CONCISE SYNTHESIS OF (±)-BREVIOXIME

Yutaka Nishimura and Takeshi Kitahara*†

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences,
The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

Abstract —Brevioxime (**1**) is a juvenile hormone (JH) biosynthesis inhibitor isolated from *Penicillium brevicompactum*. The synthesis of racemic brevioxime (**1**) was accomplished in a straightforward manner *via* the β-ketoamido aldehyde.

INTRODUCTION

Since the isolation of precocene as an anti-juvenile hormone (JH) activity substance with anti-allatotropic activity by Bowers and coworkers in 1976,[1] much attention has been focused on the discovery of new inhibitors of JHs over the past 20 years, culminating in the identification of a variety of substances, including compactin.[2] Among them, compounds inhibiting the final steps of JH biosynthesis are very attractive because the involved enzymes are specific for insects and, therefore, they might have potential as selective insecticides. Brevioxime (**1**) was isolated from *Penicillium brevicompactum* as an anti-JH agent by Primo-Yúfera and coworkers in 1997.[3] Its action as anti-JH is thought to inhibit the final steps in JH biosynthesis. The attractive nature of brevioxime (**1**) prompted us to synthesize and investigate the precise biological activities of **1** and related analogs. Herein we describe the first and facile synthesis of racemic brevioxime.

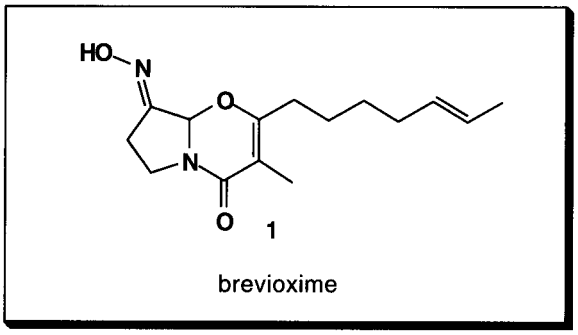


Figure 1.

† Dedicated to Professor Teruaki Mukaiyama for his 73th Birthday.

RESULTS AND DISCUSSION

Our synthetic strategy, which was based on its plausible biosynthetic route, is outlined in Figure **2**. The heterocyclic skeleton (**2**) of brevioxime (**1**) would be constructed by intramolecular oxazinone formation from **3** in a single operation.

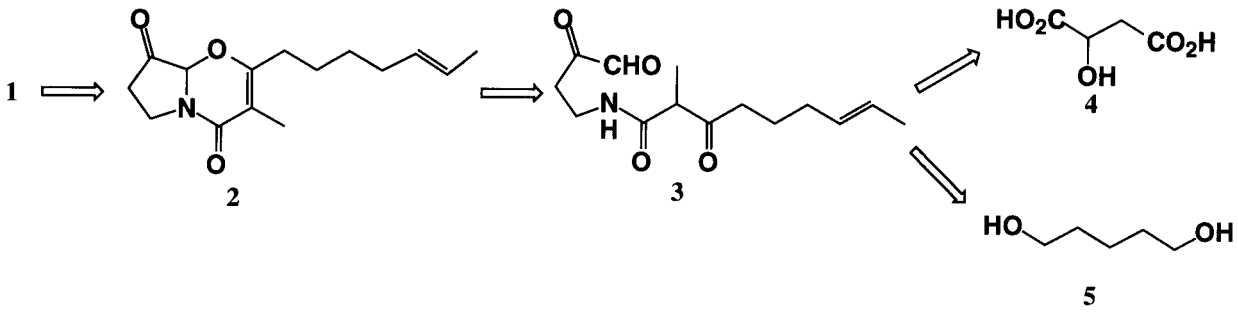
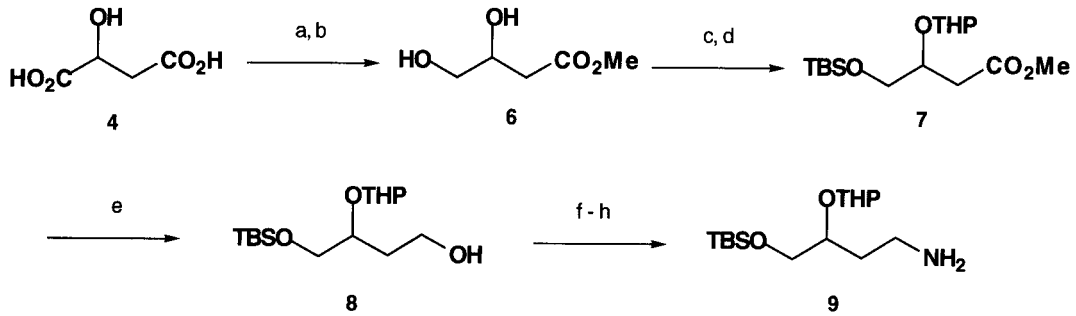


