# Preparation of 1-aryl-substituted isoindoline derivatives by sequential Morita–Baylis–Hillman and intramolecular Diels–Alder reactions†

**Kristen Nicole Clary, Masood Parvez and Thomas George Back***

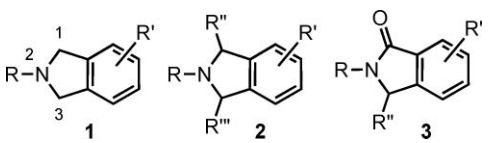
*Received 13th October 2008, Accepted 12th December 2008*
*First published as an Advance Article on the web 11th February 2009*
**DOI: 10.1039/b817954a**



Aldimines underwent Morita–Baylis–Hillman reactions with dienes activated by sulfonyl or nitrile groups. The *N*-allyl or propargyl derivatives of the products were subjected to intramolecular Diels–Alder cycloadditions to produce the corresponding partly saturated 1-arylisoindoline derivatives. The cycloadducts in the nitrile-activated *N*-propargyl series were aromatized by base-mediated elimination of HCN to afford 1-arylisoindolines, which were in turn oxidized to the corresponding 3-arylisoindolin-1-ones.

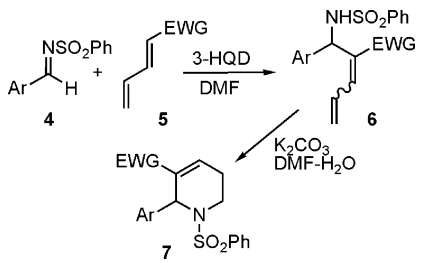
## Introduction

Isoindolines (**1**) and their congeners are privileged structures because of their diverse medicinal and other biological activities. For example, compounds of this class have been reported to inhibit the enzymes prolyl dipeptidase DPP8 and DPP9,[1] and COX-2.[2] They serve as antagonists or modulators of endothelins,[3] NMDA,[4] 5-$HT_7$, 5-$HT_{2C}$, and $5HT_{1A}$ receptors,[5] as well as of estrogen,[6] dopamine[7] and metabotropic glutamate[8] receptors. Other reported effects include the inhibition of amyloid protein aggregation,[9] selective serotonin uptake inhibition,[10] and antibacterial,[11] antitumour,[12] diuretic[13] and herbicidal[14] activity. Certain isoindoline derivatives have been investigated in potential therapies for cardiac arrhythmias,[15] hypolipemia[16] and lupus.[17] The isoindoline core is also present in several natural products, such as the alkaloids nuevamine and lennoxamine.[18] While the majority of these compounds contain substituents on the nitrogen atom or on the aromatic ring, as in **1**,[19] variously 1-substituted or 1,3-disubstituted isoindolines (**2**)[2a,3a3b,20] and 3-substituted isoindolin-1-ones (**3**)[8,13,15,21,22] are of particular importance and several approaches to them have been devised. There are, however, relatively few known syntheses of 1-aryl-substituted derivatives,[3a,20a21j] or of partially reduced[23] congeners.




**1** **2** **3**

We recently reported that aldimines **4** react with suitably activated conjugated dienes **5** to afford dienylamines **6** *via* Morita–Baylis–Hillman reactions.[24] Intramolecular conjugate additions of the products provide the corresponding functionalized 2-aryldehydropiperidines **7** (Scheme 1). We now report that the *N*-allyl or *N*-propargyl derivatives of **6** undergo intramolecular Diels–Alder (IMDA) cycloadditions,[25] leading to 1-aryl-substituted isoindolines and their partly reduced or oxidized congeners.




**Scheme 1**

## Results and discussion

The *N*-allylation of a series of Morita–Baylis–Hillman adducts **6a–6c** (EWG = *p*-toluenesulfonyl) was readily performed by their treatment with allyl iodide in the presence of potassium carbonate in DMF at room temperature to afford **8a–8c**, respectively. Only the minor *Z*-isomers[26] of **6a–6c** were utilized, as cyclization to **7** *via* Scheme 1 predominated in the case of the corresponding *E*-isomers under the basic conditions of the allylation step. The products were then refluxed in toluene and the resulting cycloadducts **11a–11c** were isolated as single diastereomers in generally high yield (Scheme 2 and Table 1, entries 1–3). The relative stereochemistry of **11b** was established by X-ray crystallography (Fig. 1), which indicated that the IMDA reaction occurred with high stereoselectivity *via* transition state **A** in Scheme 2. The similar configurations of **11a** and **11c** were assigned by analogy. Attempts to aromatize products **11a–11c** by base-catalyzed elimination of the *p*-toluenesulfonyl group, followed by DDQ oxidation, failed because the elimination step could not be achieved effectively under a variety of conditions, including the use of DBU, potassium and caesium carbonate, potassium *tert*-butoxide and lithium hexamethyldisilazane. This can be attributed to the inability of the molecule to adopt an unstrained conformation where the *p*-toluenesulfonyl group is antiperiplanar with one of its vicinal hydrogen atoms (see Fig. 1).

