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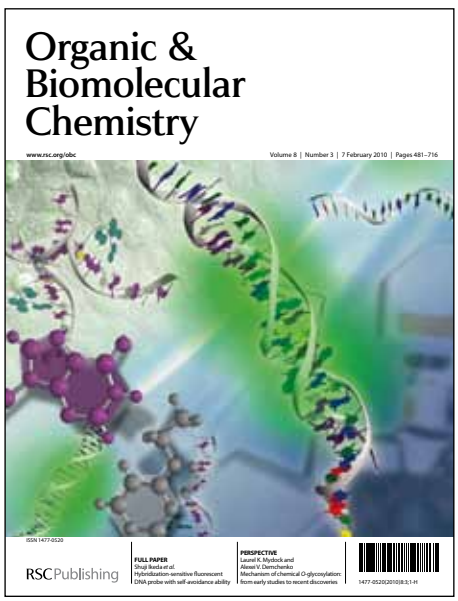

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Baylis-Hillman Acetates in Organic Synthesis: Convenient One-Pot Synthesis of α-Carboline Framework - A Concise Synthesis of Neocryptolepine†

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A convenient, facile, and one-pot methodology for synthesis of α-carbolines from the Baylis-Hillman (BH) acetates, involving three steps (reactions), that is, 1) mono alkylation of 2-nitroarylacetonitriles with BH-acetates 2) reduction of nitro group into amino group using Fe/AcOH 3) formation of two (five and six membered) rings, is presented. This methodology is successfully applied to the synthesis of bioactive alkaloid neocryptolepine (2).

Development of facile and convenient protocols for synthesis[1] of pyrido[2,3-*b*]indole (α-carboline) framework has received increasing attention from synthetic chemists due to the fact that several molecules containing this structural organization show various biological activities such as anti-inflammatory,[2a] anxiolytic,[2b] and cytotoxic.[2c] Also a number of natural products [mescengricin (**1a**),[3a] grossularine-1 (**1b**),[3b] grossularine-2 (**1c**)[3b] and neocryptolepine (**2**) (also known as cryptotackieine)[3c] (Figure 1)] possess this tricyclic skeleton as their core structure.

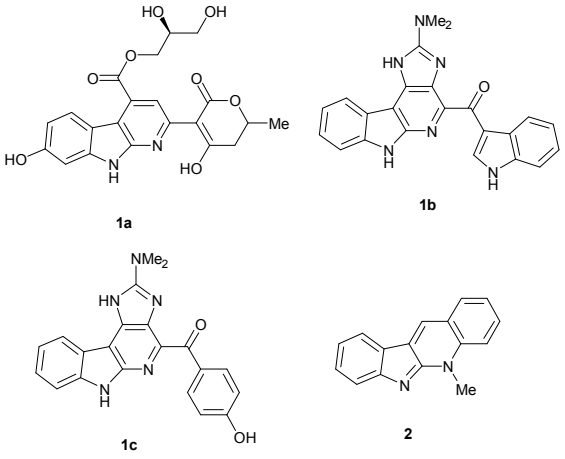
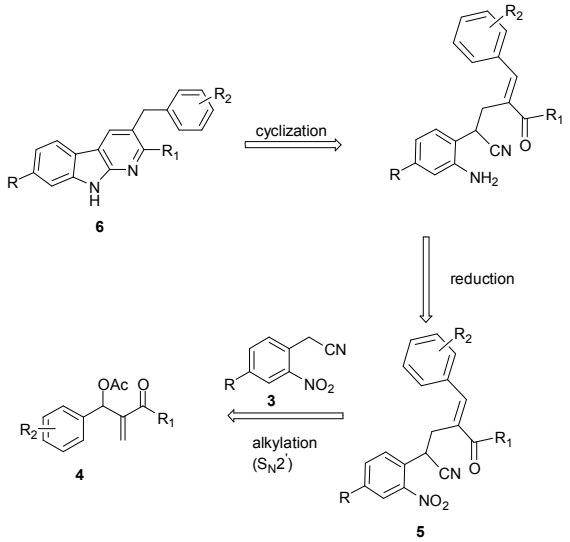


