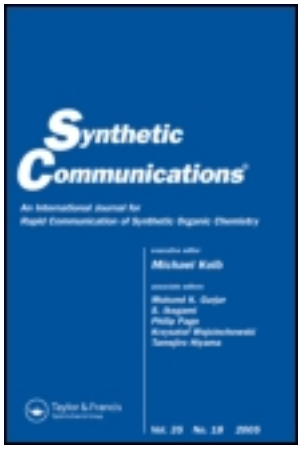


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Contiguous Generation of Quaternary and Tertiary Stereocenters: One-Pot Synthesis of Chroman-Fused S-Proline-Derived Chiral Oxazepinones

Ritesh Singh [a], Maloy Kumar Parai [a], Sankalan Mondal [a] & Gautam Panda [a]

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, Council of Scientific and Industrial Research, Lucknow, India

Accepted author version posted online: 01 Feb 2012.Published online: 18 Oct 2012.

To cite this article: Ritesh Singh , Maloy Kumar Parai , Sankalan Mondal & Gautam Panda (2013): Contiguous Generation of Quaternary and Tertiary Stereocenters: One-Pot Synthesis of Chroman-Fused S-Proline-Derived Chiral Oxazepinones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:2, 253-259

To link to this article: http://dx.doi.org/10.1080/00397911.2011.596301

Synthetic Communications®, 43: 253–259, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.596301

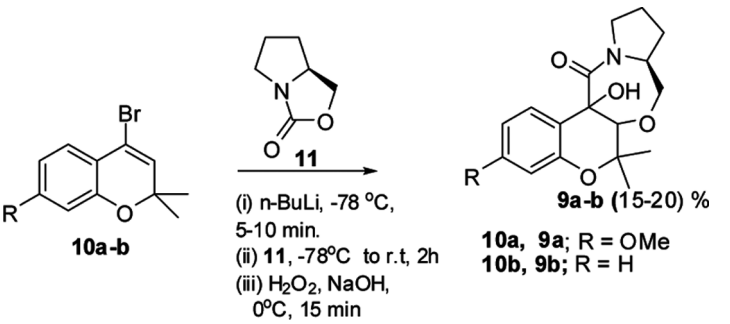
Taylor & Francis
Taylor & Francis Group

CONTIGUOUS GENERATION OF QUATERNARY AND TERTIARY STEREOCENTERS: ONE-POT SYNTHESIS OF CHROMAN-FUSED *S*-PROLINE-DERIVED CHIRAL OXAZEPINONES

Ritesh Singh, Maloy Kumar Parai, Sankalan Mondal, and Gautam Panda

Medicinal and Process Chemistry Division, Central Drug Research Institute, Council of Scientific and Industrial Research, Lucknow, India

GRAPHICAL ABSTRACT



Abstract *A new class of chroman-fused* S*-proline-derived chiral oxazepinones has been synthesized in one pot through contiguous generation of quaternary and tertiary stereocenters.*

Keywords Chromans; hydrogen peroxide; oxazepinone; α,β-unsaturated amide

INTRODUCTION

Synthesis of structurally modified heterocycles containing contiguous quaternary and tertiary stereocenters is a challenging task in synthetic organic chemistry.[1–3] Such polycycles with heteroatoms embedded at variant positions display diverse bioactivities[4] and have led to the discovery of many molecules that are now in clinical use as drugs.[5] It is known that the chroman belongs to a privileged subunit because of its abundance in numerous natural products[6] as well as in several pharmaceutically important molecules.[7–9] Examples include selective estrogen

Received May 4, 2011.

Address correspondence to Gautam Panda, Medical and Process Chemistry Division, Central Drug Rearch Institute, CSIR, Lucknow 226001, India. E-mail: gautam.panda@gmail.com; gautam_panda@cdri.res.in

receptor modulators (SERMs) (**1**),[8,9] NF-κB inhibitors[10] deguelin (**2**) and tephrosin (**3**), and natural compound suksdorfin,[11] which has anti-HIV properties (Fig. 1). In addition, the prevalence of the oxazepinone skeleton in synthetic as well as natural products, which exhibit varied bioactivities like anti-HIV (**5, 6, 7**) and antimalarial (holstiine, **8**),[12] encouraged us to design and synthesize a new scaffold **9** combining the chroman moiety with a chiral oxazepinone ring that has contiguous quaternary and tertiary stereocenters.

