Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6079–6082

First total synthesis of (±)-epocarbazolin A and epocarbazolin B, and asymmetric synthesis of (−)-epocarbazolin A via Shi epoxidation

Jan Knöll and Hans-Joachim Knölker*

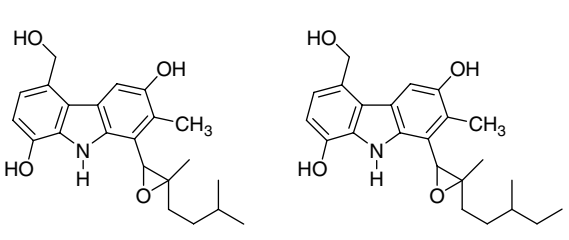
Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany

Received 10 May 2006; revised 14 June 2006; accepted 19 June 2006
Available online 10 July 2006

Abstract—Epoxidation of the trisilyl-protected carbazomadurins A and B with dimethyldioxirane followed by desilylation provides a simple route to racemic epocarbazolin A and a non-diastereoselective access to epocarbazolin B. The Shi epoxidation has been applied to an asymmetric synthesis of the non-natural (−)-epocarbazolin A.

Recent isolations emphasize that nature appears to offer an enormous reservoir of structurally interesting carbazole alkaloids with useful pharmacological activities. These findings induced a strong research activity by several groups.[1–3] In 1993 a Japanese research group of the company Bristol-Myers on screening for 5-lipoxygenase inhibitors identified epocarbazolin A **1a** and epocarbazolin B **1b** (Fig. 1).[4] These compounds were isolated from the actinomycete strain *Streptomyces anulatus* T688-8.

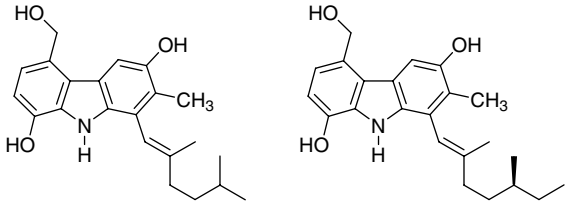
5-Lipoxygenase metabolites of arachidonic acid are known as mediators of inflammatory and allergic processes such as psoriasis, asthma, and hypersensitivity. Thus, inhibitors of 5-lipoxygenase are considered to represent potential therapeutics for the treatment of these diseases. The epocarbazolins exhibit a potent inhibition of rat 5-lipoxygenase ($IC_{50} = 2.4$ and 2.6 μM for **1a** and **1b**, respectively).[4] The 5-lipoxygenase inhibitory activity presumably relies on their radical scavenger activity. Both compounds also show weak antibacterial activity.



Epocarbazolin A **1a** Epocarbazolin B **1b**

Figure 1. Epocarbazolin A **1a** and epocarbazolin B **1b**.

The structural elucidation of the epocarbazolins was based on their spectral data. They are remarkable by their substitution pattern and the epoxide ring in the side chain. However, the absolute configuration at the stereogenic centers of the epocarbazolins has remained unknown. The framework of the epocarbazolins A **1a** and B **1b** resembles that of the carbazomadurins A **2a** and B **2b** (Fig. 2).[5] Because of the structural similarity we considered the carbazomadurins **2** as precursors for a total synthesis of the epocarbazolins **1**. In the most simple approach epoxidation of the former would lead to the latter natural products.

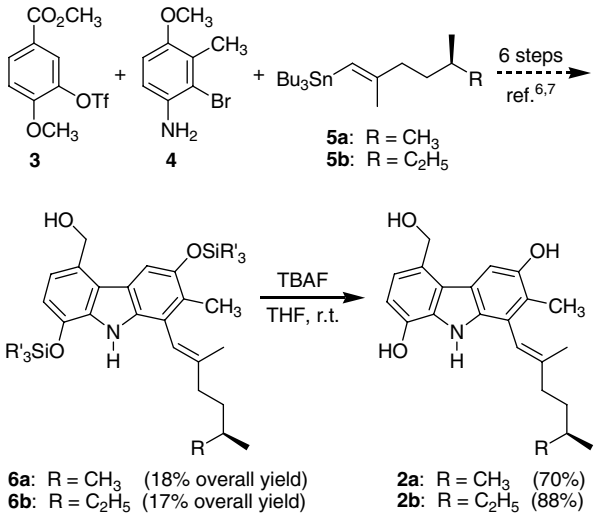


Carbazomadurin A **2a** Carbazomadurin B **2b**

Figure 2. Carbazomadurin A **2a** and carbazomadurin B **2b**.