*Department of Chemistry, University of Calgary, Calgary, AB, Canada T2N 1N4. E-mail: tgback@ucalgary.ca; Fax: +1 (403) 289-9488; Tel: +1 (403) 220-6256*

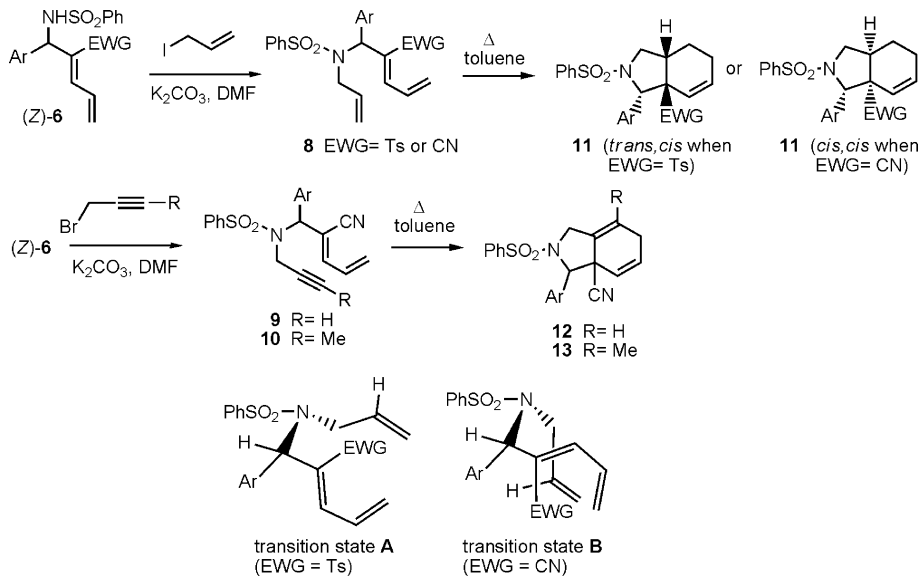
† Electronic supplementary information (ESI) available: Characterization data for new products, $^1$H and $^{13}$C NMR spectra of new products, X-ray crystallographic data for compounds **11b** and **11d**. See DOI: 10.1039/b817954a.

**Table 1** Preparation and IMDA cycloadditions of **8–10**

| Entry | Starting material | EWG | Ar | *N*-Substituent | *N*-Allyl or propargyl product (yield, %) | IMDA product[a] (yield, %) |
|---|---|---|---|---|---|---|
| 1 | **6a** | Ts | $C_6H_5$ | Allyl | **8a** (86) | **11a** (91) |
| 2 | **6b** | Ts | 2-Cl-$C_6H_4$ | Allyl | **8b** (72) | **11b** (90) |
| 3 | **6c** | Ts | 4-MeO-$C_6H_4$ | Allyl | **8c** (88) | **11c** (70) |
| 4 | **6d** | CN | $C_6H_5$ | Allyl | **8d** (94) | **11d** (85) |
| 5 | **6e** | CN | 2-Cl-$C_6H_4$ | Allyl | **8e** (63) | **11e** (83) |
| 6 | **6f** | CN | 4-Cl-$C_6H_4$ | Allyl | **8f** (78) | **11f** (76) |
| 7 | **6g** | CN | 4-NC-$C_6H_4$ | Allyl | **8g** (62) | **11g** (71) |
| 8 | **6h** | CN | 4-$MeO_2C$-$C_6H_4$ | Allyl | **8h** (74) | **11h** (89) |
| 9 | **6i** | CN | 1-Naphthyl | Allyl | **8i** (89) | **11i** (88) |
| 10 | **6d** | CN | $C_6H_5$ | Propargyl | **9d** (quant) | **12d** (94) |
| 11 | **6e** | CN | 2-Cl-$C_6H_4$ | Propargyl | **9e** (quant) | **12e** (89) |
| 12 | **6f** | CN | 4-Cl-$C_6H_4$ | Propargyl | **9f** (quant) | **12f** (79) |
| 13 | **6i** | CN | 1-Naphthyl | Propargyl | **9i** (quant) | **12i** (84) |
| 14 | **6d** | CN | $C_6H_5$ | 2-Butynyl | **10d** (quant) | **13d** (68) |

[a] Compounds **11e**, **12d–12f**, **12i** and **13d** were obtained as *ca.* 1 : 1 mixtures of diastereomers; the other products were unique diastereomers.