Figure 1. Natural products containing α-carboline core

In continuation of our ongoing long term major research program in the area of Baylis-Hillman reaction and its applications,[4] we herein report a convenient, facile, and one-pot methodology for synthesis of pyrido[2,3-*b*]indole derivatives from appropriate Baylis-Hillman (BH) acetates. This protocol involves three steps (reactions), that is, 1) mono alkylation of 2-nitroarylacetonitriles with BH-acetates 2) reduction of nitro group into amino group using Fe/AcOH 3) formation of two (five and six membered) rings in an operationally simple one-pot procedure. We have also successfully applied this protocol to the synthesis of neocryptolepine (**2**), an important bioactive alkaloid.

The Baylis-Hillman reaction has been and continues to attract the attention of various synthetic chemists because it provides diverse classes of multifunctional molecules.[5] In fact, due to the close proximity of functional groups the BH-adducts have become an attractive source/ substrates for a number of organic transformations often leading to the synthesis of several bioactive compounds and important frameworks of medicinal relevance.[5, 6] We have recently reported interesting one-pot synthetic protocols for the facile conversion of Baylis-Hillman adducts into substituted [1,8]naphthyridin-2-ones,[7a] tri-/tetracyclic azocines,[7b] 3-benzoylquinolines,[7c] tetrahydroacridines[7d] and quinolines.[7e] In all these strategies, the *in situ* reduction of nitro group using Fe/AcOH into an amino group and subsequent cyclization (mono or bis) are the key steps.[7] This experience has led us to envision that Baylis-Hillman acetates can be in principle transformed into pyrido[2,3-*b*]indole framework *via* the mono alkylation (S_N2') of 2-nitroarylacetonitriles (**3**) with BH-acetates (**4**) followed by *in situ* reduction of nitro group and then two successive cyclizations (first one forming five membered ring and the second one producing the six membered ring) according to the retro-synthetic strategy as shown in Scheme 1.



Scheme 1 Retro-synthetic strategy for the synthesis of α-carboline framework

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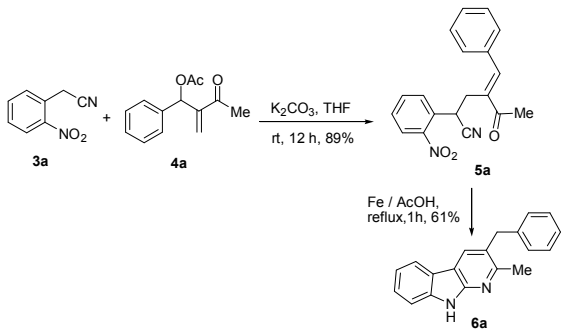
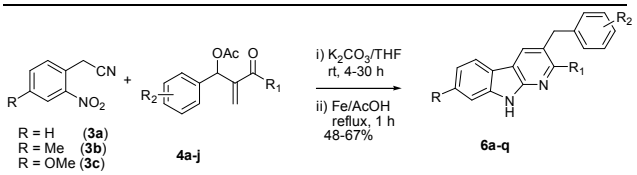
†Electronic Supplementary Information (ESI) available: Representative experimental procedures, with all spectral data of **2, 5a, 6a-q, 8-11,** crystal data and ORTEP diagram of **6n & 8** See DOI: 10.1039/b000000x.

Accordingly, we have first selected 4-acetoxy-3-methylene-4-phenylbutan-2-one (**4a)**, acetate of Baylis-Hillman alcohol (obtained *via* the reaction between benzaldehyde and methyl vinyl ketone), as a substrate for alkylation of 2-nitrophenylacetonitrile (**3a**). Best results in this direction were obtained when we treated BH-acetate **4a** (2 mmol) with 2-nitrophenylacetonitrile **3a** (2 mmol) in the presence of K_2CO_3 (2 mmol) in THF (6 mL) at room temperature for 12 h to provide (*E*)-3-benzylidine-5-cyano-5-(2-nitrophenyl)pentan-2-one (**5a**) in



