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Synthesis and characterization of chiral enantiopure bis-chromanones: a Baylis–Hillman approach

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Abstract

Enantiopure bis-chromanones were prepared from (*S*)-Binol and bromo esters via a Baylis–Hillman approach. Chiroptical studies indicate that the two-naphthyl units of the chromanone system are non-coplanar.

Keywords: Chiral bis-chromanone; Baylis–Hillman adduct; (*S*)-Binol; ORD; CD; Photoluminescence

1. Introduction

One of the most fascinating aspects of modern synthetic organic chemistry is the synthesis of chiral compounds that play a vital role in biology and in materials such as liquid crystals. The chromanone structure is abundant in natural products possessing a broad array of biological activity.[1] Due to their favorable anti-tumor and anti-inflammatory properties, flavanones have been investigated as selective estrogen receptor modulators.[2] A limited number of strategies have been developed for the asymmetric synthesis of flavanones, such as resolution of related alcohols[3] or substitution reactions.[4]

Several methods have been proposed to prepare racemic 4-chromanones,[5–9] but only a few are available for the synthesis of the same non-racemic compounds starting from enantiopure synthons,[10] by using an external chiral ligand[11] or by incorporating an enzymatic step.[12] A few examples of enantioenrich or enantiopure 3-hydroxychromanones have also been described.[13,14] Recently, asymmetric syntheses of flavanone and chromanone derivatives from α-substituted chalcones via intramolecular conjugate addition catalyzed with chiral thioureas were described.[15] The Baylis–Hillman reaction[16] has attracted the attention of organic chemists for preparing synthetically useful multifunctional molecules which have been successfully employed in various stereoselective syntheses.

Recently, we reported the synthesis of fluorescent bis-chromanones possessing methylene-dinaphthyl units along with 3-arylidene moieties from the Baylis–Hillman adducts showing antibacterial activity.[17] (*S*)-Binol is well known for the strong dependence of its optical activity due to the repulsion between the two-naphthyl rings, and hence a series of modifications of bridged binaphthyl diether linkages have been reported.[18] To the best of our knowledge, there are no reports on the synthesis of bis-chromanones containing an optically active Binol moiety. We report herein the synthesis of enantiopure bis-chromanones **6a–d** containing a chiral (*S*)-Binol as the core unit starting from bromo esters **2a–d**. All the enantiopure bis-chromanones synthesized exhibited optical and fluorescence properties.

Scheme 1 shows the synthesis of bis-chromanones **6a–d** from (*S*)-Binol (**3**). Compound **4a** was obtained in 63% yield by the etherification of (*S*)-Binol with bromo ester **2a** in the presence of K_2CO_3 in dry DMF at 60 °C for 48 h. The ^{1}H NMR spectrum of compound **4a** displayed a sharp singlet at δ 3.61 ppm for the methoxy protons. The oxymethylene protons appeared as two doublets integrating for four protons at δ 4.65 and δ 4.85 (2d,

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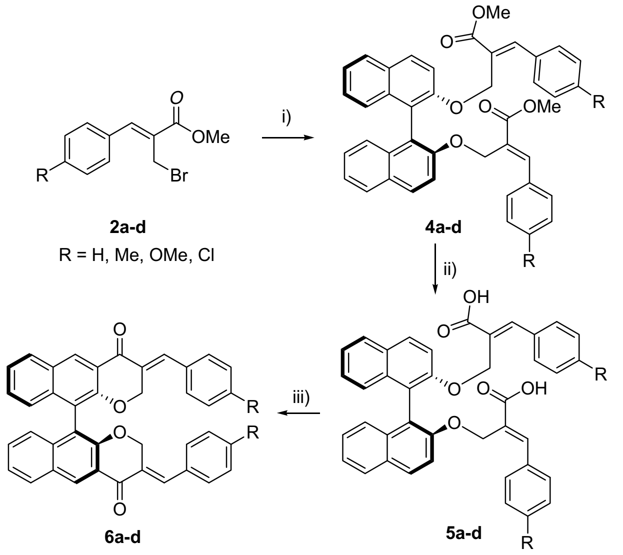


Scheme 1. Synthesis of bis-chromanones **6a–d**. Reagents and conditions: (i) (*S*)-Binol **3**, K_2CO_3, DMF, 60 °C, 48 h; (ii) KOH/H_2O, 1,4-dioxane, rt, 24 h; (iii) TFAA, 1,2-dichloroethane, 80 °C, 8 h.

