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SYNTHETIC STUDIES TOWARD VERRUCOSIDIN: SYNTHESIS OF (±)VERRUCOSAL

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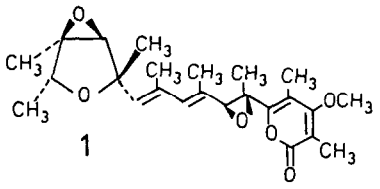
Abstract: Verrucosal, 3, a major degradation product of verrucosidin was synthesized in racemic form by a short and direct route from 4,5-dimethyl-2-furoic acid.

The structure and degradation studies of the mycotoxin verrucosidin 1 have recently been described[1a]. Although no total synthesis of 1 has been reported, several approaches[2] and one synthesis[3] of a similar compound, citreoviridin[4], 2, have appeared. Furthermore a recent report describes the preparation of intermediate 3 in chiral form[1b]. In light of these results, we report here our preliminary studies which have led to the preparation of (±)verrucosal, 3, a major degradation product of verrucosidin.



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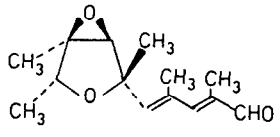

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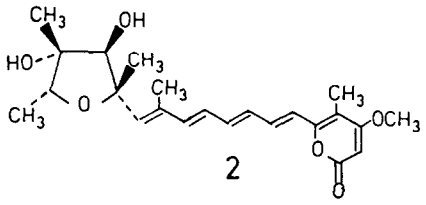

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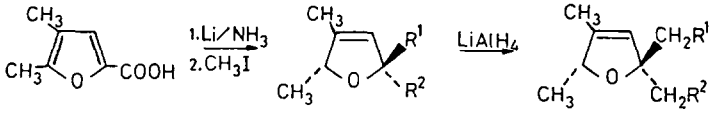
Our approach involved the Birch-type reductive methylation of 4,5-dimethyl-2-furoic acid, 4[5]. Metal-ammonia reductions of furoic acids have been described by Birch[6] and others[7], and our products were in accord with these reports. A solution of acid 4 in sufficient THF was added to a mixture of anhydrous ammonia and lithium (4 eq., -78°C). After 0.25h, excess CH_3I was added and following the usual workup[7], a 1:1 mixture of



4

5a $R^1=CH_3; R^2=COOH$
b $R^1=COOH; R^2=CH_3$
c $R^1=H; R^2=COOH$
d $R^1=COOH; R^2=H$

6a $R^1=H; R^2=OH$
b $R^1=OH; R^2=H$

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diastereomers 5a,b were obtained in >95% yield. Quenching the reduction mixture of 4, prepared as above, with NH_4Cl led to an equimixture of acids 5c,d in quantitative yield. The carboxylic acid dianion of 5c,d was then prepared (3eq. LDA in THF, -78°C, 0.25h) and quenched with CH_3I[8] leading to a 1:2 mixture[9] of diastereomers 5a,b with the undesired acid, 5b, predominating (stereochemistry determined as below). Therefore, the initially produced 1:1 mixture of 5a,b was directly reduced ($LiAlH_4$, ether, 35°C, 2 h) to 6a,b and, following chromatographic purification, affords desired 6a[9] from furan 4 in 36% yield.

In order to ascertain the relative stereochemistry of the alkylation products 6a,b, the four epoxy acetate isomers 8a-d were prepared (Table I) for spectral comparison with authentic 7, available from verrucosidin[10]. All isomers 8a-d, have easily distinguishable 400MHz ^1H NMR spectra (Table II), and it was clear that acetate 8a, derived from the less polar alcohol 6a, was identical with 7 in terms of its spectra.

