Tetrahedron Letters,Vol.30,No.41,pp 5563-5566,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# SYNTHESIS OF A CARBOCYCLIC ANALOG OF QUERCETIN VIA A BARBIER REACTION

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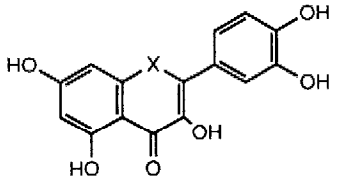
Summary: A six-step synthetic route to the carbocyclic flavanoid 2 is described. The key step involves a 1,4-addition of a tertiary bromide to a α,β-unsaturated ester by the Barbier reaction.

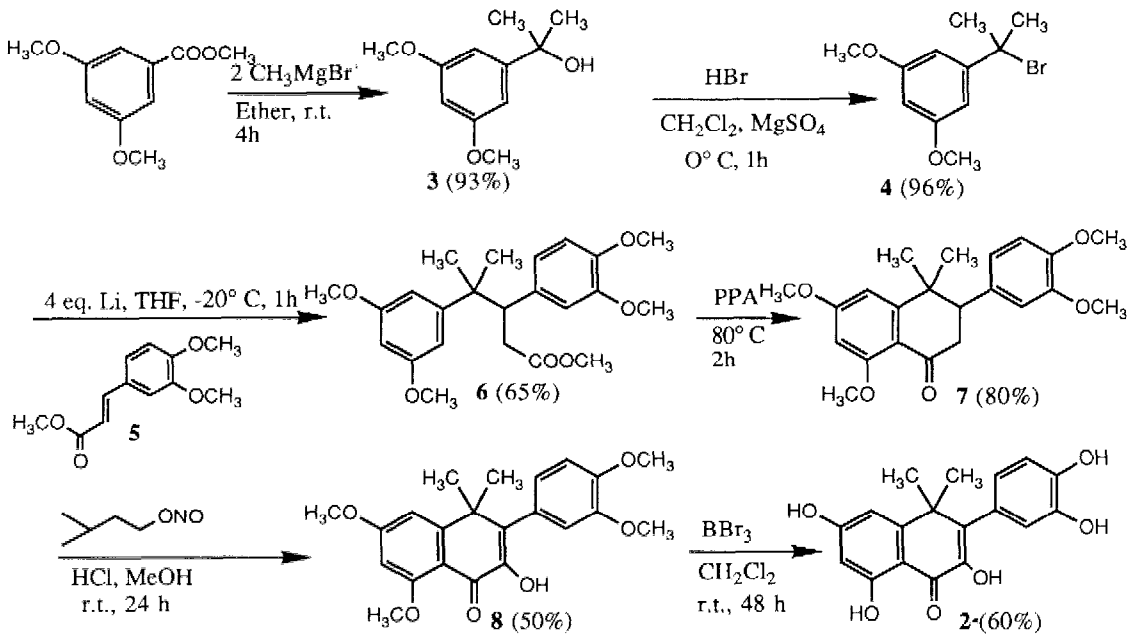
Many polyhydroxylated flavones, such as quercetin **1**, have been reported to inhibit the 5-lipoxygenase pathway of arachidonic acid metabolism.[1] They are, however, only weakly active in *in vivo* models on iv administration and are not active orally.[2] The lack of systemic activity may be partially attributed to the presence of the pyranone ring, since it has been postulated[3] that this ring, with oxygen adjacent to the double bond, is prone to metabolic cleavage. In an attempt to increase the systemic activity of these flavones, 'carbocyclic' analogs in which the oxygen moiety of the pyranone



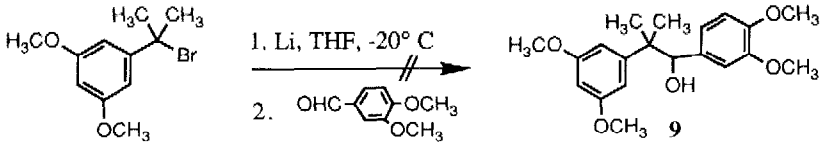

**1**, X= O
**2**, X= $C(CH_3)_2$

ring is replaced by a dimethyl substituted methylene group, e.g. **2**, were synthesized. The synthesis of one such carbocyclic flavanoid, Sch 37279 (**2**), a carbocyclic analog of quercetin, is described in Scheme 1.