A rational design and synthesis of chroman- and thiochroman-fused tetracyclic skeletons through an acid-catalyzed intramolecular Nazarov reaction has been reported.[13c] Further, synthesis and biology of *S*-amino acids–based chiral polycycles have been reported from our research group in the past.[13] More importantly, to combine the two privileged substructures (chroman and chiral oxazepines) in a single scaffold, we use a short one-pot synthetic strategy to access the desired chroman-fused *S*-proline-derived chiral oxazepinones **9** having contiguous quaternary and tertiary stereocenters.

The retrosynthetic analysis of the target molecule in Scheme **1** depicts that **9** could be obtained from two starting materials, bromo compound **10** and tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one derivative **11**. We hypothesized building the coveted tetracyclic architectures **9** through an intermediate epoxide **20** (Scheme 1).

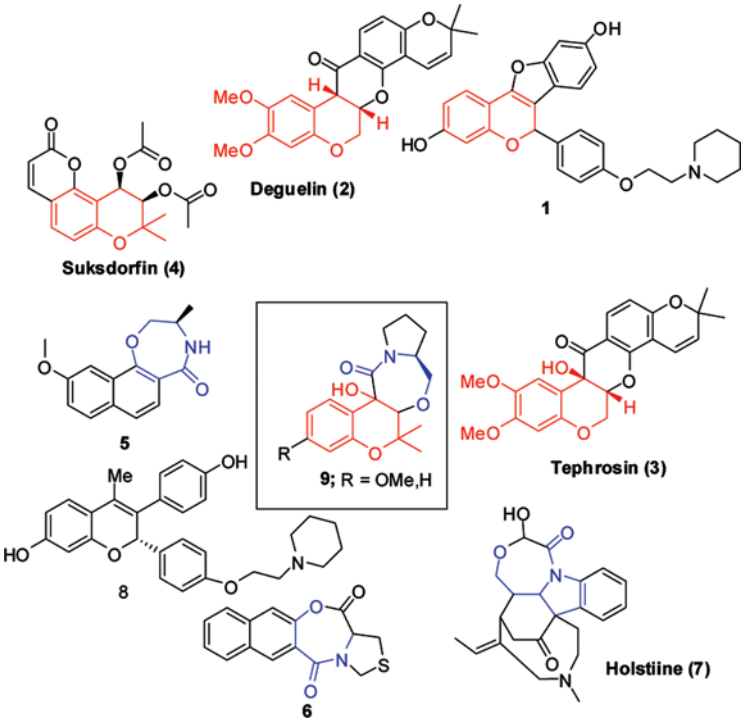
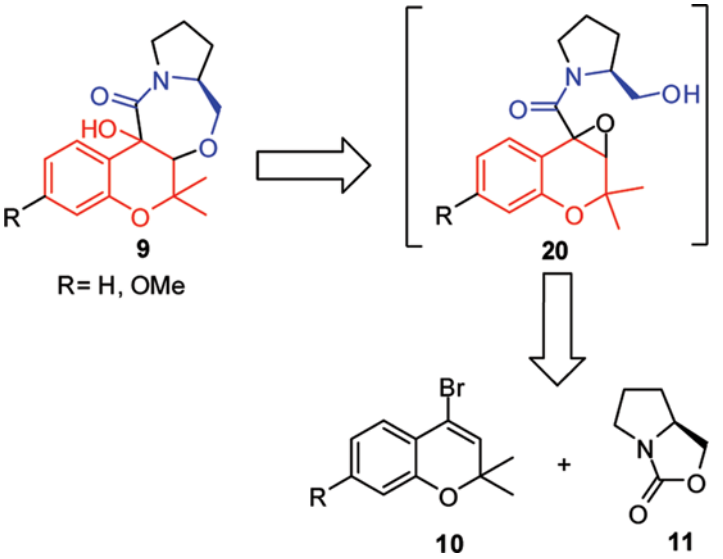


