Synthesis of Cyclohexenylamines by Ring Closing Metathesis

Martin E. Maier*[,a], Tzvetelina Lapeva

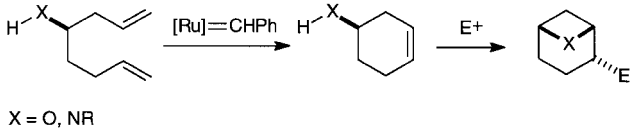
Martin-Luther-Universität Halle-Wittenberg, Fachbereich Chemie, Institut für Organische Chemie, Kurt-Mothes-Str. 2, 06120 Halle (Saale), Germany,

[a)]New address: Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany, FAX: (+49) 7071 29 5137, e-mail: martin.e.maier@uni-tuebingen.de

Received 6 June 1998

Abstract: Starting from 5-pentenaldehyde **1**, the 1-allyl-4-pentenylamines **2a-d** were prepared. The ring closing metathesis reaction of these dienes using the Grubbs catalyst **3** gave the corresponding cyclohexenylamines **4a,b** and **4d** in high yield. The secondary amine **2c** was recovered unchanged. This route to compound **4d** represents a formal total synthesis of the alkaloid epibatidine. In addition, **4b** was transformed by electrophilic transannular cyclization to the bicyclic urethanes **5a** and **5b**.

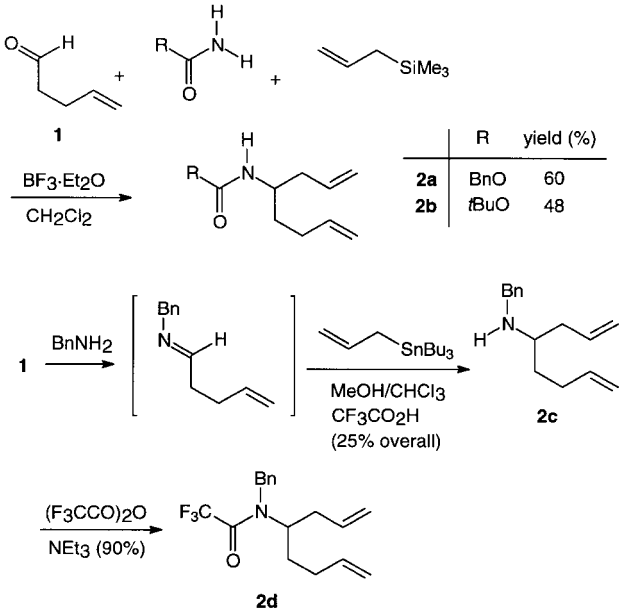
The ring-closing metathesis (rcm) is one of a few reactions that form a double bond in the cyclization step. In contrast to the intramolecular Wittig reaction or the McMurry cyclization, the starting materials, acyclic nonconjugated dienes, are stable entities and usually easily accessible. It is thus logical that the rcm reaction has found widespread use[1] since the discovery of carbene complexes that are able to mediate this reaction efficiently. In addition, some of these complexes are easily available.[2] The rcm reaction allows the formation of cyclic olefins with various ring sizes. However, as with other cyclization reactions, entropic factors and ring strain make the formation of medium-sized cycloolefins by this route difficult. Other well-known ways to some cyclic olefins include cycloaddition reactions. While, for example, cyclohexenes can be obtained by Diels-Alder reactions, not all substitution patterns are suitable for this strategy. Examples include cyclohexenes with a hetero atom at the homoallylic position. They require the use of special dienophiles, such as vinylboranes[3] or rearrangement reactions on a carboxylic substituent.[4] Such cyclohexenes are of interest for the synthesis of bicyclic heterocycles by transannular reactions (Scheme 1). In this paper we show that for cyclohexenyl amines the rcm reaction represents a useful alternative to the Diels-Alder strategy.



Scheme 1

The corresponding substrates, 1-allyl-4-pentenylamines should be available by addition of an allyl anion equivalent to a suitable 4-pentenylimine. According to this strategy, the 1,7-octadien-4-amine derivatives **2a-d** were prepared.[5] The urethanes **2a,b** were synthesized in analogy to a published procedure.[6] Thus, addition of boron trifluoride etherate to a mixture of 4-pentenal,[7] benzyl carbamate and allyl(trimethyl)silane followed by stirring of the reaction mixture over night gave the urethane **2a** in 60% yield. In a similar manner the urethane **2b** was prepared by using *tert*-butyl carbamate instead. No product was obtained with trifluoroacetamide (Scheme 2).

