CHIMERIC AZALIDES WITH FUNCTIONALIZED WESTERN PORTIONS

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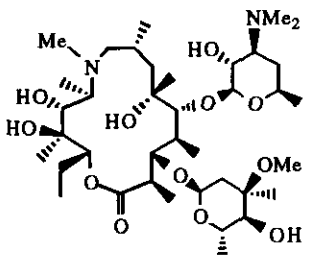
Abstract- A series of chimeric azalides which are homologous to the potent azalide antibiotic 9-deoxo-8a-aza-8a-homoerythromycin A (**2**) in their eastern halves, but which have functionally complex western halves derived from a variety of sources, including carbohydrates, is reported.

The erythromycin derived azalide antibiotics, the prototypes of which are 9-deoxo-9a-aza-9a-methyl-8a-homoerythromycin A (**1**) and 9-deoxo-8a-aza-8a-methyl-8a-homoerythromycin A (**2**), combine the safety of erythromycin with an expanded gram negative spectrum and wider tolerance to oral administration.[1] In a previous report, we described the conversion of the erythromycin-derived acyclic fragment (**3**) to a class of "chimeric" azalides[2] which have eastern portions corresponding to those found in **1** or **2**, but which have western portions (represented by "A" in the figure) simplified to a chain of methylene groups.[3] We now report the extension of our "cut and paste" method to the synthesis of chimeric 8a-azalides with more highly functionalized western portions (**4**).



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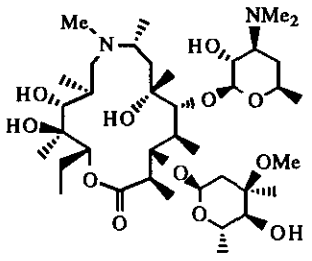

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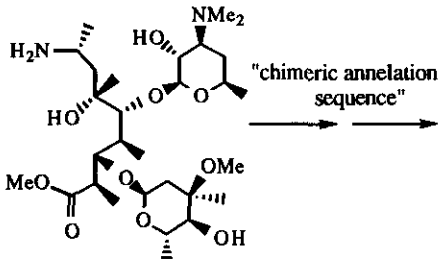

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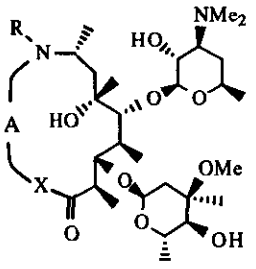
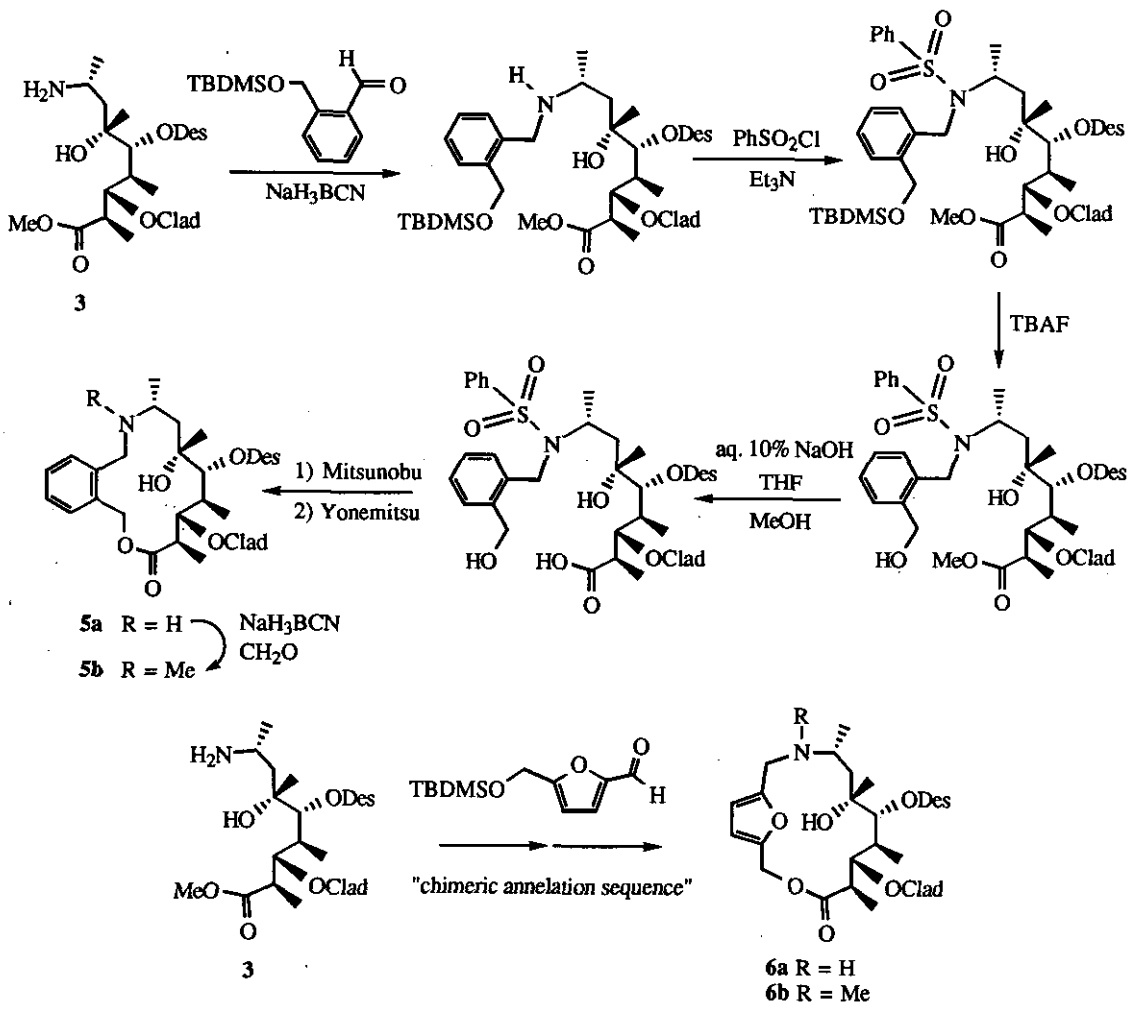