**Scheme 2**

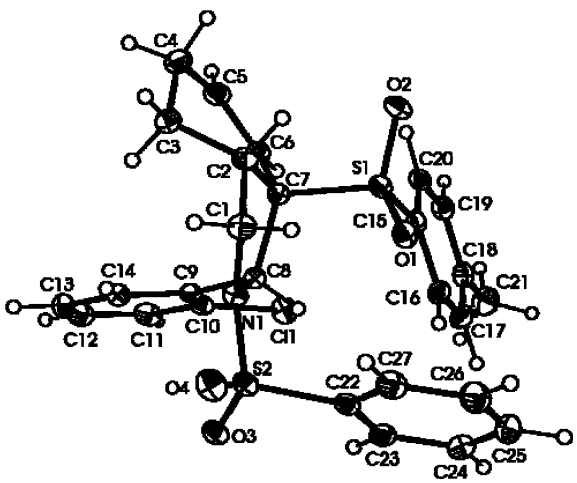



**Fig. 1** ORTEP diagram of **11b**, plotted with 50% probability thermal ellipsoids; H-atoms have been assigned arbitrary radii.

The relatively poor availability of the required *Z* isomers of **6a–6c**[24b] and the difficulty in their subsequent aromatization prompted us to examine the IMDA reactions of **6d–6i** (EWG = CN). In contrast to the sulfonyl derivatives **6a–6c**, nitriles **6d–6i** were obtained with high stereoselectivity as pure *Z* isomers from the corresponding Morita–Baylis–Hillman reactions.[24c] Allylation of **6d–6i**, followed by the IMDA reaction in refluxing toluene afforded **11d–11i** *via* the *N*-allyl derivatives **8d–8i** (Scheme 2 and Table 1, entries 4–9) as single diastereomers, except in the case of the *o*-chloro derivative **11e**, which was obtained as a *ca.* 1 : 1 mixture of two diastereoisomers.[27] An X-ray crystal structure of **11d** (Fig. 2) indicated the opposite relative stereochemistry (*cis*) between the aryl and EWG substituents compared to **11b**, suggesting that the reaction proceeds through transition state **B** (Scheme 2). The difference in stereochemistry resulting from the IMDA reactions in the nitrile series of trienes **8d–8i** and the previous *p*-toluenesulfonyl derivatives **8a–8c** can be attributed to the greater steric bulk of the tosyl group, compared to the nitrile substituent, which destabilizes

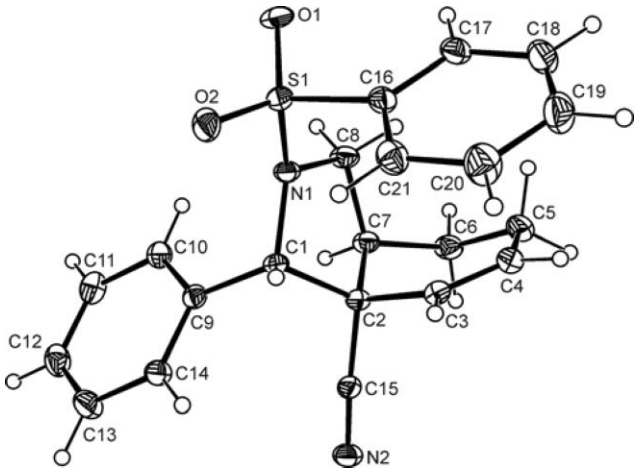



**Fig. 2** ORTEP diagram of **11d**, plotted with 50% probability thermal ellipsoids; H-atoms have been assigned arbitrary radii.

