ASYMMETRIC SYNTHESES OF UROTHION MODEL COMPOUNDS, 2-[(1*R*)-1,2-DIHYDROXYETHYL]THIENO[2,3-b]QUINOXALINE AND 2-[(1*S*)-1,2-DIHYDROXYETHYL]THIENO[2,3-b]QUINOXALINE

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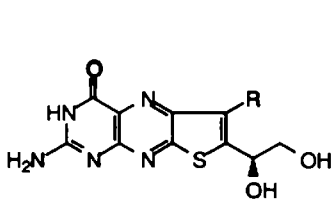
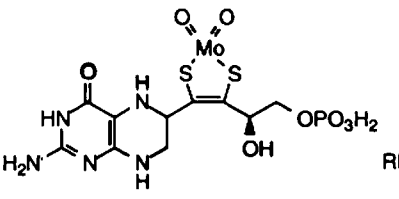
Abstract : The asymmetric syntheses of 2-[(1*R*)-1,2-dihydroxyethyl]thieno[2,3-b]quinoxaline (**5a**) and 2-[(1*S*)-1,2-dihydroxyethyl]thieno[2,3-b]quinoxaline (**5b**) were carried out as the model compounds of dephospho form-B (**5**) which is one of the degradation products of molybdopterin (**2**). The CD-spectral analysis of **5a** and **5b** supported that the chiral center of **1** has *R*-configuration, which is identical with that of **2**.

Urothion (**1**) is a yellowish pteridine pigment isolated from human urine (1, 2) and optically active by a single chiral center (3). Though its planar structure was established by syntheses (4, 5), the absolute configuration of the secondary hydroxyl group on the side chain remained elusive. Meanwhile, Johnson and Rajagopalan suggested to molybdopterin the structure **2** (6, 7, 8), with the *R*-configuration for the secondary hydroxyl group (9). Furthermore, on the basis of the metabolic study of the molybdenum cofactor, they proposed that **1** might be a urinary metabolite of **2** (10). We reported that the desulfurization of **1** with Raney-Ni afforded 2-amino-6-(3,4-dihydroxybutyl)pteridin-4(3H)-one (**3S**) (2), of which absolute configuration of the chiral center on the side chain also remained elusive. Recently, we determined the absolute configuration of the chiral center of **3S** to be *S*-configuration by application of the CD dibenzoate chirality rule to the tri-4-chlorobnenzoyl derivative **4S** prepared from **3S** (11). Moreover, we succeeded in



1: R=SCH_3
5: R=H



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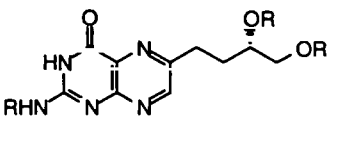
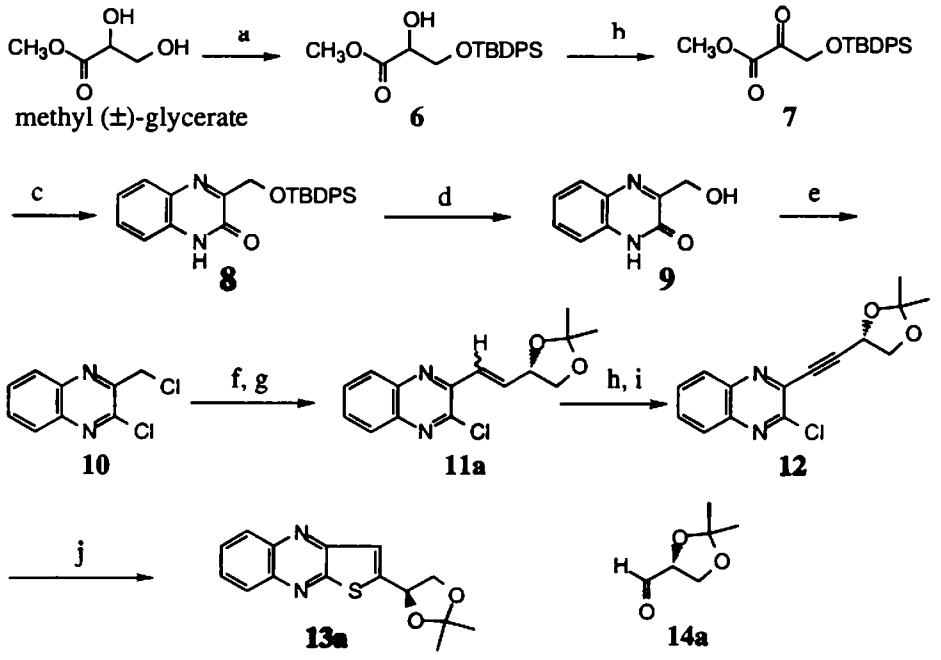


