Novel Rearrangement of the Ionophore Antibiotic X-14547A (Indanomycin) and related Derivatives induced by Lithium Tetrafluoroborate

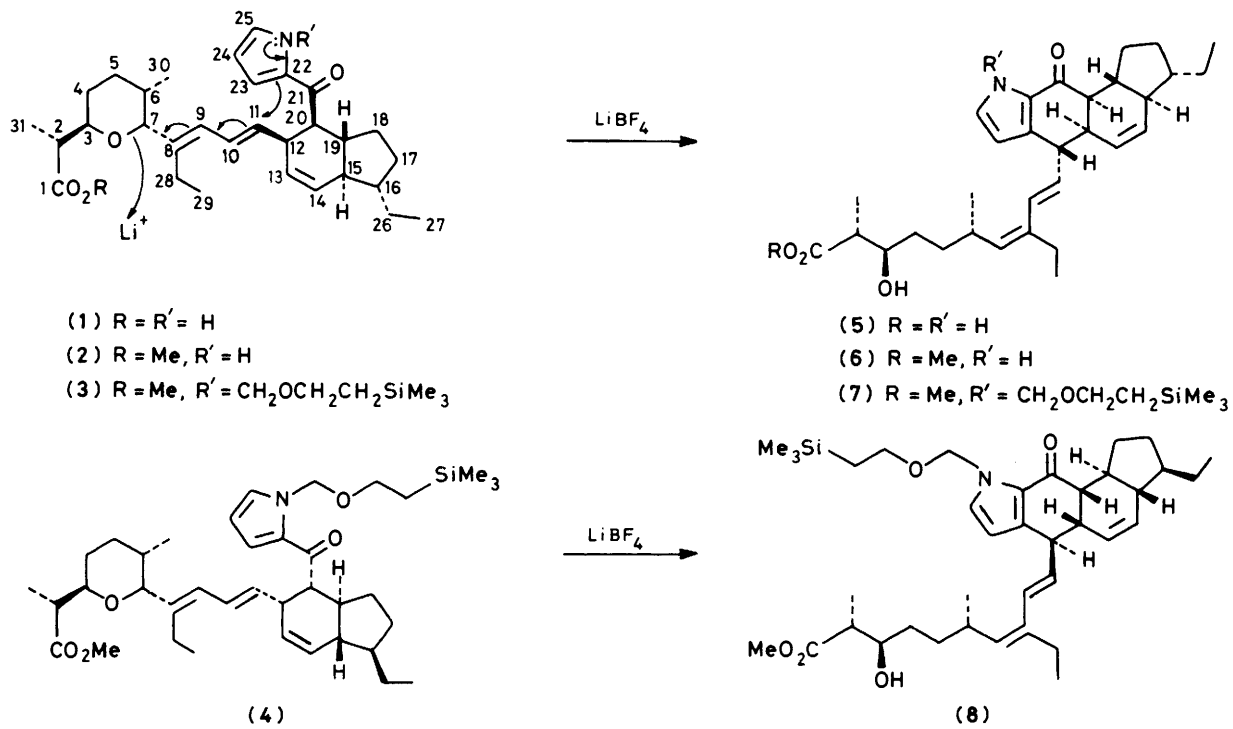
Martin P. Edwards and Steven V. Ley*
Department of Chemistry, Imperial College, London, SW7 2AY

Stereospecific rearrangement of the ionophore antibiotic X-14547A (indanomycin) and related derivatives, occurs readily at 70 °C in acetonitrile solution containing lithium tetrafluoroborate. The product of the reaction is a novel tetracyclic compound derived by ring cleavage of the tetrahydropyranyl ring, with concomitant double-bond migration and intramolecular cyclisation involving a pyrrole group.

Despite the fact that the synthesis and properties of the ionophore antibiotics have been extensively studied,[1] rearrangement reactions of these species, especially in the presence of metal ions, appear to be rare.[2] During our studies on the total synthesis of indanomycin (**1**),[3,†] we noticed an unusual rearrangement reaction the details of which we report here.

Typically we find that indanomycin (**1**)[4] and the related derivatives (**2**), (**3**), and (**4**),[3] undergo rearrangement in dry acetonitrile at 70 °C in the presence of 10 equiv. of lithium tetrafluoroborate, to afford the unusual tetracyclic products (**5**), (**6**), (**7**), and (**8**) respectively (Scheme). The yields and detailed reaction conditions for these rearrangements are as shown in the Table. The choice of lithium tetrafluoroborate as a catalyst for this rearrangement was a chance discovery in that we had intended this to be a method for the selective removal of the trimethylsilylethoxymethyl (SEM) protecting group[5] from compound (**3**).

