Tetrahedron Letters 49 (2008) 5569–5571

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Descladinosyl erythromycin in phosgene-assisted cyclic 3,6-ether formation

Audun Heggelund, Kjell Undheim *

Department of Chemistry, University of Oslo, N-0315 Oslo, Norway

ARTICLE INFO

Article history:
Received 9 January 2008
Revised 14 June 2008
Accepted 25 June 2008
Available online 1 July 2008

Keywords:
Phosgene reactions
Carbonylation
2′,3′-Cyclic carbamate
3,6-Oxa-bridge
Dess–Martin deoximation

ABSTRACT

Erythromycin A has been converted into a 3,6-bridged ether via a C-3 chloroformate by nucleophilic addition of the hydroxyl function at C-6. Further transformations afforded *N*-demethyl-3-*O*-descladinosylerythromycin A 2′,3′-carbamate-11,12-carbonate-3,6-ether in 59% overall yield over four reaction steps from (9*E*)-erythromycin A 9-(*O*-allyloxime).

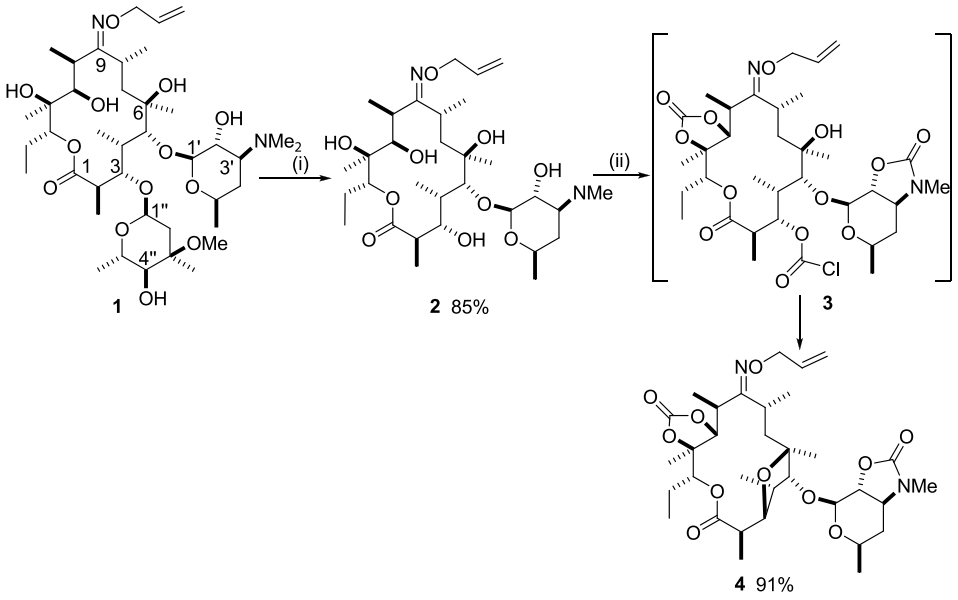
The antibacterial agent erythromycin A is widely used in treatment of upper and lower respiratory tract infections and in genital infections.[1–3] The drug suffers from some major clinical disadvantages such as poor bioavailability and frequently causes gastrointestinal side effects. These effects have been attributed to the chemical instability of erythromycin A in acidic environments. Early modifications of erythromycin A have provided chemically more stable semi-synthetic macrolides such as clarithromycin and azithromycin. We have initiated a study where the 3′-dimethylamino group in the desosamine sugar is transformed into a 2′,3′-cyclic carbamate in an effort to improve the physical and antibacterial properties.[4,5] The work described herein has provided a novel cyclic 3,6-ether bridged 2′,3′-cyclic carbamate **8**. The ether bridge is expected to confer significant conformational restrictions on the parent molecule.

