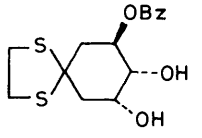

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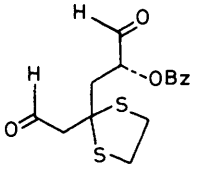

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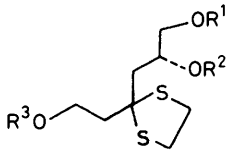
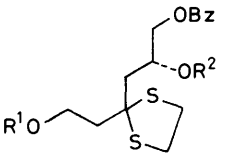


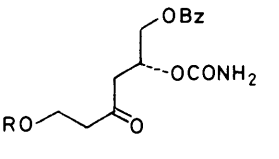
(12) R^1 = Bz, R^2 = H, R^3 = H
(13) R^1 = H, R^2 = Bz, R^3 = H
(14) R^1 = Bz, R^2 = CO—C(CF_3)(OMe)—Ph, R^3 = $MeOCH_2$

Cleavage of the *cis*-vicinal diol was achieved by the use of triphenylbismuth carbonate [14] in refluxing dichloromethane. No sulphoxide formation was detected, which would have been a problem had sodium periodate been used. The dialdehyde (11) so formed could not be converted into a crystalline derivative (oxime or 2,4-dinitrophenylhydrazone) so it was reduced with sodium borohydride. This gave the two easily separated (SiO_2) isomeric diols (12) and (13) in 50 and 25% yields, respectively. Prolonged exposure to the borohydride reaction mixture resulted in the formation of a very polar product (SiO_2). The minor product (13) was that expected and the major product was that resulting from a benzoyl migration. The secondary benzoate (13) could be converted into the primary ester (12) by treatment of a dichloromethane solution of the former with tetramethylguanidine.

We were aware that partial racemization may have occurred during the reduction of the aldehyde function. Hence, the benzoates (12) and (13) were perbenzoylated to give products which were identical spectroscopically and had the same optical rotation. In addition, an ^1H n.m.r. spectroscopic study of the α-methoxy-α-trifluoromethylphenyl acetate [15] (14) was consistent only with the non-racemized compound.



(15) R^1 = $MeOCH_2$, R^2 = H
(16) R^1 = Bu^tMe_2Si, R^2 = H
(17) R^1 = $MeOCH_2$, R^2 = $CO_2C_6H_4NO_2$-p
(18) R^1 = Bu^tMe_2Si, R^2 = $CO_2C_6H_4NO_2$-p
(19) R^1 = $MeOCH_2$, R^2 = $CONH_2$
(20) R^1 = Bu^tMe_2Si, R^2 = $CONH_2$
(23) R^1 = Bu^tMe_2Si, R^2 = $MeSO_2$
(24) R^1 = H, R^2 = $MeSO_2$



(21) R = $MeOCH_2$
(22) R = Bu^tMe_2Si

Selective protection of the primary alcohol function of compound (12) was achieved *via* its methoxymethyl or t-butyldimethylsilyl (TBDMS) ethers by treatment of compound (12) with the corresponding chloride and a base.[16] Under optimum conditions the methoxymethyl ether (15) was not obtained as the unique product; some bis-ether was formed and some starting material remained. The TBDMS ether (16) could be obtained as the only product as was evidenced by thin layer analysis of the reaction mixture.

Carbamoylation of the remaining hydroxy-group was effected by a two step procedure. The mixed carbonates (17) and (18) were prepared by using an excess of p-nitrophenyl chloroformate in pyridine and the crude products were ammonolyzed with a solution of anhydrous ammonia in 2-methylpropan-2-ol to afford the carbamates (19) and (20). The use of an aqueous ammonia solution in 2-methylpropan-2-ol resulted in some of the alcohols (15) and (16) being formed.

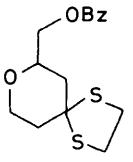
Finally, the carbonyl group in each case was liberated with phenylseleninic anhydride [17] in dichloromethane using propylene oxide as an acid scavenger. The ^1H n.m.r. shifts for the ketones (21) and (22) indicated non-cyclic products. In the case of the methoxymethyl ether (21) this was confirmed by the appearance of a peak at δ 204.7 p.p.m. in its ^{13}C n.m.r. spectra. No doubling of peaks was observed which indicated that no equilibrium existed under the n.m.r. conditions. This result was unexpected since a study of all the related systems, both natural and synthetic, given in the literature [18] revealed that they were cyclic and in the cases of synthetic compounds had cyclized spontaneously on deprotection of the carbonyl function. There are, of course, subtle

differences both in the structures, such as, in this case, the lack of a methoxy group α- to the carbonyl group, and the method of liberation of the ketone. Stork in a personal communication has mentioned similar cyclization problems with related systems. Some experiments with model systems are described later.

To finish the synthesis of our target molecule the TBDMS ether (16) was mesylated by using methanesulphonyl chloride and pyridine. The desired product (23) was obtained, but in reduced yield because of the facile loss of the silyl protecting group during work up which gave a more polar product, probably compound (24). The latter was spontaneously transformed with time to a non-polar material, possibly compound (25).

However, the next step involved the removal of the silyl group and this was achieved, not surprisingly, under mild conditions. Treatment of the ether (23) with methanol (overnight) or with dilute methanolic hydrochloric acid (1 h) gave the alcohol (24).

The primary alcohol group of compound (24) was oxidized in high yield by the excellent Swern [19] method to give the aldehyde (26), and this was subsequently protected as its 5,5-dimethyl-1,3-dioxan (27) by using 2,2-dimethylpropane-1,3-diol and toluene-*p*-sulphonic



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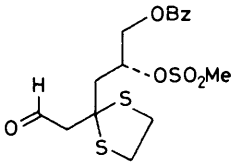

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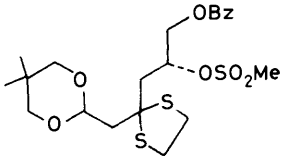

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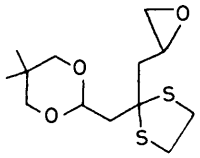

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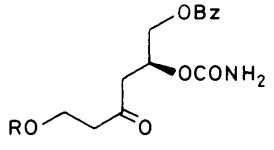
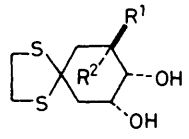


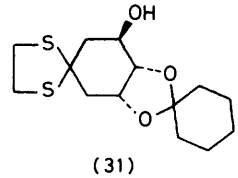
(29)

acid in benzene. The epoxide was formed smoothly with methanolic sodium methoxide. The required target molecule (28), which possessed a temporarily protected aldehyde group and a reactive terminal epoxide function was thus available.

In order to prepare, formally, the carbamate (29) with the natural (with respect to maytansine) configuration at the C-7 (maytansinoid) position it was necessary to synthesize the alcohol (36). The β-ketol (3) was treated with ethane-1,2-dithiol in the presence of zinc iodide and the resulting triol (30) was reketalized with dimethoxycyclohexane in dimethylformamide with sulphuric acid as catalyst, to afford the monohydric alcohol (31). Oxidation of compound (31) using the Swern [19] method afforded the ketone (32) in high yield with no oxidation of the sulphur atoms present.* The ketone (32) could



(30) R^1=OH, R^2=H
(35) R^1= H, R^2=OH



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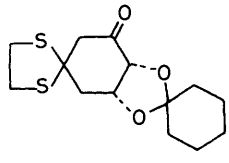

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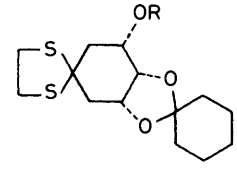
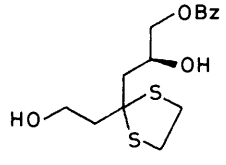


(33) R = H
(34) R = Bz



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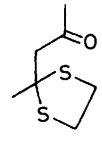


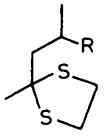
(37)

be stereoselectively reduced to the alcohol (33) by using lithium aluminium hydride (see ref. 21 for the reduction of a related system). The small quantity of undesired alcohol (31) could be readily removed by chromatography (SiO_2). Lithium tri-t-butoxyaluminium hydride did not give a better ratio of the alcohols. Benzoylation of the alcohol (33) as before gave the fully protected compound (34) which was treated with acid to afford the *cis*-vicinal diol (35). By the sequence described previously for the epimeric alcohol the diol (36) was obtained with similar physical properties to compound (12) except for its effect upon polarized light.

