Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1795–1798

A short synthesis of (+)-harzialactone A and (*R*)-(+)-4-hexanolide via proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination of aldehydes

Shriram P. Kotkar, Gurunath S. Suryavanshi and Arumugam Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India

Received 29 May 2007; accepted 28 July 2007

Abstract—An efficient and short enantioselective synthesis of the antitumor marine metabolite, (+)-harzialactone A **1** and pheromone, (*R*)-(+)-4-hexanolide **2** using L-proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination of the respective aldehydes is described.

1. Introduction

Marine microorganisms have been a rich source of bioactive metabolites, especially those with unique structural features that might represent possible leads in drug discovery processes.[1] (+)-Harzialactone A **1**, a marine metabolite isolated from the culture broth of a strain of *Trichoderma harianium* OUPS-N115, has exhibited significant antitumor and cytotoxic activities against cultured P388 cells.[2] Mereyala et al. have synthesized harzialactone A **1** starting from D-glucose[3a] and D-xylose,[3b] each in seven steps with an overall yield of 15% and 24%, respectively. Recently, Wu et al. have synthesized the antipode of harzialactone A from L-malic acid in 40% overall yield.[3c] (*R*)-(+)-4-Hexanolide **2** is a component of a pheromone secreted by the female of dermestid beetles *Trogoderma glabrum*.[4] The beetle has been reported to respond only to the (*R*)-isomer of hexanolide.[4] Several asymmetric syntheses of **2** have been reported, which include (i) the stereospecific synthesis from chiral building blocks;[5a,b] (ii) the asymmetric reduction of prochiral ketones with Baker's yeast or chiral reducing agents;[5c–e] (iii) the resolution of alcohols[5f] and other asymmetric catalytic methods.[5g,h] Some of these methods are not amenable to scale up, due to large number of steps coupled with low yields.

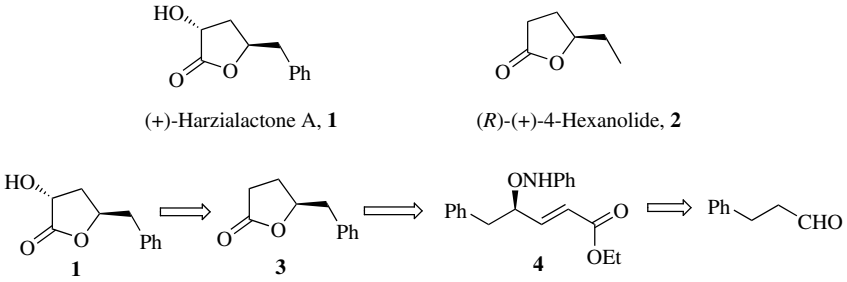
In recent years, proline has emerged as a 'universal catalyst' because of its high utility, especially in enantioselective aldol,[6] Diels–Alder,[7] Michael addition,[8] and α-functionalization of aldehydes[9] among many others.[10] Proline-catalyzed sequential transformations in particular,[11] are an emerging research field in organic synthesis. Herein we report a highly efficient and short synthesis of (+)-harzialactone A **1** and (*R*)-(+)-4-hexanolide **2** via L-proline-catalyzed sequential aminooxylation–olefination[11a,12] of the corresponding aldehydes (Schemes 2 and 3).

2. Result and discussion

Scheme 1 shows the retrosynthetic analysis of (+)-harzialactone A, wherein we envisaged the L-proline-catalyzed sequential aminooxylation–olefination strategy for introducing chirality into the molecule. Thus, 3-phenylpropanal was subjected to α-aminooxylation[13] with nitrosobenzene and L-proline at −20 °C, followed by in situ Horner–Wadsworth–Emmons (HWE) olefination with LiCl and DBU (Masamune–Roush protocol)[14] to furnish aminooxy olefinic ester **4** in 77% yield. Simultaneous reduction of both the C=C bond and the anilinoxy group in ester **4** was achieved with 10% Pd/C, H_2 (1 atm) to produce γ-hydroxy ester **5** in 92% yield. Intramolecular cyclization of hydroxyl ester **5** gave lactone **3** in 88% yield and 97% ee (determined by chiral HPLC analysis, Chiracel OD-H). Finally, diastereoselective α-hydroxylation[15] of lactone **3**

