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Synthetic Studies Towards Antibiotics Containing Phthalide Moieties

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By

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Abstract

An investigation into the synthesis of several analogues of antifungal agents related to the papulacandins was undertaken. Retrosynthetic analysis of these analogues identified phthalide (261) and allylstannane (278) as key intermediates in the synthesis of analogues of type (284).

The key step in the synthesis of phthalide (261) was the *ortho* formylation *via* ortholithiation of amide (255). The synthesis of phthalide (261) was carried out over five steps in 35% overall yield from (255).

Synthesis of the allylstannane intermediate from alcohol (351) proved problematic thus preventing further progress in this area of research.

Synthetic studies toward the anti-*helicobactericidal* phthalides CJ-12,954 (56), CJ-13,014 (57), CJ-13,015 (58), CJ-13,0102 (59), CJ-13,103 (60), CJ-13,104 (61), and CJ-13,108 (62) were undertaken. CJ-12,954 (56) and CJ-13,108 (62) were chosen as initial targets. Retrosynthetic analysis identified phthalide (288), spiroketal ylide (297) and ylide (468) as key intermediates for the synthesis of the natural products (56) and (62). The synthesis of spiroketal epoxide (300) was successfully achieved in fifteen steps starting from materials (386) and (381) in an overall yield of 8%. Unfortunately all attempts to effect ring opening of epoxide (300) were unsuccessful. The racemic synthesis of phthalide (288) was carried out in six steps starting from material 2,4-dimethoxybenzoic acid (296) in 33% overall yield. Wittig coupling of ylide (468) with phthalide (288) allowed complete total synthesis of racemic CJ-13,108 (62) from (288) in 42% overall yield.

Abbreviations

Ac	= Acetyl
Ac ₂ O	= Acetic anhydride
9-BBN	= 9-Borabicyclononane
Bn	= Benzyl
BH ₃ -DMS/BMS	= Borane-dimethyl sulphide complex
CAN	= Ceric ammonium nitrate
CSA	= Camphorsulphonic acid
DCM	= Dichloromethane
DDQ	= 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	= Diisobutylaluminium hydride
DMAP	= 4-Dimethylaminopyridine
DMDO	= 2,2-Dimethyldioxirane
DMF	= <i>N,N</i> -Dimethylformamide
DMPU	= 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidone
DMSO	= Dimethylsulphoxide
DNA	= Deoxyribonucleic acid
Et ₂ AlCl	= Diethyl aluminium chloride
EtOAc	= Ethyl acetate
EtOH	= Ethanol
Et ₃ N	= Triethylamine
HMPA	= Hexamethylphosphoramide
LDA	= Lithium diisopropylamide
LTMDA	= <i>N,N,N'</i> -Trimethylethylenediamine
<i>m</i> CPBA	= <i>meta</i> -chloroperoxybenzoic acid
MMPP	= Magnesium monoperoxyphthalate
MOM	= Methoxymethyl
MsCl	= Methanesulphonyl chloride

NBS	= <i>N</i> -Bromosuccinimide
NMO	= <i>N</i> -Methylmorpholine- <i>N</i> -oxide
PCC	= Pyridinium chlorochromate
Piv	= Pivaloyl, 2,2-dimethylacetyl
PMB	= <i>p</i> -Methoxybenzyl
PPTS	= Pyridinium <i>p</i> -toluenesulphonate
Py	= Pyridine
TBAF	= Tetrabutylammonium fluoride
TBDMS	= <i>tert</i> -Butyldimethylsilyl
TBDPS	= <i>tert</i> -Butyldiphenylsilyl
TBS	= <i>tert</i> -Butyldimethylsilyl
TES	= Triethylsilyl
Tf	= Trifluoromethanesulfonyl
TfO	= Trifluoromethanesulfonate
TFAA	= Trifluoroacetic anhydride
THF	= Tetrahydrofuran
THP	= Tetrahydropyranyl
TMEDA	= <i>N,N,N',N'</i> -Tetramethylethylenediamine
TMS	= Trimethylsilyl
TIPS	= Trisopropylsilyl
TPAP	= Tetrapropylammonium perruthenate

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