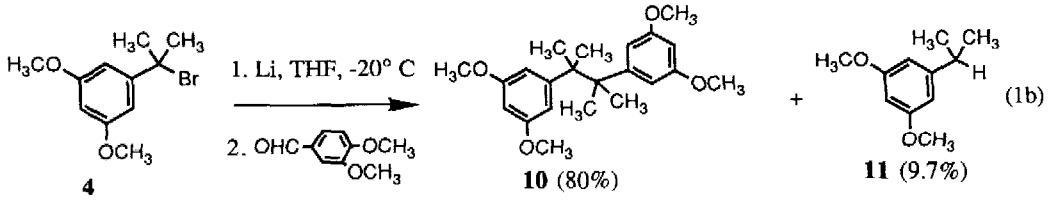
Scheme 1



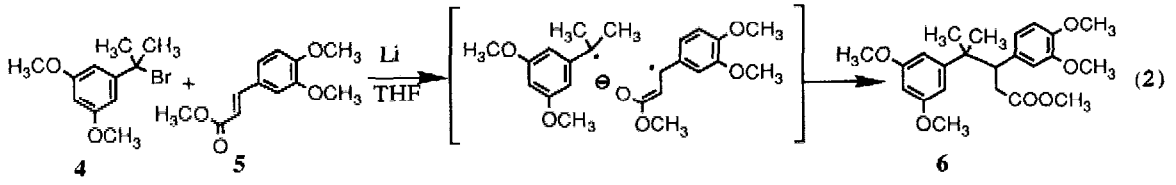

2-(3,5-dimethoxyphenyl)-propan-2-ol, **3**, prepared in 93% yield by the reaction of methyl 3,5-dimethoxybenzoate with 2 equivalents of methylmagnesium bromide in ether at room temperature, was converted to 2-(3,5-dimethoxyphenyl)-2-bromopropane, **4**[4], in 96% yield with HBr in $CH_2Cl_2$ at 0° C in the presence of anhydrous $MgSO_4$. An attempt to generate the tertiary lithium species from **4** by reaction with 4 equivalents of lithium in THF at -20° C was not successful, since subsequent quenching with 3,4-dimethoxybenzaldehyde did not yield any alkylated product **9**. Instead, the reaction generated mainly dimer **10** as well as the reduced product **11** (Eq. 1a and 1b). However, the coupling product **9** can be obtained in 65% yield, if the reaction sequence was altered by addition of a 1:1 mixture of bro-



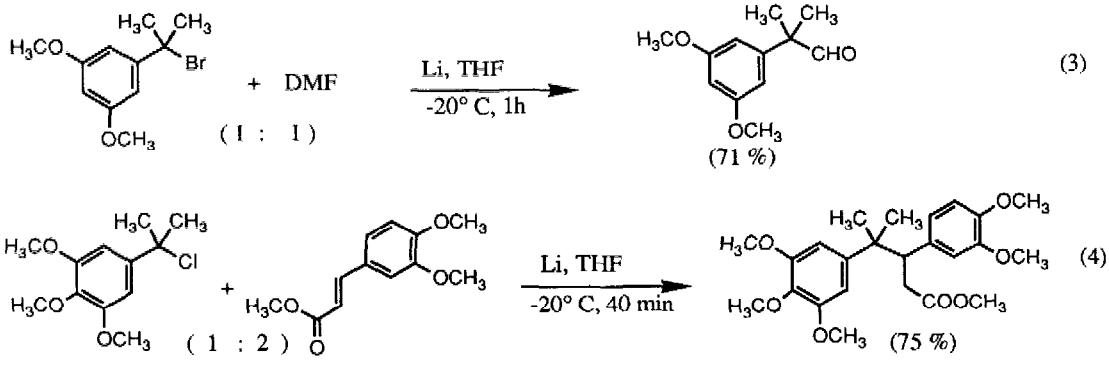

(1a)




mide **4** and 3,4-dimethoxybenzaldehyde into the lithium dispersion, i.e. following the Barbier reaction[5] conditions. Esters have been reported[6] to undergo the Barbier reaction with alkyl bromides in the presence of lithium to form tertiary alcohols. We therefore anticipated that reaction of tertiary bromide **4** with methyl 3,4-dimethoxycinnamate **5** under Barbier conditions, i.e. adding compounds **4** and **5** simultaneously into Li dispersion, might result in the production of a 1,4-coupling adduct **6** (Eq. 2). Such reaction, in THF at -15 ~ -20° C, indeed produced the desired coupling product in 30-40% yield.[7] This yield can be raised to 60-65% if two equivalents of cinnamic ester **5** are used. The mechanism of




such 1,4-addition is not clear, however, we speculate that the coupling of a radical and a radical anion intermediate[5b] is reasonable for this process. Other useful examples of such Barbier type coupling with tertiary halides are shown below (Eq. 3[8] and Eq. 4).