TABLE I

Epoxidation of Dihydrofuran 6

	SUBSTRATE	OXIDANT	CONDITIONS	PRODUCT RATIO[a]
6a	R=H, R_1=OH	mCPBA	CH_2Cl_2, RT	1:20[b]
6a	" "	$tBuO_2$-Mo(acac)$_2$	C_6H_6, 80°C	1:20[b] (β:α)
6c	R=H, R_1=OAc	mCPBA	CH_2Cl_2, RT	1:2
6b	R=OH, R_1=H	mCPBA	CH_2Cl_2, RT	3:2[b]
6b	" "	$tBuO_2$-Mo(acac)$_2$	C_5H_6, 80°C	20:1[b] (8c:8d)[c]
6d	R=OAc, R_1=H	mCPBA	CH_2Cl_2, RT	1:10

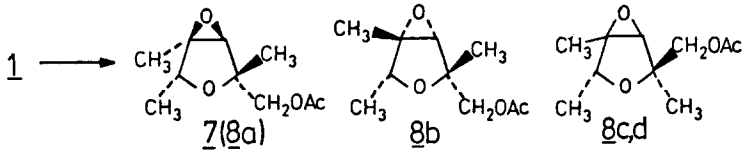
[a] Ratios determined by ^1H NMR via integration of epoxide proton. All yields were >80%.
[b] Ratio determined after acetylation.
[c] Relative stereochemistry of epoxide has yet to be established.

TABLE II

^1H NMR Spectra[a] of Epoxy Acetates 8[b]

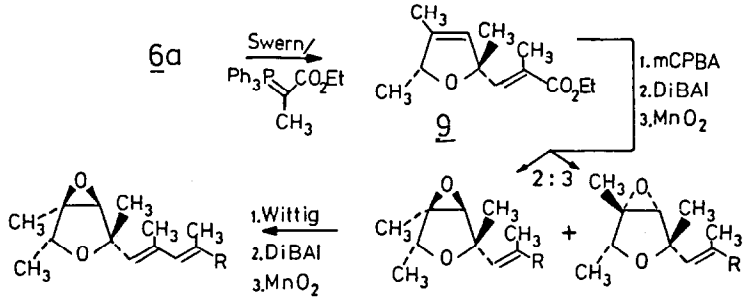
Signal	Authentic 7[10]	8a	8b	8c[c]	8d[c]
CH_3-1	1.25 (d) (6.9Hz)	1.25 (d) (6.9Hz)	1.22 (d) (6.2Hz)	1.26 (d) (6.9Hz)	1.21 (d) (6.1Hz)
CH_3-2	1.29 (s)	1.29 (s)	1.2 (s)	1.29 (s)	1.28 (s)
CH_3-3	1.46 (s)	1.46 (s)	1.46 (s)	1.49 (s)	1.45 (s)
CH_3-4	2.12 (s)	2.12 (s)	2.1 (s)	2.1 (s)	2.1 (s)
H-5	3.49 (s)	3.44 (s)	3.33 (s)	3.42 (s)	3.33 (s)
H-6	4.19 (q) (6.9Hz)	4.19 (q) (6.9Hz)	3.91 (q) (6.2Hz)	4.16 (q) (6.9Hz)	4.01 (q) (6.1Hz)
CH_2-7	3.99, (AB)	3.99, (AB)	4.08, (AB)	4.04, (AB)	4.00, (AB)
	4.1 (11.5Hz)	4.1 (11.5Hz)	4.16 (10.9Hz)	4.14 (10.7Hz)	4.16 (11.5Hz)

[a] Spectra were taken on 400MHz NMR (Vanderbilt Univ.) with $CDCl_3$ as solvent, TMS as internal standard, and δ values in ppm.
[b] Prepared by acetylation-epoxidation of 6a,b or epoxidation-acetylation. (See Table I).
[c] Relative stereochemistry of epoxide in 8c,d has yet to be established.



As expected, epoxidation of alcohol 6a with mCPBA or $tBuO_2H$-Mo(acac)$_2$[11] affords the epoxide, 8b, following acetylation. In order to inhibit hydroxyl directing effects, the acetates 6c and 6d were prepared (Ac_2O-pyr) from 6a and 6b, respectively. Unfortunately, under similar conditions, acetate 6c also leads to 8b, albeit with lower selectivity. These results can be rationalized if one assumes that a ring conformation having the two cis substituents (CH_3 and CH_2OR) in pseudoequatorial positions is preferred. The quaternary methyl group would then be pseudoaxial, thus blocking the face of the olefin.

