Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5229–5231
Tetrahedron Letters

Synthesis of optically active 6-substituted 2-(aminomethyl)chromans

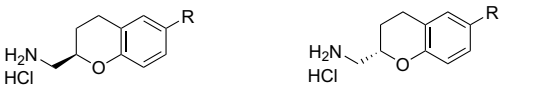
Mingbao Zhang,* Raymond Reeves, Cheng Bi, Robert Dally, Gaetan Ladouceur, William Bullock and Jefferson Chin

Department of Chemistry Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA

Received 26 March 2004; revised 29 April 2004; accepted 10 May 2004

Abstract—Three novel, optically active, 6-substituted 2-(aminomethyl)chromans were synthesized from readily available chroman 2-carboxylic acid precursors. These chroman-containing primary amines are useful building blocks for the synthesis of chroman-derived pharmaceutical agents.

Chroman-derived compounds continue to attract a great deal of attention in the pharmaceutical industry due to their potential wide-ranging pharmacological properties.[1] 2-(Aminomethyl)chroman analogues, in particular, have shown inhibition of iron-dependent lipid peroxidation, a pathophysiological process involved in many disease states.[2] Some newer generations of dopaminergic agents also contain 2-(aminomethyl) chromans.[3] In connection with a drug discovery project, we required multigram quantities of several novel optically active 2-(aminomethyl)chroman intermediates substituted at the C-6 position as building blocks for rapidly synthesizing chroman-derived analogues. In this paper, we wish to describe practical syntheses of three such novel chroman intermediates as their hydrochloride salts (Fig. 1).



(*R*) - 7: R = CH_2CO_2H
(*R*) -13: R = $CH_2CH_2CO_2$-t-Bu

(*S*) -13: R = $CH_2CH_2CO_2$-t-Bu

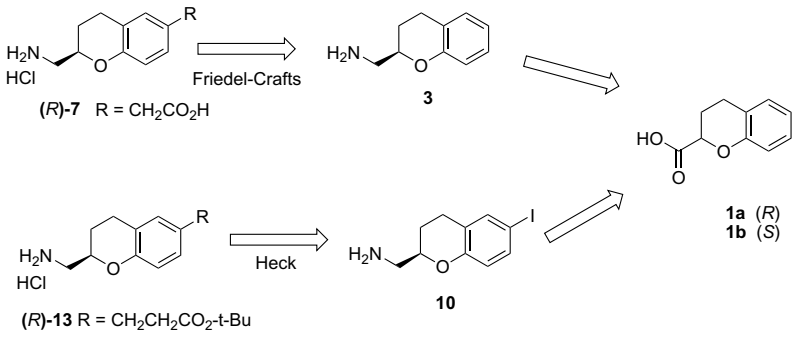
Figure 1. (*R*)- and (*S*)-2-(aminomethyl) chroman building blocks.

Retrosynthetic analysis of the targets (*R*)-**7** and (*R*)-**13** led to the identification of (*R*)-chroman-2-carboxylic acid **1a** as the key common starting material (Scheme 1). The target (*S*)-**13**, by analogy, could then be derived from (*S*)-chroman-2-carboxylic acid **1b**. The two enantiomers of **1** can be readily obtained via chemical[4] as well as enzymatic[5] resolution of the racemate for which facile syntheses have been reported.[6] For the acetic acid derivative **7**, the key step is the Friedel–Crafts alkylation of the trifluoroacetamide protected form of the chroman amine **3**. The propionic *t*-butyl ester derivative **13** involves the Heck reaction of the Cbz-protected form of chroman amine intermediate **10** as its key step.

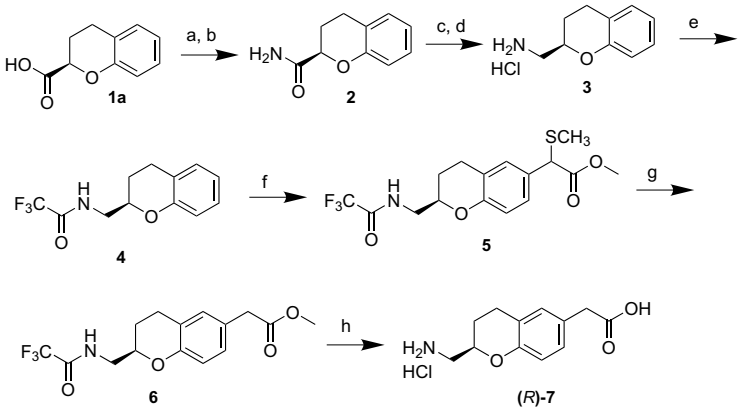
The synthesis of (*R*)-**7** is outlined in Scheme 2. The (*R*)-chroman-2-carboxylic acid **1a** was first converted to the corresponding acid chloride using oxalyl chloride followed by treatment with concentrated ammonium hydroxide in ethyl acetate to afford the chroman carboxamide intermediate **2** in near quantitative yield. A simple borane reduction,[7] after a HCl workup, converted **2** to the corresponding amine **3** as its HCl salt in 87% yield. The primary amine group was then protected as trifluoroacetamide **4** in 92% yield. Friedel–Crafts alkylation of **4** with α-chloro-2-(methylthio) acetate catalyzed by tin(IV) chloride afforded the crude intermediate **5** as a mixture of diastereomers. Removal of the thiomethyl group, upon a Raney nickel treatment, led to the penultimate precursor **6**. Heating crude **6** in 6 N HCl at reflux for 2 h removed the trifluoroacetyl group and simultaneously hydrolyzed the ethyl ester group to