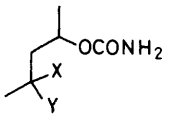
In order to study the deprotection of dithiolans with phenylseleninic anhydride and also to study the cyclization of the resulting β-carbamoyloxy-ketones two further β-carbamoyloxy-ketones were prepared.

Acetylacetone was treated [22] with ethane-1,2-dithiol and boron trifluoride (1 mol equiv.). The major product was the monoketone (37).[23] Reduction of this compound gave the alcohol (38) which was carbamoylated using the previously described two-stage procedure to afford the carbamate (39). Treatment of compound (39) with phenylseleninic anhydride gave, after silica gel chro-

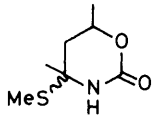
* For a subsequently published Pfitzner–Moffat oxidation of a similar system see ref. 20.



(38) R = OH
(39) R = $OCONH_2$



(40) X,Y = O
(41) X = Y = OMe
(43) X = Y = SMe



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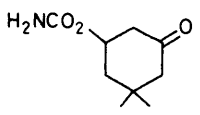

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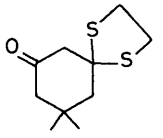


(45)

matography, a 41% yield of the required compound (40) as an unstable solid. ^1H N.m.r. shift comparison (see the Table) with known cyclized carbinol-amides suggested that it was uncyclized, as did its instability. The compound (21) was unstable even at −18 °C and could not be conveniently stored. When compound (40) was treated with trimethyl orthoformate in methanol and a trace of toluene-*p*-sulphonic acid [24] in an attempt to form the cyclic carbinol-amide, only the dimethyl acetal (41) was isolated, in high yield, as indicated by its ^1H n.m.r. spectrum and elemental analysis. In another attempt, the ketone (40) was treated with trimethylsilyl methyl sulphide (2 mol equiv.) * and a catalytic quantity of zinc iodide. A 2 : 1 mixture of the cyclized product (42), as a diastereoisomeric mixture, and the dithioacetal (43) was obtained.

* It has been noted that 8-amido-ketones cyclize only slowly to form the carbinol-amide (see ref. 25). The process was, however, accelerated by the addition of a reagent equivalent to $PhSSiMe_3$.

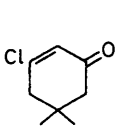
As an extreme test of the deprotection procedure, it was decided to prepare the carbamate (44). We were unable to prepare the monocarbonyl compound (45) as described for acetylacetone, and so the chloroenone (46) [26] was treated with ethane-1,2-dithiol under basic conditions to afford a moderate yield of the monoketone (45). The formation of the bis-acetal under these conditions is unlikely and the yield could probably be improved by optimization. Sodium borohydride reduction of the ketone (45) resulted in the alcohol (47) which was converted into the carbamate (48) as before.

Treatment of the latter (48) with phenylseleninic anhydride afforded the unstable carbamate (44) in 38% yield. Deprotection using periodic acid [27] gave a slightly improved yield of the ketone (44). When treated with trimethyl orthoformate, as before, compound (44) gave the dimethyl acetal (49).

It would be premature to propose hard and fast reasons for the acyclic nature of the carbamates [25] described herein, but two striking features are that the regeneration of the ketone function has previously been carried out using mercury(II) promoted hydrolyses of dithioacetals on carbamates having a methoxy-group adjacent to the liberated carbonyl. Therefore, the possibility of ring closure during hydrolysis and/or of hydrogen bonding between the newly formed hydroxy-function in the carbinol-amide and the methoxy-group cannot be ruled out. The carbonyl group would also be activated by the electron withdrawing effect of the methoxy-group. The methoxy-function in maytansine may, therefore, be of importance.

Phenylseleninic anhydride has proved to be a mild reagent for the conversion of dithiolans into ketones, even in highly sensitive systems and when other methods had failed.

The Table shows the comparative chemical shift values



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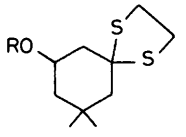
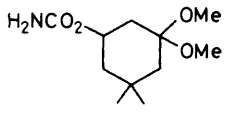
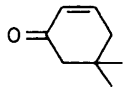


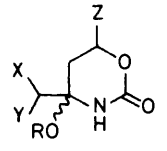
(47) R = H
(48) R = $CONH_2$



(49)



(50)



(51)

	X	Y	Z	R
a;	Me	OH	H	Me
b;	Me	OMe	H	Me
c;	Me	$Me_2C=$	Alkyl	$Me_2C=$
d;	OMe	OMe	Me_2CH	H
e;	OMe	OMe	Me_2CH	Me

Comparison of the chemical shifts observed for cyclic and acyclic β-carbamoyloxy ketones

Entry	Compound	Ref.[a]	7-H [b]	8-H	10-H	N-H
1	(42) (2 isomers)		4.83	*ca.* 2.0	1.58	6.23
			4.40		1.63	7.66
2	(40)		5.15	2.65	2.16	4.83
3	(22)		5.5	2.96	2.69	4.79
4	(21)		5.43	2.84	2.70	
5	Ansamycin P-3	2(*b*)	4.27	1.65 and 1.25	3.48	
6	(41)		4.90	1.87	1.29	
7	(44)		4.93	1.4—2.7	1.4—2.7	4.55
8	(49)		4.80	1.2—2.6	1.2—2.6	4.80
9	(51a)	18	4.44	1.97	3.92	7.20
10	(51b)	18	4.85 and 4.02	2.08—1.70	4.63	CH_2Ph
11	(51c)	18	4.71		4.01	7.71
12	(51d)	9	4.36	1.87	3.41	6.18
13	(51e)	9		1.9		6.85
14	(1)	1	4.28	0.8—2.50	3.50	6.24

[a] Where no reference is given the results are from this work. [b] Where a shift value is missing this indicates that the literature values were ambiguous or that the position of the proton was not clearly defined.

for the corresponding protons in our cyclic and acyclic carbamates and in the cyclic carbamates previously described (see the Table) with the relevant ^1H n.m.r. data. It is readily seen that the 7-H [numbering as in compound (1)] of the cyclic carbamates is always $<\delta$ 5.0, whereas in the acyclic carbamates it is always $>\delta$ 5.0, except where the carbamate function is attached to a six-membered ring. There is also a recognizable downfield shift for the 8-H of the acyclic carbamates with carbonyl free, as compared with the cyclic ones. The 10-H of the products described herein are not comparable with these in the literature since none of them contain an alkoxy-group at this position. It can be seen that cyclization (entry 1) and acetalization (entry 6), as expected, cause the 10-H to be considerably shielded as compared with the free ketone. A distinctive difference in chemical shift between the cyclized N–H and the uncyclized $N–H_2$ is characteristic and of diagnostic utility.

EXPERIMENTAL

Melting points were determined using a Reichert hot stage and are uncorrected. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. I.r. spectra were run on a Perkin-Elmer 297 spectrometer, u.v. spectra on a Jobin-Yvon Duospec 203 spectrometer, and c.d. on a Roussel-Jouan Dichrographe II.

All ^1H n.m.r. spectra were measured at 60 MHz on a Varian T-60 machine except where otherwise stated when they were measured at 250 MHz by M. Claude Merrienne at the University of Paris-Sud at Orsay. Chemical shifts are expressed in δ values downfield from $SiMe_4$.

Mass spectra were run on A.E.I. MS50 and MS9 machines and the microanalyses were carried out in the analytical department of the I.C.S.N. Gif-sur-Yvette.

Chromatographic separations were performed using Merck Kieselgel 60 PF_{254} (preparative t.l.c.) and Merck Kieselgel 60H (columns).

(3R,4R,5R)-3-*Benzoyloxy*-4,5-*dihydroxycyclohexanone* 4,5-O-*Cyclohexylidene Acetal* (7).—A solution of the alcohol (3) (5 g, 22.1 mmol) in pyridine (15 ml) was treated with benzoyl chloride (3.73 g, 26.5 mmol) and cooled with ice–water. The reaction mixture was allowed to warm to room temperature and the reaction was monitored by t.l.c. until the starting material had all been consumed. Water was then added to the mixture to precipitate the benzoate. The filtered solid was recrystallized from ethanol to give the *title compound* (7) (6.7 g, 92%), m.p. 120—121 °C, $[\alpha]_D$ +68° (*c* 1.45, in $CHCl_3$); $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ($CDCl_3$) 1.60br (10 H, s, cyclohexylidene-H), 2.80 (4 H, m, $COCH_2$), 4.50 (1 H, d, *J* 7 Hz, 3- or 4-H), 4.28 (1 H, dt, *J* 7 and 3 Hz), 5.49 (1 H, m, 3-H), and 7.21—8.1 (5 H, m, Ar-H); *m/e* 330 (M^+) (Found: C, 69.2; H, 6.55. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%).