Since the desired epoxide 8a was not readily available from 6a, we decided to construct the sidechain previous to the epoxidation. Alcohol 6a was oxidized by the Swern oxidation[12] and directly quenched[13] via Wittig chemistry to produce ester 9 in 82% yield. Treatment of 9 with mCPBA afforded a 2:3 mixture of epoxides 10a and 10b respectively, in 88% yield which were chromatographically separated. DiBAl reduction of



13 R=CO_2Et
14 R=CH_2OH
15 R=CHO ≡ 3

10a R=CO_2Et 10b R=CO_2Et
11a R=CH_2OH
12a R=CHO

10a (CH_2Cl_2, -78°C), MnO_2 oxidation (6 eq., CH_2Cl_2, RT) and subsequent reaction with triethyl phosphonopropionate anion (NaH, THF, -78°C) gave ester 13 in 71% yield. Reaction of 13 with DiBAl and MnO_2 as above proceeded smoothly to give aldehyde 15. This aldehyde produced ^1H and ^{13}C NMR spectra matching that of authentic verrucosal 3. Treatment of the epoxide, 10b, in a similar way produced a diene ester being utilized in our approach to compound 2.

Although we are presently studying the stereoselectivity in both alkylation and epoxidation steps, this report provides a short and direct synthetic route to gram quantities of racemic 3. Methods for the attachment of the required pyrone unit to 3 are presently under study.

Acknowledgements: We are grateful to Profs. Jin Cha, and T. Harris, Vanderbilt University, for an authentic sample of 7 and for the 400 MHz ^1H NMR spectra; to Prof. K. Harding for helpful discussions, and to the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the Center for Energy and Mineral Resources at TAMU.

REFERENCES

1. a) Ganguli, M; Burka, L.T.; Harris, T.M.; J. Org. Chem., (1984), 49, 3762; b) Nishiyama, S.; Shigemori, H.; Yamamura, S.; Tetrahedron Lett., (1986), 723.

2. Wilcox, C.S.; Long, G. W.,; Suh, H.; Tetrahedron Lett., (1984), 25, 395; Williams, D.R.; White, F.H.,; Tetrahedron Lett., (1985), 2529; Bowden, M.C.; Patel, P; Pattenden, G.; Tetrahedron Lett., (1985), 4793.

3. Nishiyama, S.; Shizuri, Y.; Yamamura, S.; Tetrahedron Lett., (1985), 26, 231.

4. Sakabe, N; Goto, T.; Hirata, Y.; Tetrahedron, (1977), 33, 3077.

5. In 25% yield from ethyl 2-methylacetoacetate; Klein, L.L.; Syn Comm., (1986), 431.

6. Birch, A.J.; Slobbe, J.; Tetrahedron Lett., (1975), 627; Birch, A.J.; Slobbe, J.; Tetrahedron Lett., (1976), 2079.

7. Masamune, T.; Ono, M.; Matsue, H.; Bull. Chem. Soc. Japan, (1975), 48, 491; Divanfard, H.R.; Joullie, M.M.; Org. Proceed. Prep. Inter., (1978), 10, 94.

8. Other alkylating agents were used, $(CH_3O)_2SO_2$, CH_3Br, CH_3OTs, $(CH_3O)_3PO$, along with other solvents, ether, hexane, THF-HMPA, and several temperatures ranging from -100°C to 40°C, but the ratio of 5a to 5b varied only from 1:1.2 to 1:2.7.

9. By ^1H NMR analysis via integration of the quaternary methyl group.

10. Dr. Jin Cha, Dept. of Chem., Vanderbilt University. Unpublished results.

11. Sharpless, K.B.; Michaelson, R.C.; J. Amer. Chem. Soc., (1973), 95, 6136.

12. Omura, K.; Swern, D.; Tetrahedron, (1978), 34, 1651.

13. Ireland, R.E.; Norbeck, D.W.; J. Org. Chem., (1985), 50, 2198.

14. All NMR spectra were performed on a Varian EM390 spectrometer unless otherwise stated, with values reported in ppm. $CDCl_3$ was used as solvent and TMS as an internal standard. High res. mass spectra run on Kratos 50 instrument.

