An Asymmetric Synthesis of Thiotetronic Acids using Chirality Transfer *via* an Allyl Xanthate-to-Dithiocarbonate Rearrangement. *X*-Ray Crystal Structure of (5*R*)-2,5-Dihydro-4-hydroxy-5-methyl-3-phenyl-5-prop-1′-enyl-2-oxothiophene

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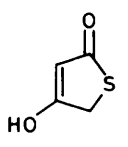
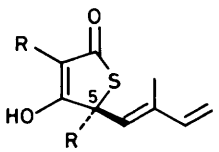
An asymmetric synthesis of thiotetronic acids has been developed which is based upon an allyl xanthate-to-dithiocarbonate rearrangement, the absolute configuration of the products being confirmed by an *X*-ray crystal structure determination.

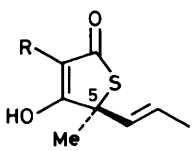
The chemistry of thiotetronic acids has been studied intermittently since Benary first synthesized the parent system (**1**) in 1913.[1] However interest in this area has recently increased because of the isolation and characterization of several thiotetronic acid antibiotics including thiolactomycin (**2**) and thiotetromycin (**3**).[2] Although a synthesis of racemic thiolactomycin has been reported,[3,4] no asymmetric synthesis of a chiral thiotetronic acid has been reported to date. We now describe a procedure for the asymmetric synthesis of thiotetronic acids as represented by the thiolactomycin analogues



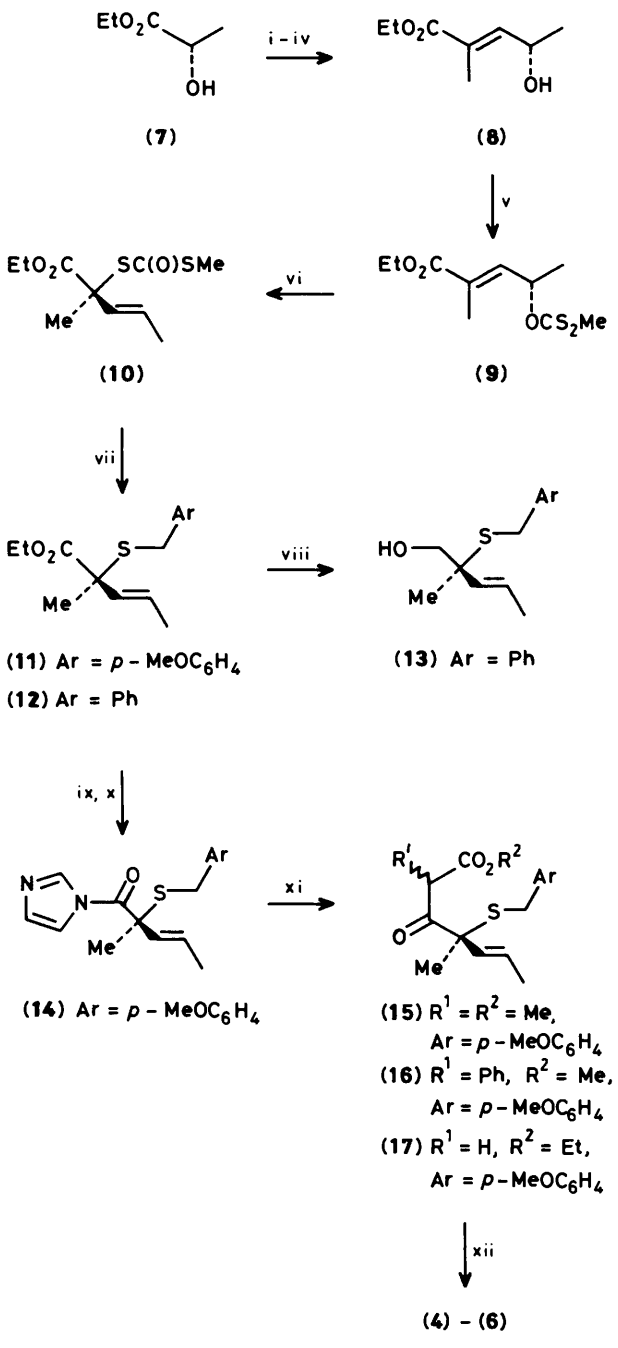
(**1**)



