Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1039–1043
Bioorganic & Medicinal Chemistry Letters

Spiro-annulation of barbituric acid derivatives and its analogs by ring-closing metathesis reaction

Sambasivarao Kotha,* Ashoke Chandra Deb and Ramanatham Vinod Kumar

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai 400076, India

Received 19 October 2004; revised 10 December 2004; accepted 11 December 2004
Available online 18 January 2005

Abstract—Barbituric acid **1** and related β-dicarbonyl compounds were dialkenylated under the phase-transfer catalyst [e.g., benzyltriethylammonium chloride (BTEAC)] conditions to generate the diallylated products. These diallylated products were subjected to the ring-closing metathesis (RCM) reaction to deliver the corresponding spiro-annulated derivatives.

1. Introduction

Barbituric acid **1**, prepared by Adolf Von Baeyer in 1864 from a fusion of the urea and malonic acid has widely been used in the manufacturing of plastics,[1] textiles,[2] polymers[3] and pharmaceuticals.[4,5] Pharmacologically active barbituric acid derivatives are either mono- or di-*C*-alkylated derivatives. The first intravenous barbituric acid was a combination, in equal parts of barbital and dial (or diallylbarbituric acid), synthesized by Fischer in the later half of the 19th century (Fig. 1).

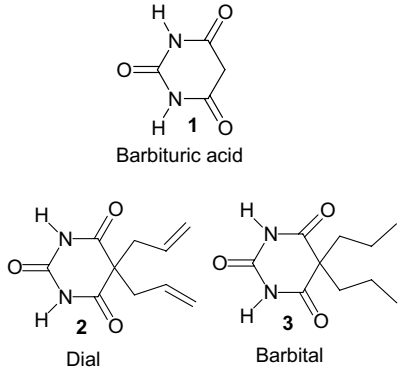


Figure 1. First examples of pharmaceutically important intravenous barbiturates.

Since then, several important drug molecules based on 5,5-dialkylated barbituric acid were discovered.[6] Generally, these compounds have been used as sedative hypnotics or local anesthetics. In addition to the pharmaceutical value, they are also useful building blocks in assembling supramolecular structures via noncovalent interactions.[7] In this respect, recently Fenniri et al. devised helical nanotubes.[8]

As part of a programme related to the application of metathesis reaction in organic synthesis, we envisioned ring-closing metathesis (RCM) reaction as a useful protocol[9] for designing new barbituric acid derivatives and its analogs. The readily available β-dicarbonyl compounds such as barbituric acid **1**, thiobarbituric acid **4**, tetronic acid **5** and thiotetronic acid **6** were selected as our starting substrates (Fig. 2).

Towards spiro-annulation of these heterocycles, we conceived two strategies based on RCM reaction. In principle, condensation of alkenylated malonate precursors with urea either before or after metathesis sequence could deliver annulated barbituric acid derivatives.

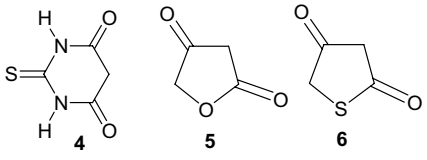
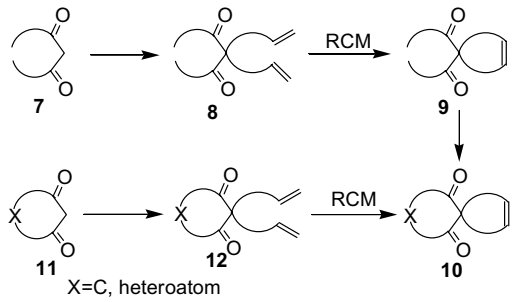


Figure 2. Examples of pharmaceutically important β-dicarbonyl compounds.

Keywords: RCM; Spirocycles; Barbituric acid; 1,3-Dicarbonyl compound.
* Corresponding author. Tel.: +91 22 2572 7160; fax: +91 22 2572 3480; e-mail: srk@chem.iitb.ac.in

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.12.034



Scheme 1.