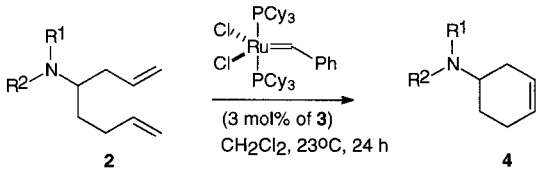
It was also of interest to study the influence of substituents at the amino function upon the rcm reaction. Therefore, the secondary amine **2c** was synthesized in a simple two-step operation by first converting the aldehyde **1** with benzylamine to the corresponding imine followed by addition of allyl(tributyl)stannane and trifluoroacetic acid.[8,9] Treatment of the benzyl amine **2c** with trifluoroacetic anhydride in the presence of triethylamine furnished the protected aminodiene **2d**.



	R	yield (%)
2a	BnO	60
2b	*t*BuO	48

Scheme 2

The crucial ring closing reactions were performed by stirring a dichloromethane solution of the dienes **2a-d** in the presence of 3 mol% of the Grubbs ruthenium carbene **3** catalyst at room temperature for 24 h. As can be seen, the 1,7-octadiene-4-amine derivatives **2a,b** and **2d** cyclized in almost quantitative yield to the corresponding cyclohexenylamines **4a,b** and **4d** (Scheme 3).[5] In contrast, the unprotected amine **2c** was recovered unchanged. This negative result supports the observation of Fürstner *et al*. who found that a chelating substituent in close proximity to one of the double bonds shuts down the catalytic cycle.[10]



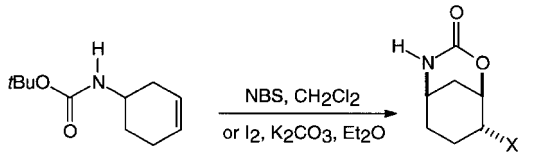
		R^1	R^2	yield (%)
2a	**4a**	H	Cbz	95
2b	**4b**	H	Boc	91
2c	**4c**	Bn	H	0
2d	**4d**	Bn	F_3CCO	98

Scheme 3

Since compound **4d** had been used in a total synthesis of the alkaloid epibatidine,[11] the present work also constitutes a formal total synthesis

of racemic epibatidine.[12] This natural product contains a 7-aza-bicyclo[2.2.1]heptane ring plus a 5-(2-chloropyridyl) substituent.[13]

The cyclohexenylamine derivative **4b** was also subjected to cyclization reactions involving electrophilic halogen atoms. Thus, treatment of **4b** with *N*-bromosuccinimide (NBS) in dichloromethane[14] provided the bicyclic urethane **5a** in good yield. Similarly, reaction of **4b** with iodine in diethyl ether[15] gave the corresponding iodo compound **5b**.[5]



4b

5a X = Br (60%)
5b X = I (74%)

Scheme 4

In summary, we have described a straightforward synthesis of cyclohexenylamines by rcm reaction of 1,7-octadiene-4-amine derivatives. This route provides a valuable alternative to the Diels-Alder strategy to cyclohexenes with an electron donating substituent in the homoallylic position. The combination of the rcm reaction with transannular cyclization should provide access to interesting natural products. Studies along these lines are currently in progress in our laboratory.

Acknowledgment. Financial support by the *Deutsche Forschungsgemeinschaft* (Graduiertenkolleg Synthese und Reaktionsverhalten von Organometallverbindungen und Metallkomplexen) and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

References and Notes

(1) Reviews: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452. (b) Schmalz, H.-G. *Angew. Chem.* **1995**, *107*, 1981-1984; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833-1836. (c) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124-2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036-2055. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1988**, *54*, 4413-4450. (f) Fürstner, A. *Top. Catal.* **1997**, *4*, 285-299.

(2) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179-2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. (c) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.

(3) (a) Singleton, D. A.; Martinez, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 7423-7424. (b) Noiret, N.; Youssofi, A.; Carboni, B.; Vaultier, M. *J. Chem. Soc. Chem. Commun.* **1992**, 1105-1107. (c) Singleton, D. A.; Redman, A. M. *Tetrahedron Lett.* **1994**, *35*, 509-512. (d) Jehanno, E.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 4439-4442.

(4) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38-40.

