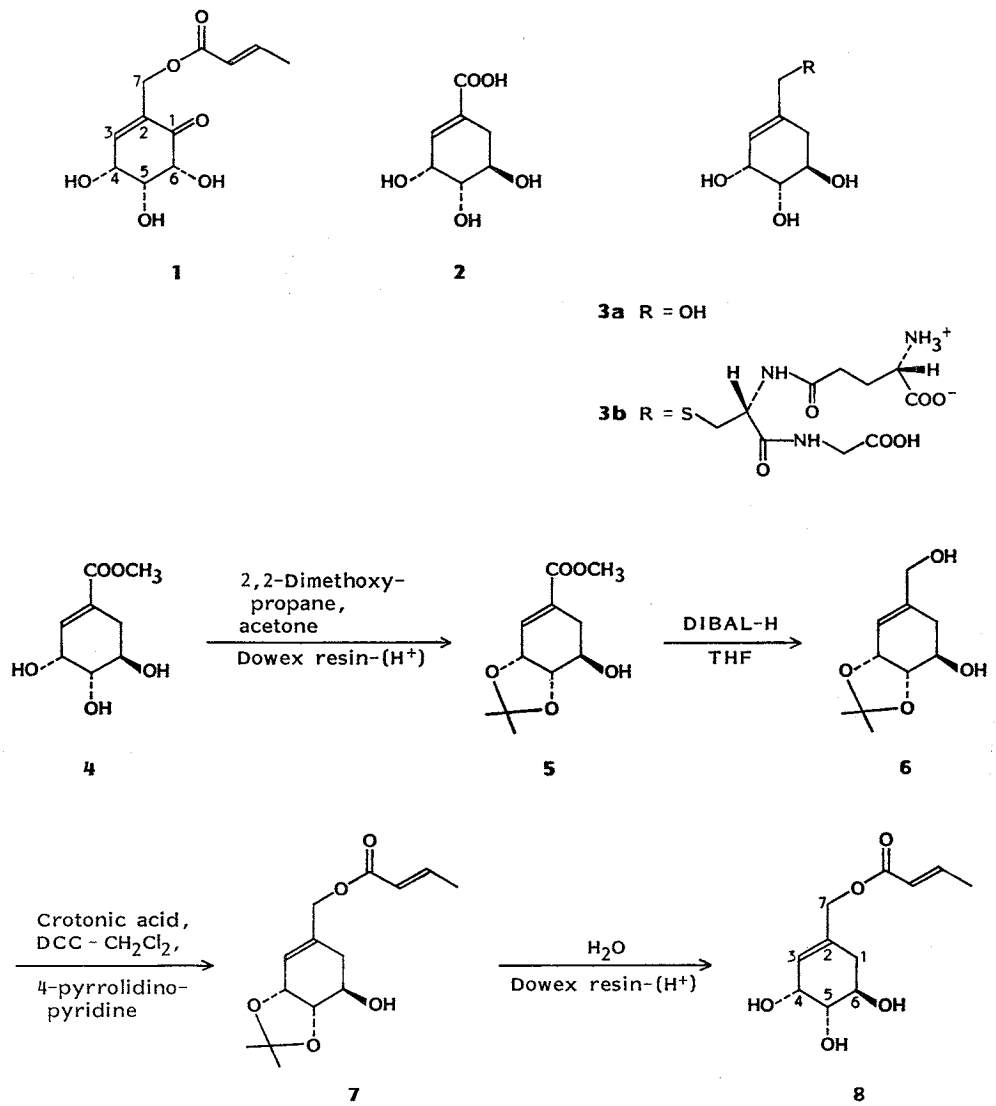
CONVERSION OF SHIKIMIC ACID INTO 2-CROTONYLOXYMETHYL-(4*R*,5*R*,6*S*)-4,5,6-TRIHYDROXYCYCLOHEX-2-ENE ANALOGOUS TO A GLYOXALASE I INHIBITOR

Sir:

Shikimic acid† was shown to occupy a major position in the formation of the essential aromatic amino acids. In comparison to chemical and biochemical studies of the shikimate pathway, the bioactivity of shikimic acid-derivatives has received considerably less attention to date††. Recently Japanese researchers discovered a glyoxalase I inhibitor, 2-crotonyloxymethyl-(4*R*, 5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone[3] (**1**), which showed a strong inhibition of growth of HeLa cells and Ehrlich ascites carcinoma and prolonged the survival period of mice inoculated with leukemia L1210 with a relatively low toxicity[3]. It was also found that inhibition of glyoxalase I is due to reaction at C-7 of **1** with

Fig. 1.



† For a comprehensive review[1].

†† Shikimic acid-derived dioxolamycin shows a moderate cytostatic activity against leukemia L1210 cells *in vitro*[2].

sulfhydryl compounds[4,5]. Recently VASELLA[6] and KOIZUMI[7] have accomplished synthesis of **1**. These findings prompted us to investigate any possibility of shikimic acid-derived antitumor agents. Thus we decided to make **8** to test its anti-neoplastic activity.

