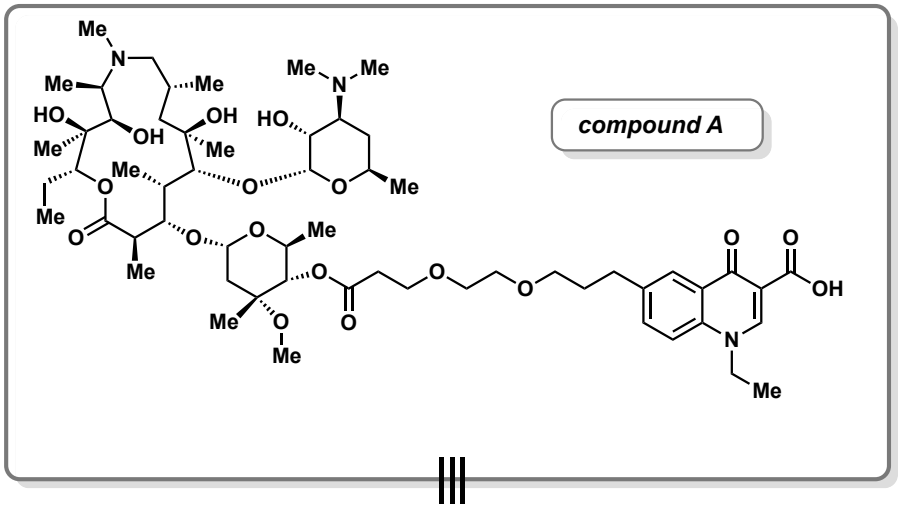
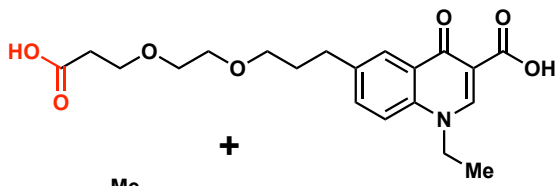
Sarlah Group

POTW: Preparation of a Lead Antibacterial Macrolone Compound



compound A



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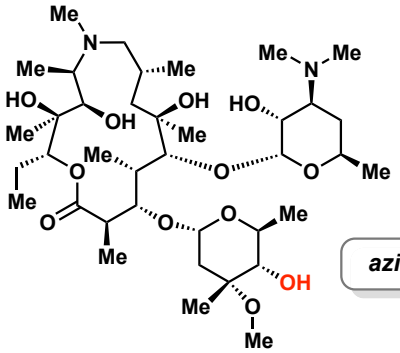
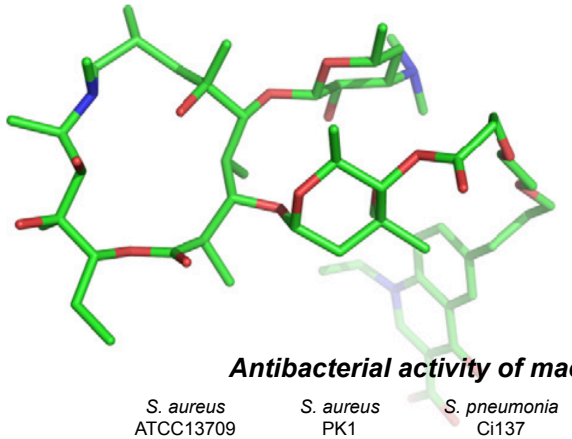


azithromycin

[coupling]



GlaxoSmithKline

Discovery route: 13 steps, several chromatographic purifications, overall yield 5-8%

This Work: 13 steps, no chromatographic purifications, adapted to 5 L reactor to prepare 350g to support preclinical in vivo safety assessment studies, overall yield 27% with 97.7% purity.

Antibacterial activity of macrolone A given as minimum inhibitory concentration (MIC) measured in units of μg/mL

	S. aureus ATCC13709 **eryS**	*S. aureus* PK1 **M**	*S. pneumonia* Ci137 **M**	*S. pyogenes* 2 Finland **M**	*S. aureus* 90256 **iMLS**	*S. pneumonia* 134 GR M **iMcLS**	*S. pyogenes* Finland 11 **iMLS**	*S. pneumoniae* 166 GR-Micro **cMLS**	*H. influenzae* ATCC 49247	*M. catarrhalis* ATCC 23246
azithromycin	0.5	>64	8	8	>64	>64	>64	>64	1	<0.125
telithromycin	<0.125	<0.125	0.25	0.5	<0.125	0.25	<0.125	16	2	<0.125
compound A	<0.125	0.25	<0.125	<0.125	0.25	0.25	<0.125	<0.125	1	<0.125

***iMLS** = inducible resistance to macrolide, licosamide and streptogramin (MLS) antibiotics; **iMcL** = inducible resistance to macrolide and constitutive resistance to lincosamide antibiotics; **cMLS** = constitutive MLS resistance; **M** = efflux mediated macrolide resistance.*

