Short Chemical Synthesis of (−)-Chorismic Acid from (−)-Shikimic Acid

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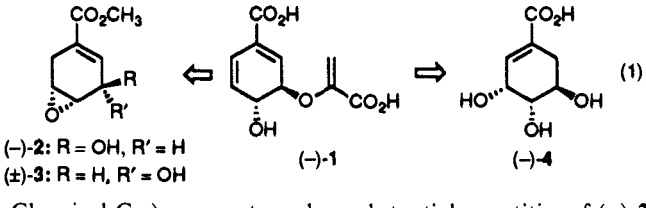
Abstract: A short and efficient partial synthesis of (−)-chorismic acid (**1**) from (−)-shikimic acid (**4**) is reported. Chorismate is the key branch-point intermediate in the shikimic acid pathway, which bacteria, fungi, and lower plants use to biosynthesize inter alia the amino acids phenylalanine, tyrosine, and tryptophan as well as the isoprenoid quinones and folate coenzymes. Reaction of (−)-methyl shikimate ((−)-**5**) with 2-acetoxyisobutyryl bromide (acetonitrile, 0 °C, 30 min) afforded (+)-methyl (3*R*,4*S*,5*R*)-3-bromo-4-acetoxy-5-hydroxy-1-cyclohexene-1-carboxylate ((+)-**7**) in 76–85% yield. Transesterification of this bromoacetate with $NaOCH_3$ (1.05 equiv, CH_3OH, 0 °C, 30 min) led quantitatively to the corresponding epoxyol, (+)-methyl 3,4-anhydroshikimate (**10**). Payne rearrangement of this *trans*-epoxyol ($NaOCH_3$–CH_3OH, 50 °C, 10 min) produced (−)-methyl (3*S*,4*S*,5*R*)-3-hydroxy-4,5-epoxy-1-cyclohexene-1-carboxylate ((−)-**2**), which has previously been converted into (−)-chorismic acid. This shikimate to chorismate transformation constitutes the first synthetic interconversion paralleling the biogenetic relationship shared by these two metabolites.

Chorismic acid (**1**) is a key branch-point intermediate in the shikimate biosynthetic pathway, which bacteria, fungi, and lower plants use to convert glucose 6-phosphate into a wide variety of primary and secondary metabolites. These include the amino acids phenylalanine, tyrosine, and tryptophan as well as the isoprenoid quinones and folate coenzymes. In 1982, the first total syntheses of racemic chorismic acid were reported by Berchtold's group at MIT[1] and by us.[2] In the following year, Hoare, Policastro, and Berchtold described an improved synthesis of (±)-**1** in 11 steps (6% overall yield) from methyl cyclohexene-4-carboxylate.[3] Most recently, a chiral synthesis of (−)-**1** was developed at MIT from *trans*-epoxyol (−)-**2**. This substance was obtained from either antipode of *cis*-epoxyol **3** by kinetically resolving the corresponding butyrate or acetate ester of (±)-**3** with bovine pancreatic cholesterol esterase,[4]

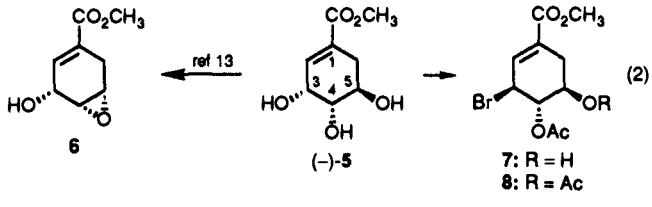
Our own longstanding interest in shikimate- and chorismate-derived metabolites[5] led us to develop an alternative approach to (−)-**2** from (−)-shikimic acid (**4**) (eq 1), thus completing a formal total synthesis of (−)-**1**. The shikimate to chorismate transformation we report constitutes the first synthetic interconversion paralleling the biogenetic relationship shared by these two metabolites. Since (−)-shikimate is commercially available (Aldrich



(−)-**2**: R = OH, R' = H
(±)-**3**: R = H, R' = OH
(−)-**1**
(−)-**4**
(1)

Chemical Co.), our route makes substantial quantities of (−)-**2** accessible for synthesizing rationally designed analogues of (−)-**1**. Chorismate analogues may be useful in elucidating the branch-point metabolism of enzymes like chorismate mutase[6] and isochorismate synthase.[7] Enantiomerically pure shikimic acid is also readily obtained in isotopically substituted forms,[8-12] so that the approach described here make it possible to prepare a variety of labeled chorismate isomers for biochemical and biological investigations.