3S: R = H
4S: R = Cl-C6H4-CO

the asymmetric syntheses of 2-amino-6-[(3*S*)-3,4-dihydroxybutyl]-pteridin-4(3H)-one (**3S**) and 2-amino-6-[(3*R*)-3,4-dihydroxybutyl]pteridin-4(3H)-one (**3R**) (11). By comparison with the CD spectra of tri-4-chlorobenzoyl derivatives **4S** and **4R**, prepared from the natural **3S** and the asymmetrically synthesized **3S** and **3R**, respectively, we concluded that the chiral centers in **3S** and **1** have *S*- and *R*-configuration,

respectively (11), the later of which was identical with that of **2** (6, 7, 8). This conclusion supports strongly that **1** might be a urinary metabolite of **2**.

However, decisive evidence for the biochemical significance of **1** will be given by the tracer studies on metabolite of **2** and bioassay of **1** with enough quantity of the sample supplied by the asymmetric synthesis. For examination on the synthesis of **1**, we attempted the asymmetric syntheses of 2-[(1*R*)-1,2-dihydroxyethyl]thieno[2,3-b]quinoxaline (**5a**) and 2-[(1*S*)-1,2-dihydroxyethyl]thieno[2,3-b]quinoxaline (**5b**) which are the model compounds of dephospho form-B (**5**) (6, 7, 8), one of the degradation products of **2**. Since the conversion from **5** to **1** has been established in our previous synthesis of (±)-**1** (4), the syntheses of **5a** and **5b** would afford important information for the asymmetric syntheses of **1** and **5**.

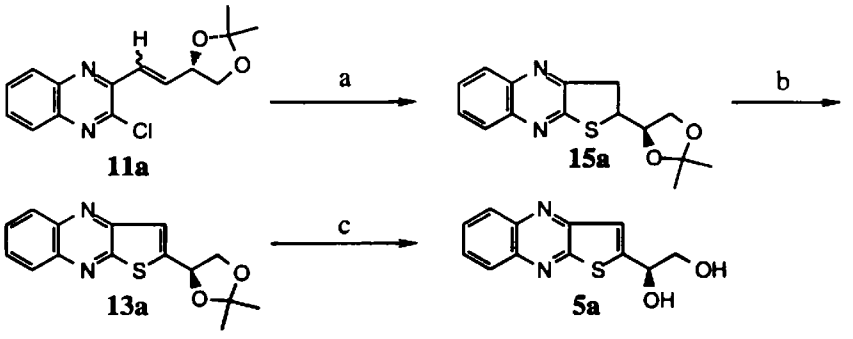


Scheme 1: a. 2.5 eq. imidazole, 1.2 eq. *tert*-butyldiphenylsilylchloride (TBDPSCl)/DMF, rt, 1.5 h, 78%; b. excess RuO_4 /$CHCl_3$, rt, 1h, 95%; c. 1.2 eq. *o*-phenylenediamine/MeOH, Ar, refl. 0.5h, 77%; d. 1.5 eq. Bu_4NF/THF, Ar, 1h, 94%; e. 6 eq. $(i\text{-}Pr)_2EtN$, 3 eq. $POCl_3$/1,1,2,2-tetrachloroethane, Ar, refl. 1.5h, 94%; f. 6 eq. Ph_3P/CH_3CN, Ar, refl. 3h; g. 1.3 eq. **14a**, 1.2 eq. Et_3N/THF, rt, 1.5h, 95%, trans/cis (2:1); h. 10 eq. Br_2/ CH_2Cl_2, Ar, 0°C, 2h; 10 eq. 2-methyl-2-butene/CH_2Cl_2, Ar, rt, 0.5h; i. 20 eq. *tert*-BuOK/THF, Ar, rt, 2h, 26% from **11a**; j. 3 eq. NaSH/EtOH, Ar, 0°C, 1h, 77%.