The first strategy (Scheme 1) involves the RCM reaction of dialkenylated malonate precursor (**7**→**8**→**9**→**10**). The second strategy (Scheme 1) rely on alkenylation of active methylene group present in compound **11** by various electrophiles containing terminal olefin. The RCM reaction of these dialkenylated derivative generates the spiro-annulated compound **10** (**11**→**12**→**10**). By varying the length of electrophile containing terminal olefin, one can generate various alkenylated barbituric acid derivatives.

Recently, RCM reaction has been used as a reliable tool for the construction of various carbo- and heterocycles. In this respect, a well-defined ruthenium-based carbene complexes **13** and **14** are useful (Fig. 3).[10,11]

To realize the strategy shown in Scheme 1, diethyl malonate was allylated with 2 equiv of allyl bromide in the presence of sodium hydride to deliver the known compound **15** (76%).[12] The RCM reaction of **15** with the Grubbs 1st generation catalyst **13** in dichloromethane at rt gave the spiro-annulated diester **16** in 92% yield (Scheme 2). The structure of **16** is well established on the basis of ^{1}H and ^{13}C NMR spectral data. The presence of six lines in ^{13}C NMR spectrum confirmed the C_2-symmetry present in the molecule **16**. Later on, we found the spirodiester **16** on reaction with various urea derivatives gave no condensation product. The hindered nature of the spirocyclic system **16** might be responsible for the failure of this reaction. Consequently, the efforts were directed towards the alternate route. Thus, barbituric acid **1** was reacted with allyl bromide under phase-transfer catalyst (PTC), BTEAC conditions to generate the diallyl barbituric acid derivative **2** in 57% yield. Since the diallyl compound **2** was insoluble in most of the organic solvents, the RCM strategy was not realized. At this juncture, protection of nitrogen atoms of **2** was considered to improve its solubility. Towards this objective, attempted *N*-tosylation gave only 10% of tosylated product. Prolonged reaction time and forcing reaction conditions did not improve the yield. Next, barbituric acid **1** was treated with 4 equivalents of allyl bromide in presence of K_2CO_3 under PTC conditions using BTEAC gave the tetra-allylated compound **18** (52% yield), which is soluble in most of the organic solvents (Scheme 3). We were pleased to note that when the tetra-allylated barbituric acid derivative **18** was subjected to RCM, the spiro compound **19** was obtained in good yield and the allyl groups attached to the nitrogen atom remained intact. It is known that *N*-allylated compounds gave deallylated products under the RCM conditions using Grubbs catalyst.[13,14] The other diallyl barbituric acid derivatives prepared under similar reaction conditions were subjected to the RCM strategy and the details are included in Table 1.

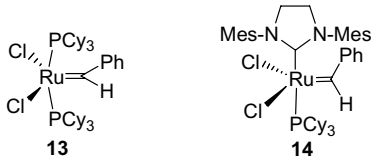
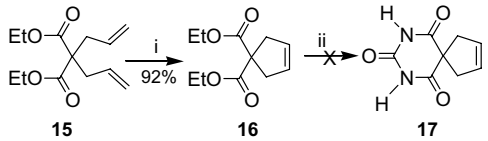


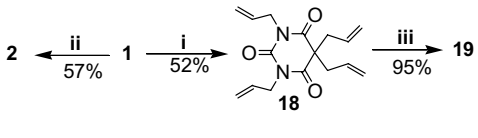
Figure 3. 1st and 2nd generation Grubbs catalysts.



Scheme 2. Reagents and conditions: (i) bis-(tricyclohexylphosphine)-benzyl ruthenium dichloride, CH_2Cl_2; (ii) urea.