Erythromycin A was the starting material for the synthetic work. The 9-keto function was initially protected as an *O*-allyloxime, structure **1** in Scheme 1.[6,7] Without oxo group protection, intramolecular cyclisation reactions between the 6-OH group and the 9-oxo group are favoured. Mild acid conditions were used to remove the cladinose sugar resulting in generation of the 3-hydroxy derivative **2** in 85% yield. A subsequent treatment with phosgene in the presence of pyridine as base resulted in several functional transformations, and a tri-cyclisation scenario led to a novel 3,6-oxa-bridged structure **4**.[8] The vicinal 11,12-dihydroxy groups were linked by carbonate formation, whereas the 2′-hydroxy and the 3′-dimethylamino groups were transformed into a mono-demethylated cyclic carbamate unit. The 3-hydroxy group was expected to react with carbonyl chloride formation and thereby furnish structure **3**. Addition of allyl alcohol to the initial reaction product, however, failed to provide an allyl carbonate function at C-3. IR analysis of the isolated product showed no hydroxyl group absorption. Using 2D NMR techniques, the product was identified as the cyclic 3,6-ether **4** which was obtained in 91% yield as a single diastereomer with the configuration at C-3 as tentatively assigned. Presumably the 3-chloroformate **3** is an intermediate structure. The formation of the cyclic 3,6-ether in **4** is rationalised as a nucleophilic attack from the 6-OH group onto C-3 with expulsion of the chloroformate functionality as carbon dioxide and a chloride. The direct displacement requires inversion of the configuration at C-3, with formation of a single C-3 epimer. When the 6-OH group is prevented from participating in the reaction by being O-methylated as in 3-*O*-descladinosylclarithromycin (**5**), the reaction with phosgene and pyridine in dichloromethane, followed by a reaction with allyl alcohol, yielded the C-3 allyl carbonate **6** (Scheme 2).[4] This finding supports a reaction path proceeding by direct nucleophilic attack of the C-6 hydroxyl group at C-3 during the formation of the cyclic 3,6-ether **4**.

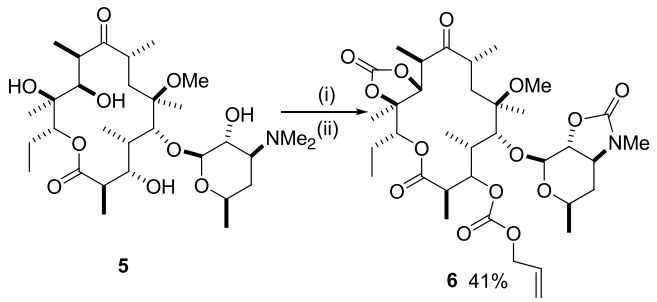
In erythromycin A chemistry, the cyclic 3,6-ether structure unit has previously been reported mainly as a result of unexpected reactions. Thus, treatment of erythromycin 6-hydroxy-3-mesylates with lithium chloride or pyridine led to the formation of 3,6-ether structures.[9] More recently, it has been reported that 6-hydroxy-3-mesylate azalides underwent cyclisation with the formation of 3,6-ethers when treated with sodium hydride.[10] The C-6 methoxy analogues gave anhydrolides under the same conditions when base-mediated elimination of the mesyl group

* Corresponding author. Tel.: +47 22 85 55 21; fax: +47 22 85 55 07.
E-mail address: kjell.undheim@kjemi.uio.no (K. Undheim).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.118



Scheme 1. Reagents and conditions for cyclic ether formation: (i) HCl, EtOH/H_2O (2:1), rt, 100 min; (ii) (a) $COCl_2$, pyridine, CH_2Cl_2, rt, 22 h, (b) MeOH, 30 min.



Scheme 2. Reagents and conditions: (i) $COCl_2$, pyridine, CH_2Cl_2, rt, 5 h; (ii) $CH_2{=}CHCH_2OH$, rt, 30 min.

occurred. Displacement of the cladinose sugar with formation of a 3,6-ether derivative has also been reported.[11] However, no reaction was observed when the corresponding 6-*O*-methyl analogue was treated under the same conditions.[11] It was suggested that cyclic ether formation was caused by a direct nucleophilic displacement by the 6-hydroxyl group. In ring azalides, however, a two-step mechanism with elimination to the conjugated ester and a subsequent addition of the C-6 hydroxy group was proposed for the cyclic 3,6-ether formation.[12]

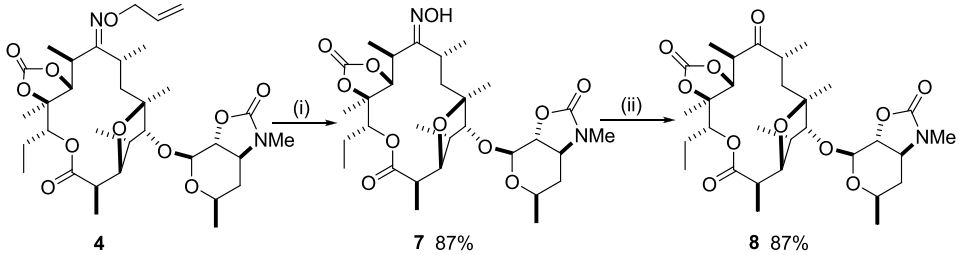
The ether oxime **4** was converted into its 9-oxo derivative (Scheme 3). The free oxime **7** was obtained in 87% yield using triethylammonium formate as the reducing agent under palladium catalysis.[13] Deoximation by treatment with sodium hydrogen sulfite, which is the most frequently reported deoximation agent for macrolide oximes, resulted in a complex product mixture. Presumably, interactions between the cyclic carbonate and the nucleophilic reagent caused side reactions. Oxidative deoximation with Dess–Martin periodinane (DMP) reagent,[14] however, proved to be excellent. Slow addition of DMP to a solution of the oxime **7** in wet dichloromethane afforded almost pure ketone **8** in high yield.[15]

