Tetrahedron Letters,Vol.27,No.45,pp 5509-5512,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

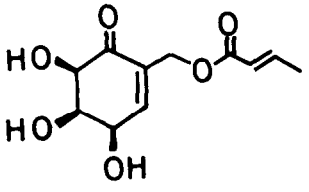
ENANTIOSELECTIVE TOTAL SYNTHESIS OF GLYOXALASE I INHIBITOR USING ASYMMETRIC DIELS-ALDER REACTION OF A NEW CHIRAL DIENOPHILE, $(\underline{S})_S$-3-(3-TRIFLUOROMETHYLPYRID-2-YLSULFINYL)ACRYLATE.

Hiromitsu Takayama, Kazuya Hayashi, and Toru Koizumi*

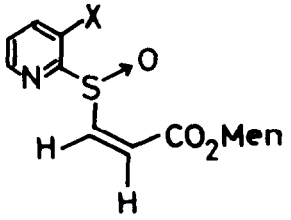
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Summary Highly enantioselective total synthesis of Glyoxalase I inhibitor (**1**) was achieved utilizing the asymmetric Diels-Alder reaction of a new chiral dienophile, $(\underline{S})_S$-menthyl 3-(3-trifluoromethylpyrid-2-ylsulfinyl)acrylate (**3**) with 2-methoxyfuran.

Glyoxalase I inhibitor(COTC) (**1**), isolated first from the culture broth of Streptomyces griseosporeus by Umezawa et al.[1], has attracted considerable interest because of its cytotoxic and cancerostatic activity.[2] The chiral synthesis of this enzyme inhibitor possessing a unique 4β, 5β, 6β-trihydroxycyclohex-2-enone system has been recently accomplished by Vasella et al[3] starting from D-mannose and the absolute configuration of **1** was confirmed unequivocally by this chemical conversion. However, the asymmetric total synthesis of this biologically important compound has not been reported so far. In this communication, we describe the first efficient enantioselective total synthesis of (-)-**1** by the asymmetric Diels-Alder reaction using chiral arylsulfinylacrylate as a dienophile.[4] In the synthetic strategy which we designed by the retrosynthetic analysis , the crucial step was the asymmetric Diels-Alder reaction of optically active 3-arylsulfinylacrylate to afford 1-methoxy-3-arylsulfinyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate system, which was transformed highly stereoselectively to compound **9**. The deprotection-ring opening - desulfenylation reactions of **9** in one step would provide the target compound, COTC **1** (see Scheme 1).

