Synthesis of a Conformationally Constrained Phenylalanine Derivative by a Strategic Combination of Ring-Closing Enyne Metathesis and Diels–Alder Reaction

Sambasivarao Kotha,* Priti Khedkar

Department of Chemistry, Indian Institute of Technology – Bombay, Mumbai 400076, India
Fax +91(22)5723480; E-mail: srk@chem.iitb.ac.in

Received 29 April 2008; revised 21 May 2008

Abstract: An efficient route towards the synthesis of a conformationally constrained phenylalanine derivative is demonstrated using the strategic combination of ring-closing enyne metathesis and Diels–Alder reaction as key steps.

Key words: constrained amino acid, phenylalanine, ring closure, metathesis, Diels–Alder

In the view of increasing demand for peptide-based drugs,[1] conformationally constrained amino acid derivatives have become useful tools in bioorganic chemistry. There are restrictions in employing peptides as drugs and these include several factors, such as instability towards proteolytic degradation, poor absorption after oral ingestion, rapid excretion through liver and kidneys, and undesired effects caused by interaction of the conformationally flexible peptides with various receptors. It has been well established that incorporation of a constrained amino acid unit in a peptide chain can modify the physiological as well as binding properties of the resulting peptide.[2] Peptide modifications[3] by incorporation of conformationally constrained amino acids in bioactive peptides and drugs can result in better substrates for structure–activity relationship studies.[4]

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic, **1**) (Figure 1) is a constrained analogue of phenylalanine (Phe). In Tic **1**, the six-membered heterocyclic ring is formed by incorporation of a methylene unit in between the amino group and the aromatic ring of the phenylalanine. This type of amino acid plays an important role in designing peptidomimetics.[5] It was found that the incorporation of Tic **1** in the second position of an opioid receptor exerts conformational restrictions and results in distinct changes in its activity and selectivity.[6] The tetrahydroisoquinoline unit is a key element in several peptide-based drugs and forms an integrated part of various biologically active molecular frameworks.[7] Commonly, Tic **1** and its derivatives are assembled via Pictet–Spengler reaction and Bischler–Napieralsky reaction or by alkylation strategies.[8] To expand the 'building block approach'[9] for the synthesis of highly functionalized Tic derivatives, our group has demonstrated that methodologies based on [2+2+2]-cyclotrimerization reactions[10] and ring-closing enyne metathesis strategies are useful.[11]

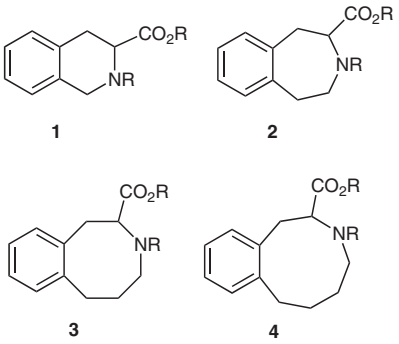


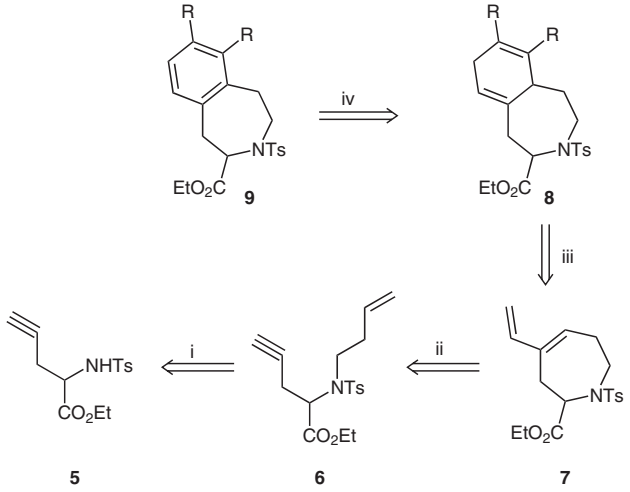
Figure 1 Conformationally constrained phenylalanine analogues (R = H)

Along similar lines, higher analogues of Tic **1** such as, 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (**2**), 1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid (**3**), and 2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-2-carboxylic acid (**4**) seem to be attractive synthetic targets[12] due to their projected utility in peptidomimetics and pharmacological studies.[13] Most of the known methods available for the preparation of these compounds start with the preformed benzene derivatives, so they provide limited opportunity for the introduction of diverse functional groups in the benzene ring.[12]

Herein, we describe our efforts towards the synthesis of highly functionalized higher analogues of Tic **1** using ring-closing enyne metathesis[14] and Diels–Alder reactions[15] as key steps (Scheme 1). This strategy provides a unique advantage over the existing methods, as diverse substituents in the aromatic ring may be introduced by the judicious selection of the reacting partners.

