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Syntheses of Aureothin, Isoaureothin, and Related Geometrical Isomers

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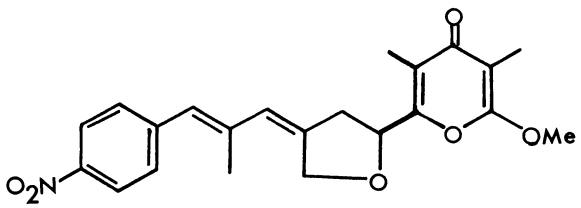
Aureothin, isoaureothin, and related compounds have been synthesized in short steps starting from 3,5-dimethyl-6-formyl-4-methoxy-2-pyrone. In addition, the geometry of the conjugated double bonds in isoaureothin and its isomers has been unambiguously determined on the basis of NOE experiments.

Both aureothin (1) and isoaureothin (2), toxic metabolites containing a nitro group, were first isolated by Maeda from the mycelium of Streptomyces thioluteus,[1] and their structures were also elucidated by Hirata et al. in 1961,[2] wherein the geometry of the exocyclic double bond attached to a tetrahydrofuran ring remained unsettled. In 1976, furthermore, spectinabilin (3) was isolated as a metabolite of Streptomyces spectabilis.[3] This metabolite has been proved to give some remarkable inhibition of RLV reverse transcriptase, and is quite similar to aureothin (1) in its structure, wherein the former contains two more propionate units than aureothin. We describe herein the synthesis of isoaureothin (2), which has been already converted into aureothin (1) through desmethylisoaureothin (4),[2,4] starting from the known 3,5-dimethyl-6-formyl-4-methoxy-2-pyrone.[5] In addition, the remaining three geometrical isomers of isoaureothin (2) have been also synthesized in connection with the geometry of the exocyclic double bond in 2, which remains unsettled. Presumably, spectinabilin (3) also has the same geometry as those of both aureothin (1) and isoaureothin (2).



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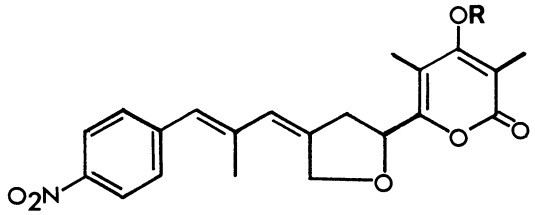
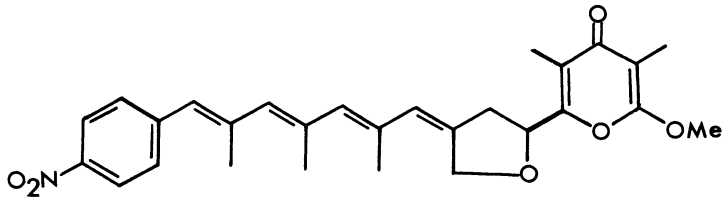


2 R = Me
4 R = H



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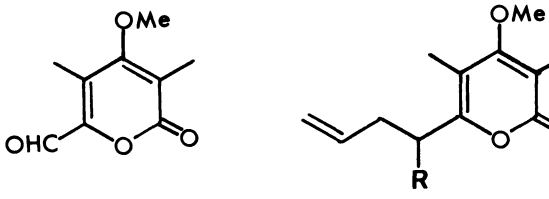
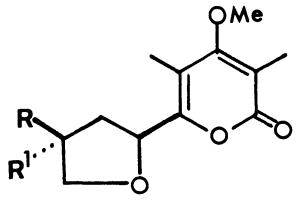
The known 3,5-dimethyl-6-formyl-4-methoxy-2-pyrone (5)[5] was treated with allylmagnesium bromide (1 equiv.) in THF under argon (0 °C, 55 min) to afford the corresponding alcohol (6),[6] in 80% yield, which was further treated with CBr_4 (2 equiv.) - Ph_3P (2 equiv.) in THF under argon (room temp, 1.5 h) to give a bromo compound (7)[6] in 81% yield. On oxidation with OsO_4 (1.2 equiv.) - pyridine (2 equiv.) in dioxane (room temp, ca. 1.7 h) followed by reduction with aq. $NaHSO_3$ (room temp, overnight), this compound (7) was readily converted into the desired tetrahydrofurans (8 and 9)[6,7] and a diol (10)[6] in 84 (8/9 = 2 : 3) and 12% yields, respectively. When treated with Et_3N (10 equiv.) in benzene (refluxing temp, overnight), the latter was readily converted into a mixture of the two tetrahydrofurans (8 and 9) in 94% yield. Therefore, the overall yield of the diastereo mixture (8 and 9) from 6 was 76%.[8] This mixture was further subjected to Jones oxidation in acetone (0 °C, 1 h) to afford the desired ketone (11)[6] as a sole product, in 80% yield. Finally, this ketone was treated with a triphenylphosphorane (12)[9] in toluene under argon (refluxing temp, overnight) to