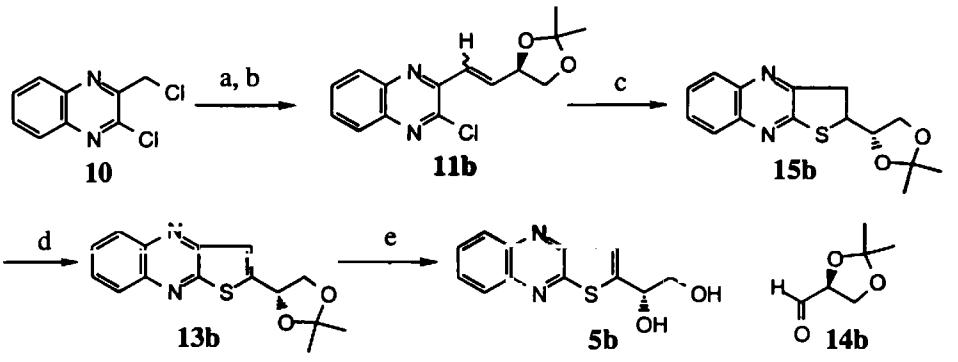
The thienoquinoxaline **13a** was at first synthesized *via* the alkynylquinoxaline **12**, utilizing a Wittig reaction of the dichloride **10** with a chiral synthon of D-glyceraldehyde acetonide **14a** which was prepared from D-mannitol according to Bear's method (11), as shown in Scheme 1 . However, the yield of **12** could not rise above 26% though the reaction conditions were examined. Therefore, we attempted the alternative cyclization reaction followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 2). The yield of **13a** from **11a** was improved twice as much by this method.

The thienoquinoxaline **5b** was synthesized by this method, utilizing a Wittig reaction of a chiral synthon, L-

glyceraldehyde acetonide **14b**, which was prepared from L-ascorbic acid according to Jung's method (13) (Scheme 3).

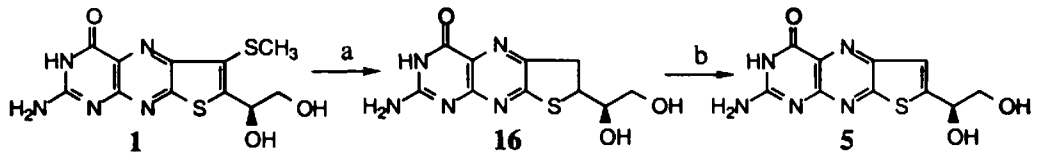


Scheme 2: a. 2 eq. NaSH/EtOH, Ar, refl. 0.5h, 82%; b. 2 eq. DDQ/THF, Ar, refl. 0.5h, 71%; c. 0.1 eq. camphorsulfonic acid (CSA)/MeOH, Ar, rt, 24h, 90% (14).



Scheme 3: a. 6 eq. Ph_3P/CH_3CN, Ar, refl. 3h; b. 1.3 eq. **14b**, 1.2 eq. Et_3N/THF, rt, 1.5h, 95%, trans/cis (2:1); c. 2 eq. NaSH /EtOH, Ar, refl. 0.5h, 71%; d. 2 eq. DDQ/THF, Ar, refl. 0.5h, 72%; e. 0.1 eq. CSA/MeOH, Ar, rt, 24h, 90%, (15)

In order to confirm the absolute configuration of **1**, the dihydrothienopteridine **16** which was prepared by desulfurization with Raney-Ni from **1** (2), was converted to the thienopteridine **5** by oxidation with selenium dioxide (6) (Scheme 4).



Scheme 4: a. H_2/Raney-Ni/aq. 0.1M NaOH, rt, 14h, 45%; b. 5 eq. SeO_2/AcOH, rt, 2h, 95% (16).

As shown in Fig. 1 and 2 the CD spectra of **5a** and **5** revealed that both have negative Cotton effects. This suggested, that **5**, as well as **1**, has *R*-configuration at the chiral center, which is agreement with the conclusion derived from the CD spectral analysis of the tri-4-chlorobenzoyl derivatives **4S** and **4R** as described above.

