An efficient strategy for the synthesis of *syn* 1,3-diols *via* iterative acetate aldol reactions and synthesis of atorvastatin lactone

Sandeep Goyal, Bhautikkumar Patel, Ratnesh Sharma, Mangilal Chouhan, Kapil Kumar, Mukesh Gangar, Vipin A. Nair

PII: S0040-4039(15)01292-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.08.011
Reference: TETL 46595

To appear in: *Tetrahedron Letters*

Received Date: 9 June 2015
Revised Date: 4 August 2015
Accepted Date: 5 August 2015

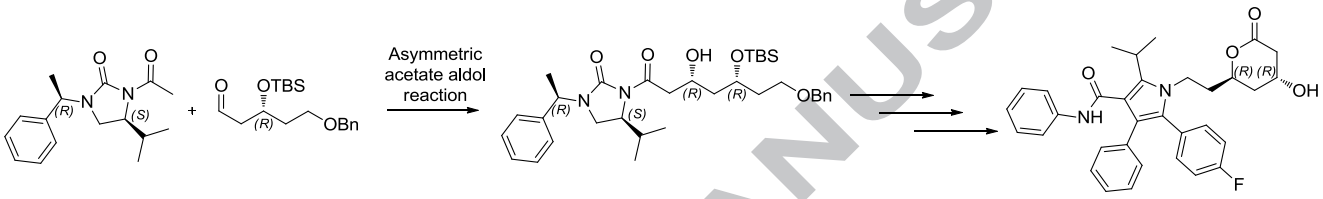
Please cite this article as: Goyal, S., Patel, B., Sharma, R., Chouhan, M., Kumar, K., Gangar, M., Nair, V.A., An efficient strategy for the synthesis of *syn* 1,3-diols *via* iterative acetate aldol reactions and synthesis of atorvastatin lactone, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.08.011

Graphical Abstract

An efficient strategy for the synthesis of *syn* 1,3-diols *via* iterative acetate aldol reactions and synthesis of atorvastatin lactone

Leave this area blank for abstract info.

Sandeep Goyal, Bhautikkumar Patel, Ratnesh Sharma, Mangilal Chouhan, Kapil Kumar, Mukesh Gangar and Vipin A. Nair*



Tetrahedron Letters
journal homepage: www.elsevier.com

An efficient strategy for the synthesis of *syn* 1,3-diols *via* iterative acetate aldol reactions and synthesis of atorvastatin lactone

Sandeep Goyal, Bhautikkumar Patel, Ratnesh Sharma, Mangilal Chouhan, Kapil Kumar, Mukesh Gangar and Vipin A. Nair*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, Mohali, Punjab 160062, India.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Atorvastatin
Aldol
Chiral auxiliary
Syn 1,3-diol
Diastereoselectivity

ABSTRACT

An efficient strategy for the synthesis of *syn* 1,3-diol has been developed, employing an imidazolidinone based chiral auxiliary *via* stereoselective and sequential double acetate aldol reactions. The *syn* 1,3-diol subunit was modified to obtain the C-7 carboxylic acid side chain and further subjected to reaction with a suitable 1,4-diketone under Paal Knorr conditions to obtain the atorvastatin lactone.

The occurrence of *syn*/*anti* 1,3-diols in natural products and drug molecules (Fig. 1) has drawn considerable attention over the years. Its stereoselective construction is of great interest to medicinal chemists,[1] and has resulted in the development of several synthetic strategies which includes diastereoselective reduction of *β*-hydroxy ketones,[2] sequential chain elongation,[3] asymmetric hydrogenation,[4] catalytic asymmetric Overman esterification,[5] enzymatic resolution[6], and enzymatic and nonenzymatic desymmetrization.[7] Based on our interests and literature reports on asymmetric aldol reactions and heterocycle synthesis,[8] we devised an aldol based strategy for the stereoselective synthesis of the 1,3-diol unit using a chiral auxiliary followed by an efficient synthesis of the atorvastatin lactone from the enantiomerically pure diol intermediate.

