A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2023** (vi) 202311954

An efficient synthesis of optically active herbicide (*S*)-metolachlor *via* reductive ring opening of 2-methoxymethylaziridine

Viswanadh Nalla,[a] Mohammad Mujahid, [ab] Murugesan Sasikumar, [a] Prashant Mujumdar, [a] and Murugan Muthukrishnan [a]*

[a]*Division of Organic Chemistry, CSIR-National Chemical Laboratory (NCL), Dr. Homi Bhabha Road, Pune 411 008, India*

[b]*Department of Chemistry, Shri. Dr. R. G. Rathod Arts & Science College, Murtizapur, Dist Akola. India*

Email: m.muthukrishnan@ncl.res.in

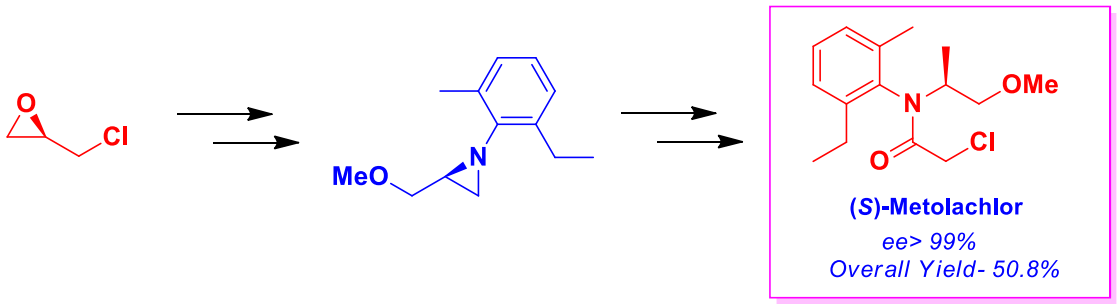
This manuscript is dedicated to Prof. Ahmed Kamal on the occasion of his 65th birthday

Received mm-dd-yyyy **Accepted Manuscript** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

An efficient synthesis of a well known chiral herbicide, (*S*)-metolachlor has been described using 2-methoxymethylaziridine ring formation and reductive ring opening as key steps using commercially available (*R*)-epichlorohydrin. The present protocol delivers the required enantiomer of metolachlor in overall yield of 50.8% and high enantiopurity (>99%).



Keywords: Metolachlor, epoxide, aziridine, herbicide synthesis, epoxide ring opening

Introduction

Many pharmaceutical and agrochemical companies have limited the use of racemates which contain both the active and inactive isomers in equimolar ratio. Due to the large variations in biological activities of the two enantiomers, development of new strategies for the production of enantiopure compounds has increased remarkably.[1] Metolachlor is a widely used herbicide which comprises four stereoisomers, of which two are inactive. The stereoisomers arise from the combination of a chiral center in the side chain and a chiral axis between the aromatic ring and nitrogen atom.[2] Previously, metolachlor was applied as a racemate with a brand name Dual®, but later it was found that about 95% of the herbicidal activity of metolachlor exists in the two 1-*S* diastereomers which means that (*S*)-enantiomers possess higher herbicidal activity than the (*R*)-enantiomers. Therefore the racemate was replaced by the active (*S*)-isomer which was marketed under the trade name Dual Magnum® (Fig.1).[3]

