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An efficient synthesis of novel tetrahydrochromeno[2,3-*b*]chromenes

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ABSTRACT

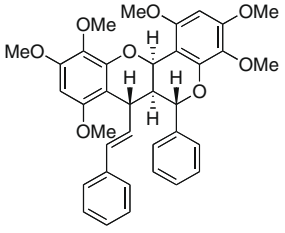
A series of novel tetrahydrochromeno[2,3-*b*]chromenes is synthesized via the acid-catalyzed dimerization reactions of 5-methoxy- or 6-methoxyflavenes. A rational mechanism for the observed rearrangement is proposed.

Phytoestrogens are naturally occurring, non-steroidal compounds present in legumes, grains and seasonings. The daily consumption of phytoestrogens has been suggested to play a protective role against cancer growth.[1] Flavonoids are a particularly widely studied class of phytoestrogens that are found throughout the plant kingdom.

Many flavonoids exist as dimers, comprising identical or non-identical units joined symmetrically or non-symmetrically through various linkages.[2] Despite their interesting range of biological activities, their use as therapeutic agents has been limited by their low abundance in nature, tedious extraction and purification procedures and scarce availability of biological data. Thus, there exists a need for the development of efficient synthetic methodologies for these compounds.

Dependensin (**1**) is a typical example of a dimeric flavonoid isolated from the root bark of the Tanzanian medicinal plant, *Uvaria dependens*, whose crude extract shows potent anti-malarial activity.[3] The heterocyclic ring system present in dependensin, a benzopyrano[4,3-*b*]benzopyran, is quite unique and contains an assortment of functionality and stereochemistry, including two fused benzopyran ring systems, four stereocentres and one *trans* double bond.[3]

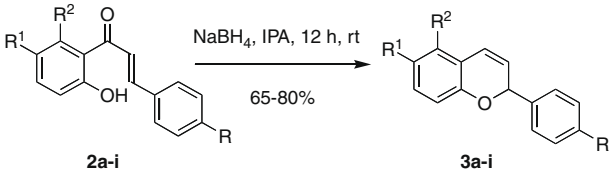
Biosynthetically, dependensin was suggested by Nkunya et al. to originate from the acid-catalyzed dimerization of 5,7,8-trimethoxyflavene, but they were unable to verify this experimentally, obtaining a ring-opened product instead of dependensin.[3] However, our group has recently demonstrated the synthesis of dependensin via this route.[4]



Dependensin (**1**)

As part of our study on the synthesis of these dimeric systems, we have investigated the acid-catalyzed reactions of 5-methoxy-, 6-methoxy- and 7-methoxyflavenes. Interestingly, instead of the expected dependensin analogues, a series of novel tetrahydrochromeno[2,3-*b*]chromenes was obtained from the acid-catalyzed dimerization reactions of 5-methoxy- and 6-methoxyflavenes.

The Claisen–Schmidt condensation of 2′-hydroxy-5′-methoxyacetophenone or 2′-hydroxy-6′-methoxyacetophenone with *para*-substituted benzaldehydes using sodium hydroxide as the base in ethanol furnished the intermediate chalcones **2a–i** in moderate to good yields. These chalcones were then subjected to sodium



2a-i **3a-i**

Scheme 1.

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borohydride reduction[5] in isopropanol to yield the desired 5-methoxy- or 6-methoxyflav-3-enes (**3a–i**) in 65–80% yield (Scheme 1).[6]

In general, we observed that flavenes **3a**, **3d**, **3e**, **3h** and **3i** bearing electron-donating or electronically neutral groups were formed in better yields when compared to the flavenes **3b**, **3c**, **3f** and **3g** bearing electron-withdrawing groups (Table 1). The flavenes so obtained were either low melting white solids or yellow oily residues.

Previous research in our group has demonstrated the acid-catalyzed reaction of 4′,7-diacetoxyflav-3-ene to yield the benzopyrano[4,3-*b*]benzopyran ring system present in the natural product, dependensin.[4] Similar reactions of 7-methoxyflavenes also yielded the same ring system, but the related 4′,5-diacetoxy- and 4′,6-diacetoxyflavenes did not. However, it has been observed that the 6-methoxyflavenes **3a–d** underwent a completely different reaction to yield the tetrahydrochromeno[2,3-*b*]chromenes **4a–d**.