Mimicking the biosynthetic conversion of **4** to **1** poses difficult problems in both selective hydroxyl group functionalization and regiospecific elimination chemistry. Besides acetal formation involving the *cis*-3,4-diol of **4**, the only other process that directly discriminates among the three secondary alcohols is the reaction of methyl shikimate (**5**) (eq 2) with triphenylphosphine–dialkyl azodicarboxylates. This dehydration does not follow the expected course but gives instead *syn*-hydroxy epoxide **6** (eq 2), presumably by selective activation of the C-5 hydroxyl group.[13]



6
(−)-**5**
7: R = H
8: R = Ac
(2)

In search of other methods for the selective modification of vicinal polyols, we turned to the chemistry of 2-acetoxyisobutyryl halides, which had been developed several years ago by Greenberg and Moffatt[14] to transform nucleoside *cis*-diols into vicinal *trans*-haloacetates via cyclic acetoxonium ion intermediates. In the event, reaction of (−)-**5** with 2-acetoxyisobutyryl bromide (CH_3CN, 0 °C, 30 min) furnished *trans*-bromoacetate **7** in 76–85% yield (eq 2). NMR decoupling studies on **7** confirmed its all-trans stereochemistry at carbons 3–5; moreover, solutions of this bromo acetate in CH_2Cl_2 rapidly deposited AgBr when treated with $AgBF_4$, as might be expected for an allylic bromide. Acetylation of **7** gave diacetate **8** as further confirmation of its

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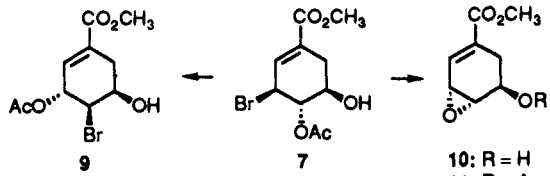
structure. This one-step differentiation of all three secondary alcohols led us to explore further the synthetic opportunities presented by halo acetates **7** and **8**.

One appealing aspect of **7** and **8** was the possibility of generating the conjugate diene pattern of chorismic acid directly by 1,4-dehydrobromination. Besides mimicking chorismate's biogenesis, such an elimination might be coupled with the regioselective attachment of an enol pyruvate at C-5 of **7** to gain rapid access to **1** and its congeners. In fact, however, all attempts to perform controlled dehydrobrominations were uniformly unsuccessful, resulting instead in ring aromatization. For example, treatment of **8** with 1,5-diazabicyclo[5.4.0]-5-undecene (DBU; 1.1 equiv, room temperature) gave exclusively methyl *m*-bromobenzoate in over 90% yield. We therefore redirected our attention to other chemistry of bromo ester **7**.

Although **7** was stable in the cold and could be purified on silica gel uneventfully, a slow isomerization took place in polar solvents, leading to bromo acetate **9** (eq 3). Thus, after **7** stood overnight



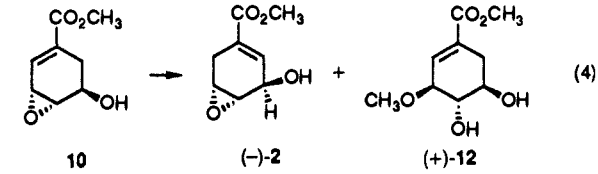
(3)

in pyridine, a 1:1 mixture of **7** and **9** was obtained. In contrast, transesterification of freshly prepared **7** with $NaOCH_3$ (1.05 equiv in CH_3OH, 0 °C, 30 min) led quantitatively to the corresponding epoxyol **10**. Interestingly, when **7** was exposed to DBU (1.1 equiv in C_6H_6), acyl migration, and then cyclization led to epoxy acetate **11** (65% yield).

The high yield of (+)-**10** obtained in the presence of methoxide is remarkable, since such 2,3-epoxy alcohols would be expected to undergo base-catalyzed Payne rearrangement. This rapid and reversible epoxyol–epoxyol interconversion was first observed in acyclic systems[15] and has since been used in conjunction with nucleophiles for the synthesis of highly functionalized diols.[16,17] In the case of **10**, isomerization to (−)-**2** would link the new chemistry of shikimic acid we had developed thus far with a key intermediate in the MIT synthesis of (−)-**1**.