Ring-closing enyne metathesis is an attractive process, which enables the generation of a diene that can easily undergo Diels–Alder reaction with various dienophiles to deliver intricate polycyclic compounds. The preparation of the diene, in the presence of reactive functional groups (-NH_2, -CO_2Et) is not a trivial task. The commercial availability of Grubbs first generation catalyst, **G-I** and Grubbs second generation catalyst, **G-II** (Figure 2)[16] has provided access to a wide range of dienes suitable for the construction of highly functionalized polycycles.

SYNTHESIS 2008, No. 18, pp 2925–2928
Advanced online publication: 22.08.2008
DOI: 10.1055/s-2008-1067237; Art ID: Z09908SS



Scheme 1 A retrosynthetic approach to a conformationally constrained phenylalanine derivative. *Reagents and conditions*: (i) 4-bromobut-1-ene, base; (ii) Grubbs catalyst; (iii) dienophile; (iv) aromatization.

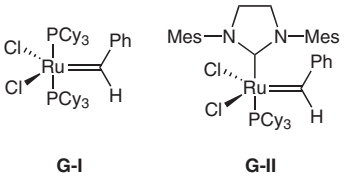
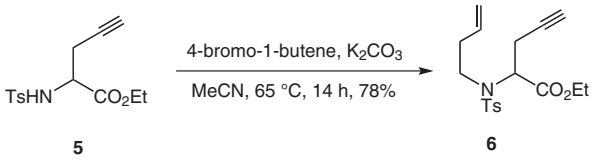


Figure 2



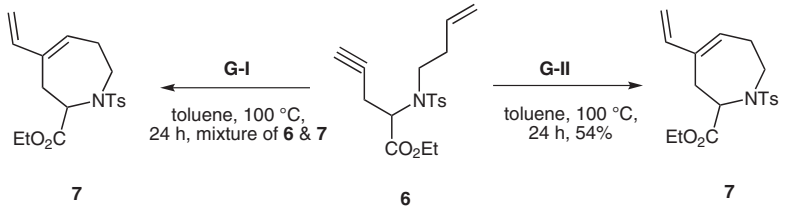
Scheme 2

The first task in our strategy involves the alkylation of the amide nitrogen of ethyl 2-(tosylamino)pent-4-ynoate (**5**) with 4-bromobut-1-ene. The substrate **6** can be subjected to enyne metathesis to generate diene **7**, which in turn may undergo a [4+2]-cycloaddition reaction with a suitable dienophile. Later on, oxidation of **8** may deliver the highly substituted seven-membered ring analogue of Tic. Thus, the enyne **6** can be used as a building block to construct various derivatives of 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid by ring-closing enyne metathesis and Diels–Alder reactions as key steps.

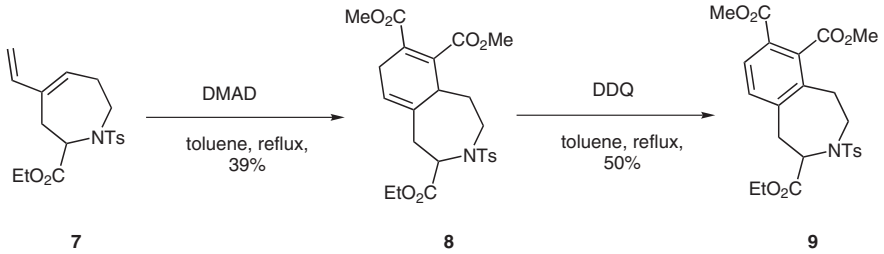
Towards the realization of this strategy, the alkyne derivative **5** was treated with 4-bromobut-1-ene and potassium carbonate in dry acetonitrile at 65 °C to obtain ethyl 2-[but-3-enyl(tosyl)amino]pent-4-ynoate (**6**) in 78% yield (Scheme 2).

