An Improved Synthesis of the Transition State Analog Inhibitor of Chorismate Mutase

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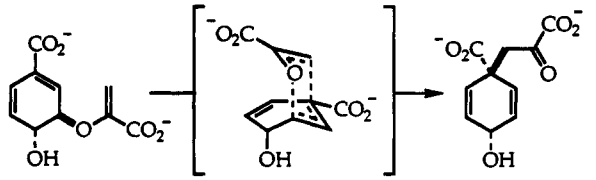
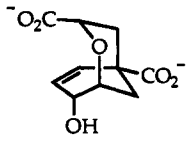
The oxabicyclic diacid **4**[1] was designed and synthesized as a mimic of the presumed transition state (**2**) for the reaction catalyzed by chorismate mutase,[2] a key enzyme in the shikimic acid pathway.[3] The enzymatic conversion of chorismic acid (**1**) to prephenic acid (**3**) is of interest because it represents the only example yet identified of a formal Claisen rearrangement in primary metabolism. As a potent inhibitor of the chorismate mutases, **4** has been useful in mechanistic[4] and structural[5] investigations, and it has served as an effective hapten for induction of antibodies that are also able to catalyze the rearrangement of **1** to **3**.[6]



1 **2** **3**



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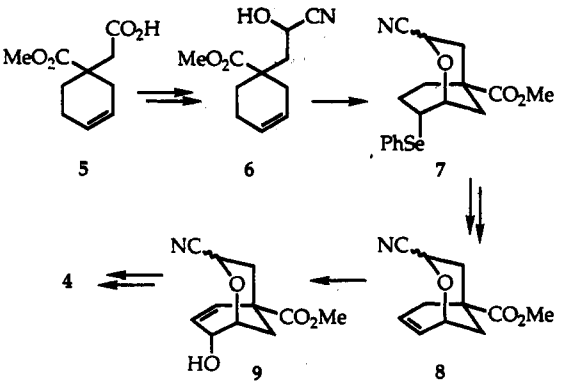
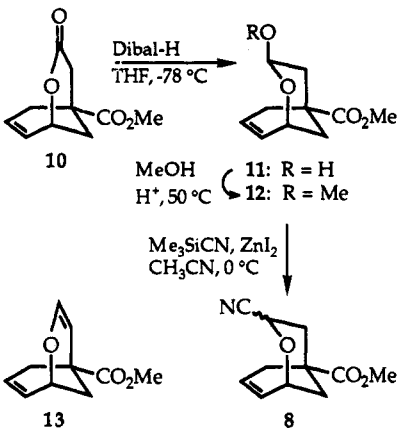
The previously reported synthesis of inhibitor **4** proceeded through the α-cyano ether **8**, as outlined in Scheme I. The steps leading up to this intermediate are cumbersome and have proven to be hard to reproduce. In particular, the cyanohydrin **6** lactonizes readily, which complicates both its generation and cyclization to the seleno ether **7**. In this Note, we describe an improved route to the α-cyano ether **8**, which streamlines the synthesis of **4** and makes it more amenable to larger scale.

Lactone **10** was described as an intermediate in the synthesis of the carbocyclic analog of **4**.[1b] It is readily available from the Diels–Alder adduct of butadiene and dimethyl itaconate by selective hydrolysis (to **5**), iodolactonization, and elimination. With DIBAL-H in THF at −78 °C, this lactone can be reduced to the hemiacetal **11** in >80% yield (Scheme II). This reaction is quite solvent-dependent, as the use of methylene chloride, toluene, or hexanes resulted in a complex mixture of products. The methyl acetal **12** is formed by warming hemiacetal **11** in methanol in the presence of an acid catalyst (Nafion NR50 beads proved to be particularly convenient).[7]

Scheme I



Scheme II



The conversion of acetals to α-cyano ethers with trimethylsilyl cyanide in the presence of a variety of Lewis acids has been reported in a number of systems.[8] However, the acetal **12** is exceedingly sensitive to elimination under Lewis-acidic conditions (perhaps through stabilization of the oxocarbonium ion by the π-bond), and most reagent combinations led to enol ether **13** as the major product. Recently, Schmidt et al. have described the use of nitrile solvents to stabilize oxocarbonium ions in glycosidic

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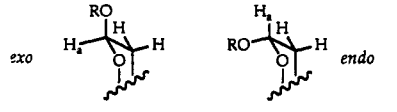
(7) The coupling constants observed for H_a in **11** and **12** serve to define the configuration of the *exo* and *endo* isomers. As initially isolated, **11** [H_a δ 5.16 (dd, J = 3.1, 10.0)] and **12** [H_a δ 4.79 (dd, J = 3.1, 9.8)] are exclusively *exo*. Interestingly, on standing in the solid state, the hemiacetal **11** isomerizes to a 2:1 *exo*/*endo* mixture [**11**-*endo* H_a δ 4.87 (dd, J = 2.4, 6.2)]; it is reconverted immediately to the *exo* epimer on redissolution in methanol. No such equilibration is seen with the acetal **12**.



