Synthesis of Isochroman and Tetrahydroisoquinoline Derivatives from Baylis-Hillman Adducts by Radical Cyclization

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Recently we were interested in radical cyclizations of modified Baylis-Hillman adducts.[1,2] We reported the synthesis of various heterocyclic compounds[1] including 2,3-dihydrobenzofuran derivatives using radical cyclization process.[2] Meantime we reasoned that six-membered heterocyclic compounds such as isochroman[3] and tetrahydroisoquinoline[4] derivatives could be prepared by radical cyclization from suitably modified Baylis-Hillman adducts (vide infra, Scheme 1).

Isochroman and tetrahydroisoquinoline derivatives are important backbone in many biologically interesting substances and their synthesis have been studied extensively.[3-5] Especially, appropriately substituted tetrahydroisoquinolines are an important class of natural and synthetic compounds, which exhibit various biological activities including antitumor, antibacterial, antiplasmodial and β-adrenergic receptor antagonism.[4,5]

As an initial trial we examined the synthesis of isochroman derivative **4a** as shown in Scheme 1. The starting material **3a** was synthesized from the reaction of Baylis-Hillman acetate **1a** and 2-bromobenzyl alcohol (**2a**) in good yield (82%). With this compound **3a** in our hand we examined the radical cyclization under the influence of *n*-Bu_3SnH/AIBN in benzene and we obtained desired 4,4-disubstituted isochroman derivative **4a** in 89% yield (Scheme 1). We did not observe the formation of seven-membered ring compound or reduction product. Most of the radical cyclizations of aryl radical toward tethered unsaturated ester occurred at the β-position of unsaturated moiety.[6] However, we observed the selective formation of six-membered ring compound **4a** presumably due to the special stability of the intermediate benzylic radical as in our previous synthesis of 2,3-dihydrobenzofuran.[2] Encouraged by the results we prepared starting materials **3b-f** (*vide infra*, Table 1 and Scheme 2) and carried out radical cyclizations under the same conditions, and the results are summarized in Table 1.

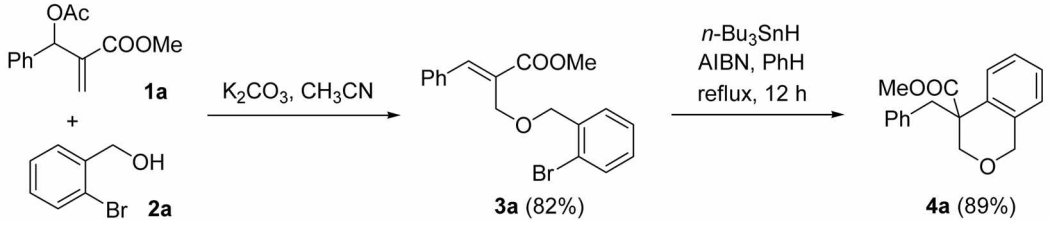
As shown we prepared three isochroman derivatives **4a-c** (entries 1-3) and two tetrahydroisoquinolines **4d** and **4e** (entries 4 and 5) in good yields (85-89%). However, unfortunately, radical cyclization was not completed in the case of nitrile derivative **3f** and we isolated isochroman **4f** and reduction compound **5** together (1:1 mixture based on ^1H NMR) as a mixture. The separation of **4f** and **5** was very difficult by column chromatography due to their same mobility on TLC. At this stage the reason for low yield of cyclized compound **4f** is not clear.

Synthesis of starting materials **3a-e** required somewhat different synthetic approaches depending upon the substrates as shown in Scheme 2. Synthesis of **3a** and **3b** was carried out by the reaction of Baylis-Hillman acetate **1a** and 2-bromobenzyl alcohol (**2a**) in the presence of K_2CO_3 in acetonitrile (79-82%). The compound **3c** was synthesized from cinnamyl alcohol **1b**[7] and 5-bromo-6-bromomethyl-1,3-benzodioxole (**2b**) in moderate yield (56%) by using potassium *tert*-butoxide in DMF. The compounds **3d** and **3e** were prepared from the reaction of rearranged *aza*-Baylis-Hillman adduct **1c**[7] and **2b** or 2-bromobenzyl bromide (**2c**) in the presence of K_2CO_3 in DMF in good yields (81-91%). Nitrile derivative **3f** was prepared by the reaction of **2a** and the corresponding Baylis-Hillman acetate in 79% yield by following the same procedure for the synthesis of **3a**.

In summary, we disclosed the synthesis of some isochroman and tetrahydroisoquinoline derivatives by the radical cyclization process starting from the Baylis-Hillman adducts.

