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A concise stereospecific synthesis of repinotan (BAY×3702)☆

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Abstract—A concise synthesis of the 2-[aminomethyl]chroman derivative BAY×3702 (**3**), a potent 5-hydroxytryptamine (5-HT_{1A}) antagonist is described. Utilization of a Mitsunobu reaction of phenol (**11**) with the non-racemic allylic alcohol (**12**) and consequent ring-closing metathesis furnishes the chroman-2-yl framework of **3** in optically active form.

2-(Aminomethyl)-1,4-benzodioxans (e.g. **1** and **2**, Fig. 1) have long been recognized as important pharmacologic tools with significant utility possessing the ability to modulate receptor activity at adrenergic, serotonergic, and dopaminergic receptors.[1] The ability of this moiety to function as a stereogenic bioisosteric replacements for another important neuropharmacologic agent, the arylpiperazine, has been documented.[2] Consequently, there exist numerous methods for the efficient, asymmetric synthesis of these compounds.[3]

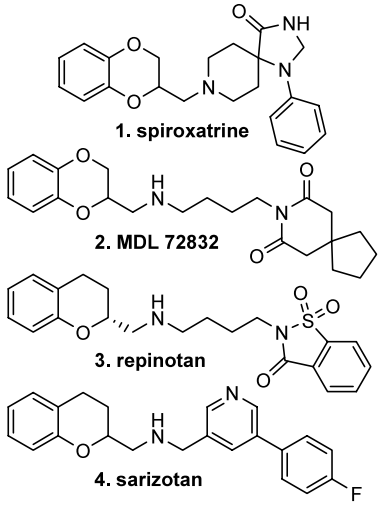

Figure 1. Selected 2-(aminomethyl)chromans/-1,4-benzodioxans.

More recently, the closely related structural analogs, 2-(aminomethyl)chromans (e.g. **3** and **4**, Fig. 1) have emerged as relevant biological agents and has generated increased pharmacological interest.[4] The lack of an efficient preparation for these molecules, coupled with their neuropharmacologic relevance and stereoselectivity of the target receptor families, has actuated synthetic effort toward their asymmetric synthesis.[5]

The 2-(aminomethyl)chroman derivative, BAY×3702 (repinotan, **3**), a high affinity 5-HT_{1A} receptor agonist,[6] currently in phase III clinical trials, is being developed by Bayer as a potential treatment for ischemic stroke and traumatic brain injury.[7] The development of repinotan as the (−)-enantiomer illustrates the potential biodiscrimination that exists for this class of molecules, and further emphasizes the importance of an asymmetric synthesis.

The previously reported synthesis of repinotan (**3**) outlined in Scheme 1 involves the formation of acid chloride (**6**) from chroman-2-carboxylic acid (**5**) via treatment with thionyl chloride.[8] Reaction of **6** with (*S*)-phenethylamine affords a 1:1 mixture of diastereomers. Separation (fractional crystallization) of the mixture provides the desired epimer in high optical purity. Subsequent reduction of the amide with diborane provides benzyl amine (**7**) followed by hydrogenolysis of **7** to afford (*R*)-2-(aminomethyl)chroman (**8**). Alkylation of **8** with *N*-(4-bromobutyl)saccharin provides repinotan (**3**), isolated as the hydrochloride salt.

Although interest in enantiomerically pure 2-(aminomethyl)chromans as pharmacologic agents has increased, their preparation generally relies upon optical resolution of a suitably functionalized 2-chromanyl

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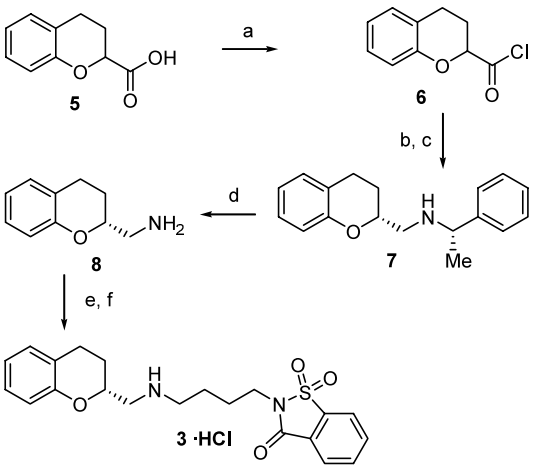
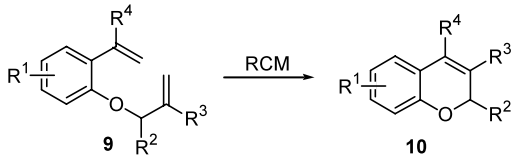