Scheme 2 Stepwise synthesis of **6a**

Table 1. Synthesis of pyrido[2,3-*b*]indoles *via* the reaction of **4a-j** with **3a**, **3b** or **3c** [a] followed by reductive cyclization

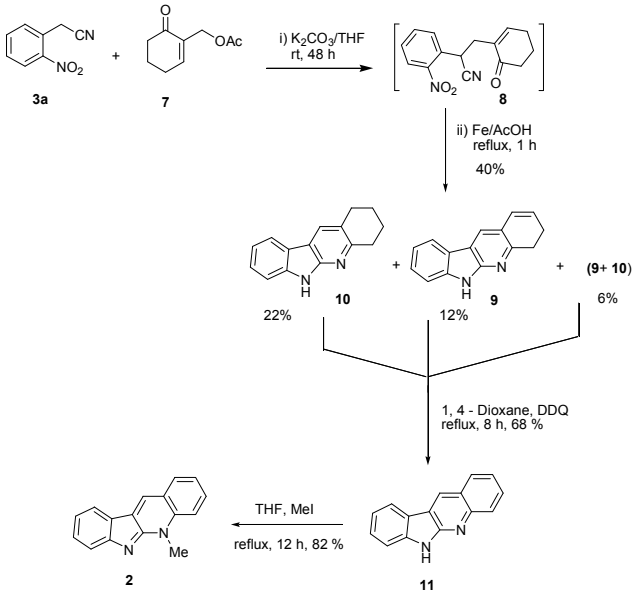


Entry	NAAN[b]	Acetate	R_1	R_2	Product[c]	Yield (%)
1	**3a**	**4a**	Me	H	**6a**	52
2	**3a**	**4b**	Et	H	**6b**	67
3	**3a**	**4c**	Me	4-Me	**6c**	53
4	**3a**	**4d**	Me	4-Cl	**6d**	55
5	**3a**	**4e**	Me	4-Br	**6e**	59
6	**3a**	**4f**	Me	3-Br	**6f**	57
7	**3a**	**4g**	Me	3-OMe	**6g**	50
8	**3b**	**4a**	Me	H	**6h**	56
9	**3b**	**4b**	Et	H	**6i**	62
10	**3b**	**4c**	Me	4-Me	**6j**	50
11	**3b**	**4d**	Me	4-Cl	**6k**	53
12	**3b**	**4e**	Me	4-Br	**6l**	58
13	**3b**	**4f**	Me	3-Br	**6m**	55
14	**3c**	**4b**	Et	H	**6n**[d]	60
15	**3a**	**4h**	Me	2-Cl	**6o**	51
16	**3a**	**4i**	Me	2-Br	**6p**	48
17	**3a**	**4j**	Me	2-Me	**6q**	52

[a]All reactions were carried out on 1 mmol scale of Baylis-Hillman acetate (**4a-j**) with 1 mmol of NAAN **(3a-c)** in the presence of K_2CO_3 (1 mmol) in THF at room temperature followed by reductive cyclization with Fe (6 eq.)/ AcOH. [b]NAAN = 2-nitroarylacetonitriles. [c]All compounds were fully characterized (see Electronic Supplementary Information). [d]Structure of this molecule was further confirmed by single crystal X-ray data (see Electronic Supplementary Information).[8]

89% isolated yield. Subsequent treatment of **5a** with Fe /AcOH at reflux temperature for 1 h, furnished 3-benzyl-2-methyl-9*H*-pyrido[2,3-*b*]indole (**6a)** in 61% isolated yield after the usual workup followed by column chromatography (Scheme 2) (in overall 54% yield for both the steps).