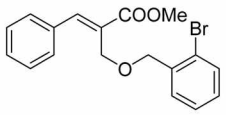
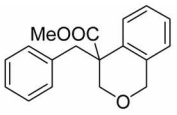
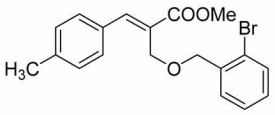
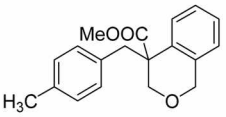
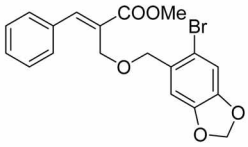
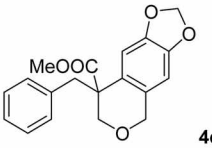
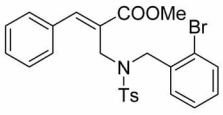
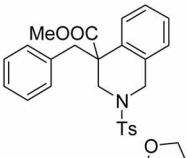
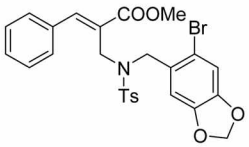
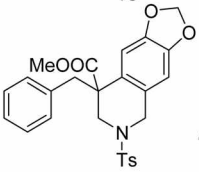
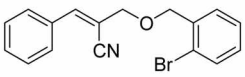
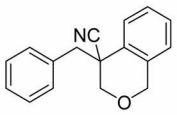
Experimental Section

Typical procedure for the synthesis of 3a. To a stirred solution of Baylis-Hillman acetate (**1a**, 200 mg, 0.85 mmol)

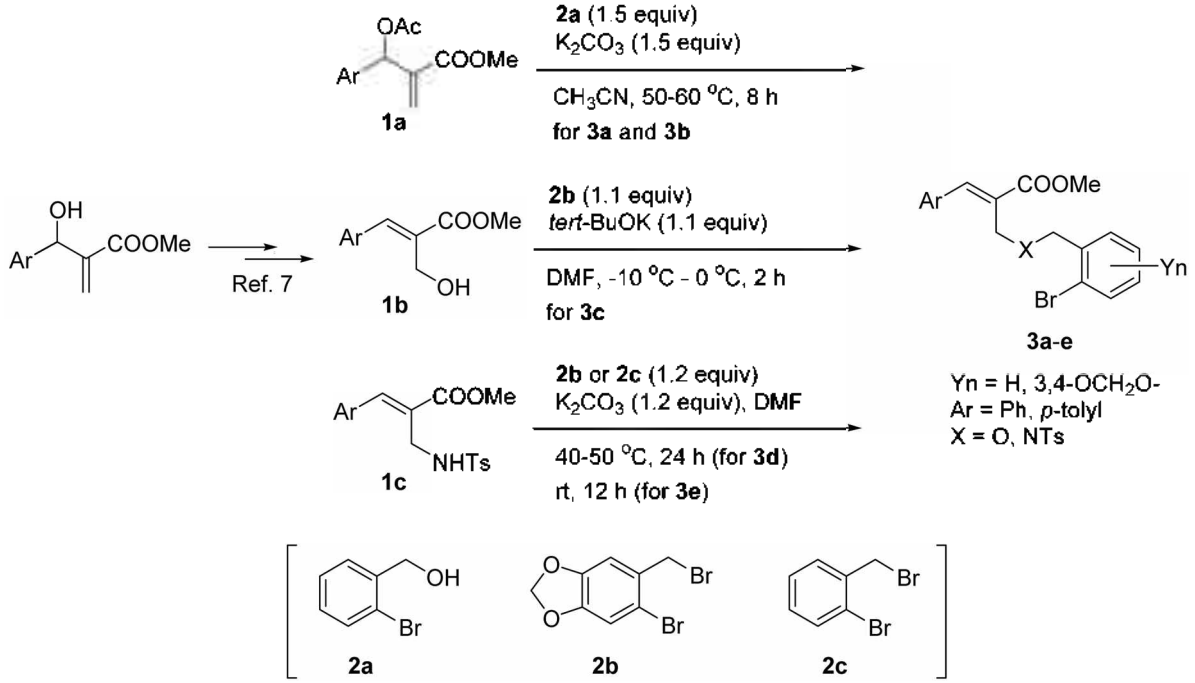


Scheme 1

Table 1. Synthesis of isochroman and tetrahydroisoquinoline derivatives

Entry	Substrate[a]		Time (h)[b]	Product (%)	
1		**3a** (82)	12		**4a** (89)
2		**3b** (79)	48		**4b** (85)
3		**3c** (56)	14		**4c** (88)
4		**3d** (91)	10		**4d** (86)
5		**3e** (81)	3		**4e** (89)
6		**3f** (79)	12		**4f** : **5** = 1 : 1 (97)[c]

[a]Synthesis of starting materials is summarized in Scheme 2. [b]Conditions: *n*-Bu_3SnH (1.5 equiv), AIBN (cat), benzene, reflux, given time. [c]Based on ^1H NMR spectrum.



