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SYNTHESIS OF STEREOISOMERS OF 1,4:3,6-DIANHYDROHEXITOL NITRATE DERIVATIVE, KF-14124

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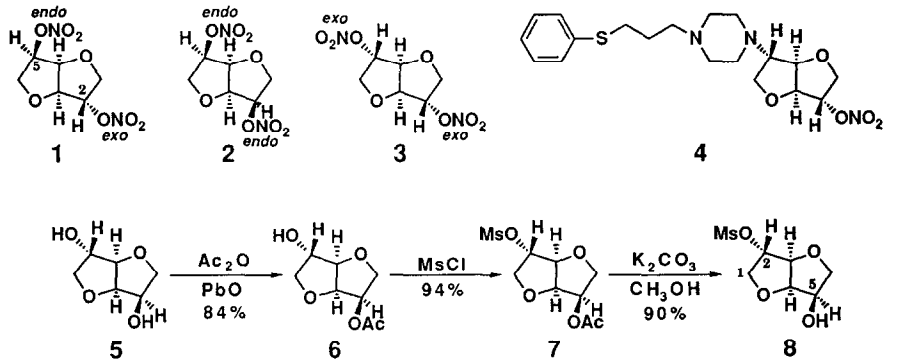
Abstract: All of the three stereoisomers of 5-deoxy-5-[4-(3-phenylthiopropyl)piperazin-1-yl]-1,4:3,6-dianhydro-L-iditol 2-nitrate (KF-14124; **4**) were synthesized from a common key intermediate (**8**).

Among modern cardiovascular therapeutic agents, organic nitrates such as nitroglycerin (GTN) and isosorbide dinitrate (**1**; ISDN) still remain the basis of therapy[1]. In the group of 1,4:3,6-dianhydrohexitol dinitrates such as ISDN (**1**) (*exo,endo*), there are two other stereoisomers, which are isomannide dinitrate [**2**; IMDN (*endo,endo*)] and isoidide dinitrate [**3**; IIDN (*exo,exo*)][2-4]. The literature indicates that IIDN is the most active among them[2-4]. Recently, we have shown that a 1,4:3,6-dianhydrohexitol nitrate derivative, KF-14124 (**4**), which has an (*exo,exo*) configuration, exhibited potent vasodilatory activity [minimum effective dose (MED) in the angina pectoris model (Table 1); MED in propranolol-induced heart failure model (LVEDP; left ventricular end diastolic pressure in dog): 0.1 mg/kg id for KF-14124 and >0.3 mg/kg for ISDN (**1**)][5]. However, it is still unclear whether an (*exo,exo*) isomer is the most potent vasodilator among the mononitrate derivatives[6]. Thus, we synthesized the other three stereoisomers of **4**.

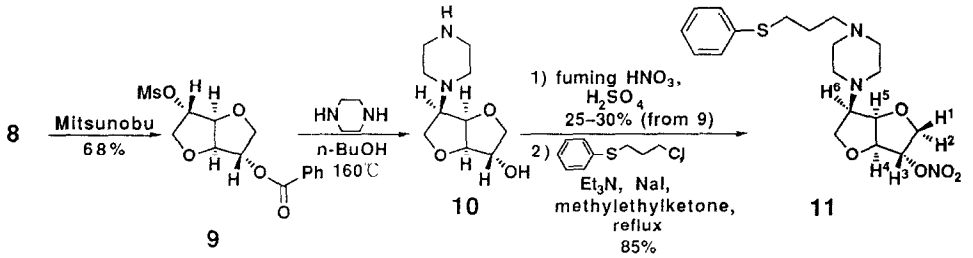


Scheme 1

First, we synthesized the monomesylate derivative **8** as a common key intermediate for the preparation of the three stereoisomers (Scheme 1)[7,8].

