Total Synthesis of (5*S*)-Thiolactomycin: Revision of the Absolute Configuration of the Natural Product

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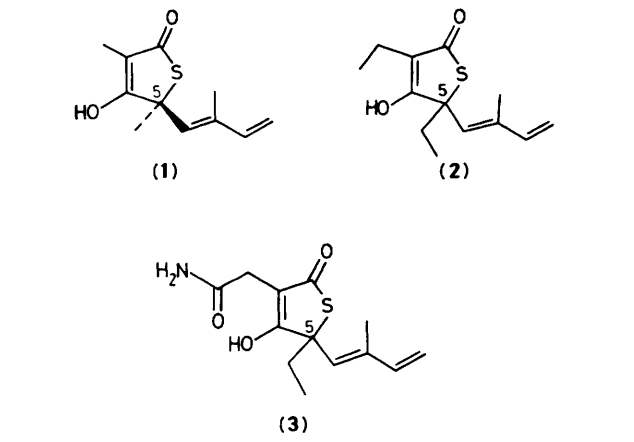
(5*S*)-Thiolactomycin (**1**) has been synthesized and found to be laevorotatory, $[\alpha]_D^{20}$ −172° (*c* 0.2, MeOH); the dextrorotatory natural product, $[\alpha]_D^{20}$ +176° (*c* 1.0, MeOH), is therefore the (5*R*)-enantiomer.

Recently a small group of antibacterial compounds has been isolated and identified as substituted thiotetronic acids. Members of this group include (+)-thiolactomycin (**1**),[1] (+)-thiotetromycin (**2**),[2] and U-68,204 (**3**).[3] Structures were assigned to these compounds on the basis of chemical and spectroscopic data, the structure of thiolactomycin being confirmed by an *X*-ray crystal determination which also indicated that the naturally occurring (+)-enantiomer had the (5*S*)-configuration shown in formula (**1**).[1]

A synthesis of racemic thiolactomycin was reported in 1984.[4] More recently an asymmetric approach to these compounds was developed[5] which was based on the use of a stereoselective allylic xanthate to allylic dithiocarbonate rearrangement. Thermolysis of the allylic xanthate (**6**) obtained from the (*S*)-lactate derived (4*S*)-hydroxypentenoate (**5**), gave the (2*S*)-dithiocarbonate (**7**). This was used to prepare the (5*S*)-thiotetronic acids (**8**)—(**10**) which were found to be laevorotatory. The (5*R*)-enantiomers (**14**) and (**15**) were also prepared from the (4*R*)-hydroxypentenoate (**11**), and the structure and absolute configuration of the (5*R*)-3-phenyl compound (**15**) was confirmed by *X*-ray crystallography (Scheme 1). We now report the application of this approach to a synthesis of (5*S*)-thiolactomycin (**1**).

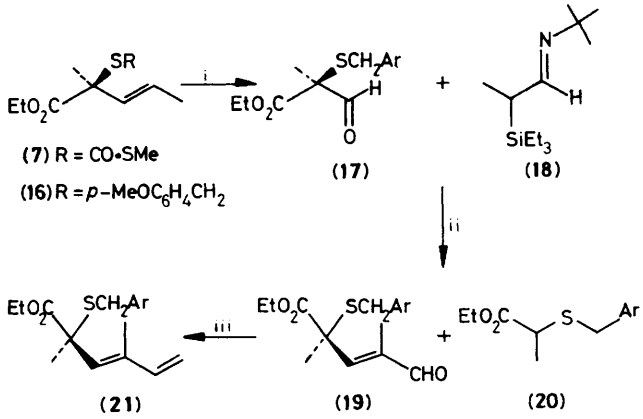


Scheme 1

Treatment of the (2*S*)-dithiocarbonate (**7**) with KOH in ethanol in the presence of *p*-methoxybenzyl chloride gave the corresponding sulphide (**16**) (99%).[5] Selective ozonolysis of this followed by decomposition of the ozonide with an excess of dimethyl sulphide gave the aldehyde (**17**) (75%) which was converted into the α,β-unsaturated aldehyde (**19**) by treatment with the lithium salt of 2-triethylsilylpropanal *N*-t-butylimine (**18**)[6] followed by hydrolysis. This gave the unsaturated aldehyde (**19**) in moderate yield (40—50%) together with the 2-(*p*-methoxybenzylthio)propanoate (**20**) (35%) formed by competing deformylation of the aldehyde (**17**). Wittig condensation of the unsaturated aldehyde (**19**) with triphenylphosphonium methylide then gave the diene ester (**21**) (75%) (Scheme 2).

Attempts to convert the diene ester (**21**) into the (5*S*)-thiolactomycin (**1**) were unsuccessful. Standard procedures[5] gave the keto-ester (**22**), but deprotection-cyclization gave no identifiable products (Scheme 3). It would appear that the conjugated diene fragment is incompatible with release of the free thiol.

To avoid this problem, the conjugated diene was hydroborated using 9-borabicyclo[3.3.1]nonane (9-BBN) to give the primary alcohol (**23**) after oxidation (70%). Conversion to the terminal selenide (**24**) was then effected using 4-chlorophenyl-



Scheme 2. *Reagents*: i, O_3 then Me_2S, 75%; ii, LDA then H_3O^+; iii, Ph_3PCH_2, 70%. Ar = *p*-$MeOC_6H_4$.

