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Chimeric Azalides with Simplified Western Portions

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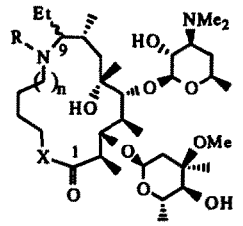
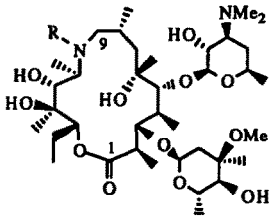
Abstract: **A series of chimeric azalides which are homologous to the azalide antibiotics 2 and 4 in their eastern halves but which have functionally simplified western halves have been semisynthesized from erythromycin A. These chimeric azalides include both macrolactones and macrolactams and vary in ring size from 13 to 16 members. The synthesis, which establishes the ring via a macrolactonization or macrolactamization reaction, requires no protecting groups on the eastern half of the molecule, including the sugars.**

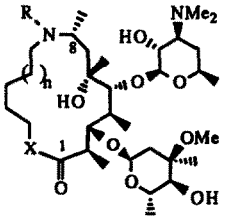
The erythromycin-derived azalide antibiotics, the prototypes of which are 9-deoxo-9a-aza-9a-methyl-9a-homo-erythromycin A (**2b**) and 9-deoxo-8a-aza-8a-methyl-8a-homoerythromycin A (**4b**), combine the safety of erythromycin with an expanded gram negative spectrum and wider tolerance to oral administration.[1] We now report the semisynthesis from erythromycin of a series of chimeric azalides **1a-h** and **3a-h**,[2] which are homologous to **2** and **4**, respectively, in their eastern halves, but which are drastically functionally simplified to a chain of methylene groups in their western halves. Further, although **2** and **4** are both 15 membered macrolactones, **1** and **3** vary in ring size from 13 to 16 members and can alternatively be macrolactams.



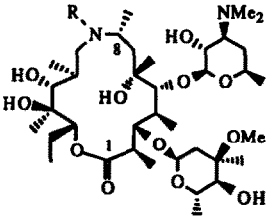
R = H	R = Me
1a X = O, n = 0	**1b** X = O, n = 0
1c X = O, n = 1	**1d** X = O, n = 1
1e X = O, n = 2	**1f** X = O, n = 2
1g X = HN, n = 0	**1h** X = HN, n = 0



2a R = H
2b R = Me

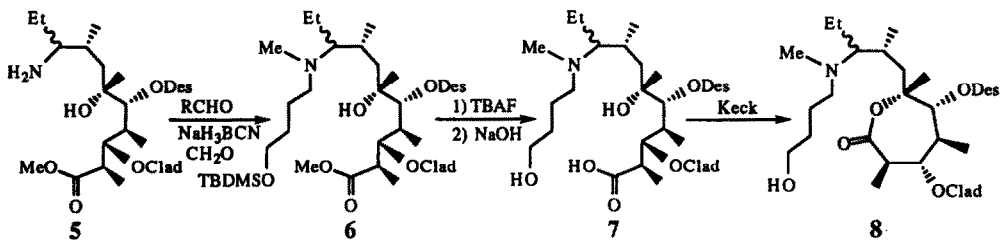


R = H	R = Me
3a X = O, n = -1	**3b** X = O, n = -1
3c X = O, n = 0	**3d** X = O, n = 0
3e X = O, n = 1	**3f** X = O, n = 1
3g X = HN, n = -1	**3h** X = HN, n = -1