Figure 2.

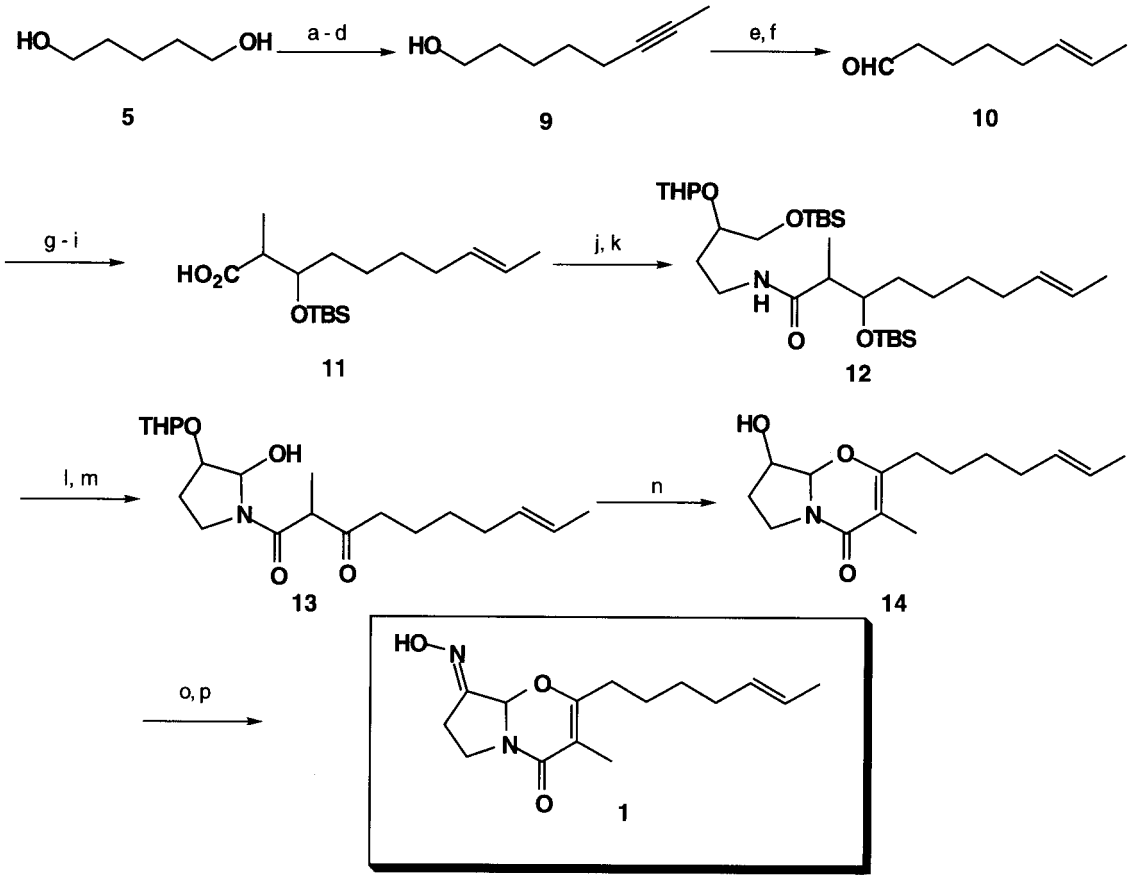
The synthesis of the amine moiety of the key intermediate (**3**) was achieved as depicted in Scheme **1**. The primary hydroxyl group of the diol ester (**6**), which was prepared from (±)-malic acid by Moriwake's method,[4] was selectively protected as *tert*-butyldimethylsilyl (TBDMS) ether and the secondary hydroxyl group was protected by the tetrahydropyranyl (THP) group to give differentially protected ester (**7**). DIBAL reduction of **7** afforded alcohol (**8**), which was then transformed to the desired amine (**4**) *via* mesylation, azidation and subsequent hydrogenation.