Cyclization of ester **6** with PPA at 80° C for 2 hr. produced a 75-80% yield of carbacyclic flavanoid **7**, which was subsequently treated with isoamylnitrite in conc. HCl and ethanol at room temperature for 24 hr. to give compound **8** in 45-55% yield. Finally, demethylation of compound **8** with $BBr_3$ in $CH_2Cl_2$ produced Sch 37279 (**2**), the carbocyclic analog of quercetin.

Sch 37279 has been found to be a potent inhibitor of 5-lipoxygenase. Detailed biological results of Sch 37279 and its analogs will be published elsewhere.

Acknowledgment

We thank Dr. Richard Friary for suggestions and assistance in the preparation of this manuscript.

Reference and Notes

1. (a) Shozo Yamamoto, Tonihiro Yoshimoto, Masayuki Furukawa, Tokunaru Horie, and Shigekatsu Watanabe-Kohno, *J. Allergy Clin. Immunol.* **1984**,*74*, 349. (b) MJ. Alcaraz and M.L. Ferrandiz, *J. Ethnopharmcology* **1987**,*21*, 209. (c) W.C. Hope, A.F. Welton, C.F. Nagy, and J.W. Coffey, *Fed. Proc.* **1981**,*40*, 1022 .

2. (a) R.M. McMillan, A.J. Millest, K.E. Proudman, and K.B. Taylor, *Brit. J. Pharmacol.* **1986,** *87*, 53P. (b) F. Carey, D. Haworth, A.E. Edmonds, and R.A. Forder, *J. Pharmacol. Methods* **1988**, *20*, 347.

3. "The Flavonoids: Advances in Research", ed. by J.B. Harborne and J.T. Mabry, London, New York, Chapman and Hall, 1975; Chap. 12, pp.681.

4. Compound **4** is a base sensitive and thermally labile molecule. It lost HBr and generated olefin when it was passed through a basic alumina column.

5. (a) C. Blomberg and F.A. Hartog, *Synthesis* **1977**,18. (b) Gérard Molle and Pierre Bauer, *J. Am. Chem. Soc.* **1982**, *104,* 3481.

6. P.J. Pearce, D.H. Richards, and N.F. Scilly, J. Chem. Soc., Perkin Trans. I. **1972**, 1655.

7. A 17% yield of dimer **10** accompanied compound **6.**

8. In contrast to our reaction conditions, ultrasonic irradiation has been applied to the Bouveault reaction, for examples: (a) J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*. **1986**, *27*, 1791. (b) C. Petrier, A.L. Gemal, and J.-L. Luche, *Tetrahedron Lett.* **1982**, *23*, 3361.

9. Spectral data for selected intermediates:

Compound **7**: m.p. 175-176° C; $^1$H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.28 (s, 3 H), 2.87 (dd, 1 H), 3.06 (dd, 1 H), 3.19 (dd, 1 H), 6.41 (d, 1 H), 6.41 (d, 1 H), 6.55 (d, 1H), 6.66 (d, 1 H), 6.7 (dd, 1 H), 6.8 (d, 1 H); $^{13}$C-NMR (CDCl) δ 25.3, 29.0, 39.3, 43.2, 49.4, 55.3, 55.7,55.8, 56.1, 96.3, 102.9, 110.7, 112.5, 115.4, 121.5, 133,9, 147.9, 148.3, 156.9, 162.2, 164.3, 196.0; MS (m/e) (%) 370 (M+) (43), 355 (6), 339 (8), 205 (65), 206 (100), 177 (17); Anal. Calcd. for $C_{22}H_{25}O_5$: C, 71.33; H, 7.08. Found: C, 71.72; H, 7.09.

Compound **8**: m.p. 161-162° C; $^1$H NMR ($CDCl_3$) δ 1.50 (s, 6H), 3.91 (s, 3 H), 3.94 (s, 6 H), 4.50 (s, 3 H), 6.51 (d, 1 H), 6.77 (d, 1 H), 6.82 (dd, 1 H), 6.99 (d, 1H); MS (m/e) (%) 384 ($M^+$) (78), 369 (39), 341 (77), 219 (100), 165 (30); Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.78; H, 6.29. Found: C, 68.91; H, 6.39.

Compound **2**: m.p. > 300° C; $^1$H NMR ($CDCl_3$) δ 1.36 (s, 6H), 6.23 (d, 1 H), 6.39 (dd, 1 H), 6.52 (d, 1 H), 6.58 (d, 1 H), 6.75 (d, 1 H); MS (m/e) (%) 328 ($M^+$) (75), 313 (44), 295 (19), 285 (49), 191 (100), 137 (45).

(Received in USA 10 July 1989)