a) Synthesis of (*exo,endo*) isomer

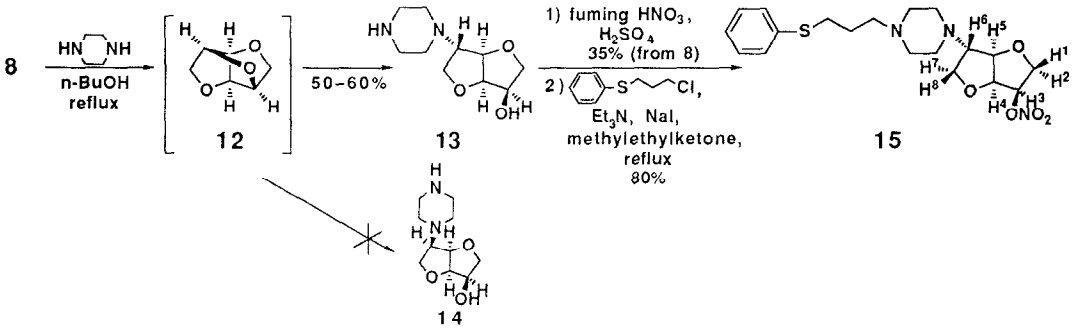
The (*exo,endo*) isomer of **4** was synthesized as shown in Scheme 2. The key intermediate **8** was subjected to the Mitsunobu reaction in order to invert the configuration of the hydroxy group at the 5-position to give the benzoate **9**. Then, **9** was reacted in a sealed tube with 10 equivalents of piperazine in n-BuOH at 160 ℃ to give the piperazine derivative **10**, which was nitrated and followed by treatment with 1-chloro-3-phenylthiopropane under a basic condition to give compound **11**, the (*exo,endo*) isomer of **4**. NMR analyses (NOE etc.) of **11** support its configuration[9].



Scheme 2

b) Synthesis of (*endo,exo*) isomer

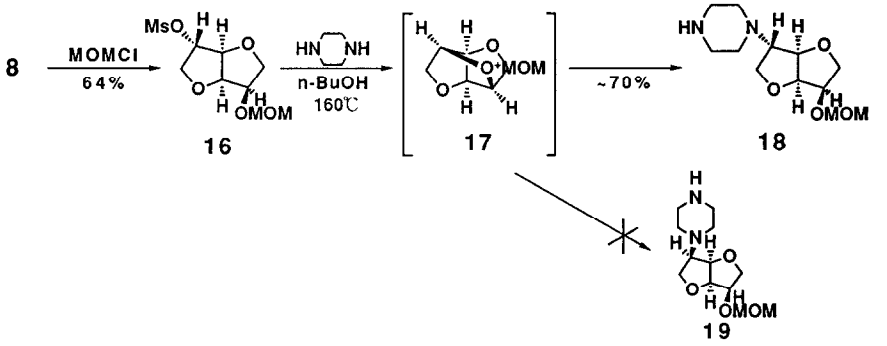
The (*endo,exo*) isomer of **4** was synthesized as shown in Scheme 3. Reaction of **8** with piperazine under reflux was originally expected to give (*endo,endo*) isomer **14**. However, (*endo,exo*) isomer **13** was obtained in a 50 to 60% yield. We assumed that an intermediate **12**[10,11] was formed by an intramolecular S_N2 reaction, which then reacted with piperazine to afford a double-inverted compound **13**. Then, **13** was nitrated and followed by treatment with 1-chloro-3-phenylthiopropane to give compound **15**, the (*endo,exo*) isomer of **4**. NMR analyses (NOE etc.) of **15** also support its configuration[12].



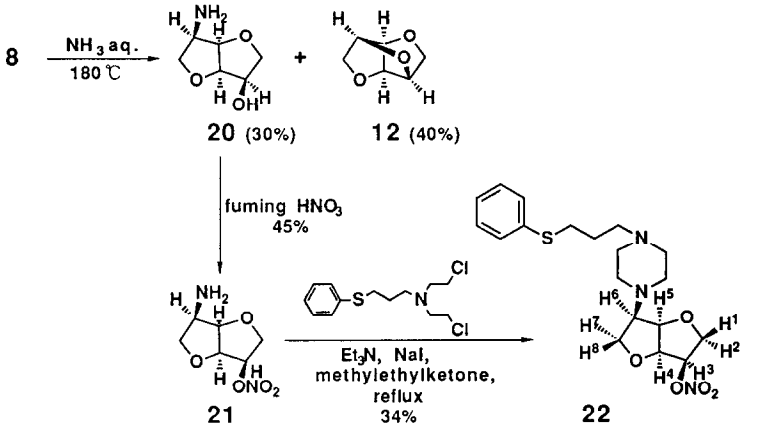
Scheme 3

c) Synthesis of (*endo,endo*) isomer

In order to avoid the formation of **12** from **8** under a basic condition, the hydroxy group of **8** was protected by a methoxymethyl (MOM) group to give **16**. Reaction of **16** in a sealed tube with 10 equivalents of piperazine in n-BuOH at 160 ℃ gave a (*endo,exo*) isomer **18** instead of the expected (*endo,endo*) isomer **19**. Presumably, an intramolecular S_N2 reaction by the O atom in the methoxymethyloxy group gave an oxonium intermediate **17**, which then suffered an attack of piperazine from an α face to afford the piperazine derivative **18** (Scheme 4).