5a: 1.34 (3H, d, 6Hz), 1.61 (3H, s), 1.75 (3H, d, 1Hz), 4.85 (1H, m), 5.44 (1H, br s), 9.66 (1H, s).

5b: 1.37 (3H, d, 6Hz), 1.53 (3H, s), 1.75 (3H, d 1Hz), 4.85 (1H, m), 5.44 (1H, br s), 9.66 (1H, br s).

5c,d: (Mixture of acids) 1.33 (3H, 2 overlapping doublets), 1.75 (3H, br s), 4.8 (1H,m), 5.15 (1H, m), 5.47 (1H, br s), 9.4 (1H, br s).

6a: 1.2 (3H, s), 1.29 (3H, d, 7Hz), 1.7 (3H, d, 1Hz), 2.48 (1H, br s), 3.49 (2H, s), 4.77 (1H, q, 7Hz), 5.3 (1H, br s).

6b: 1.24 (3H, s), 1.26 (3H, d 7Hz), 1.78 (3H, d, 1Hz), 3.21 (1H, br s), 3.42 (2H, s), 4.71 (1H, q, 7Hz), 5.28 (1H, br s).

9: 1.27 (3H, d, 7Hz), 1.33 (3H, t, 7Hz), 1.42 (3H, s), 1.7 (3H, s), 2.0 (3H, d, 1Hz), 4.14 (2H, q, 7Hz), 4.68 (1H, q, 7Hz), 5.41 (1H, br s), 6.77 (1H, br s).

10a: 1.11 (3H, d 7Hz), 1.27 (3H, t, 7Hz), 1.4 (3H, s), 1.45 (3H, s), 2.0 (3H, d, 1Hz), 3.4 (1H, s), 4.02 (1H, q, 7Hz), 4.14 (2H, q, 7Hz), 6.75 (1H br s).

11a: 1.2 (3H, d, 7Hz), 1.4 (3H, s), 1.49 (3H, s), 1.88 (3H, s), 2.78 (1H, br t, 6Hz), 3.43 (1H, s), 393 (2H, d, 6Hz), 4.1 (1H, q, 7Hz), 5.59 (1H, br s).

12a: 1.19 (3H, d, 7Hz), 1.46 (3H, s), 1.5 (3H, s), 1.95 (3H, d, 1Hz), 3.51 (1H, s), 4.15 (1H, q, 7Hz), 6.51 (1H, br s), 9.38 (1H, s).

13: 1.19 (3H, d, 7Hz), 1.29 (3H, t, 7Hz), 1.42 (3H, s), 1.48 (3H, s), 2.01 (6H, s), 3.43 (1H, s), 4.11 (1H, q, 7Hz), 4.27 (2H, q, 7Hz), 5.63 (1H, br s), 7.05 (1H, br s).

14: 1.2 (3H, d, 7Hz), 1.42 (3H, s), 1.47 (3H, s), 1.81 (3H, s), 1.94 (3H, s), 3.39 (1H, s), 4.0 (2H, d, 6Hz), 4.08 (1H, q, 7Hz), 5.41 (1H, br s), 5.82 (1H, br s).

15-(3) ^1H NMR, 200MHz: 1.13 (3H, d, 6.75Hz), 1.38 (3H, s), 1.42 (3H, s), 1.89 (3H, d, 1.27Hz), 2.1 (3H, d, 1,27Hz), 3.39 (1H, s) 4.09 (1H, q, 6.75 Hz), 5.85 (1H, br s), 6.63 (1H, br s), 9.35 (1H, s); ^{13}C NMR, 200MHz: 10.8, 13.8, 17.7, 18.9, 21.5, 67.2, 67.5, 76.8, 80.0, 135.2, 137.1, 140.2, 154.1, 195.8.
High Resolution Mass Spectra: $C_{14}H_{20}O_3$; calc. 236.141234, obs. 236.142289.

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