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ENANTIOSELECTIVE SYNTHESIS OF (+)-CITREOVIRAL USING ASYMMETRIC HYDROXYLATION OF TIGLATE ESTERS

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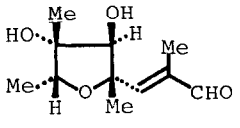
Summary: A microbial metabolite (+)-citreoviral has been synthesized enantio- and stereo-selectively using newly developed asymmetric hydroxylation of tiglate esters for the construction of the key chiral building block.

In recent years the synthesis of natural products possessing complex tetrahydrofuran systems such as polyether antibiotics, marine products, and mycotoxins has been receiving considerable attention due to their unique biological activities and molecular architectures.[1] Citreoviral (1) is a mycotoxin metabolite isolated from the mycelium of Penicillium Citreoviride B. (IF0 6050). The combination of its characteristic structural feature and its utility[2] for the synthesis of the related potent mycotoxins citreoviridin (2)[3] and verrucosidin (3)[4] makes citreoviral (1) an attractive target for synthesis.[5] We now wish to describe a novel enantioselective synthesis of (+)-citreoviral (1).



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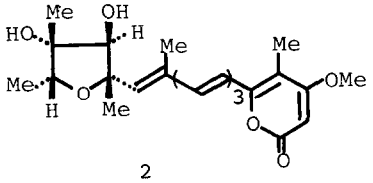

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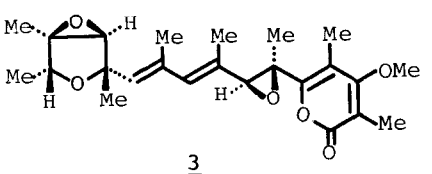
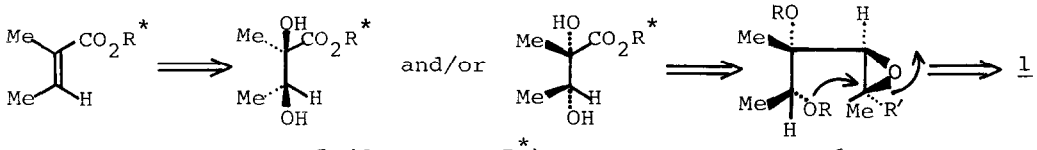


3

In view of Oppolzer's report[6] on asymmetric carbon-carbon bond construction by Lewis acid promoted Diels Alder reactions and 1,4-additions of chiral acrylates, we hoped that hydroxylation of a tiglate ester 4 having an appropriate 'enantiotopic face discriminatig element' would also proceed in a diastereoselective fashion to produce a chiral threo-diol 5 which would be convertible to 1 via an epoxide 6.



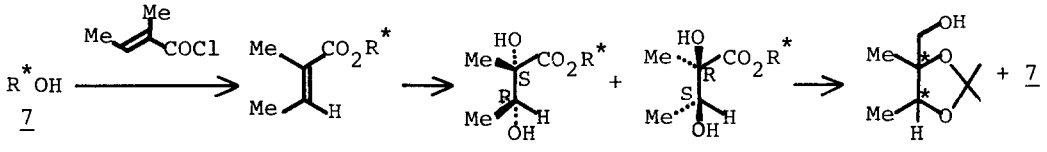
4 5 (depens on R*) 6

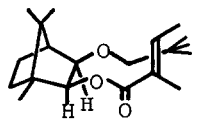
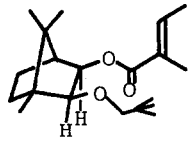
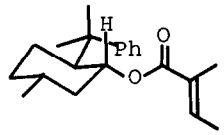
[R* =chiral auxiliary]

Scheme I

The starting tiglate esters 4a,[7] $[\alpha]_D^{30}$ -71.5° (c 1.144, $CHCl_3$), 4b, $[\alpha]_D^{28}$ +1.7° (c, 1.144, $CHCl_3$), and 4c, $[\alpha]_D^{28}$ -36.7° (c 1.064, $CHCl_3$), were prepared by acylation of the known chiral auxiliary alcohols 7a,[8] 7b,[8] and 7c[9] with tigloyl chloride (toluene, 110 °C) almost quantitatively (> 95% yield).[10] The outcome of asymmetric hydroxylation of the tiglate esters 4a-c with osmium tetroxide is summarized in Scheme II and the Table.[11] The absolute structures of 8 and 9 were determined by converting the acetonide alcohol 10 (i. 2,2-dimethoxypropane, cat. CSA, acetone, rt, ii. LAH, THF, rt) and comparing their specific rotations to that of the authentic sample prepared from known (2R,3S)-2,3-dihydroxy-2-methylbutanoic acid (9 : R^*=H).[12]