$J = 10.6$ Hz). The two vinylic protons of the α,β-unsaturated system were deshielded significantly and appeared as a doublet at δ 7.95 (d, $J = 10.8$ Hz). In the ^{13}C NMR spectrum of **4a**, a signal at δ 167.5 ppm corresponded to the ester carbonyl carbon, with the oxymethylene and methoxy carbons appearing at δ 64.9 and δ 52.2, respectively.

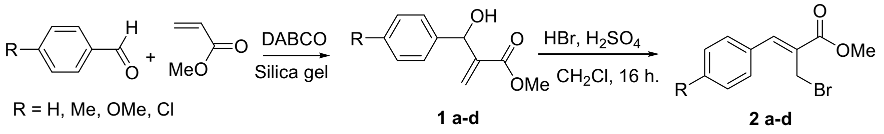
The saponification of **4a** with aqueous KOH in 1,4-dioxane afforded the diacid **5a** in 79% yield. In the ^{1}H NMR spectrum of **5a**, the oxymethylene protons appeared as two doublets integrating for four protons at δ 4.66 and δ 4.86 (d, $J = 10.0$ Hz); the two vinylic protons appeared as a doublet at δ 7.98 (d, $J = 9.0$ Hz). The ^{13}C NMR spectrum of **5a** showed signals at δ 64.9 and δ 172.7 corresponding to oxymethylene and carbonyl carbons.

The cyclization of **5a** with 2.1 equiv of trifluoroacetic anhydride in 1,2-dichloroethane under reflux gave bis-chromanone **6a** in 71% yield. In the ^{1}H NMR spectrum of **6a**, the oxymethylene protons appeared as two doublets integrating for four protons at δ 5.20 and δ 5.31 (2d, $J = 1.2$, 1.5 Hz). The two vinylic protons of the α,β unsaturated systems appeared as a singlet at δ 8.82. In the ^{13}C NMR spectrum of bis-chromanone **6a**, the chromanone carbonyl carbons appeared at δ 183.1 and the oxymethylene carbon appeared at δ 67.9. The structure of bis-chromanone **6a** was further confirmed by a molecular ion peak at m/z 570 in the mass spectrum and also from satisfactory analytical data.

Encouraged by the synthesis of bis-chromanone **6a**, we focused our attention on the synthesis of bis-chromanones containing electron-donating substituents such as R = CH_3, OCH_3 and Cl.[19] Thus, aryl aldehydes containing CH_3, OCH_3, and Cl at the *para* position were used to prepare Baylis–Hillman adducts[16] **1b–d** as shown in Scheme 2. These adducts were converted to their corresponding bromo esters **2b–d** by treatment with 47% HBr in the presence of a catalytic amount of concentrated H_2SO_4 in dichloromethane at room temperature for 16 h according to the reported procedure.[20] Bis-chromanones **6b–d** were synthesized by the cyclization of the corresponding diacids **5b–d** and characterized from spectral and analytical data.

UV–visible and photoluminescence (PL) spectra of chiral bis-chromanones **6a–d** were measured in chloroform. The absorption and emission maxima of ($\lambda_{\max}$) of the chiral bis-chromanones are given in Table 1. All the chiral bis-chromanones showed UV–visible absorption maxima at 329–345 nm. This is due to the $\pi \rightarrow \pi^*$ electron transition of the carbonyl group in the chromanone moiety. Additionally, the UV spectra of **6c** and **6d** also showed shoulders at 285 and 293 nm, and 296 and 319 nm, respectively. In the photoluminescence spectra of chiral bis-chromanones **6a–d** when excited at 331 nm, peak maxima were observed at 500 and 525 nm. Similar to the UV-spectra, the photoluminescence spectra of both the chiral bis-chromanones **6c** and **6d** also showed shoulders at 475 nm. A relatively large Stokes shift of ~170 nm was observed between the absorption and emission maxima. This large shift may be associated with the changes in the molecular structures of the bis-chromanones upon excitation, for example, (i) a change in the conformation of the α-arylidene chromanone ring from one half chair to the other; (ii) a change in the geometry of the exocyclic olefin from cis to trans and vice versa.

