Pergamon

Tetrahedron Letters 42 (2001) 3763–3766

TETRAHEDRON LETTERS

Approaches to 2-substituted chroman-4-ones: synthesis of (−)-pinostrobin

Kevin J. Hodgetts*

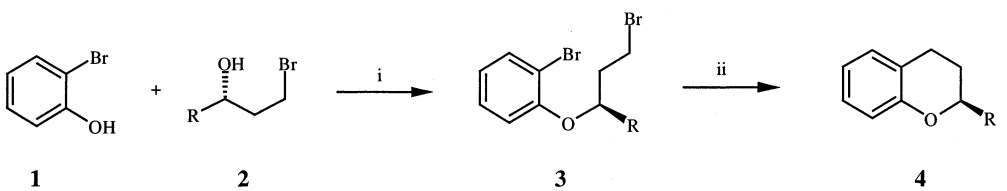
Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

Received 27 March 2001; accepted 5 April 2001

Abstract—Two approaches to optically active 2-substituted chroman-4-ones are described. The first utilized the oxidation of a preformed chroman ring and the second an intramolecular Mitsunobu cyclization. The methodology was applied to the synthesis of the biologically active natural product (−)-pinostrobin (**18**). © 2001 Elsevier Science Ltd. All rights reserved.

2-Substituted chroman-4-ones are widely distributed in nature and many show significant biological activity.[1] The preparation of 2-substituted chroman-4-ones can be problematic due to the ease with which they undergo ring-opening to the chalcone.[2] Stereocontrolled routes to these compounds are therefore limited in number. Successful examples include the diastereoselective conjugate addition of cuprates to homochiral 3-(*p*-tolylsulfinyl)chromanones[3] and an approach based on the Houben–Hoesch reaction.[4] The synthesis of related 2-substituted chromans,[5] chromenes[6] and chromanols[7] has also been reported. We recently described a general two-step synthesis of the 2-substituted chroman ring system based on an intermolecular Mitsunobu reaction between 2-bromophenol (**1**) and readily available chiral halopropanols **2**, followed by cyclization to the chroman **4** (Scheme 1).[8] In this communication we wish to describe the investigation into the oxidation of chiral 2-substituted chromans to the corresponding chroman-4-ones and an alternative route based on an intramolecular Mitsunobu reaction.

The chromium(VI) oxide catalyzed benzylic oxidation with periodic acid was recently reported and (2*S*)-(−)-phenylchroman (**4a**)[9] was subjected to the standard conditions (Table 1, entry 1).[10] The chroman-4-one **5a** was the major product (43% yield) but a substantial amount of the quinone **6a**[11] was also produced. The quinone **6a** was presumably formed by competing oxidation at the chroman-2-position of **4a**, ring-opening to the phenol and finally oxidation. Replacement of the 2-phenyl group by a 2-methyl group gave an increased yield of the chroman-4-one **5b**, although a significant amount of the quinone **6b** was also produced under the reaction conditions (entry 2). In view of the susceptibility for oxidation at the 2-position, a milder oxidizing system was sought. Treatment of **4a** with two equivalents of copper sulfate and 20 mol% peroxydisulfate[12] in aqueous acetonitrile at 65°C gave three products (entry 3). The major product was the chroman-4-one **5a** accompanied by the known benzylic alcohols **7a** and **8a**.[13] Under these conditions, none of the quinone **6a** was observed. Re-subjecting the mixture to the reaction conditions or using a larger excess of the reagents (entry 4) gave complete oxidation to (2*S*)-(−)-phenylchroman-4-one (**5a**) in 43% isolated yield ($[\alpha]_D = -66$ ($c=1$ in $CHCl_3$) [lit.[14] $[\alpha]_D = -64.4$ ($c=0.35$ in $CHCl_3$)]). Under the same conditions oxidation of