* Corresponding author. Tel.: +91 20 25902174; fax: +91 20 25902676; e-mail: a.sudalai@ncl.res.in

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.07.031



Scheme 1. Retrosynthetic analysis of (+)-harzialactone A **1**.

was achieved with KHMDS and 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (Davis oxaziridine) to afford **1** as a separable mixture of diastereomers (dr 2:1 *trans*/*cis*, as determined by ^{1}H NMR analysis of the crude mixture) with *trans*-lactone **1** [(+)-harzialactone A] as a major product (42% yield for *trans*-lactone) (>99% ee); $[\alpha]_D^{25} = +40$ (*c* 0.3, $CHCl_3$) {lit.[3c] $[\alpha]_D^{25} = -39.6$ (*c* 0.32, $CHCl_3$) for antipode of (+)-harzialactone A} (Scheme 2).

Similarly, the synthesis of (*R*)-(+)-4-hexanolide started with the same sequential protocol used for harzialctone A with *n*-butyraldehyde to produce **6** in 75% yield. Reduction of both the C=C bond and the anilinoxy group in ester **6** with 10% Pd/C, H_2 (1 atm) produced γ-hydroxy ester **7** in 84% yield, which on subsequent cyclization furnished (*R*)-4-hexanolide **2** in 95% yield and in 97% ee; $[\alpha]_D^{25} = +51.7$ (*c* 1, MeOH) {lit.[5c] $[\alpha]_D^{25} = +53.1$ (*c* 1, MeOH)} (Scheme 3).

3. Conclusion

In conclusion we have achieved a short and efficient synthesis of (+)-harzialactone A (overall yield 26.1%) and (*R*)-(+)-4-hexanolide (overall yield 59.8%) by employing proline-catalyzed sequential α-aminooxylation–HWE olefination of their respective aldehydes. Excellent yields, simple and environmentally friendly procedures, and the easy availability of the starting materials are some of the salient features of this approach.

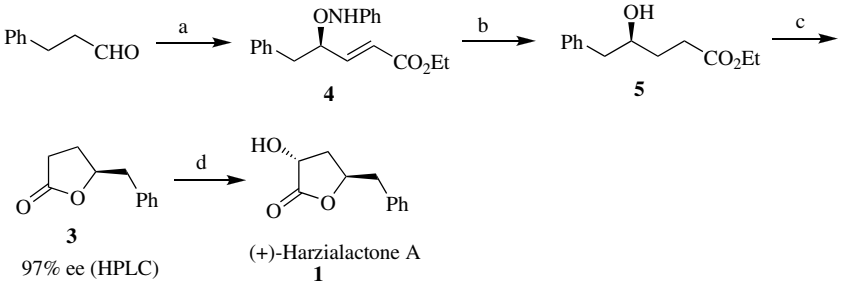
4. Experimental

4.1. General information

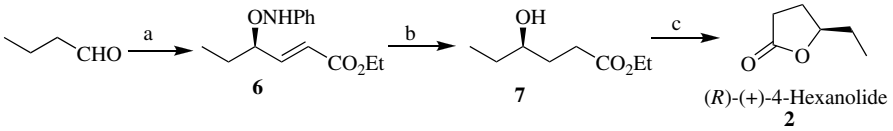
Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. Optical rotations were measured using the sodium D line on a JASCO-P-1020 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer. Enantiomeric excesses were measured using either chiral HPLC or by comparison with the specific rotation. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

4.2. (*R*)-Ethyl 4-anilinoxy-5-phenylpent-2-enoate 4

To a solution of nitrosobenzene (3 g, 28 mmol) and L-proline (483 mg, 15 mol %) in CH_3CN (60 mL) was added 3-phenylpropanal (4.5 g, 33.6 mmol) at −20 °C. The reaction mixture was stirred at the same temperature for 24 h fol-