Keywords: Alkaloids; Asymmetric catalysis; Carbazoles; Epoxides; Total synthesis.
* Corresponding author. Fax: +49 351 463 37030; e-mail: hans-joachim.knoelker@tu-dresden.de

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.095



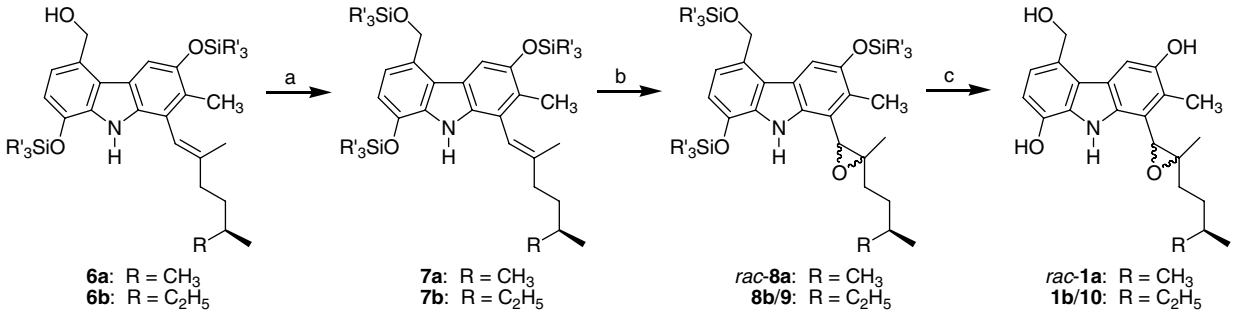
Scheme 1. Total synthesis of carbazomadurin A **2a** and B **2b**.[6,7] Protecting group: SiR'_3=Si*t*-$BuPh_2$.

Recently, we have developed a convergent synthetic route to the carbazomadurins by using a palladium-catalyzed coupling of three building blocks (Scheme 1).[6,7] The aryl triflate **3** is readily prepared from isovanillic acid (two steps, 91% yield). Starting from commercial 2-bromo-6-nitrotoluene, the arylamine **4** is obtained in five steps and 44% yield. The alkenylstannanes **5** are available via Negishi's zirconium-catalyzed carboalumination as the key-step (**5a**: two steps, 52% yield; **5b**: six steps, 11% yield). The assembly of the carbocyclic framework led to the intermediates **6a** and **6b** in six steps: (1) Buchwald–Hartwig amination, (2) palladium(II)-mediated oxidative cyclization, (3) cleavage of the methyl ethers, (4) di-*O*-silylation, (5) Stille coupling with the alkenylstannanes **5a** and **5b**, and (6) DIBAL reduction of the methyl ester. Desilylation of the disilyl-protected carbazomadurins **6a** and **6b** completed the total syntheses of carbazomadurin A **2a** and carbazomadurin B **2b**.[6,7]

All attempts to achieve a direct transformation of carbazomadurin A **2a** into epocarbazolin A **1a** by epoxidation, using either *m*-chloroperbenzoic acid in dichloromethane or dimethyldioxirane in acetone at room temperature,[8] failed and resulted in complete decomposition of starting material. Epoxidation of the disilyl-protected carbazomadurin A **6a** was unsuccessful as well. Therefore, we decided to convert compound **6a** to the trisilyl-protected carbazomadurin A **7a** by reaction with *tert*-butyldiphenylchlorosilane in the presence of stoichiometric amounts of DMAP (Scheme 2).[9] As reaction of the tri-*O*-silylcarbazomadurin A **7a** with *m*-chloroperbenzoic acid in dichloromethane also led to complete decomposition, milder epoxidizing agents were required. Dimethyldioxirane can be applied for epoxidations under neutral and almost non-aqueous reaction conditions.[8] Following a procedure of Adam, we prepared a solution of dimethyldioxirane in acetone by reaction of acetone with potassium peroxymonosulfate under buffered conditions and subsequent distillation.[10] Reaction of a solution of **7a** in dichloromethane using dimethyldioxirane in acetone at −20 °C afforded the (±)-tri-*O*-silylepocarbazolin A (±)-**8a**, representing a stable compound, which was purified by flash chromatography on silica gel. Both epocarbazolins were reported to be photolabile.[4] Thus, deprotection and workup were carried out in the absence of light. Desilylation of (±)-**8a** with tetrabutylammonium fluoride provided (±)-epocarbazolin A (±)-**1a** in only moderate yield. An intense red color, immediately generated during this reaction, indicated oxidation to quinoid systems. Several by-products have been separated by chromatography but could not be identified. However, the spectroscopic data (UV, IR, ^{1}H NMR, ^{13}C NMR, and MS) of our racemic epocarbazolin A (±)-**1a**[11] were in full agreement with those reported for the natural product.[4]