(3R,4R,5R)-3-*Benzoyloxy*-4,5-*dihydroxycyclohexanone Ethylene Dithioacetal* (10).—To the ketone (7) (5 g, 15.2 mmol) in dichloromethane (10 ml) were added ethane-1,2-dithiol (5.2 g, 37.9 mmol) and zinc iodide (1 g). The reaction was monitored until only one polar product had formed. This mixture was washed with 10% aqueous sodium carbonate and the organic layer dried (Na_2SO_4) and evaporated to give an oil. Trituration with light petroleum, in which the co-produced cyclohexanone ethylene dithioacetal is soluble, gave a solid which was pure enough for the next step. However, column chromatography (SiO_2) gave a purer material which was recrystallized from carbon tetrachloride to give the *diol* (10) (4.0 g, 81%), m.p. 115—116 °C, $[\alpha]_D$ 0° (*c* 1.47%, in $CHCl_3$); Δε + 1.75 at 223 and −5.6 at 242 nm; $\lambda_{max.}$ (EtOH) 232 (14 937), 275 (1 164), and 281 nm (s) (1 009); $\nu_{max.}$ (mull) 3 300 (OH) and 1 710 cm^{-1} (C=O); δ($CDCl_3$) 2.06—2.81 (4 H, m, CH_2CO), 3.03 (2 H, s, OH), 3.26 (4 H, s, 5 CH), 3.83 (1 H, dd, *J* 3 and 7 Hz, 4-H), 4.23 (1 H, m, 5-H), 5.39 (1 H, ddd, *J* 4 and 7 Hz, 3-H), 7.20—8.20 (5 H, m, Ar-H) (the peak at δ 3.03 was eliminated on treatment with D_2O); *m/e* 326 (M^+) (Found: C, 55.1; H, 5.65; S, 19.7. $C_{15}H_{18}O_4S_2$ requires C, 55.19; H, 5.56; S, 19.64%).

(2R)-1-*Benzoyloxy*-2,6-*dihydroxyhexan*-4-*one Ethylene Dithioacetal* (12).—A solution of the diol (10) (1 g, 3.06 mmol) in dichloromethane (30 ml) (dry) was refluxed in the presence of triphenylbismuth carbonate [14] (2.3 g, 4.6 mmol) until all the starting material had been consumed (t.l.c.) (*ca.* 6 h). The mixture was then filtered with the aid of Celite and the filtrate was evaporated to a syrup, which often solidified. This material was dissolved in 95% ethanol (100 ml) and sodium borohydride (0.116 g, 3.06 mmol) was added slowly. After 1 h the reaction was complete and aqueous ammonium chloride was added to destroy the excess of borohydride. Partial evaporation followed by dilution with dichloromethane and washing with water gave an organic phase which was evaporated to an oil. Silica gel chromatography gave the title compound (12) (0.504 g, 50%),

m.p. 51—52 °C, $[\alpha]_D$ +3.7° (*c* 0.96, in $CHCl_3$); $\nu_{max.}$ (film) 3 400 (OH) and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 2.20—2.63 (4 H, m, CH_2), 3.03 (2 H, brs, OH), 3.33 (4 H, s, 5-CH_2), 3.89 (2 H, t, *J* 6 Hz, 6-H), 4.31 (3 H, brs, 1- and 2-H), and 7.20—8.20 (5 H, m, Ar-H) (the signal at δ 3.03 disappeared on treatment with D_2O); *m/e* 328 (M^+). The *bis*-p-*nitrobenzoate* gave m.p. 64—65 °C (from hexane–$CHCl_3$), $[\alpha]_D$ +9.5° (*c* 1.48, in $CHCl_3$); *m/e* 626 (M^+) (Found: C, 55.8; H, 4.3; N, 4.4; S, 10.3. $C_{29}H_{26}N_2O_{10}S_2$ requires C, 55.58; H, 4.18; N, 4.47; S, 10.23%).

A second, more polar material, (2*R*)-2-benzoyloxy-1,6-dihydroxyhexan-4-one ethylene dithioacetal (13) was also isolated as an oil (0.25 g, 25%), $[\alpha]_D$ +23.2° (*c* 15.6, in $CHCl_3$); $\nu_{max.}$ 3 410 (OH) and 1 710 cm^{-1} (C=O); δ($CDCl_3$) 2.23 (2 H, t, *J* 6 Hz, 5-CH_2), 2.45 (2 H, d, *J* 6 Hz, 3-CH_2), 3.00 (2 H, brs, OH), 2.25 (4 H, s, 5-CH_2), 3.75 (2 H, d, *J* 6 Hz, 1-CH_2), 3.85 (2 H t, *J* 6 Hz, 6-CH_2), 5.44 (1 H, quintuplet, *J* 6 Hz, 2-H), and 7.20—8.20 (5 H, m, Ar-H); *m/e* 328 (M^+).

Perbenzoylation of the isomeric diols (12) and (13) using benzoyl chloride in pyridine gave, after chromatography (SiO_2), products with identical n.m.r. spectra and $[\alpha]_D$ values {$[\alpha]_D$ +15.3° (*c* 6.6, in $CHCl_3$) for tribenzoate derived from the secondary benzoate (13) and $[\alpha]_D$ +15.4° (*c* 3.6, in $CHCl_3$) for the tribenzoate derived from primary benzoate; compound (12), ν_{max} (film) 1 720 (C=O) and 1 600 cm^{-1} (Ar-C–H); δ($CDCl_3$) 2.37—2.67 (4 H, m, 3 and 5-CH_2), 3.32 (4 H, s, 5CH_2), 4.47—4.67 (4 H, m, 1- and 6-CH_2), 5.90 (1 H, m, 2-H), and 7.20—8.20 (15 H, m, Ar-H); *m/e* 536 (M^+).

Isomerization of the Benzoate (13) *with Bases*.—(a) *Pyridine*. The benzoate (13) (*ca.* 30 mg) in [$^2H_5$]pyridine was periodically examined by ^1H n.m.r. spectroscopy. Over a period of two weeks no change in its spectrum was observed.

(b) *Di-isopropylethylamine*. In a similar experiment the benzoate (13) in deuteriochloroform was treated with a catalytic quantity of di-isopropylethylamine. Over a period of two weeks isomerization of the secondary benzoate (13) to the primary benzoate (12) occurred giving, finally, a product ratio of *ca.* 9 : 1 primary (12) : secondary (13) benzoates, respectively.

(c) *Tetramethylguanidine*. A deuteriochloroform solution of the benzoate (13) was treated with a catalytic quantity of tetramethylguanidine. Over a period of 15 min the secondary benzoate (13) was almost completely (*ca.* 90%) converted into the primary benzoate (12).

This isomerization was applied during the course of the synthetic work in the following manner. A solution of the secondary benzoate (13) in dichloromethane (the concentration was not critical) was treated with 2 drops of tetramethylguanidine and the reaction was monitored by t.l.c. After a period of about 2 h the mixture was chromatographed to give the primary benzoate (12).

(2R)-1-*Benzoyloxy*-2-*hydroxy*-7,9-*dioxadecan*-4-*one Ethylene Dithioacetal* (15).—The diol (12) (0.5 g, 1.5 mmol) in dichloromethane (7 ml) was treated with di-isopropylethylamine (0.81 g, 6.3 mmol) rapidly followed by methoxymethyl chloride (0.49 g, 6.1 mmol) at 0 °C. The reaction was kept at 0 °C for 2 h and the reaction was monitored by t.l.c. When the quantity of the bis-ether appeared to be increasing more rapidly than the mono-ether the reaction was quenched with water and stirred for a further 1 h. The water layer was then removed and the organic layer dried (Na_2SO_4) and evaporated to give an oil which was chromatographed. The major product was the title compound (0.35 g, 62%) obtained as an oil, $[\alpha]_D$ −1.1° (*c* 18.3, in $CHCl_3$); δ($CDCl_3$) 2.20—2.62 (4 H, m, 3- and 5-CH_2), 3.30 (7 H, s, 5-CH_2 and OMe), 3.77 (2 H, t, *J* 6 Hz, 6-CH_2), 4.29 (3 H, brs, 1-CH_2 and 2-H), 4.55 (2 H, s, OCH_2O), and 7.20—8.20 (5 H, m, Ar-H); *m/e* 372 (M^+) and 371 ($M^+ - 1$).