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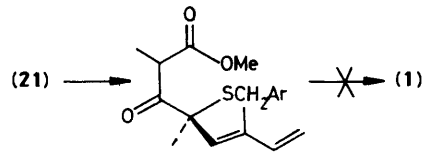
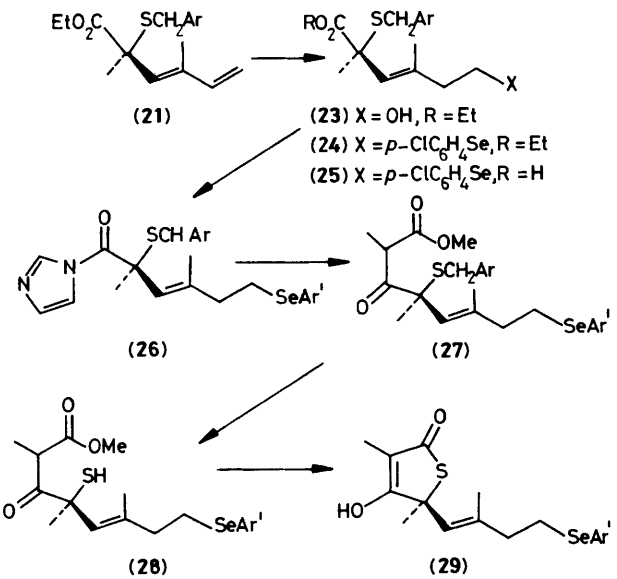


(22)

Scheme 3

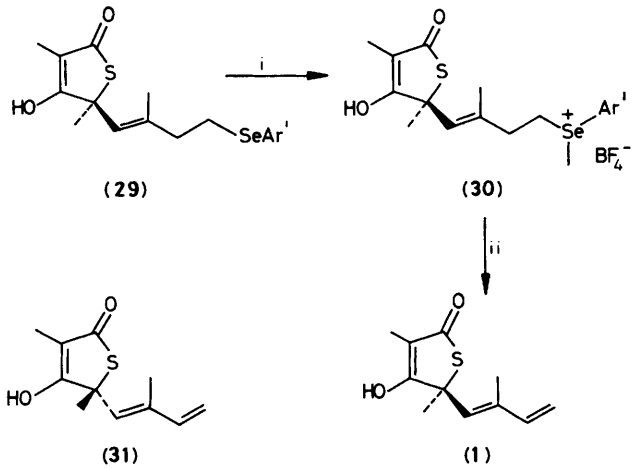


Scheme 4. Ar′ = p-ClC_6H_4.

selenocyanate and tributylphosphine (85%) and the ester converted into the acyl imidazolide (**26**) *via* hydrolysis and treatment of the acid (**25**) with N,N′-carbonyl di-imidazole. Condensation of this imidazolide with methyl propanoate gave the keto-ester (**27**) as a mixture of epimers, and this mixture was cyclized to the thiotetronic acid (**29**) by a two stage procedure involving treatment with trifluoroacetic acid-mercuric acetate-hydrogen sulphide to release the thiol (**28**) (58%) which was cyclized efficiently by KOH in EtOH (72%) (Scheme 4).

Attempts to eliminate the arylselenide substituent using oxidative procedures gave inconclusive results. However treatment with trimethyloxonium tetrafluoroborate[7] gave the selenonium salt (**30**) which was converted into (5*S*)-thiolactomycin using KOH in THF–DMSO (50% over the two steps) (Scheme 5).

The thiolactomycin so obtained had spectroscopic and physical properties identical to those reported for the natural product[1] except that it was laevorotatory, $[\alpha]_D^{20}$ −172° (*c* 0.2, MeOH). It was believed to be the (5*S*)-enantiomer (**1**) because of its mode of synthesis from (2*S*)-ethyl lactate (**4**),



Scheme 5. *Reagents*: i, $Me_3O^+BF_4^-$; ii, KOH, THF, Me_2SO.

and the assigned absolute configuration was consistent with the *X*-ray structure determination for the (5*R*)-thiotetronic acid (**15**).[5] The natural product is dextrorotatory and would therefore appear to be the (5*R*)-enantiomer (**31**).‡

This work completes the first asymmetric synthesis of a naturally occurring thiotetronic acid. All the (5*S*)-thiotetronic acids prepared during the course of this work, namely (**8**), (**9**), (**10**), and (**1**), have been laevorotatory, and so it would appear that the naturally occurring biologically active, dextrotatory enantiomers of thiotetramycin (**2**) and U-68,204 (**3**) are the (5*R*)-enantiomers.

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References

1 H. Sasaki, H. Oishi, T. Hayashi, I. Matsuura, K. Ando, and M. Sawada, *J. Antibiotics*, 1982, **35**, 396.
2 S. Omura, A. Nakagawa, R. Iwata, and A. Hatano, *J. Antibiotics*, 1983, **36**, 1781.
3 L. A. Dolak, T. M. Castle, S. E. Truesdell, and O. K. Sebek, *J. Antibiotics*, 1986, **39**, 26.
4 C.-L. Wang and J. M. Salvino, *Tetrahedron Lett.*, 1984, **25**, 5243.
5 M. S. Chambers, E. J. Thomas, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 1228.
6 R. H. Schlessinger, M. A. Poss, S. Richardson, and P. Lin, *Tetrahedron Lett.*, 1985, **26**, 2391.
7 P. G. Gassman, T. Miura, and A. Mossman, *J. Org. Chem.*, 1982, **47**, 954.

‡ This result now supersedes the original assignment (H. Sasaki, personal communication).