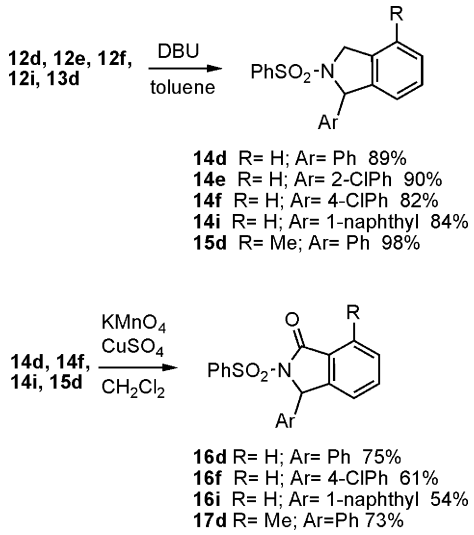
transition state **B** through increased steric interactions with the aryl moiety. In both cases, the reaction presumably involves inverse electron demand because of the presence of a strong electron-withdrawing substituent on the diene component.

The attempted elimination of nitriles **11d–11i** proved fruitless, as was observed previously with the sulfonyl derivatives **11a–11c**, presumably for similar reasons. Thus, while the IMDA reaction affords partly reduced 1-aryl-substituted isoindolines efficiently, their aromatization by elimination of the EWG and DDQ oxidation has so far proved unsuccessful.

The similar treatment of representative Morita–Baylis–Hillman adducts **6d**, **6e**, **6f**, and **6i** with propargyl bromide produced the corresponding *N*-substituted products **9d**, **9e**, **9f**, and **9i** in essentially quantitative yield (Scheme 2 and Table 1, entries 10–13). When subjected to the IMDA reaction, they afforded the corresponding cycloadducts **12d**, **12e**, **12f**, and **12i** as mixtures of diastereomers,[27,28] formed in roughly equal amounts. The butynyl derivative **10d** was obtained from **6d** in the usual manner and afforded the cycloadduct **13d** in the slightly lower yield of 68% (entry 14), again as a *ca.* 1 : 1 mixture of diastereomers.[27,28] The latter example indicates that additional substituents can be incorporated at the 4-position.

In contrast to derivatives **11a–11i**, elimination of the nitrile group from both isomers of the unseparated mixtures of diastereomers of **12d**, **12e**, **12f**, and **12i** was achieved by heating them with DBU in toluene to provide the corresponding 1-arylisoindolines **14d**, **14e**, **14f**, and **14i** in high yields, as shown in Scheme 3. The greater facility of elimination in the latter case is no doubt promoted by the accompanying aromatization. The 4-methyl derivative **13d** afforded **15d** similarly. Benzylic oxidation of **14d**, **14f**, **14i**, and **15d** with potassium permanganate and copper sulfate pentahydrate[29] provided the corresponding isoindolinones **16d**, **16f**, **16i**, and **17d** respectively.

These results demonstrate that the sequential application of Morita–Baylis–Hillman coupling of aldimines with activated dienes, followed by *N*-allylation or propargylation and IMDA cycloaddition, provides access to a variety of partially saturated 1-aryl-substituted isoindolines **11–13**, as well as the corresponding 1-arylisoindolines **14** and **15** and 3-arylisoindolin-1-ones **16** and **17**.




**Scheme 3**

## Experimental

IR spectra were recorded on a Nicolet Nexus 470 FTIR ESP spectrometer. $^{1}$H and $^{13}$C NMR spectra were acquired on a Bruker UG 300, Bruker DMX 300, or a Bruker AMX 300 spectrometer ($^{1}$H, 300 MHz; $^{13}$C, 75 MHz). Coupling constants *J* are given in Hz and chemical shifts are referenced to residual chloroform in deuteriochloroform solvent. Mass spectra were obtained by electron impact. Elemental analyses were performed by Mr J. J. Li at the University of Calgary. Compounds **6a–6i** were prepared as reported previously.[24] Chromatography refers to flash chromatography on silica-gel (230–400 mesh).

### Typical procedure for *N*-allylations and *N*-propargylations: preparation of 8d

Allyl iodide (0.627 g, 3.73 mmol), followed by potassium carbonate (0.522 g, 3.78 mmol), were added to a stirred solution of **6d** (0.811 g, 2.50 mmol) in DMF (15 mL) and the reaction was stirred at room temperature until TLC analysis indicated the disappearance of **6d** (5 h). The solution was poured into water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Chromatography (toluene : ethyl acetate, 16 : 1), afforded 0.855 g (94%) of **8d**.