(2R)-1-*Benzoyloxy*-2-*carbamoyloxy*-7,9-*dioxadecan*-4-*one Ethylene Dithioacetal* (19).—The alcohol (15) (0.2 g, 0.537 mmol) in pyridine (7 ml) was treated with *p*-nitrophenyl chloroformate (0.217 g, 1.08 mmol) and the suspension was well stirred. The course of the reaction was monitored (t.l.c.) until all the alcohol had been consumed. The reaction mixture was then washed into a saturated solution of gaseous ammonia in 2-methylpropan-2-ol and a further current of gas passed for 1 h. The reaction was left to proceed overnight after which chromatographic analysis (t.l.c.) indicated only one product and no starting carbonate. After dilution with dichloromethane the mixture was washed first with water and then with sodium carbonate solution until the aqueous washings were colourless. The organic layer was dried (Na_2SO_4) and evaporated to give an oil which was almost the pure carbamate (19). Silica gel chromatography gave the carbamate (19) as an oil (0.182 g, 81%); $\nu_{max.}$ (film) 3 500—3 150 (NH), 1 720 (C=O), and 1 600 cm^{-1} (amide II); δ($CDCl_3$) 2.38 (4 H, m, 3- and 5-CH_2), 3.31 and 3.34 (7 H, each s, 5-CH_2 and OMe), 3.83 (2 H, t, *J* 6 Hz, 6-CH_2), 4.47 (2 H, ABq, 1-CH_2), 4.63 2 H, s, OCH_2O), 4.93 (2 H, brs, NH), 5.48 (1 H, m, 2-H), and 7.30—8.30 (5 H, m, Ar-H); *m/e* 415 (M^+), 265.

(2R)-1-*Benzoyloxy*-2-*carbamoyloxy*-7,9-*dioxadecan*-4-*one* (21).—A solution of compound (19) (0.1 g, 0.24 mmol) in dry dichloromethane (5 ml) was treated with phenylseleninic anhydride (0.104 g, 0.29 mmol), as a solid and 2 drops of propylene oxide. The suspension was stirred at room temperature and over 6 h, after an initial induction period, the anhydride dissolved completely and the solution became bright yellow. Solid sodium hydrogencarbonate was then added and the solid removed by filtration. The concentrated filtrate was then chromatographed on silica gel giving (0.033 g, 40%) of unstable oil which could be recrystallized from diethyl ether–light petroleum to give the *title compound* (21), m.p. 71—72 °C; $\nu_{max.}$ 3 500—3 200 (NH), 1 720br (C=O), and 1 600 cm^{-1} (amide II); δ($CDCl_3$–D_2O) 2.70 (2 H, t, *J* 6 Hz, 5-H), 2.84 (2 H, d, *J*, 7 Hz, 3-H), 3.28 (7 H, s, 5-CH_2, OMe), 3.77 (2 H, t, *J* 6-Hz, 6-H), 4.40—4.80 (complex envelope 1-CH_2, OCH_2O, HOD), 5.43 (1 H, m, 2-H), and 7.20—8.20 (5 H, m, Ar-H); δ_C 42.8 (C-5), 44.1 (C-3), 54.8 (C-10), 62.6 (C-1), 65.6 (C-6), 68.3 (C-2), 96.5 (C-8). 156.5 [C(:O)NH_2], 166.1 (Bz), and 204.7 p.p.m. (C-4) (Found: C, 56.35; H, 6.25; N, 4.05. $C_{16}H_{21}NO_7$ requires C, 56.63; H, 6.24; N, 4.13%).

(3R,4S,5R)-3,4,5-*Trihydroxycyclohexanone Ethylene Dithioacetal* (30).—To the ketone (3) (5 g, 22.1 mmol) in dichloromethane were added ethanedithiol (5.2 g, 55.3 mmol) and zinc iodide (2 g). The reaction mixture was left overnight and then diluted with ethyl acetate and washed once with dilute sodium carbonate solution. The organic layer was separated off and the aqueous layer was washed with more ethyl acetate. The combined ethyl acetate solutions were dried (Na_2SO_4) and evaporated to give an oil. Column chromatography gave the *pure triol* (30) (3.9 g, 80%), m.p. 127—128 °C (ethanol), $[\alpha]_D$ −35° (*c* 1.25%, in EtOH); $\nu_{max.}$ (Nujol mull) 3 400 and 3 220br cm^{-1} (OH) (Found: C, 42.95; H, 6.4; S, 29.1. $C_8H_{14}O_3S_2$ requires C, 43.22; H, 6.35; S, 28.84%).

(3R,4S,5R)-4,5-O-*Cyclohexylidene*-4,5-*dioxy*-3-*hydroxycyclohexanone Ethylene Dithioacetal* (31).—A solution of the triol (30) (2 g, 9.0 mmol) in dimethylformamide (20 ml) was

treated with 1,1-dimethoxycyclohexane (5.19 g, 36 mmol) and 1 drop of concentrated sulphuric acid. The reaction was monitored by t.l.c. and after 6 h the reaction was complete. Sodium hydrogencarbonate (solid) was then added and the dimethylformamide evaporated under reduced pressure. The product in dichloromethane was washed with water. Evaporation of the resulting dried (Na_2SO_4) organic layer gave a solid product which was normally sufficiently pure for further work. Recrystallization of a portion from hexane–chloroform gave the pure *title compound* (31) (2.3 g, 85%), m.p. 143—144 °C, $[\alpha]_D$ −45° (*c* 1.76, in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 600 (OH) and 3 450br cm^{-1} (OH); δ($CDCl_3$) 1.57 and 1.74 (1 OH, each brs, cyclohexylidene-H), 1.90—2.60 (4 H, complex AB systems, 2- and 6-CH_2), 3.27 (4 H, s, 5-CH_2), 3.77—4.43 (3 H, m, 3-, 4-, and 5-H) (Found: C, 55.3; H, 7.25; S, 20.9. $C_{14}H_{22}O_3S_2$ requires C, 55.59; H, 7.33; S, 21.20%).

(4R,5R)-4,5-O-*Cyclohexylidene*-4,5-*dioxycyclohexane*-1,3-*dione* 1-(*Ethylene Dithioacetal*) (32).—The procedure of Swern was used.[19] To a solution of oxalyl chloride (0.46 g, 3.63 mmol) at −60 °C was added freshly dried and distilled dimethyl sulphoxide (0.57 g, 7.28 mmol). After 5 min the alcohol (31) (1 g, 3.3 mmol) in dry dichloromethane (2 ml) was added rapidly and the temperature of the system was kept between −50 and −60 °C for 15 min. An excess of di-isopropylethylamine was then added and after 5 min the system was brought to room temperature. Water was then added and the mixture was diluted with dichloromethane. The separated, dried (Na_2SO_4) organic layer was evaporated to give a white solid which, by chromatographic analysis, was essentially the pure title product. Several attempts to recrystallize this product resulted in gels. Sublimation at 150—160 °C (0.3 mmHg) gave the pure *ketone* (32) (0.88 g, 89%), m.p. 184—186 °C (with sublimation), $[\alpha]_D$ +15° (*c* 1.03, in $CHCl_3$); $\nu_{max.}$ (Nujol mull) 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.60 (10 H, brs, cyclohexylidene-H), 2.78 (2 H, d, *J* 4 Hz, 6-CH_2), 2.98 (2 H, s, 2-CH_2), 3.32 (4 H, s, 5-CH_2), 4.28 (1 H, d, *J* 6 Hz, 4-H), and 4.62 (1 H, dt, *J* 3 and 6 Hz, 5-H); *m/e* 300 (M^+), 272, and 257 (Found: C, 55.95; H, 6.75; S, 21.2. $C_{14}H_{20}O_3S_2$ requires C, 55.97; H, 6.71; S, 21.35%).