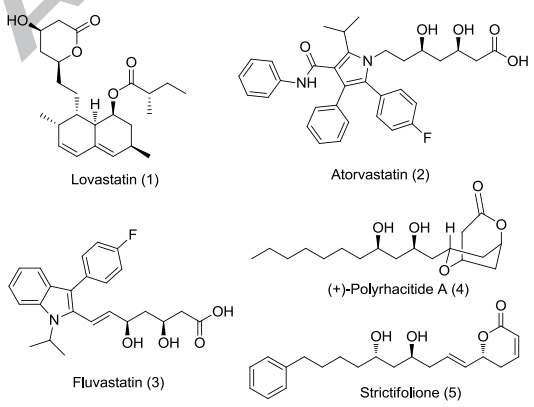


Figure 1. Structures of a few molecules containing 1,3-diol subunit

Atorvastatin (**2**, Lipitor®) is widely prescribed and well acknowledged as the world's leading cholesterol lowering drug in treating hypercholesterolemia because of its efficacy, safety and long term benefits.[9] Different methods to synthesize the statin side chains have been reported in the last two decades. This includes the chiral pool synthesis,[10] cycloaddition reaction,[11] resolution of racemates,[12] chemoenzymatic synthesis[13] and organocatalytic approaches.[14] However, low yields, expensive reagents, tedious workup procedures and significant loss in the case of resolution methods sustain considerable interests to develop newer protocols. The structure of atorvastatin comprises of a substituted pyrrole nucleus and a C-7 carboxylic acid side chain fragment bearing a *syn* 1,3-diol unit. Stereoselective synthesis of 1,3-diol unit requires the investment of chirality and an imidazolidinone based chiral auxiliary was envisaged to this objective.

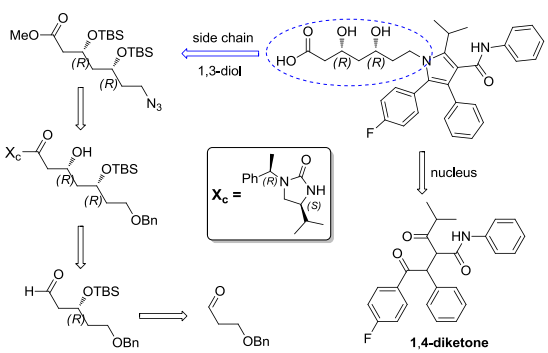
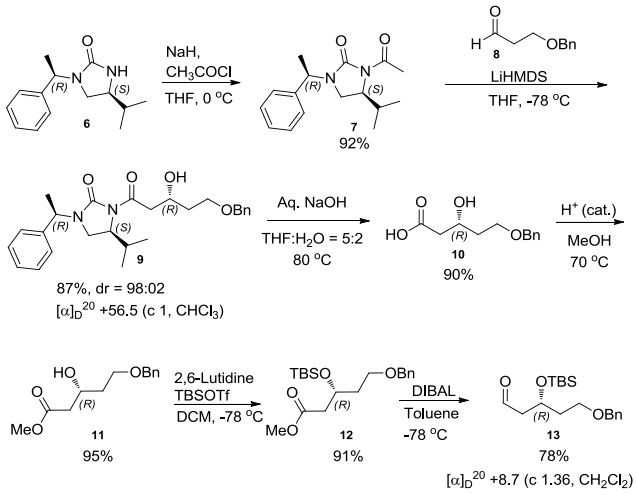


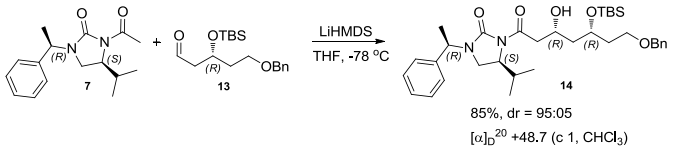
Figure 2. Retrosynthetic strategy for atorvastatin

* Corresponding author. Tel.: +91-172-229-2045; fax: +91-172-221-4692; e-mail: vn74nr@yahoo.com