Scheme 2

and **2a** (239 mg, 1.28 mmol) in CH_3CN (3 mL) was added K_2CO_3 (177 mg, 1.28 mmol), and the reaction mixture was stirred for 8 h at 50-60 °C. After the normal aqueous workup and column chromatographic purification process (hexanes/EtOAc = 15:1) we obtained **3a** as colorless oil, 251 mg (82%). Synthesis of compounds **3b**, **3d**, **3e** and **3f** was carried out similarly and the spectroscopic data are as follows.

Compound **3a**: colorless oil; 82%; IR (film) 3518, 2953, 1732, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 4.41 (s, 2H), 4.70 (s, 2H), 7.12-7.18 (m, 1H), 7.28-7.33 (m, 1H), 7.36-7.39 (m, 3H), 7.51-7.57 (m, 4H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.17, 64.86, 72.21, 123.07, 127.37, 128.42, 128.52, 129.07, 129.37, 129.78, 129.85, 132.53, 134.62, 137.37, 144.97, 168.02; ESIMS *m/z* 361 (M^++1). Anal Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74. Found: C, 60.13; H, 4.55.

Compound **3b**: colorless oil; 79%; IR (film) 3521, 2952, 1747, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 3.83 (s, 3H), 4.42 (s, 2H), 4.71 (s, 2H), 7.12-7.16 (m, 1H), 7.17-7.20 (m, 2H), 7.28-7.33 (m, 1H), 7.45-7.48 (m, 2H), 7.52-7.57 (m, 2H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.40, 52.14, 64.99, 72.17, 123.08, 127.39, 127.48, 129.05, 129.31, 129.79, 130.02, 131.84, 132.54, 137.46, 139.78, 145.17, 168.21; ESIMS *m/z* 375 (M^++1).

Compound **3d**: colorless oil; 91%; IR (film) 2958, 1705, 1344, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.56 (s, 3H), 4.37 (s, 2H), 4.38 (s, 2H), 6.99-7.04 (m, 1H), 7.12-7.16 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.34-7.49 (m, 7H), 7.64 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.47, 45.08, 51.97, 52.13, 122.15, 126.39, 127.19, 127.41, 128.48, 128.50, 129.19, 129.27, 129.64, 129.72, 132.21, 133.90, 135.71, 136.07, 143.45, 144.41, 167.41; ESIMS *m/z* 514 (M^++1). Anal Calcd for $C_{25}H_{24}BrNO_4S$: C, 58.37; H, 4.70; N, 2.72. Found: C, 58.12; H, 4.95; N, 2.58.

Compound **3e**: colorless oil; 81%; IR (film) 2925, 1714, 1479, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.62 (s, 3H), 4.25 (s, 2H), 4.36 (s, 2H), 5.89 (s, 2H), 6.83, (s, 1H), 6.96 (s, 1H), 7.28-7.35 (m, 7H), 7.65-7.68 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.48, 44.78, 51.81, 52.01, 101.58, 109.35, 112.11, 112.50, 126.34, 127.41, 128.46, 129.11, 129.31, 129.64, 129.69, 133.90, 135.76, 143.46, 144.33, 147.36, 167.40 and one carbon is overlapped; ESIMS *m/z* 558 (M^++1).

Compound **3f**: colorless oil; 79%; IR (film) 3492, 3062, 2864, 2214, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 2H), 4.69 (s, 2H), 7.13-7.21 (m, 2H), 7.28-7.36 (m, 1H), 7.39-7.44 (m, 3H), 7.51-7.58 (m, 2H), 7.75-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.68, 71.84, 107.89, 117.62, 122.84, 127.57, 128.87, 129.02, 129.32, 129.36, 130.67, 132.62, 132.92, 136.58, 145.12; ESIMS *m/z* 328 (M^++1).

Typical procedure for the synthesis of 3c. To a stirred mixture of **1b** (40 mg, 0.21 mmol) and **2b** (67 mg, 0.23 mmol) in DMF (0.5 mL) was added *t*-BuOK (26 mg, 0.23 mmol) at −10 °C, and the reaction mixture was stirred at around 0 °C for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc = 15:1) we obtained **3c** as colorless oil, 48 mg (56%). Spectroscopic data of compound **3c** are as follows.