Scheme 2. Reagents and conditions: (a) PhNO, L-proline (15 mol %), CH_3CN, −20 °C, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 77%; (b) H_2 (1 atm), Pd/C (10%), MeOH, 12 h, 92%; (c) EtOH, reflux, 5 h, 88%; (d) 2-[(4-Methylphenyl)sulfonyl]-3-phenyloxaziridine, KHMDS, THF, −78 °C, 1 h, 63%.



Scheme 3. Reagents and conditions: (a) PhNO, L-proline (15 mol %), −20 °C, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 75%; (b) H_2 (1 atm), Pd/C (10%), MeOH, 12 h, 84%; (c) EtOH, reflux, 5 h, 95%.

lowed by the addition of LiCl (1.7 g, 1.5 equiv), triethyl phosphonoacetate (9.4 g, 1.5 equiv), and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (4.2 g, 1 equiv). After stirring for 1 h, the reaction mixture was quenched with half saturated NH_4Cl and extracted with ethyl acetate (3×60 mL). Combined organic phases were concentrated and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (pet. ether–EtOAc = 88:12) afforded aminooxy olefinic ester **4**. Yield: 6.7 g, 77% yield; $[\alpha]_D^{25} = +47$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3028, 2979, 2937, 2358, 1714, 1600, 1494, 1454, 1369, 1271, 1178, 1029, 910, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, $J = 7.1$ Hz, 3H), 2.87–2.97 (dd, $J = 5.9$, 13.8 Hz, 1H), 3.04–3.15 (dd, $J = 7.7$, 13.8 Hz, 1H), 4.19 (q, $J = 7.2$, 2H), 4.58 (m, 1H), 5.97 (d, $J = 15.8$, 1H), 6.64 (d, $J = 7.9$ Hz, 1H), 6.97 (m, 3H), 7.16–7.30 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 40.0, 60.4, 83.9, 114.1, 121.9, 122.9, 126.6, 128.4, 128.8, 129.5, 136.8, 146.2, 148.1, 165.9; Elemental Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.8; N, 4.5. Found: C, 73.33; H, 6.73; N, 4.67.

4.3. (*S*)-Ethyl 4-hydroxy-5-phenylpentanoate 5

To a solution of **4** (5.0 g, 16 mmol) in MeOH was added 10% Pd/C (300 mg) carefully. The reaction mixture was then stirred in a hydrogen atmosphere (1 atm of H_2) for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite pad and concentrated to near dryness. The crude product was then purified by flash column chromatography (pet. ether–EtOAc = 75:25). Yield: 3.28 g, 92% yield; $[\alpha]_D^{25} = +14.5$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3488, 2927, 2360, 2331, 1770, 1731, 1602, 1494, 1178, 1022, 923, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.77–1.90 (m, 3H), 2.48 (dt, $J = 7.5$, 1.3 Hz, 2H), 2.65–2.75 (dd, $J = 7.9$, 13.5 Hz, 1H), 2.78–2.87 (dd, $J = 4.7$, 13.5 Hz, 1H), 3.85 (m, 1H), 4.11 (q, $J = 7.1$, 2H), 7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 30.7, 31.4, 44.0, 60.4, 71.8, 126.4, 128.4, 129.3, 138.1, 174.0; Elemental Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.14; H, 8.22.

