A Convenient Synthesis of 1-[6-Fluoro-(2*S*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol and 1-[6-Fluoro-(2*R*)-3*H*,4*H*-dihydro- 2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol

An-Guang Yu,[a] Nai-Xing Wang,*[a] Ya-Lan Xing,[b] Jun-Ping Zhang,[a] Yun-Xu Yang,[a] Wu-Wei Wang,[a] Rui-long Sheng[a]

[a] Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100101, P. R. China
Fax +86(10)64879375; E-mail: nxwang@mail.ipc.ac.cn

[b] Beijing University of Chemical Technology, Beijing 100029, P. R. China

Received 23 February 2005

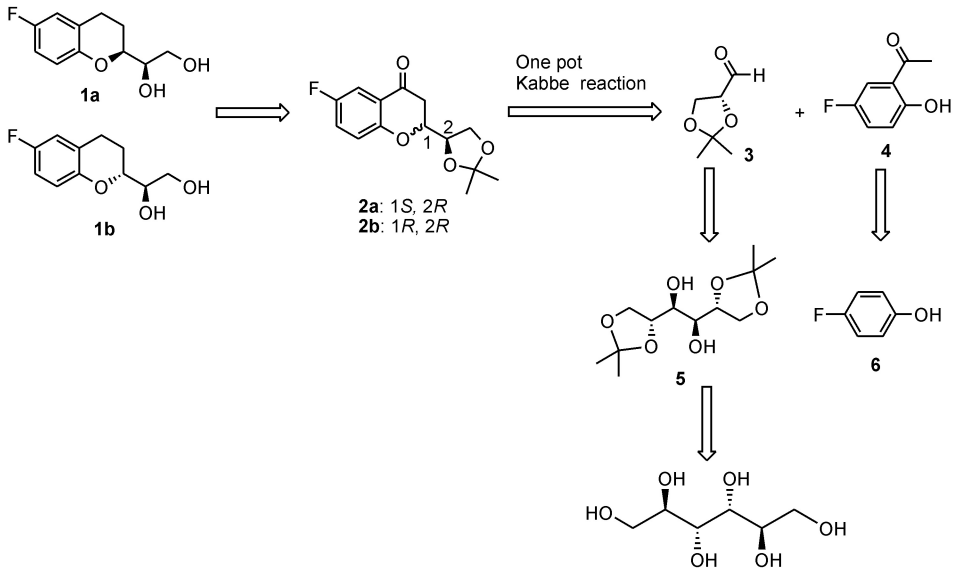
Abstract: 1-[6-Fluoro-(2*S*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol and 1-[6-fluoro-(2*R*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol, important pharmaceutical intermediates, were synthesized from natural chiral pool D-mannitol.

Key words: chiral pool, reductions, ketones, aldol reactions

Chiral chromans are a class of important compounds possessing significant biological properties. For example, vitamin E[1] and its analogs trolox[2] and MDL-73404[3] are important lipophilic antioxidants. Daurichromenic acid and rhodod-aurichromanic acid A show potent anti-HIV activity,[4] while siccanin has potent antifugal activity.[5] Our interests in synthesizing Nebivolol, a new selective β_1-adrenergic blocker with antihypertensive activity,[6] prompted us to develop a general and efficient methodology for the construction of chiral chroman intermediates **1a** (*S*,*R*) and **1b** (*R*,*R*).

Previously, Chandrasekhar et al.[7] reported the synthesis of chroman **1a** and **1b** starting from 4-fluorophenol, which involves eight and ten steps, respectively; a Sharpless asymmetric epoxidation is required for the stereoselective introduction of the two stereogenic centers. In their approach,[7] the preparation of **1** is long and tedious, discouraging practical application. Furthermore, this preparation involves multiple isolations and chromatographic purifications, rendering it unacceptable for larger kilo-scale production.