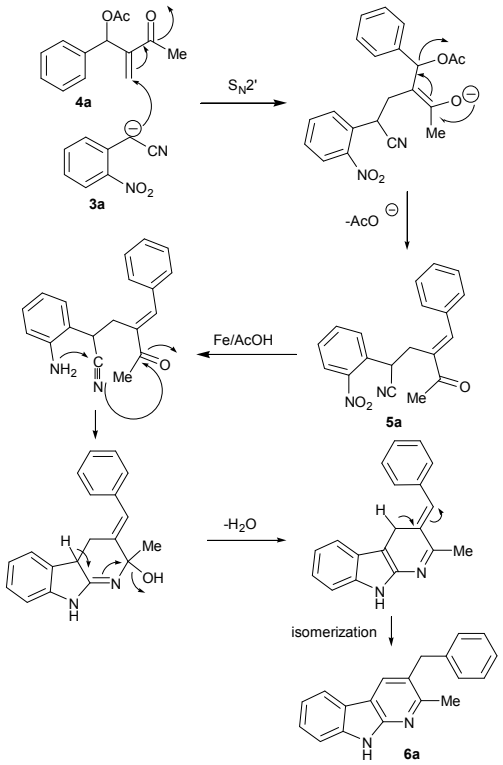
With a view to understand the feasibility of one-pot process we have directly treated the *in situ* generated **5a** (after removal of THF under reduced pressure) with Fe/AcOH under reflux temperature for 1h to afford the desired compound **6a** in 52% overall isolated yield (Table 1). Since the yields are comparable in both procedures we have selected the one-pot procedure for understanding the generality of this reaction. We have prepared representative Baylis-Hillman acetates (**4b-g**) from the corresponding alcohols (derived from selected benzaldehydes and alkyl vinyl ketones). The acetates (**4b-g**) were then subjected to similar synthetic sequence as in the case of **4a** to provide the desired α-carbolines (**6b-n**) in 50-67% isolated yields (Table 1, entries 2-14). With a view to understand the applicability of this strategy to Baylis-Hillman acetates containing *ortho* substituted aryl groups[9] we have also used allyl acetates **4h-j** (containing aryl groups with 2- chloro, 2-bromo, and 2-methyl substitution respectively). These reactions worked well and the resulting α-carbolines **6o-q** were obtained in reasonable (48-52 %) yields. In order to further confirm the formation of tricyclic ring system we also obtained single crystal for compound **6n** and established its structure by X-ray data analysis (Figure 2).[8]



Scheme 3 A simple route for synthesis of compound **2**

Then our attention was directed towards the application of this methodology for synthesis of bioactive compound neocryptolepine (**2**),[1a,10] containing the pyrido[2,3-*b*]indole skeleton. We have in fact achieved synthesis of **2** (Scheme 3) in 22% overall yield in three steps, starting from 2-acetoxymethylcyclohex-2-enone (**7**), acetate of Baylis-Hillman alcohol (obtained *via* the reaction between formaldehyde and cyclohex-2-enone). Thus treatment of the acetate **7** with **3a** followed by reductive cyclization (with Fe /AcOH) provided 3,4-dihydro-6*H*-indolo[2,3-*b*]quinoline (**9,** 12%) along with 1,2,3,4-tetrahydro-6*H*-indolo[2,3-*b*]quinoline (**10,** 22%) in over all 40% yield (including their mixture 6%). We have converted the mixture [**9** + **10** + **(9+10**)] into aromatic product (**11**)[11] *via* the

treatment with DDQ.[10b] This molecule **11** was then transformed into the natural product (**2**)[11] via alkylation with MeI following the known procedure[10c] (Scheme 3).



Scheme 4 Plausible mechanism for synthesis of α-carboline core

We have in fact in a separate experiment isolated the alkylated compound (**8**) (*S_N2 product) (in the case of acetates **4** we obtained exclusively S_N2' products*) and confirmed this structure by single crystal X-ray data analysis (Figure 3).[8]

Although the overall yield of the bioactive molecule, neocryptolepine (**2**) is not that high, this protocol is still interesting in the sense that this strategy demonstrates the importance of the BH-acetates in the synthesis of heterocyclic compounds.

