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STEREOCONTROLLED FUNCTIONALIZATION OF CYCLOHEPTADIENE; AN APPROACH TO TYLOSIN AND CARBOMYCIN B FROM A COMMON INTERMEDIATE

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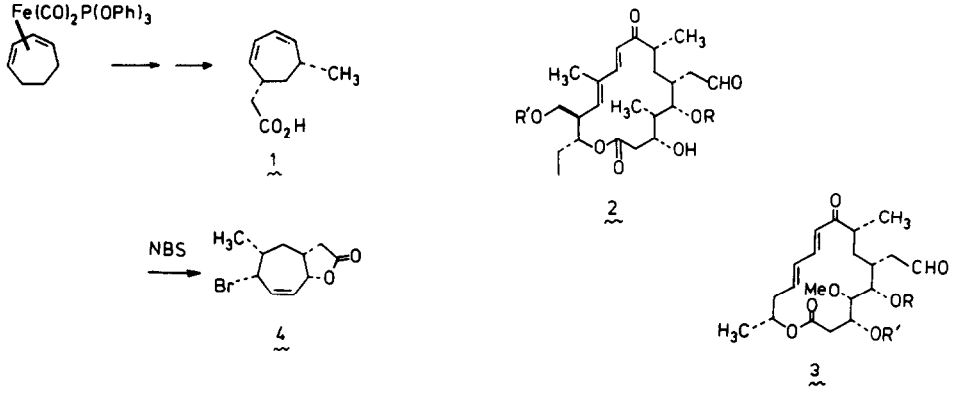
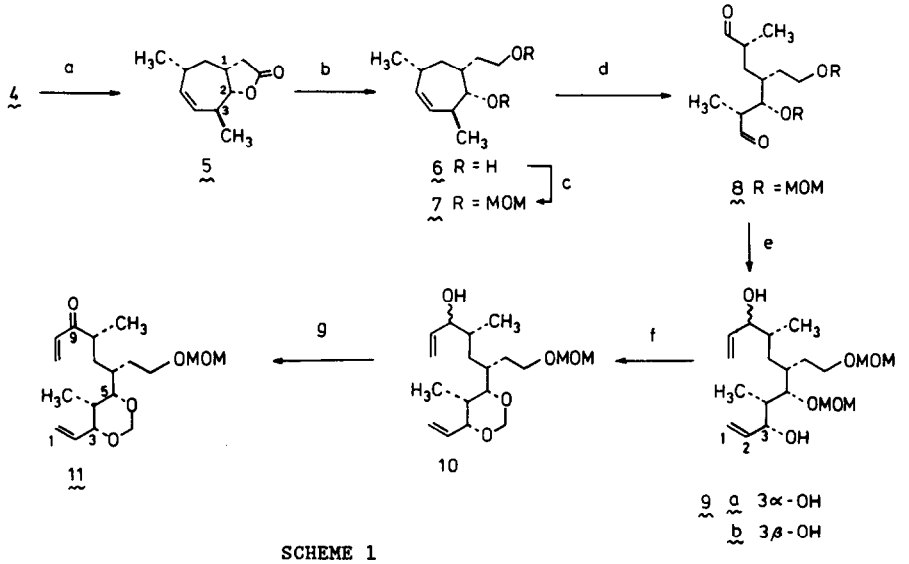
Abstract. Bromolactonization of the cycloheptadienylacetic acid 1 proceeds with good regio- and stereocontrol and provides 4 which serves as a common intermediate for right hand sections of two macrolide antibiotics, tylosin and carbomycin B.

While the six-membered ring has played a major role as a framework for stereocontrolled attachment of substituents in the synthesis of both cyclic and acyclic molecules, the homologous cycloheptane ring has remained comparatively untouched,[1] even though the presence of the extra carbon atom might lead to opportunities for introduction of additional stereocenters. We have been exploring methods for functionalizing cycloheptene and cycloheptadiene derivatives[2] using a transition metal moiety as a means of introducing conformational rigidity and achieving stereocontrolled C-C bond formation. Using organoiron complexes, we have been able to convert cycloheptadiene to the racemic carboxylic acid 1. However, for this to be of use to the synthetic organic chemist, it is essential to determine the outcome of reactions designed to functionalize the cycloheptadiene system, and for this purpose we have focussed on the right hand sections of the 16-membered ring macrolide antibiotics tylosin (2) and carbomycin (3) as synthetic targets.[3] In this Letter we report straightforward transformations of 1 and derived cycloheptene derivatives, illustrating the potential synthetic utility of this traditionally awkward ring size.



