

Synthesis of the Esperamicin A₁/Calicheamicin γ -Trisulphide Functionality: Thermal Stability and Reduction

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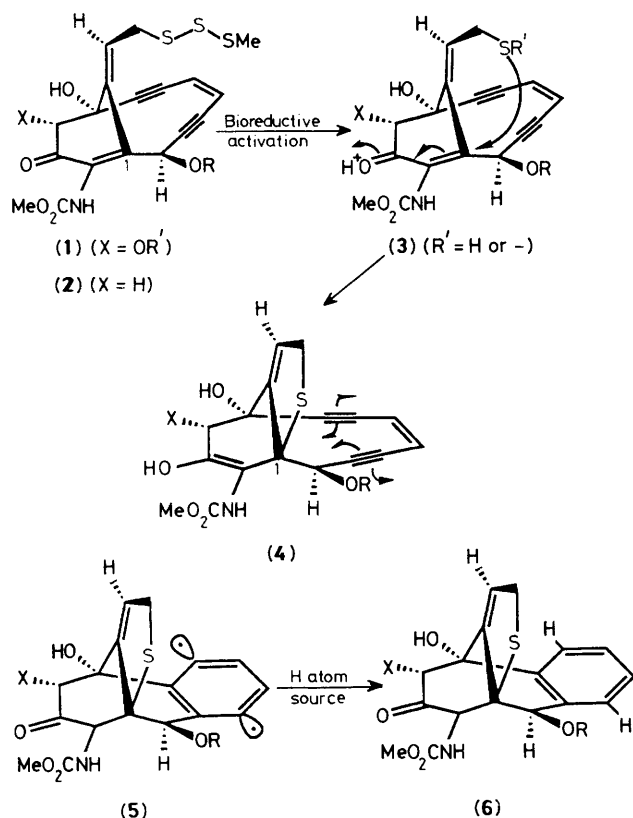
The bridgehead enone (**16**) was converted into the allylic trisulphide (**22**)/(**23**) in a completely stereospecific manner, and the thermal and reduction chemistry of some allylic trisulphides was examined.

Esperamicin A₁ (**1**) and the C-4 deoxy analogue calicheamicin γ (**2**)^{1,2} reportedly cleave DNA by a unique mechanism. It has been proposed that bioreductive cleavage of the allylic trisulphide functionality produces the thiol (**3**). This can

undergo intramolecular conjugate addition to C-1, providing (**4**). Bergman cyclization³ to the 1,4-diyl (**5**) followed by hydrogen atom abstraction (from the DNA backbone) results in the aromatic adduct (**6**) (Scheme 1).⁴

The intrinsic chemistry of allylic trisulphides has received scant attention, although good methods for their synthesis are available.⁵ Porter⁶ reported a splendidly economical experiment. Heating the bis-allylic trisulphide (**7**), (a *single* unspci-