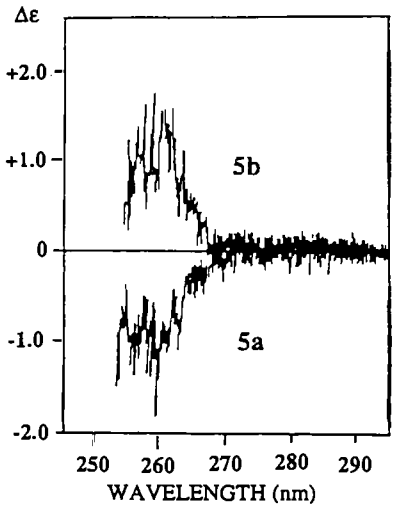


Figure 1. The CD spectra of **5a** and **5b** in EtOH.

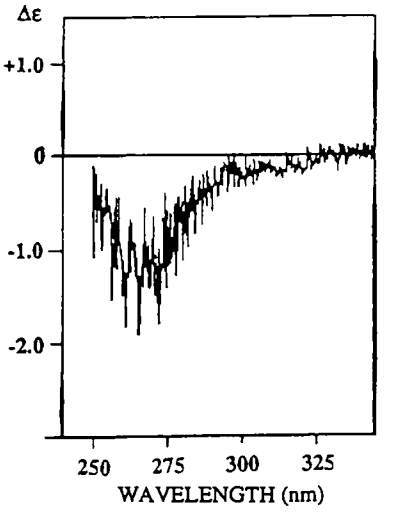


Figure 2. The CD spectrum of **5** in EtOH.

In summary, we successfully achieved the asymmetric synthesis of urothion model compounds **5a** and **5b**. *R*-Configuration of the chiral center at the 1-position of the side chain in urothion has been confirmed.

References and Notes

(1) M. Goto, A. Sakurai, and H. Yamakami, *Tetrahedron Lett.* 4507 (1967)
(2) M. Goto, A. Sakurai, K. Ohta, and H. Yamakami, *J. Biochem.* **65**, 611 (1969)
(3) A. Sakurai, H. Horibe, and Y. Okumura, *Rep. Fac. Sci. Shizuoka Univ.* **26**, 57 (1992)
(4) A. Sakurai and M. Goto, *J. Biochem.* **65**, 755 (1969).
(5) E. C. Taylor and L. A. Reiter, *J. Am Chem. Soc.* **111**, 285 (1989)
(6) J. L. Johnson, E. E. Hainline, and K. V. Rajagopalan, *J. Biol. Chem.* **255**, 1783 (1980)
(7) C. S. P. Wahl and K. V. Rajagopalan, *J. Am. Chem. Soc.* **103**, 7721 (1981)
(8) J. L. Johnson and K. V. Rajagopalan, *Proc. Natl. Acad. Sci.* USA **79**, 6856 (1982)
(9) E. C. Taylor, P. S. Darwich, J. L. Johnson, and K. V. Rajagopalan, *J. Am. Chem. Soc.* **111**, 7664 (1989)
(10) J. L. Johnson, B. E. Hainline, K. V. Rajagopalan, and B. E. Arison, *J. Biol. Chem.*, **259**, 5414 (1984)
(11) A. Sakurai, H. Horibe, N. Kuboyama, Y. Hashimoto, and Y. Okumura, *Tetrahedron Lett* in press
(12) E. Bear, *Bioch. Prep.* **2**, 31 (1952)
(13) M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.* **102**, 6304 (1980)
(14) **5a**: mp 176-177°C; MS (EI, 70 eV) M^+: Found 246.0166, Calcd for $C_{12}H_{10}N_2O_2S$, 246.0169; ^{13}C NMR ($CDCl_3$, δ ppm): 67.6 (C-2'), 72.8 (C-1'), 118.9 (C-3), 129.3, 129.7, 130.6, 130.7, 141.0, 141.8, 152.2, 157.6, and 160.3 (Ar-C); UV (EtOH): λ_{max} 258 (ε 63600) and 343 nm (ε 14800); CD (EtOH): λ_{ext} near 258 nm (Δε *ca.* -1.2)
(15) **5b**: mp 175-176°C; ^{13}C NMR was same as **5a**; UV (EtOH): λ_{max} 258 (ε 63500) and 343 nm (ε 14700); CD (EtOH): λ_{ext} near 258 nm (Δε *ca.* +1.3)
(16) **5**: UV (aq. 1% NH_3): λ_{max} 241 (ε 17800), 269 (ε 21900), and 393 nm (ε 9500); CD (aq. 1% NH_3): λ_{ext} near 269 nm (Δε *ca.* -1.3)

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