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A stereocontrolled route to 2-substituted chromans

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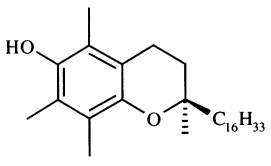
Abstract

A two-step synthesis of 2-substituted chromans of high enantiomeric purity is described. Mitsunobu reaction of homochiral halopropanols **10** with 2-bromophenol (**9**), followed by treatment with *n*-butyllithium under Parham cycloalkylation conditions generates 2-substituted chromans **7**. The methodology was applied to the synthesis of the natural product tephrowatsin E (**5**) and the antiviral BW683C (**6**).

The chroman ring system occupies a prominent position among oxygen heterocycles, occurring naturally with a variety of substituents at C-2.[1] Disubstituted examples include α-tocopherol (vitamin E) (**1**)[2] and the psychotropic tricycle Δ^9-tetrahydrocannabinol (**2**).[3] Monosubstituted examples include the anti-HIV agent calanolide A (**3**),[4] the antibiotic LL-D253α (**4**),[5] and the plant product tephrowatsin E (**5**).[6] In addition, many biologically active synthetic chromans have been reported, for example racemic 4′,6-dichloroflavan (BW683C) (**6**), a potent in vitro inhibitor of rhinovirus replication.[7]



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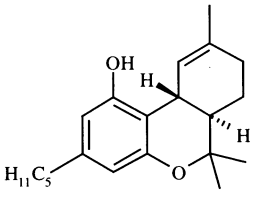

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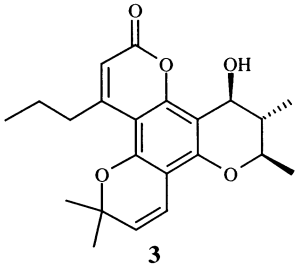

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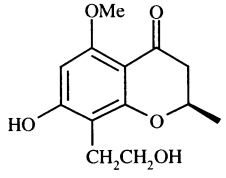

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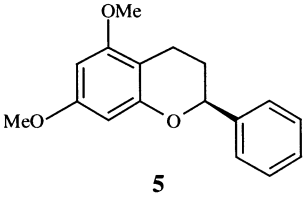

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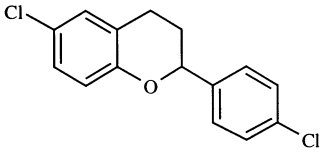

(±)-**6**

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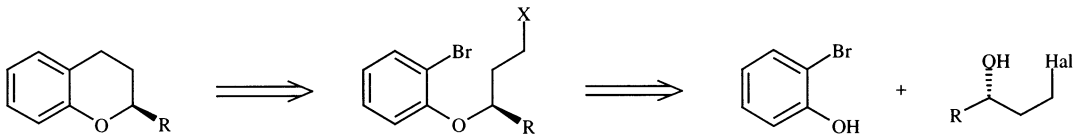
While there is extensive literature on the synthesis of chromans, most efforts are specifically directed to the synthesis of the tocopherol and tetrahydrocannabinol ring systems. We required access to a series of homochiral 2-aryl and 2-alkyl monosubstituted chromans for which there are few general routes. Knight[8] has recently reported a chroman ring synthesis based on the intramolecular trapping by alcohols of benzynes generated from 7-substituted-1-aminobenzotriazoles. Trost's synthesis of calanolide A (**3**) utilizes an asymmetric *O*-alkylation of a phenol followed by functionalization and an aromatic ring closure to the chromanol **3**.[4] Routes to 2-alkylchroman-4-ones reported in the literature include the diastereoselective conjugate addition of lithium dimethylcuprate to (*S*)-3-(*p*-tolylsulphinyl)chromanones reported by Wallace,[9] as well as an approach based on the Houben–Hoesch reaction reported by Rama Rao.[10]