(3S,4S,5R)-4,5-O-*Cyclohexylidene*-4,5-*dioxy*-3-*hydroxycyclohexanone Ethylene Dithioacetal* (33).—(a) *Sodium borohydride*. The ketone (32) (0.5 g, 1.2 mmol) in a 1 : 1 mixture of ethanol and tetrahydrofuran (THF) was treated with sodium borohydride (0.063 g, 1.7 mmol). The reaction was monitored by t.l.c. and when all of the starting material had been consumed (<0.5 h) aqueous ammonium chloride was added to consume the remaining reducing agent. Partial evaporation of the solvents was followed by dilution with dichloromethane and washing with water. The dried (Na_2SO_4) organic phase was evaporated to a solid which, after chromatography on SiO_2, gave (i) the *title compound* (33) (0.338 g, 67%), m.p. 121—122 °C (from hexane–diethyl ether), $[\alpha]_D$ +16° (*c* 3.65%, in $CHCl_3$); $\nu_{max.}$ (Nujol mull) 3 250 cm^{-1} (OH); δ($CDCl_3$) 1.60 (10 H, brs, cyclohexylidene-H), 2.1—2.5 (4 H, m, 2- and 6-CH_2), 2.62 (1 H, s, OH), 3.33 (4 H, s, 5-CH_2), 3.8—4.4 and (3 H, m, 3-, 4-, and 5-H); *m/e* 302 (M^+), 273, and 259 (Found: C, 55.55; H, 7.25; S, 20.9. $C_{14}H_{22}O_3S_2$ requires C, 55.59; H, 7.33; S, 21.20%) and (ii) the alcohol (31) (0.084 g, 16.6%).

(b) *Lithium tri-(t-butoxy)aluminium hydride*. The ketone (32) (0.1 g, 0.33 mmol) in THF (2 ml) was added to a solution of hydride (0.17 g, 0.66 mmol) also in THF. After 0.5 h the reaction was quenched by adding wet diethyl ether and then the whole was diluted with dichloromethane and washed with water. The dried organic phase was evaporated to an oil which was chromatographed to give the desired alcohol (33) (70 mg, 70%) and its epimer (31) (6 mg, 6%).

(c) *Lithium aluminium hydride*. The ketone (32) (100 mg) in dry THF was treated with lithium aluminium hydride (0.013 g, 0.33 mmol). After 0.5 h the reaction was worked up as above to give the required alcohol (33) (0.067 g, 67%) and its epimer (31) (0.088 g, 8%).

(3S,4R,5R)-3-*Benzoyloxy*-4,5-O-*cyclohexylidene*-4,5-*dioxycyclohexanone Ethylene Dithioacetal* (34).—The alcohol (33) (0.3 g, 1 mmol) in pyridine (5 ml) was treated with benzoyl chloride (0.211 g, 1.5 mmol) and the reaction mixture was left at room temperature overnight. Water was then added and the whole mixture diluted with dichloromethane and washed with dilute sodium hydrogencarbonate. Evaporation of the organic phase gave an oil which, though almost pure, requires a final chromatographic purification, to afford the *benzoate* (34) (0.335 g, 88%), m.p. 84—88 °C (from ethanol–water), $[\alpha]_D$ −24° (*c* 1.33, in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 1 710 (C=O) and 1 600 cm^{-1}; δ($CDCl_3$) 1.53 and 1.70 (10 H, each brs, cyclohexylidene-H), 2.15—2.55 (4 H, m, 2- and 6-CH_2), 3.28 (4 H, s, 5-CH_2), 4.20—4.50 (2 H, m, 4- and 5-H), 5.42 (1 H, ddd, *J* 4.6, and 10 Hz, 3-H), and 7.2—8.2 (5 H, m, Ar-H); *m/e* 406 (M^+), 376, and 362 (Found: C, 62.0; H, 6.45; S, 15.6. $C_{21}H_{26}O_4S_2$ requires C, 62.04; H, 6.45; S, 15.77%).

(3S,4R,5R)-3-*Benzoyloxy*-4,5-*dihydroxycyclohexanone Ethylene Dithioacetal* (35).—The benzoate (34) (0.2 g, 0.49 mmol) was suspended in methanolic hydrogen chloride (3 ml) (prepared by adding a few drops of acetyl chloride to methanol) and brought rapidly to reflux temperature. The reaction was soon completed as indicated by the dissolution of the starting material. After 5 min solid sodium hydrogencarbonate was added and when all effervescence had stopped water and dichloromethane were added. The organic phase was washed with water, dried (Na_2SO_4), and evaporated to give a solid which was purified by chromatography to give *the diol* (35) (0.147 g, 92%), m.p. 178—179 °C, $[\alpha]_D$ −27° (*c* 1.7, in EtOH); $\nu_{max.}$ (Nujol mull), 3 360, 3 290 (OH), 1 720 (C=O), and 1 600 cm^{-1} (Ar); δ (DMSO–$CDCl_3$–D_2O) 1.85—2.67 (4 H, complex m, 2- and 6-CH_2), 3.29 (4 H, s, 5-CH_2), 3.50—4.0 (1 H, m, partially masked by HOD peak, 5-H), 4.04 (1 H, m, 4-H), 4.97 (1 H, ddd, *J* 2.5 and 10 Hz), and 7.23—8.03 (5 H, m, Ar-H); *m/e* 326 (M^+) (Found: C, 55.4; H, 5.7; S, 19.35. $C_{15}H_{18}O_4S_2$ requires C, 55.19; H, 5.56; S, 19.64%).

(2S)-1-*Benzoyloxy*-2,6-*dihydroxyhexan*-4-*one Ethylene Dithioacetal* (36).—The diol (35) (0.1 g, 0.31 mmol) in dry dichloromethane (3 ml) was treated with triphenylbismuth carbonate (0.232 g, 0.46 mmol) and refluxed for 6 h. Work-up of the reaction mixture and reduction with sodium borohydride (0.012 g, 0.31 mmol) in 95% ethanol (20 ml), as before, gave of the *title compound* (36) (0.052 g, 51%), with i.r. and n.m.r. spectra identical with those obtained for compound (12), $[\alpha]_D$ −3.9 (*c* 1.1, in $CHCl_3$), −2.6° (*c* 0.8, in CH_2Cl_2).

The other component was not characterized, but had an R_F identical to compound (13) and is probably its enantiomer (2*S*)-2-benzoyloxy-1,6-dihydroxyhexan-4-one ethylene dithioacetal.

(2R)-1-*Benzoyloxy*-2-*hydroxy*-6-(*t-butyldimethylsilyloxy*)-*hexan*-4-*one Ethylene Dithioacetal* (16).—The diol (12) (0.2 g, 2.1 mmol) in dry dichloromethane (15 ml) was treated with

triethylamine (0.218 g, 3.15 mmol), t-butyldimethylsilyl chloride (0.38 g, 2.5 mmol), and finally a catalytic quantity of 4-dimethylaminopyridine.[16] After 10 h no further reaction seemed to be taking place. Only the starting material and one other product were present. The solution was washed rapidly with water, dried (Na_2SO_4), and evaporated to give an oil which was chromatographed (SiO_2) to give the mono-silylated product (16) (0.82 g, 88%) as an oil; $\nu_{max.}$ (film) 3 400 (OH) and 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.07 (6 H, s, SiMe), 0.93 (9 H, s, CMe_3) 2.1—2.6 (4 H, m, 3- and 5-CH_2), 3.33 (4 H, s, 5-CH_2), 3.78 (1 H, brs, OH), 3.93 (2 H, t, *J* 6 Hz, 6-CH_2), 4.37 (3 H, brs, 1-CH_2 and 2-H), and 7.2—8.2 (5 H, m, Ar-H).

(2R)-1-*Benzoyloxy*-2-*methanesulphonyloxy*-6-(*t-butyldimethylsiloxy*)*hexan*-4-*one Ethylene Dithioacetal* (23).—A cold solution of the silyl ether (16) (0.7 g, 1.58 mmol) in dichloromethane was treated with pyridine (2 ml) and methanesulphonyl chloride (0.36 g, 3.16 mmol). The reaction was monitored by t.l.c. until all the starting material had been converted into a single, less polar product. Water was then added to destroy the excess of acid chloride and the organic phase washed a further two times with water. Evaporation of the dried (Na_2SO_4) organic solution gave the almost pure product (0.76 g, 93%). Chromatographic purification of a portion gave pure (t.l.c.) compound (23) which eluded all attempts at crystallization mainly because of the facile loss of the silyl group: $\nu_{max.}$ (film) 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.03 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 2.25 (2 H, t, *J* 6 Hz, 5-CH), 2.47 (2 H, d, *J* 5 Hz), 3-CH_2), 3.07 (3 H, s, $MeSO_2$), 3.33 (4 H, s, 5-CH_2), 3.85 (2 H, t, *J* 6 Hz, 6-CH_2), 4.56 (2 H, Abq, *J* 6, 4 and 12 Hz, 1-CH_2), 5.37 (1 H, m, 2-H), and 7.2—8.2 (5 H, m, Ar-H); *m/e* 462 ($M^+ - C_4H_{10}$), 367, and 341.