Propargylations were performed similarly with propargyl bromide or 1-bromo-2-butyne.[30]

### Typical procedure for IMDA reactions: preparation of 2-benzenesulfonyl-1-phenyl-7*a*-(toluene-4-sulfonyl)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-isoindole (11a)

*N*-Allyl derivative **8a** (87.4 mg, 0.177 mmol) was dissolved in toluene (8 mL) and refluxed for 5 d. The solvent was removed under reduced pressure. The product was chromatographed (toluene : ethyl acetate, 16 : 1) to give 79.3 mg (91%) of **11a**: colourless crystals, mp 172–175 °C (from ethyl acetate). Found: C, 65.4; H, 5.8; N, 2.9%. Calc for $C_{27}H_{27}NO_4S_2$: C, 65.7; H, 5.5; N, 2.8%; $\nu_{max}$/cm$^{-1}$(film) 1596, 1348, 1300, 1165, 1143, 1083; $\delta_H$ (400 MHz) 7.82 (2 H, d, *J* 7.2), 7.68–7.65 (1 H, m), 7.60 (2 H, d,

*J* 7.9), 7.56 (2 H, d, *J* 8.3), 7.27–7.18 (7 H, m), 5.76 (1 H, ddd, *J* 10.1, 5.6, 2.6), 5.30 (1 H, s), 4.94 (1 H, dd, *J* 10.3, 1.6), 3.81 (1 H, dd, *J* 7.1, 5.3), 3.58 (1 H, dd, *J* 7.1, 2.2), 2.64–2.56 (1 H, m), 2.43 (3 H, s), 1.92–1.82 (1 H, m), 1.73–1.59 (2 H, m), 1.47–1.37 (1 H, m); $\delta_C$ (50 MHz) 145.1, 138.0, 135.6, 134.5, 133.0, 131.8, 130.7, 128.9, 128.8, 128.4, 128.2, 127.9, 127.6, 122.2, 77.2, 66.5, 54.0, 38.0, 24.8, 22.0, 21.6; (*m*/*z*,%) 338 (11), 155 (43), 91 (47), 77 (100). Exact mass found: 338.1216. Calc for $C_{20}H_{20}NO_2S$: 338.1215 ($M^+$ – Ts).

The preparations of **11b–11i** were performed similarly and their characterization data are provided in the ESI.† All of the above products except **11e** were obtained as single diastereomers.

IMDA reactions of *N*-propargyl derivatives **9d–9f** and **9i** were performed similarly and afforded *ca.* 1 : 1 mixtures of diastereomers of the cycloadducts **12d–12f** and **12i**. The IMDA reaction of the butynyl derivative **10d** required refluxing in anisole for 24 h and afforded a similar mixture of diastereomers of **13d**. These products were used in subsequent aromatizations without separation of isomers.[28]

### Typical aromatization procedure: preparation of 2-benzenesulfonyl-1-phenyl-2,3-dihydro-1*H*-isoindole (14d)

A mixture of both diastereomers of **12d** (82.6 mg, 0.228 mmol) was dissolved in toluene (20 mL). DBU was added (36 mg, 0.23 mmol) and the solution was refluxed until TLC analysis indicated completion of the reaction (9 h). The mixture was poured into water and extracted 3 times with ethyl acetate. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated. The product was chromatographed (toluene : ethyl acetate, 16 : 1) to afford 68.4 mg (89%) of **14d**: white solid, mp 155–157 °C (from ethyl acetate); $\nu_{max}$/cm$^{-1}$(film) 1350, 1164, 1101; $\delta_H$ (300 MHz) 7.62–7.59 (2 H, m), 7.45 (1 H, tt, *J* 8.4, 1.2), 7.34 (2 H, t, *J* 8.4), 7.24–7.13 (8 H, m), 6.88 (1 H, d, *J* 7.5), 5.94 (1 H, s), 4.90–4.80 (2 H, m); $\delta_C$ (75 MHz) 141.6, 140.9, 138.5, 135.0, 132.4, 128.8, 128.5, 128.0, 127.97, 127.87, 127.7, 127.2, 123.7, 122.4, 69.5, 54.0; (*m*/*z*,%) 335 (4), 258 (67), 194 (100). Exact mass found: 334.0964. Calc for $C_{20}H_{17}NO_2S$: 335.0980.

Products **14e**, **14f**, **14i** and **15d** were prepared similarly (see ESI†).