We soon found that the Payne rearrangement of epoxyol **10** *had* already found its way, undetected, into the natural products literature. This substance, also known as methyl 3,4-anhydroshikimate, was first reported in 1981 as a chemical constituent of the fungus *Charala microspora*. Its structure was confirmed by a racemic multistep synthesis and its absolute configuration subsequently established by partial resolution.[18] However, the specific rotation for **10** reported in the earlier synthesis was +95°, whereas under identical measurement conditions our analytically pure material had $[\alpha]_D = +248°$. We believe this discrepancy arose from a previously undetected Payne rearrangement of (+)-**10** to (−)-**2** under the mildly basic conditions of natural product isolation. Epoxyol **10** was stable to SiO_2 chromatography; however, prolonged exposure to $NaOCH_3$ resulted in a gradual erosion of its specific rotation, with little discernible change upon thin-layer chromatographic analysis. We subsequently established that the isolated sample of naturally occurring **10** had actually rearranged to a 1:1 mixture of epoxyols (+)-**10** and (−)-**2**, whose 100-MHz NMR spectrum did not resolve the small differences between isomers.[19]

After considerable experimentation, optimum conditions for the Payne rearrangement of **10** were developed in $NaOCH_3$–CH_3OH, which reproducibly afforded a 1:3 equilibrium mixture of (+)-**10**–(−)-**2** with a minor amount of ether **12** resulting from nucleophilic opening of the epoxide (eq 4). This finding was particularly gratifying since earlier molecular mechanics calculations indicated that **2** was the more stable epoxyol isomer by approximately 1.2 kcal/mol.[20]



(4)

As the same base–solvent combination was used to form and isomerize **10**, we were able to streamline the synthesis by converting bromo acetate **7** directly to (−)-**2** in a one-pot reaction, with an overall yield of 46%. The melting point and spectroscopic properties of epoxyol (−)-**2** obtained after medium-pressure chromatographic purification were in agreement with previously reported values for this substance.[4] The specific rotation of (−)-**2** prepared in this fashion was slightly below the reported value, indicating that our product contained 3–4% of residual (+)-**10**, which could not be detected by NMR.

In summary, the selective functionalization of (−)-shikimic acid methyl ester (**5**) provided a short enantioselective synthesis of methyl 3,4-anhydroshikimate ((+)-**10**) (75% overall yield) and of epoxyol (−)-**2** (35% overall). The synthesis of (+)-**10** led to a revision in the properties reported for this natural product. More importantly, since epoxyol (−)-**2** had previously been converted to chorismic acid ((−)-**1**), a formal total synthesis of that key branch-point metabolite of the shikimate pathway was also achieved.

Experimental Section

Proton NMR spectra were taken on a Bruker WM-300 (300-MHz) spectrometer. All chemical shifts were reported as δ scale in parts per million downfield from Me_4Si. Spectra taken in $CDCl_3$ were referenced to either Me_4Si or residual $CHCl_3$. Anhydrous CH_3OH was prepared by distillation from Mg. Other experimental details have previously been reported.[21]

(+)-Methyl (3*R*,4*S*,5*R*)-3-Bromo-4-acetoxy-5-hydroxy-1-cyclohexene-1-carboxylate (7). α-Acetoxyisobutyryl bromide (1.46 g, 6.9 mmol) was added dropwise to a stirred suspension of methyl shikimate[22] (1.19 g, 6.33 mmol) at 0 °C in acetonitrile (25 mL). After 30 min, the homogeneous solution was diluted with anhydrous ether (10 mL) and washed with saturated $NaHCO_3$ (2 × 5 mL) and brine (5 mL) and the organic layer dried over $MgSO_4$. After removal of the solvent in vacuo, the crude oil was flash chromatographed over SiO_2 (3:2 hexane–ethyl acetate) to afford bromo acetate **7**: 1.40 g, 76% as a clear oil; R_f 0.25; $[\alpha]^{25}_D$ +40° (*c* = 2.45, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) 6.84 (t, 1 H, *J* = 2.3 Hz), 5.22 (dd, 1 H, *J* = 9.4, 7.8 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* = 18.0, 5.4 Hz), 2.4 (ddt, 1 H, *J* = 18.0, 9.4, 3.1 Hz), 2.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$), 170.8, 165.7, 136.1, 129.4, 78.3, 68.7, 52.2, 45.8, 32.3, 20.8; IR (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. This substance was not sufficiently stable to obtain a satisfactory combustion analysis. It was further characterized by acetylation (Ac_2O–pyridine–(*N*,*N*-dimethylamino)pyridine) to afford **8**: R_f 0.33; ^1H NMR ($CDCl_3$) 6.91 (br s, 1 H), 5.43 (dd, 1 H, *J* = 7.5, 5.0 Hz), 5.05 (m, 1 H), 4.66 (m, 1 H), 3.67 (s, 3 H), 2.88 (dd, 1 H, *J* = 17.5, 5.0 Hz), 2.51 (m, 1 H), 2.08 and 2.03 (2 s, each 3 H).