The absolute configuration at the stereogenic center in the side chain of epocarbazolin B **1b** is still unknown.[4] We recently assigned unambiguously the absolute stereochemistry of carbazomadurin B **2b** by an enantioselective total synthesis.[7] As both natural products have been isolated from similar sources (microorganisms), we assume an identical absolute configuration at this stereogenic center.

Starting from enantiopure di-*O*-silylcarbazomadurin B **6b** (enantiopurity: >99% ee),[7] silylation to the tri-*O*-silylcarbazomadurin B **7b** and epoxidation using dimethyldioxirane provided the tri-*O*-silylepocarbazolin B **8b** and diastereoisomer **9** as a 1:1 mixture (Scheme 2). Desilylation of this mixture afforded epocarbazolin B **1b** along



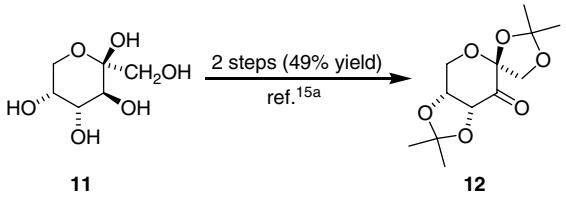
Scheme 2. Synthesis of (±)-epocarbazolin A (±)-**1a** and epocarbazolin B **1b**. Protecting group: SiR'_3=Si*t*-$BuPh_2$. Reagents and conditions: (a) *t*-$BuPh_2SiCl$ (= R'_3SiCl), DMF, DMAP, rt, 4.5 h (**7a**: 100%, **7b**: 100%); (b) dimethyldioxirane, acetone/CH_2Cl_2, −20 °C, 24 h ((±)-**8a**: 53%, **8b/9**: 53%); (c) 3 equiv TBAF, THF, rt (in the dark), 6 h ((±)-**1a**: 24%, **1b/10**: 18%).

with its diastereoisomer **10**.[12] The spectroscopic data (UV, IR, ^{1}H NMR, ^{13}C NMR, and MS) have been compared with those described for the natural product.[4]

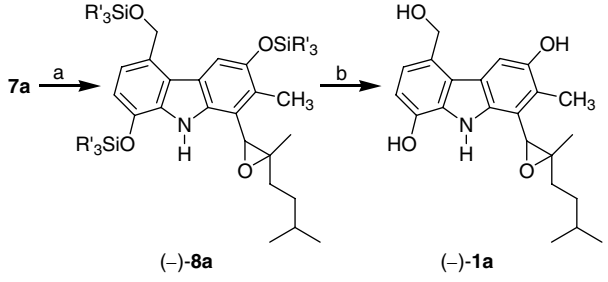
For the enantioselective synthesis of epocarbazolin A **1a** we envisaged an asymmetric epoxidation using chiral non-racemic dioxiranes.[13–15] Shi used catalytic amounts of the chiral ketone **12**, prepared from D-fructose **11** (Scheme 3), and oxone® as stoichiometric oxidizing agent for the in situ generation of a chiral dioxirane.[15a] The method of Shi has been applied to the asymmetric catalytic epoxidation of a wide variety of olefins including conjugated trisubstituted double bonds.[15–18]

Using a modified Shi procedure,[15b] the tri-*O*-silylcarbazomadurin A **7a** was transformed to the (−)-tri-*O*-silylepocarbazolin A (−)-**8a** (Scheme 4).[19] Removal of the silyl protecting groups afforded (−)-epocarbazolin A (−)-**1a**.[20] The value for the specific rotation of our synthetic (−)-**1a** is $[\alpha]_D^{26}$ −55,[20] while a value of $[\alpha]_D^{26}$ +75 has been reported for the natural product.[4] Therefore, we concluded that using catalyst **12** the non-natural enantiomer of epocarbazolin is formed preferentially. However, we have not yet been able to assign the absolute configuration of our product. Assuming a linear correlation of specific rotation and enantiomeric excess, an enantioselectivity of 73% ee can be estimated for the Shi epoxidation of **7a** described above.