Specific rotation, ORD and CD studies were carried out on bis-chromanones **6a–d** in chloroform as a solvent; the results obtained are summarized in Table 2. These structures can be expected to be rigid and optically active. This was apparent from the optical rotation of the compounds. The CD curves of the bis-chromanones (Fig. 1) indicated three absorptions due to the presence of three different chromophores in the chromanone moiety. UV and photoluminescence studies indicated a single $\lambda_{\max}$ for **6a** and **6b**, whereas for **6c** and **6d**, two additional shoulders appeared at lower wavelength. These absorptions were weak and did not appear in the UV spectra. The absorption intensity



Scheme 2. Synthesis of bromo esters **2a–d**

Table 1
Optical properties of chiral bis-chromanones **6a**–**d**

Bis-chromanone **6**	1×10^{-4} M/$CHCl_3$	
	λ_{max}, Abs. (nm)	λ_{max} PL[a] (nm)
a	329	525
b	335	525
c	285, 293, 345	475, 500
d	296, 319, 332	475, 525

[a] Excitation at 331 nm.

Table 2
Specific rotations of chiral bis-chromanones **6a**–**d**

Bis-chromanone 6	$[\alpha]_D^{25}$ in $CHCl_3$ at 25 °C	Molecular weight (g/mol)	Molar rotation
a	−201	570	−1145.70
b	−202	598	−1207.96
c	−205	630	−1291.50
d	−207	638	−1322.73

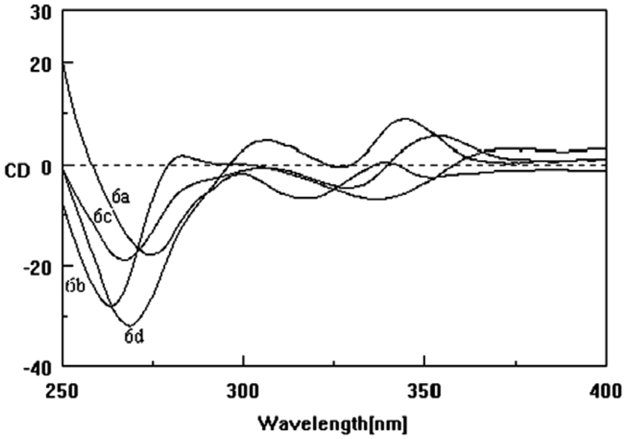


Fig. 1. Circular dichroism spectra of chiral bis-chromanones **6a**–**d**.

indicated by the shoulders is very weak because they are of high-energy transitions. Shoulder absorption may be due to the presence of canonical forms of the chromanones as shown in Figure 2. Such resonance is facilitated by the n–π overlap in **6c** and **6d** by the OCH_3 and Cl substituents. The increase in optical rotation from **6a** to **6d** although small can be explained by steric hindrance due to the *para* substituents and the electrostatic repulsion between the positively charged *para* substituents. The change in the λ_{max} from **6a** to **6d** can be explained on the basis of delocalization and inductive effects of substituents.

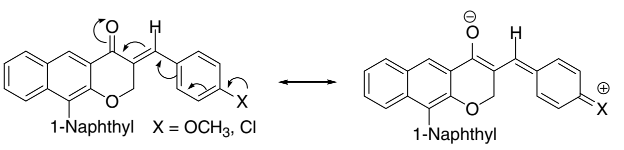


Fig. 2. Canonical forms of chromanone.

In conclusion, we have investigated the Baylis–Hillman reaction for the synthesis of chiral bis-chromanones containing a (*S*)-Binol unit. All the chiral bis-chromanones exhibited photoluminescence in the blue light region. Due to steric repulsion in the highly rigid chromanone system, the conformational mobility decreased. This is reflected in the optical rotations of the products as measured by specific rotation and CD experiments.

2. Experimental

2.1. General procedure for the synthesis of compounds **4a–d**

A mixture of (*S*)-Binol (1.0 mmol) and bromo esters **2a**–**d** (2.1 mmol) was stirred in the presence of K_2CO_3 (5 mmol) in dry DMF (20 ml) at 60 °C for 48 h. The reaction mixture was poured into 200 ml of water and stirred for 1 h and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and finally with brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude compound was purified by column chromatography using a mixture of ethyl acetate and hexane as an eluent.

2.2. General procedure for the synthesis of compounds **5a–d**

Diesters **4a**–**d** were dissolved in 25 ml of dioxane and hydrolyzed using 10% aqueous KOH at room temperature for 24 h. The reaction mixture was acidified with cold 2.0 N HCl solution. The precipitated product was filtered and thoroughly washed with cold water and dried in a $CaCl_2$ desiccator.

