Tetrahedron Letters,Vol.28,No.50,pp 6253-6256,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STEREOSELECTIVE FRAGMENTATION OF A TRICYCLIC DIESTER LEADING TO A POTENT CHORISMATE MUTASE TRANSITION STATE INHIBITOR

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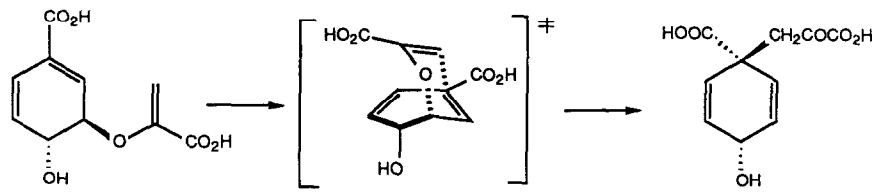
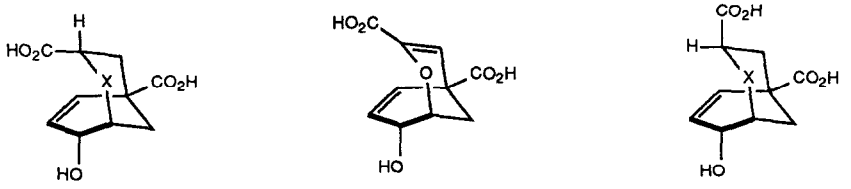
Summary: High kinetic stereoselectivity in the base-catalyzed fragmentation of 1,7-dicarbomethoxytricyclo[3.3.1.$0^{2,7}$]nonan-4-one 11 led to a convergent, high-yielding synthesis of 6.

The enzyme **chorismate mutase** catalyzes (what is apparently) the Claisen rearrangement of chorismic acid 1 to prephenic acid 2 via a chair transition state[1] as depicted below.[2] Since this reaction represents the first committed biosynthetic step to phenylalanine and tyrosine in plants and microorganisms, a potent inhibitor might possess valuable antibacterial and herbicidal properties. However, less is known about the mechanism of enzymic rearrangement[3] than of the non-enzymic process.[4] As a result, more progress has been made in the synthesis of transition state analogs than in the design of mechanism-based inhibitors.[5-8] Recently Bartlett and Johnson described the synthesis of oxabicyclic diacids 3-5, of which 3 was a more potent *E. coli* mutase inhibitor than adamantane-1-phosphonic acid (AD-PO_3H_2), the most active inhibitor known at the time.[9] Our interest in this area[4b] had led us to synthesize carbocyclic diacids 6 and 7 corresponding to 3 and 5. We now report that the endo isomer 6 is also more potent than AD-PO_3H_2 and supports the proposed picture[9] of a rearrangement transition state with the enol pyruvate carboxyl markedly tilted towards the unsaturated ring.



