Synthesis of Highly Functionalized 3,4-Dihydro-2*H*-pyrans from Baylis-Hillman Acetates†

Jae Nyoung Kim,* Jeong Mi Kim, Ka Young Lee, and Saravanan Gowrisankar

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
Received April 6, 2004

Key Words : 3,4-Dihydro-2*H*-pyrans, Baylis-Hillman acetates, Conjugate addition

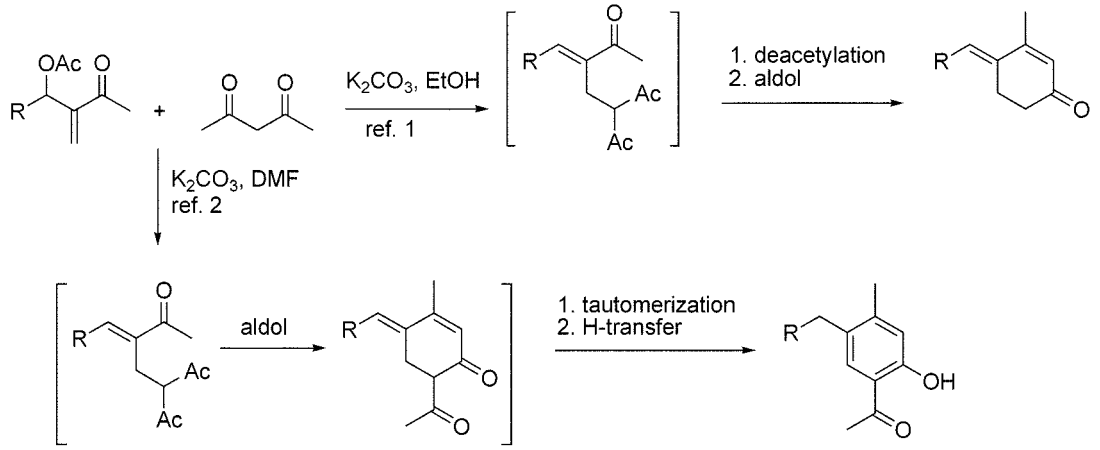
Chamakh and Amri have reported the reaction of Baylis-Hillman acetates and β-diketones in the presence of K_2CO_3 in ethanol and they obtained alkylidene cyclohexenone derivatives (Scheme 1).[1] This novel reaction has been extended by us for the synthesis of 2-hydroxyacetophenone derivatives by exchanging the solvent from ethanol to DMF (Scheme 1).[2]

We envisioned that we could synthesize another type of cyclohexenone derivatives containing exo-methylene moiety[3] by utilizing the Amri's protocol (Scheme 2). The reaction of the Baylis-Hillman acetate **1a** and 2,4-pentanedione (**2a**) in the presence of DABCO in aqueous THF would give the corresponding S_N2 type substitution product **3a** *via* the corresponding DABCO salt of the Baylis-Hillman acetate.[4] The intermediate **3a** would undergo the successive deacetylation and aldol type condensation in ethanol in the presence of K_2CO_3, and would give the methylene cyclohexenone compound **5a** as shown in Scheme 2.

However, during the synthesis of **3a** we obtained dihydropyran derivative **4a** as the minor (18%, vide infra). Dihydropyran systems are found in many natural products such as FR 182877[5a] and a number of iridoid alkaloids[5b] and can be used as the important synthetic intermediates.[6] However, the synthesis required somewhat complex procedures and is limited to rather simple dihydropyran skeletons.[6,7] In these respects we intended to examine the improved synthesis of **4a** from **1a** or from **3a**, and to report herein the results.

As a first trial we examined the reaction of the Baylis-Hillman acetate **1a** and 2,4-pentanedione (**2a**) in the presence of DABCO (1.3 equiv.) in aqueous THF at room temperature. The reaction gave the desired S_N2 product **3a** in 44% isolated yield and another compound **4a** in 18% isolated yield. The structure of **4a** was found to be as 3,5-diacetyl-6-methyl-4-phenyl substituted dihydropyran derivative. The yield of **4a** could be improved by elevating the reaction temperature (40-50 °C) to 42%. The Baylis-Hillman acetates **1b** and **1c** gave the similar results (entries 2 and 3 in Table 1). The reaction of **1a** and **2a** under the influence of K_2CO_3 in ethanol showed the formation of 4-benzylidene-2-cyclohexenone derivative as reported by Amri.[1]