Compound **3c**: colorless oil; 56%; IR (film) 2949, 2895, 1714, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3H), 4.37 (s, 2H), 4.60 (s, 2H), 5.96 (s, 2H), 7.00 (s, 1H), 7.02 (s, 1H), 7.37-7.39 (m, 3H), 7.51-7.55 (m, 2H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.17, 64.67, 72.08, 101.67, 109.78, 112.56, 113.59, 128.38, 128.51, 129.38, 129.84, 130.58, 134.61, 144.96, 147.38, 147.79, 167.98; ESIMS *m/z* 405 (M^++1).

Typical procedure for the synthesis of 4a. A stirred mixture of **3a** (80 mg, 0.22 mmol), *n*-Bu_3SnH (97 mg, 0.33 mmol), AIBN (cat) in benzene (5 mL) was heated to reflux for 12 h. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 15:1) we obtained **4a** as colorless oil, 55 mg (89%).

Compound **4a**: colorless oil; 89%; IR (film) 2950, 1734, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16 (d, J = 13.5 Hz, 1H), 3.50 (d, J = 13.5 Hz, 1H), 3.67 (s, 3H), 3.90 (d, J = 11.7 Hz, 1H), 4.13 (d, J = 11.7 Hz, 1H), 4.81 (d, J = 0.6 Hz, 2H), 6.99-7.03 (m, 1H), 7.13-7.16 (m, 2H), 7.17-7.26 (m, 5H), 7.52-7.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.48, 50.08, 52.10, 68.71, 69.11, 124.39, 126.63, 126.68, 127.08, 127.78, 128.10, 130.43, 133.92, 135.16, 138.81, 173.46; ESIMS *m/z* 283 (M^++1). Anal Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.43; H, 6.61.

Compound **4b**: colorless oil; 85%; IR (film) 2952, 1731, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 3.11 (d, J = 13.5 Hz, 1H), 3.46 (d, J = 13.5 Hz, 1H), 3.66 (s, 3H), 3.90 (d, J = 11.7 Hz, 1H), 4.14 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 0.9 Hz, 2H), 6.99-7.00 (m, 1H), 7.05 (s, 4H), 7.19-7.25 (m, 2H), 7.56-7.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.98, 43.07, 49.98, 52.04, 68.69, 69.06, 124.33, 126.60, 127.01, 127.76, 128.80, 130.24, 133.59, 133.92, 135.20, 136.17, 173.47; ESIMS *m/z* 297 (M^++1).

Compound **4c**: colorless oil; 88%; IR (film) 2951, 1728, 1484, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.10 (d, J = 13.5 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.68 (s, 3H), 3.84 (d, J = 11.7 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.95 (d, J = 1.2 Hz, 1H), 6.45 (s, 1H), 7.06 (s, 1H), 7.13-7.16 (m, 2H), 7.19-7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.64, 49.95, 52.17, 68.84, 69.19, 101.00, 104.17, 107.98, 126.76, 127.66, 128.17, 128.20, 130.36, 136.72, 146.41, 146.75, 173.58; ESIMS *m/z* 327 (M^++1).

Compound **4d**: colorless oil; 86%; IR (film) 2954, 1733, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.30 (d, J = 13.5 Hz, 1H), 3.31 (d, J = 13.5 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.65 (s, 3H), 3.93 (d, J = 14.7 Hz, 1H), 4.39 (d, J = 14.7 Hz, 1H), 7.02-7.05 (m, 1H), 7.14-7.28 (m, 7H), 7.34 (d, J = 8.4 Hz, 2H), 7.47-7.50 (m, 1H), 7.71 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.51, 44.25, 48.62, 49.14, 52.05, 52.25, 126.47, 126.79, 126.86, 127.37, 128.03 (2C), 128.61, 129.73, 130.89, 131.26, 132.14, 134.38, 136.21, 143.94, 173.01; ESIMS *m/z* 436 (M^++1). Anal Calcd for $C_{25}H_{25}NO_4S$: C,

68.94; H, 5.79; N, 3.22. Found: C, 68.75; H, 5.88; N, 3.15.