Scheme II and Table

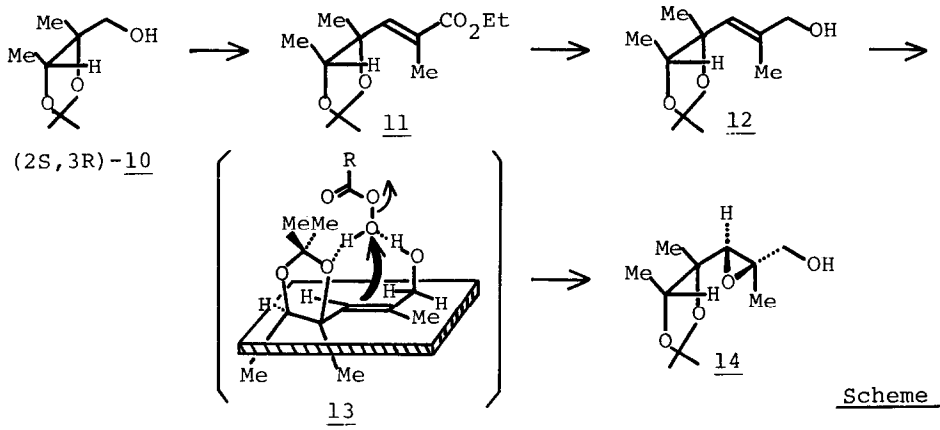


	Tiglate Ester 4	Method[a]	8/9	Yield (%)
a		A	1/4.0[b,e]	88
		B	1/2.5[b,e]	92
b		A	4.3[c,e]	95
		B	3.3[c,e]	96
c		A	5.0[d,f]	94
		B	2.5[d,f]	90

a) method A : 1 equiv. OsO_4, THF-pyridine, -78 °C; method B : 7 mol% OsO_4, 2 equiv. NMO, 10% aq. acetone, -10 °C; b) determined by comparison of the corresponding methine protones adjacent to the ester oxygen located at δ 4.63 and δ 4.81; c) determined by ^{1}H-NMR analysis using Eu(hfc)$_3$; d) determined by comparison of the corresponding methine protones adjacent to the methyl group located at δ 3.60 and δ 3.80; e) separable by SiO_2-column chromatography; f) separable by fractional recrystallization from n-hexane.

Having established asymmetric hydroxylation of tiglate esters, the synthesis of (+)-citreoviral (1) was then investigated. The easy availability of the enantiomerically pure diol 8c, mp 99-100 °C (n-hexane), through recrystallization of the crude reaction product made us start the synthesis of

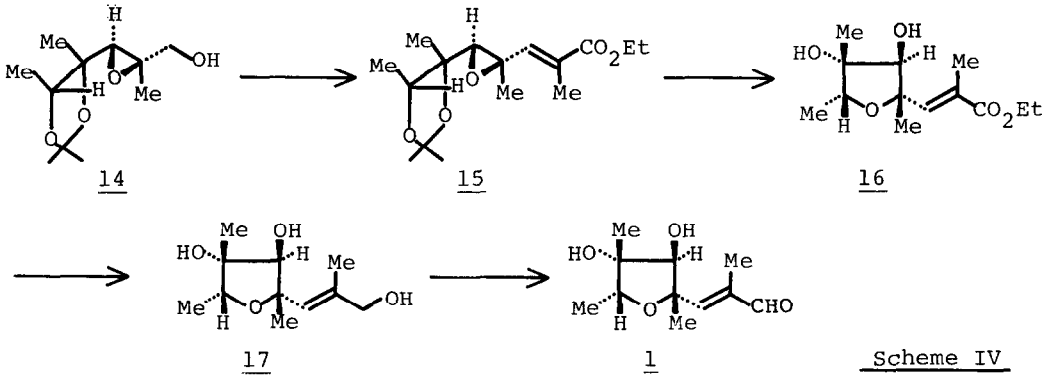
1 from 8c. The diol 8c was converted to the (2S,3R)-10, $bp_{0.8}$ 50 °C (kugelrohr), $[\alpha]_D^{25}$ -12.5° (c 0.976, $CHCl_3$), as mentioned above in 70% overall yield with quantitative recovery of the auxiliary alcohol 7c. Swern oxidation of 10 followed by Wittig reaction ($Ph_3P=C(Me)CO_2Et$, $Cl(CH_2)_2Cl$, reflux) gave the E-α,β-unsaturated ester 11, $[\alpha]_D^{22}$ -25.8° (c 1.398, $CHCl_3$) in 87% yield. After reduction of 11 (DIBAL, CH_2Cl_2, -78 °C), treatment of 12, $[\alpha]_D^{23}$ -14.3° (c 0.824, $CHCl_3$), with m-chloroperbenzoic acid (CH_2Cl_2, -30 °C) led to highly stereoselective epoxidation to give the epoxide 14, $[\alpha]_D^{24}$ +17.8° (c 0.326, $CHCl_3$), almost exclusively in 85% overall yield. The stereochemistry of the epoxide 14 was assigned based on the following experimental facts. Thus, the epoxide 14 was completely identical with the major product of Sharpless oxidation[13] of 12 using D-(-)-diethyl tartrate, while use of L-(+)-diethyl tartrate afforded the isomer of 14 mainly. One might rationalize the production of 14 as the major product of this 'm-CPBA-epoxidation' by assuming a transition state resembling 13 in which m-chloroperbenzoic acid could be complexed by two hydrogen bonds as indicated.[14]