The next task in hand was to realize the ring-closing enyne metathesis strategy as shown Scheme 1. When enyne **6** was subjected to ring-closing enyne metathesis in the presence of **G-I** for 24 hours in dry toluene, the complete conversion of starting material into diene **7** could not be achieved. However, Grubbs second generation catalyst **G-II** delivered the desired diene in 54% yield (Scheme 3). Although, the diene was characterized by ^{1}H NMR, IR, and HRMS data, the ^{13}C NMR spectrum of this material showed some minor additional peaks that may arise from decomposition of this sensitive diene. Therefore, the diene **7** was immediately subjected to Diels–Alder reaction with dimethyl acetylenedicarboxylate to furnish compound **8**. Further, functionalized 2,3,4,5-tetrahydro-1*H*-3-benzoazepine-2-carboxylic acid derivative **9** was obtained by the aromatization of **8** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 4).

In conclusion, a building block approach towards the construction of a conformationally constrained phenylalanine analogue using ring-closing enyne metathesis and Diels–Alder reactions as key steps has been demonstrated. The



Scheme 3



Scheme 4

method has several advantages over the existing procedures, as it provides an opportunity to install the desired substituents in the benzene ring under construction.

All reactions were monitored by TLC carried out on glass plates coated with Acme silica gel GF 254 (containing 13% $CaSO_4$ as a binder). Visualization of the spots on TLC plates was achieved either by exposure to I_2 vapor or UV light. Flash chromatography was performed using Acme silica gel (100–200 mesh). Hexane refers to fraction having boiling point 60–80 °C. All commercial grade reagents were used without further purification. IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer in KBr–CH_2Cl_2. ^{1}H NMR (400 MHz) and ^{13}C NMR (75 and 100.6 MHz) spectra were determined at r.t. on a Varian VXR 300 in $CDCl_3$ solns with TMS as internal reference. HRMS were determined on Micromass Q-Tof spectrometer. Starting material **5** was prepared using literature procedures.[11,17]

Ethyl 2-[But-3-enyl(tosyl)amino]pent-4-ynoate (6)

To a stirred suspension of finely powdered K_2CO_3 (100 mg, 0.72 mmol) in anhyd MeCN (15 mL) was added **5** (43 mg, 0.145 mmol) and 4-bromobut-1-ene (24 mg, 0.17 mmol). The resulting heterogeneous mixture was heated at 65 °C for 14 h under N_2. The mixture was cooled and filtered over a short Celite pad. The filtrate was concentrated under reduced pressure and diluted with H_2O (15 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL) and dried (anhyd Na_2SO_4). Removal of the solvent gave the crude product that was purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **6** (40 mg, 78%) as a colorless thick liquid; R_f = 0.5 (silica gel, 30% EtOAc–hexane).

IR (neat): 1737, 1644, 1343, 1160 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.2 Hz, 3 H), 2.01 (t, J = 2.8 Hz, 1 H), 2.42–2.46 (m, 5 H), 2.67–2.88 (m, 2 H), 3.12–3.38 (m, 2 H), 4.05 (q, J = 7.2 Hz, 2 H), 4.66–4.70 (m, 1 H), 5.06–5.08 (m, 2 H), 5.65–5.77 (m, 1 H) 7.28 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 8.2 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 21.5, 34.9, 46.0, 59.0, 61.7, 71.6, 79.4, 117.1, 127.7, 128.2, 129.4, 129.5, 130.0 134.7, 137.1, 143.5, 169.4.

HRMS (Q-Tof): m/z [M + Na]$^+$ calcd for $C_{18}H_{23}NNaO_4S$: 372.1245; found: 372.1244.

Ethyl 1-Tosyl-4-vinyl-2,3,6,7-tetrahydro-1*H*-azepine-2-carboxylate (7)

To a soln of **6** (52.2 mg, 0.149 mmol) in dry degassed toluene (20 mL) was added Grubbs' second generation catalyst **G-II** (13 mg, 0.015 mmol, 10 mol%). The mixture was heated at 100 °C for 24 h maintaining the inert atmosphere. The resulting brown soln was allowed to cool to r.t. and solvent was removed under reduced pressure to obtain a crude material that was purified by column chromatography (silica gel, 10% EtOAc–hexane) gave **7** (28 mg, 54%) as a colorless liquid; R_f = 0.5 (silica gel, 30% EtOAc–hexane).

