Sulphenylation and Halogenation Reactions leading Selectively to *cis*-Carbapenem Precursors; Stereospecific Synthesis of (±)-6-Epithienamycin

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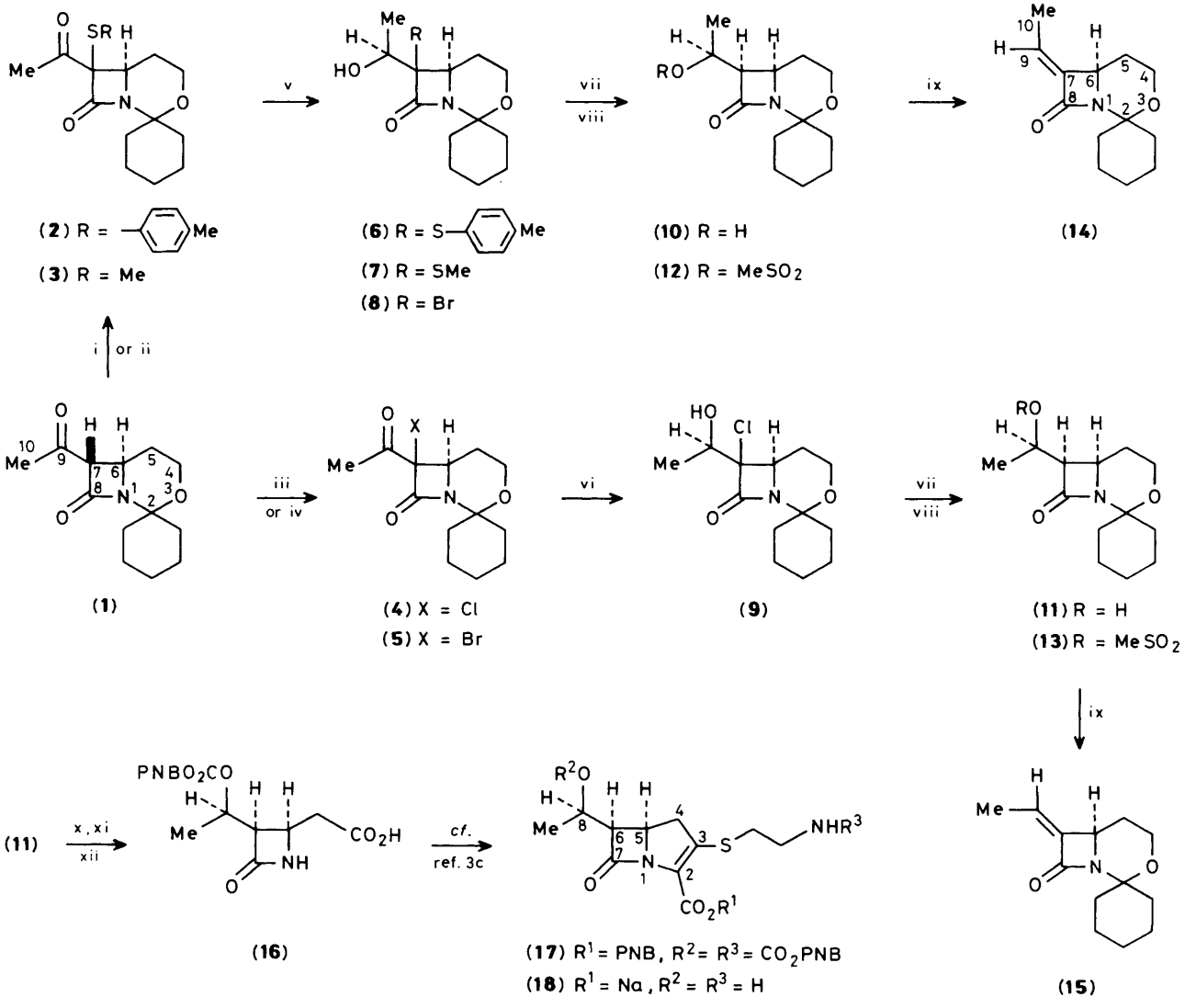
Introduction of sulphenyl or halogen substituents at C-7 of ketone (**1**), followed by stereospecific reduction steps, provides a selective route either to the (6*RS*,7*RS*,9*SR*) or to the (6*RS*,7*RS*,9*RS*) isomers, (**10**) and (**11**), of 7-(1-hydroxyethyl)-8-oxo-1-aza-3-oxabicyclo[4.2.0]octane-2-spirocyclohexane.

cis-Carbapenem derivatives comprise a significant proportion of the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid antibacterial substances isolated from natural sources.[1] In contrast to the many published syntheses of the *trans*-substituted carbapenems, relatively few stereospecific routes to their thermodynamically less stable *cis*-counterparts have been described.[2,3] We now report a versatile and efficient procedure for the synthesis of such β-lactams in the olivanic acid natural product series.[4] The sequence permits the side-chain hydroxy group to be introduced stereospecifically in either stereochemical form from a common precursor.