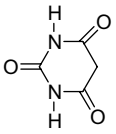
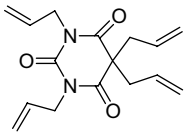
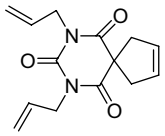
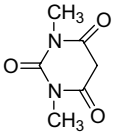
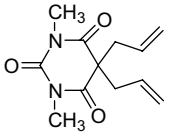
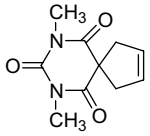
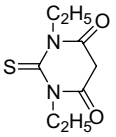
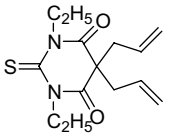
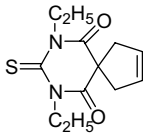
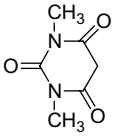
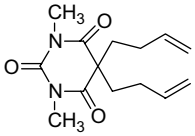
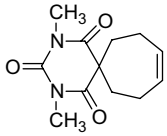
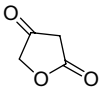
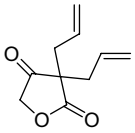
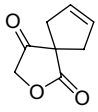
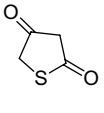
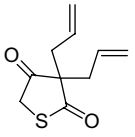
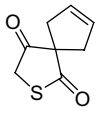
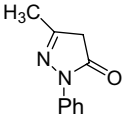
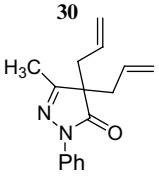
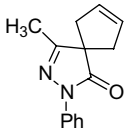
To expand the utility of this approach, tetronic acid **5** and thiotetronic acid **6** were alkylated with allyl bromide. In case of tetronic acid *O*-alkylated product was also formed along with the required diallylated compound (3:5). However, unwanted *O*-allylated derivative was converted into the desired isomer by Claisen rearrangement (Scheme 4).[15] For diallylation of thiotetronic acid **6**, similar protocol was adopted and the diallyl thiotetronic acid **30** was found to be major product when the temperature of the reaction was maintained around 0–15 °C. After successful diallylation of tetronic acid **5**, thiotetronic acid **6** was diallylated. Then, the corresponding RCM products were obtained by treating the diallylated products with catalytic quantities of 1st generation Grubbs catalyst in CH_2Cl_2 at rt for 42 h.

In conclusion, the RCM methodology has been found to be useful to generate various spiro-annulated barbituric acid derivatives. Also, the PTC conditions developed in this study for diallylation may also be applicable with other alkylating agents. In addition, various other biologically important molecules such as tetronic acids,[16] thiotetronic acids, pyrazolone derivatives[17] have been annulated via the RCM reaction. In view of extensive use of barbituric acid derivatives in medicinal chemistry, the compounds prepared in the present study and the methodology developed here may find useful applications in bio-organic and medicinal chemistry.

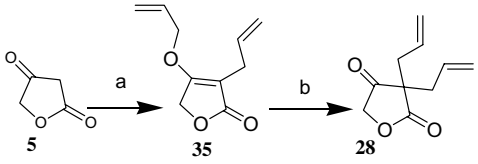


Scheme 3. Reagents and conditions: (i) allylbromide (4 equiv), K_2CO_3, BTEAC, $CHCl_3$, rt; (ii) allylbromide (2 equiv), K_2CO_3, BTEAC, $CHCl_3$, rt; (iii) Grubbs catalyst **13**.

Table 1. List of various barbituric acid derivatives and its analogs synthesized using RCM as a key step

Entry	Substrate	Diallyl products	RCM product	Yield[a] (%)
1		 **18**	 **19**	95
2	 **20**	 **21**	 **22**	88
3	 **23**	 **24**	 **25**	92
4		 **26**	 **27**	81
5	 **5**	 **28**	 **29**	69
6	 **6**	 **30**	 **31**	79
7	 **32**	 **33**	 **34**	75

[a] Yield refers to RCM yield.



Scheme 4. Reagents and conditions: (a) allylbromide, base; (b) Claisen rearrangement, silica gel support.

