Synthesis of the Esperamicin A_1/Calicheamicin γ-Trisulphide Functionality: Thermal Stability and Reduction

Philip Magnus,*† Richard T. Lewis, and Frank Bennett

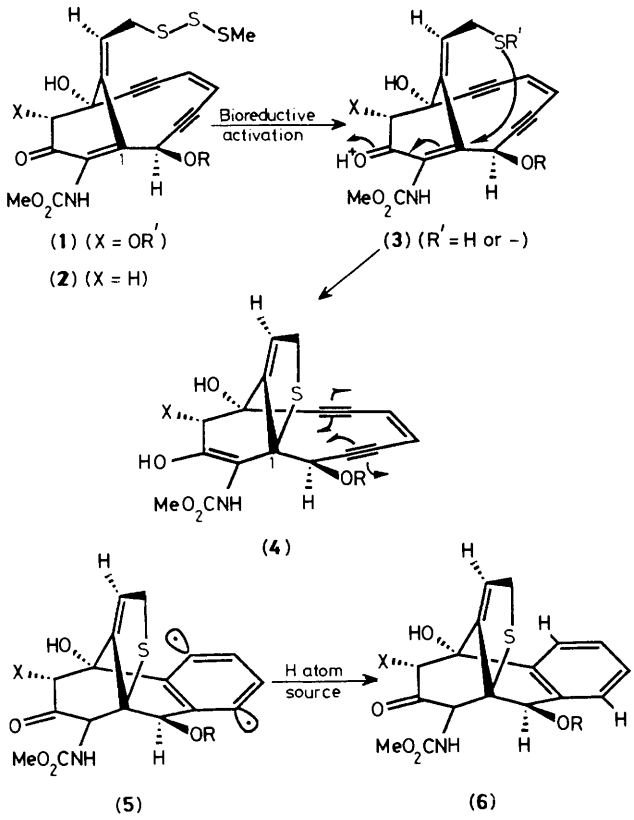
Department of Chemistry, Indiana University, Bloomington, Indiana 47405, U.S.A.

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 A_1 (**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 cyclization[3] 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] Porter[6] reported a splendidly economical experiment. Heating the bis-allylic trisulphide (**7**), (a *single* unspeci-

† Correspondence to the author at: Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712–1167, U.S.A.

