Communications to the Editor

[Chem. Pharm. Bull.]
35(1) 433-435 (1987)

SUCCESSFUL ASYMMETRIC DIELS-ALDER APPROACH TO
OPTICALLY ACTIVE C-NUCLEOSIDES. ENANTIOSELECTIVE TOTAL
SYNTHESIS OF D-SHOWDOMYCIN AND D-2,5-ANHYDROALLOSE DERIVATIVES

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Using an asymmetric Diels-Alder reaction of (S)S-3-(2-pyridyl-sulfinyl)acrylate with furan, a highly enantioselective synthesis of a common key intermediate (+)-(1) was achieved, and this was successfully converted to C-nucleosides, D-showdomycin (2) and D-3,4-O-isopropylidene-2,5-anhydroallose (3).

KEYWORDS—C-nucleoside; D-showdomycin; 3-(arylsulfinyl)-acrylate; 3-(heteroarylsulfinyl)acrylate; asymmetric Diels-Alder reaction; chiral sulfoxide; D-anhydroallose

Much attention has been focused on synthetic approaches to naturally occurring C-nucleosides because of their interesting biological activities.¹⁾ Methods hitherto developed for the synthesis of optically active C-nucleosides fall into the following three categories: 1) chemical transformation of natural carbohydrate precursors,²⁾ 2) conventional optical resolution of synthetic intermediates,³⁾ and 3) production of chiral intermediates by a chemicoenzymatic strategy.⁴⁾ There has been no report on the total synthesis of C-nucleosides using asymmetric organic reactions. The recent progress in the asymmetric reactions, especially the asymmetric Diels-Alder reaction, presents a new method for the preparation of chiral synthetic intermediates of C-nucleosides.

Recently we have introduced novel chiral dienophiles, menthyl 3-(2-pyridylsulfinyl)acrylates (S)S- and (R)S-(4),⁵⁾ which react smoothly with furan in a highly diastereoselective manner, and suggested that the asymmetric D-A reaction may be a new way to synthesize chiral C-nucleosides.

Here we report our recent results along this line, presenting the highly enantioselective synthesis of a common key intermediate (+)-1⁶⁾ using the asymmetric Diels-Alder reaction of (S)S-4 and its transformation to D-showdomycin(2)⁶⁾ and D-3,4-O-isopropylideneallose(3).⁷⁾

The major cycloadduct (5) (mp 94-96°C, [α]_D -23.8°) derived from (S)S-(4), having the desired absolute configuration for the synthesis of naturally occurring C-nucleosides, was oxidized with OsO₄ (OsO₄ and Me₃NO) then acetonized (2,2-dimethoxypropane and p-toluenesulfonic acid) to give sulfoxide (6) (mp 145°C, [α]_D -84.8°) and sulfone (7) (mp 132-133°C, [α]_D +10.4°) in 33% and 56% yields, respectively.⁸⁾ The sulfoxide (6) was converted to the corresponding sulfone (7) by

m-chloroperbenzoic acid (mCPBA) oxidation, in a quantitative yield. The menthyl ester was converted to methyl ester in sulfone (7) as follows.⁹⁾ The reduction of (7) with diisobutylaluminum hydride (DIBAH) gave the primary alcohol (8) (mp 174-175°C, $[\alpha]_D -30.7^\circ$) in 73% yield, which was then oxidized with pyridinium dichromate (PDC) and the resultant carboxylic acid was treated with diazomethane to afford the methyl ester (9) (mp 107-110°C, $[\alpha]_D -46.8^\circ$) in 83% yield. Treatment of (9) with DBU produced (+)-(1) (mp 133°C, $[\alpha]_D +54.6^\circ$) in 80% yield. The enantiomeric excess of (+)-(1) proved to be no less than 98% as checked by the 270 MHz NMR spectrum using chiral shift reagent.¹⁰⁾

- a) Me_3NO , cat. OsO_4 , acetone, rt, 12 h.
 b) dimethoxypropane, TsOH , 70°C, 6 h.
 c) DIBAH, THF, rt, 7 h.
 d) PDC, DMF, rt, 10 h; CH_2N_2 , Et_2O .
 e) DBU, CH_3CN , rt, 4 h.
 f) O_3 ; $\text{LiAlH}(\text{O}t\text{Bu})_3$; $t\text{-BuMe}_2\text{SiCl}$; DMSO-DCC;
 $\text{Ph}_3\text{P}=\text{CHCONH}_2$; CF_3COOH . g) O_3 ; NaBH_4 ; NaIO_4 .

The methyl ester (+)-(1) was successfully transformed in 9% overall yield to the optically pure D-showdomycin(2), mp 152-154°C, $[\alpha]_D +49.9^\circ$ ($c=0.51$, H_2O), lit.⁶⁾ mp 153-154°C, $[\alpha]_D +49.9^\circ$ ($c=1$, H_2O), according to the procedure reported by Just et al.¹¹⁾ in their synthesis of racemic showdomycin.

The intermediate (+)-(1) was also converted by three steps (O_3 , NaBH_4 , NaIO_4)¹²⁾ to D-(3), mp 165°C, $[\alpha]_D +6.3^\circ$ ($c=0.29$), in about 40% overall yield. The racemate (3)

had been used previously by Just *et al.*¹²⁾ as a key intermediate for the synthesis of C-nucleoside analogues.

The method developed in this work provides a new entry for the total synthesis of optically active C-nucleosides. We are currently studying the chiral synthesis of both enantiomers of natural and modified C-nucleosides using the present method starting from the chiral dienophiles, (S)₅- and (R)₅-4.

