RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Synthetic approach towards trisubstituted methanes and a chiral tertiary α-hydroxyaldehyde, a possible intermediate for tetrasubstituted methanes†

Cite this: *RSC Advances*, 2013, **3**, 12100

Received 16th April 2013,
Accepted 29th May 2013

DOI: 10.1039/c3ra41826j

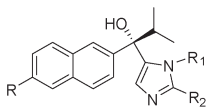
www.rsc.org/advances

Priyanka Singh, Subal Kumar Dinda, Shagufta and Gautam Panda*

A series of trisubstituted methanes containing aryl and heteroaryl rings, as well as a sulfur spacer between the central methano-carbon and benzene ring, is reported. In an approach towards asymmetric tetrasubstituted methane with high enantioselectivity, chiral tertiary α-hydroxyaldehyde has been synthesized through a Sharpless dihydroxylation on a disubstituted olefin, followed by the chemoselective oxidation of the primary alcohol.

Tri- and tetrasubstituted methanes (TRSMs) are interesting targets, which have attracted the attention of the synthetic community, not only for their interesting chemical properties but also for their pharmaceutical importance.[1] For example, they are known to possess a wide variety of biological activities such as anti-breast cancer,[2] antitubercular,[3] antiimplantation,[4] antiproliferative[5] *etc*. Clotrimazole (CLT) **1**, a membrane-permeant triarylmethane, is reported as having antimycotic and antiproliferative activity.[6,7] Related trisubstituted methanes such as econazole **2**, ketoconazole, nifedipine and miconazole are known to have diverse biological activities.[8] Recently, we have reported thiophene-containing TRSMs **3** which show significant antitubercular properties.[9] The antiproliferative activity of the non-imidazole part of clotrimazole analogs such as **4** has also been reported[10] (Scheme 1). Trisubstituted methanes (TRSMs) containing sulfide, sulfoxide or sulfone spacers have also been reported to show various biological activities.[11–14]

TRSMs have also served as suitable building blocks for the generation of dendrimers.[15] Dendrimers with specific peripheral functionalities have been used in bioconjugation,[16] cross-linking,[17] mass spectrometry,[18] fluorescence[19] and optics.[19] Triphenylmethyl (trityl) derivatives, which are also a class of TRSMs, are widely used as a family of protecting groups in organic synthesis to transiently block various functional moieties.[20]



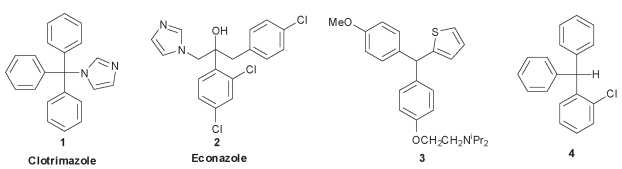
R_1, R_2=H; R=OMe

5

The tetrasubstituted methane, (1*S*)-1-(1*H*-imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanol **5**, a novel inhibitor of $C_{17,20}$-lyase and the key enzyme involved in androgen biosynthesis, is thought to be a promising target for the treatment of androgen-dependent prostate cancer[7] and is currently involved in clinical trials.[21,22] In spite of its potential bioactivity, only one stereocontrolled synthesis[22b] of compound **5** has been reported so far. Kawakami and coworkers[23] reported the large-scale racemic synthesis of **5**.

In a preliminary communication, we reported an approach towards the synthesis of TRSMs.[24] Herein, we report modified trisubstituted methanes containing benzene, naphthalene, benzopyran, imidazole and indole groups, and featuring a sulfur spacer between the central methano-carbon and the other aromatic rings. We also report a short and elegant approach towards a chiral tertiary α-hydroxyaldehyde, a possible intermediate for the asymmetric tetrasubstituted methane **5**, applying a Sharpless dihydroxylation for the introduction of chirality.