4.4. (*S*)-5-Benzyl-dihydrofuran-2(3*H*)-one 3

A solution of hydroxyl ester **5** (2 g, 9 mmol) in dry ethanol (20 mL) was refluxed for 5 h. Removal of the solvent under reduced pressure and flash chromatographic purification gave lactone **3** as a brown colored liquid. Yield: 1.39 g, 88% yield; $[\alpha]_D^{25} = +24.7$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2925, 2360, 1771, 1602, 1456, 1180, 1022, 912, 734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.86–2.05 (m, 1H), 2.17–2.53 (m, 3H), 2.87–2.98 (dd, $J = 6.29$, 14.0 Hz, 1H), 3.03–3.13 (dd, $J = 6.0$, 14.0 Hz, 1H), 4.67–4.80 (m, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 28.4, 41.0, 80.5, 126.7, 128.4, 129.2, 135.7, 176; Elemental Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.11; H, 6.77. Chiracel OD-H column; 97% ee, *n*-hexane–*i*-PrOH (90:10 v/v); flow rate 1.0 mL/min; UV 214 nm; column temperature 25 °C; retention time: 14.95 min major (*S*-isomer) and 17.53 min minor (*R*-isomer) (compared with reported conditions[16]).

4.5. (+)-Harzialactone A 1

To a solution of KHMDS in dry THF (8 mL) at −78 °C was added lactone **3** (0.5 g, 2.8 mmol) in THF and the reaction mixture was stirred for 10 min followed by the addition of [(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (Davis oxaziridine) (814 mg, 2.8 mmol). After stirring at the same temperature for 1 h, the reaction mixture was quenched with aq NH_4Cl and extracted with ethyl acetate (3×15 mL). Purification by flash column chromatography gave **1** as a colorless solid in 63% yield with dr = 2:1. The diastereomers were separated by flash column chromatography (pet. ether–EtOAc = 70:30). Yield: 229 mg, 42% yield (after diastereomeric purification and recrystallization from *n*-hexane); mp = 80 °C (lit.[11] 82–84 °C); $[\alpha]_D^{25} = +40$ (*c* 0.3, $CHCl_3$) {lit.[14] $[\alpha]_D^{25} = -39.6$ (*c* 0.32, $CHCl_3$) for antipode of (+)-harzialactone A}; IR ($CHCl_3$) ν_{max} 3373, 2921, 2360, 2343, 1772, 1456, 1188, 1031, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.27–2.43 (m, 2H), 2.43 (br s, 1H), 2.96 (d, $J = 5.7$ Hz, 2H), 3.96 (t, $J = 8.1$ Hz, 1H), 4.91 (m, 1H), 7.19–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.3, 41.1, 67.0, 78.1, 127.2, 128.4, 129.5, 135.2, 177.2; Elemental Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.55; H, 6.58.

4.6. (*R*)-Ethyl 4-anilinoxyhex-2-enoate 6

To a solution of nitrosobenzene (3 g, 28 mmol) and L-proline (476 mg, 15 mol %) in CH_3CN (60 mL) was added *n*-butyraldehyde (2.94 mL, 33.6 mmol) at −20 °C. The reaction mixture was stirred at the same temperature for 24 h, followed by the addition of LiCl (1.7 g, 1.5 equiv), triethyl phosphonoacetate (9.4 g, 1.5 equiv) and DBU (4.2 g, 1 equiv). After stirring for 1 h, the reaction mixture was quenched with half saturated NH_4Cl and extracted with ethyl acetate (3×60 mL). The combined organic phases were concentrated and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (pet. ether–EtOAc = 90:10) afforded aminooxy olefinic ester **6** as brown liquid. Yield: 5.2 g, 75% yield; $[\alpha]_D^{25} = +88$ (*c* 2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3433, 2975, 2937, 2877, 2360, 1703, 1654, 1454, 1274, 1178, 1039, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.02 (t, $J = 7.4$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.62 (s, 1H), 1.66–1.99 (m, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.30 (m, 1H), 5.77 (d, $J = 15.9$ Hz, 1H), 6.93 (m, 4H), 7.24 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5, 14.1, 26.2, 60.3, 84.0, 114.2, 121.9, 122.8, 128.8, 146.9, 148.4, 165.9 ppm. Elemental Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.15; H, 7.28; N, 5.80.