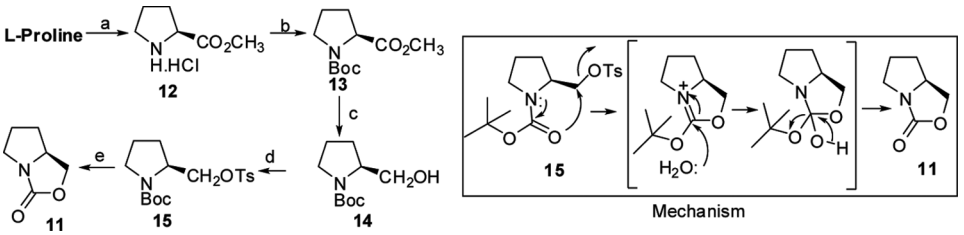
Figure 1. Representative natural (**2, 3, 4, 7**) and synthetic polycycles (**1, 5, 6, 8**) having chroman and oxazepinone rings and the designed molecule **9**. (Figure is provided in color online.)



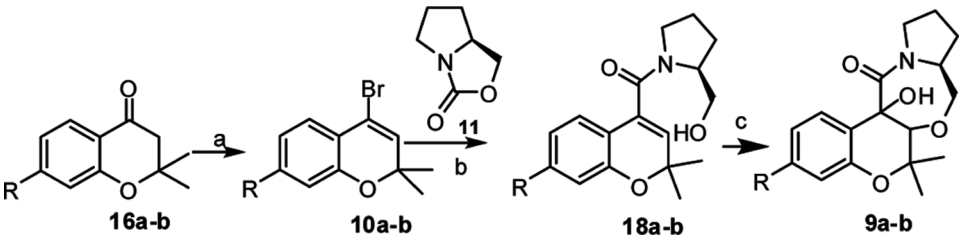
Scheme 1. Retrosynthetic analysis of **9**. (Figure is provided in color online.)

Compound **11** was synthesized from L-proline following the standard set of reaction conditions as shown in Scheme 2. L-Proline was esterified (**12**) by treating it with MeOH and thionyl chloride at 0 °C, followed by Boc protection of secondary amine in dry tetrahydrofuran (THF) using triethyl amine as base at rt, furnishing **13**, which on LAH reduction at 0 °C in dry THF provided alcohol **14**. Reaction of **14** with TsCl using pyridine as base in dry DCM furnished **15**. Compound **15** on heating at 60 °C in aqueous ethanolic solution gave tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one **11** in 5–10 min with very good yield, as shown in Scheme 2. Another starting material, compound **10**, was obtained[14,15] with 50–60% yield from corresponding ketone **16** after treatment with PBr_3 in dry benzene at 60 °C.

With both starting materials **10** and **11** in hand, we attempted the envisioned one-pot reaction to construct the desired scaffold **9** through cascade transformations including oxazolone ring opening and epoxide formation, followed by intramolecular nucleophilic substitution. In this quest, the anions generated through treatment



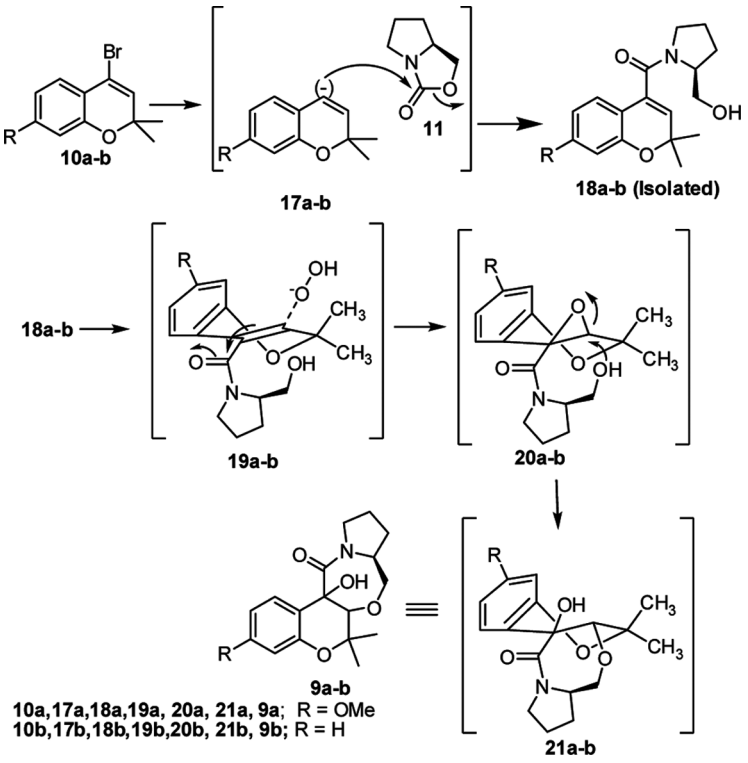
Scheme 2. Syntheses of **11**. Reagents and conditions: (a) MeOH/ $SOCl_2$, 0 °C–rt, 4 h, (b) Et_3N, $(Boc)_2O$, THF, 0 °C–rt, 5 h, 91%, (c) LAH, THF, 0 °C, 20–30 min, 97%, (d) Et_3N, TsCl, DCM, 0 °C, 3 h, 98%, (e) H_2O/EtOH, 60 °C, 5–10 min, 58%.



