that E_{act} for the conversion of **15a** into **17** is approximately 18.6 kcal mol^{-1} ($t_{1/2}$ 334 s at 300 K). Thus we have demonstrated that the diynene **15** is sufficiently strained that even at room temperature it undergoes rapid cyclization into the 1,4-diyl **16**. The products **17** and **18** are clear indications of a radical abstraction process and provide substantial vindication of the proposed mechanism. We are currently pursuing more elaborate models that contain the C-12 oxygen substituent and the C-13,14-double bond.[11]

Acknowledgment. The National Institutes of Health are gratefully thanked for their support. Dr. Terry Doyle (Bristol-Myers) is thanked for helpful discussions. Dr. John Huffman, Molecular Structure Center, Indiana University, Bloomington, IN 47405, is thanked for the X-ray structural determinations. Dr. J. Gajewski is thanked for carrying out the MMX calculations and discussions on the above problems.

(11) NMR data for **10**, **11**, **14**, and **17** are as follows. **10**: ^{1}NMR (300 MHz, $CDCl_3$) δ 5.86 (2 H, m), 4.21 (2 H, d, J = 1.8 Hz), 3.36 (3 H, s), 2.50 (4 H, m), 2.14 (4 H, t, J = 6.9 Hz), 0.87 (9 H, s), 0.21 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.68 (s), 119.57 (d), 118.81 (d), 98.75 (s), 92.90 (s), 83.40 (s), 83.01 (s), 67.75 (s), 60.21 (t), 57.61 (q), 40.14 (t), 37.40 (t), 25.80 (q), 18.13 (s), -3.00 (q). **11**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.32 (1 H, d, J = 11.0 Hz), 5.50 (1 H, d, J = 11.0 Hz), 4.59 (2 H, s), 3.19 (3 H, s), 2.55 (2 H, m), 2.23 (2 H, m), 1.8-2.1 (2 H, m), 0.95 (9 H, s), 0.22 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.77 (s), 198 (m), 136.82 (d), 109.84 (d), 102.22 (s), 94.18 (s), 83.39 (s), 81.76 (s), 73.38 (t), 67.44 (s), 58.99 (q), 39.74 (t), 37.18 (t), 25.85 (q), 18.40 (s), -2.84 (q). **14**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.88 (1 H, d, J = 9.4 Hz), 5.64 (1 H, d, J = 9.4 Hz), 3.20 (3 H, m), 2.7 (2 H, m), 2.3 (4 H, m), 0.92 (9 H, s), 0.26 (3 H, s); 0.18 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.52 (s), 198.74-199.13 (m), 142.69 (d), 109.50 (d), 102.70 (s), 99.28 (s), 88.63 (s), 83.11 (s), 69.78 (s), 56.64 (d), 45.42 (t), 41.09 (t), 36.81 (t), 35.36 (t), 25.84 (q), 18.28 (s), -3.10 (q). **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (4 H, m), 3.37 (1 H, dd, J's = 9.0 and 17.4 Hz), 2.82 (1 H, m), 2.67 (1 H, dd, J's = 6.2 and 15.7 Hz), 2.59 (1 H, m), 2.52 (1 H, dd, J's = 5.2 and 17.4 Hz), 2.31 (2 H, m), 2.16 (2 H, m), 0.87 (9 H, s), -0.06 (3 H, s), -0.19 (3 H, s).

Does Dehydroquinate Synthase Synthesize Dehydroquinate?

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Received November 2, 1987

The biosynthetic conversion of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) to 3-dehydroquinic acid (DHQ), attributed to 3-dehydroquinate synthase (EC 4.6.1.3), occurs at an early stage of the shikimate pathway.[1] The mechanistic details of the transformation (Scheme I)[2] reflect both clever functional group manipulation and stereochemical dexterity on the part of the enzyme. Temporary introduction of a ketone at C-5 of DAHP facilitates elimination of phosphate and generation of an enolpyranose **3**. From this intermediate, ring opening and rotation of the ensuing acyclic enol or enolate (→ **4**) set the stage for ring closure via an aldol condensation to provide the observed product, DHQ. We report here the nonenzymatic generation of enolpyranose **3** and observations of its chemical behavior which suggest that its biosynthetic conversion to DHQ may not be an enzyme-catalyzed process.