(−)-Shikimic acid was chosen as a chiral starting material. The conversion of (−)-shikimic acid into a potential glyoxalase I inhibitor, **8**, is outlined in Fig. 1. Thus treatment of (−)-shikimic acid, **2**, with saturated hydrogen chloride in methanol afforded crystalline methyl shikimate, **4** (reflux 1 hour, yield 91%). Direct reduction of **4** into shikimyl alcohol, **3a**[8], has been failed under various conditions (diisobutylaluminum hydride and lithium aluminum hydride). It was found that the protection of two hydroxyl groups at C-4 and C-5 of **4** is necessary for successful reduction of α,β-unsaturated methyl ester of **4**[8]. Therefore, two hydroxyl groups at C-4 and C-5 of **4** was selectively protected as acetonide, **5**[8] (2,2-dimethoxypropane, Dowex resin acidic form, acetone, 15 minutes, room temperature, yield 86%) and the reduction of methyl isopropylidene shikimate, **5**, with diisobutylaluminum hydride (10 equiv of 1.0 M diisobutylaluminum hydride (DIBAL-H) in THF, 0°C, 1 hour) provided cleanly the diol **6**[8] in excellent yield (87%, colorless oil). Selective crotonation of the allylic alcohol of **6** with crotonic acid (1 equiv) was achieved by dicyclohexylcarbodiimide (DCC) in the presence of catalytic amount of 4-pyrrolidinopyridine (methylene chloride, room temperature, 24 hours) to give **7** (yield 42%)†. It is known that treatment of isopropylideneshikimyl alcohol with dilute mineral acid, in an attempt to remove the protecting group, yielded only acetone and aromatics[1]. We found that final deprotection of the acetonide of **7** with Dowex resin (acidic form, water, 70°C, 1.5 hours) afforded cleanly the water soluble product, **8** (88%, mp 76~77°C, $[\alpha]_D^{25}$ −122° (*c* 0.1, H_2O), *Anal* Calcd for $C_{11}H_{16}O_5$: C 57.89, H 7.02, O 35.09. Found: C 57.98, H 7.20, O 35.00; IR (KBr) cm^{-1} 1710 (s, C=O); ^1H NMR (90 MHz, D_2O+DSS) δ 7.20 (1H, dq, J=14 and 6 Hz, *trans*-H), 6.05 (1H, dq, J=14 and 2 Hz, *trans*-H), 5.86 (1H, br d, J=3 Hz, 3-H), 4.70 (2H, s, CH_2O), 4.40 (1H, t, J=3 Hz, 4-H), 4.10 (1H, m, 6-H), 3.75 (1H, dd, J=3 and 9 Hz, 5-H), 2.40 (2H, ABq, J_{AB}=15 Hz, CH_2), 1.92 (3H, dd, J=2 and 6 Hz, CH_3). This compound **8** was further reacted with sulfhydryl compounds, for example, glutathione to afford **3b**. The ^1H NMR spectrum showed the presence of methylene proton attached to the C-2 position of **3b** as a doublet (J=1.3 Hz) at δ 3.79 and the absence of the crotonate moiety. In conclusion, we obtained the optically active target compound, **8** in 5 steps starting from shikimic acid in overall yield 25%. Although this final compound, **8** showed no antibacterial and anti-neoplastic activity against leukemia L1210 cell, this new synthetic compound, **8** shows a moderate anticandidal activity against *Trichophyton mentagrophytes* ATCC 9972 *in vitro* (MIC 51 μg/ml).

† The yield was not optimized.

Acknowledgment

This research was supported by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi. The author expresses his thanks to Dr. ALICE CLARK for anticandidal screening test, Dr. MAHMOUD A. ELSOHLY for helpful discussion and Mr. TIM WEST for technical assistance.

MANKIL JUNG

Research Institute of Pharmaceutical Sciences
and Department of Medicinal Chemistry,
School of Pharmacy University,
The University of Mississippi,
MS 38677, U.S.A.

(Received December 2, 1986)

References

1) BOHM, B. A.: Shikimic acid (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid). Chem. Rev. 65: 435~466, 1965
2) ZHU, B.; M. MORIOKA, H. NAKAMURA, H. NAGANAWA, Y. MURAOKA, Y. OKAMI & H. UMEZAWA: A new antitumor antibiotic, dioxolamycin. J. Antibiotics 37: 673~674, 1984
3) TAKEUCHI, T.; H. CHIMURA, M. HAMADA, H. UMEZAWA, O. YOSHIOKA, N. OGUCHI, Y. TAKAHASHI & A. MATSUDA: A glyoxalase I inhibitor of a new structural type produced by *Streptomyces*. J. Antibiotics 28: 737~742, 1975
4) CHIMURA, H.; H. NAKAMURA, T. TAKITA, T. TAKEUCHI, H. UMEZAWA, K. KATO, S. SAITO, T. TOMISAWA & Y. IITAKA: The structure of a glyoxalase I inhibitor and its chemical reactivity

with SH-compounds. J. Antibiotics 28: 743~748, 1975

5) SUGIMOTO, Y.; H. SUZUKI, H. YAMAKI, T. NISHIMURA & N. TANAKA: Mechanism of action of 2-crotonyloxymethyl-4,5,6-trihydroxycyclohex-2-enone, a SH inhibitory antitumor antibiotic, and its effect on drug-resistant neoplastic cells. J. Antibiotics 35: 1222~1230, 1982

6) MIRZA, S.; L.-P. MOLLEYRES & A. VASELLA: Synthesis of a glyoxalase I inhibitor from *Streptomyces griseosporeus* Niida et Ogasawara. Helv. Chim. Acta 68: 988~996, 1985

7) TAKAYAMA, H.; K. HAYASHI & T. KOIZUMI: Enantioselective total synthesis of glyoxalase I inhibitor using asymmetric Diels-Alder reaction of a new chiral dienophile, $(S)_S$-3-(3-trifluoromethylpyrid-2-ylsulfinyl)acrylate. Tetrahedron Lett. 27: 5509~5512, 1986

8) GREWE, R.; H. JENSEN & M. SCHNOOR: Darstellung und Eigenschaften des Shikimialkohols. Berichte 89: 898~905, 1956