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A NEW SYNTHETIC METHOD OF 3-ACYLTETRONIC ACID DERIVATIVES AND ITS APPLICATION TO THE SYNTHESIS OF ISOASPERTETRONIN A(ISOGREGATIN A)

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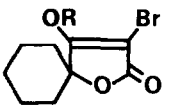
Abstract: A new synthetic method of 3-acyltetronic acid derivatives from the corresponding 3-bromo compound via lithiation with n-BuLi followed either by acylation with acid chloride or better by first reacting with aldehyde and then subsequent oxidation with active MnO_2 is described. A revised structure 10 for aspertetronin A(gregatin A) was presented based on the synthesis of the proposed structure 8 and spectral comparison of a model compound 12 with the natural product.

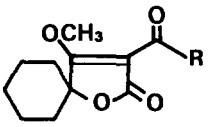
In our recent program directed towards the total synthesis of those antibiotics bearing 3-acyltetronic acid moiety such as tetrocarcin[1] (and/or kijanimicin[2]) and aspertetronins,[3] we had required a new access to this system. The existing standard method which involves Lewis acid catalyzed Friedel Crafts acylation(or Fries rearrangement of O-acylate)[4] is apparently not applicable to our target molecules possessing sensitive functionalities. For solution to this problem, it was our idea to employ 3-lithio derivative for the substrate activation. Preliminary model experiment performed on 3-lithio-5,5-pentamethylenetetronic acid methyl ester proved it to be the case. Since a similar methodology appeared very recently in this Letter,[5] we were prompted to describe our own results obtained for the above compound and application of the new method to the synthesis of aspertetronin A(gregatin A) of the proposed structure 8 leading to the correction of the structure to 10.

Methyl 3-bromo-5,5-pentamethylenetetronate(2) obtained by methylation of the corresponding acid 1[6] was treated with n-BuLi in THF at -78° and the resulting 3-lithio derivative was reacted with selected acid chlorides, RCOCl(R=i-Pr, t-Bu, MeCH=CH-, Ph). The 3-acylated product 3a-d obtained in varying yields(a,44%; b,94%; c,14%; d,100%) were characterized by infrared and ultraviolet spectra.[7] Unacceptable yields obtained in 3a and 3c might be responsible to the presence of enolizable hydrogen in the product as supported by the formation of debrominated 3-H compound as an only identifiable byproduct. Variations of experimental procedure and use of imidazolide in place of chloride did not improve the yield. However, nearly quantitative overall yields were secured by a two step sequence——first reacting with corresponding aldehydes to give carbinols 4a-d and then oxidation with active MnO_2. For 4c other oxidants, PCC and PDC, caused rapid allylic migration of the hydroxyl group and therefore the compound 5 was only characterizable product.[8] The present synthetic method of 3-acyltetronic acids should have advantage over that of Clemo and Pattenden[5] in that ours will be also useful for 5-monosubstituted cases.

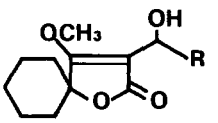
Having developed a steady route to 3-acyltetronate, we next attempted application of the methodology to the synthesis of aspertetronin A(gregatin A), to which the structure 8 had been



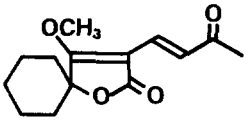
1 R = H
2 R = CH_3



3a–d



4a–d



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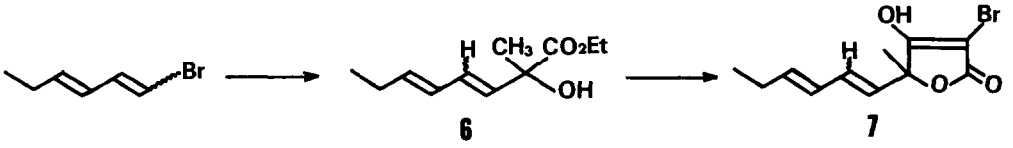
a	$(CH_3)_2CH-$
b	$(CH_3)_3C-$
c	$CH_3CH=CH-$
d	C_6H_5-