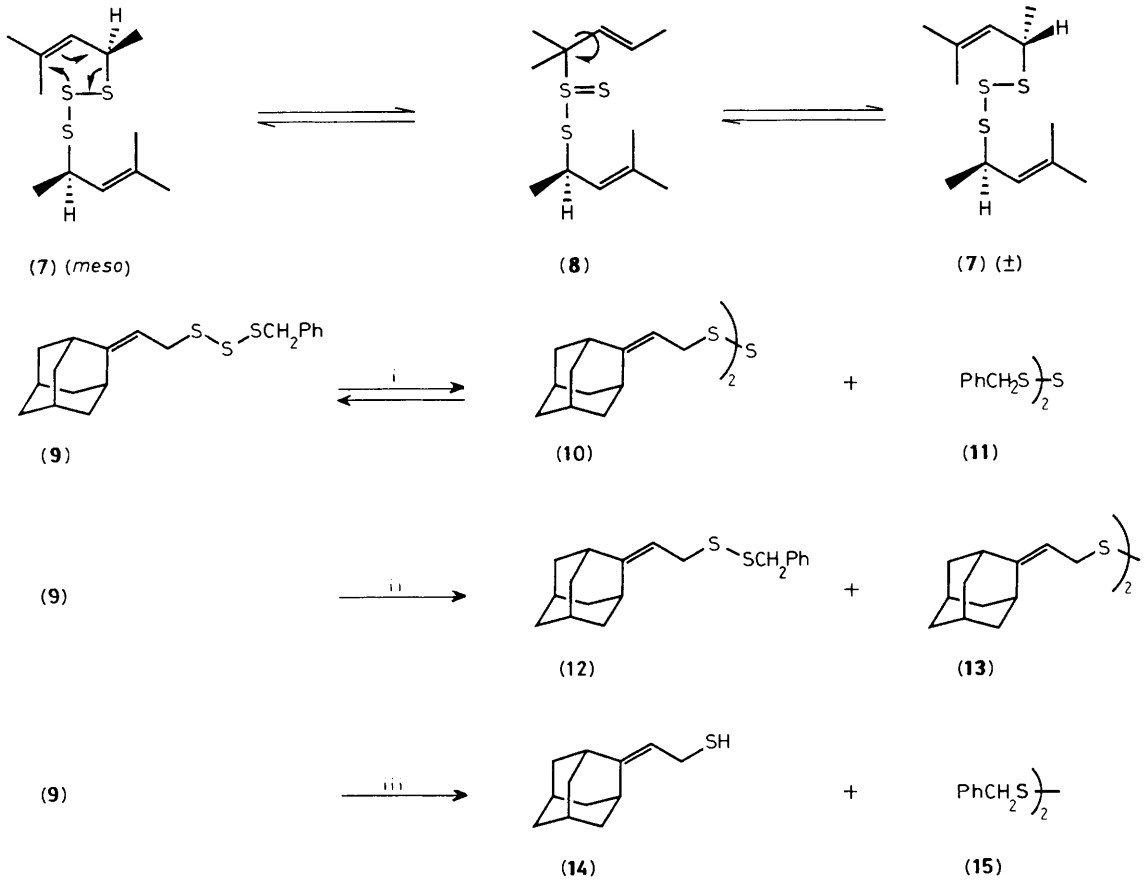


(1) (X = OR')
(2) (X = H)
(3) (R' = H or -)
(4)
(5)
(6)

Scheme 1

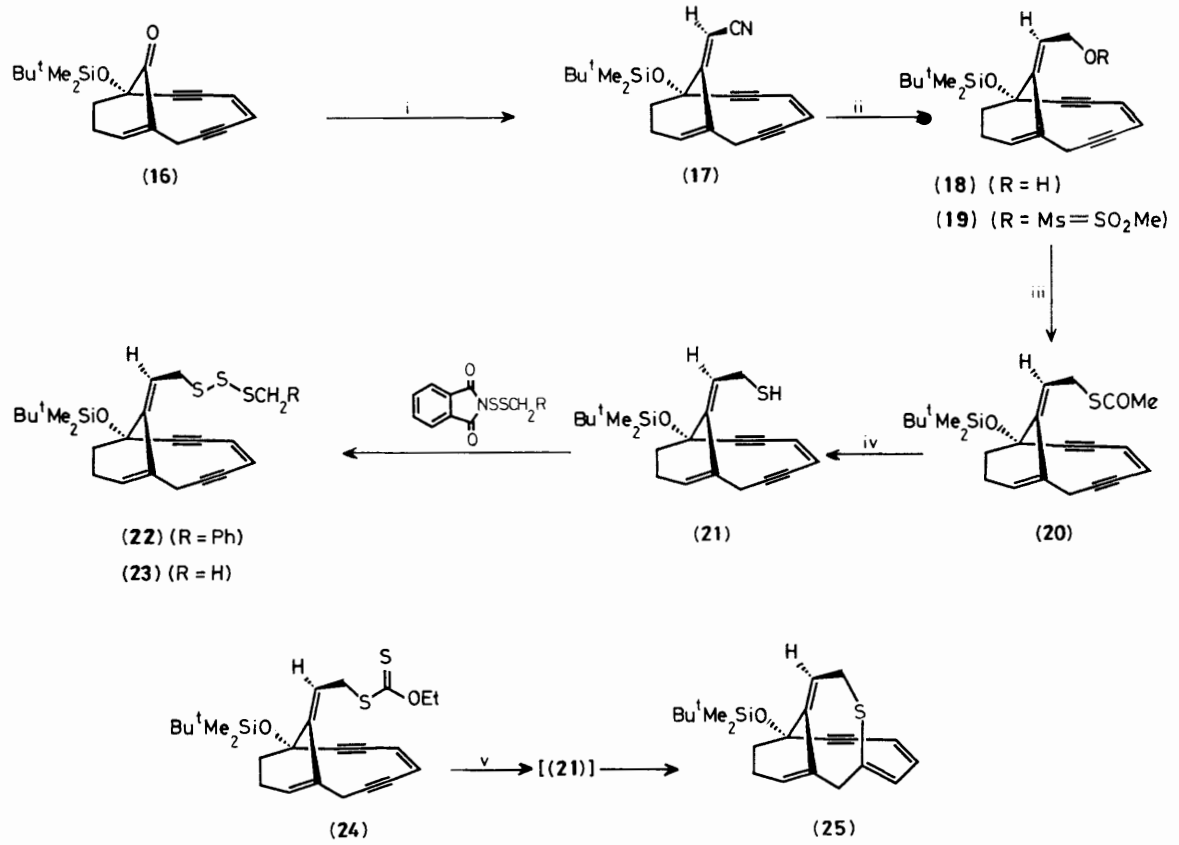
fied diastereoisomer, but probably the *meso*-isomer), at 75 °C resulted in rapid equilibration ($t_{1/2}$ 46.5 min) between the *meso*- and (±)-forms of (**7**) without detectable leakage to allylic rearranged trisulphides, disulphides, or disproportionation products. It was proposed that (**7**) undergoes a [2,3] sigmatropic rearrangement to (**8**). Baldwin[7] and Mislow[8] 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 azoisobutyronitrile (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 propanedithiol/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 Bu^i_2AlH/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%