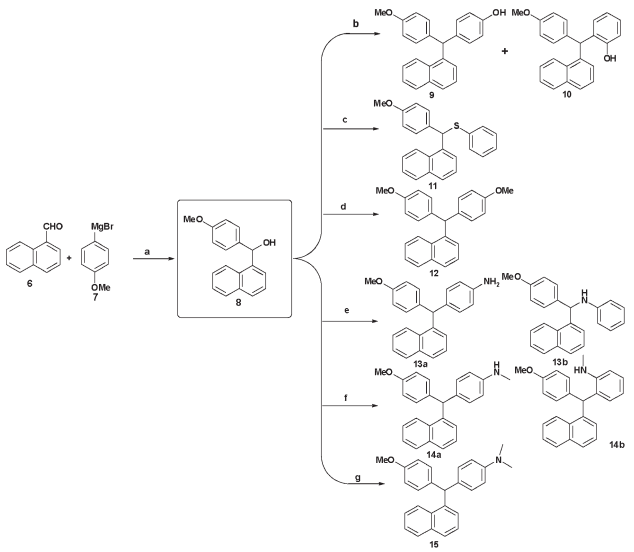
To begin with, 4-methoxy phenyl magnesium bromide **7** was reacted with naphthalene-1-carbaldehyde **6** at room temperature to generate the carbinol **8** (Scheme 2). It was treated with different nucleophiles, phenol, thiophenol, anisole, aniline, *N*-methylaniline, *N*,*N*-dimethylaniline to yield **9**, **10**, **11**, **12**, **13**,



Scheme 1 Biologically relevant trisubstituted methanes (TRSMs).

Medicinal and Process Chemistry Division, Central Drug Research Institute, CSIR, Lucknow-226001, UP, India. E-mail: gautam.panda@gmail.com; gautam_panda@cdri.res.in; Fax: 91-522-2623405; Tel: 91-522-2612411-18, Ext. 4385, 4603

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C-NMR spectra for all of the new compounds. See DOI: 10.1039/c3ra41826j



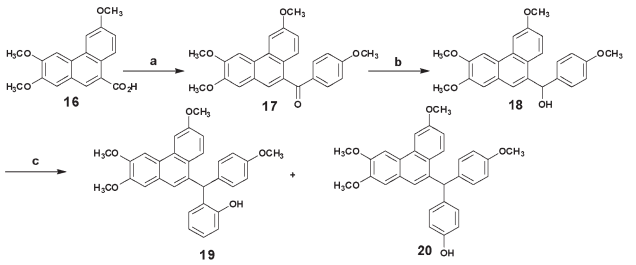
Scheme 2 Reagents and conditions: (a) THF, RT, 30 min, 58%; (b) phenol, conc. H_2SO_4, 55–60 °C, 30 min, 55%; (c) thiophenol, conc. H_2SO_4, 55–60 °C, 30 min, 82%; (d) anisole, conc. H_2SO_4, 55–60 °C, 30 min, 59%; (e) aniline, conc. H_2SO_4, 55–60 °C, 30 min, 55% (**13a**), 7% (**13b**); (f) *N*-methylaniline, conc. H_2SO_4, 55–60 °C, 30 min, 59% (**14a**) 9% (**14b**); (g) *N*,*N*-dimethylaniline, conc. H_2SO_4, 55–60 °C, 30 min, 60%.

14 and **15** as the respective alkylated products. Nucleophilic attack of the phenol and *N*-methyl aniline occurred through the *ortho* and *para* carbon atoms of the benzene ring respectively to give **9** and **14a** as the major products and **10** and **14b** as the minor products. We did not isolate any *ortho*-substituted product in the cases of anisole and *N*,*N*-dimethylaniline. It is interesting to note that nucleophilic attack occurred *via* the sulfur atom onto the carbinol carbon atom of **8** when thiophenol was used as the nuclephile. We did not isolate any *O*-alkylated product when phenol was used, but a similar *S*-alkylated product was isolated in the case of thiophenol.

Friedel–Crafts alkylation of carbinol **8** with anisole and *N*,*N*-dimethylaniline did not give any *ortho*-substituted products, possibly due to the steric hindrance between the naphthalene ring proton and the protons of the methoxy and *N*,*N*-dimethylaniline groups. Sulfur, being a good nucleophile, will prefer to attack the carbinol in the Friedel–Crafts alkylation, instead of attacking through a carbon of the benzene core.

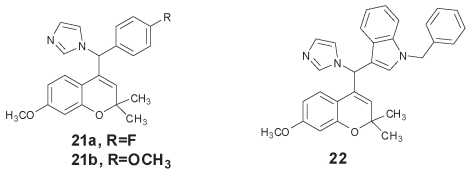
To obtain trisubstituted methanes through an alternative methodology, compound **16** was treated with anisole in the presence of polyphosphoric acid (PPA) to afford the methanone derivative **17** in 58% yield. The reduction of the carbonyl group of methanone **17** with lithium aluminium hydride (LAH) in THF at 0 °C generated the carbinol **18** in 83% yield. Further, Friedel–Crafts arylation with phenol in the presence of a catalytic amount of conc. H_2SO_4, and benzene as the solvent, gave **19** as the minor product and **20** as the major product by nucleophilic attack of the phenol through the *ortho* and *para* positions respectively on the carbon atom of carbinol **18** (Scheme 3).