Acknowledgement We are grateful to Dr. T. Komeno and Dr. M. Yoshioka of Shionogi Research Laboratory for a generous gift of showdomycin, and to Prof. G. Just of McGill University for the IR spectrum of (±)-3 for the identification. This work was supported by a grant from the Japan Research Foundation for Optically Active Compounds.

References and Notes

- 1) R. J. Suhadolnik, "Nucleoside Antibiotics"; Wiley-Interscience: New York, 1970, 354. G. D. Danes, Jr., C. C. Cheng, *Progr. Med. Chem.*, **13**, 303(1976).
- 2) A. O. Stewart and R. M. Williams, *J. Am. Chem. Soc.*, **107**, 4289(1985), and references cited therein.
- 3) T. Sato, Y. Hayakawa, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **57**, 2515(1984), and references cited therein.
- 4) M. Ohno, Y. Itoh, M. Arita, T. Shibata, K. Adachi, and H. Sawai, *Tetrahedron*, **40**, 145(1984).
- 5) H. Takayama, A. Iyobe, and T. Koizumi, *J. Chem. Soc. Chem. Commun.*, **1986**, 771.
- 6) a) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *J. Antibiot.* **17A**, 148(1964); b) Y. Nakagawa, H. Kano, H. Tsukuda, and H. Koyama, *Tetrahedron Lett.*, **1967**, 4105.
- 7) a) G. Just and M. Ramjeesingh, *Tetrahedron Lett.*, **1975**, 985; b) G. Just, M. Ramjeesingh, and T. J. Liak, *Can. J. Chem.*, **54**, 2940(1976).
- 8) All new compounds reported here gave satisfactory spectroscopic and analytical data. Optical rotations were taken in CHCl₃ (c 0.95-1.01) unless otherwise noted. Some of the spectral data are listed below.
(6). IR(KBr) cm⁻¹: 1740. NMR(CDCl₃) δ: 2.19(3H, s), 2.33(3H, s), 3.35(1H, dd, J=11.8, 5.6, C₂-H), 3.75(1H, dd, J=11.8, 5.6, C₃-H), 4.25(1H, d, J=5.6, C₄-H), 4.59(2H, d, J=5.6, C₁-&C₅), 5.20(1H, d, J=5.6, C₆-H).
(7). IR(KBr) cm⁻¹: 1740, 1325. NMR(CDCl₃) δ: 3.30(1H, dd, J=11.6, 5.6, C₂-H), 4.62(1H, dd, J=5.6, 1.0, C₄-H), 4.83(1H, dd, J=5.6, 1.0, C₁-H), 5.00(1H, d, J=5.6, C₆-H), 5.01(1H, dd, J=11.6, 5.6, C₃-H), 5.30(1H, d, J=5.6, C₅-H).
(8). IR(KBr) cm⁻¹: 3420, 3370. NMR(CDCl₃) δ: 2.90(1H, m, C₂-H), 3.88(1H, m, C₂-CHOH), 4.08(1H, dd, J=11.1, 5.6, C₃-H), 4.33(1H, m, C₂-CHOH), 4.58(1H, dd, J=5.4, 1.0, C₁-H), 4.62(1H, broad-d, J=5.6, C₄-H), 4.64(1H, d, J=5.4, C₆-H), 5.31(1H, d, J=5.4, C₅-H).
(9). IR(KBr) cm⁻¹: 1735. NMR(CDCl₃) δ: 3.18(1H, d, J=5.5, C₂-H), 3.63(3H, s, C₂-COOMe), 4.36(1H, t, J=5.5, C₃-H), 4.53(1H, d, J=5.4, C₅ or C₆-H), 4.74(1H, s, C₁-H), 4.88(1H, broad-d, J=5.4, C₄-H), 5.25(1H, J, J=5.4, C₅ or C₆-H).
(1). IR(KBr) cm⁻¹: 1710, 1605. NMR(CDCl₃) δ: 1.34(3H, s), 1.52(3H, s), 3.78(3H, s), 4.41(1H, d, J=5.2, C₅-H), 4.47(1H, d, J=5.2, C₆-H), 4.93(1H, broad-s, C₄-H), 5.03(1H, d, J=1.2, C₁-H), 7.07(1H, d, J=2, C₃-H).
9) The menthyl derivative of (1) was prepared by the DBU treatment of the sulfone (7). The O₃ oxidation of this compound followed by the metal hydride reduction [LiAlH(OtBu)₃] did not yield the corresponding diol-ester. Furthermore, the conversion of the menthyl ester into the simple alkyl ester in cycloadduct (5), the sulfone (7), or the menthyl ester derivative of (1) did not give satisfactory results, under conditions in which the 7-oxabicyclo[2.2.1]heptane system was untouched. Therefore, the menthyl ester derivatives could not be used to prepare D-showdomycin.
10) In the nmr spectrum, (±)-(1) was resolved to a pair of doublets due to the olefinic proton at 7.46 and 7.40 ppm using a chiral shift reagent Eu(hfc)₃. The spectrum of (+)-(1) showed the olefinic proton at 7.46 ppm and the corresponding enantiomer was not observed within the limit of detection (<1 %).
11) G. Just, T. J. Liak, M. Lim, P. Potvin, and Y. S. Tsantrizos, *Can. J. Chem.*, **58**, 2024(1980).
12) G. Just, A. Martel, K. Grozinger, and M. Ramjeesingh, *Can. J. Chem.*, **53**, 131(1975).

(Received October 29, 1986)