Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1787–1790

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHETIC APPROACHES TO 2-(4-HYDROXY-7-CHROMANYL)BENZOIC ACIDS AS ANTAGONISTS OF LEUKOTRIENE B_4

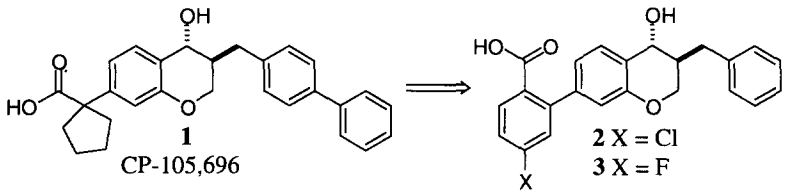
R. J. Chambers,* K. Koch, M. S. Biggers, and M. Ramchandani

Central Research Division, Pfizer Inc, Groton, CT 06340, U.S.A.

Received 26 March 1998; accepted 1 May 1998

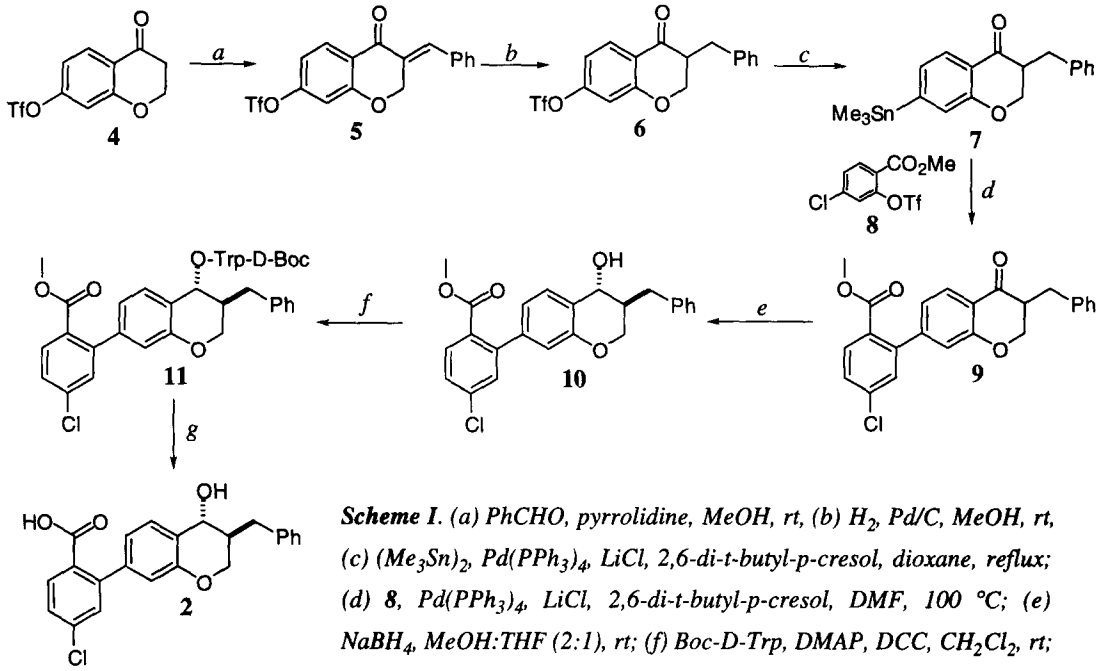
Abstract. Structural modification of **1** led to a series of 2-(4-hydroxy-7-chromanyl)benzoic acid LTB_4 antagonists exemplified by **2** and **3**. The use of an organostannane biaryl coupling, a non stereoselective reduction and a chromatographic resolution limited the utility of this synthetic route. To address these issues, a new synthetic route was developed utilizing a palladium catalyzed coupling of aryl oxazolines in tandem with a stereospecific enone reduction as key synthetic steps. Resolution was achieved by fractional crystallization of a (*S*)-(−)-α-methylbenzylamine salt. © 1998 Elsevier Science Ltd. All rights reserved.

Leukotriene B_4 (LTB_4) has been implicated as a key mediator in the progression of inflammatory diseases thus justifying the blockage of LTB_4 production as a therapeutic approach.[1] CP-105,696 **1** is a potent LTB_4 receptor antagonist which has recently undergone clinical evaluation for the treatment of inflammatory diseases.[2] In our continuing effort to identify therapeutically useful LTB_4 antagonists, structural modification of **1** led to a series of 2-(4-hydroxy-7-chromanyl)benzoic acids which demonstrate potent antagonism of LTB_4 receptors.[3] We report herein the synthetic approaches to this series as exemplified by the syntheses of **2** and **3**.