The enolpyranose **3** was expected to be unstable both toward isolation as well as under acidic or basic conditions typically utilized for removal of hydroxyl- or ketal-protecting groups. *o*-Nitrobenzyl ketal **15** was therefore chosen as the immediate precursor to **3**, since deprotection could be accomplished photochemically under neutral conditions.[3] This intermediate was synthesized from methyl 3-deoxy-D-*arabino*-heptulosonate, **5**,[4] as shown in Scheme II.[5]

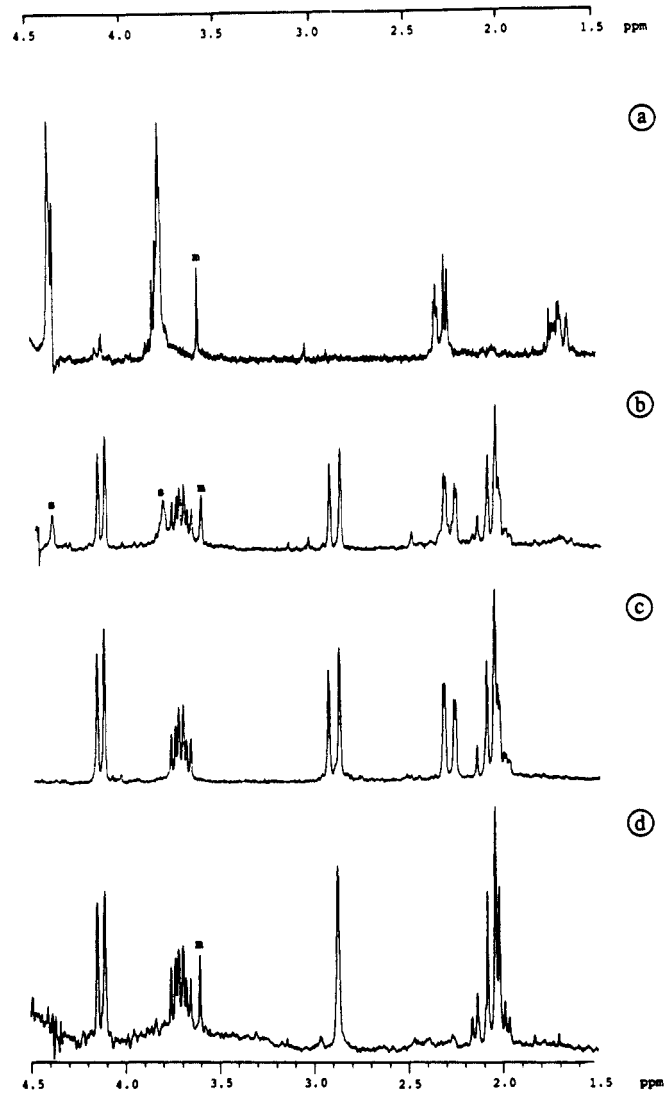
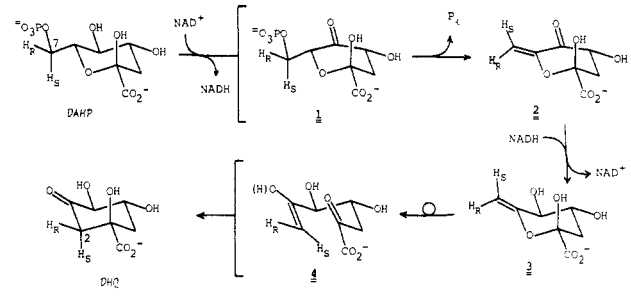