Keywords: Chromans; Friedel–Crafts alkylation; Heck reaction; Building blocks.
* Corresponding author. Tel.: +1-203-812-5906; fax: +1-203-812-2452; e-mail: mingbao.zhang.b@bayer.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.037



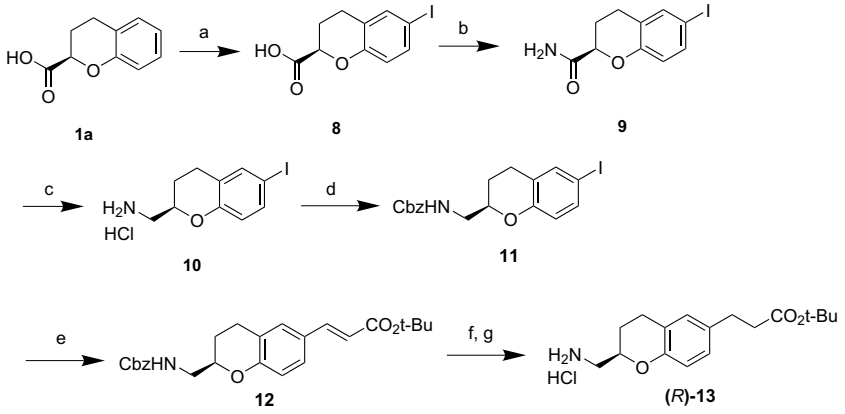
Scheme 1.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, DMF (cat.), room temperature; (b) NH_4OH (concd), EtOAc; (c) BH_3/DMS, THF, reflux; (d) MeOH, HCl/ether; (e) $(CF_3CO)_2O$/pyridine, CH_2Cl_2; (f) α-chloro-2-(methylthio)acetate, tin(IV) chloride, CH_2Cl_2; (g) Raney nickel, ethanol; (h) 6 N HCl, reflux.

afford target compound (*R*)-**7**, which precipitated out of the reaction cleanly as an HCl salt (46% yield from **4**).

The synthesis of the *tert*-butyl propionate analogue (*R*)-**13** is shown in Scheme 3. The (*R*)-chroman carboxylic acid **1a** was converted to the corresponding iodo chroman carboxylic acid **8** in 84% yield upon stirring with benzyltrimethylammonium dichloroiodate and zinc chloride in glacial acetic acid at room temperature. The amide **9**, formed via the carbonyldiimidazole route in 85% yield, was reduced to the corresponding amine intermediate (*R*)-**10** using a borane/DMS complex in 44% yield. (*R*)-**10** was then protected as the benzyl carbamate **11**, which underwent the Heck reaction smoothly to afford the vinyl intermediate **12** in near quantitative yield. Though the unprotected amine underwent Heck reaction, it gave lower yields and an impure product. Transfer hydrogenation (ammonium formate, Pearlman's catalyst, ethanol) of intermediate **12** afforded the free base amine in 88% yield, which was



Scheme 3. Reagents and conditions: (a) $C_6H_5CH_2N(CH_3)_3ICl_2$, $ZnCl_2$, HOAc; (b) CDI, DMF, NH_4OAc; (c) BH_3/DMS, THF, reflux; MeOH, HCl/ether; (d) Cbz-Cl, NaOH; (e) *tert*-butyl acrylate, $Pd(OAc)_2$ (cat.), CH_3CN; (f) NH_4CO_2H, $Pd(OH)_2$/C, ethanol; (g) 1 M HCl/diethyl ether.

readily converted to the hydrochloride salt (*R*)-**13** using 1 M HCl/diethyl ether.

The synthesis of (*S*)-**13** was achieved in similar fashion from the (*S*)-chroman carboxylic acid **1b**.

In summary, three novel 2, 6-disubstituted chiral chroman derivatives containing an amino methyl functional group at the C-2 position were synthesized from the corresponding chiral chroman-2-carboxylic acids.[8] These intermediates are useful building blocks for rapidly synthesizing novel chroman-containing compounds possessing interesting pharmacological properties.

Acknowledgements

The authors thank Donald Wolanin, Qingjie Liu and Mareli Rodriguez for helpful discussions. We are indebted to the Bayer Chemical Development group for providing the chiral chroman starting materials.