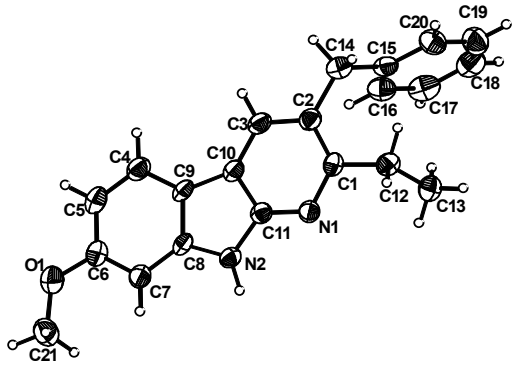


Figure 2 ORTEP diagram of compound **6n**

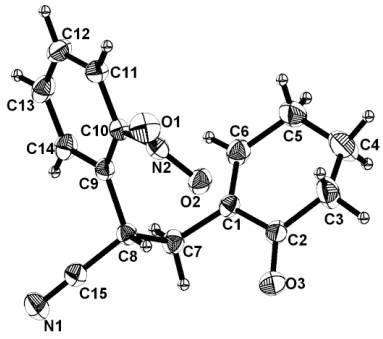
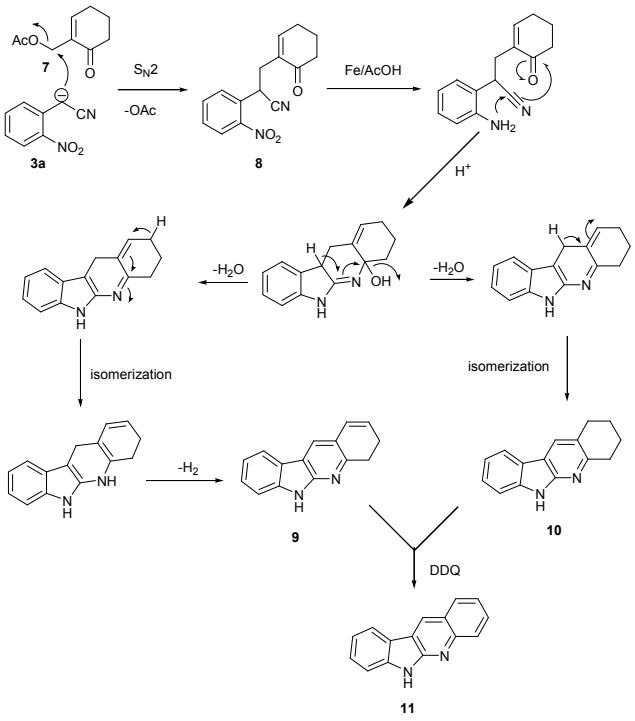


Figure 3 ORTEP diagram of compound **8**

A plausible mechanism for the formation of pyrido[2,3-*b*]indole (α-carboline) framework [taking **4a** (Baylis-Hillman acetate) and **3a** as a model case) is presented in Scheme 4. The first step involves alkylation (S_N2') to provide trisubstituted alkene (**5a**). The second step proceeds through the reduction of nitro group to provide amine followed by the simultaneous formation (third step) of five and six membered heterocycles (Scheme 4).

In case of the acetate **7** the first step proceeds through S_N2 alkylation to afford trisubstituted alkene (**8**). The second and third steps proceed as in the case of the acetates **4** to give the compounds **9** and **10** which on aromatization with DDQ provided the molecule **11** according to Scheme 5.



Scheme 5 Plausible path way for the formation of **9** and **10**

In conclusion, we have developed a convenient, operationally simple, one-pot procedure for synthesis of pyrido[2,3-*b*]indole (α-carbolines) from the BH-acetates. This strategy has also been successfully employed to the synthesis of bioactive compound neocryptolepine **2**.