(5) *Procedure for the preparation of N1-(allyl-4-pentenyl)-carbamates* (**2a,b**): To a stirred solution of aldehyde **1** (1.00 g, 12.0 mmol), allyltrimethylsilane (1.37 g, 12.0 mmol) and carbamate (12.0 mmol) in dry dichloromethane (20 ml), cooled to 0-5°C was added boron trifluoride etherate (1.48 ml, 12.0 mmol) in one portion. After 30 min of stirring the reaction mixture was allowed to warm to room temperature and further stirred for 12 h. Then the mixture was poured into satd. aqueous $NaHCO_3$ and diluted with toluene (30 ml). The organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

N1-(1-allyl-4-pentenyl)-benzylcarbamate (**2a**): Flash chromatography (heptane/ethyl acetate; 7:1) provided **2a** as a white solid (1.87 g, 60%), m.p. 26-28°C. TLC (heptane/ethyl acetate, 7:1): R_f = 0.41. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44-1.61 (m, 2 H, CH_2), 2.06-2.17 (m, 2 H, CH_2), 2.19-2.30 (m, 2 H, CH_2), 3.73 (d, br., *J* = 5.7 Hz, 1 H, CH), 4.57 (d, br., *J* = 7.4 Hz, 1 H, NH), 4.93-5.04 (m, 4 H, olefinic H), 5.07 (s, 2 H, benzylic H), 5.70-5.83 (m, 2 H, olefinic H), 7.29-7.36 (m, 5 H, aryl H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1, 33.8, 39.4 (3 *C*H_2), 50.3 (*C*H), 66.5 (benzyl C), 115.0, 117.9 (2 olefinic *C*H_2), 128.0, 128.5 (aryl *C*H), 134.0 (olefinic *C*H), 136.6 (aryl C), 137.8 (olefinic *C*H), 155.9 (CO). MS (EI), *m/z* (%): 218 (15) [M^+ - allyl], 174 (20), 91 (100). $C_{16}H_{21}NO_2$ (259.35): calcd. C 74.10, H 8.10, N 5.40; found C 73.96, H 7.82, N 5.42.

N1-(1-allyl-4-pentenyl)-tert-butylcarbamate (**2b**): Flash chromatography (petroleum ether/ethyl acetate; 5:1) provided **2b** as a colorless oil (1.3 g, 48%). TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *tert*-butyl), 1.46-1.58 (m, 2 H, CH_2), 2.03-2.40 (m, 4 H, CH_2), 3.64 (s, br., 1 H, CH), 4.33 (s, br., 1 H, NH), 4.94-5.09 (m, 4 H, olefinic H), 5.71-5.85 (m, 2 H, olefinic H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (C(*C*H_3)$_3$), 31.2, 34.9, 40.5 (3 *C*H_2), 50.7 (*C*H), 64.8 (*C*(CH$_3$)$_3$), 115.9, 118.7 (2 olefinic *C*H_2), 135.5, 139.2 (2 olefinic *C*H), 156.8 (CO). MS (ESI), *m/z* (%): 248 (100) [M + Na]$^+$. $C_{13}H_{23}NO_2$ (225.33): calcd. C 69.30, H 10.29, N 6.22; found C 69.01, H 9.94, N 6.38.

N4-benzyl-1,7-octadien-4-amine (**2c**): TLC (Al_2O_3, petroleum ether/ethyl acetate, 5:1): R_f = 0.79. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50-1.58 (m, 2 H, CH_2), 2.09-2.29 (m, 4 H, CH_2), 2.62-2.67 (m, 1 H, CH), 3.76 (s, br., 2 H, benzylic CH_2), 4.92-5.09 (m, 4 H, olefinic H), 5.73-5.84 (m, 2 H, olefinic H), 7.20-7.35 (m, 5 H, aryl H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.0, 33.2, 38.3 (3 *C*H_2), 51.1 (benzylic C), 55.8 (*C*H), 114.4, 117.2 (olefinic *C*H_2), 126.8, 128.1, 128.3 (aryl *C*H), 135.6, 138.8 (olefinic *C*H), 140.8 (aryl C). MS (ESI), *m/z* (%): 216 (100) [M + H]$^+$.

N1-(1-allyl-4-pentenyl)-N1-benzyl-2,2,2-trifluoracetamide (**2d**): TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.68. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of rotamers (ratio 58:42): δ = 0.82-0.88, 1.56-1.89 (m, 4 H, CH_2), 2.28-2.33, 2.41-2.48 (m, 2 H, CH_2), 3.58-3.63, 3.96-4.03 (2 m, 1 H, CH), 4.43, 4.70 (2 d, *J* = 15.2, 1.2 H, benzylic CH_2), 4.44-4.58 (m, 0.8 H, benzylic CH_2), 4.83-5.08 (m, 4 H, olefinic H), 5.52-5.64 (m, 2 H, olefinic H), 7.26-7.37 (m, 5 H, aryl H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.1, 31.6, 31.7, 33.0, 37.1, 39.3, 46.7, 52.5, 58.9, 60.6, 116.3, 116.5, 118.9, 119.7, 128.6, 129.4, 129.7, 129.8, 134.3, 135.7, 136.5, 137.8, 138.1, 138.5, 159.3, 159.6. MS (EI), *m/z*: 311 [M^+], 270 [M^+ - allyl]. $C_{17}H_{20}F_3NO$ (311.20): calcd. C 65.61, H 6.43, N 4.50; found C 65.98, H 6.28, N 4.50.