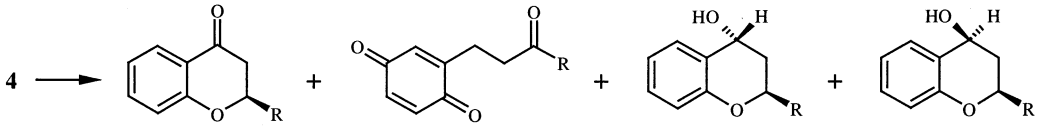
1 **2** **3** **4**

Scheme 1. *Reaction conditions*: (i) PPh_3, DEAD, THF, 64–85%; (ii) ^{n}BuLi, THF, −50°C to rt, 74–83%.

* Corresponding author. Present address: Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, USA. Tel.: 1-203-488-8201; fax: 1-203-483-7027; e-mail: khodgetts@nrgn.com

PII: S0040-4039(01)00567-6

Table 1. Oxidation of chroman **4**



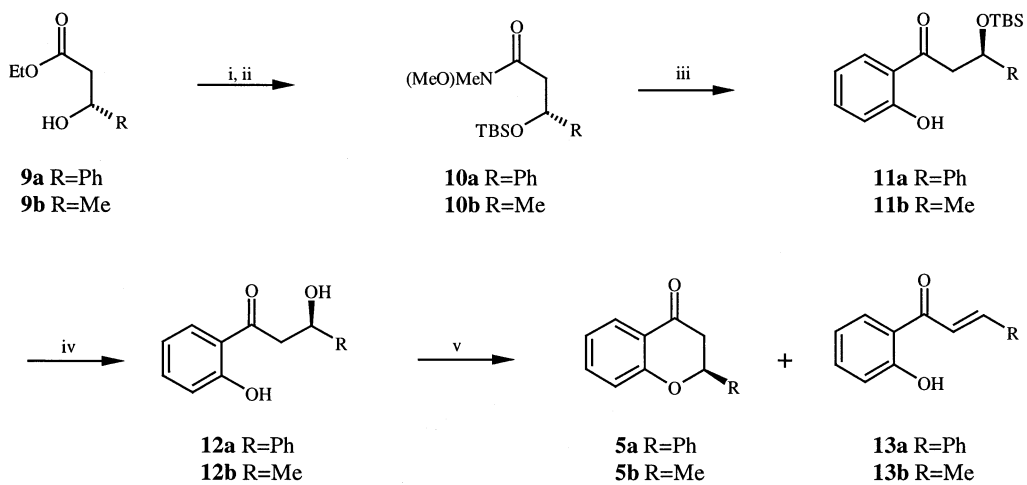
5a R=Ph **6a** R=Ph **7a** R=Ph **8a** R=Ph
5b R=Me **6b** R=Me **7b** R=Me **8b** R=Me

Entry	R	Conditions	Ratio **5**:**6**:**7**:**8**[a]	Yield **5** (%)[b]
1	Ph	(i)	57:43:0:0	43
2	Me	(i)	75:25:0:0	53
3	Ph	(ii)	75:0:19:6	35
4	Ph	(iii)	**5a** only	43
5	Me	(iii)	**5b** only	51
6	Ph	(iv)	**5a** only	39
7	Me	(iv)	**5b** only	42

Reaction conditions: (i) H_5IO_6, CrO_3 (cat.), CH_3CN, rt; (ii) $CuSO_4$ (2 mol equiv.), $K_2S_2O_8$ (0.2 mol equiv.), CH_3CN, H_2O, 65°C; (iii) $CuSO_4$ (4 mol equiv.), $K_2S_2O_8$ (0.4 mol equiv.), CH_3CN, H_2O, 65°C; (iv) CAN, AcOH, H_2O, 95°C.
[a] Determined by ^1H NMR (400 MHz) analysis of the crude reaction mixture.
[b] Isolated yield.

