Total Synthesis of the Structurally Unique Ionophore Antibiotic X–14547 A

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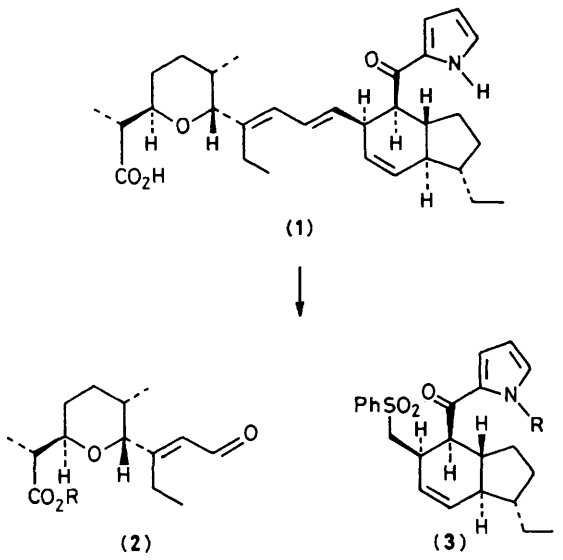
Using a convergent synthetic strategy a total synthesis of the novel ionophore antibiotic X–14547 A in its optically active form has been accomplished.

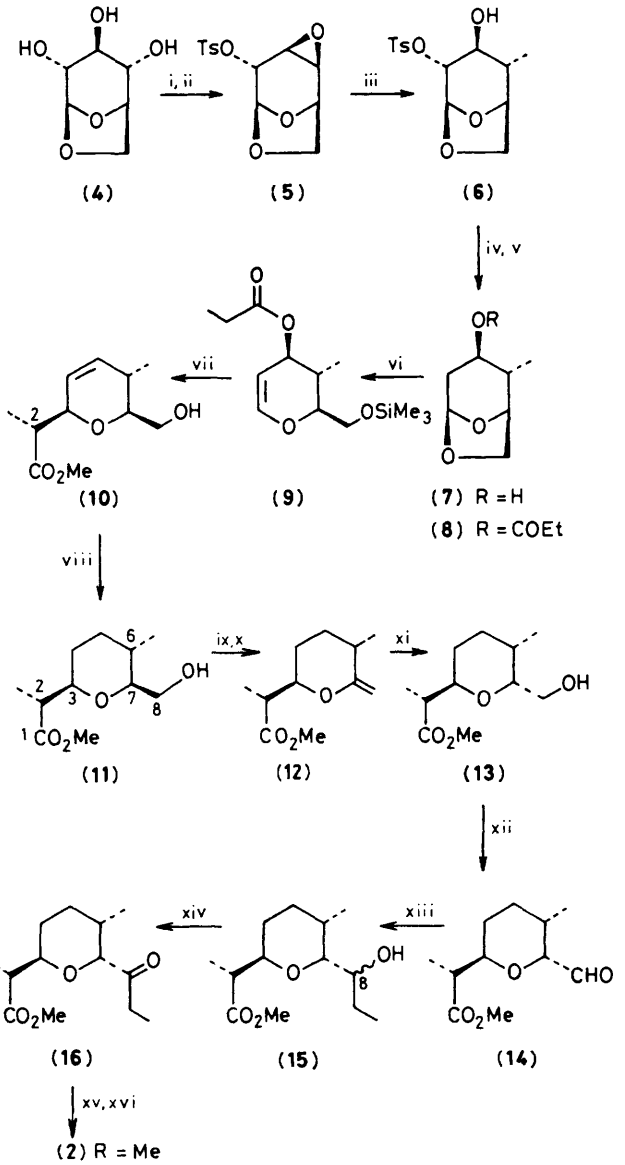
Naturally occurring antibiotics, with their wide range of structural and stereochemical features, continue to provide important, challenging synthetic targets. For example, the structurally unique carboxylic acid ionophore X-14547 A has been the subject of several investigations[1] since its isolation in 1978 from a strain of *Streptomyces antibioticus* (NRRL



8167).[2] X-14547 A, like only a few other natural ionophores (*e.g.*, lasalocid A) possesses the ability to transport divalent as well as monovalent cations. It also exhibits a range of biological activity including antibacterial, antitumour, and antihypertensive properties and promotes feed utilization in ruminants.

