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Total Synthesis of (+)-Isoaureothin· Determination of the Absolute Configurations of Aureothin, Isoaureothin and Spectinabilin

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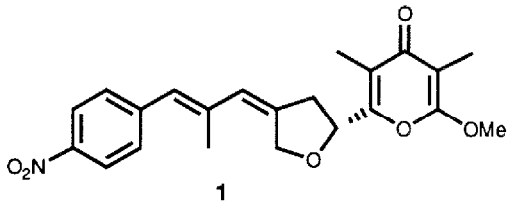
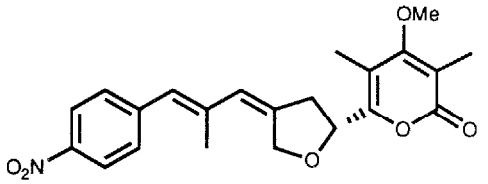
Key words *asymmetric synthesis, absolute configuration, metabolites with a nitro group*

Summary The absolute configurations of isoaureothin and related metabolites having a nitro group have been unambiguously determined by means of asymmetric synthesis of (+)-isoaureothin through (+)-isoaureonone

Both aureothin (**1**) and isoaureothin (**2**), toxic metabolites having 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] In 1976, furthermore, spectinabilin (**3**) was isolated as a metabolite of *Streptomyces spectabilis*, showing an inhibitory activity against RLV (Rauscher leukemia virus) reverse transcriptase [3] The structure of spectinabilin (**3**) is quite similar to that of aureothin (**1**) In the previous paper,[4] we could synthesize the four possible geometrical isomers of isoaureothin as racemic forms, indicating that isoaureothin has the all-trans olefinic stereochemistry as depicted in **2** We describe herein a total synthesis of (+)-isoaureothin through (+)-isoaureonone, by which the absolute configurations of these metabolites have been established



1



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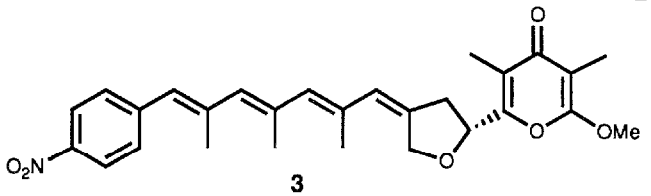
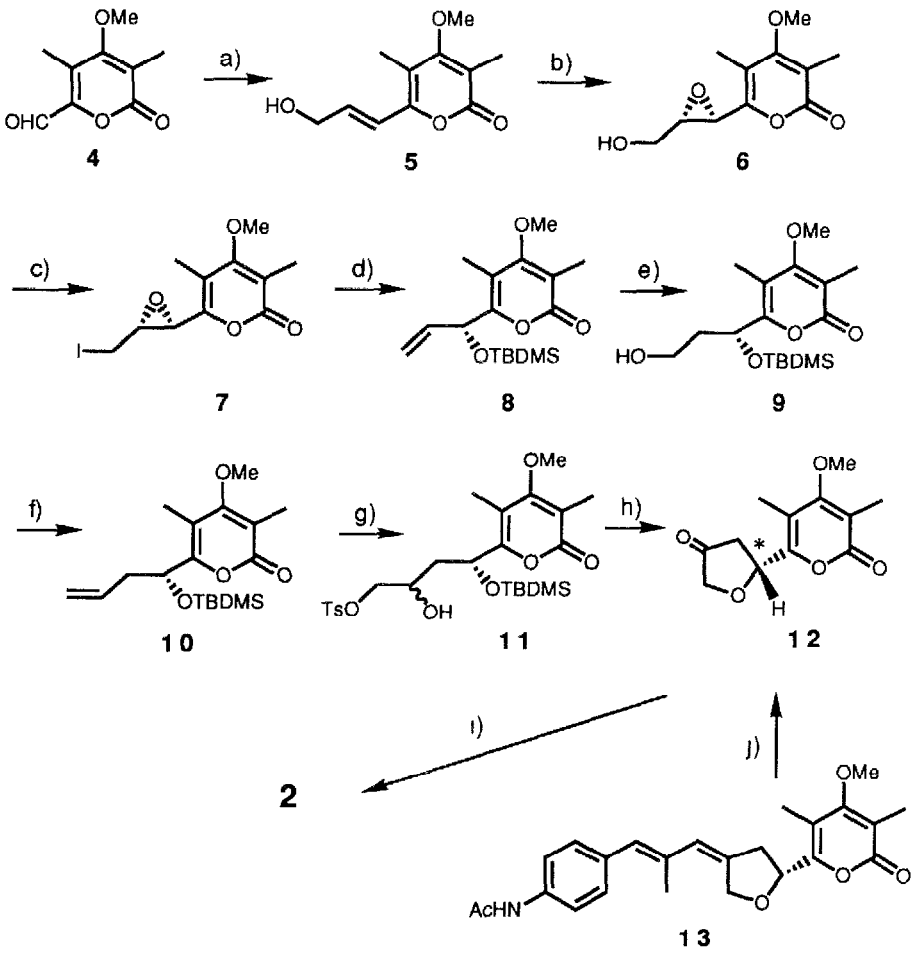