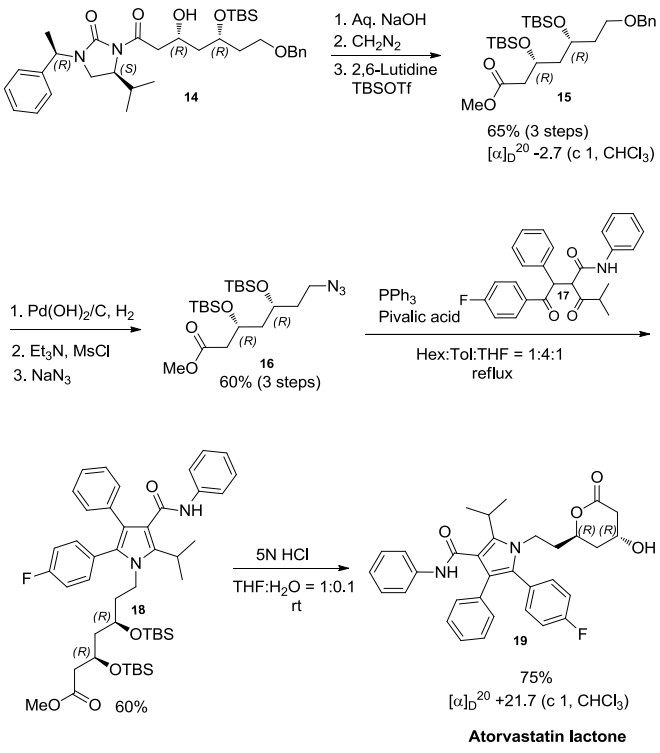
Scheme 1. Synthesis of chiral *β*-alkoxy aldehyde

A retrosynthetic analysis of the *syn* 1,3-diol unit containing carboxylic acid side chain of atorvastatin is illustrated in Figure 2. The synthesis and applications of (*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one as a chiral auxiliary in acetate aldol reactions employing LiHMDS with various aldehydes had been examined by us in detail recently.[8d] The reactions were found to afford the acetate aldol adducts stereoselectivily, bearing an *anti* relation between the newly generated hydroxy group and the resident isopropyl group of the auxiliary. The excellent selectivity imparted by the chiral auxiliary gave sufficient encouragement to carry out double acetate aldol reactions to gain access to the desired stereoisomer of the 1,3-diol subunit. The synthesis commenced with the acetylation of the chiral auxiliary (6) followed by treatment with LiHMDS to generate the corresponding lithium enolate (Scheme 1). It was reacted with 3-(benzyloxy)propanal (8) to give (*S*)-3-[(*R*)-5 (benzyloxy)-3-hydroxypentanoyl]-4-isopropyl-1-[(*R*)-1-phenylethyl] imidazolidin-2-one (9) in good yield, and a high diastereoselectivity of 98:02 as determined from the ^{1}H NMR spectra of the reaction mixture. The aldol adduct was subjected to hydrolysis using aq. NaOH under reflux condition to obtain the *β*-hydroxy acid (10). Using catalytic amount of sulfuric acid and methanol as a solvent under reflux condition gave the corresponding *β*-hydroxy ester (11). The free hydroxy group was protected thereafter using *tert*-butyldimethylsilyltriflate and 2,6-lutidine to give (*R*)-methyl-5-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)pentanoate (12). Reduction of the protected hydroxy ester was carried out using diisobutylaluminium hydride to afford (*R*)-5-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)pentanal (13). The optical rotation of the compound (13) was compared with literature[15] (reported $[\alpha]_D^{25}$ +9.8 (c 1.36, CH_2Cl_2), found $[\alpha]_D^{20}$ +8.7 (c 1.36, CH_2Cl_2), and an (*R*) configuration was unambiguously assigned to the newly generated stereocentre, confirming an *anti* relation between the hydroxy group and the isopropyl group for the major isomer of the acetate aldol adduct (9). The *β*-silyloxy aldehyde (13) was further subjected to a second acetate aldol reaction (Scheme 2) to obtain the 1,3-diol subunit. The reaction afforded good yield, and a high diastereoselectivity of 95:05 was observed in the ^{1}H NMR spectra of the reaction mixture. As before, an *anti* selectivity of the newly generated hydroxy group with respect to the isopropyl group of the auxiliary was expected again in the second acetate aldol reaction. More interestingly the newly formed hydroxy group would share a *syn* relation with the incumbent protected hydroxy group of the substrate, giving rise to a *syn* 1,3-diol subunit after desilylation.