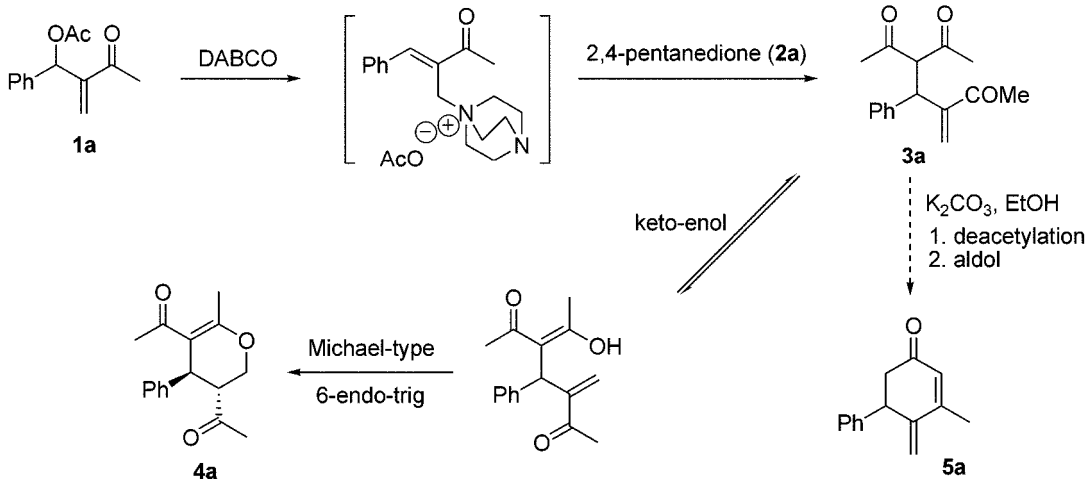
For the Baylis-Hillman acetates **1d-f**, which was derived from methyl acrylate, ethyl acrylate, and acrylonitrile we could not obtain the dihydropyrans **4d-f** directly by using DABCO. Instead, the S_N2 type products **3d-f** were formed as the major (80-89% isolated yields, see Table 1 and Scheme 3) from the Baylis-Hillman acetates **1d-f** and **2a** or ethyl acetoacetate (**2b**). Then, we examined the following Michael type cyclization of **3d-f** under the influence of K_2CO_3 in alcohol solvent and obtained the desired dihydropyrans **4d-f**. As shown in Table 1, we used catalytic amounts of K_2CO_3 for the synthesis of **4d** and **4f** in order to minimize the



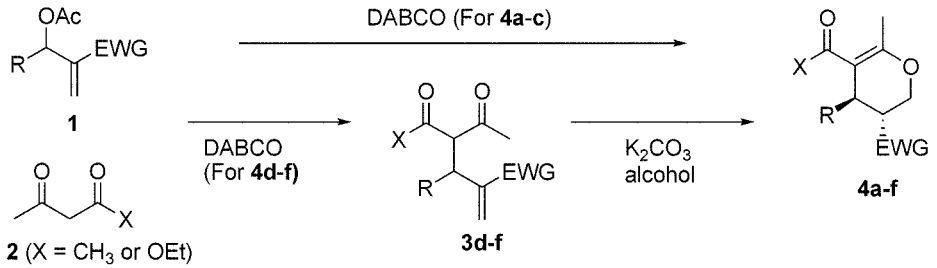
Scheme 1

†This paper is dedicated to Prof. Yong Hae Kim for his outstanding achievements in organic chemistry.

*Corresponding Author. Phone: +82-62-530-3381, e-mail: kimjn@chonnam.ac.kr



Scheme 2



Scheme 3

unwanted deacetylation process. The deacetylation process is not a severe problem for the cyclization of **3e** and we used 1.1 equivalents of K_2CO_3 for the synthesis of **4e**.

The mechanism for the formation of **4** from **3** can be regarded as cyclization of the enol-form of **3** *via* the 6-endo-trig mode as depicted in Scheme 2. The structure of **4** was confirmed from their spectroscopic data. ^1H, ^{13}C, DEPT (**4c**), ^1H-^1H COSY (**4c**), ^1H-^{13}C COSY (**4c**), and NOE (**4b**) experiments. NOE experimental results of **4b** are summarized in Figure 1. The relative stereochemistry of the substituents of **4** at the 3- and 4-position was thought to be as *anti* relationship.[8] The proton at the 4-position appeared as a broad singlet in all cases. Thus, we cannot say exactly about the relative stereochemistry between the substituents of 3- and 4-position, however, we tentatively propose the relative stereochemistry as *anti* relationships.[8]

In summary, we have synthesized some synthetically useful 3,4,5,6-tetrasubstituted 3,4-dihydro-2*H*-pyrans from Baylis-Hillman acetates in moderate yields. Further studies on the conformational characteristics of the dihydropyrans and the selective synthesis of the exo-methylene cyclohexenone derivatives are currently undergoing and will be reported in due course.

