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ON THE STRUCTURE OF NATURALLY-OCCURRING (+)-METHYL 3,4-ANHYDROSHIKIMATE

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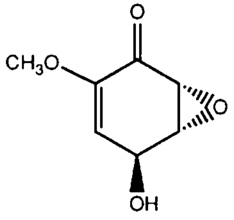
Abstract -- A two-step synthesis of enantiomerically pure (+)-methyl 3,4-anhydroshikimate **2** from (-)-methyl shikimate **3** is described, leading to a revision in the properties reported for this natural product.

Recently two new metabolites **1** and **2** were isolated from the fungus *Chalara microspora* during a systematic search for medicinally active compounds.[1] The former, chaloxone, appears related to the epoxydon family[2] while the latter, methyl 3,4-anhydroshikimate, may be derived from shikimate-3-phosphate as an offshoot of the aromatic biosynthetic pathway in plants and microorganisms.[3] The structure of **2** was subsequently confirmed by a racemic multistep synthesis and its absolute configuration reportedly established by partial resolution.[1]

As part of another project, we recently achieved a high-yielding, enantioselective synthesis of pure (+)-**2** in just two steps from (-) methyl shikimate **3**. While the NMR, IR and mass spectra of our synthetic sample agreed closely with reported values,[1] the specific rotations of synthetic and natural **2** were substantially different. Here we report our synthetic studies which indicate that **2** is a rather unstable substance, prone to a rearrangement that accounts for the observed discrepancy in chiroptical properties.



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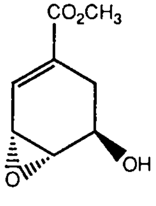

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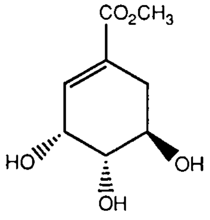

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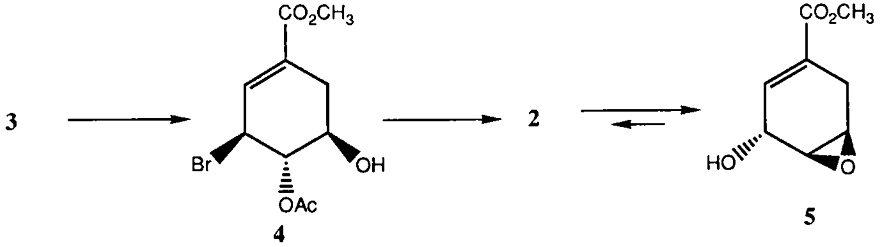
Reaction of (-)-methyl shikimate **3** with 2-acetoxyisobutyryl bromide (CH_3CN, 0°C, 30 min) gave trans-bromoacetate **4** (85%).[5] This application of a Syntex[6] procedure represents a new, highly selective functionalization of shikimic acid.[7] Treatment of **4** with base (1.3 equiv $NaOCH_3$-CH_3OH, 0°C, 30 min, immediate extractive workup) afforded analytically pure (+)-**2** in 87% yield[8] having $[\alpha]_D = +248^\circ$ (c 0.5, EtOH), lit[1] $[\alpha]_D = +95^\circ$ (c 0.5, EtOH). We now believe this discrepancy arises from a previously undetected[1] Payne rearrangement of **2** to **5** under mildly basic conditions.[9] Epoxyol **2** was stable to SiO_2 chromatography, however prolonged exposure to $NaOCH_3$ resulted in a gradual erosion of the rotation with no detectable change by tlc. Eventually an inseparable 3:7 equilibrium mixture of **2**:**5** was formed, judging from 300 MHz NMR, with $[\alpha] = +35^\circ$ (c 0.2, EtOH). The new, well-resolved NMR resonances were identical with published values for **5** described in a recent chiral synthesis of the enantiomer shown, which exhibited $[\alpha]_D = -54^\circ$ (c, 4.2, $CHCl_3$).[10] Based on these data, the reported dextrorotatory isolate of **2** may have been a 1:1 mixture of **2**:**5** which was not resolved by 100 MHz ^1H-NMR at the time.[11]



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5. For **4**: $[\alpha]_D = +40^\circ$ (c, 2.45, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) 6.84 (t, 1 H, J=2.3 Hz), 5.22 (dd, 1 H, J=7.8, 9.6 Hz), 4.68-4.62 (m, 1 H), 3.82-3.76 (m, 1 H), 3.74 (s 3 H), 2.90 (dd, 1 H, J=5.4, 18 Hz), 2.40 (ddt, 1 H, J=3.1, 9.3, 18 Hz), 2.13 (s, 3 H); IR ν_{max} (film) 3450, 2960, 1720, 1650, 1250, 750 cm^{-1}; HRMS calcd for $C_8H_9O_3Br$ (M^+-CH_3CO_2H) 231.9736; found 231.9741.
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7. For a route to methyl 4,5-anhydroshikimate derivatives, see McGowan, D.A.; Berchtold, G.A. *J. Org. Chem.* **1981,** 46, 2381.
8. For **2**; UV λ_{max} 234 nm (ε=7660, EtOH); NMR (300 MHz, $CDCl_3$) 7.13 (t, 1 H, J=3.7 Hz), 4.58-4.54 (m, 1 H), 3.75 (s, 3 H), 3.58-3.55 (m, 1 H), 3.47 (t, 1 H, J=4 Hz), 2.81 (dt, 1 H, J=2, 17.6 Hz), 2.32 (ddd, 1 H, J=3.3, 5.1, 17.6 Hz); IR ν_{max} (film) 3425, 2965, 2925, 1712, 1650, 1435, 1260 cm^{-1}; HRMS calcd for $C_8H_{10}O_4$ (M^+) 170.0579; found 170.0594.
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11. We thank the National Institutes of Health (GM 24054) for financial support and Mr. N. Nikolaides for valuable experimental assistance.

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