Scheme 2. Iterative acetate aldol reaction of *β*-silyloxy aldehyde

We envisioned that the side chain of atorvastatin constructed from 3-(benzyloxy)propanal *via* iterative double acetate aldol reactions can be condensed with the appropriate 1,4-diketone as shown in scheme 3. Hydrolytic cleavage of the chiral auxiliary from the intermediate (14) using aq. NaOH under reflux conditions followed by esterification by diazomethane,[16] freshly prepared from nitrosomethyl urea,[17] and a *tert*-butyldimethylsilyl protection of the free hydroxy group using 2,6-lutidine and *tert*-butyldimethyl silyltrifluoromethanesulfonate gave (3*R*,5*R*)-methyl-7-(benzyloxy)-3,5-bis((*tert*-butyldimethylsilyl)oxy)heptanoate (15). This intermediate was subjected to debenzylation using catalytic amount of palladium hydroxide in methanol followed by mesylation using mesyl chloride and Et_3N at 0 °C, and then treated with sodium azide to give (3*R*,5*R*)-methyl-7-azido-3,5-bis((*tert*-butyldimethylsilyl) oxy)heptanoate (16). It was reacted with the 1,4-diketone (17)[18] under Paal-Knorr conditions by *in situ* generation of the corresponding amine using triphenyl phosphine, followed by a cyclization to afford (3*R*,5*R*)-methyl-3,5-bis((*tert*-butyldimethyl silyl)oxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1-*H*-pyrrol-1-yl)heptanoate (18). Finally deprotection of the silyl groups using 5N HCl afforded the atorvastatin lactone (19) in good yield and high steroeselectivity. The optical rotation of the atorvastatin lactone (19) was found to be in good agreement with the literature reported value for the (*R*,*R*) enantiomer (reported $[\alpha]_D$ +26.05 (c 1, $CHCl_3$); found $[\alpha]_D^{20}$ +21.7 (c 1, $CHCl_3$))[14d], reiterating the high *anti* selectivity observed for the lithium enolate in acetate aldol reactions of the imidazolidinone auxiliary (6).



Scheme 3. Synthesis of atorvastatin lactone

In conclusion, a convenient synthetic strategy to prepare *syn* 1,3-diol unit stereoselectively was explored by an imidazolidinone based auxiliary mediated sequential double acetate aldol reactions. The strategy afforded the *syn* 1,3-diol of the C-7 carboxylic acid side chain fragment of atorvastatin. Subsequent reaction with the appropriate 1,4-diketone under Paal-Knorr conditions provided access to atorvastatin lactone in good yield and selectivity.

Acknowledgments

Research funding from the Department of Science and Technology, Government of India, and a research fellowship to S.G. from the University Grants Commission (UGC-RGNF) are gratefully acknowledged.

Supplementary Material

Supplementary material which includes experimental procedures and compound data can be found in the online version.