IR (neat): 1966, 1651, 1265 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.2 Hz, 3 H), 2.38–2.62 (m, 6 H), 3.00–3.16 (m, 1 H), 3.43–3.74 (m, 2 H), 3.94–4.08 (m, 2 H), 4.93–5.17 (m, 3 H), 5.75 (t, J = 6 Hz, 1 H), 6.25 (dd, J_1 = 16 Hz, J_2 = 10 Hz, 1 H), 7.27 (d, J = 8 Hz, 2 H), 7.71 (d, J = 8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 21.6, 28.7, 29.6, 42.7, 57.2, 61.3, 111.4, 117.1, 127.4, 128.3, 129.6, 130.0, 132.1, 137.1, 139.6, 143.3, 170.5.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{18}H_{24}NO_4S$: 350.1426; found: 350.1412.

2-Ethyl 6,7-Dimethyl 3-Tosyl-2,3,4,5,5a,8-hexahydro-1*H*-3-benzazepine-2,6,7-tricarboxylate (8)

To a soln of **7** (27 mg, 0.077 mmol) in dry toluene (20 mL) was added DMAD (17 mg, 0.118 mmol). The mixture was heated to reflux for 17 h maintaining the inert atmosphere. At the completion of reaction (TLC) the mixture was allowed to cool to r.t. and solvent was removed under reduced pressure. The crude material obtained was purified by column chromatography (silica gel, 20% EtOAc–hexane) to give **8** (15 mg, 39%) as a colorless liquid; R_f = 0.26 (silica gel, 30% EtOAc–hexane).

IR (neat): 1966, 1648, 1265, 1157 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3 H), 1.40–1.51 (m, 2 H), 1.96 (td, J_1 = 14 Hz, J_2 = 4 Hz, 1 H), 2.11 (dd, J_1 = 13.6 Hz, J_2 = 11.6 Hz, 1 H), 2.40 (s, 3 H), 2.79–3.03 (m, 4 H), 3.36 (dd, J_1 = 14 Hz, J_2 = 12 Hz, 1 H), 3.76 (s, 6 H), 3.96–4.06 (m, 2 H), 4.50 (dd, J_1 = 10 Hz, J_2 = 7.2 Hz, 1 H), 5.55–5.59 (m, 1 H), 7.25 (d, J = 8 Hz, 2 H), 7.64 (d, J = 8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 21.6, 28.1, 34.9, 37.7, 42.5, 43.7, 52.4, 52.4, 58.8, 61.4, 121.7, 127.3, 127.5, 129.6, 129.6, 131.9, 132.8, 137.2, 137.6, 143.4, 168.0, 168.3, 171.6.

HRMS (Q-Tof): m/z [M + Na]$^+$ calcd for $C_{24}H_{29}NNaO_8S$: 514.1512; found: 514.1524.

2-Ethyl 6,7-Dimethyl 3-Tosyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-2,6,7-tricarboxylate (9)

To a soln of **8** (50 mg, 0.10 mmol) in dry toluene (25 mL) was added DDQ (80 mg, 0.35 mmol) and the mixture was refluxed for 48 h. The mixture was then allowed to cool to r.t. and solvent was removed under reduced pressure. The crude material obtained was purified by column chromatography (silica gel, 20% EtOAc–hexane) to give **9** (25 mg, 50%) as a colorless thick liquid; R_f = 0. 27 (silica–gel, 30% EtOAc–hexane).

IR (neat): 1966, 1644, 1266 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, J = 7 Hz, 3 H), 2.38 (s, 3 H), 2.81–2.97 (m, 2 H), 3.27–3.44 (m, 4 H), 3.76–4.07 (m, 8 H), 5.16 (m, 1 H), 7.20–7.27 (m, 3 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 8 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 21.5, 32.2, 38.9, 43.4, 52.5, 52.7, 56.0, 61.4, 126.8, 127.3, 128.4, 129.6, 131.5, 135.2, 137.1, 137.9, 142.3, 143.4, 165.9, 169.0, 169.6.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{24}H_{28}NO_4S$: 490.1536; found: 490.1539.

Acknowledgement

We thank the DST, New Delhi for the financial support and SAIF-Mumbai for providing spectral facilities. P.K. thanks the CSIR, New Delhi for the award of research fellowship.