Our synthesis of X-14547 A (**1**) relies on the efficient, stereoselective coupling of two key chiral structural units designated as a left hand fragment (**2**) and a right hand fragment (**3**).

1,6-Anhydro-β-D-glucose† (**4**) (laevoglucosan) was chosen as the starting material for the synthesis of the left hand fragment. This was converted into the epoxy toluene-*p*-sulphonate (**5**) by treatment with toluene-*p*-sulphonyl chloride (2 equiv.), followed by reaction with sodium methoxide according to the literature conditions.[3] The epoxide ring in (**5**) was opened stereospecifically to give (**6**) in 86% yield by reaction with methylmagnesium chloride/copper(I) bromide–dimethyl sulphide at −10 °C in tetrahydrofuran (THF) over 4 days.[4]‡ Reduction of (**6**) with lithium triethylborohydride[5] gave (**7**) {95%, m.p. 73—76 °C, $[\alpha]_D^{25}$ −134.5° (*c* 1.87, $CHCl_3$)} which was converted into (**8**) in 97% yield by treatment with n-butyl-lithium at −78 °C, followed by quenching with propionyl chloride. The anhydrobridge in (**8**) was opened using iodotrimethylsilane at −35 °C. The presumed intermediate anomeric iodide was not isolated but was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at −35 °C and allowed to warm to room temperature to give (**9**) in 75% yield. Because of the instability of this compound it was used directly in the next step, in which chirality was transferred efficiently using the Claisen ester–enolate rearrangement recently reported by Ireland.[6] Thus reaction of (**9**) with lithium di-isopropylamide (LDA) in THF at −50 °C followed by silylation with chlorotrimethylsilane–Et_3N gave the intermediate *E*-ketene acetal.§ This was rearranged by warming in THF for 4 h and the product worked-up by brief fluoride treatment (using Bu^n_4NF) and methylation (using CH_2N_2) to give compound (**10**). This product was obtained together with the C-2 methyl epimer in the ratio 5:1, and in a combined yield of 67%. It was found more convenient to separate these diastereoisomers after hydrogenation using H_2–PtO_2 which then afforded pure (**11**) in 60% yield {$[\alpha]_D^{21}$ −6° (*c* 0.25, $CHCl_3$); ν_{max} 3560, 3490, and 1730 cm^{-1}; ^1H n.m.r. δ 0.82 (3H, d, *J* 6.57 Hz, C-6 Me), 1.12 (3H, d, *J* 7.06 Hz, C-2 Me), 1.2—1.33 (2H, m, 5-H), 1.61 (1H, m,