Owing to the fact that none of the products were crystalline,‡ their structures were derived by spectroscopic analysis. For example the i.r. spectrum of compound (**7**) showed bands corresponding to the methyl ester group ($\nu_{max.}$ 1 725 cm^{-1}), the pyrrolylcarbonyl group ($\nu_{max.}$ 1 645 cm^{-1}) and the hydroxy group ($\nu_{max.}$ 3 440 cm^{-1}). The highfield ^1H n.m.r. spectrum at 400 MHz showed resonances at δ 6.58 and 6.69 as two doublets, (*J* 3 Hz) corresponding to two pyrrole protons. Also resonances at δ 5.82 and 5.97, with a coupling constant (amongst others) of 10 Hz, are expected for the *cis*-arrangement of protons at 13-H and 14-H and thus indicated that the tetrahydroindan portion of the molecule was intact. The remaining olefinic resonances at δ 5.20 (d, *J* 10 Hz 7-H), 5.48 (dd, *J* 16 and 9.5 Hz, 10-H) and 6.13 (d, *J* 16 Hz, 9-H) are all consistent with the assigned structure. The spectrum also indicated that there was only one proton on a carbon atom adjacent to a hydroxy group at δ 3.64. Characteristic resonances were also observed for two methyl groups at C-30 and C-31, the trimethylsilylethoxymethyl



(1) R = R′ = H
(2) R = Me, R′ = H
(3) R = Me, R′ = $CH_2OCH_2CH_2SiMe_3$
(4)
(5) R = R′ = H
(6) R = Me, R′ = H
(7) R = Me, R′ = $CH_2OCH_2CH_2SiMe_3$
(8)

Scheme.

† Following discussions with Dr. J. W. Westley, Hoffmann-La Roche, Nutley, New Jersey, USA we propose the trivial name indanomycin for this ionophore antibiotic.

‡ Efforts to prepare novel crystalline metal complexed indanomycin derivatives are currently underway in our laboratories.

Table. Rearrangement of indanomycin and derivatives with $LiBF_4$

Starting material	Product	Reaction time	Yield (%)
(1)	(5)	1 h	85
(2)	(6)	40 min	63
(3)	(7)	2 h	55
(4)	(8)	3 h	44

protecting group and the methyl ester. The coupling constants for the absorption attributed to the proton at C-11 in compound (3) ($J_{10,11}$ 9.5 and $J_{11,12}$ 10 Hz) strongly indicated a *trans*-disposition relative to the C-12 proton.

In all the rearrangement reactions studied, only one product was formed which suggests that the reactions proceed in a highly stereoselective fashion. It is proposed that initial lithium cation complexation* occurs at the tetrahydropyranyl oxygen atom which is followed by synchronous rupture of the C–7 to oxygen bond, migration of the double bonds of the buta-1,3-dienyl unit, and bond formation between C-11 and the nucleophilic C-23 pyrrole carbon atom. Although indanomycin (1) is known to adopt a stable conformation in which the 6-methyl and 2-propionic acid residues of the tetrahydropyran ring are in axial environments and that (1) will also form a 2:1 complex with *R*-(+)-1-amino-1-(4-bromophenyl)ethane,[4b] the conformation in solution, in the presence of an excess of lithium cations, as in the above rearrangement reactions, is difficult to predict. From the very high stereoselectivity observed in these reactions it is clear that intimate binding and complex transition states are likely to be involved. Nevertheless the above rearrangement reactions are interesting and potentially have important implications concerning the ability of (1) to transport metal atoms in biological environments.

Experimental

I.r. spectra were recorded for solutions in chloroform on a Perkin-Elmer 298 instrument. ^1H N.m.r. spectra were recorded at 400 MHz on a Bruker WH400 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard. Mass spectra were determined with a VG Micromass 7070B instrument and optical rotations on a Perkin-Elmer 141 polarimeter. Analytical t.l.c. was performed on Merck pre-coated silica gel F_{254} plates and column chromatography on MN-Kieselgel 60 or Merck 9385 Kieselgel 60 both 230—400 mesh. All solvents were dried by standard methods. Light petroleum refers to the fraction with b.p. 40—60 °C.

