An Approach to 6-Oxygenated Shikimic Acid Derivatives by Photolysis of the Pyruvate Ester of Dimethyl Epoxychorismate

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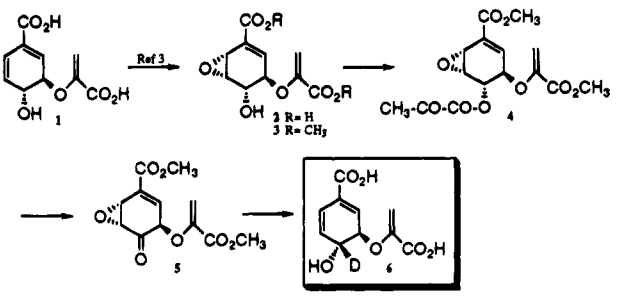
We report an unusual rearrangement of a synthetic epoxychorismic acid derivative which provides access to the 6-substituted shikimic acid framework. Photolysis of the pyruvate ester of dimethyl epoxychorismate triggered an intramolecular Paterno–Buchi photocyclization of the enol pyruvate alkene and the ketone group of the pyruvate ester, leading to a 2,2,3,3-tetrasubstituted oxetane ring. Upon standing for 1 week in $CDCl_3$ or in the presence of CF_3CO_2D, the primary photoproduct underwent a slow epoxide-opening reaction with participation by the oxetane-substituted carbomethoxy group to form an unusual fused tetracyclic lactone. The chemistry described here suggests at least one plausible pathway, with appropriate stereoelectronic constraints, by which oxidation of shikimic acid at C6 might be achieved.

As part of our longstanding interest in the metabolism of shikimic acid, we have recently been investigating shikimate branchpoint pathway enzymes which transform chorismic acid into a variety of important aromatic amino acids.[1,2] Here we report an unusual rearrangement of a synthetic epoxychorismic acid derivative which provides access to the 6-substituted shikimic acid framework. Besides their close structural relationship to certain natural products,[3] several 6-substituted shikimates have been synthesized for use as mechanistic probes of the enzyme chorismate synthase.[4,5] The chemistry described here suggests at least one plausible pathway, with appropriate stereoelectronic constraints, by which oxidation of shikimic acid at C6 might be achieved.

For mechanistic studies on chorismate lyase, we required a sample of regioselectively deuterated chorismate **6** (box, Scheme 1), which we hoped to prepare in enantiomerically pure form by partial synthesis from (−)-chorismic acid (**1**). One plan involved reduction of an appropriate ketone such as **5** with $NaBD_4$. We reasoned that ketone **5** might be obtained by oxidation of epoxy diester **3**, a substance that should be readily available in two steps from **1** using the methodology of Ife *et al.*[6]

Since enolization of **5** might trigger an unwanted tautomerization to the corresponding oxepin, oxidation of **3** under neutral conditions seemed imperative. Pyruvate esters of alcohols are known to produce the corresponding carbonyl compounds upon UV irradiation in dry benzene.[7] We therefore envisioned that photolysis of pyruvate **4** (prepared in high yield from **3** by acylation with pyruvoyl chloride)[8] would furnish **5** without exposing the carbonyl compound to an aqueous workup, since the byproducts of oxidation, CO and acetaldehyde, would easily be removed during solvent evaporation.

Scheme 1



In the event, irradiation of **4** with ultraviolet light (C_6D_6, 2 h, rt) using a medium pressure mercury lamp afforded in quantitative yield a major new product which was stable in benzene or acetone solution, or as a solid, but which decomposed slowly in $CDCl_3$. Its ^{13}C NMR spectrum showed 15 resonances, indicating that all the carbon atoms of the starting material had been preserved during photolysis. Notably absent from the ^{13}C NMR spectrum were the enol pyruvate alkene and ketone carbonyl carbon resonances. Moreover, the product's ^1H-NMR spectrum confirmed the disappearance of enol pyruvate alkene hydrogens and a solvent-dependent, upfield shift in the pyruvate methyl singlet. On the basis of extensive decoupling and nuclear Overhauser effect (NOE) measurements, the photoproduct was assigned structure **7** (eq 1) in which an intramolecular Paterno–Buchi photocyclization between the enol pyruvate alkene and the ketone group of the pyruvate ester afforded a 2,2,3,3-tetrasubstituted oxetane ring.[9]