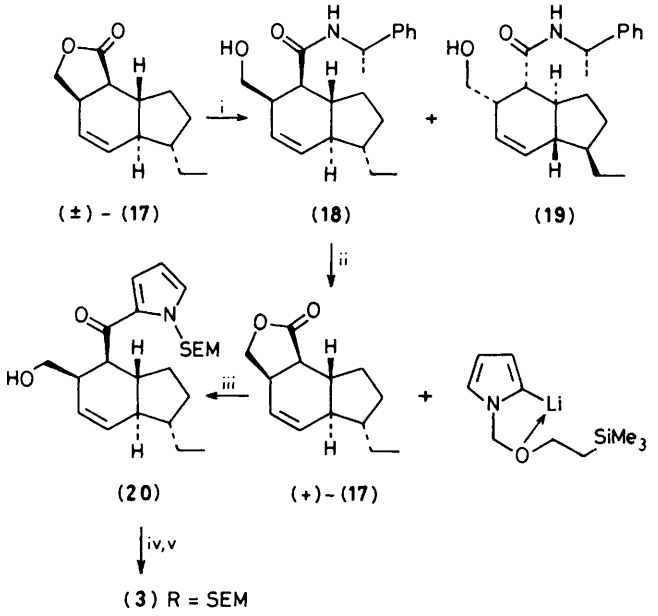


Scheme 1. Ts = *p*-$MeC_6H_4SO_2$. i, TsCl (2.0 equiv.), pyridine, 20 °C, 48 h; ii, NaOMe, MeOH (5.0 equiv.), 20 °C, 36 h; iii, MeMgCl (20.0 equiv.), CuBr·SMe_2 (10.0 equiv.), THF, −10 °C, 4 days; iv, $LiBHEt_3$ (3.4 equiv.), THF, 20 °C, 24 h; v, Bu^nLi (1.0 equiv.), THF, −78 °C, then $MeCH_2COCl$ (1.05 equiv.), 20 °C, 2 h; vi, Me_3SiI (2 equiv.), toluene, −35 °C, 4 h, then DBU (2.2 equiv.) and warm to room temp.; vii, LDA (6.7 equiv.), THF, −50 °C, 1 h, then Me_3SiCl (7.0 equiv.), Et_3N, 20 °C, 15 min; warm at 50 °C for 4 h; Bu^n_4NF and CH_2N_2 work-up; viii, PtO_2, H_2, EtOAc, 20 °C, 2 h; ix, Ph_3P (2.2 equiv.), imidazole (4.5 equiv.), I_2 (2.1 equiv.), benzene, 80 °C, 1.5 h; x, AgF (2.0 equiv.), pyridine, 20 °C, 24 h; xi, BH_3·THF (1.2 equiv.), THF, 20 °C, 1.5 h, then NaOH, H_2O_2; xii, PCC (2.0 equiv.), CH_2Cl_2, 20 °C, 48 h; xiii, EtMgBr (1.1 equiv.), THF, −30 °C, 15 min; xiv, H_2CrO_4 (1.0 equiv.), acetone, 20 °C, 15 min; xv, CH_2:CHMgBr (1.1 equiv.), THF, −30 °C, 10 min; xvi, PCC (4.8 equiv.), CH_2Cl_2, 40 °C, 5 h.

† The structurally rigid and readily available laevoglucosan is an ideal carbohydrate building block for natural product synthesis. Further uses will be reported at a later date.

‡ All new compounds were fully characterised by spectroscopic methods, elemental microanalysis, and/or accurate mass measurements.

§ The *E*-assignment was made by analogy with Ireland's work[6] and not by independent determination.



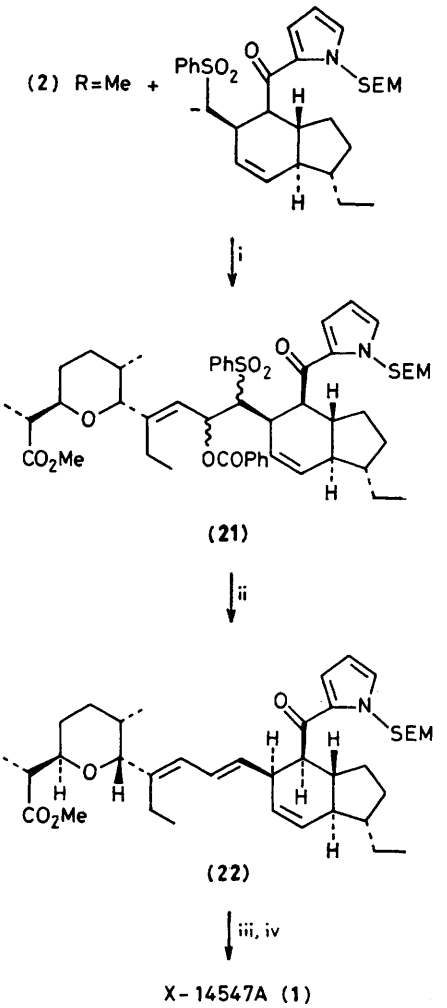
Scheme 2. i, $PhCHMeNH_2$ (2.0 equiv.), 2-hydroxypyridine (1.0 equiv.), toluene, 110 °C, 6 h; ii, 0.5 M H_2SO_4, dioxan–H_2O, 1 h; iii, 2-lithio-*N*-SEM-pyrrole (2.0 equiv.), DME, 0—20 °C, 5 min; iv, NPSS (1.6 equiv.), Bu^n_3P (1.6 equiv.), benzene, 20 °C, 3 h; v, H_2O_2 (6.0 equiv.), $(PhSe)_2$, CH_2Cl_2–Et_2O, 20 °C, 7 h.

