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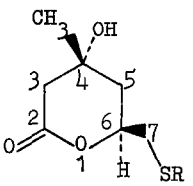
A DIASTEREOSELECTIVE SYNTHESIS OF 4(RS), 6(SR)-MERCAPTOMETHYLMEVALONOLACTONE, A KEY INTERMEDIATE IN THE PREPARATION OF A NEW CLASS OF INHIBITORS OF HMG-CoA REDUCTASE

H. Ferres*, I.K. Hatton, L.J.A. Jennings and A.W.R. Tyrrell
Beecham Pharmaceuticals, Biosciences Research Centre, Epsom, Surrey, England.
and
D.J. Williams
Chemical Crystallography Laboratory, Department of Chemistry,
Imperial College, London, England.

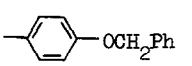
Summary: A diastereoselective synthesis of 4(RS), 6(SR)-mercaptomethylmevalonolactone (1) is described in the course of the preparation of disulphides designed as inhibitors of HMG-CoA reductase.

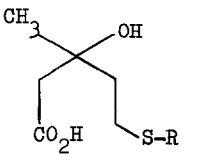
Certain disulphides, e.g. glutathione- and coenzyme A-disulphides,are known to undergo thiol-disulphide exchange reactions with several key enzymes of intermediary metabolism and are thought to play important regulatory functions in vivo ("third messengers").[1a,b] We now report the synthesis of disulphides designed to inhibit the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway.[2] The structures of the disulphides synthesised [(2a-b) and (4a-b)] were chosen by comparison with the structures of both the substrate and known inhibitors of HMG-CoA reductase.[3a,b] These "mevalonate" disulphides are therefore pharmacological tools with which to explore the potential of a thiol-disulphide exchange reaction as a means of enzyme regulation which in this case could lead to therapeutic benefit by lowering blood cholesterol levels.[4]



(±)

