Synthesis of the E Ring of Salinomycin

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To Mum, Dad, Leo and Julie
Thanks for all the support.

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Abstract

The synthesis of (2R*, 5R*, 2'S*) and (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans **331a, 331b** in a 5:1 ratio by the iodoetherification of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **330a** is described. Subsequent iodoetherification of ether derivatives **385 - 389** of hydroxyalkene **330a** was then effected to produce predominantly the *cis* iodide **331b**. (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-(2", 6"-dichlorobenzyloxy)-4-pentene **387** proved most successful in this respect affording iodides **331a, 331b** in a 1:10 ratio.

Attempted silver catalysed ring expansion of iodide **331a** proved ineffective affording only (5R*, 2'S*)-5-(2'-methyltetrahydro-2'-yl)-5-hydroxypentan-2-one **344**.

The synthesis of (E)-1-bromo-3-ethyl-3-pentene **146** is described, the key step in its formation being the diastereoselective reaction of 2-ethyl-1-butene **364** with butyl glyoxylate **367**, in the presence of a titanium catalyst formed *in situ* from diisopropoxytitanium(VI) dichloride **362** and (±)-1,1'-bi-2-naphthol **363**, to afford butyl (E)-4-ethyl-2-hydroxy-4-hexenoate **370**.

The synthesis of (2S*, 3R*, 6R*, 2'S*)-3-ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran **323** from 2-methyl-2-tetrahydrofuraldehyde **322** is described, thereby modelling the synthesis of the E ring of salinomycin. The synthesis began with the coupling of the organolithium derivative of (E)-1-bromo-3-ethyl-3-pentene **146** to 2-methyl-2-tetrahydrofuraldehyde **322** to afford (4E, 1R*, 2'S*)- and (4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **348a, 348b** in a 3:1 ratio. Following separation of the alcohols **348a, 348b** *via* formation of their acetate derivatives **383a, 383b**, iodoetherification of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **348a** afforded (2R*, 5R*, 1'S*, 2"S*)- and (2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofurans **347a** and **347b** in a 3:1 ratio. Subsequent ring expansion of iodide **347b** resulted in formation of the target pyran **323** in 77% yield.

Iodoetherification of the trimethylsilyl derivative **392** of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **348a** produced the iodides **347a** and **347b** in a 1:1 ratio, while the 2,6-dichlorobenzyl **390** and 4-bromobenzyl **391** derivatives were too sterically hindered for iodoetherification to occur.

Contents

Abbreviations

Ac	=	acetyl
acac	=	2,4-pentanedione
AD	=	asymmetric dihydroxylation
AIBN	=	2,2'-azobisisobutyronitrile
aq.	=	aqueous
BB	=	4-bromobenzyl
BOM	=	benzyloxymethyl
Bz	=	benzyl
cat.	=	catalytic
CSA	=	camphorsulphonic acid
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	=	2,6-dichlorobenzyl
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	diethyl azodicarboxylate
DHP	=	dihydropyranyl
DIBAL	=	diisobutylaluminium hydride
DMAP	=	4-dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	*N,N*-dimethylformamide
DMS	=	dimethylsulphide
DMSO	=	dimethylsulphoxide
HMDS	=	1,1,1,3,3,3-hexamethyldisilazane
HMPA	=	hexamethylphosphoramide
HMPT	=	hexamethylphosphorus triamide
HPLC	=	high performance liquid chromatography
imid.	=	imidazole
IR	=	infra-red
LDA	=	lithium diisopropylamide
MCPBA	=	*meta*-chloroperoxybenzoic acid
MOM	=	methoxymethyl
MOP	=	methoxyisopropyl
MP	=	methoxyphenyl
MPM	=	*p*-methoxyphenylmethyl
MS	=	molecular sieves
Ms	=	methanesulphonyl

NCS	=	*N*-chlorosuccinimide
NIS	=	*N*-iodosuccinimide
NMO	=	4-methylmorpholine-*N*-oxide
NMR	=	nuclear magnetic resonance
NOESY	=	nuclear Overhauser and exchange spectroscopy
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
Ph	=	phenyl
PPTS	=	pyridinium *p*-toluenesulphonate
Pv	=	pivaloyl
Py	=	pyridine
RT	=	room temperature
TBCO	=	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDMS	=	*tert*-butyldimethylsilyl
TES	=	triethylsilyl
Tf	=	trifluoromethanesulphonyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic anhydride
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TIPS	=	triisopropylsilyl
tlc	=	thin layer chromatography
TMS	=	trimethylsilyl
TSA	=	*para*-toluenesulphonic acid