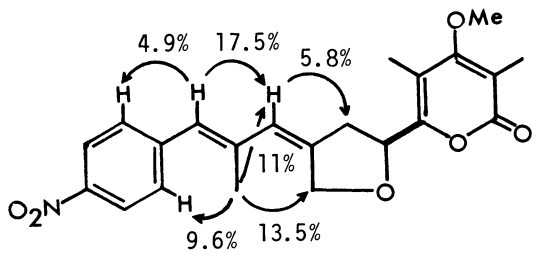


5

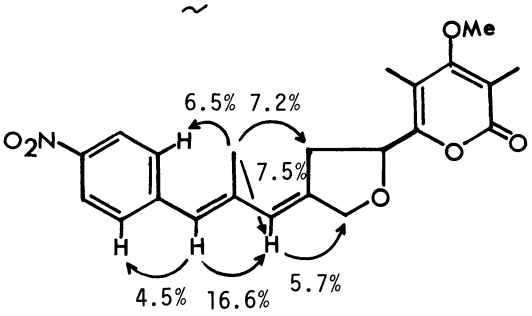
6 R = OH
7 R = Br



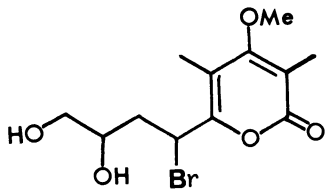
8 R = OH, R^1 = H
9 R = H, R^1 = OH
11 R·R^1 = O



[A]



[B] = 13



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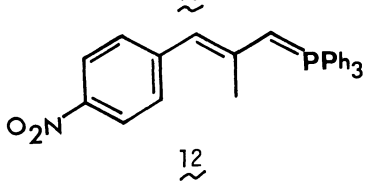

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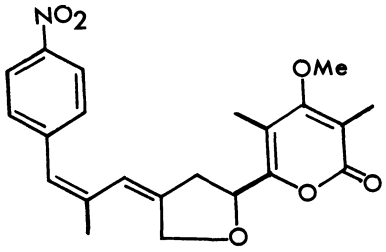

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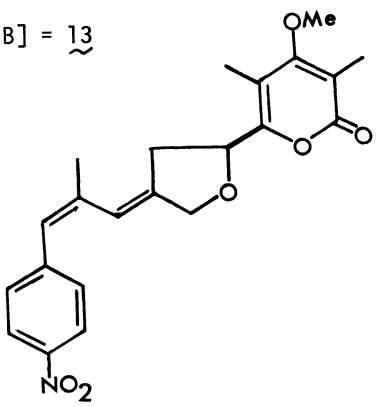

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afford two condensation products (2 and 13)[6] in 41% yield (relative ratio: 2/13 ≃ 1).[10] One of them is completely identical with natural isoaureothin (2), in all respects of IR and ^{1}H NMR spectral data and chromatographic behavior (Kieselgel PF_{254}), which has been converted into aureothin (1) through desmethylisoaureothin (4) as reported by Nakata.[4] The structures of these two geometrical isomers are based on their ^{1}H NMR spectra with aid of NOE experiments, as shown in [A] and [B], respectively. Interestingly, these two compounds (2 and 13) are not so stable as expected: when allowed to stand at room temperature for a few days, they were gradually converted into the corresponding different isomers (14 and 15),[6,11] respectively. Further synthetic study on spectinabilin (3) is in progress.

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References

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3) K. Kakinuma, C. A. Hanson, and K. L. Rinehart, Jr., Tetrahedron, 32, 217 (1976).
4) H. Nakata, Bull. Chem. Soc. Jpn., 33, 1688 and 1693 (1960).
5) E. Suzuki and S. Inoue, Synthesis, 1975, 259; E. Suzuki, H. Sekizaki, and S. Inoue, J. Chem. Res. (M), 1977, 2273.
6) The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: 6: $C_{12}H_{16}O_4$ [m/z 224.1067(M^+)]; IR (film) 3420, 1695 br., 1640, and 1568 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98(3H, s), 2.05(3H, s), 2.55(2H, br.t, J = 7.5 Hz), 3.84(3H, s), 4.66(1H, t, J = 7.5 Hz), 5.07(1H, br.d, J = 11 Hz), 5.10(1H, br.d, J = 18 Hz), and 5.73(1H, ddt, J = 11, 18, and 7.5 Hz). 7: IR (film) 1705 br., 1640, and 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.88(1H, t, J = 7.5 Hz) (any peak due to the molecular ion has not been detected). 8: mp 92 - 95 °C (from hexane - benzene); $C_{12}H_{16}O_5$ [m/z 240.1014(M^+)]; IR (film) 3435, 1690 br., 1645, and 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.0 - 2.7(2H, complex), 2.07(6H, s), 3.80(1H, overlapped with MeO signal), 3.84(3H, s), 4.02(1H, br.d, J = 10 Hz), 4.54(1H, m), and 4.96(1H, dd, J = 6, 8 Hz). 9: $C_{12}H_{16}O_5$ [m/z 240.1016(M^+)]; IR (film) 3415, 1690, 1680, 1640, and 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.9 - 2.6(2H, m), 2.05(6H, s), 3.82(3H, s), 3.8 - 3.86(1H, overlapped with MeO signal), 4.14(1H, dd, J = 4, 10 Hz), 4.66(1H, m), and 5.19(1H, dd, J = 7.5, 9.5 Hz). 10: $C_{12}H_{16}O_5$ [m/z 240.0982(M^+ - HBr)]; IR (film) 3410, 1690 br., 1640, 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.07(6H, s), 2.0 - 2.5(2H, complex), 3.35 - 3.8(3H, complex), 3.85(3H, s), and 5.1 - 5.35(1H, complex). 11: mp 89 - 90 °C (from hexane - benzene); $C_{12}H_{14}O_5$ [m/z 238.0834(M^+)]; IR (film) 1760, 1705, 1645, and 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08(6H, s), 2.62(1H, dd, J = 7.5, 18 Hz), 2.93(1H, dd, J = 7.5, 18 Hz), 3.85(3H, s), 3.91