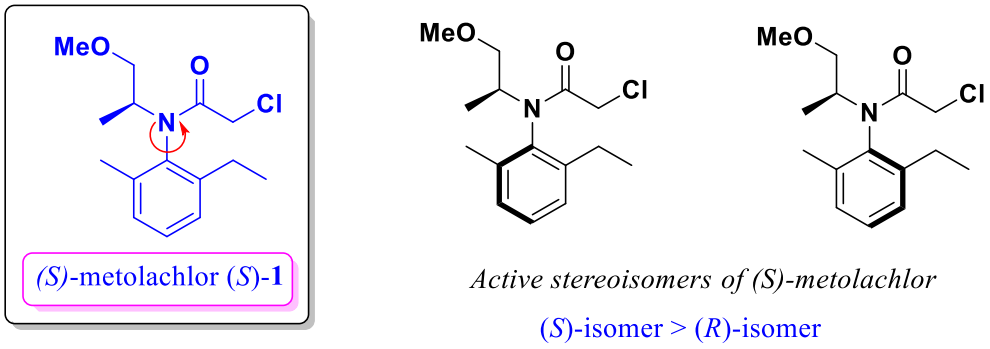


Figure 1. Active isomers of Metolachlor

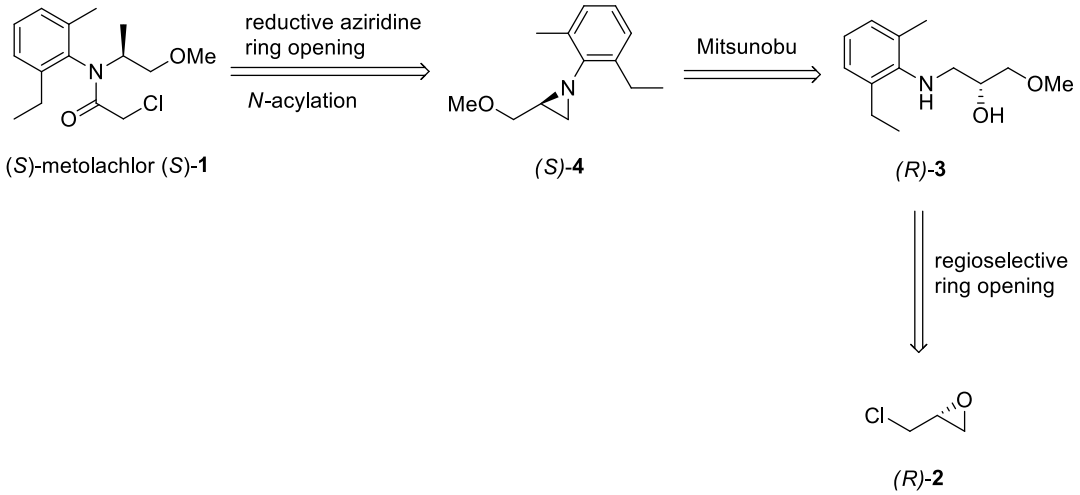
Several reports are available for the synthesis of (*S*)-metolachlor, which involves asymmetric processes: mainly hydrogenation of imines or enamides,[4] enzymatic resolution[5] and chiral pool approaches.[6] But, most of these methods suffer from at least one of the following drawbacks such as low enantioselectivity, lower overall yield, protection-deprotection sequences, expensive reagents and catalysts, drastic reaction conditions etc. Very recently, Wang and coworkers reported a new route for the synthesis of (*S*)-metolachlor. Although this method seems to be impressive, but it involves nosylation-denosylation steps that limits the superiority of the method.[7] So, still there is a scope for newer methods that can overcome these drawbacks.

Epoxides, emerged as one of the widely used functional groups in various chemical transformations because of its intrinsic strain, can be easily opened with numerous nucleophiles.[8-13] In connection with our continued interests in utilizing epoxides for the synthesis of pharmaceutically important compounds[14-18] herein, we report a new and simple synthetic strategy for the synthesis of (*S*)-metolachlor via reductive ring opening of 2-methoxymethylaziridine.[19,20]