Rearrangement of X-14547A(1) (*Indanomycin*).—X-14547A(1) (0.1 g, 2.03×10^{-4} mole was stirred with anhydrous lithium tetrafluoroborate (0.192 g, 20.3×10^{-3} mol, 10 equiv.) in dry acetonitrile (2.1 ml), at 70 °C, for 1 h. The reaction mixture was diluted with dichloromethane (35 ml) and water 50 ml). The organic phase was combined with dichloromethane (2 × 25 ml) extracts of the aqueous phase, washed with 10% aqueous hydrochloric acid (50 ml) and brine (50 ml), before being dried and concentrated under reduced pressure to give a pale yellow glassy solid. Flash chromatography (5 in silica, 10 mm diam. column) with a gradient of 5% methanol–diethyl ether up to 90% methanol–diethyl ether, followed by filtration of a dichloromethane (5 ml) solution of the concentrated fractions through sodium sulphate (1 in) in a Pasteur pipette to remove methanol-dissolved silica, gave the tetracycle (5) (85 mg, 1.72×10^{-4} mol, 85%), as a pale yellow glass that resisted crystallisation attempts; R_F 0.39, 5% methanol–diethyl ether, $[\alpha]_D^{25}$ −10° (*c* 1.0, $CHCl_3$), $\nu_{max.}$ 3 460, 3 300, 1 710, and 1 645 cm^{-1}; δ (400 MHz) 0.85 (3 H, t, *J* 7.5 Hz, 27-methyl), 0.8—1.9 (22 H, m), 2.25 (2 H, m, 28-methylene), 2.4—2.6 (3 H, m), 2.8 (1 H, m, 2-H), 3.42 (1 H, dd, *J* 10 and 9.5 Hz 11-H), 3.64 (1 H, m, 3-H), 5.2 (1 H, d, *J* 10 Hz), 5.45 (1 H, dd, *J* 16 and 9 Hz, 10-H), 5.73 (1 H, br d, *J* 10 Hz, 13-H), 5.97 (1 H, d, *J* 10 Hz, 14-H), 6.2 (1 H, d, *J* 16 Hz, 9-H), 6.6 (1 H, br s, 24-H), and 8.65 (1 H, br s, NH) (CO_2H proton not assignable).

Rearrangement of the Methyl Ester (2).—The methyl ester (2)[3] (20 mg, 3.94×10^{-5} mol) was stirred with anhydrous lithium tetrafluoroborate (37.3 mg, 3.94×10^{-4} mol, 10 equiv.) in dry acetonitrile (0.42 ml), at 70 °C, for 40 min. The reaction mixture was poured into diethyl ether (50 ml) and washed with water (2 × 10 ml) before being dried and concentrated under reduced pressure to give a dark brown gum. Microchromatography in a Pasteur pipette containing Kieselgel ($2\frac{1}{2}$ in Merck 9385) with 50% ethyl acetate–light petroleum gave the tetracycle (6) (12.6 mg, 2.48×10^{-5} mol, 63%), as a colourless glass; R_F 0.3, diethyl ether, $[\alpha]_D^{25}$ −36.2° (*c* 1.26, $CHCl_3$), $\nu_{max.}$ 3 440, 3 380, 1 725, and 1 645 cm^{-1}; δ (400 MHz) 0.92 (3 H, t, *J* 7.5 Hz, 27-Me), 1.02 (3 H, d, *J* 7 Hz, 30-Me), 1.05 (3 H, t, *J* 7.5 Hz, 29-Me), 1.22 (3 H, d, *J* H_3, 31-Me), 1.15—1.93 (13 H, m), 2.27 (2 H, m, 28-CH_2), 2.5 (1 H, m, 12-H), 2.54 (1 H, qd, *J* 7 and 6 Hz), 2.6 (1 H, dd, *J* 11 and 5.5 Hz), 2.64 (1 H, br s, OH), 2.85 (1 H, m, 2-H), 3.45 (1 H, dd, *J* 10 and 9 Hz, 11-H), 3.65 (1 H, m, 3-H), 3.73 (3 H, s, CO_2CH_3), 5.23 (1 H, d, *J* 10 Hz, 7-H), 5.47 (1 H, dd, *J* 16 and 9 Hz, 10-H), 5.73 (1 H, ddd, *J* 10, 4.5 and 2.5 Hz, 13-H), 5.97 (1 H, d, *J* 10 Hz, 14-H), 6.2 (1 H, d, *J* 16 Hz, 9-H), 6.61 (1 H, dd, *J* 3 and 2.5 Hz, 24-H), and 6.72 (1 H, dd, *J* 3 and 2 Hz, 24-H), and 8.3 (1 H, br s, NH) (Found: M^+, 507.3336. $C_{32}H_{45}NO_4$ requires *M*, 507.3346).