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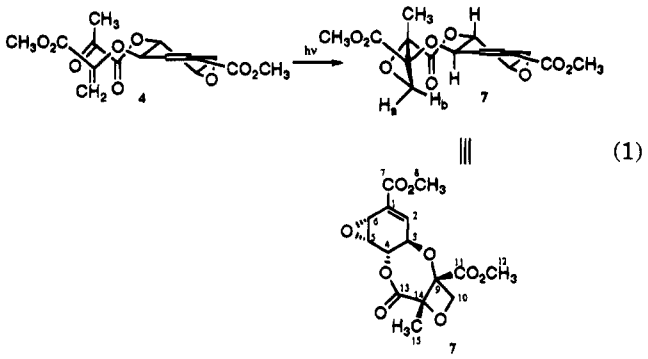
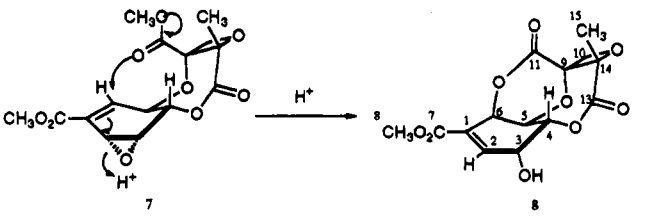


(1)

The regiochemistry of ring formation indicated in **7** not only paralleled earlier studies on the photoaddition of ketones with electron-rich enol ethers[10] but also was consistent with the observed chemical shifts of C-9 (88.3–88.4 ppm), which has two oxygens attached, and with the methylene hydrogens $H_{10\alpha}$ and $H_{10\beta}$ at 4.28 and 4.42 ppm (C_6D_6). Nuclear Overhauser effect (NOE) difference experiments in benzene-d_6 indicated a strong NOE between the geminal hydrogens at C10 and between the methyl group at C14 and the axial hydrogen at C4.

Upon standing for 1 week in $CDCl_3$, **7** underwent a slow transformation to a new oxetane (MW = 326 Da). The same material could be obtained more reproducibly (52% yield) when **7** was treated with $CF_3CO_2D/CDCl_3$, although some decomposition occurred during silica gel chromatography. Initial spectroscopic characterization indicated that the ^{1}H-NMR signals for the epoxide hydrogens at C5 and C6 were absent and a new hydroxyl group (IR, D_2O exchange) had appeared. While the new substance contained only one methyl ester, its ^{13}C NMR spectrum still revealed three carbonyl resonances.

The assignment of structure **8** (eq 2) to this new product was supported by detailed ^{1}H and ^{13}C NMR studies (Tables 1 and 2). Noteworthy in the ^{1}H-NMR



(2)

spectrum of **8** was the apparent lack of long-range coupling between the C2 and C6 hydrogens, previously observed in spectra of **3**, **4**, and **7**, suggesting that the two C—H bonds were no longer coplanar. However, a minor cross-peak in a long-range COSY spectrum of **8** (CD_3COCD_3) did indicate weak C2/C6 hydrogen coupling. Resonances at 4.42 and 4.74 ppm were assigned to the C4 and C5 hydrogens, respectively, in **8** and the observed vicinal coupling constant (11.2 Hz) suggested a *trans*-diaxial orientation. The strongly deshielded doublet at 5.76 ppm was assigned to the allylic, acyloxy-substituted hydrogen at C6. NOE difference spectra (Table 3) were consistent with structure **8**, whose tetraoxygenated cyclohexene ring embodied the 6-hydroxyshikimate framework.

One plausible mechanism for the transformation of **7** to **8** is shown in eq 2. It should be noted that the facile participation by the oxetane-substituted carbomethoxy group in the conjugate opening of **7** corroborates the NOE assignment of relative stereochemistry for the *cis*-fused intramolecular photocycloadduct of **4**. Formation of **8** further suggests that even simpler routes to 6-oxygenated shikimic acids might be realized by the conjugate opening of epoxychorismic acid (**2**) or its dimethyl ester (**3**), either by hydrolysis or with participation of the enol pyruvate