### Typical procedure for benzylic oxidation: preparation of 2-benzenesulfonyl-3-phenyl-2,3-dihydroisoindol-1-one (16d)

Potassium permanganate (200 mg) and copper sulfate pentahydrate (200 mg) were combined and crushed into a fine powder. This was added to a solution of **14d** (59.1 mg, 0.176 mmol) in dichloromethane (8 mL). The reaction was refluxed until TLC showed completion of the reaction (3 d). The solution was filtered through a pad of Celite, which was washed thoroughly with dichloromethane. The filtrate was concentrated and chromatographed (toluene : ethyl acetate, 16 : 1) to provide 46.3 mg (75%) of **16d**: colourless needles, mp 176–178 °C (from ethyl acetate). Found: C, 68.45; H, 4.3; N, 4.0%. Calc for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.3; N, 4.0%. $\nu_{max}$/cm$^{-1}$(film) 1733, 1367, 1280, 1181, 1090; $\delta_H$ (300 MHz) 7.85 (1 H, d, *J* 7.5), 7.61–7.46 (5 H, m), 7.33–7.19 (5 H, m), 7.14 (1 H, d, *J* 7.6), 7.03 (2 H, d, *J* 7.0), 6.21 (1 H, s); $\delta_C$ (50 MHz) 166.4, 146.4, 138.9, 136.7, 134.4, 133.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.1, 127.9, 124.8, 123.7, 65.6; (*m*/*z*,%) 284 (75), 219 (100), 208 (71), 130 (74). Exact mass found: 208.0760. Calc for $C_{14}H_{10}NO$ ($M^+ - SO_2Ph$): 208.0762.

Products **16f**, **16i** and **17d** were prepared similarly (see ESI†).

## Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. K.N.C. thanks NSERC and the Alberta Ingenuity Fund for postgraduate scholarships.

## References

1 (*a*) W.-T. Jiaang, Y.-S. Chen, T. Hsu, S.-H. Wu, C.-H. Chien, C.-N. Chang, S.-P. Chang, S.-J. Lee and X. Chen, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 687–691; (*b*) S. Van Goethem, P. Van der Veken, V. Dubois, A. Soroka, A.-M. Lambeir, X. Chen, A. Haemers, S. Scharpé, I. De Meester and K. Augustyns, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4159–4162.

2 (*a*) B. Portevin, C. Tordjman, P. Pastoureau, J. Bonnet and G. De Nanteuil, *J. Med. Chem.*, 2000, **43**, 4582–4593; (*b*) T. Mancilla, J. Correa-Basurto, K. S. Alaves Carbajal, E. T. J. Sanchez Escalante and J. T. Ferrara, *J. Mex. Chem. Soc.*, 2007, **51**, 96–102.

3 (*a*) P. J. Kukkola, N. A. Bilci and T. J. Ikeler, *Tetrahedron Lett.*, 1996, **37**, 5065–5068; (*b*) P. J. Kukkola, N. A. Bilci, T. Ikler, P. Savage, S. S. Shetty, D. DelGrande and A. Y. Jeng, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1737–1740.

4 (*a*) T. M. Bare, C. W. Draper, C. D. McLaren, L. M. Pullan, J. Patel and J. B. Patel, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 55–60; (*b*) A. Alanine, S. Burner, B. Buettelmann, N. M. Heitz, G. Jaeschke, E. Pinard, and R. Wyler, *Eur. Pat.* 1090917, 2001, *Chem. Abs.,* **134**, 280719.

5 (*a*) D. Hamprecht, F. Micheli, G. Tedesco, A. Checchia, D. Donati, M. Petrone, S. Terreni and M. Wood, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 428–433; (*b*) G. A. Cain, and J. F. McElroy, *PCT Int.*, WO 0000472, 2000,*Chem. Abs.,* **132**, 64183; (*c*) P. George, M. Sevrin, M. Mangane, J. P. Merly and D. Bigg, *Eur. Pat.*, 351283, 1990,*Chem. Abs.,* **113**, 58970.

6 (*a*) S. S. Bhagwat, L. M. Gayo-Fung, B. M. Stein, Q. Chao, A. R. Gangloff, J. A. McKie, and K. D. Rice, *PCT Int.*, WO 02024653, 2002,*Chem. Abs.,* **136**, 279351; (*b*) B. Barlaam and C. Dantzman, *PCT Int.*, WO 02046164, 2002,*Chem. Abs.,* **137**, 47127.

7 (*a*) C. N. Johnson and G. Stemp, *PCT Int.*, WO 00021950, 2000,*Chem. Abs.,* **132**, 279110; (*b*) H. B. Broughton, J. J. Kulagowski, P. D. Leeson and I. M. Mawer, *PCT Int. Appl.*, WO 9421628, 1994,*Chem. Abs.,* **122**, 9863.