Scheme 4



Scheme 5

In order to circumvent the formation of **18**, we prepared the (*endo,endo*) isomer **22** from the amine **20**. The amine **20** was prepared by reaction of **8** with an aqueous ammonia solution

at 180 ℃ in a sealed tube[13] (Scheme 5). During this reaction, **12**[10,11,14], which is an elucidated intermediate in the reaction of **8** with piperazine (Scheme 3), was also isolated[15]. Therefore, reactions in Scheme 3 were speculated as follows. Piperazine could not attack the carbon at the 2-position of **8** from a hindered β-face owing to its bulkiness compared with ammonia, before an intramolecular S_N2 reaction gave **12**. Then, **12** immediately suffered the attack of piperazine to give **13**, because piperazine is more nucleophilic than ammonia (Scheme 3). The amine **20** was nitrated to give **21** followed by construction of a piperazine ring by treatment with a bis(chloroethyl)amine derivative, resulting in the formation of compound **22**[16], the (*endo,endo*) isomer of **4**.

In conclusion, we have succeeded in obtaining all of the three stereoisomers of KF-14124 (**4**) from a common key intermediate **8**, using the Mitsunobu reaction, an intramolecular S_N2 reaction, and a stepwise method for the preparation of a piperazine ring, respectively. However, as can be seen from Table 1, all of these isomers exhibited less potent activity than **4** (KF-14124) which is now under preclinical studies as a new orally absorbable nitrate.

Table 1. Inhibition of T-wave Elevation in Lysine-Vasopressin-Induced Angina Pectoris Model in Rats[5,17]

Compound	MED (mg/kg, ip)	MED (mg/kg, po)
4 (KF-14124)	12.5	10
11	>25	NT[a]
15	>25	>30
22	>25	NT[a]

[a] NT: not tested.

Experimental:

Typical procedure: To a mixture of compound **8** (20.0 g, 89.3 mmol), PPh_3 (46.8 g, 178.4 mmol), benzoic acid (21.8 g, 178.5 mmol), and anhydrous THF (1.3 L) was added a solution of diethyl azodicarboxylate (27.5 mL, 178.4 mmol) in anhydrous THF (100 mL) followed by stirring at room temperature overnight. The mixture was concentrated, and the residue was purified by silica gel column chromatography with $CHCl_3$ as eluent to give compound **9** (20.0 g, 68%); $\delta_H(CDCl_3)$ 8.03(2H, d, *J* 8.0Hz), 7.60(1H, dd,*J* 7.5, 7.5Hz), 7.46(2H, dd, *J* 8.0, 7.5Hz), 5.47(1H, m), 5.18(1H, m), 4.90(1H, m), 4.84(1H, m), 4.16(1H, m), 4.08(2H, m), 4.03(1H, m), and 3.10(3H, s). A mixture of compound **9** (12.7 g, 38.7 mmol), piperazine (36.4 g, 422.8 mmol), and n-BuOH (100 mL) was heated at 160 ℃ in a sealed tube for 22 h. The mixture was concentrated, and piperazine in the residue was azeotropically evaporated with toluene several times. The residue was purified by column chromatography of DIAION SP 207 (manufactured by Mitsubishi Kasei Co) with H_2O to MeOH-H_2O (3 : 7) as eluent, and recrystallized from EtOAc to give compound **10** as a crude product; δ_H(DMSO-d_6) 5.35(1H, m), 4.50(1H, m), 4.19(1H, m), and 2 2–4 1 (14H, m). To the above crude compound **10** in H_2O (7.4 mL) was added conc. H_2SO_4 (3.9 mL) (solution A). A solution of urea (1.73 g, 28.8 mmol) in conc. H_2SO_4 (39.0 mL) was added to fuming HNO_3 (86%) (26 mL) at -15 ℃. Then,

solution A was slowly added thereto at -15 ℃ over 30 min to 1 h followed by stirring at the same temperature for further 2 h. The reaction mixture was gradually poured into H_2O (210 mL) with stirring, neutralized with 1 N NaOH at 0℃, and extracted with $CHCl_3$ 5 to 10 times. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (10 : 1 to 0 : 1) as eluent to give 5-deoxy-5-(piperazin-1-yl)-1,4:3,6-dianhydro-D-glucitol 2-nitrate (6.3 g, 27% from **9**); $\delta_H(CDCl_3)$ 5.33(1H, m), 4.50–4.75(2H, m), and 2.2–4.5(14H, m). A mixture of the compound described above (1.25 g, 4.82 mmol), 1-chloro-3-phenylthiopropane (0.91 g, 4.87 mmol), Et_3N (0.70 mL, 5.02 mmol), NaI (0.75 g, 5.00 mmol), and methylethylketone (30 mL) was refluxed for 24 h. The mixture was concentrated, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (40 : 1) as a eluent. The product was dissolved in EtOH followed by addition of EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring and the precipitated crystals were taken out by filtration and dried to afford compound **11** as the hydrochloride (2.00 g, 85%)