4

R = H or Me
A = functionalized chain of from 3-6 carbons
X = O or HN

ANSA AZALIDES

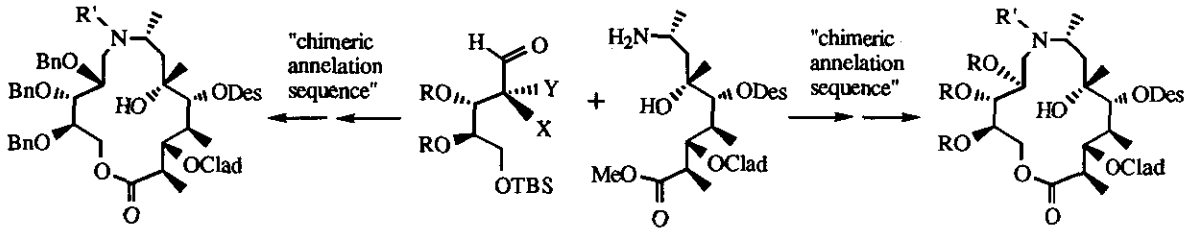
Azalides incorporating an aromatic or heterocyclic ring in the western portion (ansa azalides) have been prepared from amine fragment (3) and suitable aldehydes, following the "chimeric annelation sequence"[3] illustrated in the Scheme which follows. Two examples, **5a-b** and **6a-b**, are shown below.[4]



CHIMERIC AZALIDES WITH CARBOHYDRATE DERIVED WESTERN PORTIONS

Recognizing that carbohydrates are a commercial and generally inexpensive source of optically pure polyhydroxylated carbon chains of variable length and stereochemistry, we desired to exploit them for construction of chimeric azalides bearing highly oxygenated western portions. Shown below is a pair of examples which illustrates the facile control over stereochemistry that this approach provides. A standard series of manipulations produced **7** and **8a-b** from D-lyxose and D-xylose, respectively.[5] These aldehydes were stitched onto amine (3) in the established manner to produce chimeric azalides (**9a-b**) and (**10a-d**).[3] These

carbohydrates were chosen so that the hydroxyl group stereochemistries at positions 11 and 12 would mimic those found in **2**, while the stereochemistry of the hydroxyl at position 10 was varied. It can be seen that the choice of a suitable carbohydrate could yield almost any desired combination of hydroxyl group stereochemistries in the western portion.

