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Synthetic Chemistry Case Study: Challenging Macrolide Chemistry

Challenge:

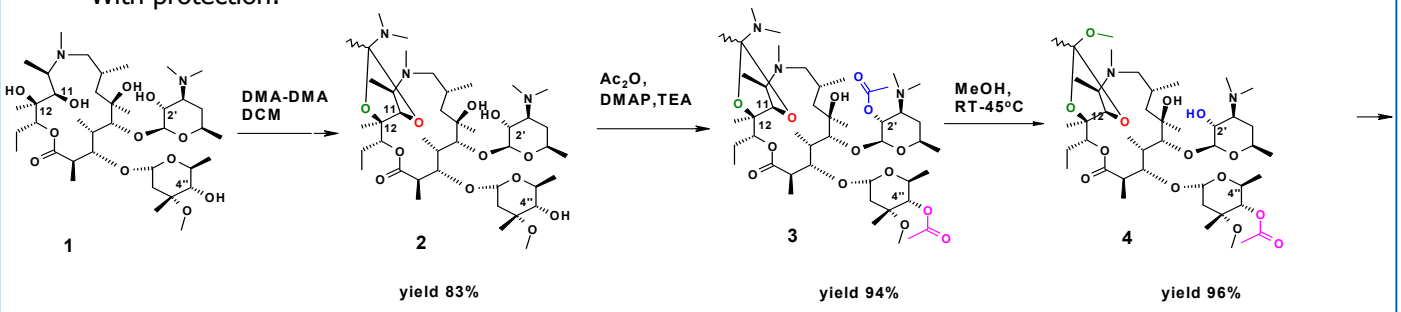
- **Reactivity and selective protection/deprotection of five OH groups**
- **Sensitivity of macrolides towards basic and acidic conditions (epimerisation on C-2, lactone opening, sugar cleavage)**
- **No chromophore – difficult to monitor reaction progress (LC-MS and TLC with H2SO4)**
- **Complex purification of final products (precipitation, acid/base extraction, solid-phase extraction)**

Summary:

- **An inventive protecting group strategy allowed regioselective alkylation at position 2′-OH**
- **100 g scale**
- **Overall yield 5% / 7 steps**
- **No column chromatography**
- **Low cost: 1g < $10**

Introducing substituents at position 2′ of azithromycin

- Without protection: mixture of products (reaction proceeded on 2′-OH, 4″-OH and 11-OH)
- With protection:

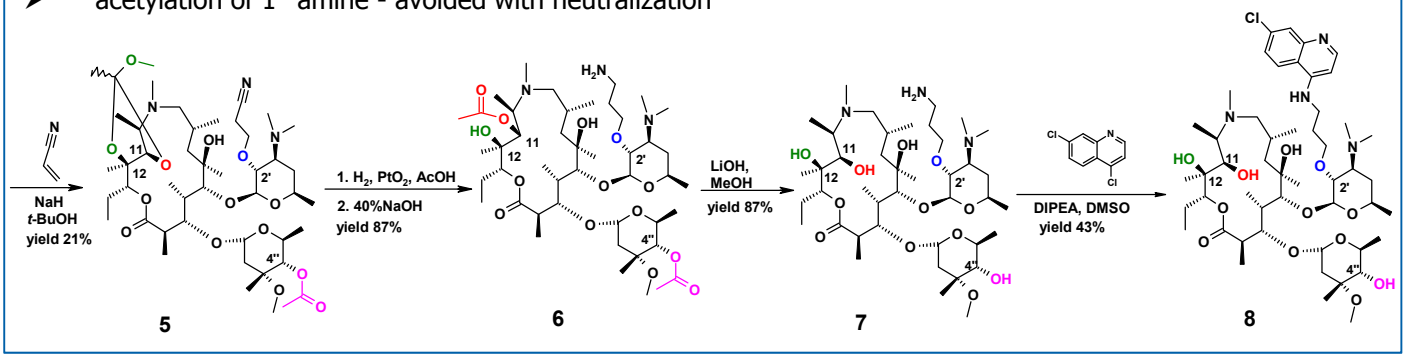


Challenge at step 3:

- hydrolysis in MeOH at RT – two products (11,12-orthoamide and 11,12-orthoester)
- 45°C – only 11,12-orthoester (used for scale-up)

Challenge at step 5:

- acetylation of 11-OH due to protecting group cleavage
- acetylation of 1° amine - avoided with neutralization



References

1. D. Pesic et al., *J. Med. Chem.* **55** (2012) 3216;
2. K. Starcevic, et al., *Eur. J. Med. Chem.* **49** (2012) 365;
3. S. Alihodzic et al. , WO2010086351;
4. S. Alihodzic et al., WO2009016142.

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