Reaction of the readily accessible *trans*-ketone (**1**)[5] with



Reagents: i, *p*-$MeC_6H_4S{\cdot}SO_2C_6H_4Me$-*p*, Et_3N, CH_2Cl_2, room temp., 6 h, 85%; ii, $MeS{\cdot}SO_2Me$, Et_3N, CH_2Cl_2, 50 °C, 3 h, 90%; iii, Na^+-$ClNSO_2C_6H_4Me$-*p*, MeCN, room temp., 30 min. 68%; iv, NBS (1 equiv.), AIBN (cat.), PhH, reflux, 5 min, 70%; v, $NaBH_4$ (0.3 molar ratio). EtOH–THF, 0 °C to room temp., 1 h, 95%; vi, K-Selectride®, THF, −70 °C, 1 h, >90%; vii, Bu_3SnH (4 equiv.), AIBN (cat.), acetone, argon, reflux, >90%; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 1 h, 90%; ix, $NaHCO_3$, MeOH, reflux, 30 min, 95%; x, Pr^i_2NLi, *p*-$O_2NC_6H_4CH_2OCOCl$, −70 °C to room temp., 30 min; xi, 2.5 M H_2SO_4, THF, 50 °C, 24 h; xii, 2.7 M CrO_3–H_2SO_4 (3.3 equiv.), acetone, 0 °C, 30 min, 86%; (**17**) → (**18**), H_2, 5% Pd–C, dioxane, –H_2O, 0.05 M pH 7 NaH_2PO_4–Na_2HPO_4 buffer, 2.5 h.

p-tolylsulphenyl toluene-*p*-sulphonate in the presence of triethylamine gave a single 7-arylsulphenyl derivative (**2**),† m.p. 120—121 °C; use of methylsulphenyl methanesulphonate provided (**3**), m.p. 83 °C. Alternatively, halogenation with chloramine-T in acetonitrile gave (**4**), m.p. 108—110 °C. With *N*-bromosuccinimide (NBS) in refluxing benzene in the presence of azoisobutyronitrile (AIBN), the corresponding bromo-derivative (**5**), m.p. 103—105 °C, was rapidly produced.‡

Reduction of (**2**) or (**3**) with sodium borohydride in ethanol–tetrahydrofuran (THF) gave alcohols (**6**) and (**7**) in excellent yield. Subsequent desulphurisation of (**6**) or (**7**) with tributyltin hydride (AIBN initiation) gave (**10**) (36 h, 93% and 60 h, 97%). In contrast, borohydride treatment of chloroketone (**4**) afforded a mixture of alcohol epimers (5 : 2 ratio). However, reduction of (**4**) with either potassium or lithium s-butylborohydrides ('Selectride'®) provided a single alcohol (**9**).§ Tributyltin hydride dechlorination of (**9**) gave (**11**) (6 h, 49%), differing from (**10**) only in stereochemistry of the hydroxyethyl grouping at C-9. N.m.r. coupling constants¶ supported the assigned stereochemistries. Alcohols (**10**) and (**11**) are attractive synthetic precursors of the *cis*-carbapenem antibiotics.

Confirmation of the structural assignments was obtained by elimination of the hydroxy groups, *via* methanesulphonates (**12**) and (**13**) under E2 conditions, producing ethylidenes (**14**) and (**15**). These were obtained in ratios (19 : 1; 98%) and (1 : 9; 96%), respectively. Correlation of n.m.r. data¶ with that from previous work in these laboratories[6] and elsewhere[7] permits the hydroxyethyl stereochemistries of (**10**) and (**11**) to be deduced as indicated.

No carbapenem antibiotic containing the relative stereochemistry present in (**11**) has yet been isolated from natural sources. We have demonstrated the utility of our procedures by the provision of an alternative synthesis of 6-epithienamycin. *p*-Nitrobenzyloxycarbonyl protection of (**11**), followed by acid hydrolysis of the tetrahydro-oxazine ring, and Jones oxidation of the resulting primary alcohol furnished acid (**16**), m.p. 144—145 °C. Using methods closely similar to those reported[3c] by Vasella for the final stages of his synthesis from glucose, we obtained (±)-(**17**). Finally, hydrogenolysis afforded the required sodium salt (**18**) (51%) [$\lambda_{max.}$ (H_2O) 288 nm; homogeneous by h.p.l.c.]. This unnatural isomer did not exhibit the broad spectrum antibacterial potency of thienamyacin.

Received, 28th April 1986; Com. 568

† All compounds prepared are racemic; one enantiomer is depicted to denote relative stereochemistry. All new compounds were fully characterised by microanalytical data and/or high resolution mass spectral measurements.

‡ For compounds (**2**)—(**5**) we have not obtained proof of the C-7 substituent stereochemistry.

§ Bromoketone (**5**) behaved in an anomalous manner: reaction with Selectride® reagents caused reversion to ketone (**1**) (59%). Reaction with sodium borohydride to compound (**8**), followed by tributyltin hydride gave alcohol (**10**) in moderate yield as the major product.

¶ Selected data: (**10**): δ (CD_3COCD_3) 3.10, (7-H); $^3J_{6,7}$ 5.3, $^3J_{7,9}$ 10.6 Hz; (**11**) δ (CD_3COCD_3) 3.10, (7-H); $^3J_{6,7}$ 5.4, $^3J_{7,9}$ 8.2 Hz. (**14**): δ ($CDCl_3$) 1.71 (3H, d, *J* 6.5 Hz, 10-H_3) and 6.11 (1H, dq, *J* 6.5 and 1 Hz, 9-H); 1 Hz allylic coupling only on olefinic signal (*E*-series). (**15**): δ ($CDCl_3$) 2.02 (3H, dd, *J* 6.5 and 1 Hz, 10-H_3) and 5.68 (1H, dq, *J* 6.5 and ~1 Hz, 9-H); homoallylic and allylic couplings respectively, on 10-H_3 and 9-H resonances (*Z*-series).

References

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