3

The known 3,5-dimethyl-6-formyl-4-methoxy-2-pyrone (**4**)[5] was subjected to Wittig reaction followed by $NaBH_4$ reduction to afford the allyl alcohol (**5**),[6] in good yield, which was further subjected to Sharpless epoxidation to give rise to the (+)-epoxide (**6**)[6] in 78% yield (>99% ee), as shown in Scheme 1 This epoxide was converted into the iodide (**7**),[6] in two steps (90% overall yield), which was treated with zinc powder in acetic acid, and then silylated in a conventional manner to give the corresponding olefin (**8**)[6] in high yield



a) 1 Ph_3P=CHCHO / benzene under Ar (room temp , 2 3 h), 2 $NaBH_4$ (1 equiv) / EtOH (0 °C, 20 min) (75% in 2 steps), b) L-DET (2 0 equiv) / $Ti(O^iPr)_4$ (2 equiv) / ^{t}BuOOH (3 0 equiv) / CH_2Cl_2 under Ar (-37 - 30 °C, 3 h) (78%), c) 1 MsCl / pyr - CH_2Cl_2 (4 1) under Ar (-35 °C, 3 h) (~100%), 2 NaI / DMF (52 °C, 5 h) (90%), d) Zn / DMF - AcOH (4 1) (room temp , 3 5 h) (79%), ^{t}BuMe$_2$SiCl / Imidazole / DMF (room temp , 14 h) (100%), e) 1 9-BBN (3 equiv) / THF under Ar (0 °C → room temp , 1 5 h), 2 H_2O_2 / sat $NaHCO_3$ (0 °C → room temp , 40 min) (81% in 2 steps), f) 1 $(COCl)_2$ / DMSO / Et_3N (-78 °C, 2 h), 2 Ph_3P=CH_2 (1 5 equiv) / THF under Ar (0 °C, 2.5 h) (57% in 2 steps), g) 1 OsO_4 (cat) / NMO (2 equiv) / CH_3CN - H_2O (3 1) (room temp , 3 7 h) (93%), 2 ^{n}Bu$_2$SnO (1 1 equiv) / toluene (refluxing temp , 2 5 h), 3 TsCl (1 5 equiv) / $CHCl_3$ (room temp , 3 h) (87% in 2 steps), h) 1 $(MeO)_2CH_2$ / P_2O_5 / $CHCl_3$ (0 °C, 10 min) (72%), 2 ^{n}Bu$_4$NF / THF under Ar (room temp , 2 5 h) (90%), 3 conc HCl - dioxane (1 12) (room temp , 1 h) (99%), 4 Jones oxid (0 °C → room temp , 2 7 h) (79%), i) Wittig reaction (see ref 4), j) 1 OsO_4 / NMO / THF - H_2O (3 1) (room temp , 2 2 h), 2 $NaIO_4$ (excess) / MeOH - H_2O (room temp , 1 3 h) (63% in 2 steps)

Scheme 1. Synthesis of (+)-Isoaureothin (2) through (+)-Isoaureonone (12).

Table 1. ^{1}H NMR Spectral Data[a] and Optical Rotations.

Aureothin (**1**)	Spectinabilin (**3**)[b]
$[\alpha]_D^{18}$ +51° ($CHCl_3$)	$[\alpha]_D^{26}$ +60° ($CHCl_3$)
γ-Pyrone moiety	
δ 1 86 (3H, s), 2 04 (3H, s), 3 95 (3H, s)	δ 1 86 (3H, s), 2 04 (3H, s), 3 99 (3H, s)
Tetrahydrofuran moiety	
2 97 (1H, br dd, J= 15 7, 6 8 Hz) 3 07 (1H, br dd, J= 15 7, 6 8 Hz)	3 04 (2H, dq , J= 15, 7 Hz)[c]
4 75 (1H, br d, J= 14 1 Hz) 4 88 (1H, br d, J= 14 1 Hz)	4 86 (2H, br q, J= 13 Hz)[d]
5 15 (1H, t, J= 6 8 Hz)	5 20 (1H, t, J= 7 Hz)

a ^{1}H NMR spectra were measured in $CDCl_3$ using TMS as an internal standard
b Spectral data of **3** are cited in ref 3
c These double quartets correspond to the two double doublets of **1**
d The broad quartet corresponds to the two doublets of **1**