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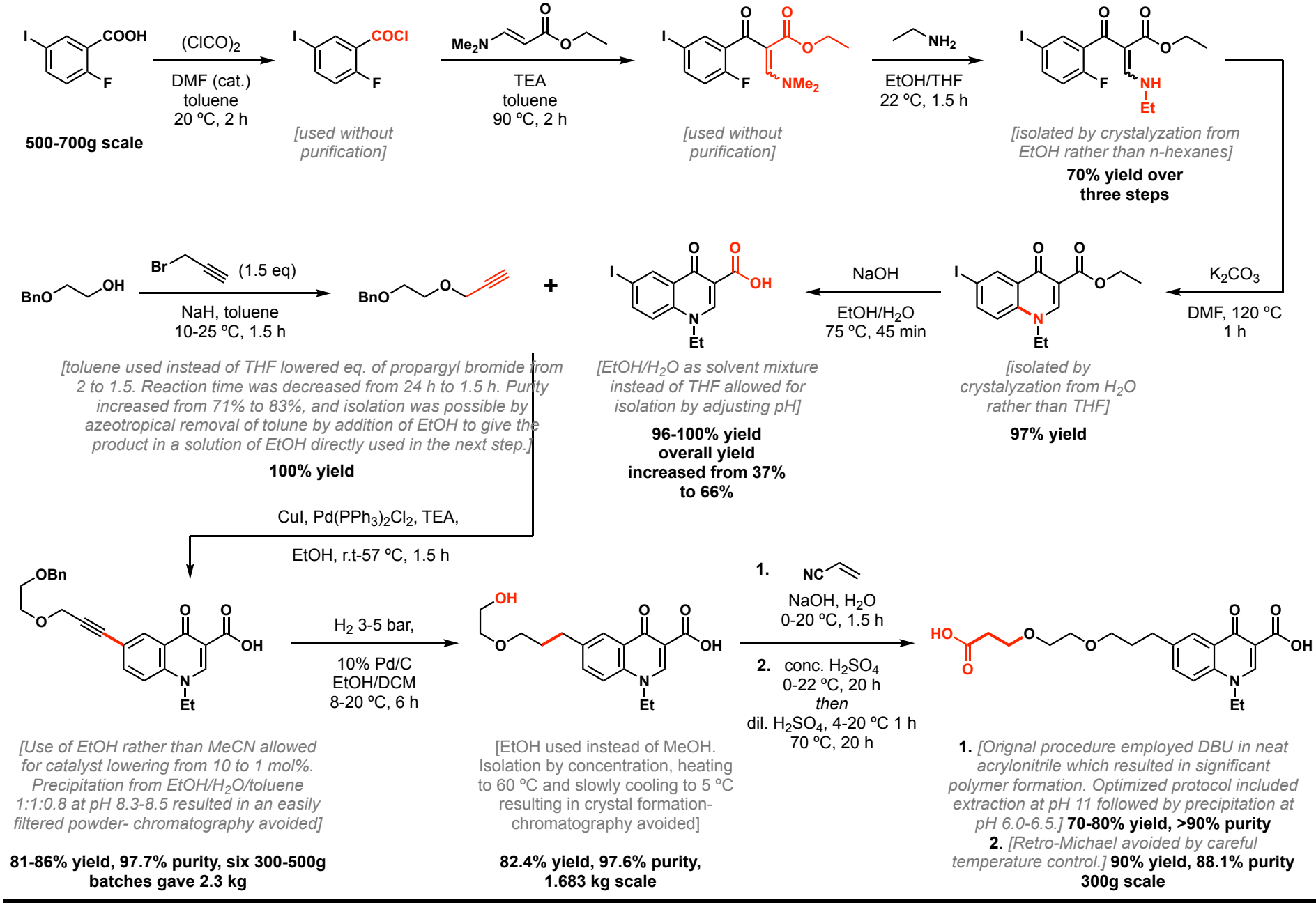

500-700g scale

[used without purification]

[used without purification]

[isolated by crystalyzation from EtOH rather than n-hexanes]

70% yield over three steps

[isolated by crystalyzation from H_2O rather than THF]

97% yield

[EtOH/H_2O as solvent mixture instead of THF allowed for isolation by adjusting pH]

96-100% yield overall yield increased from 37% to 66%

[toluene used instead of THF lowered eq. of propargyl bromide from 2 to 1.5. Reaction time was decreased from 24 h to 1.5 h. Purity increased from 71% to 83%, and isolation was possible by azeotropical removal of tolune by addition of EtOH to give the product in a solution of EtOH directly used in the next step.]