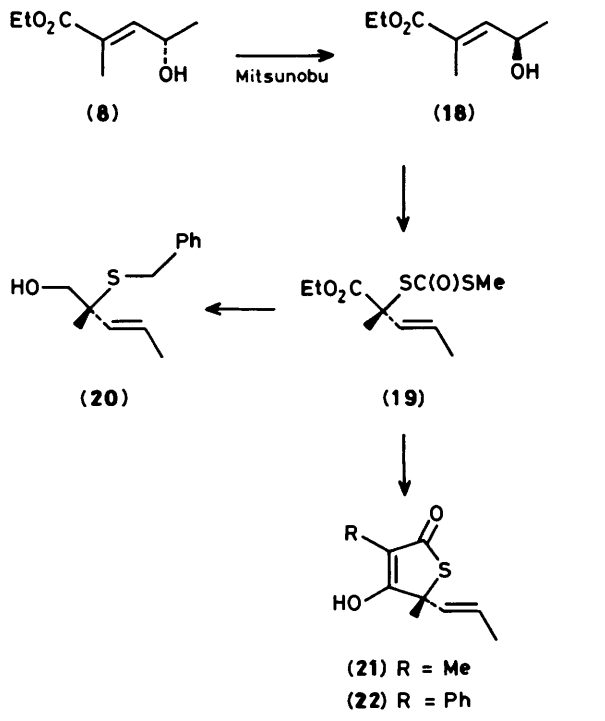
(**2**) R = Me
(**3**) R = Et



(**4**) R = Me
(**5**) R = Ph
(**6**) R = H



Scheme 1. *Reagents*: i, Bu^tMe_2SiCl, imidazole (99%), ii, DIBAL, −60 °C, 2.5 h (70%), iii, $Ph_3PC(Me)CO_2Et$ (87%); iv, NBu_4F, tetrahydrofuran (THF) (84%); v, NaH, CS_2, MeI (50—60%); vi, distil. b.p. 145 °C, 0.4 mmHg, (99%); vii, KOH, EtOH, $ArCH_2Cl$, 15 °C, 0.75 h (85—99%); viii, DIBAL (95%); ix, KOH, EtOH, 70 °C, (80%); x, carbonyldi-imidazole (95%); xi, $R^1CH_2CO_2R^2$, lithium isopropylcyclohexylamide (70%); xii, trifluoroacetic acid, 72 °C, 0.75—1.5 h (35—40%).



Scheme 2. Reagents as in Scheme 1.

(4)—(6). The key step in our synthesis is the introduction of the chiral centre at C(5) *via* the highly stereoselective rearrangement of an allylic xanthate.[5]

The chiral allylic xanthate (**9**) was prepared as shown in Scheme 1 from ethyl (*S*)-lactate (**7**) by OH protection, di-isobutylaluminium hydride (DIBAL) reduction, chain extension using a Wittig reaction, deprotection, and sequential treatment of the alcohol (**8**) with NaH, CS_2, and methyl iodide. Simple distillation of the xanthate (145 °C; 0.4 mmHg) caused rearrangement and gave the isomeric dithiocarbonate (**10**) in 99% yield. The rearrangement was found to be particularly stereoselective. Only the diastereoisomer shown, with the (*E*)-double bond, could be detected by high field (300 Mz) ^1H n.m.r. spectroscopy, and Mosher's derivatization of the derived alcohol (**13**) showed it to have an enantiomeric excess of at least 98% (see below). Also of interest is the efficiency of the rearrangement which introduced the sulphur substituent at a tertiary centre with concomitant deconjugation of the double bond.

Having obtained the tertiary thiol derivative (**10**) with a high enantiomeric excess, it was necessary to replace the relatively labile dithiocarbonate group with a more stable sulphur protecting group before proceeding with the synthesis. Thus treatment of the dithiocarbonate (**10**) with KOH in ethanol in the presence of *p*-methoxybenzyl chloride gave the corresponding sulphide (**11**) (*ca.* 99% yield). Ester saponification followed by treatment with carbonyl-1,1′-di-imidazole then gave the acyl imidazolide (**14**) which was treated with several different ester enolate anions to provide the keto-esters (**15**)—(**17**) (yields *ca.* 70%). Sulphur deprotection (CF_3CO_2H, 72 °C) was accompanied by cyclization of the intermediate thiols, and gave directly the thiotetronic acids (**4**)—(**6**).†

Structures were assigned to the thiotetronic acids (**4**)—(**6**) on the basis of spectroscopic data, and their optical purities were established by comparison with the enantiomeric series prepared from the (4*R*)-alcohol (**18**). Thus Mitsunobu inver-

† Optical rotations: (**4**) $[\alpha]_D^{20}$ −53.7° (*c* 0.74, MeOH); (**5**) $[\alpha]_D^{20}$ −75° (*c* 0.59, MeOH); (**6**) $[\alpha]_D^{20}$ −60.6° (*c* 1.30, MeOH).