Acknowledgements

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Notes and References

1 (a) A. L. Pumphrey, H. Dong and T. G. Driver, *Angew. Chem. Int. Ed.,* 2012, **51**, 5920; (b) J. K. Laha, S. M. Barolo, R. A. Rossi and G. D. Cuny, *J. Org. Chem.,* 2011, **76**, 6421; (c) A. S. Kumar and R. Nagarajan, *Org. Lett.,* 2011, **13**, 1398; (d) N. L. Chavan, S. K. Nayak and R. S. Kusurkar, *Tetrahedron*, 2010, **66**, 1827; (e) C. Schneider, D. Goyard, D. Gueyrard, B. Joseph and P. G. Goekjian, *Eur. J. Org. Chem.,* 2010, 6665; (f) C. Schneider, D. Gueyrard, F. Popowycz, B. Joseph and P. G. Goekjian, *Synlett*, 2007, 2237; (g) C. Bonini, M. Funicello and P. Spagnolo, *Synlett*, 2006, 1574; (h) P. Vera-Luque, R. Alajarin, J. Alvarez-Builla and J. J. Vaquero, *Org. Lett.,* 2006, **8**, 415; (i) O. Barun, P. K. Patra, H. Ila and H. Junjappa, *Tetrahedron. Lett*., 1999, **40**, 3797.

2 (a) T. Okamoto, T. Akase, T, Izumi, S. Inaba and H. Yamamoto, Japanese patent, 7220196, *Chem. Abstr*., 1972, **77**, 152142a; (b) G. Winters and N. Di Mola, German patent, 2442513, *Chem. Abstr*., 1975, **82**, 156255r; (c) W. Peczynska-Czoch, F. Pognan, L. Kaczmarek and J. Boratynski, *J. Med. Chem*., 1994, **37**, 3503.

3 (a) J.-S. Kim, K. Shin-ya, K. Furihata, Y. Hayakawa and H. Seto, *Tetrahedron Lett.*, 1997, **38**, 3431; (b) C. Moquin-Pattey and M. Guyot, *Tetrahedron*, 1989, **45**, 3445; (c) M. H. M. Sharaf, P. L. Schiff, Jr., A. N. Tackie, C. H. Phoebe, Jr. and G. E. Martin, *J. Heterocyclic. Chem*., 1996, **33**, 239.

4 (a) D. Basavaiah, S. Roy and U. Das, *Tetrahedron*, 2010, **66**, 5612; (b) D. Basavaiah, B. Devendar, K. Aravindu and A. Veerendhar, *Chem. Eur. J*., 2010, **16**, 2031; (c) D. Basavaiah, B. Devendar, D. V. Lenin and T. Satyanarayana, *Synlett*, 2009, 411; (d) D. Basavaiah and S. Roy, *Org. Lett*., 2008, **10**, 1819; (e) D. Basavaiah, N. Kumaragurubaran, D. S. Sharada and R. Mallikarjuna Reddy *Tetrahedron,* 2001, **57**, 8167; (f) D. Basavaiah, K. Muthukumaran and B. Sreenivasulu, *Synlett,* 1999, 1249; (g) D. Basavaiah, V. V. L. Gowriswari, P. K. S. Sarma and P. Dharma Rao, *Tetrahedron Lett.,* 1990, **31**, 1621; (h) D. Basavaiah, T. K. Bharathi and V. V. L. Gowriswari *Tetrahedron Lett*., 1987, **28**, 4351.

5 For reviews see a) T. Y. Liu, M. Xie and Y. C. Chen, *Chem. Soc. Rev*., 2012, **41**, 4101; (b) D. Basavaiah and G. Veeraraghavaiah, *Chem. Soc. Rev*., 2012, **41**, 68; (c) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev*., 2010, **110**, 5447; (d) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev*., 2009, **109**, 1; (e) V. Singh and S. Batra, *Tetrahedron*, 2008, **64,** 4511; (f) G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed.,* 2007, **46**, 4614; (g) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.,* 2007, **36**, 1581; (h) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev*., 2003, **103**, 811; (i) E. Ciganek, *Org. React.*, 1997, **51**, 201; (j) D. Basavaiah, P. Dharmarao and R. Suguna Hyma, *Tetrahedron,* 1996, **52,** 8001; (k) S. E. Drewes and G. H. P. Roos, *Tetrehedron,* 1988, **44**, 4653.