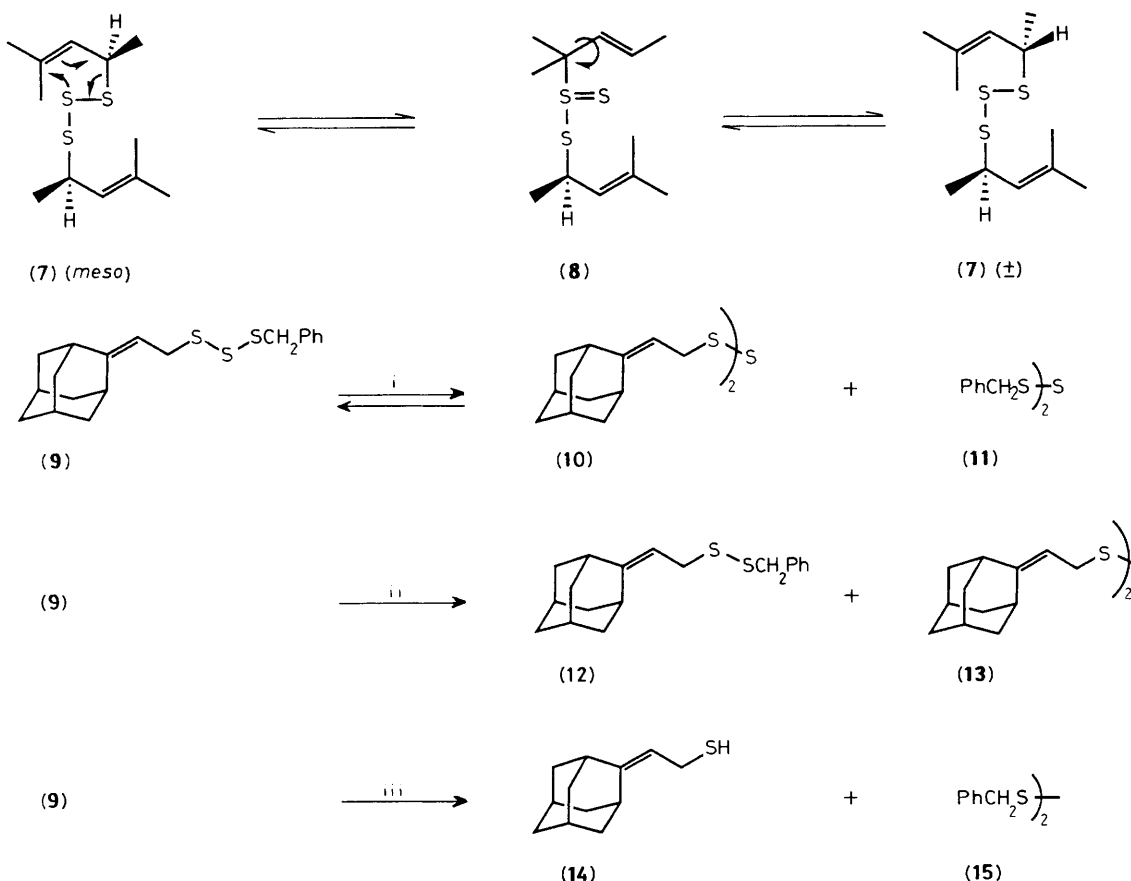
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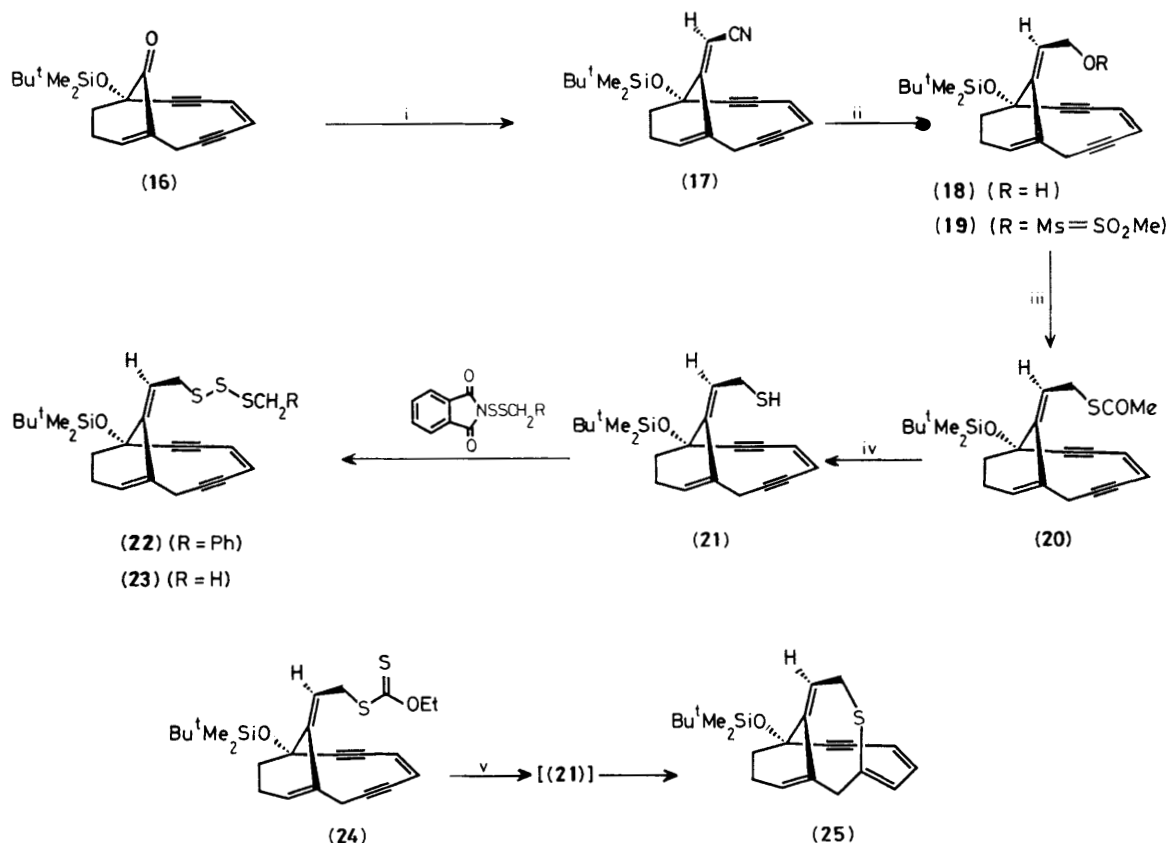
Scheme 1