2. Experimental

2.1. Typical experimental procedure for allylation of barbituric acid 1 to 18

To a suspension of barbituric acid **1** (200 mg, 1.56 mmol) in chloroform (10 mL), powdered potassium carbonate (1.29 g, 9.37 mmol) and BTEAC (889 mg, 3.9 mmol) were added. The reaction mixture was cooled to 0 °C and allyl bromide (850 mg, 7.03 mmol) was added drop-wise. After 18 h at rt, the reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted with chloroform (3×20 mL). The combined organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was removed and the crude product was purified by silica gel column chromatography using 5% ethyl acetate–petroleum ether to give **18** (234 mg, yield 52%) as a colorless thick liquid.

R_f: 0.8 (20% ethyl acetate–petroleum ether). IR (neat) ν_{max}: 1686, 1654 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.69 (d, $J = 7.4$ Hz, 4H), 4.42 (d, $J = 5.9$ Hz, 4H), 5.03 (t, $J = 6.9$ Hz, 2H), 5.12 (br s, 2H), 5.24 (d, $J = 1.2$ Hz, 2H), 5.17 (br s, 2H), 5.37–5.58 (m, 2H), 5.66–5.85 (m,

2H). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 43.1, 43.8, 56.6, 118.4, 120.8, 130.4, 131.2, 149.8, 170.2. Mass: *m/z* 311.2025 (M+Na).

2.2. Typical experimental procedure for RCM reaction

To a suspension of tetra-allyl barbituric acid **18** (90 mg, 0.313 mmol) in toluene (10 mL), first generation Grubbs catalyst (25.7 mg, 10 mol %) was added and stirred at 90 °C for 26 h under nitrogen. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography using 5% ethyl acetate–petroleum ether as an eluent to give **19** (86 mg, yield 95%) as a faint yellow solid.

Mp: 52–53 °C. R_f: 0.5 (10% ethyl acetate–petroleum ether). IR ($CHCl_3$) ν_{max}: 1692, 1646 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.99 (s, 4H), 4.45 (d, J = 5.8 Hz, 4H), 5.16–5.29 (m, 4H), 5.64 (s, 2H), 5.72–5.89 (m, 2H). ^{13}C NMR (50.38 MHz, $CDCl_3$): δ 44.1, 44.9, 54.8, 118.8, 127.2, 131.1, 150.3, 171.5. Mass: *m/z* 260 (M^+).

2.3. Typical experimental procedure for allylation of tetronic acid 5 or thiotetronic acid 6

To a solution of tetronic acid **5** (150 mg, 1.5 mmol) in chloroform (10 mL), powdered potassium carbonate (621 mg, 4.5 mmol) and tetrabutylammonium hydrogen sulfate (1.5 g, 4.5 mmol) were added. The reaction mixture was cooled to 0 °C and to this cooled solution, allyl bromide (545 mg, 4.5 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Then, the reaction temperature was maintained between 0 and 15 °C till the completion of the reaction (12 h, monitored by TLC) and the reaction mixture was quenched by addition of water (10 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography using 1% ethyl acetate–petroleum ether as an eluent to give **28** (99 mg, yield 55%) and **35** (63 mg, 35%) as a colorless liquid. Similar procedure was used for the diallylation of thiotetronic acid **6**.

2.4. Typical experimental procedure for allylation of 20 to 21

To a suspension of 1,3-dimethyl barbituric acid **20** (150 mg, 0.962 mmol) in chloroform (10 mL), powdered potassium carbonate (796 mg, 5.77 mmol) and BTEAC (548 mg, 2.41 mmol) were added. The reaction mixture was cooled to 0 °C and to this ice-cooled stirred solution, allyl bromide (407 mg, 3.37 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Then the reaction mixture was stirred at rt for 24 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with addition of water (10 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography using 3% ethyl acetate–petroleum ether as an eluent to give **21** (227 mg, yield 81%) as a colorless solid. Mp: 58–59 °C.