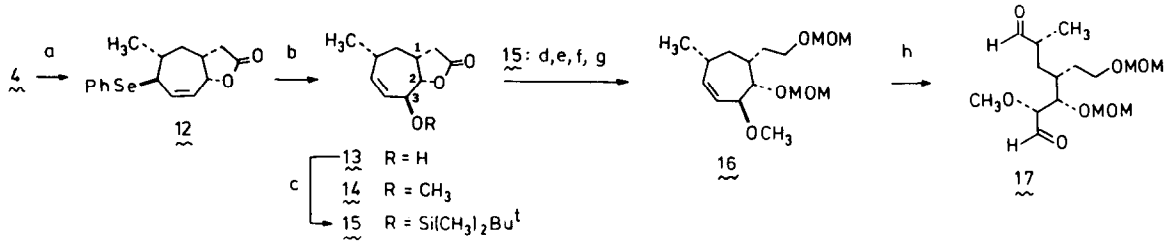
Bromolactonization of 1 (NBS, CH_2Cl_2, reflux 1.5 h) proceeded cleanly by syn- 1,4- addition to give the sensitive lactone 4 in 80% yield.[4] The stereochemical course of this reaction is identical to the previously described phenylselenolactonization,[2a] and the bromolactone has all the features of a common intermediate representing C(3)-C(9) sections of tylosin and carbomycin B, as well as many related macrolides, provided it can be further manipulated.



SCHEME 1

Reagents (yield): (a) Me_2CuLi, Et_2O, 0°C, 1h (40%). (b) $LiAlH_4$, Et_2O, 0°C, 1h (88%). (c) CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, reflux, 8h (90%). (d) O_3, CH_2Cl_2, -78°C, then Me_2S, room temperature, 2h (75%). (e) CH_2=CHMgBr, THF, 0°C, 1h (80-85%). (f) p-TsOH (cat.), acetone, room temperature 48h. (g) Pyridinium chlorochromate, CH_2Cl_2, room temperature, 2h (ca 60% overall from 9).

Conjugate anti displacement[5] of bromide occurred on treatment of 4 with Me_2CuLi, to give intermediate 5 which was converted to the protected diol 7 using standard techniques (Scheme 1).[4] Ozonolysis of 7 afforded the dialdehyde 8 which possesses four of the stereocenters of tylosin. Treatment of 8 with vinylmagnesium bromide gave 9 as a mixture of four diastereomers, in which the major and one other component were tentatively assigned as having the required relative stereochemistry at C(3).[6] Further confirmation of this will form the basis of future work. Treatment of the mixture with a catalytic amount of p-toluenesulfonic acid gave the dioxolane 10[6] which was readily oxidized to the enone derivative 11, obtained as a single diastereomer now representing a C(1)-C(11) subunit of tylosin.



SCHEME 2

Reagents (yield): (a) PhSeNa (generated from $NaBH_4$ and PhSeSePh), CH_2Cl_2, -20°C, 1h (81%). (b) H_2O_2, THF, -20°C, 2h; then Et_3N, 23°C, 10 min (72%). (c) TBDMSOTf, 1h (92%). $LiAlH_4$, Et_2O, 0°C, 1h. (e) CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, reflux, 8h (89%). (f) Bu_4NF, THF, 25°C, 1h (90%). (g) NaH, MeI, THF, reflux, 1h (82%). (h) O_3, CH_2Cl_2, -78°C; then Me_2S, room temperature, 2h (64%).

Treatment of the bromolactone 4 with PhSeNa led to clean S_N2 displacement of bromide, affording the selenolactone 12 (Scheme 2). Oxidation of 12 proceeded with concomitant [2,3]-sigmatropic rearrangement of the initially formed allylic selenoxide to give the hydroxy lactone 13.[4] It is interesting to note that *both* 12 and the epimeric selenolactone[2a] (with PhSe syn to the lactone) undergo clean oxidative conversion to allylic alcohols. Although 13 could be converted directly (CH_3I, NaH, THF) to the methyl ether 14 required as a carbomycin B intermediate, the yield of this transformation was poor. Accordingly, a less direct route was chosen, via the silyl ether 15, which was converted to the desired triol derivative 16. Finally, ozomolysis of 16 afforded the dialdehyde 17, representing a C(3) - C(9) section of carbomycin B which can be further manipulated using the methodology employed for conversion of

8 to 11. The use of organoiron methodology, coupled with manipulation of the product dienes, thus provides a potentially flexible approach to these macrolides.

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References and Notes.

1) Some approaches to the Prelog-Djerassi lactone via cycloheptane derivatives have been described. See: G. Stork and V. Nair, J. Am. Chem. Soc., 1979, 101, 1315; J. D. White and Y. Fukuyama, ibid., 1979, 101, 226; S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou and G. S. Bates, ibid., 1975, 97, 3512; A. J. Pearson and H. S. Bansal, Tetrahedron Lett., 1986, 27, 383.