Since we are involved in the design and synthesis of biologically-important TRSMs[24] as possible non-steroidal aromatase inhibitors, as well as anti-TB agents, we have undertaken the



Scheme 3 Reagents and conditions: (a) anisole, PPA, 100 °C, 2 h, 58%; (b) LAH, THF, 0 °C–RT, 2 h, 83%; (c) phenol, benzene, conc. H_2SO_4, 55–60 °C, 30 min, 10% (**19**) and 24% (**20**).

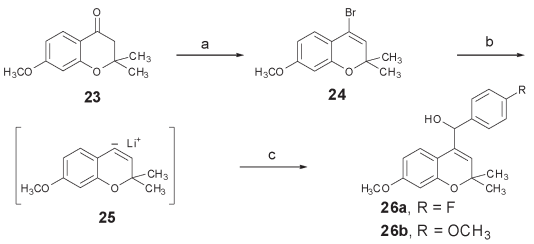
synthesis of the benzopyran and imidazole-based TRSMs **21** and **22.**



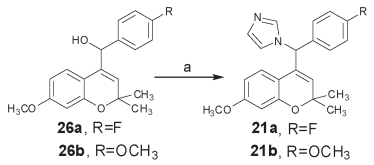
Treatment of compound[25,26] **23** with phosphorus tribromide afforded 4-bromo-7-methoxy-2,2-dimethyl-2*H*-chromene **24**, which was obtained as a pale yellow oil in 62% yield. Addition of *n*-butyl lithium to 4-bromo chromene **24** in THF at −78 °C under N_2 for 10–15 min afforded 4-chromenyl lithium **25**, which was then reacted with *para*-fluoro benzaldehyde and *para*-methoxy benzaldehyde to give **26a** and **26b** in 51% and 70% yields respectively (Scheme 4).

With compounds **26a–b** in hand, we proceeded towards the synthesis of the target compounds **21** and **22.** It was decided to convert the carbinols **26a–b** to the bromo derivatives, where the nucleophilic displacement of bromine by imidazole was expected to yield **21**. Unfortunately, reaction of carbinols **26a–b** with phosphorus tribromide (PBr_3) at 0 °C yielded no bromo derivative, but rearranged products, saturated ketones and exocyclic olefins, were isolated.[27]

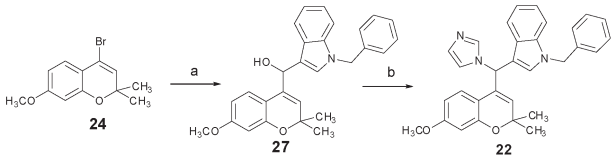
When carbinols **26a–b** did not yield the required products, an alternative strategy was adopted. A literature search revealed that the hydroxyl group can be replaced by imidazole through treatment with 1,1′-carbonyldiimidazole (CDI).[28] Towards this



Scheme 4 Reagents and conditions: (a) PBr_3, benzene, 80 °C, 6 h, 62%; (b) *n*-BuLi, THF, −78 °C, 15–20 min; (c) 1 h, *p*-fluoro benzaldehyde, 51%, *p*-methoxy benzaldehyde, 70%.



Scheme 5 Reagents and conditions: (a) CDI, THF, reflux, 12 h, 33% (**21a**) and 31% (**21b**).



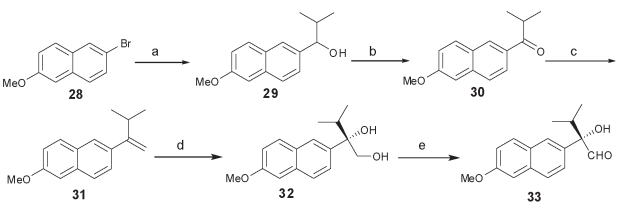
Scheme 6 Reagents and conditions: (a) i) *n*-BuLi, THF, −78 °C, 15–20 min, ii) *N*-benzylated indole-3-carboxaldehyde, 1 h, 50%; (b) CDI, THF, reflux, 12 h, 33%.

objective, **26a–b** were refluxed with CDI in THF to afford **21a** and **21b** in 33% and 31% yields respectively (Scheme 5).