In the next step, one carbon elongation of **8** was carried out in four steps Hydroboration of **8** followed by hydroxylation with hydrogen peroxide provided the primary alcohol (**9**),[6] in 81% yield, which was further subjected to Swern oxidation followed by Wittig reaction to give the desired olefin (**10**)[6] in 57% overall yield After oxidation with catalytic amounts of osmium tetroxide using 4-methylmorpholine N-oxide, **10** was selectively converted into the monotosylate (**11**)[6,7] in 81% overall yield After protection of the OH group of **11** as a methoxymethyl ether,[8] treatment with tetrabutylammonium fluoride effected a cyclization to give a tetrahydrofuran, the methoxymethyl group of which was deprotected with hydrochloric acid, and the resulting OH group was oxidized with Jones reagent to afford the corresponding ketone (**12**),[9] in 51% overall yield The synthetic compound (**12**) was completely identical with an authentic sample of isoaureonone derived from N-acetylisoaureothamine (**13**),[2] in all respects of spectral data (IR and ^{1}H NMR) and optical rotation [synthetic sample [synthetic sample $[\alpha]_D^{25}$+51 7° (*c* 1 00, $CHCl_3$), isoaureonone $[\alpha]_D^{25}$ +47° (*c* 0 56, $CHCl_3$)], indicating that isoaureonone (**12**) has the R configuration at the asterisk carbon atom

According to the same procedure as described in the previous paper,[4] finally, the optically active isoaureonone (**12**) was readily converted into natural isoaureothin (**2**) (IR, ^{1}H NMR and $[\alpha]_D$) [2] Therefore, the stereostructures of aureothin and isoaureothin , including the absolute configuration, are represented by **1** and **2**, respectively In addition, spectinabilin (**3**)[3] must have the same absolute configuration as that of aureothin as judged from an exhaustive comparison of their ^{1}H NMR spectral data and optical rotations, as shown in Table 1 Further synthetic studies on (+)-spectinabilin (**3**)[10] are in progress

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6 The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited **5** mp 138 - 139 °C (from hexane - $CHCl_3$), $C_{11}H_{14}O_4$ [m/z 210 0891 (M^+)], IR (film) 3510, 1690 and 1650 cm^{-1}, δ ($CDCl_3$) 1 99 (3H, s), 2 05 (3H, s) 3 81 (3H, s), 4 34 (2H, d, J = 3 6 Hz), 6 50 (1H, d, J = 16 2 Hz), 6 77 (1H, dt, J = 16 2, 3 6 Hz) **6** mp 121 °C (from hexane - EtOAc), $C_{11}H_{14}O_5$ [m/z 226 0857 (M^+)], $[\alpha]_D^{21}$ +48 7° (*c* 1 00, $CHCl_3$), IR (film) 3480 cm^{-1}, δ ($CDCl_3$) 2 7 - 3 15 (3H, complex) and 3 95 (1H, d, J = 1 8 Hz) **7** mp 150 - 153 °C (from hexane - EtOAc), $C_{11}H_{13}O_4I$ [m/z 335 9837 (M^+)], IR (film) 1725, 1705 and 1640 cm^{-1}, δ ($CDCl_3$) 3 1 - 3 45 (2H, complex) and 3 7 - 4 1 (2H, complex) **8** $C_{17}H_{28}O_4Si$ [m/z 324 1770 (M^+)], $[\alpha]_D^{25}$ +80 1° (*c* 1 00, $CHCl_3$), IR (film) 1730, 1710, and 1645 cm^{-1}, δ ($CDCl_3$) 0 00 (3H, overlapped with TMS), 0 07 (3H, s), 0 86 (9H, s), 1 98 (3H, s), 2 02 (3H, s), 3 79 (3H, s), 4 05 (1H, m), 4 2 - 4 5 (2H, complex), and 4 94 (1H, m) **9** $C_{17}H_{30}O_5Si$ [m/z 342 1877 (M^+)], $[\alpha]_D^{25}$ +86 6° (*c* 1 00, $CHCl_3$), IR (film) 3470 cm^{-1}, δ ($CDCl_3$) 3 6 - 3 9 (2H, overlapped with MeO signal) and 4 89 (1H, dd, J = 6 3, 9 0 Hz) **10** ,$C_{18}H_{30}O_4Si$ [m/z 338 1926 (M^+)], $[\alpha]_D^{25}$ +53 3° (*c* 1 00, $CHCl_3$), IR (film) 1715 and 1645 cm^{-1}, δ ($CDCl_3$) 2 50 (2H, t, J = 6 8 Hz), 4 62 (1H, t, J = 6 8 Hz), 4 9 -5 2 (2H, complex) and 5 72 (1H, m) **11** $C_{21}H_{29}O_8SSi$ [m/z 469 1338 (M^+ - ^{t}Bu)], IR (film) 3450, 1710, 1690 and 1640 cm^{-1}, δ ($CDCl_3$) 3 75 - 4 24 (3H, complex) and 4 93 (1H, m)

7 The ^{1}H NMR spectrum of the reaction mixture indicates an almost 1 1 mixture of two diastereoisomers at the carbon atom bearing the secondary OH group

8 When the secondary OH group of **11** was not protected, the yield of the corresponding tetrahydrofuran was not so good as expected

9 **12** mp 117 - 118 °C (from hexane - benzene), $C_{12}H_{14}O_5$ [m/z 238 0835 (M^+)], $[\alpha]_D^{25}$ +51 7° (*c* 1 00, $CHCl_3$) The IR and ^{1}H NMR spectra are identical with those of the racemic aureonone (see ref 4)

10 The all-trans stereochemistry shown for the tetraene system of **3** is speculative (see ref 3)

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