Table 1. ^{1}H-NMR Resonances for 3, 4, 7, and 8

	3 ($CDCl_3$)	**3** (CD_3COCD_3)	**4** ($CDCl_3$)	**4** (C_6D_6)	**7** (C_6D_6)	**7** ($CDCl_3$)	**7** (CD_3COCD_3)	**8** ($CDCl_3$)	**8** (CD_3COCD_3)
C2-H	6.93, dd J = 2.0, 2.0	6.82, dd J = 2.0, 2.0	6.97, dd J = 2.0, 2.0	6.83, dd J = 2.0, 2.0	6.80, dd J = 2.2, 2.2	6.98, dd J = 2.2, 2.2	7.00, dd J = 2.2, 2.2	7.20, d J = 5.7	7.19, d J = 5.7
C3-H	4.58, dd J = 8.2, 1.6	4.59, dd J = 8.0, 1.6	4.92, dd J = 8.4, 1.7	4.86, dd J = 8.4, 1.7	4.76, dd J = 9.5, 1.9	4.94, dd J = 9.6, 1.9	4.84, dd J = 9.6[b]	4.90, ddd J = 3.6, 3.6, 5.7	4.96, dt J = 5.5, 5.5, 2.9
C4-H	4.24, dd J = 8.2, 1.0	4.18, ddd J = 8.0, 5.3, 1.2	5.51, dd J = 8.4, 1.1	5.34, dd J = 8.9, 1.2	4.64, dd J = 9.5, 1.1	5.05, dd J = 9.6, 1.1	5.23, dd J = 9.6, 1.2	4.41, dd J = 3.5, 11.1	4.66–4.74 m
C5-H	3.71, dd J = 4.2, 0.8	3.64, dd J = 4.3, 1.2	3.76, dd J = 4.3, 1.0	3.15, dd J = 4.2, 1.1	3.12, dd J = 4.3, 1.0	≈3.86[a]	3.95, dd J = 4.4, 1.2	4.73, dd J = 3.8, 11.3	4.66–4.74 m
C6-H	4.10, dd J = 4.3, 2.3	3.97, dd J = 4.3, 2.3	4.17, dd J = 4.3, 2.3	3.81, dd J = 4.3, 2.3	3.80, dd J = 4.3, 2.5	4.13, dd J = 4.3, 2.4	4.06, dd J = 4.5, 2.5	5.76, d J = 3.8	5.76, d J = 3.1
C10-H_2	5.60, 4.85 AB q, J = 3.0	4.91, 5.45 AB q, J = 2.9	4.84, 5.58 AB q, J = 3.1	4.27, 5.32 AB q, J = 3.1	4.28, 4.42 AB q, J = 7.0	4.55, 4.88 AB q, J = 7.3	4.38, 4.84 AB q, J = 7.2	4.53, 5.08 AB q, J = 7.3	4.40, 4.93 AB q, J = 7.4
$COOCH_3$	3.82, s 3.83, s	3.77, s 3.80, s	3.79, s 3.84, s	3.21, s 3.29, s	3.03, s 3.25, s	3.83, s 3.85, s	3.82, s 3.83, s	3.86, s	3.82, s
C-CH_3			2.52, s	1.87, s	1.35, s	1.69, s	1.70, s	1.71, s	1.66, s

[a] Resonance partially masked by the $COOCH_3$ group at 3.85 ppm. [b] Resonance partially masked by $H_2C(2')$ group at 4.38 ppm.

Table 2. ^{13}C-NMR Resonances for 3, 4, 7, and 8

	3 ($CDCl_3$)	**3** (CD_3COCD_3)	**4** ($CDCl_3$)	**4** (CD_3COCD_3)	**7** (benzene-d_6)	**7** ($CDCl_3$)	**7** (CD_3COCD_3)	**8** ($CDCl_3$)	**8** (acetone-d_6)
C1	129.7	130.5	129.4	130.5	125.7	125.7	126.3	129.8	128.9
C2	139.3	140.0	139.0	139.4	143.9	143.6	144.6	140.3	143.4
C3/C4	70.3, 77.4	70.8, 77.8	73.8, 75.1	75.0, 75.7	73.8, 74.4	73.4, 74.5	74.4, 75.1	70.6, 73.0[a]	71.2, 73.6[a]
C5/C6	48.5, 53.7	49.1, 54.9	48.9, 51.3	49.5, 52.1	48.8, 52.5	48.7, 53.1	49.4, 53.5	64.6, 65.6[a]	66.7, 65.0[a]
C8/C12	52.4, 52.8	52.5	52.6	52.6, 52.7	51.7, 52.0	52.5	52.6, 53.3	53.0	52.8
C9	149.5	151.1	149.8	151.0	88.4	88.3		90.5	91.3
C10	99.1	97.6	99.6	100.2	74.1	74.3	74.8	74.2	73.6
C7/C11/C13	163.8, 164.8	163.8, 165.5	160.0, 162.9, 164.3	160.7, 163.5, 165.2	164.5, 168.6, 169.7	164.5, 168.4, 170.6		162.3, 163.7, 170.0	163.3, 165.1, 171.0
C14			190.5	191.2	80.1	79.8	80.9	77.8	78.6
C15			26.8	26.8	21.5	21.7	21.8	19.4	19.6

[a] Assignments may be reversed.

Table 3. NOE Difference Measurements for 8 in $CDCl_3$

irradiate	+NOE (%)
H2	H3 (12.5%)
H6	H5 (17.3%)
H10α	H10β (32.9%)
H10β	H10α (36.4%)
H3	H2 (21.2%), H4 (6.1%)
H5	H6 (17.9%)
H4	H10α (7.8%), H3 (12.9%), CH_3 (13.8%)

carboxyl group. Unfortunately, several attempts to induce this transformation of **2** or **3** using Bronsted acids, Lewis acids, or alkaline conditions proved unsuccessful. The only products of epoxide opening which could be characterized were *trans*-1,2-diols or in some cases 1,2-halohydrins. It would seem that the orientation of the participating carbomethoxy group in **7**, as well as the conformational restrictions imposed by the fused polycyclic ring system, is indicative of stereoelectronic constraints for this process.