By using similar procedure, compounds **24**, **26** and **33** were synthesized.

2.5. Selected spectral data

Compound **21**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (d, J = 7.4 Hz, 4H), 3.26 (s, 6H), 5.02–5.11 (m, 4H), 5.45–5.54 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 27.9, 42.7, 56.9, 119.9, 130.8, 150.8, 170.5. *m/z* 236 (M^+).

Compound **22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 4H), 3.30 (s, 6H), 5.66 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.8, 45.3, 54.8, 127.2, 151.3, 172.3. *m/z* 208 (M^+).

Compound **24**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J = 7 Hz, 6H), 2.67 (d, J = 7.4 Hz, 4H), 4.36 (q, J = 7 Hz, 4H), 4.97–5.97 (dd, J = 10.3, 6.9 Hz, 4H), 5.36–5.56 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.2, 43.3, 56.7, 120.6, 130.4, 168.8, 178.8. *m/z* 280 (M^+).

Compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7 Hz, 6H), 2.99 (s, 4H), 4.41 (q, J = 7 Hz, 4H), 5.63 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.1, 43.6, 44.1, 55.8, 126.9, 169.8, 179.4. *m/z* 253 (M+1).

Compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (q, J = 7, 7.5 Hz, 4H), 2.13 (t, J = 7.5 Hz, 4H), 3.29 (d, J = 5 Hz, 6H), 4.91 (dd, J = 10.5, 6.5 Hz, 4H), 5.60–5.66 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.8, 36.5, 39.3, 55.7, 115.8, 135.7, 150.3, 171.8. *m/z* 264 (M^+).

Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (m, 4H), 2.46 (m, 4H), 3.29 (s, 6H), 5.65 (t, J = 3.2 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 25.1, 34.8, 39.4, 53.9, 130.1, 141.5, 172.9. *m/z* 236 (M^+).

Compound **28**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (d, J = 6.3 Hz, 4H), 4.39 (s, 2H), 5.13–5.20 (m, 2H), 5.59–5.65 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 39.1, 54.1, 121.2, 130.2, 203.8, 209.8. *m/z* 180 (M^+).

Compound **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (d, J = 8 Hz, 4H), 4.32 (s, 2H), 5.68 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 35.2, 42.3, 66.3, 127.3, 197.1, 209.1. *m/z* 152 (M^+).

Compound **30**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40–2.42 (m, 4H), 3.75 (s, 2H), 5.08–5.12 (m, 4H), 5.54–5.65 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 40.9, 41.2, 60.6, 120.7, 130.5, 203.5, 207.7. *m/z* 196 (M^+).

Compound **31**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (s, 4H), 4.02 (s, 2H), 5.62 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 39.38, 42.3, 60.1, 127.3, 201.9, 205.01. *m/z* 168 (M^+).

Compound **33**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.29–2.30 (m, 2H), 2.59 (q, J = 7 Hz, 2H), 4.98–5.15 (dd, J = 16, 10 Hz, 4H), 5.4–5.6 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 8 Hz, 2H), 7.9 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.2, 38.8, 59.1, 118.7, 119.5, 124.8, 128.7, 130.8, 137.8, 161.7, 174.5. *m/z* 254 (M^+).

Compound **34**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.59 (d, J = 14.9 Hz, 2H), 2.90 (d, J = 15.2 Hz, 2H), 5.77 (s, 2H), 7.15 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.1, 41.1, 57.4, 118.5, 124.7, 128.4, 128.7, 138.1, 164.2, 176.9. *m/z* 227 (M+1).

Acknowledgements

We thank the DST (New Delhi) for the financial support, RSIC-Mumbai for providing the spectral data.