The antibacterial activities of compounds **4**, **7** and **8** were measured as the minimum inhibitory concentrations (MIC) of bacterial growth against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922.[16] The compounds were inactive within the limits of the analysis. Previous reports from our group on the 2′,3′-carbamate derivatives of erythromycin, however, have shown that this structural unit lowers the antibacterial activity of the macrolides due to loss of the basic dimethylamino function.[4,5] Hence, the bioeffect of the 3,6-ether element remains unknown.

In conclusion, we have shown that a 3,6-bridged ether structure is formed when a 3-*O*-descladinosylerythromycin A derivative, with a free hydroxy group at C-6, is treated with phosgene. The cyclisation is rationalised as an intramolecular nucleophilic displacement of the intermediate chlorocarbonate of the 3-hydroxyl group. When the 6-hydroxyl group is blocked as a methyl ether as in clarithromycin, cyclisation does not take place.

Acknowledgements

We thank Alpharma AS and The Norwegian Research Council for financial support and a research fellowship (A.H).



Scheme 3. Reagents and conditions for deprotection: (i) $Pd(OAc)_2$, PPh_3, HCO_2H/NEt_3, EtOH, H_2O, reflux, 55 min; (ii) DMP, wet CH_2Cl_2, rt, 30 min.

Supplementary data

Supplementary data (spectroscopic data and experimental descriptions) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.118.