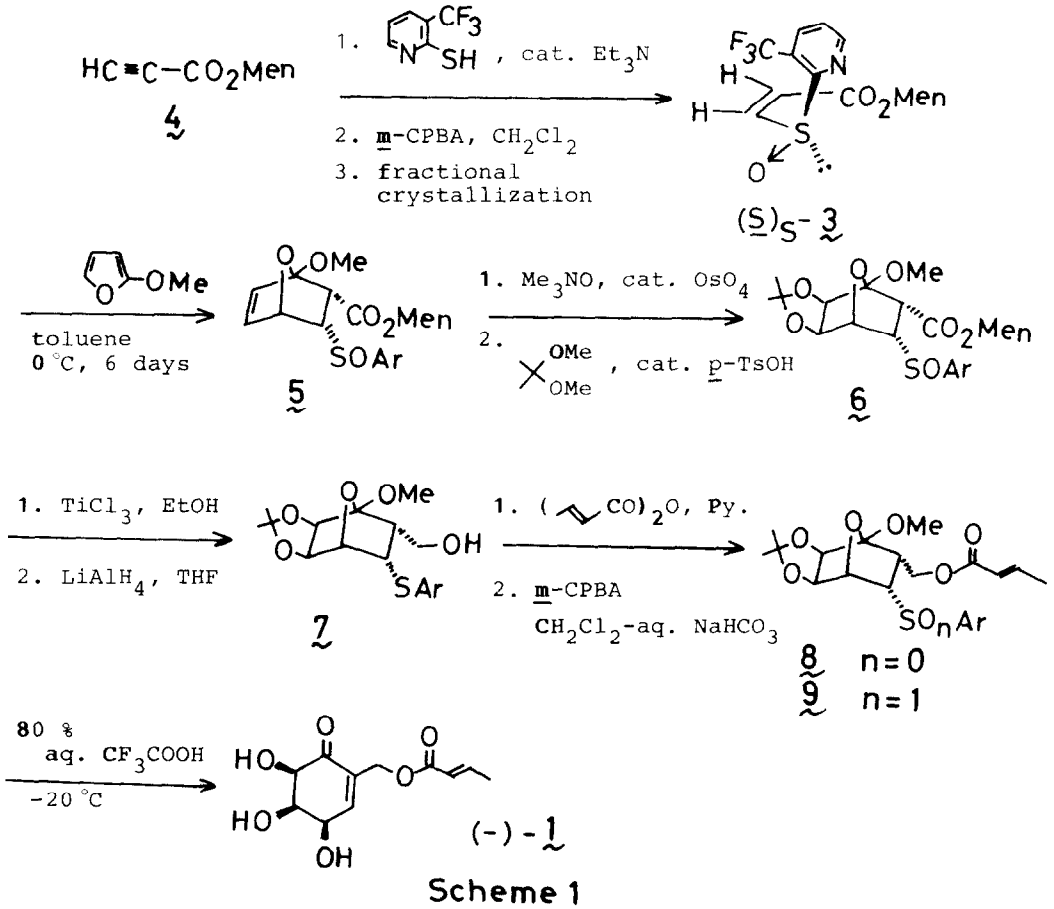


(-) - **1**



2 X = H
3 X = CF_3

For our synthetic plan, what is strongly required is the development of a novel arylsulfinyl-type chiral dienophile which reacts highly diastereoselectively with 2-methoxyfuran under non-acidic condition[5]. Chiral sulfinyl dienophiles[4] hitherto developed by our group are unfortunately not suitable for the present purpose. During our continuing studies on the asymmetric Diels-Alder reaction using chiral sulfinyl group,[4] we have quite recently found that the introduction of trifluoromethyl group at the 3-position of (±)-3-(2-pyridylsulfinyl)acrylate(2) enhanced the dienophilic reactivity considerably[6]. Furthermore, the high diastereoselectivity was observed even in the absence of Lewis acid.[6] Based on this observation, we decided to prepare the optically active sulfoxide 3 from l-menthyl propiolate (4)[7] by the same procedure reported previously[4c]. Fractional crystallization of a diastereomeric mixture(1:1) of sulfoxides from Et_2O-ethyl acetate gave nicely crystalline, optically pure sulfoxide 3[8], mp 148-149°C, $[\alpha]_D$ +189° (c 1.08), in 20% yield from 4.[9] Absolute configuration of the sulfoxide was assigned as $(S)_S$ by comparison of its CD spectrum with those of $(S)_S$- and $(R)_S$-3-(2-pyridylsulfinyl)acrylates (2).[10] On the basis of the mechanistic consideration,[4] the sulfoxide having (S) configuration should be suitable for the chiral synthesis of natural (-)-COTC (1).