Triflate **4**[4] was envisioned as an ideal starting material in the synthesis of **2**, since the triflate group allows for the introduction of the benzoic acid moeity by palladium catalyzed coupling and the ketone group allows for the introduction of the benzyl group by alkylation and subsequent reduction to furnish the requesite 3,4-*trans* sterochemistry. This analysis led to the development of our initial synthetic approach to this series of 2-(4-hydroxy-7-chromanyl)benzoic acids which is illustrated by the synthesis of **2** (Scheme I).

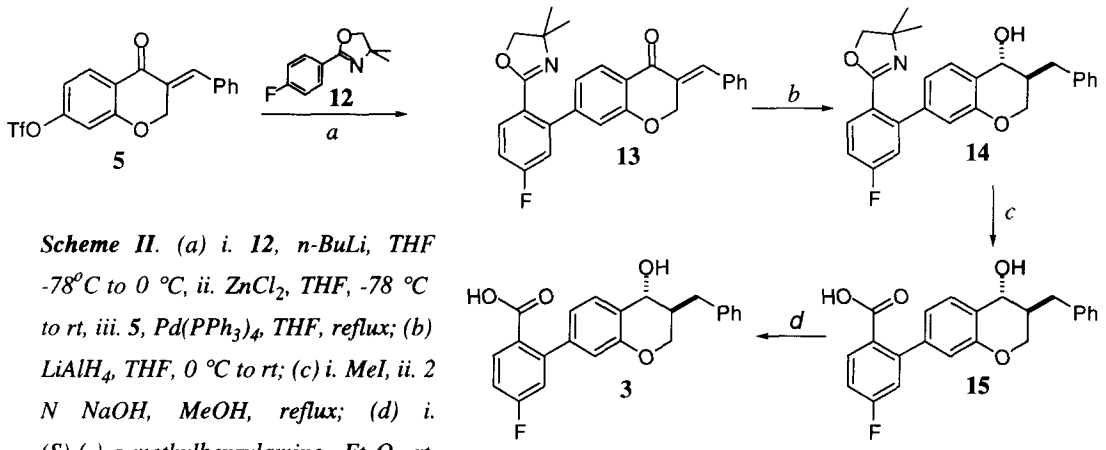
0960-894X/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(98)00276-5



Scheme I. *(a) PhCHO, pyrrolidine, MeOH, rt, (b) H_2, Pd/C, MeOH, rt, (c) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, 2,6-di-t-butyl-p-cresol, dioxane, reflux; (d) 8, $Pd(PPh_3)_4$, LiCl, 2,6-di-t-butyl-p-cresol, DMF, 100 °C; (e) $NaBH_4$, MeOH:THF (2:1), rt; (f) Boc-D-Trp, DMAP, DCC, CH_2Cl_2, rt; (g) 1N NaOH, EtOH, reflux.*

Aldol condensation of ketone **4** with benzaldehyde gave enone **5** (73%).[5] Catalytic hydrogenation of **5** afforded ketone **6** (88%). Stannylation of **6** with hexamethylditin under palladium catalysis gave stannane **7** (82%).[6] Palladium catalyzed coupling of **7** with methyl 4-chloro-2-trifluoromethanesulfonyloxy-benzoate **8**, prepared in two steps from 4-chlorosalicyclic acid, afforded keto ester **9** (34%).[7] Reduction of **9** with sodium borohydride yielded a 60/40 mixture of *cis/trans* alcohols from which the desired racemic *trans* alcohol **10** was isolated by chromatography (30%). Resolution of alcohol **10** was accomplished by esterification with Boc-D-tryptophan, isolation of the less polar diastereomer **11** by chromatography (36%), followed by saponification to yield (+)-carboxylic acid **2** (89%). The diastereomeric purity of **11** was judged to be > 95% by ^{1}H NMR and the absolute configuration of **2** was assigned to be 3*S*,4*R* based on its analogous optical rotation to **1**.[2] Although this synthetic approach was straightforward, it suffered from several drawbacks. Namely, the use of organostannanes which present purification and toxicity issues, the lack of stereoselectivity in the reduction of ketone **9** and the resolution of **10** by the chromatographic separation of diastereomer **11**, all limited the utility of this route. With regard to the lack of stereoselectivity obtained in the reduction of ketone **9**, β-aryl enones were found to undergo reduction with lithium aluminum hydride to give exclusively *trans* substituted alcohols.[8] However, in order to utilize this methodology in the current instance, the 2-benzoic acid moiety would have to be replaced by a group stable to lithium aluminum hydride and which was compatible with biaryl formation

through a palladium catalyzed coupling. Aryl oxazolines are latent benzoic acids which are stable to lithium aluminum hydride[9] and they also undergo orthometallation and subsequent palladium catalyzed coupling with aryl triflates to give biaryl oxazolines.[10] Thus aryl oxazolines had the potential not only to allow for a stereoselective reduction but would also avoid the use of organostannanes. We also reasoned that the carboxylic acid moiety might lend itself to resolution by way of fractional crystallization of diastereomeric salts, thus avoiding resolution by way of chromatographic separation of Boc-D-trytophan esters. These methods addressed all the shortfalls of our first synthetic route and we set out to apply these methods in the synthesis of **3** (Scheme II).