Results and Discussion

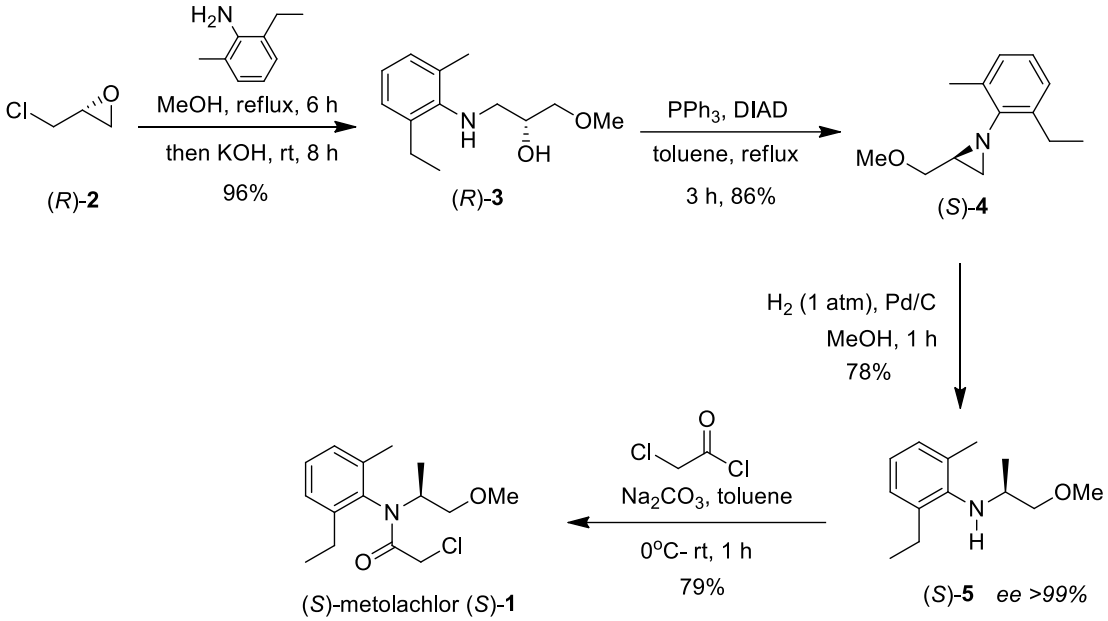
A retrosynthetic analysis of ***(S)*-1** is depicted in Scheme 1. We envisioned that enantiomerically pure epichlorohydrin **(*R*)-2** can be used as a chiral starting material for the synthesis. Based on the strategies involving regioselective ring opening and Mitsunobu reaction, aziridine ***(S)*-4** could be obtained from the epoxide **(*R*)-2**.

This aziridine **(*S*)-4** intermediate can be transformed to the final product ***(S)*-1** via reductive ring opening and subsequent reaction.



Scheme 1. Retrosynthetic analysis of (S)-metolachlor **(*S*)-1**

Accordingly, epoxide **(*R*)-2** on treatment with 2-ethyl-6-methylaniline in refluxing methanol for 6 h afforded chlorohydrin in situ. After the complete conversion of the starting material to the corresponding chlorohydrin derivative (confirmed by TLC), powdered KOH (2.5 equiv.) was added portion wise to the reaction mixture at temperature maintained below 25°C. After stirring the reaction mixture at room temperature for 8 h the required amino alcohol **(*R*)-3** was obtained in high yield (Scheme 2). Subsequently, the amino alcohol **(*R*)-3** in hand was exposed to Mitsunobu conditions (PPh_3/DIAD) to afford the key intermediate aziridine **(*S*)-4**. Here, it is noteworthy to mention that the formation of aziridine **(*S*)-4** was unsuccessful at room temperature using THF as a solvent as practiced routinely, so the reaction was carried out in toluene under reflux conditions. Further, the aziridine **(*S*)-4** on reductive ring opening using catalytic Pd/C under H_2 pressure furnished the required metolachlor intermediate **(*S*)-5** in high enantiopurity (ee>99%). Finally, **(*S*)-5** was acylated using chloroacetyl chloride under basic conditions to furnish the target compound **(*S*)-1** in overall yield of 50.8%. The structure of **(*S*)-1** was confirmed by its IR, ^{1}H NMR,[7] ^{13}C NMR,[7] and mass spectroscopic analysis. The enantiomeric purity of **(*S*)-5** was determined by chiral HPLC analysis.



Scheme 2. Synthesis for (*S*)-metolachlor **(*S*)-1**

Conclusions

In conclusion, we have developed an efficient new route for the synthesis of (*S*)-metolachlor **(*S*)-1** via reductive ring opening of 2-methoxymethylaziridine. The attractive features of the present protocol include readily available chiral starting material, simple chemical transformations, high enantiopurity and good overall yield (50.8%). We envisage that this simple protocol may find application in agrochemical industries for the large scale preparation of active isomer of metolachlor with high enantiopurity.