(2*R*)-(+)-methylchroman (**4b**) gave (2*R*)-(+)-methylchroman-4-one (**5b**) in 51% isolated yield ($[\alpha]_D=+51$ ($c=1$ in $CHCl_3$) [for the (2*S*)-enantiomer lit.[3a] $[\alpha]_D=-50$ ($c=1.2$ in $CHCl_3$)]). The magnitude of rotation of **5a** and **5b** indicated that the oxidation had proceeded without significant racemization. The use of cerium ammonium nitrate in aqueous acetic acid gave very similar results although the isolated yields of **5a** and **5b** were slightly reduced (entries 6 and 7).[15] The moderate isolated yields in the oxidation step, however, prompted the investigation of an alternative route to 2-substituted chroman-4-ones.

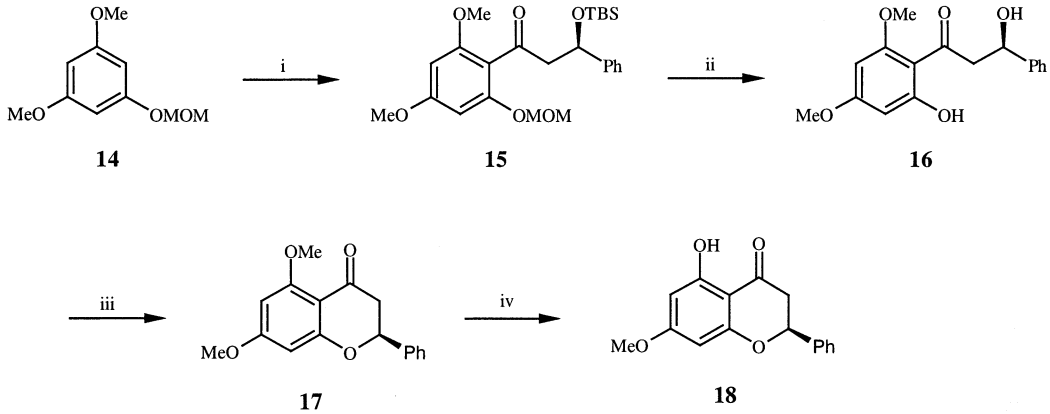
Optically active β-hydroxy esters are readily available, either commercially or via asymmetric hydrogenation of the appropriate β-keto ester.[16] Commercially available (+)-ethyl (*R*)-3-hydroxy-3-phenylpropanoate (**9a**)[17] was protected as its TBS ether and converted into the Weinreb amide **10a** under standard conditions (Scheme 2).[18] Addition of two equivalents of lithium *o*-lithiumphenoxide[19] (prepared from 2-bromophenol and two equivalents ^{n}BuLi) to the amide **10a** gave the ketone **11a** in 85% yield (based on **10a**). The TBS group was removed by treatment with 10% *p*-TsOH in aqueous THF and gave **12a** in 83% yield. Treatment of **12a** with triphenylphosphine (1 equiv.) and diethyl azodicarboxylate (DEAD) (1 equiv.) in THF at 0°C resulted in smooth cyclization to the chromanone **5a** in 86% yield ($[\alpha]_D=-67$ ($c=1$ in $CHCl_3$) [lit.[14] $[\alpha]_D=-64.4$ ($c=0.35$ in $CHCl_3$)]).[20] A minor by-product was identified as the elimination product **13a** which was isolated in 5% yield. Several groups have used an intramolecular Mitsunobu reaction to prepare six- and seven-membered cyclic ethers,[21] but we believe this to be the first example of the formation of an optically active chroman-4-one via this approach. Repeating the sequence with ethyl (*S*)-(+)-3-hydroxybutyrate (**9b**) gave (2*R*)-(+)-methylchroman-4-one (**5b**) in excellent



9a R=Ph **10a** R=Ph **11a** R=Ph
9b R=Me **10b** R=Me **11b** R=Me

12a R=Ph **5a** R=Ph **13a** R=Ph
12b R=Me **5b** R=Me **13b** R=Me

Scheme 2. *Reaction conditions*: (i) TBSCl, imidazole, CH_2Cl_2 (93%); (ii) MeONHMe·HCl, Me_3Al, CH_2Cl_2, (82%); (iii) 2-bromophenol (2 equiv.), ^{n}BuLi, ether, −78°C to rt; (85%); (iv) *p*-TsOH (10%), THF/H_2O (9:1), 55°C (83%); (v) PPh_3, DEAD, THF, 0°C (86%).