fied diastereoisomer, but probably the *meso*-isomer), at 75 °C resulted in rapid equilibration ($t_{1/2}$ 46.5 min) between the *meso*- and (\pm)-forms of (7) without detectable leakage to allylic rearranged trisulphides, disulphides, or disproportionation products. It was proposed that (7) undergoes a [2,3] sigmatropic rearrangement to (8). Baldwin⁷ and Mislow⁸ have made similar observations for bis-allylic disulphides, which undergo [2,3] sigmatropic shifts at room temperature. Importantly, alkyl allyl disulphides are considerably more stable and can be distilled, without change, at 50 °C. Extrapolation suggests that alkyl allyl trisulphides should be relatively stable (at least below *ca.* 100 °C). Before proceeding directly to an esperamicin trisulphide system we examined the chemistry of adamantylidene-ethyl benzyl trisulphide (9). Treatment of the allylic thiol (14) with *N*-(benzylthiosulphenyl)phthalimide (A)⁹ gave the allyl trisulphide (9) (67%). Heating a solution of (9) in toluene at 110 °C for 36 h gave (9), (10), and (11) (4:1:1). Further heating for 36 h established the equilibrium mixture of trisulphides (9), (10), and (11) (2:1:1), which did not change upon continued heating. Addition of azobutyronitrile (AIBN) to the above solution of (9) caused the equilibrium mixture of trisulphides (9), (10), and (11) (2:1:1) to be established at 100 °C in 16 h.¹⁰ Reduction of (9) using $Ph_3P/CDCl_3$ at room temperature gave (12), (13), (14), and (15) (4:1:2:2). Similarly, treatment of (9) with propane-1,2-dithiol/EtOH/KOH gave (12), (13), and (15) (2:2:1).¹¹

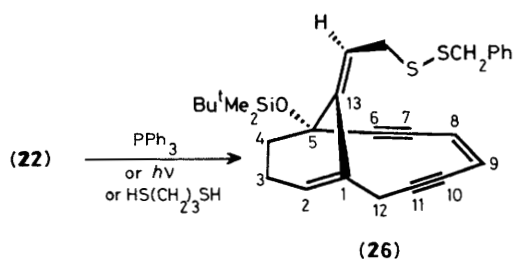
Treatment of the enone (16)⁴ with $(EtO)_2P(O)CH_2CN/NaH$ /dimethoxyethane (DME) at -45 to 20 °C gave (17) (90%) as a single stereoisomer. Successive reduction of (17) with $BuLi/AlH/toluene$ gave the allylic alcohol (18) (84%). The derived mesylate (19) ($MeSO_2Cl/NEt_3/-15$ °C) was treated with $NaSCOMe/MeOH$ to give the thioacetate (20) [92%



Reagents and conditions: i, PhMe, 110 °C, 36 h; ii, Ph_3P (1.0 equiv.), $CDCl_3$; iii, $HSCH_2CH_2CH_2SH$, KOH, EtOH.