Scheme 3. Synthesis of target molecules **9**. Reagents and conditions: (a) PBr_3, benzene, 60 °C, 50–60%; (b) (i) *n*-BuLi, THF, −78 °C, 5–10 min; (ii) **11**, −78 °C to rt, 2 h; (c) H_2O_2, NaOH, EtOH, 0 °C, 15 min.

of *n*-BuLi on bromo derivatives **10** were reacted with **11** at −78 °C in dry THF for a period of 2 h. Further sequential addition of sodium hydroxide and hydrogen peroxide in ethanol medium at 0 °C furnished the desired product **9a** and **b**, albeit in poor yields (Schemes 3 and 4).

It is believed that initially the oxazolone ring in **11** was opened by the lithiated bromo derivatives **17a** and **b**, generating intermediate alcohols **18a** and **b**. The alkene present in **18a** and **b** furnished epoxidized product via hydrogen peroxide/NaOH,[16] at 0 °C. Inspection of the six-membered half-chair-like transition state of **19a** and **b**



Scheme 4. Probable mechanism for the formation of **9a** and **b**.

revealed that attack of hydroperoxide anion on alkene was obstructed from the proline side by steric hindrance, giving rise to epoxide **20a** and **b**. Intermediate **20a** and **b** on attack of primary alcohol might have furnished chroman fused *S*-proline derived chiral oxazepinones with contiguous quaternary and tertiary stereocenters. Isolation of compound **18a** and **b** indicates this pathway of reaction mechanism (Scheme 4). However, we could not confirm the existence of any other diastereomer either from ^{1}H or ^{13}C of the crude reaction mixture.

The structure and stereochemistry of *S*-proline-derived chiral oxazepinones were determined through incisive analysis of ^{1}H NMR, ^{1}H-^{1}H correlation spectroscopy (COSY), and ^{13}C spectra. Although the epoxidation of electron-deficient alkene using chiral catalyst followed by ring opening to install the chiral hydroxyl substituted quaternary stereocenter is well precedented,[17–19] epoxidation via hydrogen peroxide followed by ring opening in one pot was hitherto unknown.

In conclusion, a new class of chroman-fused *S*-proline-derived chiral oxazepinones has been synthesized in one pot through efficient cascade reactions, installing contiguous chiral quaternary and tertiary stereocenters. In addition, the scope of the reaction sequence is much broader, allowing high atom economy and synthesis of this type of tetracycles having close resemblance with natural product motifs.

EXPERIMENTAL

General Procedure for One-Pot Cyclization

n-BuLi (2.99 mmol) was added to a solution of bromo derivative **10a** and **b** (2.85 mmol) in THF (15 ml) at −78 °C and stirred for 5–10 min. Tetrahydropyrrolo[1,2-c]oxazol-3-one **11** (254 mg, 2.0 mmol) in THF (10 ml) was added and stirred at −78 °C for another 30 min and was brought to room temperature for a period of 2 h. Subsequently the compound was dissolved in ethanol, and sodium hydroxide solution (0.5 ml, 1 M)was added at 0 °C. Then the mixture was charged with 50% hydrogen peroxide solution (0.06 ml). After the completion of reaction (as observed on thin-layer chromatography; TLC) saturated solution of sodium sulfite was added and the resulting solution was evaporated. Then ethyl acetate was added, and the organic mixture was extracted by performing the usual workup. Column chromatography over silica gel and elution with ethylacetate in hexane furnished the desired compounds **9a** and **b** along with intermediate **18a** and **b**.