The target compound **22** was also synthesized following the above-mentioned route. 4-Chromenyl lithium **25** synthesized from bromo derivative **24** was reacted with *N*-benzylated indole-3-carboxaldehyde at −78 °C under N_2 to give carbinol **27**, which was then converted to **22** by using CDI in THF at room temperature with 33% yield, (Scheme 6).

With the aim of accessing asymmetric TRSM-like structures,[29] the synthesis of chiral tertiary α-hydroxyaldehyde was undertaken which could be an advanced intermediate for the synthesis of **5**. The Sharpless dihydroxylation[30] was envisaged as a powerful tool to introduce chirality on disubstituted olefins, a precursor for asymmetric TRSMs.

The synthesis was initiated with the lithiation of commercially available 2-bromo-6-methoxy naphthalene **28** with *n*-BuLi at −78 °C, followed by addition of isobutyraldehyde to yield the benzyl alcohol **29**. The Swern oxidation of **29** provided ketone **30** which, after a Wittig olefination using methylene triphenylphosphorane (generated *in situ*) in THF, generated **31** in 78% yield. The Sharpless asymmetric dihydroxylation of olefin **31** with AD-mix-α[30,32] in *t*-BuOH–H_2O (1 : 1) at 0 °C for 28 h provided the crude product which, on recrystallisation twice from EtOAc–petroleum ether, gave the pure diol **32** in 72% yield with 92% ee. The selective oxidation of the primary alcohol of **32** was achieved under standard Swern oxidation conditions to furnish the asymmetric α-hydroxyaldehyde **33** in 81% yield, which could be an advanced intermediate for the synthesis of **5** (Scheme 7). The van Leusen imidazole synthesis,[31] a unique multicomponent reaction, may allow access to novel imidazoles from aldehydes using substituted TosMIC reagents in the presence of suitable amines. Other suitable methods may also yield **5** and will be reported elsewhere.



Scheme 7 Reagents and conditions: (a) i) *n*-BuLi, THF, −78 °C, 20 min, ii) isobutyraldehyde, 2 h, 88%; (b) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2, 2 h, 80%; (c) $Ph_3P^+CH_3I^-$, *t*-BuOK, THF, 0 °C– RT, 10 h, 78%; (d) AD-mix-α, *t*-BuOH–H_2O (1 : 1), 0 °C, 24 h, 72%; (e) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2, 2 h, 81%.

Conclusion

We have developed a very short and easy synthetic route for the preparation of trisubstituted methanes (TRSMs) containing aryl and heteroaryl rings, as well as featuring a sulfur spacer between the central methano-carbon and the aromatic ring. A new enantioselective synthesis of chiral tertiary α-hydroxyaldehyde, which could be an advanced intermediate of asymmetric tetrasubstituted methanes (TRSMs), is developed. Both enantiomers of the TRSM could be obtained by varying the ligands in the Sharpless asymmetric dihydroxylation.

Acknowledgements

This research project was supported by the Department of Science and Technology (DST), New Delhi, India. Priyanka, Subal and Shagufta thank CSIR for providing fellowships. Sailaja IReddy is thanked for the preparation of some of the starting materials. This is CDRI commn no 8468.