Scheme 1. a) AcCl, MeOH, rt, 90%. b) BH_3·SMe_2, $NaBH_4$, THF, MeOH. c) TBSCl, imidazole, DMF, rt, 67% in 2 steps. d) DHP, TsOH, CH_2Cl_2, rt, 90%. e) DIBAL, CH_2Cl_2, –78 °C, 87%. f) MsCl, pyridine, CH_2Cl_2, 4 °C. g) NaN_3, DMF, 90 °C. h) H_2, 10% Pd-C, MeOH, rt, 86% in 3 steps.

The other half of **3**, the carboxylic acid (**11**), was prepared starting from 1,5-pentanediol (**5**). The diol (**5**) was converted to the known aldehyde (**10**)[5] as shown in Scheme **2**. The aldehyde (**10**) was then reacted with ethyl α-bromopropionate under Reformatsky conditions to give the corresponding hydroxy ester, whose hydroxyl group was protected as TBDMS ether and subsequent hydrolysis afforded the carboxylic acid (**11**). Reaction of the acid (**11**) with oxalyl chloride and treatment of the resulting acid chloride with the amine (**9**) led to the amide (**12**). Initially, we tried simultaneous oxidation of triol to give diketo aldehyde (**3**) directly, but the result was not satisfactory. So we deprotected the TBDMS group selectively to give a diol, which on Swern oxidation, afforded hemiacetal (**13**) and a trace amount of aldehyde as an equilibrium mixture. The mixture was treated with *p*-toluenesulfonic acid to promote cyclization with concomitant deprotection of the THP group affording a diastereomeric mixture of

oxazinones (**14**) with a bicyclic skeleton in *ca* 1:1 ratio. Finally, the hydoxyl group was oxidized with Dess-Martin reagent and the resultant ketone was treated with hydroxylamine under mild conditions[6] to give the oxime (**1**). Although this reaction gave both geometrical isomers in a ratio of *ca.* 1:1, recrystallization of the mixture caused epimerization *via* equilibration to crystallize only natural (±)-brevioxime (**1**) (mp 142 °C) out from the solution as a single product. The spectral data (^{1}H and ^{13}C-NMR, IR, HR-MS)[7] were identical with those of the natural sample.



Scheme 2. a) NaH, TBSCl, THF, 85%. b) TsCl, pyridine, CH_2Cl_2, 4 °C. c) NaI, $NaHCO_3$, acetone, refrux, 81%. d) propyne, *n*-BuLi, HMPA, THF; conc. HCl, 81%. e) Li, $EtNH_2$, –78 °C, 96%. f) Swern ox., 78%. g) ethyl α-bromopropionate, Zn, benzene, 91%. h) TBSCl, imidazole, DMF, rt, 84%. i) LiOH, H_2O, THF, MeOH, rt, 92%. j) $(COCl)_2$, benzene, rt. k) **9**, Et_3N, CH_2Cl_2, 0 °C, 87% in 2 steps. l) TBAF, THF, rt, quant. m) Swern ox. n) TsOH,CH_2Cl_2; MeOH, 0 °C, 56% in 2 steps. o) Dess-Martin ox., 66%. p) $HONH_2$·HCl, NaOAc, MeOH, rt, 62%.