(8aS)-13a-Hydroxy-3-methoxy-6,6-dimethyl-8,8a,9,10,11,13a-hexahydro-6H-chromeno[4,3-f]pyrrolo[2,1-c][1,4]oxazepin-13(6aH)-one (9a)

IR (neat): 2933, 1687, 1348, 1216 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (dd, 1H, $J = 2$, 8.1), 6.58 (dd, 1H, $J = 2$, 8.1), 6.34 (s, 1H), 4.56–4.53 (m, 1H), 3.96–3.90 (m, 1H), 3.75 (s, 3H), 3.72–3.71 (m, 2H), 3.67–3.49 (m, 2H), 2.16–2.10 (m, 1H), 1.88–1.67 (m, 3H), 1.44 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 161.1, 154.0, 131.5, 118.4, 109.1, 101.9, 86.3, 78.3, 70.8, 55.6, 55.6, 48.2, 32.5, 30.1, 27.4, 22.5, 20.4; MS (ESI): m/z 334 $[M + H]+$. Anal. calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20; O, 24.00. Found: C, 67.76; H, 6.91; N, 4.34.

(2-Hydroxymethyl-pyrrolidin-1-yl)-(7-methoxy-2,2-dimethyl-2H-chromen-4-yl)-methanone (18a)

IR (neat): 2918, 1612, 1442, 1145, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (dd, 1H, $J = 2$, 8.1), 6.42 (dd, 1H, $J = 2$, 8.1), 6.40 (s, 1H), 5.56 (s, 1H), 4.99 (bs, 1H), 4.32–4.29 (m, 1H), 3.77 (s, 3H), 3.71–3.67 (m, 1H), 3.46–3.40 (m, 1H), 3.29–3.26 (m, 1H), 2.12–2.08 (m, 1H), 1.83–1.61 (m, 3H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 161.7, 154.4, 131.4, 126.1, 125.4, 111.5, 107.6, 103.0, 76.2, 67.2, 64.0, 61.4, 60.2, 55.7, 50.0, 46.3, 28.8, 27.9, 24.8, 22.5; MS (ESI): m/z 318 [M+H]+. Anal. calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41; O, 20.16. Found: C, 68.71; H, 7.90; N, 4.39.

ACKNOWLEDGMENTS

This research project was supported by Department of Science and Technology, New Delhi, India, in the form of a grant. Ritesh, Maloy, and Sankalan thank the Council of Scientific and Industrial Research for research fellowships. This is CDRI Communication No. 7345.

REFERENCES

1. Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388.
2. Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105.
3. Chrisotoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688.
4. (a) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Beyeler, A. L.; Potts, G. O.; Arnold, A. *J. Am. Chem. Soc.* **1959**, *81*, 1513; (b) Kierstead, R. W.; Faraone, A.; Boris, A. *J. Med. Chem.* **1967**, *10*, 177; (c) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Neumann, H. C.; Chritiansen, R. G.; Clarke, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 1478; (d) Li, X.; Singh, S. M.; Lourdusamy, M.; Merand, Y.; Veitleux, R.; Labrie, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1061; (e) Gupta, R.; Pathak, D.; Jindal, D. P. *Eur. J. Med. Chem.* **1996**, *31*, 241; (f) Anastasiou, A.; Catsoulacus, P.; Epitheor, K. *Farmakol. Farmakokinet. Int. Ed.* **1992**, *6*, 130; (g) Singh, H.; Jindal, D. P.; Yadav, M. R.; Kumar, M. *Prog. Med. Chem.* **1991**, *28*, 223; (h) Burbiel, J.; Bracher, F. *Steroids* **2003**, *68*, 587.
5. (a) Rossum, J. M.; Ariens, E. J. *Experientia* **1957**, *13*, 161; (b) Morand, P.; Lyall, J. *Chem. Rev.* **1968**, *68*, 85.
6. (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968; (c) Yenesew, A.; Kiplagat, J. T.; Derese, S.; Midiwo, J. O.; Kabaru, J. M.; Heydenreich, M.; Peter, M. G. *Phytochemistry* **2006**, *67*, 988.
7. Wallace, O. B.; Lauwers, K. S.; Dodge, J. A.; May, S. A.; Calvin, J. R.; Hinklin, R.; Bryant, H. U.; Shetler, P. K.; Adrian, M. D.; Geiser, A. G.; Sato, M.; Burris, T. P. *J. Med. Chem.* **2006**, *49*, 843.
8. Jain, N.; Xu, J.; Kanojia, R. M.; Du, F.; Jian-Zhong, G.; Pacia, E.; Lai, M. T.; Musto, A.; Allan, G.; Reuman, M.; Li, X.; Hahn, D.; Cousineau, M.; Peng, S.; Ritchie, D.; Russell, R.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2009**, *52*, 7544, and references cited therein.
9. Hajela, K.; Jha, A. K.; Pandey, J. *Bioorg. Med. Chem.* **2004**, *12*, 2239.
10. Nair, A. S.; Shishodia, S.; Ahn, K. S.; Kunnumakkara, A. B.; Sethi, G.; Aggarwal, B. B. *J. Immunol.* **2006**, *177*, 5612.

11. Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K. H. *J. Med. Chem.* **1999**, *42*, 2662.
12. (a) Frederich, M.; Hayette, M. P.; Tits, M.; De Mol, P.; Angenot, L. *Antimicrobial Agents Chemo.* **1999**, 2328; (b) Cherif, A.; Martin, G. E. *J. Nat. Prod.* **1990**, *53*, 793.
13. (a) Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S.; Panda, G. *Bioorg Med Chem.* **2006**, *14*, 1497; (b) Das, S. K.; Shagufta; Panda, G. *Tetrahedron Lett.* **2005**, *46*, 3097; (c) Singh, R.; Parai, M. K.; Panda, G. *Org. Biomol. Chem.* **2009**, *7*, 1858; Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881; (d) Mishra, J. K.; Rao, J. S.; Sastry, G. N.; Panda, G. *Tetrahedron Lett.* **2006**, *47*, 3357; (e) Shagufta; Panda, G. *Org. Biomol. Chem.* **2007**, *5*, 360; (f) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321; (g) Mishra, J. K.; Garg, P.; Dohare, P.; Kumar, A.; Siddiqi, M. I.; Ray, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1326; (h) Srivastava, A. K.; Panda, G. *Chem.-Eur. J.* **2008**, *14*, 4675; (i) Srivastava, A. K.; Das, S. K.; Panda, G. *Tetrahedron* **2009**, *65*, 5322; (j) Parai, M. K.; Panda, G. *Tetrahedron Lett.* **2009**, *50*, 4703; (k) Das, S. K.; Srivastava, A. K.; Panda, G. *Tetrahedron Lett.* **2010**, *51*, 1483; (l) Samanta, K.; Chakravarti, B.; Mishra, J. K.; Dwivedi, S. K. D.; Nayak, L. V.; Choudhry, P.; Bid, H. K.; Konwar, R.; Chattopadhyay, N.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 283; (m) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244; (n) Samanta, K.; Panda, G. *Org. Biomol. Chem.* **2010**, *8*, 2823–2828.
14. Ko, S. K.; Jang, H. J.; Kim, E.; Park, S. B. *Chem. Commun.* **2006**, *28*, 2962, and references cited therein.
15. (a) Gabbutt, C. D.; Hartley, D. J.; Hepworth, J. D.; Heron, B. M.; Kanjia, M.; Rahman, M. M. *Tetrahedron* **1994**, *50*, 2507; (b) Shagufta; Raghunandan, R.; Moulik, P. R.; Panda, G. *Tetrahedron Lett.* **2005**, *46*, 5337; (c) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 653; (d) Shagufta; Parai, M. K.; Panda, G. *Tetrahedron Lett.* **2005** *46*, 8849–8852; (e) Shagufta; Srivastava, A. K.; Panda, G. *Tetrahedron Lett.* **2006**, *47*, 1065–1070; (f) Parai, M. K.; Shagufta, Srivastava, A. K.; Kassack, M.; Panda, G. *Tetrahedron* **2008**, *64*, 9962–9976.
16. Sanchez, J.; Myers, T. N. Peroxides and peroxide compounds, organic peroxides; In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley-VCH Verlag, 2000.
17. Orru, R. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, *54*, 859.
18. Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1999**, *40*, 7303.
19. Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013.