2.3. General procedure for the synthesis of bis-chromanones **6a–d**

Diacids **5a**–**d** (1.0 mmol) were treated with trifluoroacetic anhydride (TFAA) (2.1 mmol), and the reaction mixture was refluxed in 1,2-dichloroethane for 8 h. The solvent was removed under vacuum and the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $NaHCO_3$ solution (3 × 100 ml) and brine, then dried over anhydrous $MgSO_4$ and the solvent evaporated. The crude compound was purified by column chromatography using a mixture of ethyl acetate and hexane as an eluent.

Bis-chromanone **6a**: Yield: 71%; IR (KBr, cm^{-1}) 1665; ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (d, 2H, $J = 1.2$ Hz), 5.31 (d, 2H, $J = 1.5$ Hz), 7.21–8.06 (m, 20H), 8.82 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.9, 118.2, 123.0, 124.3, 124.5, 128.6, 129.1, 129.6, 130.0, 130.5, 131.4, 134.2, 137.0, 138.0, 154.1 and 183.1; MS (EI) 570 [M^+]; mp: 230–233 °C; $C_{40}H_{26}O_4$ Anal. Calcd: C, 84.19; H, 4.59. Found: C, 84.25; H, 4.50.

Bis-chromanone **6b**: Yield: 69%; IR (KBr, cm^{-1}) 1668; ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 6H), 5.11 (d, 2H, $J = 10.5$ Hz), 5.17 (d, 2H, $J = 10.8$ Hz), 7.05–7.93 (m, 18H) and 8.68 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

21.3, 68.0, 118.3, 123.3, 124.7, 125.0, 129.2, 128.6, 129.4, 130.2, 130.5, 131.7, 137.1, 140.0, 154.3, 183.0; MS (EI) m/z 598 [M^+]; mp: 200–203 °C; $C_{42}H_{30}O_4$ Anal. Calcd: C, 84.26; H, 5.05. Found: C, 84.20; H, 5.16.

Bis-chromanone **6c**: Yield: 64%; IR (KBr, cm^{-1}): 1662; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 6H), 5.17 (d, 2H, $J = 6.0$), 5.23 (d, 2H, $J = 6.6$ Hz), 6.76–7.94 (m, 18H), 8.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.0, 113.5, 114.2, 118.1, 123.2, 124.7, 126.9, 129.3, 130.2, 132.2, 133.2, 136.9, 137.8, 154.1, 160.8, 183.1; MS (EI) 630 [M^+]; mp: 178–181 °C; $C_{42}H_{30}O_6$ Anal. Calcd: C, 79.98; H, 4.79. Found: C, 79.84; H, 4.70.

Bis-chromanone **6d**: Yield: 66%; IR (KBr, cm^{-1}) 1667; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (d, 2H, $J = 10.4$ Hz), 5.22 (d, 2H, $J = 10.8$ Hz), 6.82–7.94 (m, 18H), 8.61 (s, 2H);^{13}C NMR (75 MHz, $CDCl_3$): δ 68.0, 118.2, 120.0, 123.3, 124.9, 126.9, 128.5, 129.5, 130.2, 130.5, 131.4, 132.0, 133.3, 134.8, 137.0, 138.5, 154.1, 183.1; MS (EI) 638 [M^+]; mp: 163–166 °C; $C_{40}H_{24}Cl_2O_4$ Anal. Calcd: C, 75.12; H, 3.78. Found: C, 75.19; H, 3.69.