Experimental Section

General. Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. Monitoring of reactions was carried out using TLC plates Merck Silica Gel 60 F254 and visualization with UV light (254 and 365 nm), I_2 and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a JASCO P 1020 digital polarimeter. Mass spectra were recorded at ionization energy 70 eV on API Q Star Pulsar spectrometer using electrospray ionization. Enantiomeric excess was determined by chiral HPLC.

(*R*)-1-((2-Ethyl-6-methylphenyl)amino)-3-methoxypropan-2-ol (*R*)-3. To a stirred solution of (*R*)-epichlorohydrin **(*R*)-2** (2 g, 21.6 mmol) in methanol (15 mL) was added 2-ethyl-6-methyl aniline (3.2 g, 23.7 mmol) and the resulting mixture was refluxed for 6 h. After completion of the reaction (monitored by TLC), crushed KOH (3.0 g, 54.0 mmol) was added portion wise at temperature <25 °C. After completing the addition, the reaction mixture was stirred vigorously for 8 h at room temperature. After completion of the reaction (monitored by TLC), excess methanol was evaporated under reduced pressure. The reaction mixture was then

poured into water (20 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (90:10) as eluent to furnish (*R*)-1-((2-ethyl-6-methylphenyl)amino)-3-methoxypropan-2-ol **(*R*)-3** as a pale brown oil (4.6 g, 96%); $[\alpha]^{21}_D$ = +4.9 (*c* 2.09, $CHCl_3$); IR ($CHCl_3$, cm-1): ν_{max} 3421, 3009, 2966, 1593, 1466, 1377, 1216, 1129, 968, 667; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.26 (t, *J* 7.6 Hz, 3H), 2.33 (s, 3H), 2.66-2.71 (m, 2H), 2.98 (dd, *J* 12.5, 7.0 Hz, 1H), 3.10 (dd, *J* 12.5, 4.0 Hz, 1H), 3.42 (s, 3H), 3.47 (dd, *J* 9.4, 6.4 Hz, 1H), 3.51 (dd, *J* 9.7, 3.6 Hz, 1H), 3.96-4.00 (m, 1H), 6.91 (apparent t, *J* 7.2 Hz, 1H), 7.02 (d, *J* 7.3 Hz, 1H), 7.04 (d, *J* 7.6 Hz, 1H); ^{13}C NMR (50 Hz, $CDCl_3$): δ_C 145.0, 136.2, 130.6, 128.8, 126.7, 122.6, 75.3, 69.6, 59.2, 51.5, 24.2, 18.5, 14.8; MS: m/z 224 $[M+1]^+$, 246 $[M+Na]^+$.

(*S*)-1-(2-Ethyl-6-methylphenyl)-2-(methoxymethyl)aziridine (*S*)-4. A solution of DIAD (3.0 mL, 15.4 mmol) in dry toluene (5 mL) was added dropwise to a solution of **(*R*)-3** (2.3 g, 10.3 mmol) and triphenylphosphine (4.0 g, 15.4 mmol) in a dry toluene (25 mL) under N_2 atmosphere at 0 °C. The reaction mixture was refluxed for 3 h. After completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh, petroleum ether/ethyl acetate, 95:5) to afford (*S*)-1-(2-ethyl-6-methylphenyl)-2-(methoxymethyl)aziridine **(*S*)-4** as a yellow oil (1.8 g, 86 %); $[\alpha]^{21}_D$ = -120.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3419, 2967, 2875, 1915, 1745, 1592, 1460, 1378, 1355, 1276, 1217, 1188, 1108, 965, 929, 900, 666; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.28 (t, *J* 7.6 Hz, 3H), 2.04 (d, *J* 6.3 Hz, 1H), 2.39 (s, 3H), 2.41-2.50 (m, 1H), 2.80 (q, *J* 7.5 Hz, 2H), 3.46 (s, 3H), 3.49-3.54 (m, 1H), 3.93 (dd, *J* 10.4, 4.3 Hz, 1H), 6.88 (apparent t, *J* 7.3 Hz, 1H), 6.95-7.04 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 149.9, 134.9, 129.1, 128.8, 126.9, 122.0, 74.0, 59.1, 39.4, 34.9, 24.3, 19.3, 14.3; MS: m/z 206 $[M+1]^+$, 228 $[M+Na]^+$.