References and notes

1. Wu, Y.-J. *Curr. Pharm. Des.* **2000**, *6*, 181–223.
2. Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem.* **2003**, *3*, 961–989.
3. Pal, S. *Tetrahedron* **2006**, *62*, 3171–3200.
4. Heggelund, A.; Undheim, K. *Bioorg. Med. Chem.* **2007**, *15*, 3266–3277.
5. Heggelund, A.; Rømming, C.; Undheim, K. *Eur. J. Med. Chem.* **2008**, in press. doi:10.1016/j.ejmech.2007.10.013.
6. (a) Morimoto, S.; Adachi, T.; Matsunaga, T.; Kashimura, M.; Watanabe, Y.; Sota, K. *Eur. Pat. Appl.* **1988**, *0260*, 938 B1; (b). *Chem. Abstr.* **1988**, *109*, 6898q.
7. Gasc, J.-C.; Gouin D'Ambrieres, S.; Lutz, A.; Chantot, J.-F. *J. Antibiot.* **1991**, *44*, 313–330.
8. (9E)-N-Demethyl-3-O-descladinosylerythromycin A 9-(O-allyloxime) *2′,3′-urethane-11,12-carbonate-3,6-ether (4)*: Phosgene (20% in toluene, 7.3 mL, 14 mmol) was added to a solution of (9*E*)-3-*O*-descladinosylerythromycin A 9-(*O*-allyloxime) (**2**) (1.74 g, 2.76 mmol) in dichloromethane (30 mL) and pyridine (2.3 mL, 28 mmol). The reaction mixture was stirred at room temperature for 22 h. Methanol (1.1 mL, 27 mmol) was added to the resulting yellow solution in order to destroy excess phosgene. The mixture was stirred for 30 min, aqueous sodium hydroxide was added and the product was extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and the solvents were removed under reduced pressure. Any remaining pyridine was removed by azeotroping with toluene. Drying at 80 °C and 0.5 mbar provided 1.63 g (91%) of **4** as a pale yellow solid. Purification of the product was not necessary, but the discolouration could be removed by flash chromatography on silica gel using hexane/EtOAc/NEt_3 49:49:2. The product was a white solid with mp 175–181 °C (cyclohexane). Anal. Calcd for $C_{33}H_{50}N_2O_{11}$: C, 60.91; H, 7.74. Found: C, 61.08; H, 7.84. HRMS, ESI pos.: Found 651.3462. Calcd for $M+H^+ = C_{33}H_{51}N_2O_{11}$ 651.3487. IR (ATR, cm^{-1}): 3083w, 2973s (C–H), 2937s (C–H), 2879s (C–H), 2253w, 1799s (C=O), 1767s (C=O), 1743s (C=O), 1646w, 1458s, 1425m, 1382s, 1355s, 1327s, 1282m, 1236s, 1173s, 1154m, 1110s, 1086s, 1079s, 1055m, 1045s, 1021s, 1008s; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, ddt, J = 5.6, 10.5, 17.3 Hz, H-2‴), 5.21 (1H, dq, J = 1.7, 17.3 Hz, H-3‴a), 5.11 (1H, dd, J = 1.6, 10.5 Hz, H-3‴b), 4.97 (1H, dd, J = 2.3, 10.6 Hz, H-13), 4.63–4.61 (2H, m, H-11, H-1′), 4.50 (2H, d, J = 5.6 Hz, H-1‴a+b), 3.71–3.68 (1H, m, H-5′), 3.65 (1H, dd, J = 7.8, 11.4 Hz, H-2′), 3.62–3.54 (1H, m, H-8), 3.58 (1H, d, J = 1.4 Hz, H-5), 3.49 (1H, dd, J = 6.4, 9.8 Hz, H-3), 3.24 (1H, dt, J = 3.5, 11.8 Hz, H-3′), 2.77 (3H, s, NMe), 2.65 (1H, q, J = 7.0 Hz, H-10), 2.50 (1H, dq, J = 6.9, 9.7 Hz, H-2), 1.99–1.96 (1H, m, H-4′a), 1.90 (1H, quin., J = 7.5 Hz, H-4), 1.84–1.74 (3H, m, H-7a+b, H-14a), 1.58–1.47 (2H, m, H-14b, H-4′b), 1.46 (3H, s, Me at C-12), 1.29 (3H, d, J = 6.2 Hz, Me at C-5′), 1.22 (3H, d, J 7.6 Hz, Me at C-4), 1.18 (3H, d, J 6.9 Hz, Me at C-10), 1.09 (3H, d, J = 5.6 Hz, Me at C-2), 1.09 (3H, s, Me at C-6), 1.02 (3H, d, J = 7.0 Hz, Me at C-8), 0.85 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR(125 MHz, $CDCl_3$): δ 174.9 (C-1), 164.8 (C-9), 159.7 (O–(C=O)–N), 154.5 (O–(C=O)–O), 134.4 (C-2‴), 116.8 (C-3‴), 98.8 (C-1′), 92.4 (C-5), 85.8 (C-3), 85.2 (C-12), 84.3 (C-6), 83.6 (C-11), 78.7 (C-2′), 75.5 (C-13), 74.5 (C-1‴), 71.2 (C-5′), 61.2 (C-3′), 46.7 (C-4), 46.4 (C-2), 40.9 (C-7), 36.1 (C-4′), 33.8 (C-10), 30.0 (NMe), 27.2 (C-8), 21.5 (C-14), 20.8 (Me at C-6), 20.7 (Me at C-5′), 20.2 (Me at C-4), 20.1 (Me at C-8), 15.8 (Me at C-10), 13.8 (Me at C-2), 13.5 (Me at C-12), 10.1 (C-15); MS, ESI pos. *m/z* (% rel. int.): 673.2 (22, [M+Na]), 651.2 (100, [$M+H^+$]), 485.7 (5), 481.7 (6), 453.7 (3).