(2R)-1-*Benzoyloxy*-6-*hydroxy*-2-*methanesulphonyloxy*-*hexan*-4-*one Ethylene Dithioacetal* (24).—(a) *Methanol.* The silyl ether (23) (0.6 g, 1.15 mmol) in methanol overnight gave a single more polar product. Evaporation of the methanol gave an oil a portion of which was chromatographed (0.1 g) to give the title compound (24) (0.085 g, 85%) which resisted all attempts at crystallization; $\nu_{max.}$ (film) 3 540 and 3 420br (OH) and 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 2.16 (1 H, s, OH), 2.29 (2 H, t, 6 Hz, 5-CH_2), 2.50 (2 H, d, *J* 6 Hz, 3-CH_2), 3.07 (3 H, s, $MeSO_2$), 3.32 (4 H, s, 5-CH_2), 3.90 (2 H, t, *J* 6 Hz, 6-CH_2), 4.54 (2 H, ABq, *J* 4, 6 and 12 Hz, 1-CH_2), 5.33 (1 H, m, 2-H), and 7.2—8.2 (5 H, m, Ar-H) (the addition of D_2O caused the loss of the singlet at δ 2.16); *m/e* 406 (M^+), 360, and 264.

(b) *Hydrochloric acid.* The same product could also be obtained in 1 h by the addition of 1 drop of concentrated hydrochloric acid to the methanolic solution. It was observed that on standing this alcohol produced a very non-polar product.

(2R)-1-*Benzoyloxy*-2-*methanesulphonyloxy*-6-(N-*phenylcarbamoyloxy*)*hexan*-4-*one Ethylene Dithioacetal.*—Phenyl isocyanate (0.17 g, 0.98 mmol) was added to a solution of the alcohol (24) (0.1 g, 0.24 mmol) in dichloromethane (5 ml) and refluxed for 5 h. The solvent and the excess of phenyl isocyanate were then removed by evaporation under reduced pressure and the resulting oil was chromatographed. The title compound was obtained as a *foam*, $[\alpha]_D$ +98° (*c* 5.64, in $CHCl_3$); $\nu_{max.}$ (film) 3 350 (NH), 1 720 (C=O), and 1 600 cm^{-1} (amide II); $\delta(CDCl_3)$ 2.39 (2 H, t, *J* 7 Hz, 5-CH_2), 2.50 (2 H, d, *J* 5 Hz, 3-CH_2), 3.04 (3H, s, SO_2Me), 3.28 (4 H, s, 5-CH_2), 4.38 (2 H, t, *J* 6 Hz, 6-CH_2), 4.56 (2 H, ABq, *J* 3.6, and 12 Hz, 1-CH_2), 5.40 (1 H, m, 2-H), and 7.0—8.2 (10 H, m, Ar-H) (Found: C, 52.25; H, 5.2; N, 2.35; S, 18.05. $C_{23}H_{22}NO_7S_3$ requires C, 52.55; H, 5.18; N, 2.66; S, 18.30%).

(2R)-1-*Benzoyloxy*-5-*formyl*-2-*methylsulphonyloxypentan*-4-*one Ethylene Dithioacetal* (26).—The alcohol (24) (0.5 g, 1.23 mmol) was added to a mixture of oxalyl chloride (0.17 g, 1.35 mmol) and dimethyl sulphoxide (0.21 g, 2.7 mmol) at −60 °C in dry dichloromethane, following the method of Swern.[19] After 0.5 h as excess of di-isopropylethylamine was added and the reaction mixture was allowed to reach room temperature. Water was then added and the mixture diluted further with dichloromethane and washed twice with water. Evaporation of the dried (Na_2SO_4) dichloromethane solution gave a yellow oil which was almost exclusively the aldehyde (t.l.c.). Chromatography (SiO_2) gave the pure aldehyde (26) (0.42 g, 85%) as an oil; $\nu_{max.}$ (film) 2 730 (aldehyde C-H) and 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 2.58 (2 H, dd, *J* 4 and 6 Hz, 3-CH_2), 3.09 (3 H, s, $MeSO_2$), 3.23 (2 H, brs, 5-CH_2), 3.30 (4 H. s, 5 CH_2), 4.60 (2 H, ABq, *J* 4, 6, and 12 Hz, 1-CH_2), 5.32 (1 H, m, 2-H), 7.22—8.22 (5 H, m, Ar-H), and 9.73 (1 H, brs, CHO); *m/e* 404 (M^+).

(2R)-1-*Benzoyloxy*-5-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)-2-*methanesulphonyloxypentan*-4-*one Ethylene Dithioacetal* (27).—The aldehyde (26) (0.4 g, 0.99 mmol) in benzene (10 ml) was treated with 2,2-dimethylpropane-1,3-diol (2 g) and a trace of toluene-*p*-sulphonic acid. The solvent was slowly distilled and fresh benzene was added to attain a constant volume. After 3 h the reaction mixture was left at room temperature overnight. Solid sodium hydrogencarbonate was added and after 5 min the solution was washed twice with water. Evaporation of the dried (Na_2SO_4) organic layers gave an oil which, by t.l.c. and n.m.r. analysis was the almost pure *dioxan derivative* (27) (0.44 g, 91%). A portion was purified by preparative t.l.c. to give the pure compound (27); $\nu_{max.}$ 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.70 (3 H, s, Me), 1.16 (3 H, s, Me), 2.40 (2 H, d, *J* 5 Hz, 5-H), 2.52 (2 H, d, *J* 6 Hz, 3-H), 3.08 (3 H, s, $MeSO_2$), 3.33 (4 H, s, 5-CH_2), 3.48 (4 H, m, OCH_2), 4.57 (2 H, ABq, *J* 3, 6, and 12 Hz, 1-H), 4.62 (1 H, t, *J* 5 Hz, OCHO), 5.36 (1 H, m, 2-H), and 7.2—8.2 (5 H, m, Ar-H); *m/e* 490 (M^+) (Found: C, 51.7; H, 5.25; S, 19.9. $C_{21}H_{30}O_7S_3$ requires C, 51.41; H, 6.16; S, 19.61%).

(2S)-5-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)-1,2-*epoxypentan*-4-*one Ethylene Dithioacetal* (28).—The benzoate (27) (0.3 g, 0.61 mmol) in methanol (5 ml) was treated slowly at room temperature with 1M sodium methoxide in methanol solution (1.75 ml, 2.9 mmol) and the reaction was monitored by t.l.c. When all the starting material had been consumed the reaction mixture was diluted with 10% ammonium chloride solution and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase yielded an oil which was chromatographed to yield the title compound (28) as an oil (0.145 g, 82%); $\nu_{max.}$ 2 920, 2 820 (C-H), and 1 273 (epoxide C-O); $\delta(CDCl_3)$ 1.70 (3 H, s, Me), 1.17 (3 H, s, Me), 2.23 (2 H, dd, *J* 5.5 and 7 Hz, 3-H), 2.41 (2 H, d, *J* 4.5 Hz, 5-H), 2.59 (1 H, dd, *J* 3 and 5 Hz, 1-H), 2.79 (1 H, dd, *J* 4, 3 and 5 Hz, 1-H), 3.2 (1 H, m, 2-H), 3.31 (4 H, s, SCH_2CH_2S), 3.52 (3 H, ABq, OCH_2), and 4.65 (1 H, t, *J* 4.5 Hz, OCHO); *m/e* 290 (M^+).

1-(2-*Methyl*-1,3-*dithiolan*-2-*yl*)*propan*-2-*one* (37).[23]—Pentane-2,4-dione (5 g, 50 mmol) in dichloromethane (20 ml) was treated with boron trifluoride–ether (7.1 g, 50 mmol) and slowly (1 h) with ethane-1,2-dithiol (4.7 t, 50 mmol). The mixture was stirred at room temperature overnight (the reaction was essentially over within 3 h). Aqueous sodium hydrogencarbonate (10%) was then added and the mixture was stirred a further hour. The organic solution

was washed once more with water, dried (Na_2SO_4), and evaporated to an oil which was distilled over a short path to give the monodithioacetal (37) (3.8 g, 43%) as an oil, b.p. (oven temp.) 200 °C/18 mmHg (Kugelrohr); $\nu_{max.}$ (film) 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.79 (3 H, s, Me), 2.12 (3 H, s, Ac), 3.13 (2 H, s, CH_2), and 3.22 (4 H, s, 5CH_2); *m/e* 176 (M^+).

