SECO-DERIVATIVES OF 15-MEMBERED AZALIDES

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Introduction

Polyketide macrolides are a large group of natural products produced mainly by microorganisms and in most cases these compounds contain polihydroxy macrocyclic lactones gylcosylated with one or more deoxy- and/or aminosugar moieties. Erythromycin A is a 14-membered macrolactone first isolated from *Saccharopolyspora erythraea.* It quickly became a largely used antibacterial agent in treatment of respiratory and soft tissue infections. Fast growing bacterial resistance, pharmacokinetic and gastrointestinal problems set off the quest for new semisynthetic analogues. Azithromycin, the most notable member of the azalide family was developed in the 1980's.[1,2] Its macrolactone is enlarged to a 15-membered ring by introduction of a nitrogen atom in the "northern" part of the molecule (Figure 1). In general the macrolide lactone moiety is stable under neutral conditions. Under highly acidic or basic conditions, however, transformations in the lactone become prominent.[3-5] Other hydroxyl groups present in the molecule participate in translactonisations thus enabling enlargement or shrinking the original ring, while in some cases complete hydrolysis of the macrocycle to ω-hydroxy acid were reported.[6] It was found that such seco-macrolides have no antibacterial activity.[9]

Objective

In the course of our investigations on 15-membered azalides we found that some of these compounds are susceptible to solvolysis even without addition of external acids or bases. We performed an investigation on the influence of azalide structure on the course of methanolysis and succeeded to isolate and characterise some of the products of this process. Later on we investigated activity of some of these seco-azalides in palladium catalysed allylic alkylation and in our newly developed tandem allylic alkylation/Michael addition reaction, thus allowing formation of highly substituted morpholine derivatives .

Results and discussion

Heating of methanol solution of compound **1a** led to macrolide's gradual degradation and formation of the corresponding methyl ester **2a** (Scheme 1). Reaction was slow and complete conversion was achieved in a sealed vessel at 80°C for 3 days. Performing the reaction for 20 hours allowed us to isolate intermediate and it proved to be 13-membered azalide **3a**, a product of translactonisation (Scheme 2).[5] 14- and 15-Membered analogues of **3a** are described in the literature and it is known that the process of translactonisation and ring shrinking is in equilibrium.[5] Refluxing methanol solution of **3a** for one hour afforded a mixture of **3a**, **2a** and **1a** with the latter a predominant compound of the reaction mixture. After 12 hours seco derivative **2a** was the predominant component of the mixture. It might be assumed that **1a** and **3a** are in an equilibrium that is shifted to the left. Methanolysis of **3a**, however slowly leads to the seco-derivative **2a**. As it was mentioned earlier solvolysis of the macrolactone was triggered by external base.[6] There are no data about the role of the base but most likely alkoxyde formed after deprotonation of 11-OH group attacks proximal lactone leading to ring size changes and subsequent hydrolysis. In our case however, except for the elevated temperature reaction proceeded under mild conditions without addition of a base.
Having these results in hands we concluded that key factors for macrolactone ring opening were 1) basicity of macrolide itself, 2) presence of adjacent hydroxyl group at C-11 that participate in translactonisation and 3) conformation of the aglycone. We treated a set of azalides under the same reaction conditions in order to prove if anticipated mechanism was operative. All tested compounds contained highly basic desosamine moiety[16] but differ in functionalisation of the aglycone nitrogen atom. Azithromycin (**1b**) was used as a tertiary amine analogue of **1a**. Compound **1c** was also a tertiary amine but had 11-OH group blocked as methyl ether while 9a-lactam **1d** was used as a representative of azalides that contain no basic nitrogen atoms in the aglycone part of the molecule. Contrary to **1a** all other azalides were much more stable. Thus **1b** gave conversion of 30 % of **2b** for more than a week, while **1c** for the same period of time gave only 9% conversion to **2c**. Compound **1d** remained stable and no **2d** was formed. Obviously high basicity of the macrolides governed by desosamine sugar moiety was not the main factor in the process. Presence and type of nitrogen containing function in close proximity to the reaction centre seems more important (basic amines **1a** and **1b** reacted while amide **1d** remained intact). Results with **1c** seemed reasonable taking into account that there were no free hydroxyl groups that could participate in the assumed translactonisation.