Figure 1. (a) There is 5.6 mg of **15** in 0.65 mL of 0.1 M phosphate buffer (0.39 mmol of NaH_2PO_4 and 0.61 mmol of Na_2HPO_4 in 10.0 mL of D_2O): m = methanol. (b) Solution from (a) after irradiation for 15 min at 0 °C: m = methanol, s = residual **15**. (c) Authentic DHQ in phosphate buffer. (d) Solution from irradiation of (7*Z*)-(7-^{2}H)-**15** (94% stereoisomeric purity) under the same conditions as (a): m = methanol.

Scheme I



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(4) Compound **5** was prepared by Dowex 50W X8-catalyzed hydrolysis of the corresponding diacetonide as described in the following: Frost, J. W.; Knowles, J. R. *Biochemistry* **1984**, *23*, 4465-4469.

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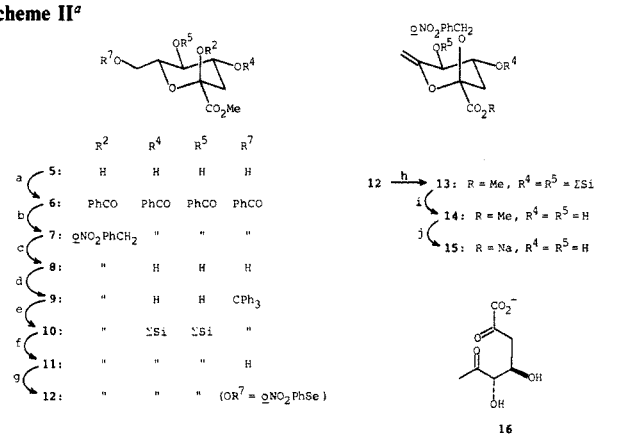
Scheme II[a]

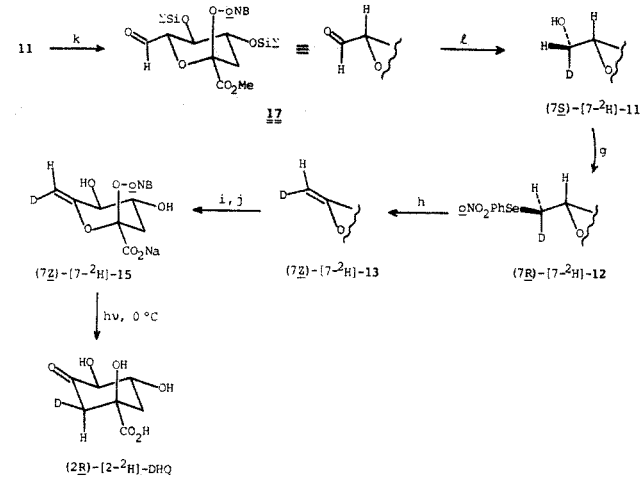


[a](a) PhCOCl, pyridine, 85%; (b) *o*-NO_2PhCH_2OH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 66%; (c) NaOMe, MeOH/THF, (98%); (d) Ph_3CCl, pyridine, 90 °C, 76%; (e) ΣSiO_3SCF_3, 2,6-lutidine, 89%; (f) MeOH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 85%; (g) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF, 85%; (h) 30% H_2O_2, THF, 80 °C, 88%; (i) *n*-Bu_4NF, THF, 72%; (j) NaOH, MeOH.