Herein, we report a convenient method for the preparation of enantiomerically pure 1-[6-fluoro-(2*S*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol (**1a**) and 1-[6-fluoro-(2*R*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol (**1b**) from readily available starting material D-mannitol in four steps. The general retrosynthetic analysis is illustrated in Scheme 1. In the synthesis of chromanone **2a** (*S*,*R*) and **2b** (*R*,*R*), the Kabbe reaction[8,9] was applied



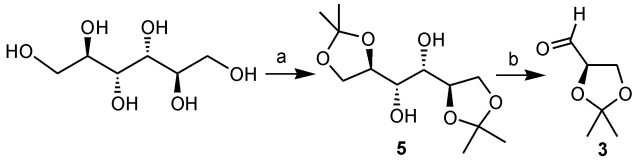
Scheme 1

SYNLETT 2005, No. 9, pp 1465–1467
Advanced online publication: 29.04.2005
DOI: 10.1055/s-2005-868508; Art ID: U05005ST

to build up the pyranone skeleton of chromanone. The first asymmetric centere of (*R*)-2,3-isopropyrideneglyceralaldehyde (**3**) was incorporated into the backbone of the chromanone **2** (only C2*R*), while the second chiral center (C1*R* or C1*S*) was generated during the ring closing. The resulting diastereomeric compounds **2a** and **2b** could be isolated easily. Then **2a** and **2b** were reduced to **1a** (*S*,*R*) and **1b** (*R*,*R*); intermediates **1a** and **1b** are the precursors to (*S*,*R*,*R*,*R*)-nebivolol which was obtained by a coupling reaction. Therefore, our new synthetic methodology reported here not only has the advantage of atom economy but also requires fewer synthetic steps.

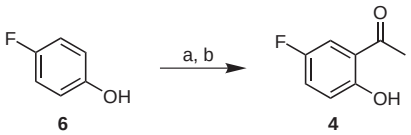
Multigram quantities of (*R*)-2,3-isopropyrideneglycerolaldehyde can be readily obtained from cheap and commercially available D-mannitol as previously reported[10] and acetylfluorophenol (**4**) was obtained from 4-fluorophenol.

D-Mannitol was converted to (*R*)-2,3-isopropyrideneglycerolaldehyde in two steps in 40% overall yield on a 100-g scale (Scheme 2).



Scheme 2 Reagents and conditions: (a) glyme, 2,2-dimethoxypropane, $SnCl_2$ (54%); (b) $NaIO_4$, CH_2Cl_2, $NaHCO_3$ (77%).

4-Fluorophenol (**6**) was converted to its acetate, which was used in the next step without work-up. Acetylfluorophenol **4** was obtained by Fries rearrangement of the acetate in 89% overall yield on an 80 g scale (Scheme 3).



Scheme 3 Reagents and conditions: (a) AcCl; (b) $AlCl_3$, heating, 130 °C (89%).

With the required building blocks in hand, the stage was set for the crucial segment couplings (Scheme 4). Kabbe reaction of the fragments **3** and **4** gave chromanone **2a** and **2b**;[11] a mixture of **3**, **4**, and pyrrolidine in toluene was allowed to stand for a while and then heated to reflux in an apparatus fitted with a water separator. The chromanone was obtained as a mixture of two diastereoisomers in 40% yield [**2a**(*S*,*R*)/**2b**(*R*,*R*), 60:40], which were isolated easily by flash column chromatography.

Initially both **2a** and **2b** were reduced by the Wolff–Kishner reduction under different conditions including at different temperatures; however changing the ratio of potassium hydroxide to hydrazine hydrate failed because the high temperature resulted in the degradation of the product; therefore the Clemmensen reduction was exploited and good results were obtained. Treatment of chromanone **2a** and **2b** with zinc amalgam in 15% hydrochloric acid gave chroman **1a** and **1b**[12] in good yield (62%).

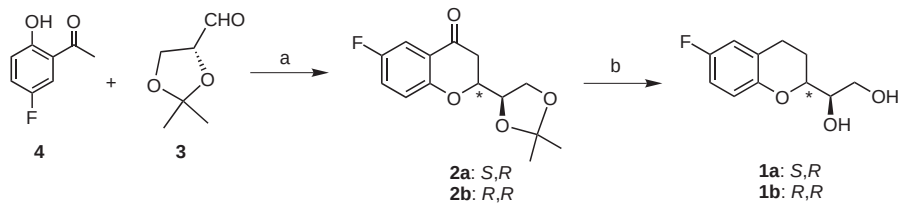
In conclusion, an efficient and convenient synthetic methodology for the synthesis of 1-[6-fluoro-(2*S*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol and 1-[6-fluoro-(2*R*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol was presented. Chromans **1a** and **1b** prepared by this method possessed excellent chemical and enantiomeric purity; this route is shorter than previously reported. The utilization of the natural chiral pool makes the synthesis quite efficient with overall atom economy.