The ^{1}H NMR spectrum of compound **4b** showed the presence of four aliphatic protons corresponding to H11, H11a and H12 between δ 2.84 and δ 3.46. The protons on the *trans* double bond, H_α and H_β appeared as a doublet of doublets and a doublet at δ 6.24 (J = 9.8 Hz, 15.8 Hz) and δ 6.47 (J = 15.8 Hz), respectively.[7] The HMBC experiment showed two-bond and three-bond proton to carbon couplings from the four aliphatic protons to C5a at δ 100.4. DEPT-135 along with a broadband decoupled ^{13}C NMR spectrum indicated the presence of one CH_2 group in the structure.

A single crystal of compound **4b** was obtained for X-ray crystallographic analysis[8] (Fig. 1), further confirming the structure indicated.

This unique structure consists of two symmetrically fused benzopyran units, flanked by the two aromatic rings on either side of the fused ring system together with an exocyclic *trans* double bond.

By correlation of the ^{1}H NMR and ^{13}C NMR spectra, the other dimeric products **4a**, **4c** and **4d** resulting from the acid-catalyzed reactions of 6-methoxyflavenes **3a**, **3c** and **3d** were concluded to contain the same structure (Scheme 2).

The reaction mechanism for the formation of this new dimeric system is thought to involve the protonation of the flavene **5**, followed by ring-opening and formation of the stabilized benzylic carbocation intermediate **6**. A second molecule of the flav-3-ene can isomerize in situ to the corresponding flav-2-ene **7** under acidic conditions and attack the carbocation intermediate **6** giving another stable benzylic intermediate **8**, which can then undergo cyclization to give the dimer **4b** (Scheme 3).

In a similar fashion, the acid-catalyzed reactions of 5-methoxyflav-3-enes **3e–i** gave the tetrahydrochromeno[2,3-*b*]chromenes **9a–e** (Scheme 4). The dimerization reaction mechanism is believed to be similar to the pathway taken by the 6-methoxyflavenes.

The dimeric flavonoids **4a–d** and **9a–e** were obtained in moderate to good yields (Table 2). The identity and purity of all compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, thin layer chromatography and elemental analyses.

Table 1
Synthesis of 5-methoxy- and 6-methoxyflavenes

Chalcone	R^1	R^2	R	Flavene	Yield[a] (%)
2a	OMe	H	H	**3a**	72
2b	OMe	H	Br	**3b**	65
2c	OMe	H	Cl	**3c**	68
2d	OMe	H	Me	**3d**	74
2e	H	OMe	H	**3e**	77
2f	H	OMe	Br	**3f**	70
2g	H	OMe	Cl	**3g**	70
2h	H	OMe	OMe	**3h**	80
2i	H	OMe	Me	**3i**	79

[a] Yield of isolated pure product.