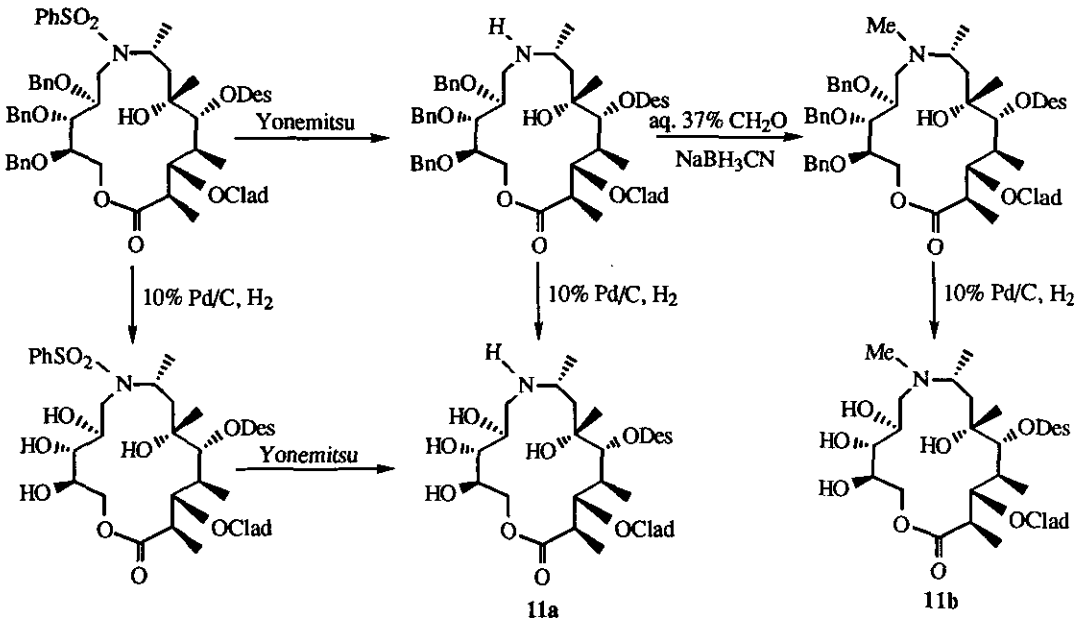


9 a R' = H
b R' = Me

7 X = OBn, Y = H, R = Bn
8a X = H, Y = OMe
b X = H, Y = OBn

10 a R = Me, R' = H
b R = Me, R' = Me
c R = Bn, R' = H
d R = Bn, R' = Me

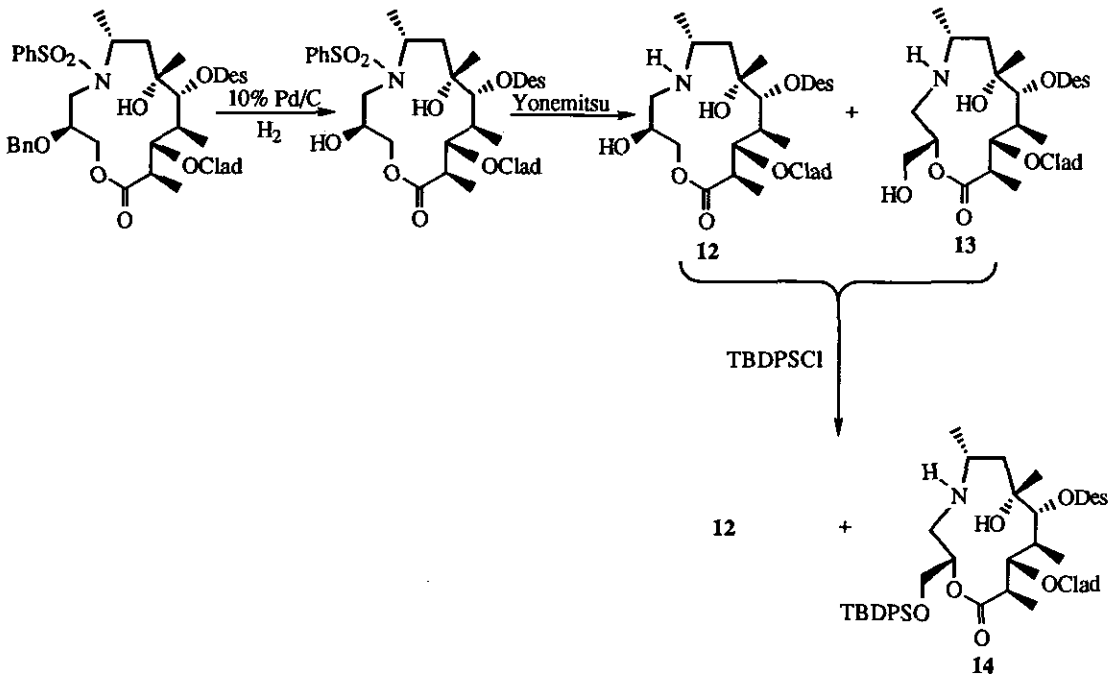
Unprotected hydroxyl groups on the sidechain are incompatible with Mitsunobu cyclization, and must be rendered non-nucleophilic by some protecting group: the above sequence shows that methyl and benzyl are suitable for this purpose. Liberation of the benzyl protected hydroxyls in the western portion was accomplished by hydrogenolysis, as shown in the following Scheme. This operation could be carried out either before or after the Yonemitsu photoreductive cleavage[6] of the benzenesulfonamide. The fully deprotected final products (**11a-b**) in this, the xylose series, had poor solubility and were difficult to purify.