References

(1) (a) Pillai, O.; Panchagnula, R. *Drug Discovery Today* **2001**, *6*, 1056. (b) Fletcher, K. *Pharm. Sci. Technol. Today* **1998**, *1*, 49. (c) Cochran, A. G. *Chem. Biol.* **2000**, *7*, R85. (d) van Hest, J. C. M.; Tirrell, D. A. *Chem. Commun.* **2001**, 1897.

(2) (a) Wang, W.; Cai, M.; Xiong, C.; Zhang, J.; Trivedi, D.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 7365. (b) Rajesh, B. M.; Iqbal, J. *Curr. Pharm. Biotechnol.* **2006**, *7*, 247.

(3) (a) Kotha, S.; Lahiri, K. *Curr. Med. Chem.* **2005**, *12*, 849. (b) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 305.
(4) Griffiths, E. C. In *A Text Book of Drug Design and Development*; Krogsgaard, L.; Bundgaard, P., Eds.; Harwood Academic Publishers: Tokyo, **1992**, 487–528.
(5) (a) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. (b) Kazmierski, W.; Hruby, V. J. *Tetrahedron* **1988**, *44*, 697.
(6) (a) Schiller, P. W.; Nguyen, T. M.; Weltrowska, G.; Wilkes, B. C.; Marsden, B. J.; Lemieux, C.; Chung, N. N. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11871. (b) Kazmierski, W. M.; Yamamura, H. I.; Hruby, V. J. *J. Am. Chem. Soc.* **1991**, *113*, 2275. (c) Lazarus, L. H.; Bryant, S. D.; Cooper, P. S.; Guerrini, R.; Balboni, G.; Salvadori, S. *Drug Discovery Today* **1998**, *3*, 284.
(7) (a) Austin, N. E.; Avenell, K. Y.; Boyfield, I.; Branch, C. L.; Coldwell, M. C.; Hadley, M. S.; Jeffrey, P.; Johns, A.; Johnson, C. N.; Nash, D. J.; Riley, G. J.; Smith, S. A.; Stacey, R. C.; Stemp, G.; Thewlis, K. M.; Vong, A. K. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 179. (b) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 567.
(8) For selected examples: (a) Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005**, *13*, 5154. (b) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327. (c) Chen, H. G.; Goel, O. P. *Synth. Commun.* **1995**, *25*, 49. (d) Jansa, P.; Machacek, V.; Bertolasi, V. *Heterocycles* **2006**, *68*, 59. (e) Liu, Z. Z.; Tang, Y. F.; Chen, S. Z. *Chin. Chem. Lett.* **2001**, *12*, 947. (f) Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P. *Tetrahedron* **2001**, *57*, 8297. (g) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2002**, 116. (h) Mash, E. A.; Williams, L. J.; Pfeiffer, S. S. *Tetrahedron Lett.* **1997**, *38*, 6977. (i) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (j) Kotha, S.; Sreenivasachary, N. *J. Indian Inst. Sci.* **2001**, *81*, 277; and references cited therein. (k) Liu, C.; Thomas, J. B.; Brieaddy, L.; Berrang, B.; Carroll, F. I. *Synthesis* **2008**, 856. (l) Wohlgemuth, R.; Benz, P. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 1082. (m) Aubry, S.; Pellet-Rostaing, S.; Faure, R.; Lemaire, M. *J. Heterocycl. Chem.* **2006**, *43*, 139. (n) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716. (o) Shchetnikov, G. T.; Osipov, S. N.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2008**, 578.
(9) For the 'building block approach' see: (a) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342. (b) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, **1989**.
(10) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1413.
(11) (a) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503. (b) Kotha, S.; Sreenivasachary, N. *Eur. J. Org. Chem.* **2001**, 3375.
(12) (a) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447. (b) Gibson, S. E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743.
(13) (a) Gibson, S. E.; Guillo, N.; Jones, J. O.; Buck, I. M.; Kalindjian, S. B.; Roberts, S.; Tozer, M. J. *Eur. J. Med. Chem.* **2002**, *37*, 379. (b) Gibson, S. E.; Guillo, N.; Kalindjian, S. B.; Tozer, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1289.
(14) For selected reviews on enyne metathesis, see: (a) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. (b) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (d) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1.
(15) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; John Wiley & Sons: Chichester, **2002**.
(16) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (c) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(17) Brahmachary, E. *PhD Thesis*; IIT-Bombay: India, **2000**.