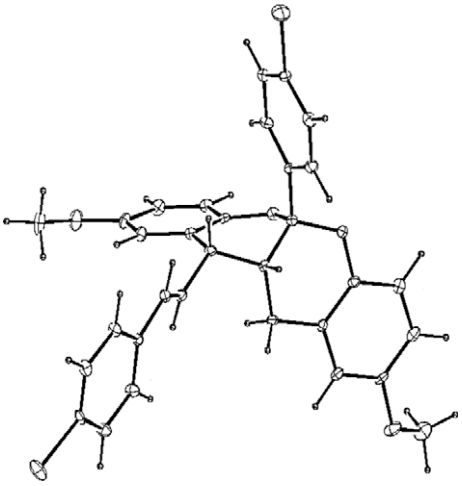
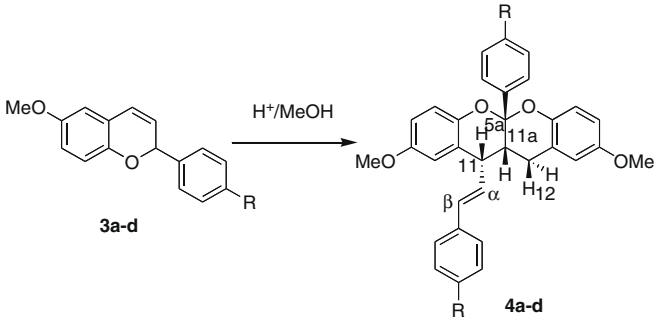
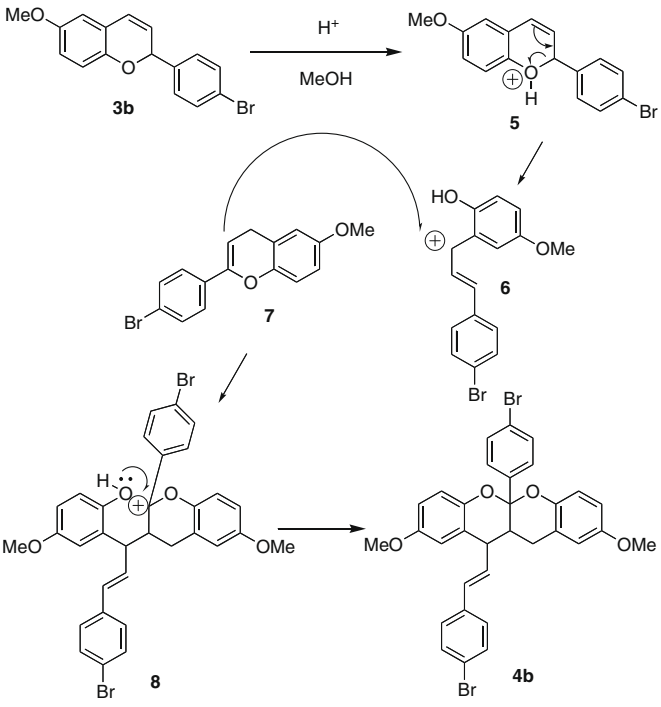


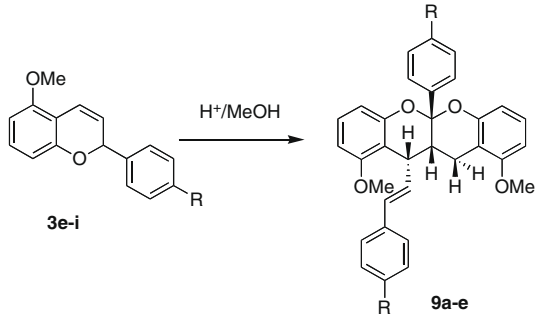
Figure 1. ORTEP diagram of compound **4b**.



Scheme 2.



Scheme 3.



Scheme 4.

Table 2
Dimerization products of 5-methoxy- and 6-methoxyflavenes

Flavene	R	Chromeno-chromene	Yield[a] (%)
3a	H	**4a**	70
3b	Br	**4b**	73
3c	Cl	**4c**	74
3d	Me	**4d**	72
3e	H	**9a**	75
3f	Br	**9b**	69
3g	Cl	**9c**	72
3h	OMe	**9d**	58
3i	Me	**9e**	56

[a] Yield of isolated pure product.

In summary, an efficient methodology for the synthesis of a series of tetrahydrochromeno[2,3-*b*]chromenes has been developed via the acid-catalyzed dimerization reactions of 6-methoxy- and 5-methoxyflavenes.