a: Ar = Ph

b: Ar = 



(1) R = H

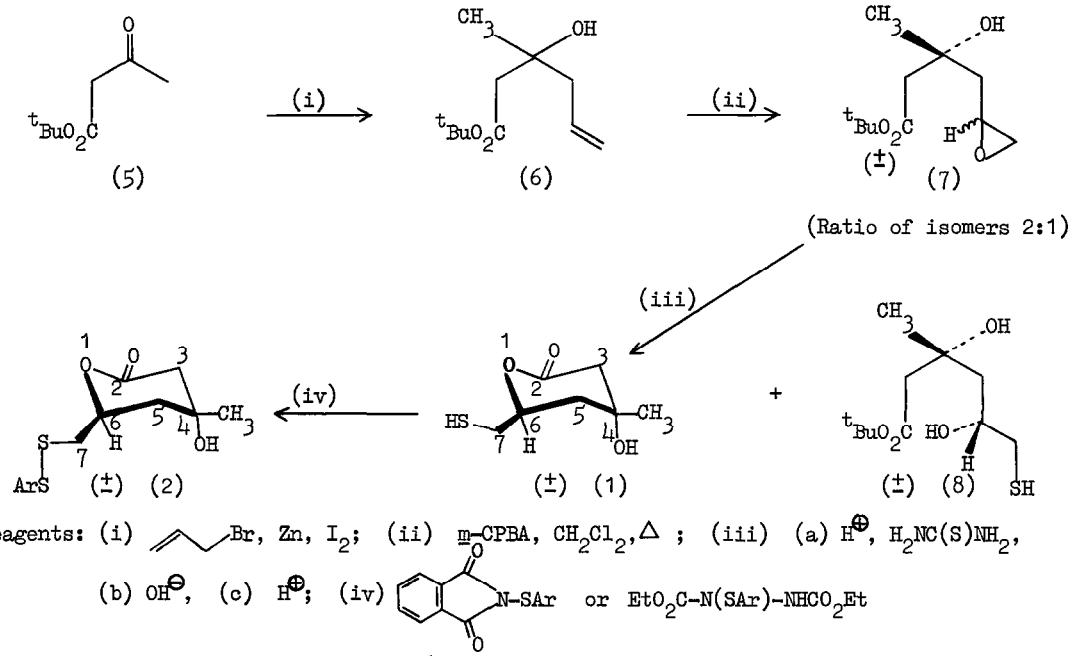
(2) R = S-Ar

(3) R = H

(4) R = S-Ar

To prepare racemic disulphides of type (2) a synthetic route to the thiol (1) was devised. From this key intermediate, it was expected that a series of (2) could be prepared by standard methods. Compound (6)(b.p.$_{0.8}$77-80°) was synthesised[5] in 30% yield and treated with m-chloroperbenzoic acid in refluxing CH_2Cl_2 to give the epoxide[13] (7) in 63% yield. The product was a 2:1 mixture of diastereoisomers, as shown by g.l.c. of their $^{t}Bu(Me)_2Si$-ethers. The isomer ratio was confirmed by reference to the ^{1}H and ^{13}C nmr spectra [^{1}H nmr δ1.32 (s,Me) and 1.35 (s,Me*); ^{13}C nmr δ27.67 (q,Me) and 26.95 (q,Me*). (* Denotes minor

Scheme



isomer)]. The epoxide (7) was opened[6] by treatment with 1 equivalent of both thiourea and 1M H_2SO_4 for 2 hours at 0° followed by 4 equivalents of 2M NaOH for 30 min. On acidification and work up, the minor diastereoisomer was converted into (8) (15% yield), while the major product was found to be the lactone (1) (59% yield), an oil; IR:ν_{max}(film) 3390, 2560, 2245 and 1715 cm^{-1}; mass spectrum: m/z (M^+) requires 176.0507, found 176.0515; δ($CDCl_3$) 1.42 (s,3H,C<u>H</u>$_3$), 1.84 (dd,$^3J_{5ax,6}$ 11Hz, $^2J_{5ax,5eq}$ 14Hz,1H,5ax-<u>H</u>), 1.98 (ddd, $^4J_{5eq,3eq}$ 2.5 Hz, $^3J_{5eq,6}$ 3Hz, $^2J_{5eq,5ax}$ 14Hz,1H,5eq-<u>H</u>), 2.46 (d, $^2J_{3ax,3eq}$ 18Hz,1H,3ax-<u>H</u>), 2.68 (dd, $^4J_{3eq,5eq}$ 2.5Hz, $^2J_{3eq,3ax}$ 18Hz,1H,3eq-<u>H</u>), 2.74 (½ABX,$^3J_{7,6}$ 5Hz, $^2J_{7,7'}$ 14Hz,1H,½-C<u>H</u>$_2$-SH) 2.90 (½ABX $^3J_{7',6}$ 5.5Hz, $^2J_{7',7}$ 14Hz,1H,½-C<u>H</u>$_2$-SH), and 4.85 (m, 12 lines,1H,6-<u>H</u>); ^{13}C nmr δ($CDCl_3$) 171.19 (s,C-2), 77.47 (d,C-6), 67.96 (s,C-4), 43.93 (t,C-3), 39.29 (t,C-5), 29.70 (q,CH_3) and 29.21 (t,C-7). The relative stereochemistry of (1) was determined as follows. The equatorial protons at C-3 and C-5 were assigned in the p.m.r. spectrum by the observation of W-coupling, ^4J 2.5 Hz between them; this fixes the 5 axial signal at δ1.84. $^3J_{5ax,6}$ has a value of 11 Hz which is only consistent with vicinal diaxial coupling, thus the C-6 proton is axial. The stereochemistry at C-4 was tentatively assigned with the hydroxyl group axial by comparison of the ^{13}C nmr shift of the methyl group at C-4, with values[7] calculated for the diastereoisomers of 4-hydroxy-4-methyl-1-t-butylcyclohexane. A solution of (1) in ethyl acetate was converted[8] into the disulphide (2a) in 31% yield by refluxing with phenylthiophthalimide[9] in benzene. Similarly, the p-benzyloxyphenyl disulphide[13] (2b)(m.p. 93-5°) was isolated in 36% yield by treating (1) with p-benzyloxyphenylthiophthalimide[11] (m.p. 139-41°) in refluxing benzene. The yield of (2a) was improved to 94% by treating (1) with EtO_2C-N(SPh)-$NHCO_2Et$ according to the method of Mukaiyama and Takahashi.[10] The product was the single diastereoisomer (2a), m.p. 92-5°; (found: C 54.76; H 5.64; S 22.59%; M^+ 284.0532.