Our approach is outlined in Scheme 1. Parham[11] cyclization of an aryl bromide **8** should give the chroman ring system **7**. The aryl bromide **8** should be accessible via a Mitsunobu[12] inversion reaction between 2-bromophenol (**9**) and the appropriately substituted halopropanol **10**.[13] Chiral propanols **10** are either commercially available or readily prepared via asymmetric reduction of the corresponding ketone.[14]

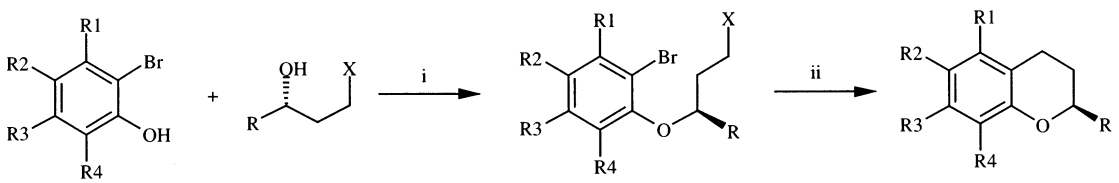


7 **8** **9** **10**

Scheme 1.

Our preliminary results are shown in Table 1. Commercially available (*R*)-(+)-3-chloro-1-phenyl-1-propanol (**12**)[15] was treated with 2-bromophenol (**11**) under standard Mitsunobu inversion conditions to give, following chromatography, the (*S*)-phenyl ether **13a** in 78% yield

Table 1
Reaction conditions: (i) PPh_3, DEAD, THF, rt, 8–36 h; (ii) ^{n}BuLi, THF, −50°C to rt

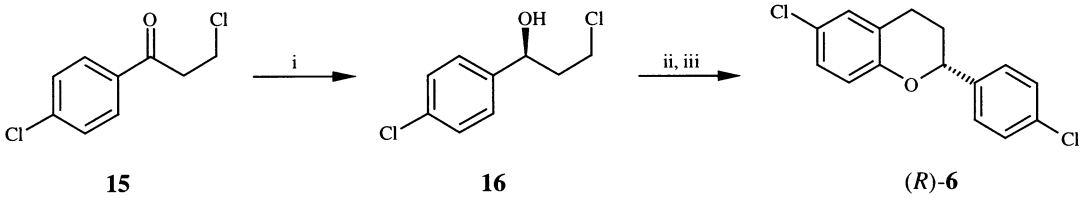


11 **12** **13 a-f** **14 a-e**

Entry	R1	R2	R3	R4	R	X	Yield **13** (%)	Yield (%)	
a	H	H	H	H	Ph	Cl	78	**14a**	83
b	H	Me	H	H	Ph	Cl	82	**14b**	77
c	H	Cl	H	H	Ph	Cl	81	**14c**	78
d	H	H		–$(CH)_4$–	Ph	Cl	64	**14d**	74
e	H	H	H	H	Me	Br	67	**14e**	81
f	MeO	H	MeO	H	Ph	Cl	76	**5**	78

(entry a, Table 1). Initially, we subjected **13a** to the cyclization conditions originally described by Parham, but these led to only moderate yields of the 2-phenylchroman (**14a**).[11] Optimal conditions for the Parham cyclization were found to be a modified version of those recently described by Spoors[16] for the cyclization of 2-(*o*-bromophenoxy)ethyl bromides to benzodihydrofurans; addition of **13a** to one equivalent of *n*-butyllithium in THF at −50°C and allowing the reaction to warm to room temperature. Under these conditions, (2*S*)-(−)-phenylchroman (**14a**), $[\alpha]_D = -15$ (*c* 3.0 in $CHCl_3$) [lit.[17] $[\alpha]_D = -15.3$ (*c* 3.48 in $CHCl_3$)] was obtained. The sign and magnitude of rotation confirmed that the Mitsunobu reaction occurred with inversion and the two steps without significant racemization. A single recrystallization from methanol gave material of >99% e.e. by HPLC analysis.[18] In order to investigate the utility of the methodology, a variety of readily available substituted bromophenols **11** (entries b, c, d and f) were studied in the reaction with (*R*)-(+)-3-chloro-1-phenyl-1-propanol (**12**). The Mitsunobu reaction and cyclization all proceeded in good yields and without significant racemization to furnish the (2*S*)-phenylchromans **14b**, **14c**, **14d**, and **5**, respectively. Tephrowatsin E (**5**) was previously isolated from the aerial parts of *Tephrosia Watsoniana*.[6] The spectral properties of our synthetic sample were in close agreement with the reported spectral data.[6] Replacement of the 2-phenyl substituent with an alkyl substituent was possible by repeating the sequence with 2-bromophenol (**11**) and (*S*)-4-bromobutane-2-ol (**12e**)[19], which gave (2*R*)-methylchroman (**14e**) in 54% yield over the two steps (entry e).