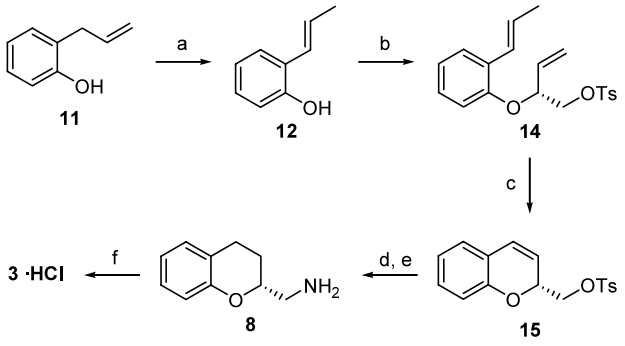
Scheme 1. Bayer synthesis of BAY×3702. *Reagents and conditions*: (a) $SOCl_2$. (b) (*S*)-Phenethylamine. (c) BH_3/THF. (d) H_2, Pd–C. (e) *N*-(4-bromobutyl)saccharin, Et_3N. (f) HCl.

derivative, as demonstrated for repinotan.[9] Although resolution ultimately provides the desired enantiomer, the remaining material is inevitably discarded. It is noted for repinotan that 'epimerization of the undesired diastereomer is feasible'. However, the axiomatic implication of this iterative cycle demonstrates an inherent shortcoming of resolution.

Of the many reports of chromene synthesis, Grubb's and co-workers have demonstrated a non-stereospecific, facile and practical methodology via ring-closing olefin metathesis (RCM) of a series of 2-styrenyl allyl ethers (**9**, Scheme 2) to afford chromene derivatives (**10**).[10]



Scheme 2. Grubb's synthesis of chromenes.



Scheme 3. Asymmetric synthesis of BAY×3702. *Reagents and conditions*: (a) $PdCl_2(MeCN)_2$, CH_2Cl_2. (b) (*S*)-2-Hydroxy-3-buten-1-yl *p*-tosylate (**13**), PPh_3, DEAD, PhMe (64%). (c) $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2 (78%). (d) NaN_3, DMSO. (e) H_2, Pd–C, MeOH (83%, two steps). (f) *N*-[4-Bromobutyl]saccharin, DMSO then HCl/Et_2O (62%).

Interest in utilization of the extant methodology indicated that 2-'styrene-like' phenols (i.e. **12**, Scheme 3) would also serve as exemplary substrates for elaboration into 2-(aminomethyl)chromans such as **3**. Rearrangement of the double bond present in **11** is accomplished by treatment with bis(acetonitrile)dichloropalladium(II) in refluxing dichloromethane to afford styrene (**12**).[11] Mitsunobu reaction of **12** with the commercially available (*S*)-2-hydroxy-3-buten-1-yl *p*-tosylate (**13**) provided the requisite diene (**14**) for the envisioned RCM.[12] Cyclization of **14** was effected using 0.2 equiv. of Grubb's catalyst to afford the metathesis adduct 2-(hydroxymethyl)chromene (**15**) as the *p*-toluenesulfonyl ester.[13] Azide displacement of the tosylate in **15** followed by subsequent reduction of the azido group with concomitant reduction of the chromene provided 2-(aminomethyl)chroman (**8**). Alkylation of **8** with *N*-[4-bromobutyl]saccharin and conversion to the hydrochloride salt provides repinotan (**3**) as a single enantiomer.

The unmediated preparation of styrenes such as **12** from their corresponding phenols via allylation, Claisen rearrangement, and olefin rearrangement significantly expands the pool of available phenols. This observation, coupled with the ability of these compounds to serve as reacting partners in the RCM further amplifies the number of targets accessible utilizing this process.