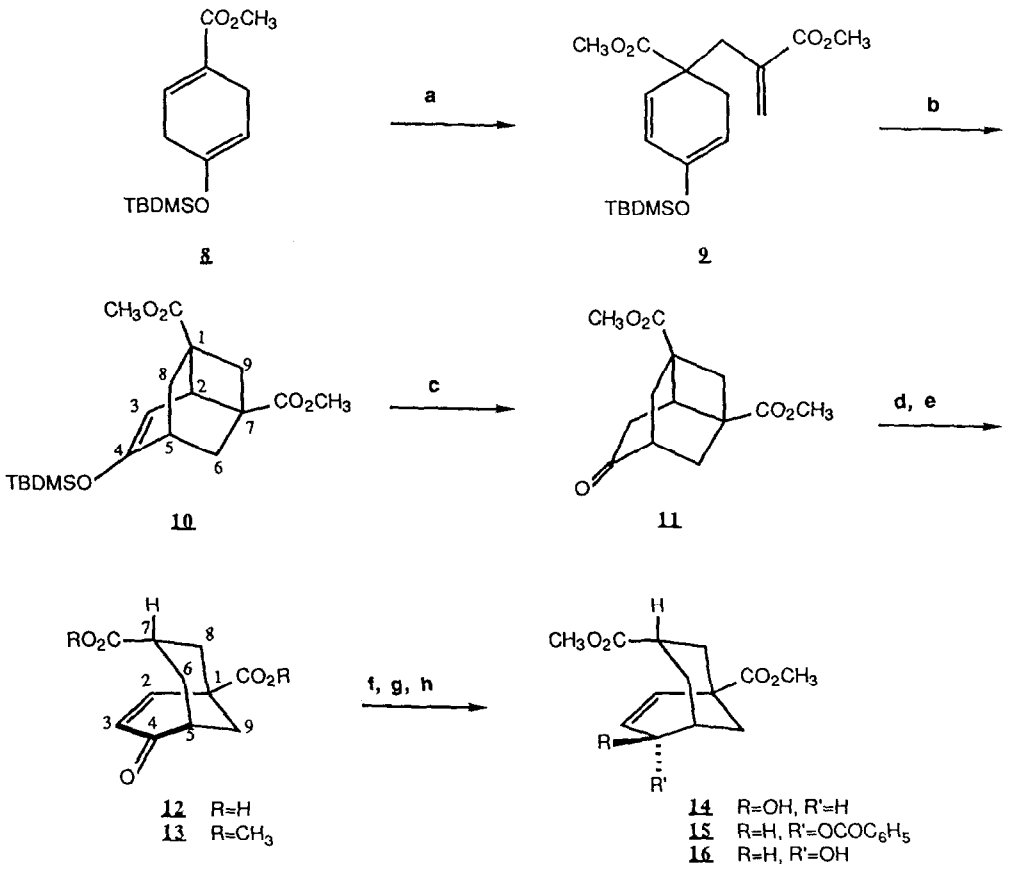


Methyl vinyl ketone was converted to 2-(tert-butyldimethylsilyloxy)-buta-1,3-diene by analogy with a known procedure.[10] Heating the diene with methyl propiolate furnished cycloadduct 8 which could be alkylated [lithium isopropylcyclohexylamide, methyl (2-bromomethyl)-acrylate] to afford diester 9 (Scheme).[11] In toluene at reflux, 9 underwent a smooth intramolecular Diels-Alder cycloaddition to furnish the symmetrical tricyclo[3.3.1.$0^{2,7}$]non-3-ene diester 10 in 90% yield.[12] Hydrolysis of the enol silyl ether group in 10 afforded symmetrical ketone 11 (96%). It was hoped that intramolecular β-elimination of 11 would occur with kinetically controlled protonation of the resultant bicyclo[3.3.1]non-2-en-4-one ester enolate from the less hindered (exo) face. In the event, exposure of 11 to $NaOCH_3$-CH_3OH at room temperature produced endo enone-diacid 12 as the exclusive product (waxy solid, 97%). The C7-hydrogen resonance of the corresponding diester 13 (t, δ=2.77, J=6.7 Hz)[13] conclusively established the axial configuration of its C7-carboxyl group. Reduction of 13 with $NaBH_4$-$CeCl_3$ furnished allylic alcohol 14 (100%) which could be transformed by the Mitsunobu reaction into allylic benzoate 15 (92%).[14] Exposure of this triester to excess NaOH (CH_3OH-H_2O, rt, 9 h, 78%) furnished endo-hydroxydiacid 6. Alternatively, 15 could be epimerized (KH-THF, then TFA) to a new triester (90%) which, when saponified as above, gave exo-hydroxydiacid 7 (tt, δ=2.45, J=4.3, 13.1 Hz; C7-hydrogen).[15]

Racemic samples of 6 and 7 along with AD-PO_3H_2 were evaluated as inhibitors of E. coli chorismate mutase/prephenate dehydrogenase. The enzyme was partially purified according to SampathKumar and Morrison,[16] then further purified by Blue Dextran-Sepharose chromatography using a method similar to that reported by Hudson et al.[17] Assays were performed at 30°C and pH 7.5 according to a published procedure.[16] Results with 7 [I_{50}=1.85 mM; I_{50}/K_m = 20.6] indicated that this exo-diacid was a weaker inhibitor than AD-PO_3H_2 [I_{50} = 0.70mM; I_{50}/Km = 7.8] when assayed under identical conditions.[18] In contrast, the endo-diacid 6 was more potent than AD-PO_3H_2, with an I_{50} = 0.43mM [I_{50}/K_m = 4.8 at pH 7.5]. While a direct comparison of 6 with oxabicyclic diacid 3 was not possible, our findings taken together with Bartlett's results[9] suggest interesting design strategies for useful new inhibitors of chorismate mutase.