9. LeMahieu, R. A.; Blount, J. F.; Kierstead, R. *J. Antibiot.* **1975**, *28*, 705–706.
10. Istuk, Z. M.; Mutak, S.; Kujundzic, N.; Kragol, G. *Bioorg. Med. Chem.* **2007**, *15*, 4498–4510.
11. Huang, X.-M.; Reamer, D. M.; Miller, L. H.; Gracey, H. E.; Montgomery, S. H.; Pagano, T. G.; Henry, R. F.; Liu, J.-H. *J. Antibiot.* **1996**, *49*, 318–320.
12. Waddell, S. T.; Santorelli, G. M.; Blizzard, T. A.; Graham, A.; Occi, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1321–1326.
13. Yamada, T.; Goto, K.; Mitsuda, Y.; Tsuji, J. A. *Tetrahedron Lett.* **1987**, *28*, 4557–4560.
14. Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **1999**, 760–764.
15. *N-Demethyl-3-O-descladinosylerythromycin A 2′,3′-carbamate-11,12-carbonate-3,6-ether* (8): Dess–Martin periodinane reagent[14] (125 mg, 0.29 mmol) was added slowly over 5 min to a solution of (9*E*)-*N*-demethyl-3-*O*-descladinosylerythromycin A 9-oxime 2′,3′-carbamate-11,12-carbonate-3,6-ether (**7**) (120 mg, 0.20 mmol) in wet dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 30 min. Aqueous sodium hydroxide was added, the product was extracted into dichloromethane, the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and the filtrate was evaporated. The residual white solid (127 mg) was subjected to flash chromatography on silica gel (2 g) using Et_2O:2-PrOH:NEt_3 96:2:2 to yield 102 mg (87%) of a white solid with mp 116–119 °C (acetone/hexane). Calcd for $C_{30}H_{45}NO_{11}$: C, 60.49; H, 7.61. Found: C, 60.28; H, 7.50. HRMS, ESI pos.: Found 618.2859. Calcd for $M+Na^+ = C_{30}H_{45}NNaO_{11}$ 618.2884. IR (ATR, cm^{-1}): 3057w, 2970s (C–H), 2938s (C–H), 2880s (C–H), 1800s (C=O), 1764s (C=O), 1738s (C=O), 1706s (C=O), 1552w, 1457m, 1426m, 1381s, 1356s, 1328s, 1291w, 1274m, 1234s, 1173s, 1153m, 1109s, 1080s, 1044s, 1016s; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.95 (1H, dd, J = 3.0, 10.0 Hz, H-13), 4.73 (1H, s, H-11), 4.63 (1H, d, J = 7.8 Hz, H-1′), 3.73–3.70 (1H, m, H-5′), 3.66 (1H, dd, J = 7.8, 11.3 Hz, H-2′), 3.56 (1H, d, J = 3.0 Hz, H-5), 3.49 (1H, dd, J = 7.6, 9.5 Hz, H-3), 3.25 (1H, dt, J = 3.2, 11.6 Hz, H-3′), 3.00 (1H, q, J = 7.1 Hz, H-10), 2.86–2.82 (1H, m, H-8), 2.79 (3H, s, NMe), 2.47 (1H, dq, J = 6.9, 9.5 Hz, H-2), 2.04–1.98 (2H, m, H-7a, H-4′a), 1.92 (1H, dquin., J = 3.0, 7.3 Hz, H-4), 1.79 (1H, ddq, J = 3.1, 7.5, 14.2 Hz, H-14a), 1.67 (1H, dd, J = 4.1, 15.6 Hz, H-7b), 1.60–1.51 (2H, m, H-14b, H-4′b), 1.48 (3H, s, Me at C-12), 1.30 (3H, d, J = 6.2 Hz, Me at C-5′), 1.21 (3H, d, J = 7.2 Hz, Me at C-4), 1.20 (3H, d, J = 7.0 Hz, Me at C-10), 1.15 (3H, s, Me at C-6), 1.15 (3H, d, J = 6.7 Hz, Me at C-8), 1.11 (3H, d, J = 6.9 Hz, Me at C-2), 0.89 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9 (C-9), 174.8 (C-1), 159.6 (O–(C=O)–N), 153.9 (O–(C=O)–O), 99.3 (C-1′), 92.5 (C-5), 85.0 (C-3), 84.9 (C-12), 83.5 (C-6), 81.2 (C-11), 78.7 (C-2′), 76.4 (C-13), 71.3(C-5′), 61.2 (C-3′), 46.4 (C-4), 46.0 (C-2), 42.5 (C-8), 41.3 (C-10), 41.1 (C-7), 36.1 (C-4′), 30.1 (NMe), 21.9 (C-14), 21.2 (Me at C-6), 20.7 (Me at C-5′), 19.3 (Me at C-8), 19.1 (Me at C-4), 14.0 (Me at C-12), 13.9 (Me at C-2), 12.0 (Me at C-10), 10.2 (C-15); MS, ESI pos. *m/z* (% rel. int.): 1212.8 (9, [2M+Na^+]), 617.9 (100, [$M+Na^+$]), 613.0 (6), 534.0 (4).
16. Vorland, L. H.; Ulvatne, H.; Andersen, J.; Haukland, H.; Rekdal, O.; Svendsen, J.; Gutteberg, T. J. *Scand. J. Infect. Dis.* **1998**, *30*, 513–517.