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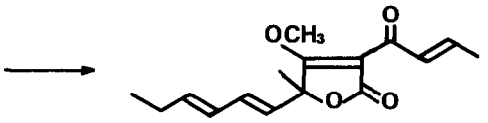

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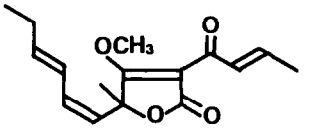

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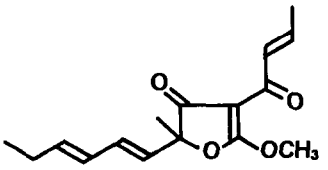

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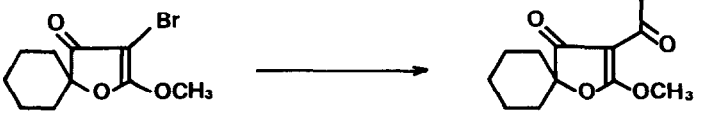

11 **12**

assigned.[3] α-Hydroxyester 6[9] was obtained in 44% yield by the reaction of ethyl pyruvate with 1-lithio-1,3-hexadienes generated by reacting a ca. 1:1 mixture of (1E,3E) and (1Z,3E) 1-bromo-1,3-hexadienes[10] with t-BuLi. The compound 6 was acetylated with acetic anhydride in the presence of 4-dimethylaminopyridine and the acetate product isolated in 84% yield by usual manner was successively treated with 2 equiv of LDA(in THF, -78°)[11] and 1 equiv of Br_2 to give 3-bromotetronic acid 7.[9] The compound 7 without purification was treated with ethereal diazomethane to give 4-methoxy-3-bromo-2-furanone[12] in 23% overall yield after silica gel chromatography. The latter compound was subjected to lithiation with n-BuLi followed by condensation with crotonic aldehyde. The crude carbinol so produced was immediately oxidized with active MnO_2 to give a 1:1 mixture of geometrical isomers 8 and 9 in 34% overall yield. They were separated by HPLC and were fully characterized by spectral data.[13] The spectral data of the (E,E) isomer 8, however, did not coincide with those of aspertetronin A(gregatin A). Careful comparison of the spectral data of 8 with those of gregatin A[14] urged us to assign the alternative structure 10 for the natural product,[15] the same conclusion drawn very recently by Clemo and Pattenden[5] who named the compound as isoaspertetronin A. In order to confirm the revised structure 10 by spectral means, we had decided to synthesize the model compound 12 possessing the same furanone chromophore as 10.

3-Bromo-2-methoxy-5,5-pentamethylene-5H-furan-4-one(11) obtained as a byproduct during O-methylation of 1 with diazomethane was treated with n-BuLi in THF at -100° for several minutes,[16] and the resulting lithio derivative was reacted with crotonic aldehyde. The carbinol product isolated by usual manner was immediately oxidized with active MnO_2 in CCl_4 at room temperature giving the desired model compound 12[17] which was isolated in 12% overall yield[18] by preparative TLC. The compound 12 exhibited characteristic NMR feature for the crotonyl group observed with gregatin A(10)— α-H is unusually more deshielded than β-H. The fact could be responsible to the conformation of the side chain as depicted in the structures. The IR and UV spectra obtained with 12 were also supported the corrected structure 10 for aspertetronin A(gregatin A).[19]

Based on the model experiment described above, we are currently engaging in the total synthesis of aspertetronin A and the result will be reported elswhere.

References and Notes

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7) IR cm^{-1}: 3a(mp 60°)(KBr), 1750, 1680, 1615; 3b(mp 73°)(KBr), 1750, 1680, 1635; 3c(oil)(film), 1750, 1675, 1655, 1625; 3d(mp 154°)(KBr), 1745, 1660, 1630. UV(MeOH) λmax nm(log ε): 3a, 244 (3.89); 3b, 224(3.96); 3c, 223(3.67); 3d, 256(4.12).

8) IR(KBr) cm^{-1}: 1740, 1615, 1590; NMR(CCl_4, 90 MHz) δppm: 2.26(3H, s), 4.36(3H, s), 7.33(1H, d, J=18 Hz), 7.54(1H, d, J=18 Hz).