8 B. Van Wagenen, R. Ukkiramapandian, J. Clayton, I. Egle, J. Empfield, M. Isaac, F. Ma, A. Slassi, G. Steelman, R. Urbanek and S. Walsh, *PCT Int.*, WO 07021309, 2007,*Chem. Abs.,* **146**, 274221.

9 C. E. Augelli-Szafran, Y. Lai, A. T. Sakkab and L. C. Walker, *PCT Int.*, WO 0076969, 2000,*Chem. Abs.,* **134**, 56565.

10 K. J. Kapples and G. M. Shutske, *J. Heterocycl. Chem.*, 1997, **34**, 1335–1338.

11 M. Yamada, S. Hamamoto, K. Hayashi, K. Takaoka, H. Matsukura, M. Yotsuji, K. Yonezawa, K. Ojima, T. Takamatsu, K. Taya, H. Yamamoto, T. Kiyoto and H. Kotsubo, *PCT Int.*, WO 9921849, 1999,*Chem. Abs.,* **130**, 311706.

12 (*a*) D. Berger, R. Citarella, M. Dutia, L. Greenberger, W. Hallett, R. Paul and D. Powell, *J. Med. Chem.*, 1999, **42**, 2145–2161; (*b*) G. W. Muller, and H.-W. Man, *PCT Int.*, WO 06025991, 2006,*Chem. Abs.,* **144**, 369911; (*c*) C. Murakata, N. Amishiro, T. Atsumi, Y. Yamashita, T. Takahashi, R. Nakai, H. Tagaya, H. Takahashi, J. Funahashi, J. Yamamoto and Y. Fukuda, *PCT Int.*, WO 06112479, 2006,*Chem. Abs.,* **145**, 454932; (*d*) L. A. Funk, M. C. Johnson, P.-P. Kung, J. J. Meng and J. Z. Zhou, *PCT Int.*, WO 06117669, 2006,*Chem. Abs.,* **145**, 489014.

13 E. J. Cornish, G. E. Lee and W. R. Wragg, *Nature*, 1963, **197**, 1296–1297.

14 M.-Z. Huang, K.-L. Huang, Y.-G. Ren, M.-X. Lei, L. Huang, Z.-K. Hou, A.-P. Liu and X.-M. Ou, *J. Agric. Food Chem.*, 2005, **53**, 7908–7914.

15 A. Bjoere, J. Bostroem, O. Davidsson, H. Emtenaes, U. Gran, T. Iliefski, J. Kajanus, R. Olsson, L. Sandberg, G. Strandlund, J. Sundell and Z.-Q. Yuan, *PCT Int.*, WO 08008022, 2008,*Chem. Abs.,* **148**, 168577.