1-(2-*Methyl*-1,3-*dithiolan*-2-*yl*)*propan*-2-*ol* (38).—*The* ketone (37) (3 g, 7 mmol) in ethanol (10 ml) was treated slowly with sodium borohydride (0.65 g, 17 mmol). After 1 h of agitation, a 10% solution of ammonium chloride was added slowly and the mixture was then diluted with dichloromethane and washed twice with water. Evaporation of the dried (Na_2SO_4) organic layer gave, in an almost pure form, the alcohol (38) (3 g, 99%) as an oil, b.p. 220 °C/18 mmHg (Kugelrohr); $\nu_{max.}$ 3 420 cm^{-1} (OH); δ($CDCl_3$) 1.18 (3 H, d, *J* 6 Hz, Me), 1.78 (3 H, s, Ac), 2.06 2 H, dd, *J* 5 and 6 Hz, $COCH_2$), 3.22 (4 H, s, 5-CH_2 and OH), and 4.20 (1 H, tq, *J* 6 and 5 Hz, CHOH) (the addition of deuterium oxide caused the sharpening of the signals at 4.20 and the loss of a proton at δ 3.22); *m/e* 178 (M^+) and 119.

1-(2-*Methyl*-1,3-*dithiolan*-2-*yl*)*propan*-2-*yl Carbamate* (39). —Acylation of the alcohol (38) (3 g, 17 mmol) was effected in pyridine (12 ml) and dichloromethane (5 ml) by treatment with *p*-nitrophenyl chloroformate (6.85 g, 34 mmol) and stirring for 4 h. The mixed carbonate, so formed, was then poured into 2-methylpropan-2-ol which had been saturated with anhydrous ammonia. Ammonia gas was passed through the mixture for a further hour and the whole left overnight at room temperature. The yellow mixture was diluted with dichloromethane and then washed with water and several times with 10% sodium carbonate solution until the washings were no longer yellow. Evaporation of the dried (Na_2SO_4) solvents gave a crude solid (3.42 g, 91%). Recrystallization from hexane–diethyl ether gave the pure *carbamate* (39) (2.64 g, 70%), m.p. 58—59 °C; $\nu_{max.}$ (solid film) 3 500—3 150 (NH), 1 710 (C=O), and 1 600 cm^{-1} (amide II); δ 1.28 (3 H, d, *J* 6 Hz, Me), 1.76 (3 H, s, Ac), 2.22 (2 H, ABq, *J* 4.8 and 14 Hz, $COCH_2$), 3.30 (4 H, s, 5-CH_2), 4.87 (2 H, brs, NH_2), and 5.03 (1 H, m, CHO) (deuterium oxide addition caused the disappearance of the broad singlet at δ 4.87); *m/e* 221 (M^+) and 160 ($M^+ - H_2NCO_2H$) (Found: C 43.55; H 7.0; N, 6.35; S, 29.25. $C_7H_{15}NO_2S_2$ requires C, 43.41; H, 6.83; N, 6.33; S, 28.97%).

4-*Oxopentan*-2-*yl Carbamate* (40).—The carbamate (39) (1 g, 4.5 mmol) in dichloromethane (10 ml) was treated with freshly regenerated phenylseleninic anhydride (1.95 g, 5.4 mmol) and propylene oxide (100 mg) and the reaction mixture was stirred for 4 h, during which time all the anhydride dissolved and a clear yellow solution resulted. Some of the dichloromethane was then removed by evaporation at or below room temperature and then the mixture of products was column chromatographed. The pure ketone (40) was obtained as a solid (0.268 g, 41%) which could be recrystallized from hexane–diethyl ether to give *needles*, m.p. 88—89 °C; $\nu_{max.}$ (Nujol mull) 3 400, 3 320, 3 250, 3 200 (NH), 1 680, 1 710 (C=O), and 1 610 (amide II); δ($CDCl_3$) 1.25 (3 H, d, *J* 6 Hz, Me), 2.13 (3 H, s, Ac), 2.62 (2 H, ABq, *J* 4, 6, and 16 Hz, $COCH_2$), 5.05 (1 H, brs, NH), and 5.15 (1 H, tq, *J* 6 Hz, CHO) (treatment with deuterium oxide caused the disappearance of the signal at δ 5.05); *m/e* 146 (M^+H), 104, 102, and 84 ($M^+ - H_2NCO_2H$) (Found: C, 49.6; H, 7.7; N, 9.5. $C_6H_{11}NO_3$ requires C, 49.65; H, 7.64; N, 9.65%).

4,4-*Dimethoxypentan*-2-*yl Carbamate* (41).—The ketone (40) (0.1 g, 0.69 mmol) in dry methanol (1 ml) was treated with trimethyl orthoformate (0.5 ml) and a trace of toluene-*p*-sulphonic acid and the mixture was left for 0.5 h at room temperature. Solid sodium hydrogencarbonate was then added and after 5 min the mixture was filtered and evaporated to give an almost pure solid product. Recrystallization from hexane–diethyl ether gave the title compound as *prisms* (0.087 g, 66%), m.p. 72—73 °C; $\nu_{max.}$ (CH_2Cl_2) 3 520 and 3 410 (NH), 1 720 (C=O), and 1 580 cm^{-1} (amide II); δ($CDCl_3$) 1.24 (3 H, d, *J* 6 Hz, Me), 1.29 (3 H, s, COMe), 1.87 (1 H, d, *J* 4 Hz, COCH), 1.86 (1 H, d, *J* 7 Hz, COCH), 3.11 (6 H, s, OMe), 4.95 (1 H, m, CHO), and 4.98 (2 H, brs, NH_2) (treatment with deuterium oxide caused the disappearance of the signal at δ 4.98) (Found: C, 50.3; H, 8.9; N, 7.25. $C_8H_{17}NO_4$ requires C, 50.25; H, 8.96; N, 7.33%).

4,6-*Dimethyl*-4-*methylthio*-1-*oxa*-3-*azacyclohexan*-2-*one* (42).—The ketone (0.1 g, 0.69 mmol) in dry dichloromethane (3 ml) was treated with trimethylsilyl methyl sulphide (0.166 g, 1.38 mmol) and finally with a catalytic quantity of zinc iodide. After 1 h water was added to destroy any remaining reagent and then the mixture was washed with sodium carbonate solution. The dried organic solution was evaporated to an oil which was chromatographed (SiO_2) to give (*a*) the title compound (42) as a mixture of isomers (0.069 g, 57%), m.p. 104—106 °C (from hexane–diethyl ether); $\nu_{max.}$ (solid film) 3 600—3 100 (NH) and 1 700 br cm^{-1} (C=O); δ($CDCl_3$) 1.38 (3 H, d, *J* 6 Hz, Me), 1.58 and 1.63 (3 H, each s, Me), 1.98 (2 H, ABq, CH_2), 2.10 and 1.17 (3 H, each s, 5-Me), 4.40 and 4.83 (1 H, each m, 6-H), and 6.23 and 7.66 (1 H, brs, NH); *m/e* 176 ($M^+ + 1$) and 127 ($M^+ - MeSH$) (Found: C, 47.75; H, 7.55; N, 7.8; S, 18.05. Calc. for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48; N, 7.99; S, 18.30%) and (*b*) 4-carbamoyloxypentan-2-one dimethyl thioacetal (43) (0.04 g, 26%), m.p. 70—71 °C; $\nu_{max.}$ (CH_2Cl_2) 3 530 and 3 420 (NH), 1 720 (C=O), and 1 580 cm^{-1} (amide II); δ($CDCl_3$) 1.27 (3 H, d, *J* 6 Hz, Me), 1.53 (3 H, s, Ac), 1.99 and 1.22 [(each s, Me) and obscuring completely the 3-H signals, total 8 H], 4.73 (2 H, brs, NH_2), and 5.16 (1 H, m, 4-H); *m/e* 223 (M^+), 176 ($M^+ - MeS$), and 115 ($M^+ - MeS - H_2NCO_2H$).

5,5-*Dimethylcyclohexane*-1,3-*dione* 1-(*Ethylene Dithioacetal*) (45).—The chloroenone (46) [26] (4 g, 25.2 mmol was added to a mixture of ethanedithiol (2.60 g, 27.8 mmol) and potassium hydroxide (1.55 g, 27.8 mmol) in a mixture of tetrahydrofuran and water (1 : 1, 15 ml). After 2 h the mixture was diluted with dichloromethane and washed twice with water. Evaporation of the dried (Na_2SO_4) solution gave a solid which was a mixture of the required product and dimedone. Column chromatography (SiO_2) gave pure compound (45) (3.3 g, 61%), m.p. 88—89 °C; $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ($CDCl_3$) 1.12 (6 H, s, Me), 2.20 (2 H, s, CH_2), 2.37 (2 H, s, CH_2), 2.85 (2 H, s, CH_2), and 3.27 (4 H, s, 5-CH_2); *m/e* 216 (M^+).