The range of potential substituents located at the chroman 2-position can be extended further by taking advantage of the asymmetric reduction of suitable prochiral ketones,[14] as exemplified by the first synthesis of enantiomerically pure (*R*)-4′,6-dichloroflavan (**6**) (Scheme 2). Catalytic asymmetric reduction of 3,4′-dichloropropiophenone (**15**) with (*R*)-oxazaborolidine and borane, under the conditions described by Corey,[20] gave (*S*)-3-chloro-1-(4-chlorophenyl)-1-propanol (**16**) in 91% yield and 94% e.e. as judged by ^{1}H NMR analysis of the MTPA (Mosher) ester.[21] Mitsunobu reaction of **16** with 2-bromo-4-chlorophenol and cyclization with one equivalent of *n*-butyllithium gave, following recrystallization from methanol, BW683 (**6**) of >99% e.e. by HPLC analysis.[18] Racemic BW683C (**6**) is a potent in vitro inhibitor of rhinovirus replication and was previously isolated in enantiomerically pure form following preparative HPLC using the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate).[22]



15 **16** (*R*)-**6**

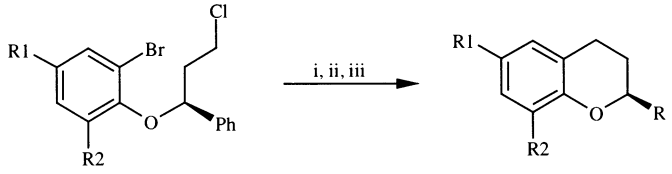
Scheme 2. *Reaction conditions*: (i) BH_3, (*R*)-oxazaborolidine, THF, 0°C, 91%; (ii) 2-bromo-4-chlorophenol, PPh_3, DEAD, THF, rt, 16 h, 85%; (iii) ^{n}BuLi, THF, −50°C to rt, 78%

Bradsher has examined the selectivity of *n*-butyllithium towards aromatic dibromides in the Parham cyclization.[23] It was reported that the bromide adjacent to the ether preferentially reacts with one equivalent of *n*-butyllithium to initiate cyclization between −100 and −78°C. The second bromide was then exchanged by the addition of further *n*-butyllithium at −100°C followed by in situ trapping with an electrophile. As expected, replication of these conditions with the dibromide **17** was complicated by the relatively slow cyclization step and a mixture of

products was obtained. Treatment of the dibromide **17** (entry a, Table 2) with one equivalent of *n*-butyllithium, under our modified conditions, gave the 6-bromo-2-phenylchroman (**18a**) in 84% yield, confirming the selectivity for the *ortho*-bromide described by Bradsher. This reaction was repeated, but when the cyclization was judged to be complete, the reaction mixture was re-cooled to −50°C and two equivalents of *n*-butyllithium were added followed by an excess of DMF. This time the desired 6-carbaldehyde-2-phenylchroman (**18b**) was isolated in 81% yield (entry b). A range of other electrophiles were screened in the double lithiation reaction and each gave the desired 6-substituted-2-phenylchroman **18** in good to moderate yields (entries c, d and e). Repeating the sequence with the 2,6-dibromoether **17** (entries f and g) gave the expected 8-bromo-2-phenylchroman (**18f**) and 8-carbaldehyde-2-phenylchroman (**18g**) in good yields, further extending the synthetic utility of this procedure.