(*S*)-2-eEhyl-*N*-*(*1-methoxypropan-2-yl)-6-methylaniline (*S*)-5. To a solution of **(*S*)-4** (1.0 g, 4.8 mmol) in methanol (10 mL) was added palladium on activated carbon (0.065 g, 10-20 wt %) and the reaction mixture was stirred under hydrogen atmosphere (balloon) for 1 h. After completion of the reaction (monitored by TLC) the catalyst was filtered over the celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (100-200 mesh, petroleum ether/ethyl acetate, 98:2) to afford (*S*)-2-ethyl-*N*-(1-methoxypropan-2-yl)-6-methylaniline **(*S*)-5** (0.78 g, 78 %) as a pale yellow oil; $[\alpha]^{21}_D$ = +11.7 (*c* 2.0, $CHCl_3$); ee >99% [Chiral HPLC analysis: Chiralcel OD-H (250 x 4.6 mm) column; eluent: n-hexane/isopropanol = 99.75:0.25; flow rate: 0.5mL/min; detector: 220 nm]; IR ($CHCl_3$, cm^{-1}): ν_{max} 3409, 3019, 2969, 2877, 2401, 1593, 1465, 1385, 1215, 1103, 928, 669. ^{1}H NMR (200 MHz, $CDCl_3$)[7]: δ_H 1.19 (d, *J* 6.4 Hz, 3H), 1.26 (t, *J* 7.5 Hz, 3H), 2.31 (s, 3H), 2.67 (q, *J* 7.6 Hz, 2H), 3.32-3.37 (m, 3H), 3.39 (s, 3H), 6.88 (apparent t, *J* 7.4 Hz, 1H), 7.00-7.06 (m, 2H); ^{13}C NMR (50 Hz, $CDCl_3$): δ_C 144.2, 135.5, 129.8, 128.7, 126.5, 121.7, 76.2, 58.9, 52.9, 24.2, 18.9, 18.5, 14.5; MS: m/z 208 $[M+1]^+$, 230 $[M+Na]^+$.

(*S*)-2-Chloro-*N*-(2-ethyl-6-methyl-phenyl)-*N*-*(*2-methoxy-1-methyl-ethyl)-acetamide ((S)-metolachlor (*S*)-1). To a stirred solution of **(*S*)-5** (0.1 g, 0.48 mmol) and sodium carbonate (0.102 g, 0.96 mmol) in toluene (3 mL) was added chloroacetyl chloride (0.065 g, 0.57 mmol, 46 µL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), toluene was removed under reduced pressure and the residue was diluted with water (3 mL) and extracted with EtOAc (3 x 5 mL). The phases were separated, and the organic phase was washed with brine (2 x 5 mL), dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 90:10) to yield **(*S*)-1** as colorless oil (0.108 g; 79%); $[\alpha]^{21}_D$ = -5.73 (*c* 2.80, n-hexane) {lit.5 $[\alpha]^{25}_D$ = -8.2 (*c* 2.1, n-hexane}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3464, 3019, 1664, 1462, 1215, 1112, 765, 669; ^{1}H NMR (200 MHz, $CDCl_3$)[7]: δ_H 1.13-1.18 (m, 3H), 1.25 (t, *J* 7.5 Hz, 3H), 2.23 (s, 3H, major + minor), 2.48-2.69 (m, 2H), 3.28 (s, 3H, major + minor), 3.45-3.54 (m, 1H), 3.61 (s, 2H, major + minor), 3.66-3.78 (m, 1H), 4.15-4.28 (m, 1H), 7.11-7.31 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)[7]: δ_C 166.79, 142.56, 142.46, 137.15, 136.92, 136.81, 128.89,

126.90, 126.79, 74.54, 58.53, 55.35, 55.18, 42.87, 42.82, 23.86, 23.59, 18.89, 15.50, 15.32; 14.17, 13.92 MS: m/z 284 $[M+1]^+$, 306 $[M+Na]^+$.