After irradiation of **15** as a 2.5 mM solution in 0.1 M phosphate buffer in D_2O, pD 7.0, at 0 °C for 15 min, examination of the mixture by ^1H NMR revealed complete conversion to DHQ (Figure 1b), rather than formation of enolpyranose **3**. The deprotection and rearrangement steps could be monitored more closely by conducting the photolysis at −78 °C in 70% CD_3OD/D_2O and 0.01 M NaOAc/HOAc buffer (pH 6.1 at −25 °C) and observing the subsequent cascade of intermediates by ^1H NMR at −25 °C. While a number of such intermediates were observed, none predominated prior to formation of DHQ, indicating that conversion of **3** to DHQ is at least as rapid as the steps involved in disconnection of the *o*-nitrobenzyl moiety.[6,8,10]

A hallmark of enzymatic transformations is their stereospecificity, particularly in comparison with many solution counterparts. A crucial aspect of the formation of enolpyranose **3** and cyclization of ketoenol(ate) **4** is the stereochemical fate of the methylene hydrogens from C-7 of DAHP. The overall course of the biosynthetic transformation,[2a,b] coupled with the syn stereochemistry of the enzymatic elimination step (**1** → **2**),[2e] requires that ring closure occur through a chairlike transition state **4**.[2e] To probe the conformation of the solution rearrangement, precursor **15** was synthesized in isotopically labeled form as shown in Scheme III.[11]

Scheme III[a]



[a](k) ClCOCOCl, DMSO, CH_2Cl_2, Et_3N, −78 °C, 83%; (l) $NaBD_4$, MeOD, 0 °C, 60 s, (93%); (g–j as in Scheme II).

Upon photolysis, (7*Z*)-[7-^{2}H]-**15** is converted cleanly to (2*R*)-[2-^{2}H]-DHQ,[15] reflecting a chairlike conformation for the ring closure step (e.g., **4**). Within the limits set by the stereochemical purity of the starting material, none of the stereoisomeric material is formed (Figure 1d). Thus, the spontaneous rearrangement of enolpyranose **3** to DHQ is identical stereochemically with the biosynthetic transformation.

C-Protonation of enols and enolates is relatively sluggish;[16] hence it is not surprising that aldol cyclization of the acyclic species **4** competes successfully with ketonization nor is it unexpected that cyclization of **4** proceeds via the most stable transition-state conformation.[2e] In view of the spontaneous rearrangement of enolpyranose **3** to DHQ, there would appear to be no reason to suggest that the biosynthetic transformation requires enzymatic catalysis. Indeed, it is unlikely that an enzyme would evolve to catalyze a transformation that occurs rapidly in its absence. We suggest that the chemistry catalyzed by "3-dehydroquinate synthase" concludes with reduction of ketone **2** and that enolpyranose **3** is the actual product of the enzymatic reaction. The possibility that related enolpyranose isomerizations in aminocyclitol biosynthesis[17] may also be nonenzymatic remains to be explored.

(5) Of a variety of sequences investigated for formation of the desired ketal, that involving initial perbenzoylation (→ **6**) followed by Lewis acid-catalyzed substitution at the anomeric position (→ **7**) was found to be the most efficient. The axial configuration of the *o*-nitrobenzyloxy moiety was demonstrated by a chemical shift of δ 2.25 ppm for H_{3eq} (observed for the free acid of compound **8**): Dabrowski, V.; Friebolin, H.; Brossner, R.; Supp, M. *Tetrahedron Lett.* **1979**, 4637–4640.

(6) Adlersberg and Sprinson[7] have shown that the acyclic diketone **16** is converted to DHQ in a nonenzymatic process; however, this transformation is too slow at neutral pH for **16** to be an intermediate in the observed rearrangement of **3**.

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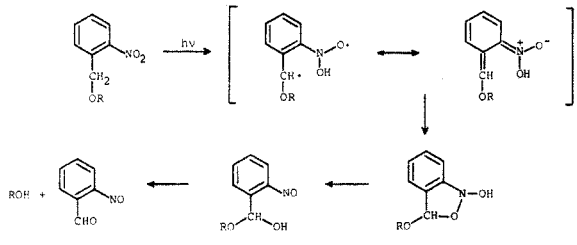
(8) The mechanism of photochemical deprotection of an *o*-nitrobenzyl group proceeds through a number of intermediates, culminating in the collapse of a hemiacetal to form *o*-nitrosobenzaldehyde.[9]