Compound **4e**: colorless oil; 89%; IR (film) 2924, 1730, 1487, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.24 (d, J = 13.8 Hz, 1H), 3.25 (d, J = 12.0 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 3.54 (d, J = 12.0 Hz, 1H), 3.64 (s, 3H), 3.83 (d, J = 14.4 Hz, 1H), 4.24 (d, J = 14.4 Hz, 1H), 5.89 (d, J = 1.2 Hz, 1H), 5.93 (d, J = 1.2 Hz, 1H), 6.46 (s, 1H), 7.01 (s, 1H), 7.22-7.24 (m, 5H), 7.34 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.50, 44.38, 48.69, 49.02, 51.91, 52.26, 101.19, 105.86, 108.41, 124.89, 126.93, 127.69, 128.02, 128.09, 129.73, 130.81, 132.14, 136.12, 143.95, 146.62, 146.96, 173.05; ESIMS m/z 480 (M^++1).

Compound **4f** and compound **5** were not separated, however, we could assign their ^1H NMR data as follows: Compound **4f**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18 (d, J = 12.0 Hz, 1H), 3.23 (d, J = 12.0 Hz, 1H), 3.85 (d, J = 11.4 Hz, 1H), 4.11 (d, J = 11.4 Hz, 1H), 4.88 (d, J = 15.0 Hz, 1H), 4.90 (d, J = 15.0 Hz, 1H), 7.25-7.79 (m, 9H); Compound **5**: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.26 (s, 2H), 4.63 (s, 2H), 7.17 (s, 1H), 7.74-7.79 (m, 10H).

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References and Notes

1. For our recent papers on the radical cyclizations using modified Baylis-Hillman adducts, see: (a) Gowrisankar, S.; Kim, S. J.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4419-4422. (b) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 3105-3108. (c) Gowrisankar, S.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 5785-5788. (d) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 2097-2100. (e) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 929-932. (f) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859-4863.
2. Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440-1442.
3. For the synthesis and biological activities of isochroman moiety-containing compounds, see: (a) Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954-961. (b) Grigg, R.; Savic, V.; Sridharan, V.; Terrier, C. *Tetrahedron* **2002**, *58*, 8613-8620. (c) Rakhimov, R. G.; Galin, F. Z.; Tomilov, Y. V.; Le, V. T. *Russ. J. Org. Chem.* **2002**, *38*, 1629-1634. (d) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 7471-7474. (e) Anwar, U.; Fielding, M. R.; Grigg, R.; Sridharan, V.; Urch, C. J. *J. Organometal. Chem.* **2006**, *691*, 1476-1487.
4. For the synthesis and biological activities of tetrahydroisoquinoline moiety-containing compounds, see: (a) Smissman, E. E.; Reid, J. R.; Walsh, D. A. *J. Med. Chem.* **1976**, *19*, 127-131. (b) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017-9019. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Masciocchi, N.; Sottocornola, S. *Org. Lett.* **2006**, *8*, 4521-4524. (d) Raju, B. C.; Neelakantan, P.; Bhalerao, U. T. *Tetrahedron Lett.* **2004**, *45*, 7487-7489. (e) Klumpp, D. A.; Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Dang, H. *J. Org. Chem.* **2004**, *69*, 8108-8110. (f) Chandrasekhar, S.; Mohanty, P. K.; Harikishan, K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877-878. (g) Navarro-Vazquez, A.; Rodriguez, D.; Martinez-Esperon, M. F.; Garcia, A.; Saa, C.; Dominguez, D. *Tetrahedron Lett.* **2007**, *48*, 2741-2743. (h) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527-1528. (i) Martinez, E.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **2001**, *57*, 1973-1979. (j) Pedrosa, R.; Andres, C.; Iglesias, J. M.; Obeso, M. A. *Tetrahedron* **2001**, *57*, 4005-4014.
5. For the synthesis and biological activities of isochromans and tetrahydroisoquinolines having methylene dioxy moiety, see: (a) Fishlock, D.; Williams, R. M. *Org. Lett.* **2006**, *8*, 3299-3301. (b) Baxendale, I. R.; Ley, S. V. *Ind. Eng. Chem. Res.* **2005**, *44*, 8588-8592. (c) Machocho, A. K.; Bastida, J.; Codina, C.; Vildomat, F.; Brun, R.; Chhabra, S. C. *Phytochemistry* **2004**, *65*, 3143-3149. (d) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336-12337. (e) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1995**, *60*, 1013-1019. (f) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959-6964.
6. For the radical cyclizations involving Baylis-Hillman adducts, see: (a) Singh, V.; Batra, S. *Tetrahedron Lett.* **2006**, *47*, 7043-7045. (b) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369-3372. (c) Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939-942. (d) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283-9285. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612-1620. (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913-1914.
7. Synthesis of starting materials **1b** and **1c**, please see: (a) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 413-414. (b) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209-6211. (c) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417-425.