References and notes

1. (a) Witiak, D. T.; Heilman, W. P.; Sankarappa, S. K.; Cavestri, R. C.; Newman, H. A. *J. Med. Chem.* **1975**, *18*, 934; (b) Oka, M.; Matsumoto, Y.; Sugiyama, S.; Tsuruta, N.; Matsushima, M. *J. Med. Chem.* **2000**, *43*, 2479; (c) Yasunaga, T.; Naito, R.; Kontani, T.; Tsukamoto, S.; Nomura, T.; Yamaguchi, T.; Mase, T. *J. Med. Chem.* **1997**, *40*, 1252; (d) Caldirola, P.; Chowdhury, R.; Unelius, L.; Mohell, N.; Hacksell, U.; Johansson, A. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1583.
2. Jacobsen, E. J.; vanDoornik, F. J.; Ayer, D. E.; Belonga, K. L.; Braughler, J. M.; Hall, E. D.; Houser, D. J. *J. Med. Chem.* **1992**, *35*, 4464.
3. (a) Mewshaw, R. E.; Kavanagh, J.; Stack, G.; Marquis, K. L.; Shi, X.; Kagan, M. Z.; Webb, M. B.; Katz, A. H.; Park, A.; Kang, Y. H.; Abou-Gharbia, M.; Scerni, R.; Wasik, T.; Cortes-Burgos, L.; Spangler, T.; Brennan, J. A.; Piesla, M.; Mazandarani, H.; Cockett, M. I.; Ochalski, R.; Coupet, J.; Andree, T. H. *J. Med. Chem.* **1997**, *40*, 4235; (b) Gross, J. L. *Tetrahedron Lett.* **2003**, *44*, 8563.
4. Schaaf, T. K.; Johnson, M. R.; Constantine, J. W.; Bindra, J. S.; Hess, H.-J.; Elger, W. *J. Med. Chem.* **1983**, *26*, 328.
5. Urban, F. J.; Moore, B. S. *J. Heterocycl. Chem.* **1992**, *29*, 431.
6. (a) Augstein, J.; Monro, A. M.; Potter, G. W. H.; Scholfield, P. *J. Med. Chem.* **1968**, *11*, 844; (b) Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. *J. Med. Chem.* **1971**, *14*, 758; (c) For this work, we obtained both the (*R*)-chroman-2-carboxylic acid and (*S*)-isobutyl-chroman-2-carboxylate from the Bayer Chemical Development group in Wuppertal, Germany, both in >98% ee.
7. Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441.
8. (a) Compound characterization data: (*R*)-**7**: white solid; IR (KBr) 3001, 2910, 1703, 1502, 1257, 1220 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.46 (s, broad, 3H), 6.94 (m, 2H), 6.71 (d, $J = 8.1$, 1H), 4.25 (m, 1H), 3.43 (s, 2H), 3.13 (dd, $J = 13.1$, $J = 3.3$, 1H), 2.99 (dd, $J = 13.2$, $J = 8.4$, 1H), 2.72 (m, 2H), 2.04 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 172.03, 151.44, 129.78, 127.58, 126.37, 120.92, 115.71, 71.87, 42.43, 39.98, 24.35, 23.61; LCMS (+esi) m/z 222 ($M+H^+$); Anal. Calcd for $C_{12}H_{15}NO_3 \cdot HCl$: C, 55.93; H, 6.26; N, 5.43. Found: C, 56.20; H, 6.12; N, 5.17; $[\alpha]_D^{25}$ −90.0 (*c* 1.02, DMSO). (*R*)-**13**: white solid; IR (KBr): 2983, 2904, 1730, 1502, 1250, 1147 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.46 (s, broad, 3H), 6.89 (m, 2H), 6.67 (d, $J = 8.3$, 1H), 4.23 (m, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.61–2.82 (m, 4H), 2.42 (t, $J = 7.4$, 2H), 2.04 (m, 1H), 1.66 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 170.61, 150.95, 131.78, 128.63, 126.39, 120.79, 115.65, 79.32, 71.75, 42.37, 36.69, 29.81, 27.85, 24.35, 23.64; LCMS (+esi) m/z 292 (M+H); Anal. Calcd for $C_{17}H_{25}NO_3 \cdot HCl$: C, 62.28; H, 7.99; N, 4.27. Found: C, 61.97; H, 8.26; N, 4.28; $[\alpha]_D^{25}$ −71.3 (*c* 1.02, DMSO). (*S*)-**13**: white solid, its spectroscopic characteristics are identical to those of (*R*)-**13**. Anal. Calcd for $C_{17}H_{25}NO_3 \cdot HCl$: C, 62.28; H, 7.99; N, 4.27. Found: C, 62.16; H, 8.27; N, 4.25; $[\alpha]_D^{25}$ +73.4 (*c* 1.03, DMSO). (b) The optical purities of (*R*)- and (*S*)-**13** were determined to be 98% and 97% ee, respectively, using ^1H NMR in $CDCl_3$ with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate as the chiral resolving agent (in the presence of excess pyridine). The optical purity of (*R*)-**7** was similarly determined to be >96% ee using the same chiral resolving agent in CD_3OD.