Finally, the utility of the chiral, non-racemic allylic alcohol (**13**) serves as the cornerstone for this synthesis of repinotan, affording the opportunity for extraneous installation of the stereogenic center present in **3**. The allylic alcohol present in **13** undergoes stereospecific inversion of configuration to provide a single enantiomer. Additionally, the functional differentiation of the diol permits facile preparation of diene **14** and, following metathesis cyclization, straightforward conversion to amine **8**.

In summary, this paper describes a stereospecific synthesis of repinotan (**3**), a 2-(aminomethyl)chroman reported to be in development for stroke. The synthesis of **3** is achieved in 25% overall yield in six steps, beginning with 2-allyl phenol (**11**). This approach provides a succinct route to a single stereoisomer, demonstrating an effective method for the preparation of a diverse array of derivatives in this class of molecules.

1. Supplementary material

Experimental procedures and characterization data for compounds **3**, **8**, **14**, and **15**.

Acknowledgements

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References

1. For example, see: (a) Quaglia, W.; Pigini, M.; Piergentili, A.; Gianella, M.; Marucci, G.; Poggesi, E.; Leonardi, A.; Melchiorre, C. *J. Med. Chem.* **1999**, *42*, 2961; (b) Matsuda, T.; Yoshikawa, T.; Suzuki, M.; Asano, S.; Somboonthum, P.; Takuma, K.; Nakano, Y.; Morita, T.; Nakasu, Y.; Kim, H. S.; Egawa, M.; Tobe, A.; Baba, A. *Jpn. J. Pharmacol.* **1995**, *69*, 357.
2. (a) Birch, A. M.; Bradley, P. A.; Gill, J. C.; Kerrigan, F.; Needham, P. L. *J. Med. Chem.* **1999**, *42*, 3342; (b) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. N.; Fozard, J. R. *J. Med. Chem.* **1988**, *31*, 1087.
3. For example, see: (a) Satoh, S.; Powers, C.; Toledo, L. M.; Kowalski, T. J.; Peters, P. A.; Kimble, E. F. *J. Med. Chem.* **1995**, *38*, 68; (b) Delgado, A.; Leclec, G.; Lobato, M. C.; Mauleon, D. *Tetrahedron Lett.* **1988**, *29*, 3671.
4. 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.
5. (a) Gross, J. L.; Stack, G. P. PCT Int. Appl. WO 0331429; (b) Gross, J. L. PCT Int. Appl. WO 0331428; (c) Goujon, J. Y.; Zammattio, F.; Pagnoncelli, S.; Boursereau, Y.; Kirschleger, B. *Synlett* **2002**, 322; (d) Bouzbouz, S.; Goujon, J. Y.; Deplanne, J.; Kirschleger, B. *Eur. J. Org. Chem.* **2000**, 3223; (e) Dean, F. M.; Jones, M. A. *Tetrahedron Lett.* **1983**, *24*, 2495; (f) Bravo, P.; Ticozzi, C. *J. Heterocyclic Chem.* **1978**, *15*, 1051.
6. De Vry, J.; Schohe-Loop, R.; Heine, H.-G.; Greuel, J. M.; Mauler, F.; Schmidt, B.; Sommermeyer, H.; Glaser, T. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 1082.
7. Lutsep, H. L. *Curr. Opinion Invest. Drugs* **2002**, *3*, 924.
8. De Vry, J.; Dietrich, H.; Glaser, T.; Heine, H.-G.; Horvath, E.; Jork, R.; Maertins, T.; Mauler, F.; Opitz, W.; Scherling, D.; Schohe-Loop, R.; Schwartz, T. *Drugs Fut.* **1997**, *22*, 341.
9. (a) Mewshaw, R. E.; Zhao, R.; Shi, X.; Marquis, K.; Brennan, J. A.; Mazandarani, H.; Coupet, J.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 271; (b) Scott, J. W.; Parrish, D. R.; Saucy, G. US Patent 4 003 919, 1977; (c) Junge, B.; Schohe, R.; Seidel, P.-R.; Glaser, T.; Traber, J.; Benz, U.; Schuurman, T.; De Vry, J.-M. V. US Patent 5 137 901, 1992.
10. Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.
11. Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453.
12. Misunobu, O. *Synthesis* **1981**, 1.
13. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.