9) A mixture of geometrical isomers as indicated in the structural formula.

10) Prepared after the method of D.R. Williams, K. Nishitani, W. Bennett, and S.Y. Sit, Tetrahedron Lett., 22, 3745(1981).

11) R.E. Ireland and W.J. Thompson, J. Org. Chem., 44, 3041(1979).

12) O-Methylation of 3-bromotetronic acids with diazomethane usually affords mainly 4-methoxy-2-furanones(e.g. 2) accompanied by 2-methoxy-4-furanones(e.g. 11). For 7, however, we did not observe the formation of 2-methoxy-4-furanone isomer (by NMR) which could have served as a key intermediate for the preparation of the revised structure 10. We are currently investigating the regiospecific O-methylation of tetronic acids leading to 2-methoxy-4-furanones. So far, application of the method of A.S. Wengel et al.(Tetrahedron, 35, 2181(1979)) to 7 provided no fruitful result, only decomposition of the substrate being observed.

13) 8: NMR($CDCl_3$, 200 MHz) δppm, 0.98(3H, t, J= 7 Hz), 1.56(3H, s), 1.94(3H, dd, J=7, 1 Hz), 2.10 (2H, quintet, J=7 Hz), 4.02(3H, s), 5.55(1H, d, J=16 Hz), 5.84(1H, dt, J=16, 7 Hz), 6.01(1H, dd, J=16, 10 Hz), 6.36(1H, dd, J=16, 10 Hz), 6.70(1H, dq, J=16, 1 Hz), 6.94(1H, dq, J=16, 7 Hz); IR(film) cm^{-1}, 1750, 1675, 1655, 1625; UV(MeOH) λmax nm(log ε), 226(4.59), 266(sh, 4.13); Mass spectrum(m/e), 276(M^+), 219, 69, 43, 41, 39. 9: NMR($CDCl_3$, 200 MHz) δppm, 0.99(3H, t, J=7 Hz), 1.61(3H, s), 1.92(3H, dd, J=7, 1 Hz), 2.13(2H, quintet, J=7 Hz), 4.04(3H, s), 5.26 (1H, d, J=12 Hz), 5.81(1H, dt, J=16, 7 Hz), 6.07(1H, t, J=12 Hz), 6.59(1H, ddt, J=16, 12, 1 Hz), 6.70(1H, dq, J=16, 1 Hz), 6.95(1H, dq, J=16, 7 Hz); IR(film) cm^{-1}, 1760, 1680, 1660, 1625.

14) We are grateful to Dr. K. Kobayashi, Hokkaido University for providing us the spectral data of gregatin A and B.

15) In NMR, remarkably deshielded vinyl protons of the crotonyl group in aspertetronin A[δppm: 7.32(α-H), 7.18(β-H)] strongly suggested the structure 10 for the natural product. Note δppm: 6.70(α-H) and 6.94(β-H) for our synthetic isoaspertetronin(8). For the interpretations of IR and UV spectral data, we agree with the view of Clemo and Pattenden.

16) We found that 3-lithio compound derived from 11 was readily transformed to the lithiation product of 2, especially at elevated temperatures and/or by prolonged lithiation reaction. This remarkable isomerization will be a subject of further investigation.

17) mp 135°. IR($CHCl_3$) cm^{-1}, 1700, 1665, 1620, 1545; UV(MeOH) λmax nm(log ε), 243(4.47), 275(4.27); NMR($CDCl_3$, 200 MHz) δppm, 1.88(3H, dd, J=7, 1 Hz), 4.21(3H, s), 7.00(1H, dq, J=16, 7 Hz), 7.23 (1H, d, J=16 Hz); Mass spectrum(m/e), 250(M^+), 124, 69.

18) The low yield of 12 should be responsible largely to the isolation technique, since the reaction products were revealed by NMR to be a mixture of 12(67%), 3c(8%), and debrominated products——4-furanone(18%) and 2-furanone(7%).

19) The UV λmax at 298 nm for 10, bathochromic shifted when compared with the corresponding band 275 nm for 12, could be interpreted as due to a partial pi conjugation of the diene system to the furanone chromophore.

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