6 (a) L. Huang, Y. Wei and M. Shi, *Org. Biomol. Chem*., 2012, **10**, 1396; (b) Y. Suman Reddy, P. Kadigachalam, R. K. Basak, A. P. J. Pal and Y. D. Vankar, *Tetrahedron Lett*., 2012, **53**, 132; (c) B. R. Park, K. H. Kim, J. W. Lim and J. N. Kim, *Tetrahedron. Lett.,* 2012, **53**, 36; (d) A. Mishra, N. Rastogi and S. Batra, *Tetrahedron*, 2012, **68**, 2146; (e) J-R. Huang, H-L. Cui, J. Lei, X-H. Sun and Y-C. Chen, *Chem. Commun*., 2011, **47**, 4784; f) K. R. de Luna Freire, C. F. Tormena and F. Coelho, *Synlett*, 2011, 2059; (g) J. W. Lim, K. H. Kim, B. R. Park and J. N. Kim, *Tetrahedron Lett.,* 2011, **52**, 6545; (h) P. Shanbhag, P. R. Nareddy, M. Dadwal, S. M. Mobin and I. N. N. Namboothiri, *Org. Biomol. Chem*., 2010, **8**, 4867; (i) G. W. Amarante, M. Cavallo and F. Coelho, *Tetrahedron Lett.,* 2010, **51**, 2597; (j) M. Bakthadoss, G. Sivakumar and D. Kannan, *Org. Lett.,* 2009, **11**, 4466; (k) B. Das, K. Damodar, N. Bhunia and B. Shashikanth, *Tetrahedron Lett.,* 2009, **50**, 2072; (l) Y.-Q. Jiang, Y.-L. Shi and M. Shi, *J. Am. Chem. Soc*., 2008, **130**, 7202; (m) V. K. Aggarwal, A. Patin and S. Tisserand, *Org. Lett*.; 2005, **7**, 2555; (n) M. E. Krafft, E-H. Song and R. J. Davoile, *Tetrahedron Lett*., 2005, **46**, 6359; (o) S. R. S. S. Kotti, X. Xu, G. Li and A. D. Headley, *Tetrahedron Lett*., 2004, **45**, 1427; (p) D. Basavaiah and T. Satyanarayana, *Chem. Commun*., 2004, 32; (q) D. Basavaiah, M. Krishnamacharyulu, R. Suguna Hyma, P. K. S. Sarma and N. Kumaragurubaran, *J. Org. Chem*., 1999, **64**, 1197.

7 (a) D. Basavaiah and K. R. Reddy, *Tetrahedron*, 2010, **66,** 1215; (b) D. Basavaiah and K. Aravindu, *Org. Lett*., 2007, **9**, 2453; (c) D. Basavaiah, R. J. Reddy and J. Srivardhana Rao, *Tetrahedron Lett*., 2006, **47**, 73; (d) D. Basavaiah, J. Srivardhana Rao and R. J. Reddy, *J. Org. Chem*., 2004, **69**, 7379; (e) D. Basavaiah, R. M. Reddy, N. Kumaragurubaran and D. S. Sharada, *Tetrahedron,* 2002, **58,** 3693.

8 Detailed X-ray crystallographic data is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK for compounds **6n (**CCDC # 873380**)** and **8 (**CCDC # 873381).

9 We thank one of the referees for suggesting to examine the applicability of this strategy to the BH-acetates containing *ortho* substituted aryl groups.

10 (a) T. Dhanabal, R. Sangeetha and P. S. Mohan, *Tetrahedron*, 2006, **62**, 6258; (b) G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila and H. Junjappa, *J. Org. Chem*., 2004, **69**, 5760; (c) T.-L. Ho and D.-G. Jou, *Helv. Chim. Acta.,* 2002, **85**, 3823; (d) P.M. Fresneda, P. Molina and S. Delgado, *Tetrahedron*, 2001, **57**, 6197; (e) C. Shi, Q. Zhang and K. K. Wang, *J. Org. Chem.,* 1999, **64**, 925; (f) P. Molina, P. M. Fresneda and S. Delgado, *Synthesis*, 1999, 326.

11 Compounds **11** (ref. 10b and S. J. Holt and V. Petrow, *J. Chem. Soc.* 1948, 922) and **2** (ref. 1a, and 10c) are known in the literature. Melting points and spectral data are in agreement with that reported in the literature.