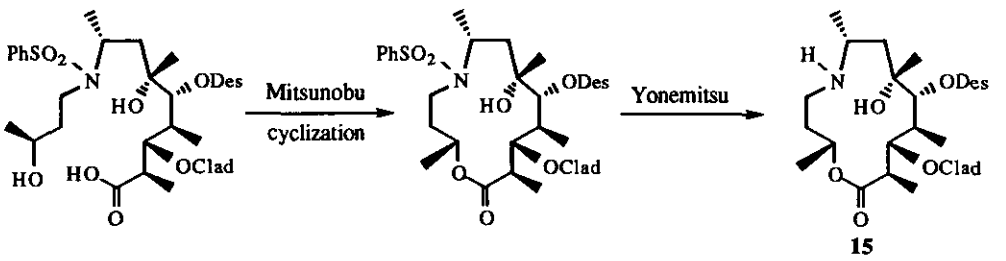
11a

11b

Shown in the Scheme below is the deprotection of a chimera incorporating a sidechain derived from D-glyceraldehyde.[7] Here, translactonization to a difficult to separate one to one mixture of the 12 and 13 membered lactones (**13** and **12** respectively) occurred during the cleavage of the benzenesulfonamide. Treatment of the mixture with *t*-butyldiphenylsilyl chloride resulted in the selective silylation of the primary alcohol in the 12 membered ring compound to give **14**, after which separation by silica chromatography became trivial. The 13 membered ring lactone (**12**) isolated in this manner does not reequilibrate quickly to the original mixture by translactonization during normal handling.