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systems.[9] Following their lead, we explored reactions in acetonitrile and were able to achieve yields of cyano ether 8 of >85%, with less than 5% of the enol ether 13. Compound 8, produced as a 1:2 mixture of *exo/endo* isomers,[10] is then carried on to inhibitor 4 as described previously. These procedures circumvent the troublesome steps in the original synthetic route and improve the yield of intermediate 8 from compound 5 from 28 to 47% over six steps.

Experimental Section

Methyl 3-Hydroxy-2-oxabicyclo[3.3.1]non-7-ene-5-carboxylate (11). Lactone 10[1b] (4.0 g, 20.4 mmol) was dissolved in 100 mL of THF under nitrogen and cooled to −78 °C. Diisobutylaluminum hydride (DIBAL-H) (1 M solution in THF, 41 mL, 41 mmol) was added dropwise over 20 min and the reaction mixture was stirred at −78 °C for 1.5 h. The reaction was quenched by the addition of 20 mL of cold MeOH followed by 50 mL of 1 M HCl and allowed to warm to room temperature. The mixture was then extracted with 50 mL of ether and twice with 50 mL of CH_2Cl_2. The organic extracts were combined and washed with saturated $NaHCO_3$ solution until neutral. The organic layer was washed with 50 mL of water and 50 mL of brine and dried over $MgSO_4$, and the mixture was evaporated to yield 3.2 g of crude lactol. Immediate purification by flash chromatography with 50% ethyl acetate/hexanes gave 2.40 g (60% yield) of lactol 11 as a white powder. Smaller scale preparations provided purified product in as much as 82% yield: mp 96.0–98.0 °C; IR (KBr) 3340, 1725, 1260 cm^{-1}; ^1H NMR (CD_3OD) δ 6.05–6.08 (m, 1), 5.78–5.81 (m, 1), 5.16 (dd, 1, J = 3.1, 10.0), 4.35–4.37 (m, 1), 3.69 (s, 3), 1.59–2.54 (m, 6); ^{13}C NMR ($CDCl_3$) δ 176.18, 131.58, 123.76, 89.33, 66.21, 52.04, 42.26, 40.40, 34.39, 31.92. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.36; H, 7.12.

Methyl 3-Methoxy-2-oxabicyclo[3.3.1]non-7-ene-5-carboxylate (12). Lactol 11 (0.500 g, 2.52 mmol) was dissolved in 25 mL of methanol under N_2 and stirred in the presence of five Nafion NR50 beads (ca. 30 mg) at 50 °C. After 15 h, the solution was filtered and the solvent was evaporated to yield 0.5 g of a clear oil. Flash chromatography with 40% ethyl acetate/hexanes gave 0.468 g (87% yield) of methyl acetal 12 as a clear oil: IR 1745, 1230, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00 (m, 1), 5.80 (m, 1), 4.79 (dd, 1, J = 3.1, 9.8), 4.40 (m, 1), 3.66 (s, 3), 3.40 (s, 3), 1.62–2.52 (m, 6); ^{13}C NMR ($CDCl_3$) δ 176.3, 131.4, 124.2, 96.5, 66.0, 56.1, 52.1, 40.4, 40.3, 34.7, 32.2. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.88; H, 7.55.

Methyl 3-Cyano-2-oxabicyclo[3.3.1]non-7-ene-5-carboxylate (8). Acetal 12 (3.36 g, 15.5 mmol) was dissolved in 80 mL of acetonitrile and cooled to 0 °C under N_2 with stirring. Zinc iodide (1.0 g, 3.1 mmol) was added quickly. After 5 min, trimethylsilyl cyanide (7.4 mL, 55.6 mmol) was added dropwise over 10 min and the solution was stirred for 2.5 h. Cold, saturated $NaHCO_3$ (40 mL) was added and the mixture was warmed to room temperature. The mixture was extracted three times with 40 mL of CH_2Cl_2, and the organic layers were combined, washed with brine, and dried over $MgSO_4$. The solvent was evaporated to give a yellow oil, which was purified by flash chromatography using 33% ether/hexanes to give 2.80 g (88% yield) of a clear oil, identified as cyanohydrin ether 8 as a 1:2 exo/endo mixture of epimers. Spectral data agreed with those reported previously:[1b] IR (film) 2280, 1750, 1450, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) endo epimer δ 6.22 (m, 1), 5.98 (m, 1), 4.85 (dd, 1, J = <1, 8.3), 4.40 (m, 1), 3.69 (s, 3), 1.82–2.65 (m, 6); exo epimer δ 6.22 (m, 1), 5.72 (m, 1), 4.70 (dd, 1, J = 3.5, 12.5), 4.44 (m, 1), 3.68 (s, 3), 1.82–2.65 (m, 6); ^{13}C NMR ($CDCl_3$) endo epimer δ 175.7, 135.2, 124.0, 119.8, 65.7, 57.1, 38.6, 38.2, 35.5, 34.0, 31.3; exo epimer δ 175.0, 133.8, 122.1, 118.3, 66.6, 56.8, 52.3, 38.6, 37.4, 34.0, 31.5. Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.16; H, 6.32; N, 6.76. Found: C, 62.97; H, 6.39; N, 6.42.

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(10) The configurations of the epimers were also assigned from the coupling constants of the nitrile α-hydrogen, as listed in the Experimental Section.