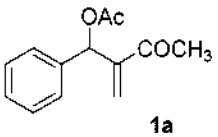
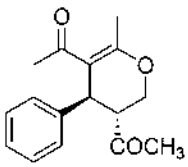
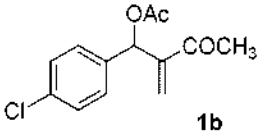
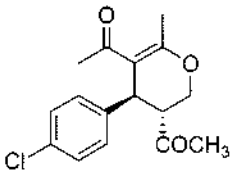
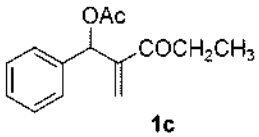
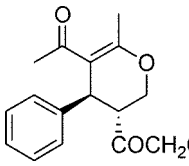
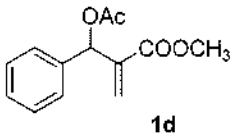
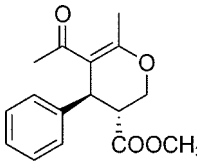
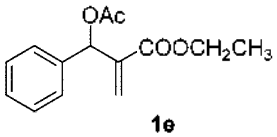
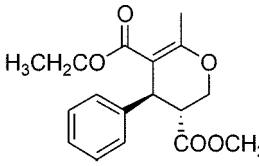
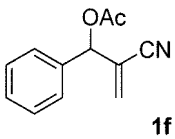
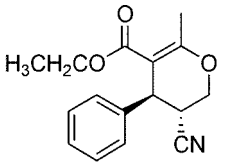
Experimental Section

Typical procedure for the synthesis of 4a: A solution of **1a** (436 mg, 2 mmol) and DABCO (291 mg, 2.6 mmol) in aqueous THF (THF/H_2O = 3 : 1, 10 mL) was stirred for 10 min. at room temperature. Complete salt formation was observed. To the reaction mixture 2,4-pentanedione (200 mg, 2 mmol) was added and heated to 40-50 °C for 2 days. After usual aqueous workup and column chromatographic purification process (hexane/ether = 5 : 1) analytically pure **4a** was isolated in 42% yield, 217 mg.

Typical procedure for the synthesis of 4d: A solution of **1d** (468 mg, 2 mmol) and DABCO (448 mg, 4 mmol) in aqueous THF (THF/H_2O = 3 : 1, 10 mL) was stirred for 10 min. at room temperature. Complete salt formation was observed. To the reaction mixture 2,4-pentanedione (200 mg, 2 mmol) was added and heated to 40-50 °C for 24 h. After usual aqueous workup and column chromatographic purification process (hexane/ether = 5 : 1) we could obtain the corresponding S_N2 type product **3d** in 83% yield, 455 mg. To a stirred solution of **3d** (274 mg, 1 mmol) in methanol (5 mL) was added K_2CO_3 (14 mg, 0.1 mmol) and heated to 40-50 °C for 3 h. After usual aqueous workup and column chromatographic purification process (hexane/ether = 5 : 1) analytically pure **4d** was isolated in 30% yield, 83 mg. The spectroscopic data of prepared compounds (**4a-c**, **3d-f**, and **4d-f**) are as follows.

4a (42%): IR (KBr) 1712, 1674, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.23 (d, J = 1.2 Hz, 3H), 2.24 (s, 3H), 2.74 (app q, J = 3.0 Hz, 1H), 3.97 (dd, J = 11.4 and 3.0 Hz, 1H), 4.38 (ddd, J = 11.4, 3.0, and 1.6 Hz, 1H), 4.45 (br s, 1H), 7.16-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.46, 28.03,

Table 1. Synthesis of Dihydropyran Derivatives **4a-f** from B-H Acetates

Entry	Substrate	Conditions	Products (% yield)
1	 **1a**	1. DABCO (1.3 equiv.) H_2O / THF, rt, 10 min. 2. **2a** (1.0 equiv.) 40-50 °C, 48 h	 **4a** (42)[a]
2	 **1b**	1. DABCO (2.0 equiv.) H_2O / THF, rt, 10 min. 2. **2a** (1.0 equiv.) rt, 72 h	 **4b** (44)[a]
3	 **1c**	1. DABCO (1.1 equiv.) H_2O / THF, rt, 10 min. 2. **2a** (1.0 equiv.) 40-50 °C, 48 h	 **4c** (30)[a]
4	 **1d**	1. DABCO (2.0 equiv.) **2a** (1.0 equiv.) H_2O / THF, 40-50 °C 24 h, **3d** (83%) 2. K_2CO_3 (0.1 equiv.) MeOH, 40-50 °C, 3 h	 **4d** (30)[b]
5	 **1e**	1. DABCO (2.0 equiv.) **2b** (1.0 equiv.) H_2O / THF, 40-50 °C 24 h, **3e** (89%)[c] 2. K_2CO_3 (1.1 equiv.) EtOH, reflux, 30 min.	 **4e** (62)
6	 **1f**	1. DABCO (2.0 equiv.) **2b** (1.1 equiv.) H_2O / THF, 40-50 °C 24 h, **3f** (80%)[c] 2. K_2CO_3 (0.1 equiv.) EtOH, 40-50 °C, 48 h	 **4f** (63)[d]