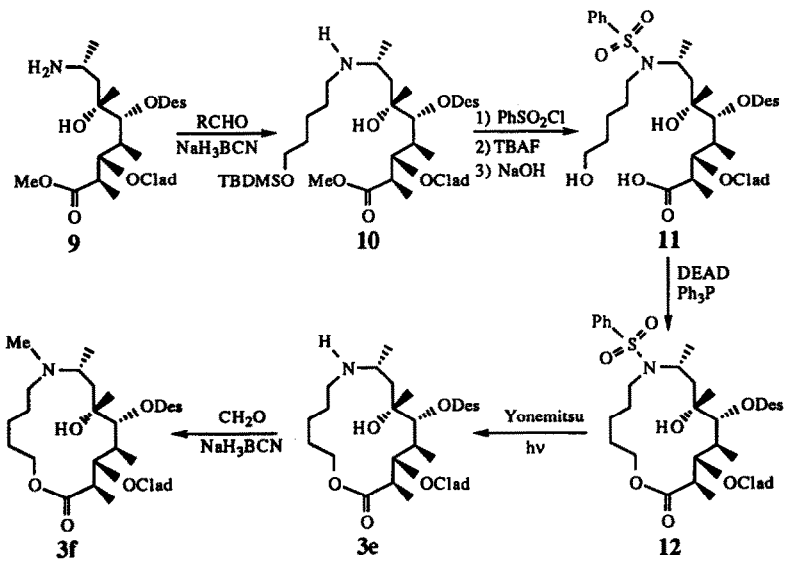
4a R = H
4b R = Me

Our aim was to develop a flexible synthesis of chimeric azalides which would allow any of a large number of western portions to be grafted onto fragments **5** and **9**.[3] We required that all synthesis steps tolerate the unprotected sugars, and generally sought to keep protecting groups to a minimum. Our initial approach to the macrolactones is illustrated below for the attempted synthesis of **1c** (X = O, n = 1). Reductive amination of **5** with 4-t-butyldimethylsilyloxybutanal[4] and sodium cyanoborohydride, followed by addition of formaldehyde, provided the "seco ester" **6** in one pot in 85% yield. Removal of silicon with tetrabutylammonium fluoride and saponification with aq. NaOH/MeOH/THF gave the "seco acid" **7**, which when subjected to the Keck conditions for macrolactonization[5] gave the undesired 7 membered lactone **8**.[6]



5 **6** **7** **8**

In any protocol involving the activation of the carboxylate, it seemed likely that the 6-hydroxy would enjoy a kinetic advantage over the remote ω-hydroxy, and so we turned our attention to the Mitsunobu cyclization, which makes the hydroxy group the leaving group. This approach is illustrated below by the synthesis of **3f** (X = O, n = 1), and began with the 8a-aza fragment **9**. Reductive amination of **9** with 5-t-butyldimethylsilyloxypentanal[4] and sodium cyanoborohydride gave **10**. Protection of the "ring" nitrogen with benzenesulfonyl chloride, removal of the silyl group with fluoride, and saponification with aq. NaOH/MeOH/THF gave the "seco acid" **11**, which when subjected to Mitsunobu conditions for macrolactonization[7] gave the desired 15 membered macrolactone **12** in 66% yield.

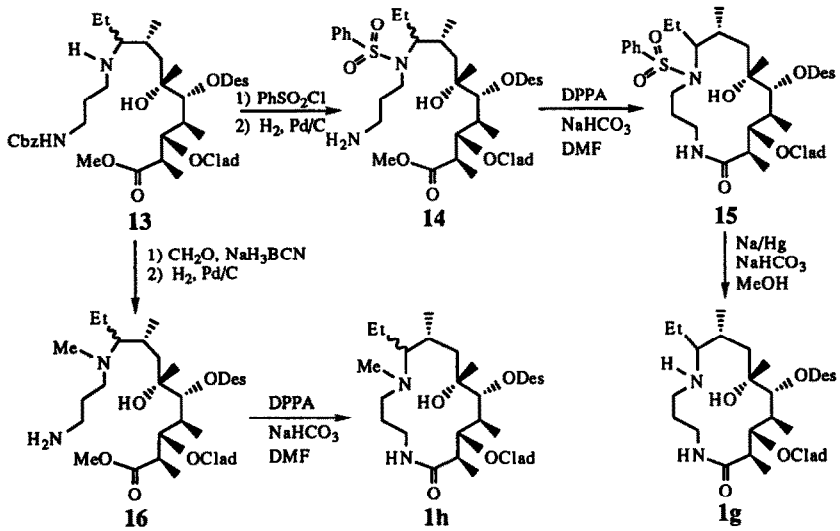


9 **10** **11** **12** **3e** **3f**

The cyclization to form **12** is remarkable because it occurs very efficiently in an erythromycin-like framework that (a) is not only fully glycosylated, but which bears the sugars in a completely unprotected form; and (b) not only contains no cyclic protecting groups (e. g. acetonide) to provide rigidity but also has an unusually floppy western portion that is utterly free of substituents that limit conformational flexibility.[8]

The benzenesulfonyl group could be removed from **12** to form **3e** using Na/Hg in MeOH with solid $NaHCO_3$, but these conditions gave irregular results because of the high pH: ring opening of the macrolactone by methoxide was a serious side reaction. A superior method of deprotection proved to be Yonemitsu's procedure of photolysis of **12** in EtOH through borosilicate glass in the presence of 1,8-dimethoxynaphthalene and either ascorbic acid or hydrazine.[9] These mild conditions provided **3e** cleanly in yields averaging 70%. Reductive amination of **3e** with formaldehyde and sodium cyanoborohydride proceeded in 85% yield to provide **3f**.

Following the above scheme, compounds **1a-f** and **3a-f** were easily prepared. In every case, the yield of the cyclization step was between 60% and 70% of theoretical. It should be noted that the cyclization precursor for compounds **1a-f** was approximately a 1 : 1 diastereomeric mixture at C-9. In the case of compounds **1a-b** and **1c-d** only one of the diastereomers cyclized, yielding a product which was a single diastereomer of uncertain configuration at C-9; for **1e-f**, however, the product of the cyclization was a mixture of diastereomers (presumably because the larger ring size allows the disfavored diastereomer to "reach".)