Table 2

Reagents and conditions: (i) ^{n}BuLi, THF, −50°C to rt 2 h; (ii) −50°C, ^{n}BuLi, 30 min; (iii) E^+ (4–6 equivalents), −50°C to rt



17 **18**

	Dibromide			Product		
Entry	R1	R2	Electrophile	R1	R2	Yield (%)
a	Br	H	–	Br	H	84
b	Br	H	DMF	CHO	H	81
c	Br	H	CO_2 (g)	CO_2H	H	78
d	Br	H	MeI	Me	H	80
e	Br	H	$(CH_2O)_n$	CH_2OH	H	57
f	H	Br	–	H	Br	79
g	H	Br	DMF	H	CHO	76

In conclusion, we have developed a general and flexible synthesis of 2-substituted chromans of high enantiomeric purity from readily available starting materials. A natural product tephrowatsinE (**5**) and a biologically active synthetic compound BW683 (**6**) were prepared using the methodology. Further studies in this area will be the subject of future reports.

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References

1. Dean, F. M. *Naturally Occuring Oxygen Ring Compounds*; Butterworths: London, 1963. (b) Ellis, G. P.; Lockhart, I. M. *Chromans and Tocopherols*; Wiley: New York, 1977. (c) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465–475.
2. For some recent approaches to vitamin E see: Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527–532; Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495–5497; Hubsher, J.; Barner, R. *Helv. Chim. Acta* **1990**, *73*, 1068; Mizuguchi, S.; Suzuki, T.; Achiwa, K. *Synlett* **1996**, 743; Tietze, L. F.; Gorlitzer, J. *Synthesis* **1997**, 877–885.
3. For a recent synthesis see: Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193–3194.
4. For a recent synthesis see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074–9075 and references cited therein.
5. Chandler, I. M.; McIntyre, C. R.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2271–2284.
6. Gomez, F.; Quijano, L.; Calderon, J. S.; Rodriquez, C.; Tirso, R. *Phytochemistry* **1985**, *24*, 1057–1059.
7. Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell, I. C.; Young, D. A. *Nature* **1981**, *292*, 369–370.
8. Knight, D. W.; Little, P. B. *Tetrahedron Lett.* **1998**, *39*, 5105–5108; Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. *Tetrahedron* **2000**, *56*, 1013–1023.
9. Saengchantara, S. T.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1592–1595; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1990**, *46*, 6553–6564.
10. Rama Rao, A. V.; Gaitonde, A. S.; Prakash, K. R. C.; Prahlada Rao, S. *Tetrahedron Lett.* **1994**, *35*, 6347–6350.
11. Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184–1191.
12. Mitsunobu, O. *Synthesis* **1981**, 1–28.
13. Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916–2920.
14. Singh, V. K. *Synthesis* **1992**, 605–617.
15. Purchased from Aldrich Chemical Company, 99% e.e. by G.C.
16. Plotkin, M.; Chen, S.; Spoors, P. G. *Tetrahedron Lett.* **2000**, *41*, 2269–2273.
17. Corey, E. J.; Mitra, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 2938–2941.
18. CHIRALCEL®OJ-R™ HPLC analysis.
19. Prepared directly by reaction of Ph_3P and Br_2 with commercially available (2*S*)-butanediol. See: Benvegnu, T.; Schio, L.; Le Floc'h, Y.; Gree, R. *Synlett* **1994**, 505–506.
20. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.
21. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
22. Quaglia, M. G.; Desideri, N.; Bossu, E.; Sestili, I.; Conti, C. *Chirality* **1992**, *4*, 65–67.
23. Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384–1388.