Scheme II. *(a) i.* ***12****, n-BuLi, THF -78°C to 0 °C, ii.* $ZnCl_2$*, THF, -78 °C to rt, iii.* ***5****,* $Pd(PPh_3)_4$*, THF, reflux; (b)* $LiAlH_4$*, THF, 0 °C to rt; (c) i. MeI, ii. 2 N NaOH, MeOH, reflux; (d) i. (S)-(-)-a-methylbenzylamine,* Et_2O*, rt, ii. HCl.*

Lithiation of 2-(4-fluorophenyl)-4,4-dimethyloxazoline **12**[11] followed by transmetallation with zinc chloride and subsequent palladium catalyzed coupling with enone **5** afforded oxazoline **13** (58%). Reduction of **13** with lithium aluminum hydride yielded *trans* alcohol **14** (64%). The corresponding *cis* alcohol could not be detected in the reaction mixture indicating that the reduction is highly stereoselective. Treatment of **14** with methyl iodide followed by basic hydrolysis gave racemic carboxylic acid **15** (93%).[12] Resolution was achieved by fractional crystallization of the *S*-(–)-α-methylbenzylamine salt of **15** to afford, after regeneration of the free acid, (+)-carboxylic acid **3** (21%). The absolute configuration of **3** was assigned as 3*S*,4*R* based on its analogous optical rotation to **1** and its optical purity determined to be > 99% by chiral HPLC.

The synthetic route depicted in Scheme II is highly efficient with **3** being obtained in five synthetic steps from **4** in 5% overall yield whereas in the synthetic route depicted in Scheme I, **2** is obtained in seven synthetic steps from **4** in 2% overall yield. The route depicted in Scheme II also has the potential to introduce a greater

array of functionality into the benzoic acid moiety due to the great diversity of commercially available benzoic acids which are precursors to 2-phenyloxazolines. In contrast, the commercial availability of diversely funtionalized salicyclic acids, the precursors to benzoic triflates used in the route depicted in Scheme I, is somewhat limited. However, the route in Scheme I does allow for the incorporation of functionality which would be incompatible with the use of lithium aluminum hydride as in the route depicted in Scheme II.

By structural modification of **1**, a new series of LTB_4 antagonists, exemplified by **2** and **3**, has been identified. Issues in our initial synthetic approach such as the use of organostannanes, lack of stereoselectivity and a chromatographic resolution, limited the utility of the synthetic route to **2**. In an effort to address these issues, a new synthetic route was developed utilizing a palladium catalyzed coupling of ortho metallated aryl oxazolines in tandem with a stereospecific enone reduction as key steps. Resolution was achieved by fractional crystallization of the (*S*)-(–)-α-methylbenzylamine salt of **15** to give **3** in five synthetic steps, 5% yield overall and an optical purity >99%.

References and Notes

1. Brooks, C. D. W.; Summers, J. B. *J. Med. Chem.* **1996**; *39*, 2629.
2. Reiter, L. A.; Melvin, L. S.; Crean, G. L.; Showell, H. J.; Koch, K.; Biggers, M. S.; Cheng, J. B.; Breslow, R.; Conklyn, M. J.; Farrell, C. A.; Hada, W. A.; Laird, E. R.; Martin, J. J.; Miller, G. T.; Pillar, J. S. *Bioorg. Med. Chem. Lett.* **1997**; *17*, 2307.
3. For an account of the discovery and structure–activity relationships of this series, see: Reiter, L. A.; Koch, K.; Piscopio, A. D.; Showell, H. J.; Alpert, R.; Biggers, M. S.; Chambers, R. J.; Conklyn, M. J.; Cooper, K.; Cortina, S. R.; Dibrino, J. N.; Dominy, B. W.; Farrel, C. A.; Hingorani, G. P.; Martinelli, G. J.; Ramchandani, M.; Wright, K. F. *Bioorg. Med. Chem. Lett.* immediately preceding article.
4. Koch, K.; Biggers, M. S. *J. Org. Chem.* **1994**, *59*, 1216.
5. Levai, A.; Schag, J. B. *Pharmazie* **1979**, *34*, 749.
6. Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49.
7. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
8. Koch, K.; Smitrovich, J. H. *Tetrahedron Lett.* **1994**, *35*, 1137.
9. Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.
10. Koch, K.; Chambers, R. J.; Biggers, M. S. *Synlett* **1994**, *5*, 347.
11. Yamaguchi, M.; Koga, T.; Kamei, K.; Akima, M.; Maruyama, N.; Kuroki, T.; Hamana, M.; Ohi, N. *Chem. Pharm. Bull.* **1994**, *42*, 1850.
12. Meyers, A. I.; Slade, J. *J.Org. Chem.* **1980**, *45*, 2785.