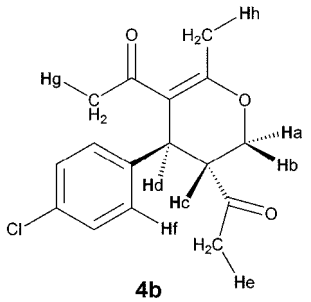
[a]The corresponding addition-elimination product **3** was formed as the minor product. [b]Deacetylated compound of **3d** was formed as the side product. [c]Diastereomeric mixture.[8] [d]The other stereoisomer was mixed in about 20% in ^{1}H NMR.

29.37, 38.88, 53.64, 62.57, 111.51, 127.05, 128.01, 128.96, 143.97, 163.89, 199.59, 205.91; HRMS calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1263.

4b (44%): mp 84-85 °C; IR (KBr) 1712, 1674, 1577 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 2.15 (d, J = 0.9 Hz, 3H), 2.23 (s, 3H), 2.91 (app dd, J = 2.7 and 2.4 Hz, 1H), 3.75 (dd, J = 11.7 and 3.0 Hz, 1H), 4.36 (br s, 1H), 4.46 (dt, J = 11.7 and 2.1 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 20.43, 27.59, 29.46, 37.00, 51.96, 62.20, 111.27, 128.53, 129.93, 131.29, 143.60, 163.50, 198.00, 206.06; HRMS calcd for $C_{16}H_{17}ClO_3$ 292.0866, found 292.0867.

4c (30%): IR (KBr) 1712, 1674, 1577 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 6.6 Hz, 3H), 2.01 (s, 3H), 2.23 (d, J = 1.2 Hz, 3H), 2.36-2.47 (m, 1H), 2.50-2.63 (m, 1H), 2.76 (app q, J = 3.6 Hz, 1H), 3.97 (dd, J = 11.4 and 3.3 Hz, 1H), 4.33 (ddd, J = 11.4, 3.9, and 1.2 Hz, 1H), 4.43 (br s, 1H), 7.15-7.35 (m, 5H); DEPT results were inserted in ^{13}C NMR data. ^{13}C NMR ($CDCl_3$) δ 7.58 (CH_3), 20.35 (CH_3), 29.40 (CH_3), 33.98 (CH_2), 39.32 (CH), 53.07 (CH), 62.90 (CH_2), 111.84 (C), 127.00 (CH), 127.93 (CH), 128.91 (CH), 143.91 (C), 163.55 (C), 199.60 (CO), 208.73 (CO); HRMS calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1417.

4d (30%): IR (KBr) 1739, 1674, 1577 cm^{-1}; ^{1}H NMR



4b

irradiation	NOE increment (%)
Ha (δ = 4.46)	Hb (23.4), Hc (3.3), He (3.3)
Hb (δ = 3.75)	Ha (23.8), Hc (4.1), Hf (2.8)
Hc (δ = 2.91)	Ha (2.1), Hb (2.6), Hd (2.4), He (2.1), Hf (2.4)
Hd (δ = 4.36)	Hc (2.4), He (1.1), Hf (4.2), Hg (3.8)

Figure 1

($CDCl_3$) δ 2.03 (s, 3H), 2.28 (d, J = 1.2 Hz, 3H), 2.80 (app q, J = 2.7 Hz, 1H), 3.76 (s, 3H), 3.89 (dd, J = 11.1 and 3.0 Hz, 1H), 4.40 (ddd, J = 11.1, 2.7, and 1.5 Hz, 1H), 4.48 (br s, 1H), 7.20-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.63, 29.22, 39.55, 45.79, 52.41, 62.41, 110.66, 127.11, 128.04, 128.91, 143.71, 164.31, 171.55, 199.33; HRMS calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1207.