Acknowledgment

This work was supported by the National Natural Science Foundation (No.20472090) and National 863 Program (No.2003AA323030) Foundation.

References

(1) Machlin, L. J. *Vitamin E*; Marcel Dekker: New York USA, **1980**.
(2) Terao, K.; Niki, E. *J. Free Radical Biol. Med.* **1986**, *2*, 193.
(3) Grisar, J. M.; Petty, M. A.; Bolkenius, F. N.; Dow, J.; Wagner, J. E.; Wagner, R. D.; Haegele, K.; Jong, W. D. *J. Med. Chem.* **1991**, *34*, 257.
(4) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K. H. *Tetrahedron* **2001**, *57*, 1559.
(5) Isabashi, K. *J. Antibiot. Ser. A* **1962**, *15*, 161.
(6) (a) De Cree, J.; Geukens, H.; Leempoels, J.; Verhaegen, H. *Drug Dev. Res.* **1986**, *8*, 109. (b) De Cree, J.; GeukensH, ; Cobo, C.; Verhaegen, H. *Angiology* **1987**, *38*, 440. (c) Van de Water, A.; Janssen, W.; Van Nueten, J.; Xhonneux, R.; De Cree, J.; Verhaegen, H.; Reneman, R. S.; Janssen, P. A. *J. Cardiovasc. Pharmacol.* **1988**, *11*, 552.



Scheme 4 Reagents and conditions: (a) pyrrolidine, toluene (40%); (b) Zn amalgam, 15% HCl, EtOH (62%).