$C_{13}H_{16}O_3S_2$ requires: C 54.90; H 5.67; S 22.55%; M^+ 284.0540); IR: ν_{max} (KBr) 3350, 1740 cm^{-1}; ^1H nmr $\delta(CDCl_3)$ 1.34 (s,3H,C<u>H</u>$_3$), 1.62 (dd, $^3J_{5ax,6}$ 12Hz, $^2J_{5ax,5eq}$ 14Hz, 1H, 5ax-<u>H</u>), 2.05 (ddd, $^4J_{5eq,3eq}$ 2.5 Hz, $^3J_{5eq,6}$ 3Hz, $^2J_{5eq,5ax}$ 14Hz, 1H, 5eq-<u>H</u>), 2.39 (d, $^2J_{3ax,3eq}$ 17Hz, 1H, 3ax-<u>H</u>), 2.62 (dd, $^4J_{3eq,5eq}$ 2.5Hz, $^2J_{3eq,3ax}$ 17Hz, 1H, 3eq-<u>H</u>), 2.95 ($\frac{1}{2}$ABX, $^3J_{7,6}$ 6.5Hz, $^2J_{7,7'}$ 14Hz, 1H, $\frac{1}{2}$-C<u>H</u>$_2$-SH), 3.14 ($\frac{1}{2}$ABX, $^3J_{7',6}$ 5Hz, $^2J_{7',7}$ 14Hz, 1H, $\frac{1}{2}$-C<u>H</u>$_2$-SH), 4.90 (m, 14 lines, 1H, 6-<u>H</u>), ~ 7.30 (m, 3H,Ar) and ~ 7.55 (m, 2H,Ar); ^{13}C nmr $\delta(CDCl_3)$ 170.10 (s,C-2), 137.12 (s,Ar), 129.31 (s, 2xAr), 128.69 (s, 2xAr), 127.59 (s,Ar), 68.21 (s,C-4), 44.04† (t,-<u>C</u>H$_2$SH), 43.95† (t,C-3), 40.43† (t,C-5) and 30.11 (q,<u>C</u>H$_3$). († assignments may be interchanged). The relative configuration of (2a) was initially deduced from ^1H and ^{13}C nmr spectra in a similar manner to that of the precursor (1). Also no NOE was observed in (2a) for the C-6 proton signal at δ4.90 when the methyl signal at δ1.34 was irradiated. Thus, as the C-6 proton has been assigned as axial, the C-4 methyl group is probably equatorial. Finally, the relative stereochemistry of this molecule was confirmed by a single crystal X-ray diffraction study (Figure).