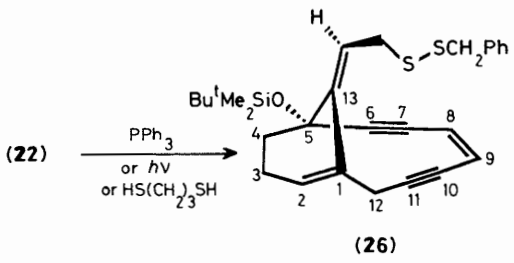


(7) (*meso*) (8) (7) (±)
(9) (10) (11)
(9) (12) (13)
(9) (14) (15)

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

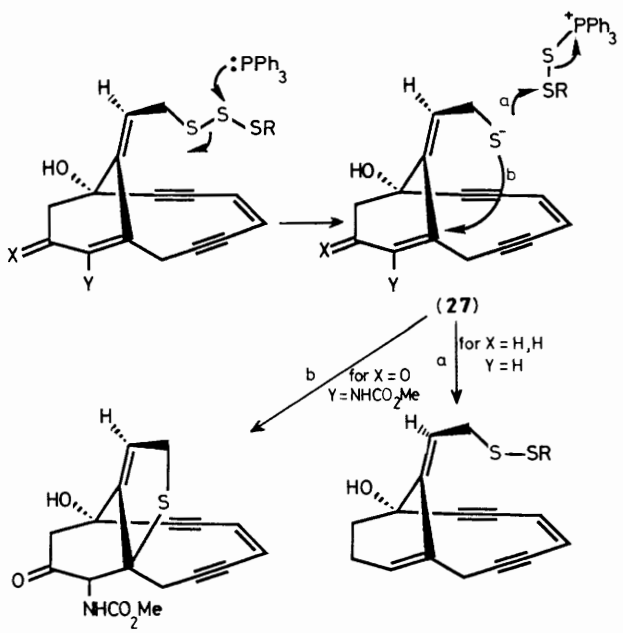


Reagents and conditions: i, $(EtO)_2P(O)CH_2CN$, NaH, dimethoxyethane (DME); ii, Bu^i_2AlH, PhMe, then HCl, H_2O, then Bu^i_2AlH, $MeSO_2Cl/Et_3N/DCM$; iii, NaSCOMe; iv, $LiAlH_4$, 0 °C, then Na_2HPO_4; v, $H_2NCH_2CH_2NH_2$.



from (**18**)]. Reduction of (**20**) using $LiAlH_4/Et_2O/0$ °C, and work-up with aqueous Na_2HPO_4 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 $[^2H_8]$toluene at 85 °C for 113 h produced no change. Exposure of (**22**) to PPh_3/CH_2Cl_2/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 PPh_3 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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