In conclusion, we have accomplished the first synthesis of (±)-brevioxime, in 5.9% overall yield from 1,5-pentanediol (**5**) in 16 steps, and 14% overall yield from the known aldehyde (**10**) in 10 steps. As we noticed that diastereomers of oxazinones (**14**) were easily separable, it implies that both enantiomers of brevioxime (**1**) must be synthesized starting from natural (–)-malic acid. Synthesis of brevioxime to determine the absolute configuration of the natural enantiomer is now in progress. We are also extremely interested to know the biological activity of both enantiomers of **1** and the geometrical isomers of the oxime portion. Those results will be published in due course.

REFERENCES AND NOTES

1. W. S. Bowers, T. Ohta, J. S. Cleere, and P. A. Masella, *Science,* **1976**, *193*, 542.

2. (a) review; G. B. Staal, *Ann. Rev. Entmol.,* **1986**, *31*, 391. (b) A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp, and R. H. Thompson, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 1165. (c) D. J. Monger, W. A. Lim, F. J. Kezdy, J. H. Law *Biochem. Biophys. Res. Commun.* **1982**, *105*, 1374-1380. (d) J. P. Edwards and N. R. Price, *Insect Biochem.*, **1983**, *13*, 185. (e) D. L. J. Clive, P. L. Wickens, and G. V. J. da Silva, *J. Org. Chem.*, **1995**, *60*, 5532. (f) G. Solladié, C. Bauder, and L. Rossi, *J. Org. Chem.,* **1995**, *60*, 7774.

3. (a) P. Moya, M. Castillo, E. Primo-Yúfera, F. Couillaud, R. Martínez-Máñez, M. Garcerá, M. A. Miranda, J. Primo, and R. Martínez-Pard, *J. Org. Chem.*, **1997**, *62,* 8544. (b) M. Castillo, P. Moya, F. Couillaud, M. D. Garcerá, and R. Martinez-Pardo , *Arch. Insect. Biochem. Physiol.*, **1998**, *37*, 287. (c) P. Moya, Á. Cantín, M-A. Castillo, J. Primo, M. A. Miranda, and E. Primo-Yúfera, *J. Org. Chem.*, **1998**, *63*, 8530. (d) Á. Cantín, P. Moya, M-A. Castillo, J. Primo, M. A. Miranda, and E. Primo-Yúfera, *Euro. J. Org. Chem.*, **1999**, 221.

4. S. Saito, T. Hasegawa, M. inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, *Chem. Lett.,* **1984**, 1389.

5. S. E. Denmark, M. S. Dappen, and C. J. Cramer, *J. Am. Chem. Soc.*, **1986**, *108*, 1306.

6. E. J. Corey, L. S. Melvin, Jr, and M. F. Haslanger, *Tetrahedron Lett.*, **1975**, *36*, 3117.

7. Spectral data for synthetic brevioxime - ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.4 (m, 4H), 1.6 (m, 3H), 1.83 (s, 3H), 2.0 (m, 2H), 2.3 (m, 2H), 2.9 (m, 2H), 3.5 (m, 1H), 4.5 (m, 1H), 5.4 (m, 2H), 5.56 (s, 1H), 8.0 (m, H). - ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 10.0, 17.8, 23.6, 26.2, 29.1, 30.5, 32.1, 41.5, 84.0, 106.9, 125.1, 130.8, 158.0, 163.2, 163.6. - IR (KBr): υ 1640 cm^{-1}(C=O), 1450 cm^{-1}. - HRMS m/z [MH^+] 279.1662 (calcd for $C_{15}H_{23}N_2O_3$ 279.1708).

Received, 1st May, 1999