4.7. (*R*)-Ethyl 4-hydroxyhexanoate 7

To a solution of **6** (3.0 g, 12 mmol) in MeOH was added 10% Pd/C (200 mg) carefully. The reaction mixture was then stirred under a hydrogen atmosphere (1 atm of H_2) for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad and concentrated to near dryness. The crude product was then purified by flash column chromatography (pet. ether–EtOAc = 80:20). Yield: 1.6 g, 84% yield; $[\alpha]_D^{25} = +27$ (*c* 2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3523, 2970, 2939, 2881, 2358, 2331, 1770, 1602, 1461, 1353, 1182,

960, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, $J = 7.4$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.48 (m, 2H), 1.76 (m, 2H), 2.44 (m, 3H), 3.53 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.64, 13.8, 29.8, 30.4, 31.4, 59.9, 71.8, 173.9 ppm. Elemental Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.69; H, 10.3.

4.8. (*R*)-(+)-4-Hexanolide 2

A solution of hydroxyl ester **7** (1 g, 6.2 mmol) in ethanol was refluxed for 5 h. Removal of the solvent under reduced pressure and flash chromatographic purification gave hexanolide **2** in 95% yield. Yield: 676 mg, 95% yield; $[\alpha]_D^{25} = +51.7$ (*c* 1, MeOH) {lit.[6] $[\alpha]_D^{25} = +53.1$ (*c* 1, MeOH)}; IR ($CHCl_3$) ν_{max} 754, 970, 1176, 1353, 1458, 1602, 1770, 2360, 2941, 2970, 3020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (t, $J = 7.4$ Hz, 3H), 1.58–1.96 (m, 3H), 2.31 (m, 1H), 2.50–2.59 (m, 2H), 4.44 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.35, 27.4, 28.4, 28.7, 82.13, 177.2 ppm. Elemental Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.0; H, 8.54.

Acknowledgements

S.P.K. thanks CSIR, New Delhi, for the award of senior research fellowship. The authors are thankful to Dr. B.D. Kulkarni, Head, Chemical Engineering and Process Development Division, for his support and encouragement.

References

1. Sims, J. J.; Rose, A. F.; Izac, R. R. In *Marine Natural Products*; Scheuer, P. J., Ed.; Chemical and Biological Perspectives; Academic Press: New York, 1978; Vol. 2, p 297.
2. Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A. *J. Antibiot.* **1998**, *51*, 33.
3. (a) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2305; (b) Mereyala, H. B.; Joe, M.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4071; (c) Jian, Y.-J.; Wu, Y.; Li, L.; Lu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2649.
4. Yarger, R. G.; Silverstein, R. M.; Burkholder, W. E. *J. Chem. Ecol.* **1975**, *1*, 323.
5. (a) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449; (b) Dhotare, B.; Hassarajni, S. A.; Chattopadhyay, A. *Enantiomer* **1999**, *4*, 431; (c) Mori, K.; Mori, H.; Sugai, T. *Tetrahedron* **1985**, *41*, 919; (d) Ghosh, S. K.; Chattopadhyay, S.; Mamdapur, V. R. *Tetrahedron* **1991**, *47*, 3089; (e) Ramachandran, P. V.; Brown, H. C.; Pitre, S. *Org. Lett.* **2001**, *3*, 17; (f) Jacobs, H. K.; Mueller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, *48*, 8891; (g) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928; (h) Arceo, E.; Odriozola, J. M.; Garcia, J. M.; Gonzalez, A.; Gil, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1617.
6. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
7. (a) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353; (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Synlett* **2003**, 1910.
8. Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.
9. For α-functionalization reviews: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjarsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296; (b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
10. For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.
11. (a) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637; (b) Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001; (c) Zhao, G.-L.; Liao, W.-W.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 4929; (d) Liao, W.-W.; Ibrahem, I.; Cordova, A. *Chem. Commun.* **2006**, 674; (e) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189.
12. Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.
13. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112; (d) Bøgevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109; (e) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
14. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
15. (a) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron Lett.* **1992**, *33*, 671; (b) Caputo, R.; Cecere, G.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **2002**, 3050.
16. Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219.