16 N. Harada, M. Yato, H. Kamaya, K. Nagata and H. Iwai, *PCT Int.*, WO 02098872, 2002,*Chem. Abs.,* **138**, 24729.

17 J. B. Zeldis, P. E. W. Rohane and P. H. Schafer, *US Pat.*, 155791,2007,*Chem. Abs.,* **147**, 110212.
18 E. Valencia, A. J. Freyer, M. Shamma and V. Fajardo, *Tetrahedron Lett.*, 1984, **25**, 599–602.
19 (*a*) For examples, see: E. R. Bonfield and C.-J. Li, *Adv. Synth. Catal.*, 2008, **350**, 370–374; (*b*) Q. Sun, X. Zhao, K. Islam and D. J. Kyle, *Tetrahedron Lett.*, 2001, **42**, 6495–6497; (*c*) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1357–1364; (*d*) H. J. Kim, U. C. Yoon, Y.-S. Jung, N. S. Park, E. M. Cederstrom and P. S. Mariano, *J. Org. Chem.*, 1998, **63**, 860–863.
20 (*a*) For examples, see: D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661–5665; (*b*) O. Gaertzen and S. L. Buchwald, *J. Org. Chem.*, 2002, **67**, 465–475; (*c*) A. Mueller, K. Polborn and K. T. Wanner, *J. Heterocycl. Chem.*, 2007, **44**, 575–590; (*d*) D. F. Ewing, C. Len, G. Mackenzie, J. P. Petit, G. Ronco and P. Villa, *J. Pharm. Pharmacol.*, 2001, **53**, 945–948; (*e*) Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133–6135.
21 (*a*) For examples, see: J. M. Chitanda, D. E. Prokopchuk, J. W. Quail and S. R. Foley, *Organometallics*, 2008, **27**, 2337–2345; (*b*) A. Couture, E. Deniau, D. Ionescu and P. Grandclaudon, *Tetrahedron Lett.*, 1998, **39**, 2319–2320; (*c*) M. Lamblin, A. Couture, E. Deniau and P. Grandclaudon, *Synthesis*, 2006, 1333–1338; (*d*) D. M. Duckworth, S. Lee-Wong, A. M. Z. Slawin, E. H. Smith and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1996, 815–821; (*e*) K. Kobayashi, M. Hase, K. Hashimoto, S. Fujita, M. Tanmatsu, O. Morikawa and H. Konishi, *Synthesis*, 2006, 2493–2496; (*f*) N. G. Kundu and M. W. Khan, *Tetrahedron*, 2000, **56**, 4777–4792; (*g*) D. L. Comins, S. Schilling and Y. Zhang, *Org. Lett.*, 2005, **7**, 95–98; (*h*) D. L. Comins and A.-C. Hiebel, *Tetrahedron Lett.*, 2005, **46**, 5639–5642; (*i*) E. Deniau, D. Enders, A. Couture and P. Grandclaudon, *Tetrahedron: Asymmetry*, 2005, **16**, 875–881; (*j*) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5326–5337.
22 For a review, see: G. Stájer and F. Csende, *Curr. Org. Chem.*, 2005, **9**, 1277–1286.
23 For examples, see: (*a*) D.-R. Hou, M.-S. Wang, M.-W. Chung, Y.-D. Hsieh and H.-H. G. Tsai, *J. Org. Chem.*, 2007, **72**, 9231–9239; (*b*) H.-Y. Lee, H. Y. Kim, H. Tae, B. G. Kim and J. Lee, *Org. Lett.*, 2003, **5**, 3439–3442; (*c*) R. Pedrosa, C. Andrés and J. Nieto, *J. Org. Chem.*, 2000, **65**, 831–839; (*d*) T. Schmidlin, D. Wallach and C. Tamm, *Helv. Chim. Acta*, 1984, **67**, 1998–2008; (*e*) D. J. R. O'Mahony, D. B. Belanger and T. Livinghouse, *Org. Biomol. Chem.*, 2003, **1**, 2038–2040.
24 (*a*) T. G. Back, D. A. Rankic, J. M. Sorbetti and J. E. Wulff, *Org. Lett.*, 2005, **7**, 2377–2379; (*b*) J. M. Sorbetti, K. N. Clary, D. A. Rankic, J. E. Wulff, M. Parvez and T. G. Back, *J. Org. Chem.*, 2007, **72**, 3326–3331; (*c*) K. N. Clary and T. G. Back, *Synlett*, 2007, 2995–2998.
25 (*a*) The use of Morita–Baylis–Hillman reactions to generate the dienophile component for subsequent intramolecular Diels–Alder cycloadditions has been employed in the syntheses of mniopetal F and sordarin analogues; see: J. Jauch, *Eur. J. Org. Chem.*, 2001, 473–476; (*b*) H. Liang, A. Schulé, J.-P. Vors and M. A. Ciufolini, *Org. Lett.*, 2007, **9**, 4119–4122.
26 The *E : Z* ratio of **6** (EWG = Ts) is typically *ca.* 70 : 30 when prepared *via* the method of ref. 24*b*.
27 It is possible that the diastereomers obtained for product **11e** are rotamers resulting from restricted rotation about the bond between C-1 and the 2-chlorophenyl group. The stereoisomers obtained for compounds **12d**, **12e**, **12f**, **12i** and **13d** are presumably *cis* and *trans* isomers, but rotamers cannot be entirely precluded, especially in **12e** and **12i**, which contain bulkier aryl groups. High temperature NMR experiments (DMSO-$d_6$, up to 390 K) with diastereomer mixtures of **11e**, **12e** and **12i** did not show coalescence of signals, indicating that either hindered rotation is not responsible for the presence of diastereomer mixtures, or that it has a very high energy barrier.
28 In each case, one stereoisomer could be isolated in the pure state by repeated recrystallization (see ESI†), while the other stereoisomer could not be obtained free from the first.
29 N. A. Noureldin, D. Zhao and D. G. Lee, *J. Org. Chem.*, 1997, **62**, 8767–8772. Other oxidants that were investigated but afforded lower yields include pyridinium dichromate, pyridinium chlorochromate, manganese dioxide and copper(II) chloride-*tert*-butyl hydroperoxide-tetrabutylammonium bromide.
30 L. F. Tietze, T. Eicher, U. Diederichsen and A. Speicher, *Reactions and Syntheses*, Wiley-VCH, Weinheim, 2007, pp. 54–56.