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Synthesis of 3-Aminochroman Derivatives by Radical Cyclization

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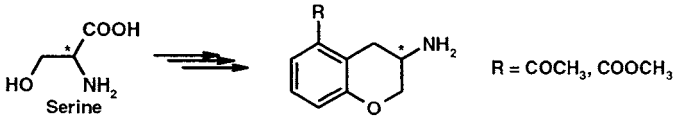
ABSTRACT



Enantiomerically pure 5-acetyl-3-amino-3,4-dihydro-2*H*-1-benzopyran and methyl 3-amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxylate were successfully synthesized starting from D- or L-serine. The formation of the benzopyran ring involved a radical cyclization step. The enantiomeric purities of the final aminochroman derivatives were determined by capillary electrophoresis using *β*-cyclodextrins as a chiral selector.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter of the central nervous system. The identification of multiple serotonin receptor subtypes has triggered the discovery of new drugs that alter 5-HT neurotransmission.[1] Due to its neuroprotective properties[2] and its key role in many (patho) physiological processes,[3] the 5-HT_{1A} receptor is a major target for neurobiological research and drug development. The 5-HT_7 receptor is the most recent addition to the serotonin subfamily of G-protein-coupled receptors.[4] At the present time, the biological functions of this receptor are still unknown. Recent reports suggest that it could be involved in the control of circadian rhythms[5] or in the etiology of depression.[6] Due to the role of 5-HT_{1A} and 5-HT_7 receptors in anxiety and depression, the synthesis of agonists appears to be very attractive. In our laboratory, previous works[7] have led to new potential therapeutic agents that demonstrated promising affinity and high selectivity toward the 5-HT_{1A} and 5-HT_7 receptors. For example, compound **1a** (Figure 1) showed 0.3 and 3.9 nmol affinities toward these receptors, respectively.[7c]

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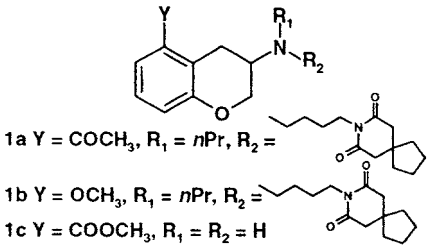


Figure 1.

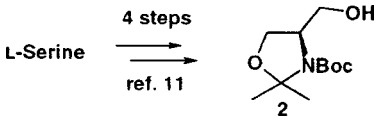
Parallel to our works, Johansson et al.[8] achieved the racemic syntheses of several 3-aminochroman derivatives possessing a carbonyl group (ketone, ester, and amide) at their C-5 position. These compounds were also used as ligands for the serotoninergic receptors 5-HT_{1A}. In this study, enantiomerically pure amines were obtained by resolution with tartric acid. Dixneuf et al. reported also an easy access to 3-aminochroman derivatives by way of ruthenium-catalyzed enantioselective hydrogenation of enamides[9] and ene carbamate.[10] As the enantioselectivities observed in the asymmetric hydrogenation were sometimes relatively low, it appears to us that this methodology was not general enough to be applied successfully to the synthesis of enantiopure 3-aminochromans.

In a previous paper,[7e] we reported the synthesis of both enantiomers (−)-**1b** and (+)-**1b** starting from Garner's aldehyde and an appropriate electrophile. This reaction involved an anionic step that could not be used due to the presence of the carbonyl group.

Herein, we wish to report a stereocontrolled synthesis of compound **1a** and methyl 3-amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxylate (**1c**), a promising intermediate for the synthesis of several C-5-functionalized 3-aminochroman derivatives.[8]

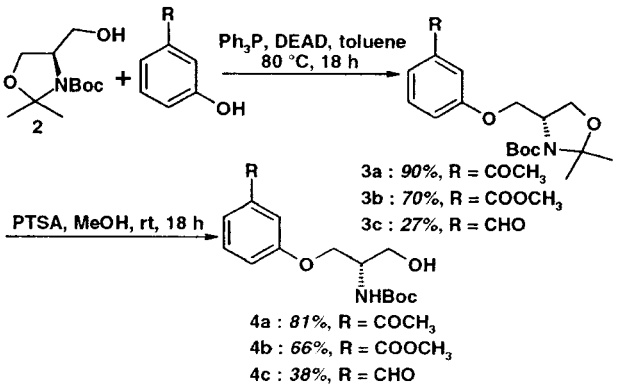
Our synthesis began with the preparation of the chiral alcohol **2** obtained in four steps starting from L-serine (Scheme 1).[11]

Scheme 1



Treatment of the chiral alcohol **2** with triphenylphosphine and diethyl azodicarboxylate at 80 °C in toluene with 1-(3-hydroxy-phenyl)-ethanone, methyl 3-hydroxybenzoate, or 3-hydroxybenzaldehyde provided ethers **3a**−**c** in 90% yield (R = $COCH_3$), 70% yield (R = $COOCH_3$), and 27% yield (R = CHO), respectively (Scheme 2). Cleavage of the