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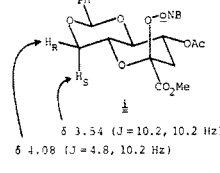
(11) Reduction of aldehyde **17** with $NaBD_4$ in methanol-d_4 at 0 °C proceeds with high stereoselectivity[12] (94:6 ratio of isomers) to afford (7*R*)-[7-^{2}H]-**11**. Conversion to benzylidene acetal **i**, in which the diastereotopic hydrogens at the 7-position are readily distinguished and identified by ^1H NMR, allowed the *R* configuration to be assigned to the deuteriated reduction product. Subsequent assignment of the *Z* configuration to enol ketal (7*Z*)-[7-^{2}H]-**15** follows from the known stereochemistry of the selenide formation[13] and elimination[14] reactions.



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Supplementary Material Available: Experimental procedures and full characterization for all compounds reported in this communication (12 pages). Ordering information is given on any current masthead page.

A Convergent, Enantiospecific Total Synthesis of the Novel Cyclodepsipeptide (+)-Jasplakinolide (Jaspamide)

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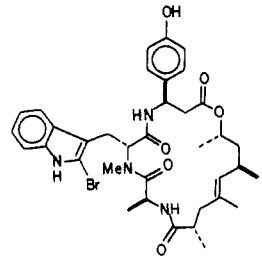
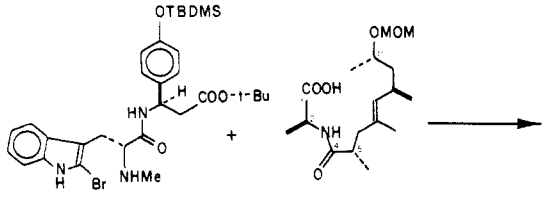
Jasplakinolide (**1**),[2] a novel cyclodepsipeptide isolated from a soft-bodied sponge, *Jaspis* sp., contains a new amino acid, 2-



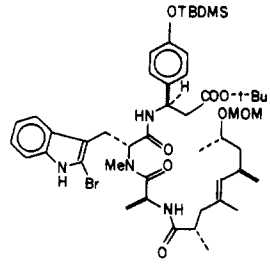
1

bromoabrine, possessing the unnatural D configuration and the rare amino acid (*R*)-β-tyrosine.[3] The potent insecticidal, antifungal, and anthelminthic properties[2] of jasplakinolide have been responsible for considerable synthetic activity in both industrial and academic laboratories. We wish to record the first total synthesis of (+)-jasplakinolide. The approach detailed below is both highly convergent and enantiospecific.

Our strategy for elaboration of jasplakinolide centered around the coupling of dipeptide **2** with the L-alanine derived acyclic fragment **3**. Construction of dipeptide **2** necessitated prior development of synthetic routes to the unnatural amino acids, (*R*)-β-tyrosine and D-bromoabrine.



2 3



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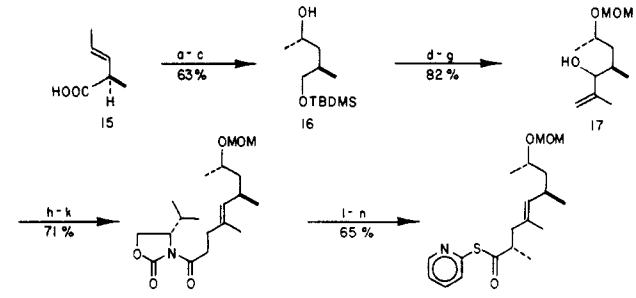
(3) Natural (*S*)-β-tyrosine was first found in two peptide antibiotics, edeine A and edeine B, obtained from cultures of *Bacillus brevis* Vm 4.[4]