2) (a) Use of organoiron complexes, see: A. J. Pearson, S. L. Kole and T. Ray, J. Am. Chem. Soc., 1984, 106, 6060; A. J. Pearson and T. Ray, Tetrahedron, 1985, 41, 5765.
(b) Use of organomolybdenum complexes, see: A. J. Pearson and M. N. I. Khan, J. Org. Chem., 1985, 50, 5276; A. J. Pearson, M. N. I. Khan, J. C. Clardy, and H. Gun-heng, J. Am. Chem. Soc., 1985, 107, 2748.

3) For a recent review of macrolide synthesis covering the tylosin and carbomycin B literature, see: I. Paterson and M. M. Mansuri, Tetrahedron, 1985, 41, 3569.

4) All new compounds were obtained as racemic mixtures and were fully characterized by IR and NMR spectroscopy. Elemental composition was confirmed by combustion analysis and/or high resolution mass spectrometry, except for bromolactone 4 whose sensitivity precluded rigorous purification. Selected NMR data ($CDCl_3$) is as follows: 5: δ5.43 (1H, br., d, J = 11.4 Hz), 5.12 (1H, ddd, J = 11.4, 3.3, 2 Hz), 4.34 (1H, dd, J = 10.7, 7.4 Hz, 2-H), 2.84-2.7 (2H, m), 2.33 -2.22 (2H, m), 1.85-1.55 (3H, m), 1.16 (3H,d, J = 6.9 Hz), 1.05 (3H, d, J = 7.0 Hz). 8: δ 9.69 (1H, s), 9.53 (1H, d, J = 2 Hz), 4.61 and 4.55 (each 1H, ABq, J = 6.9 Hz, secondary O $\underline{CH_2}$O diastereotopic), 4.56 (2H, s, primary O$\underline{CH_2}$O), 3.93 (1H, t, J = 5 Hz) 3.52 (2H, t, J = 6.3 Hz), 3.3 (3H, s), 3.27 (3H, s), 1.13 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 7 Hz). 11: δ 6.40 (1H, dd, J = 16, 9.8 Hz), 6.24 (1H, dd, J = 16, 2.3 Hz), 5.73 (1H, dd, J = 9.8, 2.3 Hz), 5.7 (1H, m), 5.24 (1H, d, J = 16.5 Hz), 5.12 (1H, d, J = 9.4 Hz), 5.00 and 4.59 (each 1H, d, J = 5.9 Hz, dioxolane OCH_2O), 4.58 (2H, s), 4.1 (1H, m), 3.53 (2H, t, J = 7.2 Hz), 3.37 (1H, m), 3.34, (3H, s), 3.04 (1H, sextet, J = 6.5 Hz, 8-H), 1.95-1.05 (5H, m), 1.08 (3H, d, J = 7.0 Hz), 0.90 (3H, d, J = 6.9 Hz). 13: δ 5.48 (1H, br. d, J = 12 Hz), 5.45 (1H, br. d, J = 12 Hz). 4.72 (1H, br. d, J = 9.8 Hz, 3-H), 4.50 (1H, dd, J = 9.8, 7.9 Hz, 1-H), 2.80 (2H, m), 2.31 (2H, m). 1.66 (2H, m), 106 (3H, d, J = 7 Hz).

5) In agreement with this result, Goering has recently shown that γ-alkylation of sterically unbiased allylic acetates, using organocuprates proceeds with anti stereochemistry, see: H. L. Goering and C. C. J. Tseng, J. Org. Chem., 1983, 48, 3986 and references cited therein. The yield of this reaction is low (40%) due to competing debromolactonization to regenerate the acid 1 which can be extracted and recycled. The assignment of stereochemistry of 5 is consistent with the large diaxial coupling of 2-H and 3-H (J = 10.7 Hz). Compounds prepared by us, having α-stereochemistry at C(3) show $J_{2,3}$ ~ 1-2 Hz (ref 2a). Similarly, 13 shows $J_{2,3}$ = 9.8 Hz.

6) This stereochemical result is expected from Cram addition, and in practice an inseparable, approximately 5:2:2:1 mixture of diastereomers is obtained. The dioxolane 10 is obtained as a mixture of two diastereomers, converted to a single enone 11 on oxidation, indicating that one C(3) stereoisomer does not cyclize. It may be noted that chelation effects from a β-alkoxy substituent during addition of vinyl Grignard reagents are known to be rather weak, see: W. C. Still and J. H. McDonald, Tetrahedron Lett., 1980, 21, 1035.

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