In summary, we have demonstrated the feasibility to transform the carbazomadurins **2** into the epocarbazolins **1**. Epoxidation of the tri-*O*-silyl-protected carbazomadurins A and B with dimethyldioxirane provides a non-stereoselective access to the epocarbazolins A and B. Moreover, our initial investigation shows that the Shi epoxidation can be utilized for an asymmetric synthesis of the epocarbazolins **1**. Application of the chiral catalyst enantiomeric to **12**, which can be prepared from L-fructose,[15a] should lead to natural (+)-epocarbazolin A (+)-**1a**.



Scheme 3. Synthesis of the Shi catalyst **12** from D-fructose **11**.[15a]



Scheme 4. Synthesis of (−)-epocarbazolin A (−)-**1a**. Protecting group: SiR'_3=Si*t*-BuPh$_2$. Reagents and conditions: (a) oxone®, K_2CO_3, 5 equiv **12**, Bu_4NHSO_4, buffer, H_2O/DME/hexane, rt, 8 h (18%); (b) 3 equiv TBAF, THF, rt (in the dark), 6 h (18%).

Acknowledgments

We thank the Fonds der Chemischen Industrie for financial support of our project.

References and notes

1. Transition Metal Complexes in Organic Synthesis, Part 80. For part 79, see: Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006** *1*, in press.
2. Reviews: (a) Chakraborty, D. P.; Roy, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Steglich, W., Tamm, C., Eds.; Springer: Wien, 1991; Vol. 57, p 71; (b) Chakraborty, D. P. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, p 257; (c) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303; (d) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309.
3. For recent novel synthetic approaches to carbazoles, see: (a) Aygün, A.; Pindur, U. *J. Heterocycl. Chem.* **2003**, *40*, 411; (b) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Eur. J. Org. Chem.* **2003**, 740; (c) Knölker, H.-J.; Reddy, K. R. *Heterocycles* **2003**, *60*, 1049; (d) Knölker, H.-J.; Wolpert, M. *Tetrahedron* **2003**, *59*, 5317; (e) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323; (f) Rawat, M.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329; (g) Knölker, H.-J.; Krahl, M. P. *Synlett* **2004**, 528; (h) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513; (i) Benavides, A.; Peralta, J.; Delgado, F.; Tamariz, J. *Synthesis* **2004**, 2499; (j) Knölker, H.-J.; Fröhner, W.; Heinrich, R. *Synlett* **2004**, 2705; (k) Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5411; (l) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413; (m) Kataeva, O.; Krahl, M. P.; Knölker, H.-J. *Org. Biomol. Chem.* **2005**, *3*, 3099; (n) Pelly, S. C.; Parkinson, C. J.; van Otterlo, W. A. L.; de Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474; (o) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620; (p) Czerwonka, R.; Reddy, K. R.; Baum, E.; Knölker, H.-J. *Chem. Commun.* **2006**, 711.
4. Nihei, Y.; Yamamoto, H.; Hasegawa, M.; Hanada, M.; Fukagawa, Y.; Oki, T. *J. Antibiot.* **1993**, *46*, 25.
5. Kotada, N.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 770.
6. Knölker, H.-J.; Knöll, J. *Chem. Commun.* **2003**, 1170.
7. Knöll, J.; Knölker, H.-J. *Synlett* **2006**, 651.
8. (a) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 45; (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187; (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.
9. (a) Hanessian, S.; Lavalee, P. *Can. J. Chem.* **1975**, *53*, 2975; (b) Hanessian, S.; Lavalee, P. *Can. J. Chem.* **1977**, *55*, 562.
10. Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
11. (±)-Epocarbazolin A (±)-**1a**: colorless powder; mp 150 °C (dec.). UV (MeOH): $\lambda = 233$, 250, 299, 345, 359 nm. IR (DRIFT): $\nu = 3461$, 2955, 2929, 2869, 1620, 1585, 1523, 1446, 1388, 1367, 1266, 1168, 1119, 1070, 988, 807 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 0.970$ (d, $J = 6.4$ Hz, 3H), 0.972 (d, $J = 6.4$ Hz, 3H), 1.05 (s, 3H), 1.49–1.56 (m, 2H), 1.63–1.70 (m, 1H), 1.81–1.88 (m, 2H),