Acknowledgements

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6. *Representative procedure for 5-methoxy- and 6-methoxy-flav-3-enes* **3b**: The chalcone **2b** (1.0 g, 3.00 mmol) was dissolved in isopropanol (25 mL) at 50 °C, and $NaBH_4$ (9.00 mmol) was slowly added. The reaction mixture was then cooled to room temperature and allowed to stir overnight. The solvent was evaporated, ice was added and the resulting solution was acidified using 10% glacial AcOH to pH 5. The solution was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. Purification of the residue by column chromatography over silica gel (20% CH_2Cl_2/hexane) eluted the flavene **3b** as a white solid (0.62 g, 65%); mp 98–100 °C; UV (MeOH): λ_{max} 202 (ε 34,171 cm^{-1} M^{-1}), 232 (39,101), 330 (4329) nm; IR (KBr): ν_{max} 3441, 3006, 2958, 2931, 2831, 1608, 1580, 1490, 1462, 1427, 1271, 1219, 1152, 1028, 971, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.76 (s, 3H, CH_3O), 5.80 (dd, *J* = 3.0, 10.9 Hz, 1H, H3), 5.83 (dd, *J* = 1.5 Hz, 3.0 Hz, 1H, H2), 6.52 (dd, *J* = 1.5 Hz, 10.9 Hz, 1H, H4), 6.61 (d, *J* = 3.0 Hz, 1H, H5), 6.68 (dd, *J* = 3.0 Hz, 8.7 Hz, 1H, H7), 6.74 (d, *J* = 8.7 Hz, 1H, H8), 7.32 (d, *J* = 8.3 Hz, 2H, H2′, H6′), 7.49 (d, *J* = 8.3 Hz, 2H, H3′, H5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.6 (CH_3O), 76.0 (C2), 111.8 (C5), 114.6 (C7), 116.5 (C8), 121.8 (C4a), 122.2 (C4′), 124.5 (C4), 125.1 (C3), 128.7 (C2′, C6′), 131.7 (C3′, C5′), 139.6 (C1′), 146.7 (C8a), 154.1 (C6); MS (ESI) *m*/*z* $[M+1]^+$ 316.95 (100%); Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13. Found: C, 60.82; H, 4.26.
7. *Representative procedure for the synthesis of dimer* **4b**: The flavene **3b** (0.10 g, 0.32 mmol) was dissolved in MeOH (20 mL), 10 drops of acid (10 M HCl, TFA or glacial AcOH) were added and the solution was heated to 60–70 °C for 12 h. The solvent was partially removed under reduced pressure, and EtOAc was added. The organic layer was washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and evaporated. Purification of the crude product by column chromatography over silica gel (50% CH_2Cl_2/hexane) eluted the dimer **4b** as a white solid (0.15 g, 73%); mp 212–214 °C; UV (MeOH): λ_{max} 203 (ε 61,384 cm^{-1} M^{-1}), 220 (35,949), 230 (28,486), 263 (34,167), 291 (17,870), 299 (12,616) nm; IR (KBr): ν_{max} 3444, 3006, 2929, 2833, 1615, 1489, 1464, 1427, 1275, 1230, 1200, 1154, 1041, 971, 951, 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 2.84 (s, 3H, H11a, H12), 3.46 (dd, *J* = 3.4 Hz, 9.8 Hz, 1H, H11), 3.70 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 6.24 (dd, *J* = 9.8 Hz, 15.8 Hz, 1H, H_α), 6.47 (d, *J* = 15.8 Hz, 1H, H_β), 6.55 (d, *J* = 2.3 Hz, 1H, H10), 6.60 (d, *J* = 3.0 Hz, 1H, H1), 6.72 (dd, *J* = 3.0 Hz, 8.6 Hz, 1H, H3), 6.80 (dd, *J* = 2.3 Hz, 8.3 Hz, 1H, H8), 6.87 (d, *J* = 8.6 Hz, 1H, H4), 6.96 (d, *J* = 8.3 Hz, 1H, H7), 7.24 (d, *J* = 8.6 Hz, 2H, H2″, H6″), 7.37 (d, *J* = 8.3 Hz, 2H, H3′, H5′), 7.41 (d, *J* = 8.3 Hz, 2H, H2′, H6′), 7.44 (d, *J* = 8.6 Hz, 2H, H3″, H5″); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 23.6 (C12), 37.8 (C11a), 42.3 (C11), 55.5 (CH_3O), 55.6 (CH_3O), 100.4 (C5a), 113.6 (C1), 113.7 (C10), 114.0 (C3), 114.4 (C8), 117.2 (C7), 117.5 (C4), 121.3 (C4′), 121.6 (C12a), 122.1 (C10a), 123.1 (C4″), 125.8 (C2″, C6″), 127.8 (C2′, C6′), 128.5 (C_α), 131.6 (C3′, C5′), 131.7 (C3″, C5″), 133.2 (C_β), 135.4 (C1′), 139.5 (C1″), 145.5 (C4a), 145.9 (C6a), 154.2 (C9), 154.3 (C2); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{26}Br_2O_4Na$ $(M+Na)^+$ 655.0098. Found 655.0086; Anal. Calcd for $C_{32}H_{26}Br_2O_4$: C, 60.59; H, 4.13. Found: C, 60.32; H, 4.13.
8. Crystallographic data for the structure of compound **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 769425. The X-ray crystal structure was obtained by Don Craig, Crystallography Laboratory, Analytical Centre, The University of New South Wales, Sydney, Australia.