5-*Hydroxy*-3,3-*Dimethylcyclohexanone Ethylene Dithioacetal* (47).—The ketone (45) (3 g, 14 mmol) in ethanol (15 ml) was treated with sodium borohydride (0.53 g, 14 mmol) for 10 min. After the mixture had been vigorously stirred for 1 h a saturated solution of ammonium chloride was added and, when all the effervescence had stopped, the mixture was diluted with dichloromethane and washed several times with water. Evaporation of the dried (Na_2SO_4) solvent gave the almost pure alcohol (47) (2.95 g, 98%) which was recrystallized from hexane–chloroform to give *crystals*, m.p. 89—90 °C; $\nu_{max.}$ (CH_2Cl_2) 3 600 (OH), 2 925, 1 290, 1 120, and 1 020 cm^{-1}; δ($CDCl_3$) 1.02 (3 H, s, Me), 1.12 (3 H, s, Me), 1.95 (2 H, s, 2-CH_2), 2.04 (1 H, s, OH), 1.4—2.8 (4 H, m, 4- and 6-CH_2), 3.28 (4 H, m, 5-CH_2), and 3.95 (tt, *J* 9

and 10 Hz C*H*OH) (the addition of deuterium oxide caused the disappearance of the peak at δ 2.04 and the sharpening of the signal at δ 3.95); *m/e* 218 (M^+) (Found: C, 54.9; H, 8.2; S, 29.35. $C_{10}H_{19}OS_2$ requires C, 55.00; H, 8.31; S, 29.29%).

5-Carbamoyloxy-3,3-dimethylcyclohexanone Ethylene Dithioacetal (48).—The alcohol (47) (2 g, 9.17 mmol) in pyridine (10 ml) was treated with *p*-nitrophenyl chloroformate (3.7 g, 18.3 mmol) and stirred for 4 h. The pyridine solution was then washed into a saturated solution of ammonia in 2-methylpropan-2-ol with dichloromethane. Ammonia gas was passed through the mixture for a further hour and the whole was left overnight. The resulting yellow mixture was diluted with dichloromethane and washed with *ca.* 5% sodium carbonate solution until the washings were colourless. The dried organic layer was then evaporated to yield a crude solid which, on recrystallization from hexane–diethyl ether gave the pure *carbamate* (48) (1.86 g, 78%), m.p. 136—137 °C; $\nu_{max.}$ (CH_2Cl_2) 3 530 and 3 420 (NH), 1 625 (C=O), and 1 580 cm^{-1} (amide II); δ($CDCl_3$) 1.0 (3 H, s, Me), 1.15 (3 H, s, Me), 1.3—2.7 (6 H, complex ABq, 2-, 4-, and 6-CH_2), 3.28 (4 H, m, 5-CH_2), 4.78 (2 H, brs, NH_2), 4.94 (1 H, tt, *J* 4 and 11 Hz, 5-H) (treatment with deuterium oxide caused the loss of the signal at δ 4.78); *m/e* (dideuteriated) 263 (M^+), 200 ($M^+ - H_2NCO_2H$) (Found: C, 50.65; H, 7.45; N, 5.35; S, 24.35. $C_{11}H_{18}NO_2S_2$ requires C, 50.54; H, 7.33; N, 5.36; S, 24.53%).

5-Carbamoyloxy-3,3-dimethylcyclohexanone Dimethyl Acetal (49).—The carbamate (48) (0.1 g, 0.38 mmol) in dichloromethane (3 ml) was treated with phenylseleninic anhydride (0.207 g, 0.57 mmol) and 2 drops of propylene oxide, and the suspension was stirred for 4 h when chromatographic analysis indicated that all the starting material had been consumed. Some of the solvent was evaporated off at or below room temperature and then the mixture was chromatographed to give a solid material (0.027 mg, 38%), believed to be the ketone (34). This material was, however, very labile and began to yellow rapidly. I.r. and ^1H n.m.r. spectroscopy indicated a mixture of the carbamate (44) and the α,β-unsaturated ketone (50); [25] $\nu_{max.}$ ($CHCl_3$) 3 530 and 3 420 (NH), 1 725 and 1 710 (saturated C=O), 1 675 (C=O) α,β-unsaturated), and 1 580 cm^{-1} (amide II); δ($CDCl_3$) 0.93 and 1.03 (each s, Me), 1.06 (s, Me of α,β-unsaturated ketone), 1.4—2.7 (m, CH_2), 4.55 (brs, NH_2), 4.93 (m, 5-H), 5.9 (m, vinylic H), and 6.8 (m, vinylic H).

This compound was treated with trimethyl orthoformate (0.5 ml) in dry methanol (1 ml) and a catalytic quantity of toluene-*p*-sulphonic acid. After 1 h at room temperature solid sodium hydrogencarbonate was added and then the mixture was filtered and evaporated to give a solid material (0.031 g, 91%), based on the ketone (44), which was recrystallized from hexane–diethyl ether to give the pure *acetal* (49), m.p. 139—140 °C; $\nu_{max.}$ ($CHCl_3$) 3 530, 3 475, and 3 420 (NH), 1 720 (C=O), and 1 580 cm^{-1} (amide II); δ($CDCl_3$) 1.97 (3 H, s, Me), 1.05 (3 H, s, Me), 1.2—2.6 (6 H, complex m, 2-, 4-, 6-CH_2), 3.12 and 3.14 (6 H, each s, OMe), 4.80 (2 H, brs, NH_2), and 4.80 (1 H, tt, *J* 4 and 12 Hz, 5-H) (treatment with deuterium oxide caused the disappearance of the broad singlet at δ 4.80); *m/e* 231 (M^+) (Found: C, 56.85; H, 8.95; N, 6.00. $C_{11}H_{21}NO_4$ requires C, 57.12; H, 9.15; N, 6.05%).

The dithiolan (48) (0.1 g, 0.38 mmol) in dichloromethane–methanol (2 ml, 1 : 1) was treated with periodic acid (0.105 g, 0.46 mmol) in water (0.5 ml). After 5 min the mixture was diluted with dichloromethane and water and then the organic layer was successively washed with water and 10% sodium thiosulphate solution to remove some liberated iodine. The dried (Na_2SO_4) dichloromethane solution was evaporated to give a crude product which, by t.l.c. analysis, contained only the desired product and a polar impurity. This crude material was treated with trimethyl orthoformate (0.5 ml) and a trace of toluene-*p*-sulphonic acid in methanol (1 ml). After 4 h the reaction was quenched with solid $NaHCO_3$ and work-up was as before. In this way the *acetal* (49) (0.037 g, 42%) was obtained with spectral data identical to those obtained above.

Mosher Ester (14).[15]—The secondary alcohol (15) (0.020 g, 0.054 mmol) in pyridine (0.5 ml) was treated with (+)-α-trifluoromethyl-α-methoxyphenylacetyl chloride (0.027 g, 0.107 mmol) and the reaction mixture was left at room temperature overnight. Water was then added and after 1 h the mixture was diluted with dichloromethane and washed with water. The solvent and an excess of pyridine were then removed under reduced pressure and the resulting material was chromatographed to remove a mobile (SiO_2) impurity. The product (14) (0.028 g, 89%) was obtained as an oil; $\nu_{max.}$ ($CHCl_2$) 1 745 cm^{-1} (ester C=O); δ($CDCl_3$, 250 MHz) 2.20 (2 H, m, 3-H), 2.34 (2 H, t, *J* 6 Hz 5-H), 3.26 (4 H, m, 5-CH_2), 3.32 (3 H, s, OMe), 3.56 (3 H, s, OMe), 3.10 (2 H, t, *J* 6 Hz, 6-H), 4.38 (1 H, dd, *J* 7 and 12 Hz, 1-H), 4.56 (2 H, s, OCH_2O), 4.64 (1 H, dd, *J* 3 and 12 Hz, 1-H), 5.84 (1 H, m, 2-H), and 7.2—8.0 (10 H, m, Ar-H) (irradiation at δ 4.64, 4.38, and 2.20 resulted in some modifications to the signal at δ 5.84, but not complete resolution of its component peaks).

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