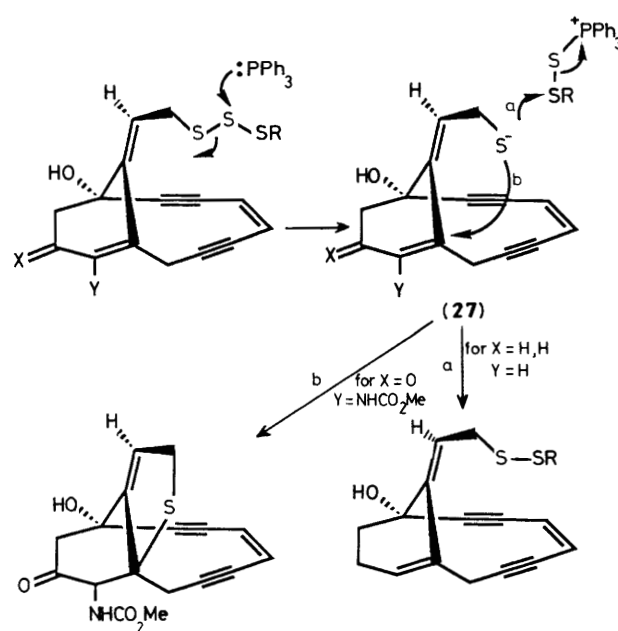


Reagents and conditions: i, (EtO)₂P(O)CH₂CN, NaH, dimethoxyethane (DME); ii, Bu₂AlH, PhMe, then HCl, H₂O, then Bu₂AlH, MeSO₂Cl/Et₃N/DCM; iii, NaSCOMe; iv, LiAlH₄, 0°C, then Na₂HPO₄; v, H₂NCH₂CH₂NH₂.



from (18)]. Reduction of (20) using LiAlH₄/Et₂O/0°C, and work-up with aqueous Na₂HPO₄ gave the allylic thiol (21), which was immediately treated with N-(benzylthiosulphenyl)phthalimide to give the trisulphide (22) [92% from (20)] contaminated with traces of the corresponding di- and tetra-sulphides. The *S*-methyltrisulphide (23) was similarly prepared, but in a less pure state as a result of significant disulphide formation (*ca.* 1.3:1). The allylic xanthate (24) [prepared from (19)] on treatment with neat ethylenediamine gave the cyclic sulphide (25) (60%), thus providing compelling evidence for the assigned stereochemistry of the C-13 double bond.

Thermolysis of the trisulphide (22) (0.02 M) in [2H₈]toluene at 85°C for 113 h produced no change. Exposure of (22) to PPh₃/CH₂Cl₂/room temp. or *hν* (Hg) gave as the major product the disulphide (26).¹¹ Similarly, treatment of (22) with propanedithiol gave the disulphide (26). If the allylic thiol (21) or its derived *sym*-disulphide are formed, they are in trace amounts.



The Lederle group (Lee *et al.*)¹ have shown that a calicheamicin derivative (2) on treatment with PPh₃ gave (6; X = H), presumably *via* (3) and conjugate addition to C-1. Clearly, the intermediate thiolate (27) is intercepted by conjugate addition. However, for the unactivated case, the usual disulphide is formed. The chemistry described here

demonstrates that the allylic trisulphide functionality can be made from the corresponding C-13 ketone with complete control of stereochemistry. Furthermore, the allylic trisulphide is thermally stable, thus precluding potential problems of [2,3] sigmatropic rearrangement, and can be reductively cleaved to a disulphide without thiol (acid-catalysed or radical) addition to C-1 or C-11.