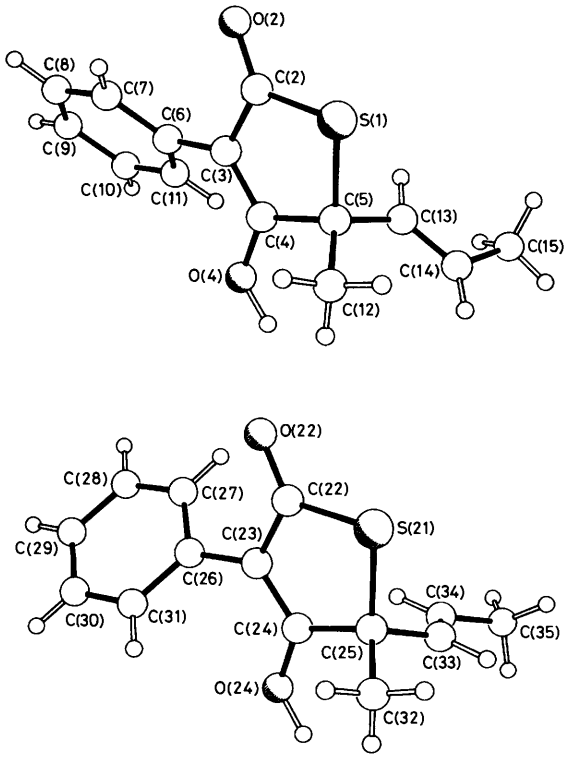


Figure 1. The two crystallographically independent conformations of (**22**) in the crystal. There are strong intermolecular hydrogen bonds between O(4) and O(22′), 2.59 Å [H(4) · · · O(22′) = 1.64 Å, O–H–O angle 162°] and between O(24) and O(2′), 2.63 Å [H(24) · · · O(2′) = 1.66 Å, O–H–O angle 172°].

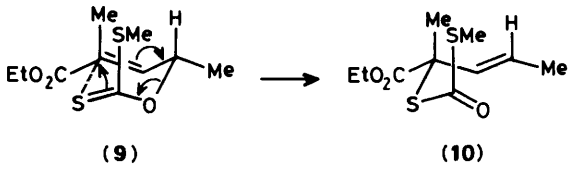


Figure 2. Chirality transfer from (**9**) to (**10**).

sion of the alcohol (**8**) gave (**18**) which was converted into the dithiocarbonate (**19**) *via* xanthate rearrangement (Scheme 2). The Mosher's derivative of the corresponding *S*-benzyl alcohol (**20**) was readily distinguished (high field ^{1}H n.m.r., ^{19}F n.m.r.) from that of the alcohol (**13**) and confirmed that both series were of high optical purity. The inverted dithiocarbonate (**19**) was used to prepare the (5*R*)-thiotetronic acids (**21**) and (**22**), and the absolute configuration of the 3-phenyl-(5*R*)-thiotetronic acid (**22**) was confirmed by an *X*-ray crystal structure determination.‡ Figure 1 shows projections of the two crystallographically independent molecules of (**22**), and illustrates the absolute configuration at C(5). The 3,3-sigmatropic rearrangement of the xanthate (**9**) to the dithiocarbonate (**10**) had therefore involved chirality transfer *via* a chair-like transition state as shown in Figure 2.

Although the 3-phenylthiotetronic acid (**5**) was found to be essentially 100% enolic in $CDCl_3$, the ^{1}H n.m.r. spectrum of the 3-methyl analogue (**4**) in this solvent showed minor peaks which were attributed to the 4-keto tautomers (**23**) [mixture of epimers at C(3)]. The 3-unsubstituted thiotetronic acid (**6**) was found to be exclusively ketonic in $CDCl_3$, *i.e.*, with stucture (**24**), and enolic in [$^2H_6$]dimethyl sulphoxide. In the past only enol tautomers have been described for thiotetronic acids.[6]

This work has opened up an approach for the asymmetric synthesis of thiotetronic acids related to the thiolactomycin and thiotetromycin antibiotics, and is being continued to provide access to the optically active antibiotics themselves.

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‡ *Crystal data*: $C_{14}H_{14}O_2S$, M = 246.3, monoclinic, a = 9.696(1), b = 12.094(2) c = 11.140(2)Å, β = 98.61(1)°, U = 1292 Å^3, space group $P2_1$, Z = 4 (2 independent molecules), D_c = 1.26 g cm^{-3}, μ(Cu-K_α) = 21 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically using absorption corrected data to give R = 0.034, R_w = 0.041 for 1788 independent observed reflections [$|F_o| \geq 3\sigma(|F_o|)$, $\theta \leq 58°$]. The absolute configuration was determined by (a) an R-factor test, (b) refinement of a free variable η which multiplies all f'', and (c) measurement of 20 selected Bijvoet pairs. All three methods gave consistent results. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.