References and notes

1. Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, *4*, 557.
2. (a) Narasaka, K.; Pai, F.-C. *Chem. Lett.* **1980**, 1415; (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233; (c) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155; (d) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923; (e) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190; (f) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009; (g) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419; (h) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868; (i) Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046.
3. (a) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2000**, 249; (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322; (c) Restorp, P.; Somfai, P. *Org. Lett.* **2005**, *7*, 893; (d) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801; (e) Kaneko, Y.; Matsuo, T.; Kiyooka, S.-i. *Tetrahedron Lett.* **1994**, *35*, 4107; (f) Kiyooka, S.-i.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett.* **1997**, *38*, 3553; (g) Kiyooka, S.-i.; Maeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371.
4. (a) Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron* **1993**, *49*, 1997; (b) Everaere, K.; Franceschini, N.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2002**, *43*, 2569; (c) Blandin, V.; Carpentier, J.-F.; Mortreux, A. *Eur. J. Org. Chem.* **1999**, 3421; (d) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629; (e) Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 87; (f) Fan, Q.-h.; Yeung, C.-h.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 4041; (g) Blanc, D.; Ratovelomanana-Vidal, V.; Marinetti, A.; Genêt, J.-P. *Synlett* **1999**, 480; (h) Cossy, J.; Eustache, F.; Dalko, P. I. *Tetrahedron Lett.* **2001**, *42*, 5005.
5. Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164 and references therein.
6. (a) Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942; (b) Levayer, F.; Rabiller, C.; Tellier, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1675; (c) Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237; (d) Bonini, C.; Chiummiento, L.; Funicello, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2755.
7. (a) Bonini, C.; Racioppi, R.; Viggiani, L.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1993**, *4*, 793; (b) Bonini, C.; Racioppi, R.; Righi, G.; Viggiani, L. *J. Org. Chem.* **1993**, *58*, 802; (c) Chênevert, R.; Rose, Y. S. *J. Org. Chem.* **2000**, *65*, 1707; (d) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9; (e) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120; (f) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161; (f) Devine, P. N.; Oh, T. *Tetrahedron Lett.* **1991**, *32*, 883.
8. (a) Kumar, V.; Khatik,G. L.; Nair, V. A. *Synlett* **2011**, 2997; (b) Chouhan, M.; Sharma, R.; Nair, V. A. *Appl. Organometal. Chem.* **2011**, *25*, 470; (c) Sharma, R.; Chouhan, M.; Sood, D.; Nair, V. A. *Appl. Organometal. Chem.* **2011**, *25*, 305; (d) Khatik, G. L.; Kumar, V.; Nair, V. A. *Org. Lett.* **2012**, *14*, 2442; (e) Chouhan, M.; Sharma, R.; Nair, V. A. *Org. Lett.* **2012**, *14*, 5672; (f) Kumar, V.; Kumar, K.; Pal, A.; Khatik, G. L.; Nair, V. A. *Tetrahedron* **2013**, *69*, 1747; (g) Goyal, S.; Patel, J. K.; Gangar, M.; Kumar, K.; Nair, V. A. *RSC Adv.* **2015**, *5*, 3187; (h) Laina, M. G.; Philip, G. H. *Tetrahedron: Asymmetry.* **2009**, *20*, 131.
9. (a) Tobert, J. A. *Nat. Rev. Drug Discovery*. **2003**, *2*, 517; (b) Pfefferkorn, J. A.; Song, Y.; Sun, K.-L.; Miller, S. R.; Trivedi, B. K.; Choi, C.; Sorenson, R. J.; Bratton, L. D.; Unangst, P. C.; Larsen, S. D.; Poel, T.-J.; Cheng, X.-M.; Lee, C.; Erasga, N.; Auerbach, B.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G.; Robertson, A.; Olsen, K.; Mertz, T.; Sekerke, C.; Pavlovsky, A.; Harris, M. S.; Bainbridge, G.; Caspers, N.; Chen, H.; Eberstadt, M. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 4538; (c) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. *J. Med. Chem.* **1991**, *34*, 357; (d) Hu, L.; Xiong, F.; Chen, X.; Chen, W.; He, Q.; Chen, F. *Tetrahedron: Asymmetry.* **2013**, *24*, 207; (e) Gao, J.; Guo, Y. H.; Wang, Y. P.; Wang, X. J.; Xiang, W. S. *Chin. Chem. Lett.* **2011**, *22*, 1159; (f) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160.
10. Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2279.
11. Pandey, P. S.; Srinivasa Rao, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129.
12. Bonini, C.; Chiummiento, L.; Funicello, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2755.
13. (a) Muller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 362; (b) Liu, J.; Hsu, C.-C.; Wong, C.-H., *Tetrahedron Lett.* **2004**, *45*, 2439; (c) Riise Moen, A.; Hoff, B. H.; Hansen, L. K.; Anthonsen, T.; Jacobsen, E. E. *Tetrahedron: Asymmetry* **2004**, *15*, 1551; (d) Tao, J.; Zhao, L.; Ran, N. *Org. Process Res. Dev.* **2007**, *11*, 259; (e) Bergeron, S.; Chaplin, D. A.; Edwards, J. H.; Ellis, B. S. W.; Hill, C. L.; Holt-Tiffin, K.; Knight, J. R.; Mahoney, T.; Osborne, A. P.; Ruecroft, G. *Org. Process Res. Dev.* **2006**, *10*, 661.
14. (a) Kawato, Y.; Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2011**, *67*, 6539; (b) Kawato, Y.; Chaudhary, S.; Kumagai, N.; Shibasaki, M. *Chem.-Eur. J.* **2013**, *19*, 3802; (c) George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 8544; (d) Sawant, P.; Maier, M. E. *Tetrahedron* **2010**, *66*, 9738.
15. Bates, R. W.; Song, P. *Synthesis* **2010**, *17*, 2935.
16. Arndt, F. *Organic synthesis* **1943**, *2*, 165.
17. Arndt, F. *Organic synthesis* **1943**, *2*, 461.
18. Cheekati, C. WO2012143933A1 2012.