The Diels-Alder reaction of $(\underline{S})_S$-**3** with 5 equiv. of 2-methoxyfuran was carried out in toluene at 0°C for 6 days to afford the endo cycloadducts **5** almost exclusively. The crude cycloadducts[11] were subjected to OsO_4 oxidation(catalytic amount of OsO_4 and Me_3NO) followed by the ketalization(2,2-dimethoxypropane and p-TsOH)to give exclusively the exo diol derivative **6** in 72% overall yield from the dienophile **3**. HPLC analysis[12] of the crude acetonide **6** showed the presence of diastereoisomers in a ratio of 98:2, indicating that the Diels-Alder reaction of $(\underline{S})_S$-**3** with 2-methoxyfuran and the subsequent vicinal hydroxylation proceeded with high stereo- and diastereoselectivity. The diastereomerically pure sulfoxide **6** which was obtained by the recrystallization of the crude sulfoxides[13] was reduced with $TiCl_3$ in ethanol and then with $LiAlH_4$ in THF to provide the primary alcohol **7**[14] in 78% yield. The enantiomeric excess of **7** was proved to be no less than 98% as checked by the NMR spectrum of the corresponding (-)-MTPA ester[15]. The sulfide **8**[16], $[\alpha]_D$ +40.5°(c 1.33), obtained by esterification of the alcohol **7** with crotonic anhydride and pyridine in quantitative yield, was oxidized with mCPBA in CH_2Cl_2-aq. $NaHCO_3$ to afford a diastereoisomeric mixture(10:1) of sulfoxides **9**[17] in 85% yield. Next is the final stage of our synthetic plan which is the direct conversion of **9** to the objective natural product by deketalization-ring opening-desulfenylation reaction. After various unsuccessful attempts due to the instability of COTC toward alkali and silica gel, we finally succeeded to obtain (-)-COTC **1** in 62% yield from **9**. Thus, treatment of **9** with 80% aq. CF_3CO_2H at -20°C for 5 hr, and subsequent purification by use of Sephadex LH-20 chromatography with methanol afforded crystalline (-)-COTC **1**. The spectral data(IR and NMR)of the synthetic COTC **1** (mp 179-181 °C, $[\alpha]_D$ -108°(c 0.23, MeOH), lit,.[1] mp 181°C, $[\alpha]_D$ -109°(c 1.5, MeOH)) were identical with those of natural compound.

The successful enantioselective synthesis of (-)-COTC presented here demonstrates that optically active 3-trifluoromethylpyrid-2-ylsulfinyl group has the potential to be an efficient chiral auxiliary. Furthermore, the methodology developed in this work should provide an expedient route to the naturally occurring highly functionalized cyclohexane derivatives having biological activities.[18]

Acknowledgement---We thank Dr. H. Suzuki, Institute of Applied Microbiology, University of Tokyo, for providing us IR and NMR spectra of natural COTC.
This work was supported in part by Grant-in-Aid from scientific research from the Ministry of Education, Science and Culture , Japan(59570888) and by the Tamura Foundation for the Promotion of Science and Technology.

References and Notes

1a) T. Takeuchi, H. Chimura, M. Hamada, H. Umezawa, O. Yoshioka, N. Oguchi, Y. Takahashi, and A. Matsuda, J. Antibiot., 1975, **28**, 737.

b) H. Chimura, H. Nakamura, T. Takita, T. Takeuchi, H. Umezawa, K. Kato, S. Saito, T. Tomizawa, and Y. Iitaka, ibid., 1975, **28**, 743.

2a) Y. Sugimoto, H. Suzuki, H. Yamaki, T. Nishimura, and N. Tanaka, ibid., 1982, **35**, 1222.

b) K. T. Douglas, S. Shinkai, Ang. Chem., Int. Ed. Engl., 1985, **24**, 31.

3) S. Mirza, L-P. Molleyres, and A. Vasella, Helv. Chim. Acta., 1985, **68**, 988.

4a) T. Koizumi, I. Hakamada, and E. Yoshii, Tetrahedron Lett., 1984, **25**, 87.

b) Y. Arai, S. Kuwayama, Y. Takeuchi, and T. Koizumi, ibid., 1985, **26**, 6205.

c) H. Takayama, A. Iyobe, and T. Koizumi, J. Chem. Soc., Chem. Commun., 1986, 771.

5) 1-Methoxy-7-oxabicyclo[2.2.1]hept-5-ene ring system was found to be unstable to acidic condition.

6) H. Takayama, K. Hayashi, Y. Takeuchi, and T. Koizumi, Heterocycles, In Press.

7) H. R. Pfaendler, J. Gosteli, and R. B. Woodward, J. Am. Chem. Soc., 1979, **101**, 6306.