Scheme III

Swern oxidation of 14 and subsequent Wittig reaction ($Ph_3P=C(Me)CO_2Et$, $Cl(CH_2)_2Cl$, reflux) gave the E-α,β-unsaturated ester 15, $[\alpha]_D^{21}$ -46.5° (c 1.088, $CHCl_3$), in 94% yield. Upon treatment of 15 with 50% aqueous trifluoroacetic acid at room temperature for 3 days allowed stereoselective cyclization to give the tetrahydrofuran 16, mp 111-113 °C (Et_2O-n-hexane), $[\alpha]_D^{21}$ +2.2° (c 1.084, $CHCl_3$) in 58% yield. Finally the total synthesis of (+)-citreoviral (1) was achieved by reduction of 16 (DIBAL, CH_2Cl_2, -78 °C) followed by selective oxidation of 17 under Swern oxidation conditions in 50% overall yield (63% overall yield based on consumed 17). The synthetic material, $[\alpha]_D^{24}$ +22.6° (c 0.24, $CHCl_3$) (lit.[2] +21.1°), exhibited spectral properties (^{1}H-NMR, IR, Hi-MS) in accord with those reported.[2] Since (+)-citreoviral (1) has already been

converted to (-)-citreoviridin (2) by Yamamura and co-workers,[2] the synthesis of 1 constitutes a formal synthesis of 2.



14 15 16 17 1

Scheme IV

References and Notes

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2. Conversion of (+)-citreoviral (1) to (-)-citreoviridin (2) has been achieved by Yamamura and co-workers: S. Nishiyama, Y. Shizuri, and S. Yamamura, Tetrahedron Lett., 26, 231 (1985).
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5. Recently citreoviral (1) has been synthesized both in racemic form and in enantiomerically pure form. For the synthesis of racemic 1, see: a) Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, J. Chem. Soc. Chem. Commun., 1985, 292; b) D. R. Williams and F. H. White, Tetrahedron Lett., 26, 2529 (1985); c) Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, 50th Annual Meeting of The Chem. Soc. Jap., April 1985 (Tokyo), Abstract Papers II, p. 874. For the synthesis of (+)-1, see ref. 2.
6. Review on regio-, diastereo-, and enantio-selective carbon-carbon bond formation; W. Oppolzer, in 'Selectivity-a Goal for Synthetic Efficiency' ed. W. Bartmann and B. M. Trost, Verlag Chemie, Weinheim; Deerfield Beach, Florida; Basel, 1984, pp. 137-167.
7. All new compounds reported in this work gave satisfactory spectral (^{1}H-NMR, IR, MS) and analytical (high resolution MS) data.
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10. Under usual acylation conditions (Et_3N, DMAP, CH_2Cl_2), deconjugation of the olefin moiety of 4 giving the β,γ-unsaturated isomer was observed.
11. The following compounds showed the indicated specific rotations $[\alpha]_D^{25}$ ($CHCl_3$): 8a, -44.8° (c 0.540); 9a, -62.1° (c 1.236); 8b, -17.4° (c 1.492); 9b, -42.7° (c 0.422); 8c, -16.1° (c 1.02). The enantiomerically pure 9c was not obtained.
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