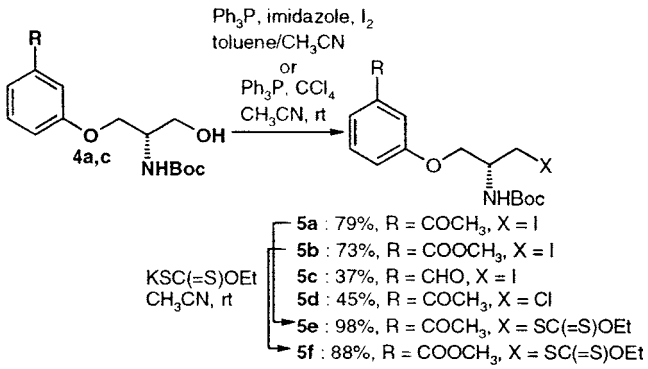
Scheme 2



isopropylidene protective group was accomplished by addition of *p*-toluenesulfonic acid on **3a**−**c** in methanol at room temperature. This reaction furnished the expected alcohols **4a**−**c** in 81% yield (R = $COCH_3$), 66% yield (R = $COOCH_3$), and 38% yield (R = CHO), respectively.

To realize the ring closure of alcohols **4** into their corresponding 3-aminochroman derivatives by a radical cyclization reaction, different activated compounds were synthesized (Scheme 3). According to the literature,[12] iodide

Scheme 3



derivatives are more reactive than other halogeno compounds. Then, the next step involved the replacement of the hydroxyl group with an halogen and more interestingly by an iodide.

Treatment of alcohols **4a**−**c** with triphenylphosphine, imidazole, and iodide in a mixture of toluene and acetonitrile

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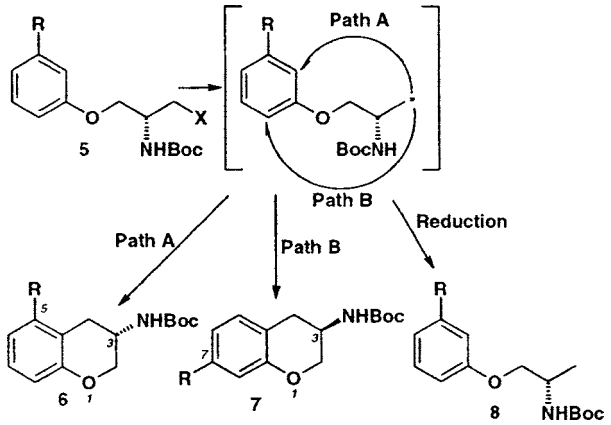
led to the expected iodide derivatives **5a** in 79% yield (R = $COCH_3$), **5b** in 73% yield (R = $COOCH_3$), and **5c** in 37% yield (R = CHO).[13] Compound **8c** was obtained with a poor overall yield. The cyclization step starting from this compound was not envisaged. Starting from alcohol **4a**, the chloride derivative **5d** was synthesized by addition of triphenylphosphine and carbon tetrachloride in acetonitrile in 45% yield. According to the high reactivity of xanthate derivatives,[14] their numerous advantages (e.g., no heavy or toxic metals, concentrated solutions, etc.) and their known utility as an easy and convenient source of radicals, xanthate analogues of alcohols **4a**,**b** were also obtained. The displacement of iodide with the potassium salt of *O*-ethylxanthic acid in acetonitrile at room temperature furnished the xanthate derivatives **5e** and **5f** in 98 and 88% yields, respectively.

At this stage, several comments on the radical cyclization can be made in anticipation of the results that will be shortly described. As shown in Scheme 4, three compounds could

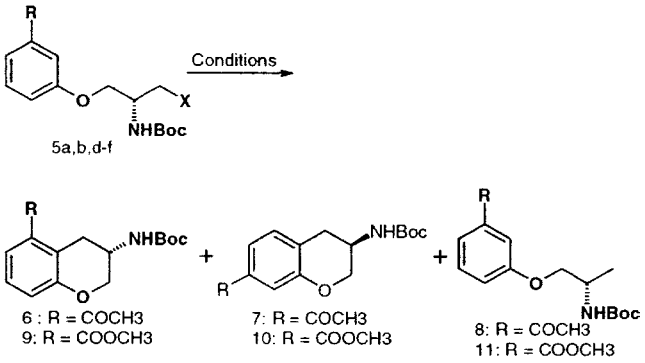
Scheme 4



be generated starting from **5**. After the formation of the radical moiety, ring closure occurred between two positions. On one hand, it can link between both substituents following path A. This sequence leads to the expected 3-aminochroman derivative **6** having the substitution in its C-5 position. On the other hand, if the cyclization occurs on the other accessible position (path B), the 3-aminochroman derivative **7** substituted in its C-7 position could be formed. Finally, reduction of the radical is also possible and leads to compound **8**.