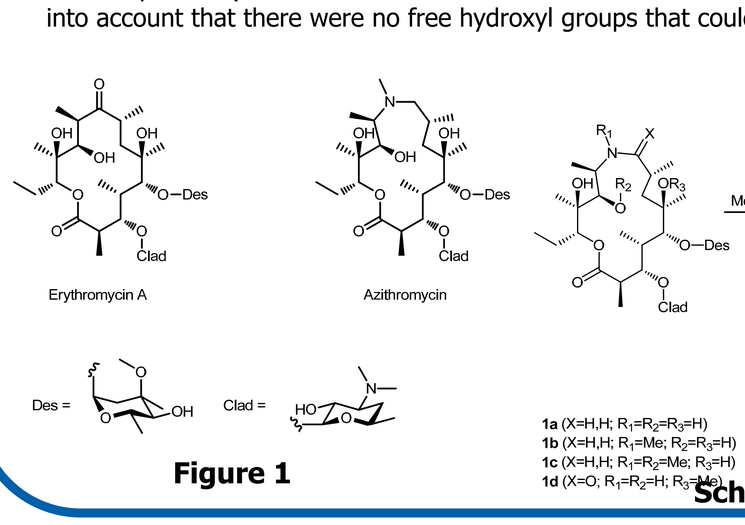
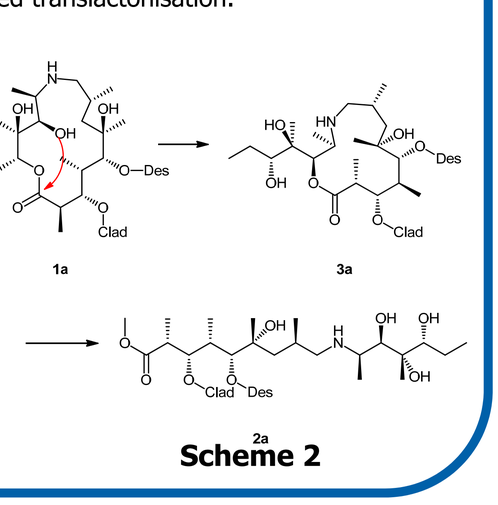


Figure 1



Scheme 2

1a (X=H,H; R_1=R_2=R_3=H)
1b (X=H,H; R_1=Me; R_2=R_3=H)
1c (X=H,H; R_1=R_2=Me; R_3=H)
1d (X=O; R_1=R_2=H; R_3=Me)

2a (X=H,H; R_1=R_2=R_3=H)
2b (X=H,H; R_1=Me; R_2=R_3=H)
2c (X=H,H; R_1=R_2=Me; R_3=H)
2d (X=O; R_1=R_2=H; R_3=Me)

Scheme 1

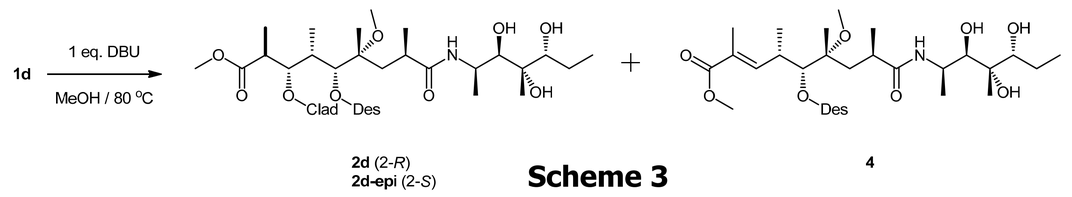
Results and discussion

Tandem allylic alkylation/Michael addition

Recently we reported a one-pot highly stereoselective tandem allylation/intermolecular Michael addition reaction in which 9a-sec. amino group and adjacent 11-OH group in the molecule of **1a** participated in formation of bicyclic macrolide containing highly substituted morpholine ring.[15] Having **2a** in hands we decided to check if it can participate in regioselective allylation reactions and further on in annulation process. In the later case the stereoselectivity of the reaction was not clear taking into account that seco-macrolide molecule had much higher conformational freedom and thus lesser bias on the stereogenic annulations process.
Palladium catalysed reaction of **2a** with methyl-allyl carbonate (**5**) in toluene proceeded regioselectively giving *N*-allyl seco-azalide **6** in 70% yield (Scheme 4). Allylation with BoC-activated 4-hydroxy crotonate derivatives **7** and **8**[15] was also *N*-regioselective giving unsaturated ester **9** and nitrile **10** in moderate yields. It is worth noting that even though **8** was used as a mixture of geometric isomers exclusively *E*-product was obtained. Obviously π-σ-π interconversion of palladium-π-allyl complex to its more stable *syn*-isomer[17] is much faster than the nucleophilic attack of secondary amine. HPLC-MS analyses of the reaction mixtures revealed that process of annulations had started even in the absence of external base. In the presence of DBU in toluene **9** was converted to morpholine derivative **11** with moderate diastereoselectivity (4:1 isomeric ratio). The main diastereomer had ester group occupying *pseudo*-equatorial position in the morpholine ring. Compound **12** on the other hand was obtained as the only isomer in a one pot protocol where DBU was added to the reaction mixture after completion of allylation and without isolation of **10** (Scheme 4). *Pseudo*-equatorial position of the methylcyano group and 22-*R* configuration of **12** were confirmed by nOe experiments where strong interactions between protons H-11 and H-22 were observable. (Figure 2).