References and notes

1. (a) *The Flavonoids. Advances in Research Since 1980*; Harborne, J. B., Ed.; Chapman and Hall: New York, 1988; (b) Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **1995**, *12*, 639; (c) Chang, L. C.; Kinghorn, A. D. In *Bioactive Compounds from Natural Sources: Isolation Characterization and Biological Properties*; Tringali, C., Ed.; Taylor & Francis Ltd: London, 2001. Chapter 5; (d) *Flavonoids: Chemistry, Biochemistry and Applications*; Andersen, Ø. M., Markham, K. R., Eds.; Taylor & Francis Ltd: London, 2006.
2. (a) Chen, H. Y.; Dykstra, K. D.; Birzin, E. T.; Frisch, K.; Chan, W.; Yang, Y. T.; Mosley, R. T.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1417; (b) Tan, Q.; Blissard, T. A.; Morgan, J. D.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Pai, L.-Y.; Hayes, E. C.; DaSilva, C. A.; Warrier, S.; Yudkovitz, J.; Wilkinson, H. A.; Sharma, N.; Fitzgerald, P. M. D.; Li, S.; Colwell, L.; Fisher, J. E.; Adamski, S.; Reszka, A. A.; Kimmel, D.; DiNinno, F.; Freedman, P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1675.
3. (a) Ramadas, S.; Krupadanam, G. L. D. *Tetrahedron: Asymmetry* **2004**, *15*, 3381; (b) Rakosi, M.; Tokes, A. L.; Bognar, R. *Tetrahedron Lett.* **1970**, *26*, 2305.
4. (a) Noda, Y.; Wantanabe, M. *Helv. Chim. Acta* **2002**, *85*, 3473; (b) Hodgetts, K. J. *Tetrahedron* **2005**, *61*, 6860.
5. (a) Nakib, T. A.; Bezjak, V.; Meegan, M. J.; Chandy, R. *Eur. J. Med. Chem.* **1990**, *25*, 55; (b) Santhosh, K. C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 7727; (c) Mandal, P.; Venkateswaran, R. V. *J. Chem. Res. (S)* **1998**, 88.
6. (a) Barlocco, D.; Cignarella, G.; Curzu, M. M. *Synthesis* **1985**, 876; (b) Jain, A. C.; Tyagi, O. D.; Saksena, R. *Indian J. Chem.* **1989**, 15; (c) Valenti, P.; Belluti, F.; Rampa, A.; Bisi, A. *Synth. Commun.* **1999**, *29*, 3895; (d) Draper, R. W.; Hu, B.; Iyer, R. V.; Li, X.; Lu, Y.; Rahman, M.; Vater, E. J. *Tetrahedron* **2000**, *56*, 1811.
7. (a) Loubinoux, B.; Colin, J. L.; Antonot-Colin, B. *Tetrahedron* **1987**, *43*, 93; (b) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* **1990**, *46*, 2031; (c) Srikanth, N.; Kon, O.-L.; Ng, S.-C.; Sim, K.-Y. *J. Chem. Res. (S)* **1997**, 202.
8. Lipinski, C. A.; Aldinger, C. E.; Beyer, T. A.; Bordne, J.; Burdi, D. F.; Bussolotti, D. L.; Inskeep, P. B.; Siegel, T. W. *J. Med. Chem.* **1992**, *35*, 2169.
9. (a) Okuro, K.; Alpe, H. *J. Org. Chem.* **1997**, *62*, 1566; (b) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125.
10. (a) Loiodice, F.; Longo, A.; Bianco, P.; Tirtirella, V. *Tetrahedron: Asymmetry* **1995**, *6*, 1001; (b) Woydowski, K.; Liebscher, J. *Synthesis* **2000**, 1444; (c) Tanada, Y.; Mori, K. *Eur. J. Org. Chem.* **2001**, 1963.
11. (a) Vicario, J. L.; Badia, D.; Dominguez, E.; Rodriguez, M.; Carrillo, L. *Tetrahedron Lett.* **2000**, *41*, 8297; (b) Vicario, J. L.; Badia, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489.
12. Loubinoux, B.; Viriot-Chauveau, C.; Sinnes, J. L. *Tetrahedron Lett.* **1992**, *33*, 2145.
13. (a) Davis, F. A.; Chen, B. C. *J. Org. Chem.* **1993**, *58*, 1751; (b) Woydowski, K.; Ziemer, B.; Liebscher, J. *J. Org. Chem.* **1999**, *64*, 3489; (c) Hansen, K. B.; Rabbat, P.; Springfield, S. A.; Devine, P. N.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 8743.
14. (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298; (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899.
15. Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.
16. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (b) Ciganek, E. *Org. React.* **1997**, *51*, 201; (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
17. Rajan, Y. C.; Kanakam, C. C.; Selvam, S. P.; Murugaesan, K. *Tetrahedron Lett.* **2007**, *48*, 8562.
18. Van Es, J. J. G. S.; Biemans, H. A. M.; Meijer, E. W. *Tetrahedron: Asymmetry* **1997**, *8*, 1825.
19. Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *J. Chem. Soc., Chem. Commun.* **1998**, 1639.
20. Bucholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.