According to our strategy, the activated compounds **5a**,**b**,**d**−**f** were involved in the radical cyclization step (Scheme 5). As shown in Table 1, slow addition of tributyltin

Scheme 5



hydride on the iodide derivative **5a** gave the best overall yield of cyclized aminochromans **6** and **9** (entries 1 and 2; 37 and 47% yields, respectively). Starting from the chloride derivative **5c** (less reactive than the corresponding iodide compound), we noticed that the reduced compound **8** was obtained preferentially in 47% yield (entry 3). When tributyltin chloride[15] (5 equiv) was added to the reaction (entry 4), aminochroman **7** was obtained preferentially in 35% yield. Indeed, as expected, this result is due to coordination between the carbonyl group of the C-5 substituent and tributyltin chloride as a Lewis acid. A steric repulsion occurs. We also used tris(trimethylsilyl)silane[16] (TTMSS) as a free-radical mediator because this reagent has kinetic and thermodynamic properties comparable to tributyltin hydride (entry 5). Then, with the iodide derivative **5a**, addition of TTMSS led to the expected 3-aminochroman in 36% yield. Finally, starting with xanthate **5e**, addition of dilauroyl peroxide (DLP, 1.5 equiv) in refluxing chlorobenzene led to cyclized products (89%), including our expected bicyclic derivative **6** in 69% yield. The favored formation of the 3-aminochroman derivative **6** may be explained by a reversible and degenerated pathway into the catalytic cycle of the radical reaction.[14] As described for the generation of compound **6**, xanthate **5f** was involved

Table 1. Radical Cyclization: Conditions and Results

entry	R	X	conditions	compounds (yields)			**6** + **7** or **9** + **10**
1[a]	$COCH_3$	I	Bu_3SnH, AIBN, PhH, reflux	**6** (23%)	**7** (14%)	**8** (32%)	37%
2[b]	$COCH_3$	I	Bu_3SnH, AIBN, PhH, reflux	**6** (31%)	**7** (16%)	**8** (34%)	47%
3[b]	$COCH_3$	Cl	Bu_3SnH, AIBN, PhH, reflux	**6** (21%)	**7** (12%)	**8** (47%)	33%
4[b]	$COCH_3$	I	Bu_3SnH, Bu_3SnCl, AIBN, PhH, reflux	**6** (33%)	**7** (35%)	**8** (23%)	68%
5	$COCH_3$	I	$(Me_3Si)_3SiH$, AIBN, $PhCH_3$, reflux	**6** (36%)	**7** (18%)	**8** (12%)	54%
6	$COCH_3$	SCSOEt	DLP, PhCl, 80 °C	**6** (69%)	**7** (20%)	**8** (<5%)	89%
7[c]	$COOCH_3$	SCSOEt	DLP, PhCl, 80 °C	**9** (56%)	**10** (17%)	**11** (<5%)	73%

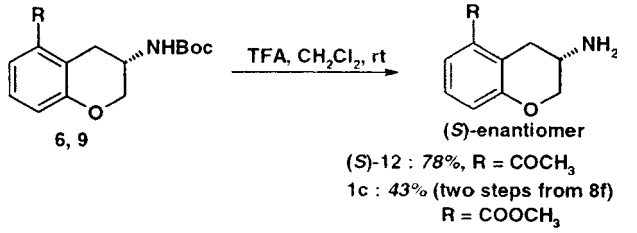
[a] Manual addition of Bu_3SnH. [b] Syringe pump addition of Bu_3SnH. [c] Yield determined by NMR.

in the radical cyclization step using DLP in refluxing chlorobenzene. This reaction led to the 3-aminochroman **9** with the ester function on C-5.

Unfortunately, carbamate **9** could not be isolated by flash chromatography and was obtained in an unseparable mixture of compounds **10** and **11**.

The *tert*-butoxycarbonyl group of compounds **6** and **9** was removed with trifluoroacetic acid in methylene chloride to give the desired aminochroman (*S*)-**12** in 78% yield (Scheme 6). Amine **1c** was easily isolated by flash chromatography

Scheme 6



in 43% yield (in two steps starting from **5f**). The final step, leading to the (+)-**1a** derivative, involved N,N-dialkylation of compound (*S*)-**12**.[7a]

(3*R*)-5-Acetyl-3-amino-3,4-dihydro-2*H*-1-benzopyran (*R*)-**12** was prepared according to the same synthetic pathway starting from D-serine. All compounds were fully characterized (IR, ^{1}H, ^{13}C NMR, mass, and specific rotation), and physical data are identical to those described for their enantiomers.

The enantiomeric purities of aminochromans **12** and **1c** were determined by capillary electrophoresis using β-cyclodextrin as a chiral selector. In each case, we obtained the desired enantiomer with an ee >99%.[17]

In conclusion, the syntheses of enantiomerically pure (3*S*)-5-acetyl-3-amino-3,4-dihydro-2*H*-1-benzopyran (*S*)-**12** and (3*S*)-3-amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxylic acid methyl ester **1c** were accomplished starting from alcohol **2** obtained from L-serine. The (*R*)-**12** was synthesized using an analogous route starting from D-serine with similar overall yield. The key step of our synthesis was the radical cyclization of the xanthate derivative into the 3-aminochroman skeleton.

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Supporting Information Available: Characterization for compounds **2** to **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Enantiomeric excess was determined by comparison of each enantiomer with a racemic mixture of the corresponding amine.