The synthesis of the macrolactams **1g-h** and **3g-h** paralled that of the macrolactones, and is illustrated above for **1g-h**. The cyclization precursor was prepared by reductive amination of **9** with 3-benzyloxycarbonyl-aminopropanal[10] to give compound **13**. This compound could be elaborated in analogy with the macrolactonization sequence to produce the N-benzenesulfonylated cyclization precursor **14**, and then cyclized with diphenylphosphorylazide/sodium bicarbonate[11] in DMF at -15 °C. Only one of the two diastereomers of **14** cyclized, and so **15** was produced as a single diastereomer of unknown configuration at C-9. Deprotection of the ring nitrogen with sodium amalgam or the Yonemitsu procedure produced **1g**. Compound **1h** can be produced by reductive amination of **1g** with formaldehyde as in the macrolactone series, but here an alternate, shorter sequence

exists: the 9a nitrogen of **13** can be methylated to produce **16**, which cyclizes with DPPA to produce **1h** directly. Here, in contrast to **1g**, the product is a mixture of diastereomers, presumably because the cyclization precursor **16** is conformationally more flexible than **15**. Compounds **3g-h** were prepared in a similar fashion.

In conclusion, chimeric azalides with high homology to erythromycin A in their eastern halves but with simplified western halves can be prepared by a "cut and paste" method, in which an independently synthesized western half is grafted onto fragment **5** or **9** and annealed to form a macrocycle. Macrolactams as well as macrolactones may be produced and ring size may be varied. Further reports on the preparation of chimeric azalides with more highly functionalized western halves and on the bioactivity of the chimeric azalides will be forthcoming.

Acknowledgements: We are grateful to Amy Bernick and Larry Colwell for FAB mass spectra and to Ronald Ratcliffe for many helpful discussions.

References and Notes

1. (a) The term "azalide", originally coined by Pfizer, refers here to ring nitrogen containing derivatives of erythromycin. (b) Compounds **2a-b** are described in Djokic, S. et al. *J. Chem. Soc., Perkin Trans I* **1986**, 1881 and Bright, G. M. et al. *J. Antibiotics* **1988**, *41*, 1029. Compound **2b** is also called azithromycin and marketed by Pfizer as Zithromax™. (c) Compounds **4a-b** are described in Wilkening, R. R.; Ratcliffe, R. W.; Doss, G. A.; Bartizal, K. F.; Graham, A. C.; Herbert, C. M. *Bioorganic and Medicinal Chemistry Letters*, in press.
2. *Chimeric* describes the state of being assembled from disparate pieces, and here refers to an azalide with an eastern half from erythromycin and a western half from an exogenous source.
3. (a) Waddell, S. T.; Blizzard, T. A. *Tetrahedron Lett.* **1992**, *33*, 7827. (b) Waddell, S. T.; Blizzard, T. A. *Bioorganic and Medicinal Chemistry Letters*, in press.
4. 4-t-Butyldimethylsilyloxybutanal was prepared by monoprotection of 1,3-butanediol with TBDMSCl as described in McDougal, P. et al. *J. Org. Chem.* **1986**, *51*, 3388, followed by Swern oxidation. 4-t-Butyldimethylsilyloxypentanal was prepared similarly.
5. Boden, E.; Keck, G. *J. Org. Chem.* **1985**, *50*, 2394.
6. Martin also observed lactonization onto the 6-hydroxy in the cyclization of his glycosylated precursor to erythromycin B. Many erythronolides bearing an unprotected 6-hydroxy group have been cyclized without forming this 7-membered lactone, but they have all contained a 6-membered cyclic acetonide group linking positions 3 and 5. See Martin, S.; Yamashita, M. *J. Am. Chem. Soc.* **1991**, *113*, 5478 and references therein.
7. Mitsunobu, O. *Synthesis* **1981**, 1.
8. To the best of our knowledge, Martin's paper (see footnote 6) is the only report to date of the macrocyclization of a glycosylated erythromycin-like molecule. It should be noted, however, that Martin uses a cyclic acetal protecting group between carbons 9 and 11 to rigidify the western portion of his substrate, whereas we need no such constraint, and in Martin's substrate the desosamine sugar is protected as a carbamate, whereas our method requires no such protection. Further, Martin's Yamaguchi cyclization gave product contaminated with the 7-membered lactone (see footnote 6), so that to effect clean cyclization Martin had to resort to a substrate lacking the 6-hydroxy. In contrast, our Mitsunobu strategy allows the 6-hydroxy to be tolerated without formation of side products.
9. Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.
10. 3-Benzyloxycarbonylaminopropanal was prepared by reaction of 3-aminopropanol with CbzCl, followed by Swern oxidation.
11. (a) de Laszlo, S.; Ley S.; Porter, R. *J. Chem. Soc., Chem. Commun.* **1986**, 344. (b) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

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