Rearrangement of the Methyl Ester (3).—(−)-Methyl 2-{(2*R*)-[6-(6-{(1*S*,3a*R*,5*R*,7a*R*)-1-ethyl-2,3,3a,4,5,7a-hexahydro-4-[*N*-(2-trimethylsilylethoxymethyl)pyrrol-2-ylcarbonyl]-indan-5-yl}hexa-3*E*,5*E*-dien-3-yl)]}-[(2R,5*S*,6*R*)-pyran-2-yl]-propionate (3)[3] (16 mg, 2.5×10^{-5} mol) was stirred with anhydrous lithium tetrafluoroborate (24 mg, 2.5×10^{-4} mol, 10 equiv.) in dry acetonitrile (0.263 ml) at 70 °C for 2 h. Work-up and microchromatography, as above gave the tetracycle (7) (8.8 mg, 1.38×10^{-5} mol, 55%) as a colourless gum, R_F 0.16, 90% diethyl ether–light petroleum, $[\alpha]_D^{25}$ *ca.* 0 °C (*c* 0.88, $CHCl_3$), $\nu_{max.}$ 3 480, 1 725, and 1 645 cm^{-1}; δ (400 MHz) 0.0 (9 H, s), 0.85 (2 H, m, CH_2SiMe_3), 0.92 (3 H, t, *J* 7.5 Hz, 27-Me), 1.1 (3 H, t, *J* 7.5 Hz, 29-Me), 1.1 (3 H, d, *J* 7 Hz, 30-Me), 1.2 (3 H, d, *J* 7 Hz, 31-Me), 1.15—1.19 (13 H, m), 2.25 (2 H, m, 28-CH_2), 2.48 (1 H, m), 2.51 (1 H, m), 2.55 (1 H, dd, *J* 3 and 2.5 Hz), 2.57 (1 H, d, *J* 6 Hz), 2.77 (1 H, m, 2-H), 3.4 (2 H, m, CH_2O), 3.5 (1 H, dd, *J* 10 and 9.5 Hz, 11-H), 3.65 (1 H, m, 3-H), 3.71 (3 H, s, CO_2CH_3), 5.0 (1 H, d, *J* 10 Hz, CH_2N), 5.2 (1 H, d, *J* 10 Hz, 7-H), 5.42 (1 H, d, *J* 10 Hz, CH_2N), 5.48 (1 H, dd, *J* 16 and 9.5 Hz, 10-H), 5.82 (1 H, ddd, *J* 10, 4.5 and 2.5 Hz, 13-H), 5.97 (1 H, d, *J* 10 Hz, 14-H), 6.13 (1 H, d, *J* 16 Hz, 9-H), 6.58 (1 H, d, *J* 3 Hz, 24-H), and 6.69 (1 H, d, *J* 3 Hz, 24-H) (Found: M^+, 637.4157. $C_{38}H_{59}NO_5Si$ requires *M*, 637.4159).

Rearrangement of the Diastereoisomer Methyl Ester (4).—(−)-Methyl 2-{(2*R*)-[6-(6-{(1*R*,3a*S*,5*S*,7a*S*)-1-ethyl-2,3,3a,4,5,7a-hexahydro-4-[*N*-(2-trimethylsilylethoxymethoxy)pyrrol-2-ylcarbonyl] indan-5-yl}hexa-3*E*,5*E*-dien-3-yl)]}-[(2*R*,5*S*,6*R*)-pyran-2-yl]propionate (4)[3] (12.1 mg, 1.9×10^{-5} mol) was stirred with anhydrous lithium tetrafluoroborate (18 mg, 1.9×10^{-5} mol, 10 equiv.) in dry acetonitrile (0.25 ml) at 70 °C for 3 h. Work-up as above and microchromatography in a

* $LiBF_4$ is known to dissociate[5] under thermal conditions and it is conceivable that trace amounts of BF_3 could also catalyse the rearrangement.