References

1 V. Nair, S. Thomas, S. C. Mathew and K. G. Abhilash, *Tetrahedron*, 2006, **62**, 6731–6747.
2 Shagufta, A. K. Srivastava, R. Sharma, R. Mishra, A. K. Balapure, P. S. R. Murthy and G. Panda, *Bioorg. Med. Chem.*, 2006, **14**, 1497–1505.
3 (*a*) Shagufta, A. Kumar, G. Panda and M. I. Siddiqi, *J. Mol. Model.*, 2007, **13**, 99–109; (*b*) G. Panda, Shagufta, A. K. Srivastavaa, M. K. Parai, S. K. Das, A. K. Srivastava, V. Chaturvedi, A. N. Gaikwad and S. Sinha, *Eur. J. Med. Chem.*, 2007, **42**, 410–419.
4 N. Srivastava, Sangita, S. Ray, M. M. Singh, A. Dwivedi and A. Kumar, *Bioorg. Med. Chem.*, 2004, **12**, 1011–1021.
5 R. A. Al-Qawasmeh, Y. Lee, M. Y. Cao, X. Gu, A. Vassilakos, J. A. Wright and A. Young, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 347.
6 (*a*) M. Terrier, T. Boubaker, L. Xiao and P. G. Farrell, *J. Org. Chem.*, 1992, **57**, 3924; (*b*) R. Muthyala, A. R. Katritzky and X. Lan, *Dyes Pigm.*, 1994, **25**, 303; (*c*) R. Aldag, Photochromism Based on Dissociation Processes, in *Photochromism: Molecules and Systems*, ed. H. Durr and H. Bouas-Laurent, Elsevier, London, 1990, and references cited therein.
7 M. Recanatini, A. Cavalli and P. Valenti, *Med. Res. Rev.*, 2002, **22**, 282.
8 A. S. Bhatnagar, A. Hausler, K. Schieweck, M. Lang and R. Bowman, *J. Steroid Biochem. Mol. Biol.*, 1990, **37**, 1021.
9 M. K. Parai, G. Panda, V. Chaturvedi, Y. K. Manju and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 289–292.