(1H, d, J = 16.5 Hz), 4.22(1H, d, J = 16.5 Hz), and 5.35(1H, t, J = 7.5 Hz). 2: $C_{22}H_{23}O_6N$ [m/z 397.1506(M^+)]; ^1H NMR ($CDCl_3$) δ 2.04(6H, s), 2.06(3H, s), 2.90(1H, dd, J = 7.5, 16.1 Hz), 3.13(1H, dd, J = 7.5, 16.1 Hz), 3.83(3H, s), 4.66(1H, d, J = 14.2 Hz), 4.88(1H, d, J = 14.2 Hz), 4.99(1H, t, J = 7.5 Hz), 6.15(1H, s), 6.35(1H, s), 7.40(2H, d, J = 9.0 Hz), and 8.20(2H, d, J = 9.0 Hz). 13: $C_{22}H_{23}O_6N$ [m/z 397.1533(M^+)]; IR (film) 1705, 1645, 1580 br., and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04(3H, s), 2.06(3H, s), 2.12(3H, s), 3.07(1H, dd, J = 7.3, 16.0 Hz), 3.18(1H, dd, J = 7.3, 16.0 Hz), 3.83(3H, s), 4.48(1H, d, J = 13.7 Hz), 4.72(1H, d, J = 13.7 Hz), 5.06(1H, t, J = 7.3 Hz), 6.07(1H, s), 6.48(1H, s), 7.41(2H, d, J = 10.8 Hz), and 8.20(2H, d, J = 10.8 Hz). 14: $C_{22}H_{23}O_6N$ [m/z 397.1536(M^+)]; IR (film) 1705, 1645, 1590, 1575, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02(3H, s), 2.06(6H, s), 2.84(1H, dd, J = 7.1, 16.1 Hz), 3.06(1H, dd, J = 7.1, 16.1 Hz), 3.82(3H, s), 4.42(1H, d, J = 14.2 Hz), 4.65 (1H, d, J = 14.2 Hz), 4.98(1H, t, J = 7.1 Hz), 6.29(1H, s), 6.37(1H, s), 7.43 (2H, d, J = 8.8 Hz), and 8.18(2H, d, J = 8.8 Hz). 15: $C_{22}H_{23}O_6N$ [m/z 397.1524 (M^+)]; IR (film) 1705, 1645, 1590, 1575, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (3H, s), 2.06(3H, s), 2.14(3H, s), 2.87(1H, dd, J = 7.1, 16.1 Hz), 2.97(1H, dd, J = 7.1, 16.1 Hz), 3.81(3H, s), 4.42(1H, d, J = 14.2 Hz), 4.66(1H, d, J = 14.2 Hz), 5.04(1H, t, J = 7.1 Hz), 6.20(1H, s), 6.40(1H, s), 7.42(2H, d, J = 8.8 Hz), and 8.18(2H, d, J = 8.8 Hz).

7) These two diastereoisomers could be easily separated by preparative TLC [Kieselgel PF_{254}] using $CHCl_3$ - MeOH (15 : 1). However, they were directly used for the next experiment, without separation.

8) Although some direct preparation of the desired tetrahydrofurans from 6 has been attempted, any satisfactory result has not yet been obtained.

9) The triphenylphosphorane (12) was prepared from p-nitrobenzaldehyde in five steps [1) EtCHO - 40% aq NaOH in EtOH - H_2O (1 : 1) (room temp, 30 min); 2) $NaBH_3CN$ (2 equiv.) in MeOH - AcOH (7 : 3) (room temp, 7.5 h); 3) CBr_4 (3 equiv) - PPh_3 (3 equiv.) in THF (room temp, overnight); 4) PPh_3 (1.1 equiv.) in MeCN under argon (room temp - refluxing temp, 10 h); 5) NaH in THF - DMSO (5 : 1) under argon (room temp, 30 min).

10) These two isomers were readily separated by preparative HPLC [Develosil ODS-5 (ϕ 10 mm x 500 mm); MeOH - H_2O (7 : 3); flow rate: 1.5 ml/min]. At the present stage, the reaction condition is not always optimum. However, it is quite useful to obtain the two geometrical isomers (2 and 13) in order to decide the geometry of the exocyclic double bond attached to the tetrahydrofuran ring in isoaureothin as well as in aureothin.

11) The structures of these two isomers (14 and 15) are also based on their ^1H NMR spectra with aid of NOE experiments.

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