Influence of external base on solvolysis

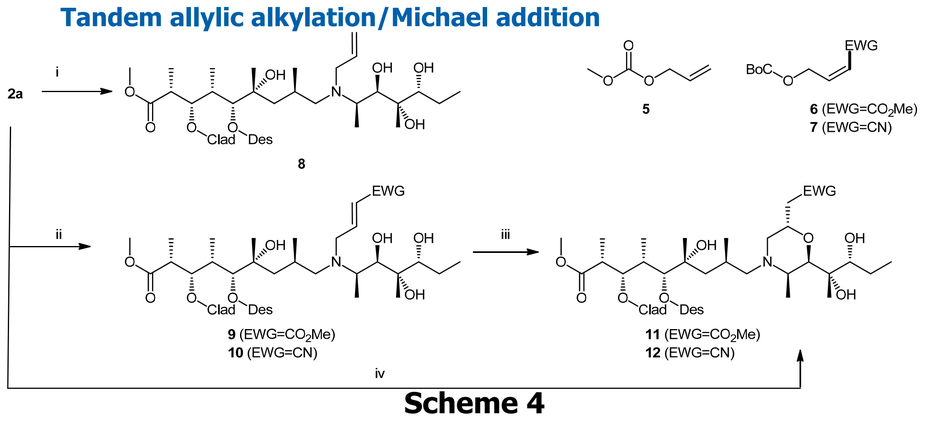
Addition of external base in the reaction mixture facilitated ring opening of the investigated azalides. Thus nonreactive **1d** was completely transferred to seco-azalide derivatives when treated with 1 equivalent of DBU in refluxing methanol. In this case however, further transformations on the molecule occurred. Expected product **2d** was isolated in a mixture with its C-2 epimer (**2d**-*epi*) in 32 % combined yield) accompanied with α,β-unsaturated ester **4** (18 %) (Scheme 3). The later was product of base catalyzed elimination of the neutral sugar moiety. 2D-NMR and nOe experiments revealed *E* configuration of the double bond, a result of antiperiplanar elimination of β-*O*-cladinosyl substituents from **2d**. Reducing the amount of DBU to 0.1 equivalents suppresses elimination process and formation of **4**. In this case however, the rate of the reaction is also low. Thus **2d** and **2d**-*epi* were obtained in 23 % combined yield (4:1 ratio) after three days in refluxing methanol.



2d (2-*R*)
2d-epi (2-*S*)

Scheme 3

Tandem allylic alkylation/Michael addition



Scheme 4

Reagents and conditions: (i) **5** (1.2 eq.), $Pd_2(dba)_3.CHCl_3$ (1 mol%), dppb (2mol %), toluene, r.t; (ii) **6** or **7** (1.2 eq.) $(dba)_3.CHCl_3$ (1 mol%), dppb (2mol %), toluene, 80 °C; (iii) DBU (0.2eq.), toluene, 80 °C; (iv) (a) 7 (1.2 eq.) $(dba)_3.CHCl_3$ (1 mol%), dppb (2mol %), toluene, 80 °C; (b) DBU (0.2eq.), toluene, 80 °C;

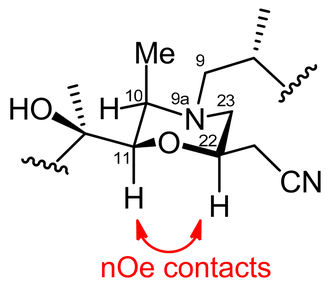


Figure 2

nOe interactions in compound **12** confirming 22-*R* stereochemistry

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Conclusion

In conclusion we have developed a method for mild transformation of 15-membered azalides to methyl esters of corresponding seco-derivatives. Process depends on structure of the starting azalide and presence of suitably oriented hydroxyl groups in them. Some of the seco-derivatives were transformed to highly substituted morpholine analogues by tandem palladium catalysed allylic alkylation/Michael addition reaction.

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