Pasteur pipette containing Kieselgel ($2\frac{1}{2}$ in, Merck 9385) with 90% diethyl ether–light petroleum gave the tetracycle (**8**) (5.3 mg, 8.3×10^{-6} mol, 44%), as a colourless gum, t.l.c.: R_F 0.44, diethyl ether, $[\alpha]_D^{25}$ + 33° (*c* 0.5, $CHCl_3$), $\nu_{max.}$ 3 440, 1 725, and 1 645 cm^{-1}; δ (400 MHz) 0.0 (9 H, s), 0.89 (2 H, m, CH_2SiMe_3), 0.95 (3 H, t, *J* 7.5 Hz, 27-Me), 1.14 (3 H, t, *J* 7.5 Hz, 29-Me), 1.14 (3 H, d, *J* 7 Hz, 30-Me), 1.25 (3 H, d, *J* 7.5 Hz, 31-Me), 1.0—2.1 (14 H, m), 2.28 (2 H, q, *J* 7.5 Hz, 28-CH_2), 2.47—2.62 (3 H, m, 20-H, 12-H, and 6-H), 2.8 (1 H, m, 2-H), 3.43 (2 H, m, CH_2O), 3.52 (1 H, dd, *J* 9.5 and 9.5 Hz, 11-H), 3.68 (1 H, m, 3-H), 3.75 (3 H, s, CO_2CH_3), 5.04 (1 H, d, *J* 10 Hz, CH_2N), 5.23 (1 H, d, *J* 10 Hz, 7-H), 5.45 (1 H, d, *J* 10 Hz, CH_2N), 5.5 (1 H, dd, *J* 16 and 9.5 Hz, 10-H), 5.83 (1 H, ddd, *J* 10, 4.5, and 2.5 Hz 13-H), 6.0 (1 H, d, *J* 10 Hz, 14-H), 6.17 (1 H, d, *J* 16 Hz, 9-H), 6.61 (1 H, d, *J* 3 Hz, 24-H), and 6.73 (1 H, d, *J* 3 Hz, 25-H) (Found M^+, 637.4179. $C_{38}H_{59}NO_5Si$ requires *M*, 637.4159).

Acknowledgements

We thank the S.E.R.C. and Pfizer Central Research, Sandwich, U.K. for financial support, the Royal Society of Chemistry for the Hickinbottom Research award to (S.V.L.) and Dr. J. W. Westley, Hoffmann La Roche, for generous supplies of X-14547A. We also thank Dr. G. E. Hawkes, Queen Mary College London, for the 400 MHz ^1H n.m.r. spectra.

References

1 (*a*) W. Wierenga in 'Total Synthesis of Natural Products', ed. J. ApSimon, J. Wiley, New York, 1981, vol. 4, p. 263. (*b*) M. Dobler 'Ionophores and Their Structures', J. Wiley, New York, 1981; (*c*) 'Polyether Antibiotics, Naturally Occurring Acid Ionophores', ed. J. W. Westley, Marcel Dekker, New York and Basel, 1983, vol. **II**.

2 For a discussion of other chemical transformations of polyether antibiotics see ref. 1*c*, p. 51.

3 M. P. Edwards, S. V. Ley, S. G. Lister, and B. D. Palmer, *J. Chem. Soc., Chem. Commun.*, 1983, 630.

4 (*a*) J. W. Westley and C.-M. Liu, U.S.P., 4100171; (*b*) J. W. Westley, R. H. Evans, Jr., C.-M. Liu, T. Hermann, and J. F. Blount, *J. Am. Chem. Soc.* 1978, **100**, 6784; (*c*) C.-M. Liu, T. E. Hermann, M. Liu, D. N. Bull, N. J. Palleroni, B. L. T. Prosser, J. W. Westley, and P. A. Miller, *J. Antibiot.*, 1979, **32**, 95; (*e*) J. W. Westley, R. H. Evans, Jr., L. H. Sello, N. Troupe, C.-M. Liu, and J. F. Blount, *J. Antibiot.*, 1979, **32**, 100.

5 B. H. Lipshutz, J. J. Pergram, and M. C. Morey, *Tetrahedron Lett.*, 1981, 4603.

Received 8th December, 1983; *Paper* 3/2172