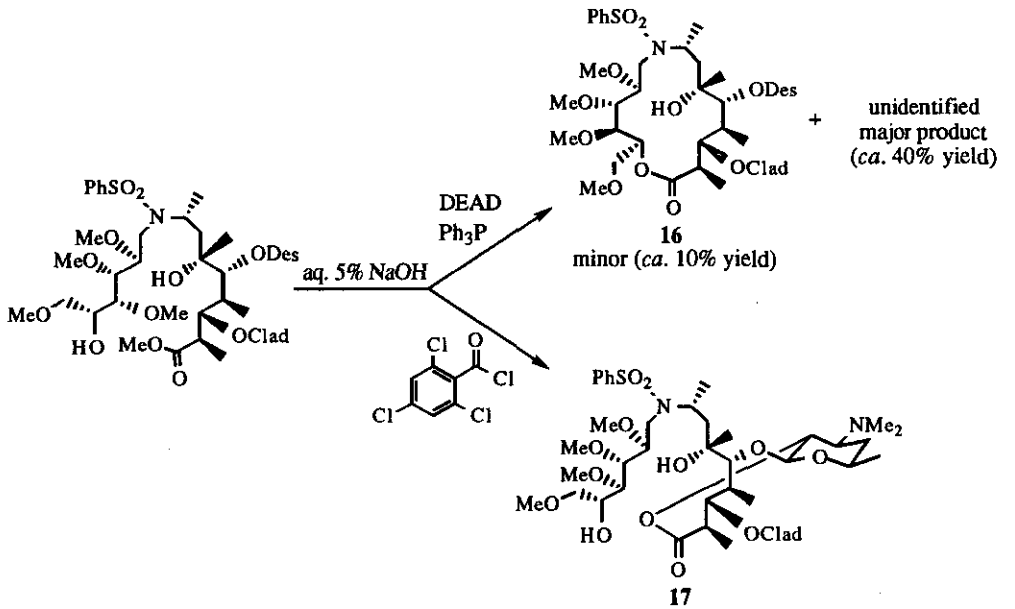


Since the paradigmatic compounds (**1**) and (**2**) have substitution on the carbon bearing the ring oxygen, we desired to extend our method to the preparation of chimeric azalides substituted at this carbon. This requires cyclization onto a secondary carbon atom. In a simple system, this cyclization worked quite well, as illustrated below for the synthesis of the 13 membered chimeric macrolactone (**15**). Yields were similar to those obtained for cyclization onto a primary carbon (60-75%). Reasoning mechanistically, we assume the stereochemistry at the cyclization carbon is inverted by the Mitsunobu displacement, but we have no hard structural data to support this assignment.



15

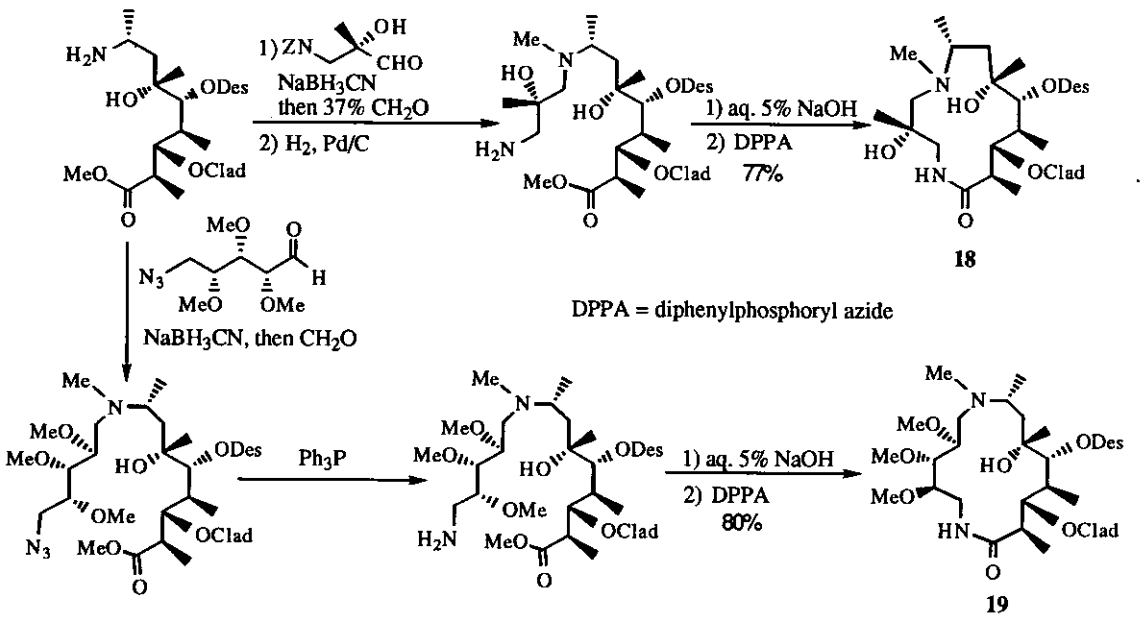
We next attempted cyclization onto a secondary carbon in a highly functionalized system in which the western portion was derived from glucose. Our usual Mitsunobu conditions gave the desired product (16) in low yield (10%) as the minor product of a mixture of two compounds. The major product is unidentified, but appears to be uncyclized and to have incorporated DEAD. An alternative set of cyclization conditions (the Yamaguchi protocol)[8] gave compound (17) by exclusive cyclization onto the 2'-hydroxyl of the desosamine moiety.



MACROLACTAM CHIMERIC AZALIDES WITH OXYGENATED WESTERN PORTIONS

Chimeric macrolactams with functionalized western portions were prepared following a sequence similar to that previously reported for the preparation of simpler lactams.[3] Since the polarity of the macrocyclization is reversed vis a vis the macrolactonization (i. e., here the carboxyl group is the electrophilic partner), the macrolactamization tolerates unprotected nucleophilic groups on the side chain, e. g. hydroxyl groups, and tertiary amines may be present. This greatly simplifies access to chimeras with hydroxylated side chains by

all but eliminating the need for protecting groups, as the short synthesis of the 13-membered chimeric macrolactam (**18**) with the hydroxylated western portion illustrates.[9] Chimeric macrolactams with western portions derived from carbohydrates can be prepared using a variation on the method described above for macrolactones. Here, the carbohydrate derived azido aldehydes are useful and easily prepared sidechain synthons.[10] As shown below for the synthesis of the lyxose derived chimeric lactam (**19**), the azide group allows the reductive amination to procede without complication, and is then selectively reduced to the amine immediately prior to cyclization.