6-H), 1.67—1.86 (2H, m, 4-H), 2.10 (1H, br., OH), 2.54 (1H, dq, $J_{2\text{-Me}}$ 7.06 and $J_{2,3}$ 8.19 Hz, 2-H), 3.09 (1H, ddd, $J_{6,7}$ 9.80, $J_{7,8}$ 2.6, $J_{7,8'}$ 7.23 Hz, 7-H), 3.48 (2H, m, 3,8-H), 3.68 (1H, m, 8'-H), and 3.69 (3H, s, CO_2Me)}.

Epimerisation at the C-7 position of (**11**) was achieved by transforming the alcohol (**11**) into the corresponding iodide (using I_2–Ph_3P) in 85% yield followed by facile elimination of HI using silver fluoride in pyridine[7] to provide the enol ether (**12**) (96%). Hydroboration of (**12**) with BH_3·THF at room temperature and oxidation with basic hydrogen peroxide gave (**13**) in 55% overall yield from the iodide.¶ The epimeric alcohol (**11**), also formed in this reaction, was recycled to afford a further quantity of (**13**) (15%).

The remaining steps to the left hand fragment were straightforward. Oxidation of (**13**) with pyridinium chlorochromate (PCC) in CH_2Cl_2 gave the aldehyde (**14**) in 62% yield, with no observable epimerisation at C-7. Treatment of (**14**) with ethylmagnesium bromide at −30 °C in THF gave the C-8 diastereoisomeric alcohols (**15**) in the ratio 1.6:1 (*i.e.*, very little chelation control) in 55% yield. Oxidation with Jones' reagent gave the ethyl ketone (**16**) in 96% yield. This ketone had previously been prepared by a different route and converted into the left hand fragment (**2**) in 70% yield by reaction with vinylmagnesium bromide and oxidative rearrangement with PCC[1b]** (Scheme 1). The enal (**2**; R = Me) was identical in all respects to a sample prepared from methylated X-14547 A by ozonolysis at −78 °C (95%) {m.p. 75—78.5 °C, $[\alpha]_D^{22}$ −44.5° (*c* 0.85, $CHCl_3$)}.

We had previously developed an efficient, highly stereoselective, multigram, route to the racemic tricyclic lactone (**17**) using an intramolecular Diels–Alder reaction as the key step.[1a] Synthesis of the optically pure right hand fragment was therefore achieved by resolution of this lactone (**17**). Reaction of (±)-(**17**) with *S*-(−)-α-phenylethylamine in the presence of 2-hydroxypyridine[8] gave a diastereoisomeric mixture of lactams which were readily separated by flash chromatography to provide (**18**) and (**19**) in 49 and 47% yields, respectively. Hydrolysis of (**18**) with 0.5 M sulphuric acid in dioxane at 80 °C gave the optically pure (+) tricyclic lactone (**17**) {98%, $[\alpha]_D^{25}$ + 136° (*c* 1.02, $CHCl_3$), (lit.[1e] $[\alpha]_D^{25}$ + 113°)}.



Scheme 3. i, THF–HMPA, −78 °C, 45 min, then PhC(O)Cl (2.0 equiv.), 20 °C, 2 h; ii, Na–Hg (8 equiv.), THF–MeOH, −20 °C, 3 h; iii, Bu^n_4NF (10 equiv.), THF, 0—20 °C, 45 min; iv, NaOH (20 equiv.), MeOH–H_2O, 60 °C, 3 h.