8) All new compounds reported here gave satisfactory spectroscopic and analytical data. Optical rotations were measured in $CHCl_3$ at 24-26°C, unless otherwise noted.

9) $(\underline{R})_S$-**3**, mp 93-94°C (hexane-Et_2O), $[\alpha]_D$ -286°(c 0.32), was also isolated in 2% yield. (The yield is not optimized.) These diastereoisomers, $(\underline{S})_S$-**3** and $(\underline{R})_S$-**3**, can be easily distinguished by means of 270MHz NMR spectra; $(\underline{S})_S$-**3**, δ 0.77(d, J=6.9Hz, CH_3), 6.42(d, J=10.2Hz, olefinic H), $(\underline{R})_S$-**3**, δ 0.59(d, J=6.9Hz), 6.40(d, J=10.2Hz).

10) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., J. Am. Chem. Soc., 1965, **87**, 1958.

11) Since the retro Diels-Alder reaction of the cycloadducts was observed during the purification using silica gel chromatography, the crude products were directly subjected to the next step.

12) Develosil, n-hexane-Et_2O(1:9); major diastereomer, Rt.34 min., minor diastereomer, Rt.31 min.

13) Diastereomerically pure isomer **6** was obtained by the recrystallization from n-hexane-AcOEt in 60 % overall yield from **3**. mp 193-194°C; $[\alpha]_D$ +41.6°(c 0.54); NMR(270MHz, $CDCl_3$) 1.34(3H, s),1.55(3H, s),3.61(1H, d, J=11.2), 3.66(3H, s), 4.33(1H,d, J=5.3), 4.53(1H, dd, J=11.2, 5.1), 4.76(1H, d, J=5.1), 5.29(1H, d, J=5.3).

14) **7**:$[\alpha]_D$ +39.2°(c 0.87); IR($CHCl_3$) 3425 cm^{-1} ;NMR($CDCl_3$) 2.90(1H, m), 3.68(3H, s), 3.80(2H, m), 4.30(1H, d, J=6.0),4.48(1H, bs),4.51(1H, d, J=4.0),4.66(1H, d, J=6.0).

15) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 1969, **34**, 2543. In the 270MHz NMR spectrum of the (-)-Mosher ester [(-)-α-methoxy-α-trifluoromethylphenylacetate] of the racemate **7**, a pair of singlets due to the C_1-OMe at 3.59ppm and 3.55ppm was observed. The spectrum of the (-)-Mosher ester derivative of (+)-**7** showed these signals in the ratio of 1:107(d.e. 98%).

16) **8**:$[\alpha]_D$ +40.5°(c 1.33); IR($CHCl_3$) 1710 cm^{-1}; NMR($CDCl_3$) 1.79(3H, dd, J=7.1, 1.7), 3.09(1H, dt, J=11.2, 8), 3.63(3H, s) 4.22(2H, d, J=8.1), 4.43(1H, d, J=5.6), 4.47(1H, d, J=5.6), 4.69(1H, d, J=5.6), 4.82(dd, J=11.2, 5.6), 5.56(1H, J=16.0, 1.7), 6.80(1H, dq, J=16.0, 7.1).

17)major diastereomer **9** : IR($CHCl_3$) 1710, 1030 cm^{-1} ; NMR($CDCl_3$) 1.36(3H,s), 1.52(3H, s), 1.88(3H, dd, J=7.1, 1.7), 3.05(1H, dt, J=11.7, 5.4),3.59(3H, s) 3.69(1H, dd, J=11.7, 5.4) 4.26(1H, d, J=5.4), 4.45(1H, d, J=5.6), 4.50(2H, d, J=7.8), 5.71(1H, dd, J=16.0, 1.7), 5.75(1H, d, J=5.6), 6.97(1H, dq, J=16.0, 7.1).

18) A. Ichihara, R. Kimura, K. Oda, and S. Sakamura, Tetrahedron Lett., **1976**, 4741 and references cited therein.

(Received in Japan 26 July 1986)