General procedure for preparation of cyclohexenylamines (**4a-d**) *using rcm:* To a solution of diene **2a-d** (0.3 – 0.9 μmol, 0.006 M) in dry and degassed dichloromethane was added ruthenium carbene **3** (3 mol%). After stirring the reaction mixture for 24 h at room temp., the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel.

N1-(3-cyclohexenyl)benzylcarbamate (**4a**): Cyclization of **2a** (250 mg, 964 μmol) in 160 ml of dichloromethane in the presence of **3**

(24 mg, 28 μmol) gave after flash chromatography (heptane/ethyl acetate, 7:1) **4a** as white crystals (212 mg, 95%). TLC (heptane/ethyl acetate, 7:1): R_f = 0.26. m.p.: 61-63°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49-1.59 (m, 1 H, CH_2), 1.86-1.98 (m, 2 H, CH_2), 2.12-2.13 (m, 2 H, CH_2), 2.38 (d, br., *J* = 15.6 Hz, 1 H, CH_2), 3.84 (s, br., 1 H, CH), 4.75 (s, br., 1 H, NH), 5.08 (s, 2 H, benzylic CH_2), 5.58-5.67 (m, 2 H, olefinic H), 7.29-7.35 (m, 5 H, aryl H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 28.1, 31.9 (3 *C*H_2), 46.1 (*C*H), 66.5 (benzylic C), 124.3, 127.1 (2 olefinic *C*H), 128.16, 128.21, 128.6 (aryl *C*H), 136.7 (aryl C), 158.8 (CO). IR (KBr): = 3322 cm^{-1}, 1687, 1542. MS (ESI), *m/z* (%): 254 (100) $[M + Na]^+$. $C_{14}H_{17}NO_2$ (231.16): calcd. C 72.70, H 7.41, N 6.06; found C 72.93, H 7.54, N 6.13.

8-Bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (**5a**): To a cooled (-78°C) solution of cyclohexenylamine **4b** (20 mg, 0.10 mmol) in dichloromethane (2 ml) was added at once *N*-bromosuccinimide (22 mg, 0.12 mmol). After being stirred for 18 h at this temp., the reaction mixture was allowed to warm up to room temp. Stirring was continued for 3 d (TLC monitoring), and then the reaction was quenched by addition of satd. aqueous Na_2SO_3. The mixture was diluted with ether and the organic layer washed with brine, satd. aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil which solidified on standing. Recrystallization from pentane/ether provided **5a** as white crystals (13 mg, 60%). m.p.: 157°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (d, *J* = 13.6 Hz, 1 H), 1.92-2.01 (m, 3 H, CH_2), 2.28-2.38 (m, 1 H), 2.53 (dd, *J* = 2.0, 13.8 Hz, 1 H), 3.64 (s, br., 1 H, CHN), 4.46 (s, 1 H, CHBr), 4.64 (s, 1 H, CH-O), 6.04 (s, br., 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 24.7, 26.9 (3 CH_2), 45.2 (*C*NH), 48.1 (*C*Br), 75.4 (*C*-O), 154.0 (C=O). MS (ESI), *m/z* (%): 244 (40) $[M + Na]^+$, 221 (98) $[M + H]^+$.

(6) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997-1000.

(7) Rossiter, J. T.; James, D. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1909-1913.

(8) Wuts, P. G. M.; Jung, J.-W. *J. Org. Chem.* **1991**, *56*, 365-372.

(9) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378-1380.

(10) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792-803.

(11) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771-1778.

(12) Recent syntheses: (a) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1857-1858. (b) Ikeda, M.; Kugo, Y.; Kondo, Y.; Yamazaki, T.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3339-3344. (c) Pandey, G.; Bagul, T. D.; Sahoo, A. *J. Org. Chem.* **1998**, *63*, 760-768. (d) Sirisoma, N.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059-2062.

(13) Review: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179-1193.

(14) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z.-i. *J. Org. Chem.* **1988**, *53*, 5491-5501.

(15) Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888-4895.