Acknowledgements

M. Mujahid thanks DST, New Delhi for a research grant under SERB-TARE scheme (TAR/2021/000110).

Supplementary Material

Supplementary information includes copies of ^{1}H NMR, ^{13}C NMR of all the compounds & chiral HPLC chromatograph of compound (*S*)-5.

References

1 Federsel, H. J., *CHEMTECH* **1993**, *23*, 24-33.
2 Cho, B. T.; Chun, Y. S., *Tetrahedron: Asymmetry* **1992**, *3*, 337-340. https://doi.org/10.1016/S0957-4166(00)80268-2
3 Blaser, H.-U., *Adv. Synth. Catal.* **2002**, *344*, 17-31. https://doi.org/10.1002/1615-4169(200201)344:1<17::AID-ADSC17>3.0.CO;2-8
4 Brunel, J. M.; Buono, G., *Synlett* **1996**, 177-178; http://doi.org/10.1055/s-1996-5343
5 Zheng, L.; Zhang, S.; Wang, F.; Gao, G.; Cao, S., *Can. J. Chem.* **2006**, *84*, 1058-1063. https://doi.org/10.1139/v06-129
6 Zhu, H.; Li, Y.; Chen, W.; Yu, G.; Du, G.; Lv, L.; Chu, Q. *Chinese Patent* CN 101367746A, 2009.
7 Yang, P.; Wang, X.; Peng, L.; Chen, F.; Tian, F.; Tang, C.-Z.; Wang, L.-X., *Org. Process Res. Dev.* **2017**, *21*, 1682-1688. https://doi.org/10.1021/acs.oprd.7b00216
8 *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. http://doi.org/10.1002/3527607862
9 Li, D-D.; Niu, L-F.; Ju, Z-Y.; Xu, Z.; Wu, C. *Eur. J. Org. Chem* **2016**, 3090-3096. https://doi.org/10.1002/ejoc.201600335
10 Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem* **2007**, *79*, 269-279. http://dx.doi.org/10.1351/pac200779020269
11 Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987. https://doi.org/10.1021/cr068367v
12 Moschona, F.; Savvopoulou, I.; Tsitopoulou, M.; Tataraki, D.; Rassias, G. *Catalysts* **2020**, *10*, 1117-1182. https://doi.org/10.3390/catal10101117
13 Singh, G. S.; Mollet, K.; D'hooghe, M.; De Kimpe, N.; *Chem. Rev*. **2013**, *113*, 1441–1498. https://doi.org/10.1021/cr3003455
14 Mujahid, M.; Mujumdar, P.; Sasikumar, M.; Deshmukh, S. P.; Muthukrishnan, M., *Tetrahedron: Asymmetry* **2017**, *28*, 983-986.

https://doi.org/10.1016/j.tetasy.2017.06.001
15 Mujahid, M.; Subramanian, J.; Nalla, V.; Sasikumar, M.; Kunte, S. S.; Muthukrishnan, M., *New J. Chem* **2017**, *41*, 824-829.
https://doi.org/10.1039/C6NJ02928K
16 Viswanadh, N.; Mujumdar, P.; Sasikumar, M.; Kunte, S. S.; Muthukrishnan, M., *Tetrahedron Lett.* **2016**, *57*, 861-863.
https://doi.org/10.1016/j.tetlet.2016.01.032
17 Reddi, A.; Mujahid, M.; Sasikumar, M.; Muthukrishnan, M., *Synthesis* **2014**, *46*, 1751-1756
http://doi.org/10.1055/s-0033-1341104
18 Mujahid, M.; Muthukrishnan, M., *Chirality* **2013**, *25*, 965-969.
https://doi.org/10.1002/chir.22253
19 D'hooghe, M.; De Kimpe, N.; *Arkivoc*. **2008**, (ix), 6-19.
https://doi.org/10.3998/ark.5550190.0009.902
20 Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V. V.; De Kimpe, N.; Ha, H-J.; *Chem. Soc. Rev.*, **2012**,*41*, 643-665.
https://doi.org/10.1039/C1CS15140A