(7) Chandrasekhar, S.; Venkat, R. M. *Tetrahedron* **2000**, *56*, 6339.
(8) Kabbe, H. J. *Synthesis* **1978**, 886.
(9) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247.
(10) Schmid, C. R.; Bryant, J. D.; Dowlatzadeh, M.; Philips, J. L.; Prather, D. E.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.
(11) Selected data for compound **2a**: pale yellow solid: mp 94–95 °C; $[\alpha]_D$ +30.65 (*c* = 0.0802, MeOH); IR (KBr): 2997, 2916, 2900, 1687, 1621, 1487, 1371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (dd, 1 H, *J* = 8.2 Hz, 3.1 Hz, C_6H_3F), 7.24–7.17 (m, 1 H, C_6H_3F), 6.96 (dd, 1 H, *J* = 9.0 Hz, 4.1Hz, C_6H_3F), 4.36–4.32 (m, 2 H, CH_2O), 4.23–4.18 (m, 1 H, FC_6H_3OCH), 4.06–4.02 (m, 1 H, $CHCHCH_2$), 2.93–2.75 (m, 2 H, $O{=}CCH_2$), 1.45 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3); ^{13}C NMR (100 Hz,$CDCl_3$): δ = 25.0 (CH_3), 26.2 (CH_3), 39.0 ($O{=}CCH_2$), 66.4 (CH_2O), 76.3 (CH_2CHO), 78.4 (*C*HOC), 110.3 (CH_3CCH_3), 112.1 (FC_6H_3), 119.5 (FC_6H_3), 123.7 (FC_6H_3), 156.1 (FC_6H_3), 157.1 (FC_6H_3), 158.5 (FC_6H_3), 190.8 (O=C); EIMS: *m*/*z* = 266, 101, 43; Anal. Calcd for $C_{14}H_{15}FO_4$: C, 63.15; H, 5.68; F, 7.14; O, 24.04. Found: C, 63.47; H, 5.92. Selected data for compound **2b**: pale yellow solid: mp 84–86 °C; $[\alpha]_D$ 13.53 (*c* = 0.2142, $CHCl_3$); IR (KBr): 2997, 2916, 2900, 1687, 1622, 1487, 1371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (dd, 1 H, *J* = 8.1 Hz, 3 Hz, C_6H_3F), 7.25–7.18 (m, 1 H, C_6H_3F), 7.04 (dd, 1 H, *J* = 9 Hz, 4.1 Hz, C_6H_3F), 4.51–4.46 (m, 1 H, C_6H_3OCH), 4.41–4.35 (m, 1 H, CHOC), 4.15 (dd, 1 H, *J* = 8.3 Hz, 6.3 Hz, $OCCH_2$), 4.03 (dd, 1 H, *J* = 8.3 Hz, 6.3 Hz, $OCCH_2$), 2.87 (dd, 1 H, *J* = 16.8 Hz, 12.9 Hz, $O{=}CCH_2$), 2.66 (dd, 1 H, *J* = 16.8 Hz,12.9 Hz, $O{=}CCH_2$), 1.43 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR (100 Hz,$CDCl_3$): δ = 25.2 (CH_3), 26.1 (CH_3), 38.6 ($O{=}CCH_2$), 64.9 (CH_2O), 76.4 (CH_2CHO), 77.5 (*C*HOC), 110.3 (CH_3CCH_3), 112.0 (FC_6H_3), 119.6 (FC_6H_3), 123.7 (FC_6H_3), 156.1 (FC_6H_3), 157.3 (FC_6H_3), 158.5 (FC_6H_3), 190.6 (O=C); EIMS: *m*/*z* = 266, 101, 43; Anal. Calcd for $C_{14}H_{15}FO_4$: C, 63.15; H, 5.68; F, 7.14; O, 24.04. Found: C, 63.48; H, 5.89.
(12) Selected data for compound **1a**: mp 87–89 °C; $[\alpha]_D$ +70.30 (*c* = 0.1, MeOH); IR (KBr): 3590, 3518, 2967, 2937, 2849, 1607, 1493, 1217, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96–6.84 (m, 3 H, C_6H_3F), 4.18–4.05 (m, 1 H, FC_6H_3OCH), 4.05–3.99 (m, 3 H, CHOH, CH_2OH), 3.01–2.94 (m, 2H, $FC_6H_3CH_2$), 2.32–2.27 (m, 1H, $FC_6H_3CH_2CH_2$), 2.03–2.01 (m, 1 H, $FC_6H_3CH_2CH_2$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 23.0 ($FC_6H_3CH_2CH_2$), 24.5 ($FC_6H_3CH_2CH_2$), 63.3 (CH_2OH), 73.5 (*C*HOH), 76.5 (O*C*HCH), 113.9 (C_6H_3F), 115.5 (C_6H_3F), 117.5 (C_6H_3F), 123.1 (C_6H_3F), 150.1 (C_6H_3F), 158.1 (C_6H_3F); EIMS: *m*/*z* = 212, 150; Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17; F, 8.95; O, 22.62. Found: C, 61.97; H, 6.12. Selected data for compound **1b**: mp 92–94 °C; $[\alpha]_D$ +63.08 (*c* = 0.1, MeOH); IR (KBr): 3406, 3281, 2960, 2924, 2885, 1496, 1217, 1081, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82–6.73 (m, 3 H, C_6H_3F), 4.07–4.04 (m, 1 H, FC_6H_3OCH), 3.84–3.78 (m, 3 H, CHOH, CH_2OH), 2.88–2.78 (m, 2 H, $FC_6H_3CH_2$), 2.40 (s, 2 H, OH), 2.00–1.93 (m, 2 H, $FC_6H_3CH_2CH_2$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 23.5 ($FC_6H_3CH_2CH_2$), 24.6 ($FC_6H_3CH_2CH_2$), 63.6 (CH_2OH), 73.6 (*C*HOH), 76.7 (O*C*HCH), 113.9 (C_6H_3F), 115.3 (C_6H_3F), 117.6 (C_6H_3F), 123.1 (C_6H_3F), 150.1 (C_6H_3F), 158.1 (C_6H_3F); EIMS: *m*/*z* = 212, 151, 57; Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17; F, 8.95; O, 22.62. Found: C, 62.13; H, 6.08.