Elaboration of the lactone (**17**) to an appropriately substituted right hand fragment required a 2-pyrrole anion equivalent which would be compatible with later synthetic steps. As none of the literature procedures seemed satisfactory, a new reagent was developed. We found that *N*-β-trimethylsilylethoxymethyl pyrrole (*N*-SEM-pyrrole) could be lithiated in the 2-position with n-butyl-lithium in dimethoxyethane (DME) at 0 °C. Reaction of this 2-lithiopyrrole with the (+) lactone (**17**) gave the alcohol (**20**) in 62% yield. Conversion of the hydroxy group in (**20**) into phenylsulphone and hence the right hand fragment (**3**; R = SEM) was achieved by formation of the phenylsulphide, by reaction with *N*-phenylsulphenylsuccinimide (NPSS)–Bu^n_3P,[9] followed by oxidation with $(PhSe)_2$–H_2O_2[10] to give (**3**; R = SEM) in

¶ Other hydroborating reagents were less successful in producing the required isomer (**13**).

** In our hands this reaction was less stereoselective and afforded an *E*:*Z* ratio of 3:1 as opposed to the literature ratio of 6:1.

56% overall yield {$[\alpha]_D^{25}$ −79° (*c* 1.05, $CHCl_3$); ν_{max} 1635, 1520 cm^{-1}; ^1H n.m.r. δ −0.2 (9H, s), 0.85 (2H, m, CH_2SiMe_3), 0.9 (3H, t, *J* 7 Hz), 0.9—2.0 (9H, m), 3.1 (1H, m, CH_2SO_2Ph), 3.13 (1H, m, 5-H), 3.43 (1H, m, CH_2SO_2Ph), 3.44 (1H, m, 4-H), 3.52 (2H, m, CH_2O), 5.55 and 5.73 (both 1H, d, *J* 9.8 Hz, NCH_2O), 5.96 (2H, m, 6-H and 7-H), 6.13 (1H, dd, *J* 4.3 and 2.4 Hz, pyrrole C-4′-H), 6.88 (1H, dd, *J* 4.3 and 1.2 Hz, C-3′-H), 7.08 (1H, dd, *J* 2.4 and 1.2 Hz, C-5′-H), 7.35—7.55 (5H, m)} (Scheme 2).

Coupling of the fragments (**2**; R = Me) and (**3**; R = SEM) was achieved using the Lythgoe–Kocienski modification[11] of the Julia reaction. Treatment of the sulphone (**3**; R = SEM) with n-butyl-lithium in THF–hexamethylphosphoramide (HMPA) at −78 °C gave the corresponding anion which was allowed to react with the enal (**2**; R = Me) and the product trapped with benzoyl chloride to give a diastereoisomeric mixture of benzoyloxy-sulphones (**21**). Stereospecific reduction with sodium amalgam in methanol–THF at −20 °C then afforded the desired *E,E*-diene (**22**) in 53% overall yield. Removal of the SEM protecting group from (**22**) required reaction with 3 M tetra-n-butylammonium fluoride in THF and proceeded in 72% yield. Finally hydrolysis of the methyl ester was most conveniently accomplished using aqueous sodium hydroxide in methanol to give X-14547 A (**1**) in 90% yield (Scheme 3). The synthesised material was identical in all respects (^1H n.m.r., t.l.c., i.r., m.p., and optical rotation) to the natural product.

The above synthesis is sufficiently flexible to provide a range of structural analogues of X-14547 A for biological studies.

We thank the S.E.R.C. and Pfizer Central Research, Sandwich, Kent, U.K. for financial support, the Royal Society of Chemistry for the Hickinbottom Research Award (to S. V. L.), Dr. G. E. Hawkes, Queen Mary College, London for high field ^1H n.m.r. experiments, Professor M. Černý, Charles University, Praha, Czechoslovakia, for generous supplies of the epoxy toluene-*p*-sulphonate (**5**), and Dr. J. W. Westley, Hoffmann-La Roche, Nutley, New Jersey, U.S.A. for quantities of X-14547 A.

Received, 9th March 1983; Com. 315

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