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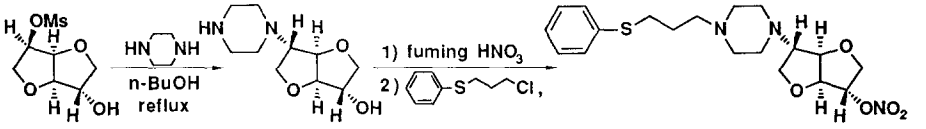
KF-14124 (**4**) was prepared as follows:



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6. Stoss, P.; Hemmer, R. *Adv. Carbohydrate Chem. Biochem.* **1991**, *49*, 93.
7. The starting material **5** is commercially available from Lancaster.
8. Stoss, P.; Merrath, P.; Schlüter, G. *Synthesis* **1987**, 174.
9. **11** (HCl salt); mp 204.5–205.5℃; $[\alpha]^{20}$ = +33.0°(c = 0.10, H_2O); δ_H(DMSO-d_6) 2.03 (2H, m), 3.06(2H, t, *J* 7.2Hz), 3.23(2H, t, *J* 7.9Hz), 3.82(1H, m), 3.2-3.9(9H, m),

4.07(1H, m), 4.22(1H, m), 4.27(1H, dd, *J* 12.0, 4.2Hz), 4.80-4.93(2H, m), 5.48 (1H, m), 7.18-7 27(1H, m), and 7 28-7.45(4H, m); NOE 14.6%(from H^1 to H^3), 9.1% (from H^2 to H^3), 30.3%(from H^6 to H'); IR(KBr) ν 1656cm^{-1}; MS(m/e) 409(M^+).

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12. **15** (HCl salt); mp 198.5–201.0℃; $[\alpha]^{20}$ = +118.0°(c = 0.10, H_2O); δ_H(DMSO-d_6) 2.00 (2H, m), 3.06(2H, t, *J* 7.2Hz), 3.23(2H, t, *J* 7.9Hz), 3.23(1H, dd, *J* 9.3, 5.0Hz), 3.68(1H, dd, *J* 9.3, 5.0Hz), 3.96(1H, dd, *J* 11.3, 5.4Hz), 4.12(1H, dd, *J* 11.3, 2.5Hz), 4.23(1H, m), 3.0-4 4(8H, m), 4.67(1H, m), 5.00(1H, dd, *J* 5.3, 5.3Hz), 5.56(1H, m), 7.17-7.27(1H, m), and 7 26-7.44(4H, m); NOE 0%(from H^3 to H^1), 5.7%(from H^3 to H^2), 12.3%(from H^3 to H^4), 0%(from H^5 to H^6), 0%(from H^6 to H^7), 18.0%(from H^6 to H^8); IR(KBr) ν 1649cm^{-1}; MS(m/e) 409(M^+).
13. Klessing, K.; Chatterjee, S. S. Eur. Patent 44 927, 1982; *Chem. Abstr.* **1982**, *96*, 218190r.
14. **12**; δ_H($CDCl_3$) 3.88(2H, d, *J* 8.9Hz), 3.98(2H, d, *J* 8.9Hz), 4.46(2H, s), 4.54(2H, s); MS(m/e) 128(M^+).
15. **12** was reacted with piperazine in n-BuOH under reflux to afford **13** in a 60–70% yield.
16. **22** (HCl salt); mp 197–199℃; $[\alpha]^{20}$ = +106.0°(c = 0.10, H_2O); δ_H(DMSO-d_6) 2.03 (2H, m), 3.06(2H, t, *J* 7.2Hz), 3.22(2H, t, *J* 7.8Hz), 3.1-4.3(13H, m), 4.67(1H, m), 4.99(1H, m), 5.55(1H, m), 7.16-7.27(1H, m), and 7.25-7.45(4H, m); NOE 0%(from H^3 to H^1), 2.6%(from H^3 to H^2), 5.9%(from H^3 to H^4), 2.5%(from H^6 to H^5), 5.3% (from H^6 to H^7), 0%(from H^6 to H^8), IR(KBr) ν 1651cm^{-1}; MS(m/e) 409(M^+).
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