CONCLUSIONS

Although still somewhat limited, our explorations suggest that this "cut and paste" method has considerable scope for converting erythromycin A into a class of chimeric 8a- and 9a-azalides with highly variable western portions. This method is convergent, using separately synthesized western portions which can be derived from an essentially unlimited number of exogenous sources. Carbohydrates are a particularly rich source of highly oxygenated western portions with well defined stereochemistry. It appears that diligent application of this method should allow for detailed therapeutic optimization of the western portion of azalide antibiotics.

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 A. (b) Compound **(1)** , also called azithromycin and marketed by Pfizer as Zithromax™, is described in S. Djokic, G. Kobrehel, G. Lazarevski, N. Loppotar, Z. Tamburasev, B. Kamenar, A. Nagl, and I. Vickovic, *J. Chem. Soc., Perkin Trans.I*, **1986**, 1881 and G. Bright, A. Nagel, J. Bordner, K. Desai, J. Dibrino, J. Nowakowska, L. Vincent, R. Watrous, F. Sciavolino, A. English, J. Retsema, M. Anderson, L. Brennan, R. Borovoy, C. Cimochowski, J. Faiella, A. Girard, D. Girard, C. Herbert, M. Manousos, and R. Mason, *J. Antibiotics*, 1988, **41**, 1029. (c) Compound **(2)** is described in R. Wilkening, R. Ratcliffe, G. Doss, K. Bartizal, A. Graham, and C. Herbert, *Bioorg. and Med. Chem. Lett.*, 1993, **6**, 1287.
2. Chimeric describes the state of being assembled from disparate pieces, and here refers to an azalide with an eastern half derived from erythromycin and a western half derived from an exogenous source.
3. The "chimeric annelation sequence" has been previously described in S. Waddell and T. Blizzard, *Tetrahedron Lett.*, 1993, **34**, 5385.
4. The sidechain for compound **(7)** was prepared by treatment of the commercial 5-(hydroxymethyl)furfural with TBDMS-Cl. The sidechain for compound **(8)** was prepared by selective monosilylation of 1,2-benzenedimethanol (see P. McDougal, J. Rico, Y. Oh,and B. Condon, *J. Org. Chem.* , 1986, **51**, 3389) followed by oxidation with PDC.
5. Carbohydrate-derived sidechains **(7)** and **(8a,b)** were prepared by permethylation or perbenzylation (RI/NaH in DMF) of the appropriate methyl glycoside (here xylose, lyxose or glucose) followed by dithioacetal formation (1,3-propanedithiol/BF_3-OEt_2), protection of the liberated hydroxy with TBDMS-Cl, and conversion of the dithioacetal to the aldehyde (MeI, collidine, acetone.)
6. For photoreductive cleavage of benzenesulfonamides see T. Hamada, A. Nishida, and O. Yonemitsu, *J. Am. Chem. Soc.* , 1986, **108**, 140.
7. The synthesis of 2-(OBn)-glyceraldehyde (sidechain for compounds **(12)** and **(13)**) is described in V. Jager and V. Wehner, *Ang. Chem., Int. Ed. Eng.*, 1989, **28**, 469.
8. a) M. Hikota, Y. Sakurai, K. Horita, and O. Yonemitsu, *Tetrahedron Lett.*, 1990, **31**, 6367. b) J. Inanaga, K. Hirata, H. Saeki, and T. Katsuki, *Bull. Chem. Soc. Jap.*, 1979, **52**, 1989.
9. The sidechain for compound **(9)** was prepared from commercial optically pure (R)-2-methylglycidol by ring opening with azide (see K. B. Sharpless and C. Behrens, *J. Org. Chem.* , 1985, **50**, 5696), reduction of azide by catalytic hydrogenation, protection of the resulting amine with CbzCl, and oxidation of the

primary alcohol to the aldehyde using SO_3/pyridine with DMSO (see J. Parikh and W. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.)

10. Carbohydrate derived azidoaldehyde sidechains (e. g. the sidechain for compound **(19)**) were prepared by a modification of the route described in footnote 5: mesylation followed by azide displacement (nBu_4NN_3, benzene, 65 °C) was substituted for reaction with TBDMS-Cl.

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