2.35 (s, 3H), 3.90 (t, $J = 5.7$ Hz, 1H), 4.24 (s, 1H), 4.99 (d, $J = 5.7$ Hz, 2H), 6.76 (d, $J = 7.7$ Hz, 1H), 6.91 (d, $J = 7.7$ Hz, 1H), 7.64 (s, 1H), 7.94 (br s, 1H), 8.64 (br s, 1H), 9.29 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): $\delta = 12.86$ (CH_3), 17.48 (CH_3), 23.26 (CH_3), 23.40 (CH_3), 29.53 (CH), 35.40 (CH_2), 36.89 (CH_2), 63.81 (C), 64.36 (CH_2), 64.70 (CH), 108.59 (CH), 110.58 (CH), 118.58 (C), 119.60 (CH), 122.09 (C), 123.04 (C), 123.35 (C), 129.00 (C), 131.04 (C), 134.24 (C), 143.43 (C), 150.03 (C). MS (EI): m/z (%) = 369 (23) [M^+], 270 (11), 200 (9), 199 (10), 153 (25), 136 (12), 107 (10), 106 (10), 89 (34), 77 (39), 71 (32), 58 (26), 43 (100). HRMS: m/z calcd for $C_{22}H_{27}NO_4$ [M^+]: 369.1940; found: 369.1934.

12. Epocarbazolin B **1b** and diastereoisomer **10**: pale yellow powder; mp 180 °C (dec.); $[\alpha]_D^{20}$ +9 (c 0.1, MeOH). UV (MeOH): $\lambda = 233$, 243, 249, 289 (sh), 299, 344, 359 nm. IR (DRIFT): $\nu = 3471$, 2958, 2874, 1623, 1587, 1523, 1506, 1447, 1270, 1158, 1080, 1061, 999, 815 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 0.91$–0.96 (m, 6H), 1.05 (s, 3H), 1.23–1.29 (m, 1H), 1.44 (m, 3H), 1.62–1.69 (m, 1H), 1.74–1.93 (m, 2H), 2.35 (s, 3H), 3.95 (br s, 1H), 4.24 (s) and 4.25 (s, $\Sigma = 1$H), 4.99 (br s, 2H), 6.76 (d, $J = 7.7$ Hz, 1H), 6.91 (d, $J = 7.7$ Hz, 1H), 7.64 (s, 1H), 7.98 (br s, 1H), 8.68 (br s, 1H), 9.29 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): $\delta = 12.09$ and 12.13 (CH_3), 12.83 (CH_3), 17.41 and 17.47 (CH_3), 19.88 and 19.95 (CH_3), 30.41 and 30.56 (CH_2), 32.95 (CH_2), 35.88 and 35.90 (CH), 36.50 (CH_2), 63.85 (C), 64.33 (CH_2), 64.70 (CH), 108.55 (CH), 110.55 (CH), 118.55 (C), 119.57 (CH), 122.05 (C), 123.00 (C), 123.32 (C), 128.96 (C), 131.01 (C), 134.20 (C), 143.40 (C), 150.00 (C). MS (EI): m/z (%) = 383 (11) [M^+], 365 (4), 270 (6), 254 (5), 199 (41), 139 (7), 77 (21), 58 (27), 43 (100). HRMS: m/z calcd for $C_{23}H_{29}NO_4$ [M^+]: 383.2097; found: 383.2092.
13. Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.
14. Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.
15. (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224; (b) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475; (c) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521.
16. Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675.
17. Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.
18. Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
19. (−)-Tri-*O*-(*tert*-butyldiphenylsilyl)epocarbazolin A (−)-**8a**: colorless crystals; mp 85–86 °C; $[\alpha]_D^{20}$ −5.7 (c 0.5, $CHCl_3$).
20. (−)-Epocarbazolin A (−)-**1a**: colorless powder; mp 160 °C (dec.); $[\alpha]_D^{26}$ −55 (c 0.067, MeOH); for spectroscopic data, see above.[11]