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References

- 1 J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K.-i. Saitoh, and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3462; M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, and D. B. Borders, *ibid.*, 1987, **109**, 3464; M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M., Siegel, G. O. Morton, W. J. McGahren, and D. B. Borders, *ibid.*, 1987, **109**, 3466.
- 2 For a study on the cleavage of double-stranded DNA, see: N. Zein, A. M. Sinha, W. J. McGahren, and G. A. Ellestad, *Science*, 1988, **240**, 1198.
- 3 R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25; T. P. Lockhart, P. B. Comita, and R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4082; T. P. Lockhart and R. G. Bergman, *ibid.*, 1981, **103**, 4691.
- 4 For previous synthetic work in this area see: P. Magnus and P. A. Carter, *J. Am. Chem. Soc.*, 1988, **110**, 1626. For the synthesis of (16) see: P. Magnus, R. T. Lewis, and J. C. Huffman, *ibid.*, 1988, **110**, 6921; S. J. Danishefsky, N. B. Mantlo, and D. S. Yamashita, *ibid.*, 1988, **110**, 6890; K. C. Nicolaou, G. Zuccarello, Y. Ogawa, E. J. Schweiger, and T. Kumazawa, *ibid.*, 1988, **110**, 4866; A. S. Kende and C. A. Smith, *Tetrahedron Lett.*, 1988, **29**, 4217; S. L. Schreiber and L. L. Kiessling, *J. Am. Chem. Soc.*, 1988, **110**, 631.
- 5 D. N. Harpp, K. Steliou, and T. H. Chen, *J. Am. Chem. Soc.*, 1978, **100**, 1222; D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem. A*, 1971, **1**, 211; A. B. Sullivan and K. Boustany, *ibid.*, 1971, **1**, 207; A. W. Mott and G. Barany, *Synthesis*, 1984, 657; for general reviews on polysulphides and thiosulphoxides: D. N. Harpp, in 'Studies in Organic Chemistry 28. Perspectives in The Organic Chemistry of Sulphur,' eds. B. Zwanenburg and A. J. H. Klunder, Elsevier, Amsterdam, 1987; G. W. Kuthey and K. Turnbull, *Chem. Rev.*, 1982, **82**, 333. It is interesting to note that diallyl trisulphide and methyl allyl trisulphide are natural products: K. T. Augusti and P. T. Mathew, *Experientia*, 1974, **30**, 468; T. Ariga, S. Oshiba, and T. Tamada, *Lancet*, 1981, **1**, 150.
- 6 D. Barnard, T. H. Houseman, M. Porter, and B. K. Tidd, *Chem. Commun.*, 1969, 371.
- 7 G. Höfle and J. E. Baldwin, *J. Am. Chem. Soc.*, 1971, **93**, 6307.
- 8 R. D. Baechler, J. P. Hummel, and K. Mislow, *J. Am. Chem. Soc.*, 1973, **95**, 4442.
- 9 K. Mori and Y. Nakamura, *J. Org. Chem.*, 1969, **34**, 4170.
- 10 The thermal behaviour of dialkyl polysulphides has been studied in connection with vulcanization chemistry. T. L. Pickering, K. J. Saunders, and K. Tobolsky, *J. Am. Chem. Soc.*, 1967, **89**, 2364; C. D. Trivette and A. Y. Coran, *J. Org. Chem.*, 1966, **31**, 100. Heating a mixture of EtS₃Et and PrS₃Pr established an equilibrium containing the latter and EtS₃Pr.
- 11 For the desulphurization of trisulphides and polysulphides with PPh₃ see: S. Hayashi, M. Furukawa, J. Yamaoto, and K. Hamamura, *Chem. Pharm. Bull.*, 1967, **15**, 1310. D. N. Harpp and D. K. Ash, *Chem. Commun.*, 1970, 811; C. G. Moore and B. R. Trego, *Tetrahedron*, 1962, 205. For an extensive study of the thiol-disulphide interchange process, see: J. Houk and G. M. Whitesides, *J. Am. Chem. Soc.*, 1987, **109**, 6825. The analysis of the thermolysis and reduction mixture was readily achieved by ¹H n.m.r. spectroscopy: (9) δ 4.09 (CH₂Ph) and 3.50 (CH₂); (12) 3.91 (CH₂Ph) and 3.09 (CH₂); (22) 4.08 (CH₂Ph); (23) 2.55 (CH₂Ph); (26) 3.91 (CH₂Ph); see: D. Grant and J. R. Van Wazer, *J. Am. Chem. Soc.*, 1964, **86**, 3012.