References and notes

1. Thetford, D.; Chorlton, A. P.; Hardman, J. *Dyes Pigments* **2003**, *59*, 185.
2. Bartzatt, R. *J. Pharm. Biomed. Anal.* **2002**, *29*, 909.
3. (a) Andreu, R.; Garin, J.; Orduna, J.; Alcala, R.; Villacumpa, B. *Org. Lett.* **2003**, *5*, 3143; (b) McClenaghan, N. D.; Absalon, C.; Bassani, D. M. *J. Am. Chem. Soc.* **2003**, *125*, 13004.
4. (a) Meusel, M.; Ambrozak, A.; Hecker, T. K.; Gutschow, M. *J. Org. Chem.* **2003**, *68*, 4684; (b) Brunner, H.; Ittner, K. P.; Lunz, D.; Schmatloch, S.; Schmidt, T.; Zabel, M. *Eur. J. Org. Chem.* **2003**, *855*.
5. (a) Neumann, D. M.; Jursic, B. S.; Martin, K. L. *Tetrahedron Lett.* **2002**, *43*, 1603; (b) Jursic, B. S.; Neumann, D. M. *Tetrahedron Lett.* **2001**, *42*, 8435; (c) Jursic, B. S.; Neumann, D. M. *Tetrahedron Lett.* **2001**, *42*, 4103; (d) Jursic, B. S. *Tetrahedron Lett.* **2000**, *41*, 5325.
6. Westhorpe, R. N.; Ball, C. *Int. Congress Series* **2002**, *1242*, 57.
7. (a) Prins, L. J.; Jolliffe, K. A.; Hulst, R.; Timmerman, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2000**, *122*, 3617; (b) Timmerman, P.; Prins, L. J. *Eur. J. Org. Chem.* **2001**, *3191*.
8. Fenniri, H.; Mathivanan, P.; Vidale, K. L.; Sherman, D. M.; Hallenga, K.; Wood, K. V.; Stowell, J. G. *J. Am. Chem. Soc.* **2001**, *123*, 3854.
9. *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Berlin, 2003; Vols. 1–3.
10. For review articles on olefin metathesis, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199; (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (d) Kotha, S.; Sreenivasachary, N. *Indian J. Chem.* **2001**, *40B*, 763; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (g) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75; (h) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (i) Amstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
11. For our recent work related to metathesis reaction, see: (a) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Tetrahedron Lett.* **1998**, *39*, 2805; (b) Kotha, S.; Manivannan, E.; Ganesh, T.; Sreenivasachary, N.; Deb, A. *Synlett* **1999**, 1618; (c) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503; (d) Kotha, S.; Halder, S.; Brahmachary, E.; Ganesh, T. *Synlett* **2000**, *22*, 853; (e) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, 787; (f) Kotha, S.; Halder, S.; Brahmachary, E. *Tetrahedron* **2002**, *58*, 9203; (g) Kotha, S.; Manivannan, E. *Arkivoc* **2003**, *iii*, 67; (h) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585; (i) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 1391; (j) Kotha, S.; Singh, K. *Tetrahedron Lett.* **2004**, *45*, 9607.
12. Nugent, W. A.; Feldman, J.; Calabrene, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992.
13. Alcaide, B.; Almendros, P.; Alonso, J. M. *Tetrahedron Lett.* **2003**, *44*, 8693.
14. Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793.
15. Kotha, S.; Mandal, K.; Deb, A. C.; Banerjee, S. *Tetrahedron Lett.* **2004**, *45*, 9603.
16. For example, the tetronic acid based drug losigamone is used to decrease the frequency of spontaneous action potentials and suppresses receptive firing of neurons. For details, see: Gebhardt, C.; Breustedt, J. M.; Noldner, M.; Chatterjee, S. S.; Heinemann, U. *Brain Res.* **2001**, *920*, 27; Koehr, G.; Heinemann, U. *Epilepsy Res.* **1990**, *7*, 49.
17. Some pyrazolone derivatives are useful for hypoxic ischemic brain disorders, especially ones of newborns caused by labor. For details, see: Tomoaki, I.; Tsuyomu. *PCT Int. Appl.* **2003**, *29*; WO 2003078401.