(+)-Methyl 3,4-Anhydroshikimate (10). A solution of $NaOCH_3$ in anhydrous methanol (0.83 M, 5.39 mL, 4.47 mmol) was added dropwise under Ar to a 0 °C solution of bromo acetate **7** (1.19 g, 4.06 mmol) in CH_3OH (10 mL). After 30 min, saturated NH_4Cl solution (2 mL) was added and CH_3OH removed in vacuo. The remaining aqueous phase was extracted with ethyl acetate (6 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford pure **10**: 0.68 g, 99% as an oil; R_f 0.30 (3:2 hexane–ethyl acetate); $[\alpha]_D$ +248° (*c* = 0.5, ethanol); ^1H NMR ($CDCl_3$) 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* = 17.6, 2.0 Hz), 2.32 (ddd, 1 H, *J* = 17.6, 5.1, 3.3 Hz); ^{13}C NMR ($CDCl_3$) 166.5, 133.4, 139.9, 63.5, 56.0, 52.0, 46.2, 29.4; IR (film) 3425, 2965, 2925, 1710, 1650, 1435, 1260 cm^{-1}; HRMS calcd for $C_8H_{10}O_4$ (M^+) 170.0579, found 170.0594.

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Acetate 11 of (+)-Methyl 3,4-Anhydroshikimate. A solution of bromo acetate **7** (65 mg, 0.22 mmol) in benzene (2 mL) was treated with DBU (36 μL, 1.1 equiv) under Ar at room temperature. The solution turned cloudy, the CH_2Cl_2 was added dropwise to restore homogeneity. After 30 min, the reaction mixture was diluted with ether (3 mL), washed with 5% H_2SO_4 (2 × 3 mL), and dried over $MgSO_4$ and the solvent removed in vacuo to produce crude **8** (46 mg). Flash chromatography on SiO_2 (3:2 hexanes–ethyl acetate) gave pure **8**: 26 mg, 60% as a clear oil; R_f 0.57; $[\alpha]_D$ +233° (c = 0.39, EtOH); ^{1}H NMR ($CDCl_3$) 7.12 (t, 1 H, J = 3.7 Hz), 5.59 (m, 1 H), 3.75 (s, 3 H), 3.59 (m, 1 H), 3.48 (t, 1 H, J = 4.0 Hz), 2.80 (dt, 1 H, J = 18.1, 1.9 Hz), 2.33 (ddd, 1 H, J = 18.1, 5.4, 3.2 Hz) 2.02 (s, 3 H); IR (film) 2950, 1740, 1720, 1650 cm^{-1}; HRMS calcd for $C_{10}H_{13}O_5$ (M + 1) 213.0763, found 213.0763.

(−)-Methyl (3*S*,4*S*,5*R*)-3-Hydroxy-4,5-epoxy-1-cyclohexene-1-carboxylate (2) Directly from 7. A solution of $NaOCH_3$ in anhydrous CH_3OH (0.84 M, 1.86 mL, 1.56 mmol) was added dropwise under Ar to a 0 °C solution of bromo acetate **7** (0.435 g, 1.48 mmol) in CH_3OH (3.7 mL). The reaction mixture was stirred for 30 min at 0 °C and then placed in a 50 °C oil bath for 10 min and more $NaOCH_3$ solution added (1.86 mL). After it was stirred for 25 min at 50 °C, the reaction mixture was neutralized at that temperature with saturated NH_4Cl solution (1 mL) and the bulk of the solvent removed in vacuo. The aqueous residue was then extracted with ethyl acetate (6 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Crude product (0.278 g) containing the desired (−)-**2**, unisomerized (+)-**10**, and ring-opened product (+)-**12** was purified by flash chromatography (9:1 ether–hexanes) to isolate (+)-**12**. The epoxyol mixture (3:1 **2**–**10**, 0.165 g) was further purified by medium-pressure liquid chromatography (Prep-PAK 500 SiO_2 column, 3:7 ether–hexanes), and the products were eluted in that order.