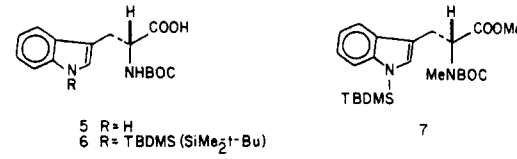
Scheme I. Synthesis of the C(4)-C(11) Fragment **19**[a]



18 19

[a] (a) $NaHCO_3$, I_2, H_2O, MeOH; (b) $LiAlH_4$, Et_2O, 0 °C; (c) *t*-$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → room temeprature; (e) Bu_4NF, THF; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (g) isopropenylmagnesium bromide, THF, -78 °C; (h) $CH_3C(OEt)_3$, propionic acid (catalyst), 120 °C, 3 h; (i) KOH, MeOH, H_2O; (j) *t*-BuCOCl, Et_3N, Et_2O; (k) lithio-(*S*)-4-isopropyl-2-oxazolidinone, THF, -78 °C; (l) $NaN(TMS)_2$, THF, -78 °C, MeI; (m) KOH, MeOH, H_2O; (n) $(PyS)_2$, Ph_3P, CH_2Cl_2.

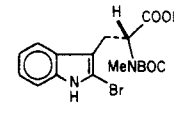
Our initial efforts were focused on the preparation of N^{α}-*t*-BOC-D-bromoabrine (**9**). Sequential treatment of a 0.2 M solution of commercially available N^{α}-*t*-BOC-D-tryptophan (**5**) in tetra-



5 R = H
6 R = TBDMS ($SiMe_2$-t-Bu)

7

hydrofuran at -78 °C with 3.0 equiv of sodium hexamethyldisilazide and 1.0 equiv of *tert*-butyldimethylchlorosilane provided in near quantitative yield N^{α}-*t*-BOC-N^{i}-*tert*-butyldimethylsilyl-D-tryptophan (**6**), $[\alpha]_D$ -21.2 ° (*c* 1.70, $CHCl_3$). Simultaneous N- and O-methylation (NaH, xsMeI, THF-DMF, 10:1, 60 °C) of **6** gave rise in ca. 80% yield to **7**, $[\alpha]_D$ +39.0° (*c* 1.27, $CHCl_3$), which upon exposure (0 °C → 25 °C, 3 h) to 2.0 equiv of pyridinium bromide perbromide in ether-chloroform, 1:1, afforded directly 2'-bromo-$N\alpha$-*t*-BOC-D-abrine methyl ester (**8**), $[\alpha]_D$ +69.4° (*c* 1.14, $CHCl_3$), in 50% yield. Saponification (1 N



8 R = Me
9 R = H

NaOH, H_2O-THF, 1:1) of **8** gives rise to a 96% yield of 2'-bromo-N^{α}-*t*-BOC-D-abrine (**9**), $[\alpha]_D$ +83.4° (*c* 1.28, MeOH). The formation of **9** proceeds without any racemization as evidenced by the proton NMR of 2'-bromo-D-abrine methyl ester in the presence of tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III).

Preparation of the (*R*)-β-tyrosine derivative **13** commenced with commercially available L-4-hydroxyphenylglycine. *tert*-Butyloxycarbonylation (BOC-ON, Et_3N, H_2O-dioxane, 1:1)[5] of L-4-hydroxyphenylglycine followed by silylation [(a) *t*-$Bu(Me)_2SiCl$, imidazole, DMF; (b) K_2CO_3, MeOH, H_2O] provided **10**, $[\alpha]_D$ +81.0° (*c* 1.34, $CHCl_3$) in 98% overall yield. *N*-*t*-BOC amino acid **10** was converted (ClCOOEt, Et_3N, Et_2O) into a mixed anhydride which upon treatment with ethereal diazomethane generated diazoketone **11** in 81% yield. Wolff rearrangement of **11** proceeded smoothly in the presence of silver benzoate and triethylamine in *tert*-butyl alcohol giving rise to **12**, $[\alpha]_D$ +22.6°

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