Scheme 3. *Reaction conditions*: (i) ^{t}BuLi, PhMe, −78°C then **10a** (0.5 equiv.) (72%); (ii) *p*-TsOH (10%), THF/H_2O (9:1), 55°C (86%); (iii) PPh_3, DEAD, THF, 0°C (88%); (iv) $AlCl_3$, CH_3CN, reflux (79%).

overall yield ($[\alpha]_D = +51$ ($c = 1$ in $CHCl_3$) [for the (2*S*)-enantiomer lit.[3a] $[\alpha]_D = -50$ ($c = 1.2$ in $CHCl_3$)]).

Pinostrobin (**18**) has been isolated from several natural sources[22] and shown to inhibit aromatase, a cytochrome P450 enzyme converting C19 androgens such as androstenedione to estrone and testosterone to estradiol.[23] This mode of action could prevent the development of estrogen related tumors such as breast and prostate cancer.[24] In addition, pinostrobin (**18**) has been isolated from *T. graveolens*, a plant used in traditional Mexican medicine for the treatment of gastrointestinal ailments such as diarrhoea and stomach pain.[25] It was recently demonstrated that pinostrobin (**18**) was an active ingredient in *T. graveolens* and inhibited intestinal smooth muscle contractions by a calcium-mediated mechanism.[26] The interesting biological activity makes pinostrobin an attractive target for synthesis. Under standard conditions, 3,5- dimethoxyphenol was protected as the MOM ether **14** and following *o*-lithiation, treated with the amide **10a** (Scheme 3). Under these conditions ketone **15** was isolated in 72% yield. The protecting groups on **15** were conveniently cleaved by treatment with 10% *p*-TsOH in aqueous THF which gave the cyclization precursor **16**. Intramolecular Mitsunobu cyclization of **16** gave an 88% yield of dimethylpinocembrin (**17**).[27] Regioselective demethylation of **17** with aluminum chloride[3b] gave, following chromatography, (−)-pinostrobin (**18**) ($[\alpha]_D = -48$ ($c = 1$ in $CHCl_3$) [lit.[22a] $[\alpha]_D = -52.7$ ($c = 1$ in $CHCl_3$)].

In conclusion, two general methods have been described for the synthesis of optically active 2-substituted chroman-4-ones from readily available starting materials. A biologically active natural product, (−)-pinostrobin (**18**), was prepared in six steps with an overall yield of 33% starting from commercially available 3,5-dimethoxyphenol and (+)-ethyl (*R*)-3-hydroxy-3-phenylpropanoate.

Acknowledgements

The University College Dublin and Schering-Plough (Avondale) are thanked for the funding of this research under the Newman Fellowship program. John Hill (Kent mass spectrometry) is thanked for mass spectra and Robertson analytical for elemental analysis and optical polarimetry.