10 H. Vanden Bossche, G. Willemsens, I. Roels, D. Bellens, H. Moereels, M. C. Coene, L. Le Jeune, W. Lauwers and P. A. Janssen, *Biochem. Pharmacol.*, 1990, **40**, 1707.
11 F. Novelli, B. Tasso and F. Sparatore, *Farmaco*, 1999, **54**, 354–358.
12 C. S. Rouvier, B. Pradines, M. Berthelot, D. Parzy and J. Barbe, *Eur. J. Med. Chem.*, 2004, **39**, 735–744.
13 U. Galli, L. Lazzarato, M. Bertinaria, G. Sorba, A. Gasco, S. Parapini and D. Taramelli, *Eur. J. Med. Chem.*, 2005, **40**, 1335–1340.
14 J. Z. Vlahakis, R. T. Kinobe, K. Nakatsu, W. A. Szarek and I. E. Crandall, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2396–2406.
15 L. A. Baker, L. Sun and R. M. Crooks, *Bull. Korean Chem. Soc.*, 2002, **23**, 647.
16 H. Koster, S. Beck, J. M. Coull, T. Dunne, B. D. Gildea, C. Kissinger and T. O'Keeffe, *Nucleic Acids Symp. Ser.*, 1991, **24**, 318.
17 (*a*) M. Kwiatkowski and J. B. Chattopadhyaya, *Nucleic Acids Symp. Ser.*, 1984, **14**, 299; (*b*) R. Ramage and F. O. Wahl, *Tetrahedron Lett.*, 1993, **34**, 7133; (*c*) R. L. Letsinger and J. L. Finnan, *J. Am. Chem. Soc.*, 1975, **97**, 7197.
18 (*a*) M. S. Shchepinov, R. Chalk and E. M. Southern, *Tetrahedron*, 2000, **56**, 2713; (*b*) J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1978, 639.
19 (*a*) R. Breslow, L. Kaplan and D. LaFollette, *J. Am. Chem. Soc.*, 1968, **90**, 4056; (*b*) E. F. Fisher and M. H. Caruthers, *Nucleic Acids Res.*, 1983, **11**, 1589; (*c*) J. L. Fourrey, J. Varenne, C. Blonski, P. Dousset and D. Shire, *Tetrahedron Lett.*, 1987, **28**, 5157; (*d*) H. Meier and S. Kim, *Eur. J. Org. Chem.*, 2001, 1163; (*e*) A. Noack and H. Hartmann, *Chem. Lett.*, 2002, 644; (*f*) S. Brasselet, F. Cherioux, P. Audebert and J. Zyss, *Chem. Mater.*, 1999, **11**, 1915.
20 M. S. Shchepinov and V. A. Korshun, *Chem. Soc. Rev.*, 2003, **32**, 170.
21 (*a*) O. O. Clement, C. M. Freenman, R. W. Hartmann, V. D. Handratta, T. S. Vasaitis, A. M. H. Brodie and V. C. O. Njar, *J. Med. Chem.*, 2003, **46**, 2345; (*b*) J. Kawakami, K. Kimura and M. Yamaoka, *Synthesis*, 2003, 677; (*c*) A. M. H. Brodie and V. C. O. Njar, *J. Med. Chem.*, 2003, **46**, 2345; (*d*) J. Kawakami, K. Kimura and M. Yamaoka, *Synthesis*, 2003, 677.
22 (*a*) N. Matsunaga, T. Kaku, A. Ojida, T. Tanaka, T. Hara, M. Yamaoka, M. Kusaka and A. Tasaka, *Bioorg. Med. Chem.*, 2004, **12**, 4313; (*b*) N. Matsunaga, T. Kaku, A. Ojida and A. Tasaka, *Tetrahedron: Asymmetry*, 2004, **15**, 1555; (*c*) N. Matsunaga, T. Kaku, A. Ojida and A. Tasaka, *Tetrahedron: Asymmetry*, 2004, **15**, 2021.
23 J. Kawakami, K. Kimura and M. Yamaoka, *Org. Process Res. Dev.*, 2007, **11**, 206.
24 (*a*) G. Panda, Shagufta, J. K. Mishra, V. Chaturvedi, A. K. Srivastava, R. Srivastava and B. S. Srivastava, *Bioorg. Med. Chem.*, 2004, **12**, 5269–5276; (*b*) G. Panda, Shagufta, A. K. Srivastava and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5222–5225; (*c*) G. Panda, J. K. Mishra, S. Sinha, A. K. Gaikwad, A. K. Srivastava, R. Srivastava and B. S. Srivastava, *ARKIVOC*, 2005, **2005**(2), 29–45.
25 H. J. Kabbe, *Synthesis*, 1978, 886–887.
26 (*a*) C. D. Gabbutt, D. J. Hartley, J. D. Hepworth, B. M. Heron, M. Kanjia and M. M. Rahman, *Tetrahedron*, 1994, **50**, 2507–2522; (*b*) C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *J. Chem. Soc., Perkin Trans. 1*, 1994, 653–657.
27 M. K. Parai, Shagufta, A. K. Srivastava, M. Kassack and G. Panda, *Tetrahedron*, 2008, **64**, 9962–9976.
28 (*a*) M. Pascal, M. Le Borgne, M. Palzer, G. Le Baut and R. W. Hartmann, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1553–1555; (*b*) M. Le Borgne, P. Marchand, B. Delevoye-Seiller, J. M. Robert, G. Le Baut, R. W. Hartmann and M. Palzer, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 333–336; (*c*) R. Whomsley, E. Fernandez, P. J. Nicholls, H. J. Smith, P. Lombardi and V. J. Pestellini, *J. Steroid Biochem. Mol. Biol.*, 1993, **44**, 675–676; (*d*) S. Yahiaoui, C. Pouget, C. Fagnere, Y. Champavier, G. Habrioux and A. Chulia, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5215–5218.
29 (*a*) M. K. Parai, G. Panda, V. Chaturvedi, Y. K. Manju and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 289–292; (*b*) G. Panda, M. K. Parai, A. K. Srivastava, V. Chaturvedi, Y. K. Manju and S. Sinha, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2009, **48**, 1121–1127; (*c*) M. K. Parai, G. Panda, V. Chaturvedi, Y. K. Manju and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 289–292; (*d*) S. K. Das, G. Panda, V. Chaturvedi, Y. S. Manju, A. K. Gaikwad and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5586–5589; (*e*) Shagufta, A. Kumar, G. Panda and M. I. Siddiqi, *J. Mol. Model.*, 2007, **13**, 99–109; (*f*) G. Panda, M. K. Parai, S. K. Das, Shagufta, M. Sinha, V. Chaturvedi, A. K. Srivastava, Y. S. Manju, A. N. Gaikwad and S. Sinha, *Eur. J. Med. Chem.*, 2007, **42**, 410–419.
30 (*a*) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483; (*b*) H. Becker and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 448.
31 (*a*) A. M. van Leusen, J. Wilderman and O. H. Oldenzeil, *J. Org. Chem.*, 1977, **42**, 1153; (*b*) A. M. van Leusen, *Lect. Heterocycl. Chem.*, 1980, **5**, S–111.
32 (*a*) A. Ramacciotti, R. Fiaschi and E. Napolitano, *Tetrahedron: Asymmetry*, 1996, **7**, 1101; (*b*) S. A. Weissman, K. Rossen and P. Reider, *Org. Lett.*, 2001, **3**, 2513; (*c*) N. J. Lawrence and S. M. Bushell, *Tetrahedron Lett.*, 2001, **42**, 7671.