Experimental Section[11]

Synthesis of Dimethyl Epoxychorismate (3). To a rapidly stirred solution of the known[6] epoxychorismic acid (**2**) (0..28 g) in anhydrous MeOH (45 mL) under argon at −78 °C was added dropwise an ethereal solution of diazomethane over *ca.* 90 min with frequent monitoring by TLC. After removal of the solvents under reduced pressure, the pale yellow oil was purified on a 17.5 × 2 cm silica gel column by flash chromatography (1:4 CH_3CN/CH_2Cl_2) to afford **3** (0.16 g, 50% yield from **1**): mp 101.5−103.5 °C; $[\alpha]^{27}_D = -162°$ (*c* = 0.76, $CHCl_3$); ^1H NMR and ^{13}C NMR, see Tables 1 and 2; IR (film) 3440, 2975, 1720, 1620, 1445 cm^{-1}; CIMS (NH_3) *m/z* (rel intensity) 288 ($M + NH_4^+$, 100), 271 (M + 1, 56).

Synthesis of Dimethyl Epoxypyruvoylchorismate (4). A solution of **3** (18.4 mg, 0.07 mmol) and freshly distilled dry pyridine (6.2 μL, 0.07 mmol) in anhydrous benzene (455 μL) under argon was stirred in a cold water bath during dropwise addition of pyruvoyl chloride (8.2 mg, 0.07 mmol)[12] in anhydrous benzene (230 μL). The resulting white suspension was stirred for 1 h before being filtered through Celite. The eluant was concentrated to dryness, redissolved in CCl_4 (2 mL), and stirred for an additional 2 h at rt. The solution was filtered through Celite, rinsed with CCl_4 (5 × 1.5 mL), and evaporated under reduced pressure to yield **4** (22.4 mg, 97% yield) as a pale yellow oil which was used without further purification: $[\alpha]^{22}_D = -130°$ (*c* = 0.19, CH_3OH); ^1H NMR and ^{13}C NMR, see Tables 1 and 2; IR (film) 2975, 1740, 1625, 1445, 1260 cm^{-1}; CIMS (NH_3) *m/z* (rel intensity) 358 ($M + NH_4$, 100), 341 (M + 1, 4).

Photolysis of 4 To Form 7. A C_6D_6 solution (1.5 mL) of pyruvate ester **4** (21.7 mg, 0.08 mmol) in a quartz NMR tube was degassed with Ar for 1 h. The tube was positioned 1 cm from an unfiltered 450-W medium pressure mercury lamp and the sample irradiated for 2 h at rt, at which time NMR analysis indicated quantitative conversion to a new product. The solution was concentrated *in vacuo* to afford a whitish foam which was purified by column chromatography (2.5:97.5 CH_3OH/CH_2Cl_2, partial decomposition). Oxetane **7** was isolated as a white solid (16.6 mg, 77% yield): $[\alpha]^{22}_D = +31°$ (*c* = 0.068, CH_3OH); ^1H NMR and ^{13}C NMR, see Tables 1 and 2; IR (film) 2950, 1760, 1740, 1725, 1645, 1445, 1250 cm^{-1}; CIMS (NH_3) *m/z* (rel intensity) 358 ($M + NH_4$, 100), 341 (M + 1, 28).

Rearrangement of 7 to 8. To a solution of **7** (9.1 mg, 0.027 mmol) in $CDCl_3$ was added 54 μL (0.035 mmol) of 5% $CF_3COOD/CDCl_3$ (v/v). The reaction was monitored by ^1H-NMR spectroscopy. After standing 72 h at rt, the solvents were removed under reduced pressure and the resulting colorless oil was purified by silica gel chromatography (15:85 CH_3CN/CH_2Cl_2, partial decomposition noted). Triturating with CH_2Cl_2/hexane and removal of the solvents under reduced pressure yielded 4.0 mg of **8** (52% yield based on recovered starting material) as a white solid: $[\alpha]^{26}_D = -50°$ (*c* = 0.2, acetone); ^1H NMR and ^{13}C NMR, see Tables 1 and 2; IR (KBr) 3505, 2980, 1770, 1740, 1720, 1295, 1105, 990 cm^{-1}; CIMS (NH_3) *m/z* (rel intensity) 344 ($M + NH_4$, 100); EIMS (70 eV) 327 (M + 1, 7), 326 (M^+, 2.8).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of new compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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