References

1. (a) Dean, F. M. *Naturally Occurring 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. (a) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247–256; (b) Anastasis, P.; Brown, P. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 197–200 and references cited therein.
3. (a) Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1990**, *46*, 6553–6564; (b) For a recent application to the synthesis of a flavanone, see: Solladié, G.; Gehrold, N.; Maignan, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2739–2747.
4. Rama Rao, A. V.; Gaitonde, A. S.; Prakash, K. R. C.; Prahlada Rao, S. *Tetrahedron Lett.* **1994**, *35*, 6347–6350.
5. (a) Sato, K.; Tomoyuki, Y.; Mitsuru, S.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309–314; (b) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. *Tetrahedron* **2000**, *56*, 1013–1023.
6. (a) Wipf, P.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321–5324; (b) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347 and references cited therein.
7. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074–9075.
8. Hodgetts, K. J. *Tetrahedron Lett.* **2000**, *41*, 8655–8659.
9. Starting material >99% e.e. by CHIRALCEL®OJ-R™ HPLC analysis.
10. Yamazaki, S. *Org. Lett.* **1999**, *1*, 2129–2132.
11. All new compounds were characterized by ^1H and ^{13}C NMR and gave satisfactory mass spectra and/or elemental analysis.
12. (a) Carter, S. D.; Wallace, T. W. *Synthesis* **1983**, 1000–1002; (b) Bhatt, M. V.; Perumal, P. T. *Tetrahedron Lett.* **1981**, *22*, 2605–2608; (c) For a review of the mechanistic and synthetic implications of peroxydisulfate reactivity,

see: Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27–32.
13. Alcohols **10a** and **11a** were assigned on the basis of their ^{1}H and ^{13}C NMR spectra, see: Momose, T.; Ozaki, Y. *Tetrahedron Lett.* **1976**, 3699–3702; Hanaya, K.; Kudo, H.; Gohke, K.; Imaizumi, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2163–2164; Senda, Y.; Ishiyama, J.; Imaizumi, S.; Hanaya, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 217–220.
14. Rakosi, M.; Tokes, A. L.; Bognar, R. *Tetrahedron Lett.* **1970**, 2305–2308.
15. Kanvinde, M. N.; Kulkarni, S. A.; Paradkar, M. V. *Synth. Commun.* **1990**, *20*, 3259–3264.
16. (a) Noyori, R.; Okuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858; (b) For a review, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994; p. 56.
17. Purchased from Fluka, >99% e.e. by GC.
18. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
19. Talley, J. T.; Evans, I. A. *J. Org. Chem.* **1984**, *49*, 5267–5269.
20. Mitsunobu, O. *Synthesis* **1981**, 1–28.
21. (a) Shih, T. L.; Wyvratt, M. J.; Mrozik, H. *J. Org. Chem.* **1987**, *52*, 2029–2033; (b) Sugihara, H.; Mabuchi, H.; Hirate, M.; Inamoto, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1930–1952; (c) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123–126; (d) Aristoff, P. A.; Harrison, A. W.; Huber, A. M. *Tetrahedron Lett.* **1984**, *25*, 3955–3958.
22. For examples, see: (a) Erdtman, H. *Svensk Kem. Tidskr.* **1944**, *56*, 95–101; (b) Lindstedt, G. *Acta Chem. Scand.* **1950**, *4*, 1042–1046; (c) Wollenweber, E. *Phytochemistry* **1982**, *20*, 1462–1464; (d) Jaipetch, T.; Reutrakul, V.; Tuntiwachwuttikul, P.; Santisuk, T. *Phytochemistry* **1983**, *22*, 625–626; (e) Haberlein, H.; Tschiersch, K.-P. *Biochem. Syst. Ecol.* **1998**, *26*, 97–103.
23. Le Bail, J.-C.; Aubourg, L.; Habrioux, G. *Cancer Lett.* **2000**, 37–44.
24. Joshi, S. C.; Strauss, L.; Makela, S.; Santti, R. *J. Med. Food* **1999**, *2*, 235–238.
25. Mata, R.; Navarrete, A.; Alvarez, L.; Pereda, R.; Delgado, G.; Romo del Vivar, R. *Phytochemistry* **1987**, *26*, 191–193.
26. Meckes, M.; Paz, D.; Acosta, J.; Mata, R. *Phytomedicine* **1998**, *5*, 459–463.
27. Bick, I. R. C.; Brown, R. B.; Hillis, W. E. *Aust. J. Chem.* **1972**, *25*, 449–451.