4e (62%): IR (KBr) 1736, 1705, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.34 (d, J = 1.2 Hz, 3H), 2.75 (app q, J = 3.3 Hz, 1H), 3.88-4.02 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.35 (ddd, J = 11.1, 3.6, and 1.5 Hz, 1H), 4.45 (br s, 1H), 7.15-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.89, 14.12, 19.93, 38.94, 45.97, 59.61, 61.12, 63.09, 102.74, 126.50, 127.70, 128.42, 144.64, 164.97, 167.62, 171.24; HRMS calcd for $C_{18}H_{22}O_5$ 318.1467, found 318.1441.

4f (63%): IR (KBr) 2245, 1704, 1624 cm^{-1}; The *syn* diastereomer appeared in the ^{1}H NMR spectra in about 20% and we could not separate them in pure state. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 3H), 2.43 (d, J = 1.2 Hz, 3H), 2.98 (app q, J = 2.7 Hz, 1H), 3.88-4.05 (m, 3H), 4.20 (ddd, J = 11.4, 3.3, and 1.8 Hz, 1H), 4.35 (br s, 1H), 7.17-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.85, 19.95, 31.90, 40.54, 59.98, 61.61, 101.34, 118.74, 127.48, 127.67, 128.78, 142.04, 165.32, 166.72; HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1210.

3d (83%): ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H), 2.20 (s, 3H), 3.69 (s, 3H), 4.56 (d, J = 12.3 Hz, 1H), 4.79 (d, J = 12.3 Hz, 1H), 5.73 (s, 1H), 6.29 (s, 1H), 7.17-7.30 (m, 5H).

3e (89%): 1 : 1 diastereomeric mixture; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 1.5H), 1.18-1.26 (m, 4.5H), 1.97 (s, 1.5H), 2.28 (s, 1.5H), 3.91 (q, J = 7.2 Hz, 1H), 4.07-4.20 (m, 3H), 4.35 (d, J = 12.3 Hz, 0.5H), 4.38 (d, J = 12.3 Hz, 0.5H), 4.70 (d, J = 12.3 Hz, 0.5H), 4.72 (d, J = 12.3 Hz, 0.5H), 5.67 (s, 0.5H), 5.75 (s, 0.5H), 6.27 (s, 0.5H), 6.30 (s, 0.5H), 7.18-7.27 (m, 5H).

3f (80%): 3 : 2 diastereomeric mixture: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H, major), 1.30 (t, J = 7.2 Hz, 3H, minor), 2.06 (s, 3H, minor), 2.38 (s, 3H, major), 3.93 (qd, J = 7.2 and 3.0 Hz, 2H, major), 4.23 (qd, J = 7.2 and 0.9 Hz, 2H, minor), 4.31-4.45 (m, 2H, major + minor), 5.89 (s, 1H, major), 5.90 (s, 1H, minor), 5.94 (s, 1H, major), 5.95 (s, 1H, minor), 7.25-7.37 (m, 5H, major + minor).

Acknowledgments. This work was supported by the grant (R05-2003-000-10042-0) from the Basic Research Program of the Korea Science & Engineering Foundation. Spectroscopic data was obtained from the Korea Basic Science Institute, Kwangju branch.

References

1. Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375.
2. Kim, J. N.; Im, Y. J.; Kim, J. M. *Tetrahedron Lett.* **2002**, *43*, 6597.
3. For the exo-methylene cyclohexenones, see: (a) Davis, B. R.; Johnson, S. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2840. (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197. (c) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.
4. For the introduction of nucleophile in a S_N2 fashion via using the DABCO salt concept, see: (a) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85. (b) Im, Y. J.; Kim, J. M.; Mun, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 349. (c) Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 328. (d) Gong, J. H.; Kim, H. R.; Ryu, E. K.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 789. (e) Basavaiah, D.; Jaganmohan, R.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811 and further references cited therein.
5. Dihydropyran skeleton in natural products, see: (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1986**, *108*, 4974 and references cited therein.
6. Dihydropyrans as synthetic intermediates, see: (a) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585. (b) Venkataraman, H.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 3509. (c) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419.
7. Synthesis of dihydropyrans, see: (a) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751. (b) Wolinsky, J.; Hauer, H. S. *J. Org. Chem.* **1969**, *34*, 3169. (c) Ito, N.; Etoh, T.; Hagiwara, H.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1571. (d) Padwa, A.; Filipkowski, M. A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 588.
8. Construction of dihydropyran skeleton via the hetero Diels-Alder reaction and spectroscopic studies, see: (a) Aben, R. W. M.; de Gelder, R.; Scheeren, H. W. *Eur. J. Org. Chem.* **2002**, 3126. (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3059. (c) Juhl, K.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498. (d) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (e) Koehler, A. N.; Shamji, A. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 8420.