(−)-**2**: 0.113 g, 46% yield; R_f 0.33 (9:1 ether–hexanes); mp 64–65.5 °C (lit.[4] mp 65–66.5°C); $[\alpha]_D$ −41° (c = 1.5, $CHCl_3$) (lit.[4] $[\alpha]_D$ −53.9°); ^{1}H NMR ($CDCl_3$) 6.78 (m, 1 H), 4.65 (m, 1 H), 3.74 (s, 3 H), 3.43 (m, 1 H), 3.28 (m, 1 H), 2.94 (dm, 1 H, J = 20.0 Hz), 2.65 (dq, 1 H, J = 20.0, 2.5 Hz); ^{13}C NMR ($CDCl_3$) 170.0, 133.8, 126.9, 63.1, 52.8, 52.1, 50.5, 24.4; IR 3250, 3000, 2960, 1720, 1660, 1250 cm^{-1}.

(+)-**12**: 85 mg, 28% yield; mp 66–67 °C; $[\alpha]_D$ +21° (c = 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.80 (br s, 1 H), 3.83 (m, 2 H), 3.74 (s, 3 H), 3.58 (dd, 1 H, J = 9.9, 8.0 Hz), 3.49 (s, 3 H), 2.86 (dd, 1 H, J = 15.0, 5.7 Hz), 2.25 (m, 1 H); IR 3400, 2910, 1715, 1650, 1250, 1100 cm^{-1}; HRMS calcd for $C_9H_{14}O_5$ (M^+) 202.0841, found 202.0839.

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Crystal Structure of Two Retro-Inverso Sweeteners

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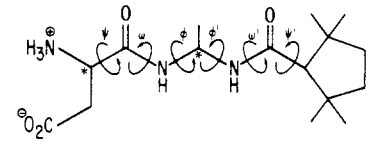
Abstract: We have solved the structure of a crystal composed of two diastereomers, *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (L,*R* isomer) and *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (L,*S* isomer). Both diastereomers are intensely sweet and are retro-inverso stereoisomers of dipeptides. We have related the crystal structure of these molecules to our model to explain the sweetness of peptide-based ligands. The "L shape" postulated on the basis of molecular mechanics and NMR spectroscopy is in full agreement with the crystal structures.

Introduction

As part of a program to relate structure of molecules to their taste, the conformations of four diastereomeric retro-inverso and dipeptide amides were recently reported,[1] The retro-inverso modification allows the examination of the effect of the backbone structure on taste and has led to many sweet-tasting compounds.[2] These molecules are sterically constrained as a result of the incorporation of a bulky substituent, the tetramethylcyclopentanyl group. The conformational preferences of the molecules were determined with use of high-resolution NMR and flexible geometry energy minimizations. The results from these experimental and theoretical approaches were found to be in good agreement. The favored conformations were then related to taste properties. From these results a model was developed to explain the sweet taste. In the molecular array of the sweet molecules the zwitterionic ring of the N-terminal L-aspartyl residue is coplanar and essentially perpendicular to the tetramethylcyclopentanyl ring leading to an "L shape" with the aspartyl moiety as the stem of the L and the tetramethylcyclopentanyl group the base of the L.

In this paper we present the X-ray diffraction analysis of a crystal composed of the following two diastereomeric retro-inverso amides: *N*-L-aspartyl-*N'*-[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*R*)-1,1-diaminoethane (Asp-R-gAlaTMCP) and *N*-L-aspartyl-*N'*[(2,2,5,5-tetramethylcyclopentanyl)carbonyl]-(*S*)-1,1-diaminoethane (Asp-S-gAlaTMCP). The similarities and differences of the solid-state structures are discussed and compared to the calculated conformations and those found in solution. The crystal structures are also compared to the solid-state conformation reported for aspartame,[3]



structure of Asp-(*R* and *S*)-gAla-TMCP

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