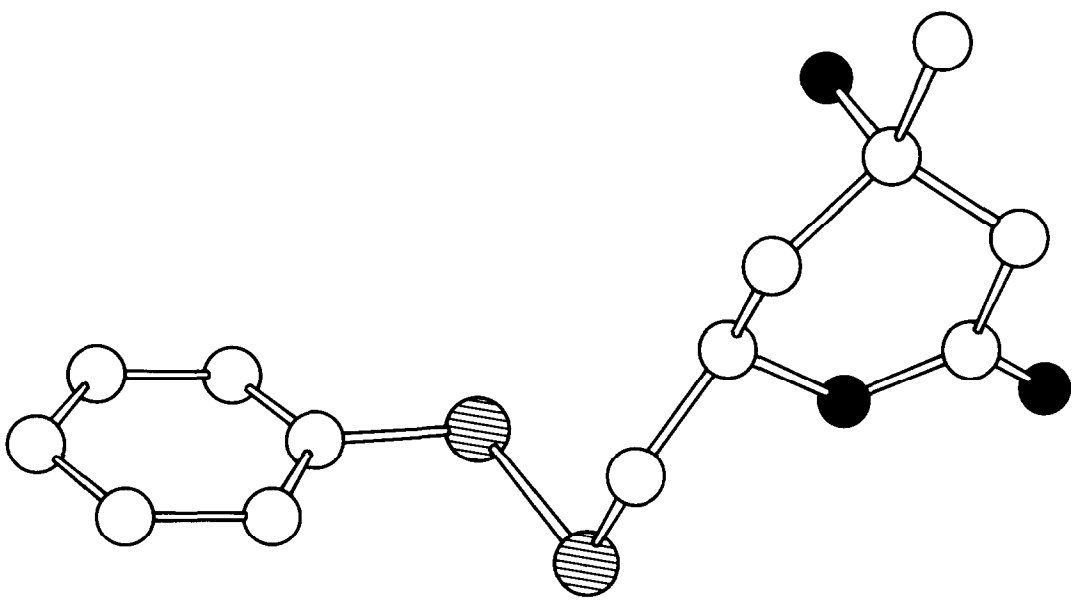


FIGURE The crystal structure of (2a)

Selected bond lengths: S-S 2.021(2), 2.031(3); S-Ph 1.782(6), 1.774(7); S-C(sp^3) 1.803(6), 1.794(6)Å. The two values given in each case refer to two independent molecules, only one of which is shown.

<u>Crystal Data</u>. Compound (2a), $C_{13}H_{16}O_3S_2$, monoclinic, a = 10.510(4), b = 9.972(4), c = 27.56(1) Å, β = 94.37(3)°, U = 2880Å^3, space group $P2_1/n$, Z = 8 (2 independent molecules in the asymmetric unit). A total of 2958 independent reflections were measured on a diffractometer ($\theta \leq 50°$) using Cu-K_α radiation and of these, 2441 had $|Fo| > 3\sigma(|Fo|)$ and were considered observed. The structure was solved by direct methods and refined anisotropically to R = 0.077*. The two molecules differ only in the relative orientation of the phenyl ring to the

S-S bond, the angle being 9° in one molecule and 113° in the other. Accompanying this rotation is a small difference in the CSSPh torsion angle (84° and 75° respectively). There are intermolecular hydrogen bonds (2.77 and 2.79Å) between the hydroxy and carbonyl oxygen atoms of like molecules.

To prepare the simpler disulphides (4a) and (4b) the intermediate (3) was obtained as its ethyl ester, O-acetate[12] and was liberated by careful hydrolysis with 1M NaOH solution at 60° under N_2, controlling the pH to 10. The thiol (3) was separately heated with phenyl and p-benzyloxyphenylthiophthalimides in benzene giving (4a) and (4b) in 25% and 28% yields respectively[13].

Disulphides (2b) and (4b) showed some inhibition of cholesterogenesis in rat liver slices in vitro but this was of a much lower magnitude than that exhibited by compactin[2]. However, (1) is a versatile intermediate which enables structural modifications within a new class of disulphide inhibitors of HMG-CoA reductase to be explored.

References

1. (a) H.F. Gilbert, J. Biol. Chem., 257, 12086, (1982); (b) H.F. Gilbert and M.D. Stewart, J. Biol. Chem., 256, 1782, (1981).

2. R. Fears, Biochem. J., 199, 1, (1981).

3. (a) A.G. Brown, T.C. Smale, T.J. King, R. Hasenkamp and R.H. Thomson; J. Chem. Soc. (Perkin I), 1165, (1976); (b) A. Sato et al, Chem. Pharm. Bull., 28, 1509, (1980).

4. H. Mabuchi et al, New Eng. J. Med., 305, 478, (1981).

5. R. Tschesche and H. Machleidt, Ann., 631, 61, (1960).

6. F.G. Bordwell and H.M. Andersen, J. Amer. Chem. Soc., 75, 4959, (1953).

7. H-J. Schneider and V. Hoppen, J. Org. Chem., 43, 3866, (1978).

8. D.N. Harpp et al, Tett. Lett., 3551, (1970).

9. M. Behforouz and J.E. Kerwood, J. Org. Chem., 34, 51, (1969).

10. T. Mukaiyama and K. Takahashi, Tett. Lett., 5907, (1968).

11. p-Benzyloxyphenylthiophthalimide was prepared by the method of ref. 9 but using SO_2Cl_2 to form the sulphenyl halide from the corresponding disulphide, and reacting this halide with potassium phthalimide.

12. H.U. Daeniker and J. Druey, Helv. Chim. Acta., 43, 983, (1960).

13. Satisfactory spectral and analytical data were obtained for all compounds but yields are not optimised.

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* The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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