ACKNOWLEDGMENT: We thank the National Institutes of Health (GM 24054) for generous financial assistance and Mrs. J. Widom for conducting the enzyme purification and assays. Support of the Cornell Nuclear Magnetic Resonance Facility by NSF (CHE 7904825, PCM 8018643) and NIH (RR02002) is gratefully acknowledged.

SCHEME



12 R=H
13 R=CH_3

14 R=OH, R'=H
15 R=H, R'=$OCOC_6H_5$
16 R=H, R'=OH

LEGEND:

(a) Lithium isopropylcyclohexylamine, THF, -78°C under Ar, then methyl (2-bromomethyl)acrylate (1.2 equiv); 95%
(b) Toluene, reflux , under Ar, 68 hours; 90%.
(c) Trifluoroacetic acid, methanol, rt under Ar, 6 hours; 96%.
(d) Sodium methoxide (4 equiv, 0.3M), methanol, rt under Ar, 19 hours; 97%.
(e) Diazomethane, ether, -78°C under Ar, until TLC monitoring indicated complete reaction; 87%.
(f) Sodium borohydride (1.3 equiv), cerium (III) chloride (1.2 equiv), methanol, rt, 5 min, then 10% HCl; 100%.
(g)Triphenylphosphine (2 equiv), benzoic acid (2 equiv), diisopropyl azodicarboxylate (2 equiv), THF, rt under Ar, 18 hours; 92%.
(h) Sodium hydroxide (4 equiv), 10:1 methanol:water, rt under Ar, 9 hours, 78%.

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11. NMR data for 9: δ ($CDCl_3$) 6.21 (d, 1 H, J=1.4 Hz), 5.94 (d, 1 H, J=10 Hz), 5.75 (dd, 1 H, J=2.1, 10 Hz), 5.48 (br. s, 1 H), 4.81 (m, 1 H), 3.62, 3.70 (2s, each 3 H), 2.76 (d, 1 H, J=13.5 Hz), 2.62 (d, 1 H, J=17.3 Hz), 2.61 (d, 1 H, J=13.3 Hz), 2.32 (dd, 1 H, J=5.5, 17.3 Hz), 0.90 (s, 9 H), 0.11 (s, 6 H).

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13. Prepared by brief CH_2N_2 treatment. NMR data for 13: 6.99 (dd, J=2.1, 10.2 Hz, H-2), 5.91 (d, J=10.2 Hz, H-3), 2.77 (t, J=6.7 Hz, H-7), 3.75, 3.55 (2s, each 3 H, OCH_3), 2.54-2.69 (m, 3 H), 2.36 (br. d, J=12.8 Hz, H-9α), 2.08 (dd, J=6.5, 13.9 Hz, H-8β), 2.04 (ddd, J=2.4, 2.4, 12.8 Hz, H-9β), 1.80 (ddd, J=4.6, 6.9, 14 Hz, H-6β).

14. NMR data for 15: 8.00, 7.50, 7.40 (3m, total=5 H, benzoate), 6.09 (d, J=10 Hz, H-2), 5.85 (ddd, J=1.1, 4.5, 10 Hz, H-3), 5.39 (d, J=4.4 Hz, H-4), 3.72, 3.63 (2s, each 3 H, OCH_3), 2.50-2.70 (m, 3 H), 2.34 (m, H-5), 2.18 (br. d, J=12.6 Hz, H-9α), 1.91 (dd, J=6.3, 13.6 Hz, H-8β), 1.70-1.80 (m, 2 H).

15. NMR of dimethyl ester of 7: 6.08, 6.03 (ABq, J=10.4 Hz, H-2, H-3), 3.87 (br. s, H-4), 3.73, 3.66 (2s, each 3 H, OCH_3), 2.51 (tt, J=4.7, 12.8 Hz, H-7), 2.26 (br. s, H-5), 2.04 (br. d, J=12 Hz, H-6α), 1.91 (m, 2 H), 1.79 (d, J=12.6 Hz, H-8β), 1.71 (br. d, J=11.5 Hz, H-6β), 1.63 (dd, J=4.3, 13.8 Hz, H-9β).

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18. It is difficult to compare reported values for I_{50} and K_m, which vary widely depending on the particular enzyme preparation and assay conditions used.

(Received in USA 15 September 1987)