# The Bisspiroketal Moiety of *epi*-17-Deoxy-(O-8)-salinomycin.

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To my family for their
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## Abstract.

The synthesis of 2-(3,4-epoxy-3-methylbutan-1-yl)-1,7-dioxaspiro[5.5]undec-4-ene **188** is described, the key step in it's formation being an addition of the lithium acetylide derivative of 5-*tert*-butyldiphenylsilyloxy-2-methyl-2-trimethylsilyloxy-7-octyn-1-*p*-toluenesulphonate **182** to δ-valerolactone. The epoxide **188** was then converted to the hydroxy spiroketal 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-2-methyl-2-butanol **149** which underwent a Barton-type oxidative cyclisation to afford both the *cis*- and *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **192** and **152**. The ring system of this latter compound is analogous to the unsaturated bisspiroketal present in the polyether antibiotic *epi*-17-deoxy-(O-8)-salinomycin **8**.

Subsequently the route was modified to afford the *trans*- and *cis*-(2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanols **211-214**, since it was expected this terminal hydroxyl group would provide a 'handle' by which these molecules could be further elaborated. This required conversion of the epoxide **188** to 4-(1,7-dioxaspiro[5.5]undec-4-en-2-yl)-1-iodo-2-methyl-2-butanol **200**, which was followed by a Barton-type oxidative cyclisation, to give the *cis*- and *trans*-2-iodomethyl-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **201-204**, which were then converted to the alcohols **211-214**.

The techniques used to construct these relatively simple bisspiroketal analogues were then applied to an enantioselective synthesis of the bisspiroketal portion of *epi*-17-deoxy-(O-8)-salinomycin. The two key intermediates required for this were (1'*S*, 3*R*, 5*S*, 6*S*)-(+)-6-[1'-(*tert*-butyldiphenylsilyloxymethyl)propyl]-3,5-dimethyl-tetrahydropyran-2-one **84** and (5*R*, 2*S*)- and (5*S*, 2*S*)-2-methyl-2,5-bis(trimethylsilyloxy)-7-octyn-1-*p*-toluenesulphonate **231**. The lactone **84** was prepared, using Evans' directed aldol methodology, from (4*R*, 5*S*)-(+)-4-methyl-3-(1'-oxobutyl)-5-phenyloxazolidin-2-one **219** and (*S*)-(+)-2,4-dimethyl-4-pentenal **218**. The acetylene **231** was prepared from levulinic acid **174**, and the procedure incorporated a resolution step which enabled the 2*S* configuration of **231** to be introduced. The lactone **84** and the the lithium acetylide derivative of acetylene **231** were combined and subsequently converted to the (1"*S*, 2*S*, 2'*S*, 6'*R*, 8'*S*, 9'*S*, 11'*R*)-(-)- and (1"*S*, 2*S*, 2'*R*, 6'*R*, 8'*S*, 9'*S*, 11'*R*)-(+)-4-{8-[1-(*tert*-butyldiphenylsilyloxymethyl)propyl]-9,11-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-2-yl}-1-iodo-2-methyl-2-butanols **245** and **246**. These hydroxy spiroketals were transformed, again using the Barton-type oxidative cyclisation methodology, to the *cis*-(1'*S*, 2*S*, 5*R*, 7*S*, 9*S*, 10*S*, 12*R*)-(-)- and the *trans*-(1'*S*, 2*S*, 5*S*, 7*S*, 9*S*, 10*S*, 12*R*)-(-)-9-[1-(*tert*-butyldiphenylsilyloxymethyl)propyl]-2-iodomethyl-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene **248** and **247**, the latter of which resembles precisely the corresponding portion of *epi*-17-deoxy-(O-8)-salinomycin. In addition, the termini of the bisspiroketal **247** are selectively functionalised, which will allow further elaboration to the entire natural product **8**.

The synthesis of the *cis*- and *trans*-2,2-dimethyl-15-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **156** and **159**, and of *cis*-2,2-dimethyl-13-hydroxy-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **268** is described. These were formed firstly by allylic bromination of the *cis*- and *trans*-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **192** and **152** to give the *cis*- and *trans*-15-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes **262** and **265**, and *cis*-13-bromo-2,2-dimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-14-ene **261**. These bromides were then displaced by an oxygen nucleophile to afford the alcohols **268**, **156**, **159**, a procedure which involved both $S_N2$ and *anti*-$S_N2'$ processes.

Contents.

Abbreviations.

| | | |
|---|---|---|
| AIBN | = | 2,2'-azobisisobutyronitrile |
| ax | = | axial |
| Bzl | = | benzyl |
| cat. | = | catalytic |
| COSY | = | correlation spectroscopy |
| CSA | = | camphorsulphonic acid |
| DDQ | = | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DHP | = | dihydropyranyl |
| DIBAL | = | diisobutylaluminium hydride |
| DMAP | = | 4-dimethylaminopyridine |
| DMF | = | *N, N*-dimethylformamide |
| DMSO | = | dimethylsulphoxide |
| eq | = | equatorial |
| equiv. | = | equivalent |
| HETCOR | = | heteronuclear correlation spectroscopy |
| imid | = | imidazole |
| MCPBA | = | *meta*-chloroperoxybenzoic acid |
| Ms | = | methanesulphonyl |
| NBS | = | *N*-bromosuccinimide |
| NCS | = | *N*-chlorosuccinimide |
| NMO | = | *N*-methylmorpholine-*N*-oxide |
| nmr | = | nuclear magnetic resonance |
| PCC | = | pyridinium chlorochromate |
| PPTS | = | pyridinium *p*-toluenesulphonate |
| Py | = | pyridine |
| RT | = | room temperature |
| Tf | = | trifluoromethanesulphonyl |
| TFA | = | trifluoroacetic acid |
| TFAA | = | trifluoroacetic anhydride |
| THF | = | tetrahydrofuran |
| THP | = | tetrahydropyranyl |
| tlc | = | thin layer chromatography |
| TMS | = | trimethylsilyl |
| Ts | = | *p*-toluenesulphonyl |
| TSA | = | *p*-toluenesulphonic acid |