100% yield

[Use of EtOH rather than MeCN allowed for catalyst lowering from 10 to 1 mol%. Precipitation from EtOH/H_2O/toluene 1:1:0.8 at pH 8.3-8.5 resulted in an easily filtered powder- chromatography avoided]

81-86% yield, 97.7% purity, six 300-500g batches gave 2.3 kg

[EtOH used instead of MeOH. Isolation by concentration, heating to 60 ºC and slowly cooling to 5 ºC resulting in crystal formation- chromatography avoided]

82.4% yield, 97.6% purity, 1.683 kg scale

1. *[Orignal procedure employed DBU in neat acrylonitrile which resulted in significant polymer formation. Optimized protocol included extraction at pH 11 followed by precipitation at pH 6.0-6.5.]* **70-80% yield, >90% purity**
2. *[Retro-Michael avoided by careful temperature control.]* **90% yield, 88.1% purity 300g scale**

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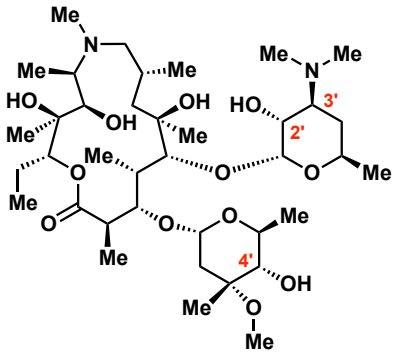
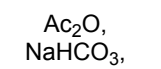
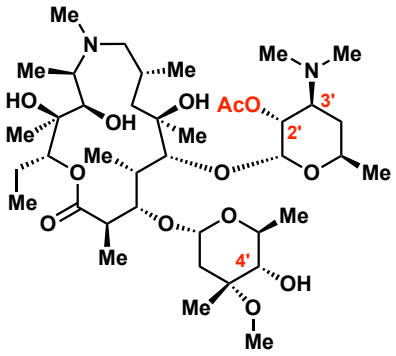


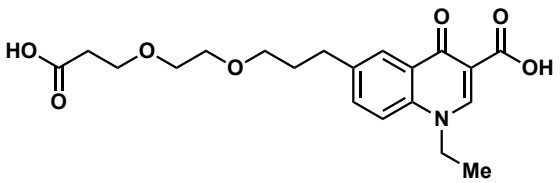
Azithromycin



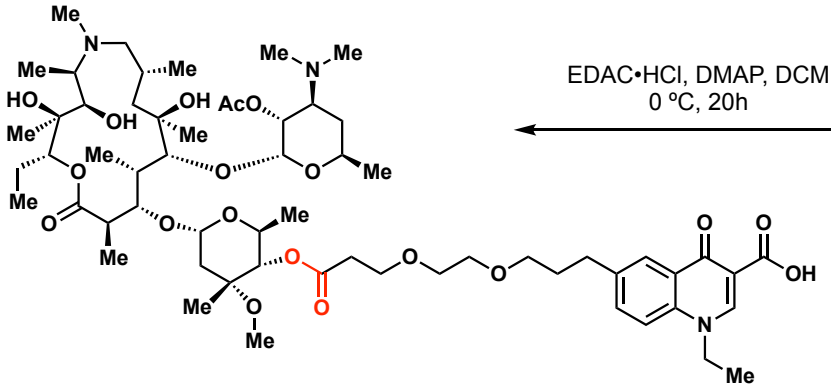


[because the reaction rate of the desired acylation at the 2' hydroxyl is enhanced by intramolecular catalysis of the vicinal dimethylamino group on the 3' position, iPrOH could be used to out-compete reactivity at the 4' hydroxyl. Purified by dilution with H_2O and adjusting pH to 9.3-9.5 resulted in crystalline product]

88% yield, 98.0% purity, 700g scale



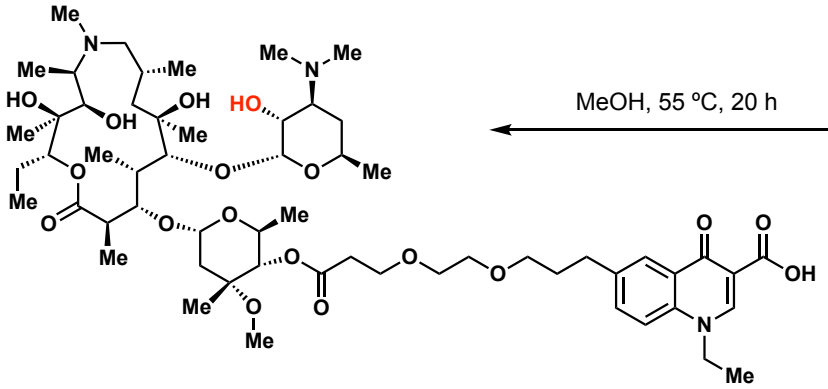
[selective reactivity at the most acidic site consistent with known mechanism for coupling]



EDAC•HCl, DMAP, DCM
0 ºC, 20h

[desired quantity for preclinical trials formed- no further optimization was needed]

1.178kg produced



MeOH, 55 ºC, 20 h

[reaction mixture concentrated, gradient extractions between H_2O and iPrOAc: pH 4.0 extracted quinolone diacid and DMAP; pH 4.8, 5.0 and 5.8 extracted macrolide byproduct; pH 5.8 extracted pure product as HCl salt; pH 8.8 extracted pure product as free base]

65% yield over two steps, 96.4% purity, 682g prepared

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