Diastereoselective Synthesis of Merucathin: The Singlet Oxygen Ene Reaction (Schenck Reaction) as a Key Step Towards an *E*-Configured β-Amino Allylic Alcohol

Waldemar Adam, Hans-Günter Brünker*

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

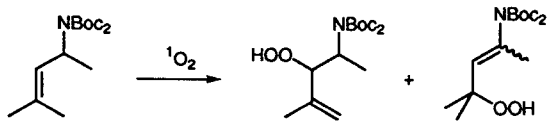
Fax +49(931)8884756; E-mail Adam@vax.rz.uni-Wuerzburg.d400.de

Received 3 April 1995

An enantio- and diastereoselective synthesis of the naturally occurring merucathin is reported. The singlet oxygen ene reaction of the bis-Boc-protected allylic amine **3**, which was prepared from L-alanine, was employed as key step for this regio- and diastereoselective synthesis. The ene reaction is highly *erythro*-selective and the newly formed double bond in the allylic hydroperoxide **5** is exclusively *E*-configured. Reduction of the allylic hydroperoxide **5** and base-catalyzed deprotection provides a convenient and unprecedented synthesis of the optically active *E*-configured β-amino allylic alcohol merucathin from the corresponding acylated allylic amine **3**.

The β-amino alcohol functionality is an important structural unit in amino sugars,[1] unusual amino acids,[2] and numerous naturally occurring compounds.[3] In view of the high interest in these natural, biologically active compounds, especially for peptidomimetic applications,[4] much work has been conducted recently on the diastereoselective synthesis of β-amino alcohols.[4,5] In the case of merucathin,[6,7] an *erythro*- and *E*-configured β-amino allylic alcohol found in the CNS-active khatamines of *Catha edulis* Forsk. (Celastraceae),[8] we show herein that the diastereoselective Schenck[9] reaction of Boc-protected allylic amines constitutes a convenient methodology for the diastereoselective synthesis of this natural product.

Recently[10,11] it was shown that the Schenck reaction of acylated allylic amines gives in high regio- and diastereoselectivity the corresponding *erythro*-configured β-amino allylic hydroperoxides, provided two requisites are met: (a) the olefin possesses 1,3-allylic strain, and (b) the nitrogen-containing functionality is sterically demanding. Thus, from the bis-Boc-protected allylic amine **1**, the hydroperoxides **2** and **2′** were obtained in regio- and diastereoselectivities of more than 90:10 (Scheme 1). High regioselectivity in the singlet oxygen ene reaction has been known for some time, as described by the so-called PSEA rule[12] (Preference of the Syn Ene Addition) or the *cis* effect.[13] In contrast, the excellent diastereoselectivity found in the photooxygenation of chiral, acyclic, allylic substrates[10,11,14] is a recent accomplishment for the singlet oxygen ene reaction. The observed high stereoselectivity was mechanistically explained in terms of the *threo* exciplex, Ex, in which the electrostatic repulsion and 1,3-allylic strain operate in conjunction as a stereocontrolling feature.[11]



1 | **2** 90 : **2′** 10 (*erythro/threo* 95 : 5; *Z/E* 95 : 5)

Scheme 1

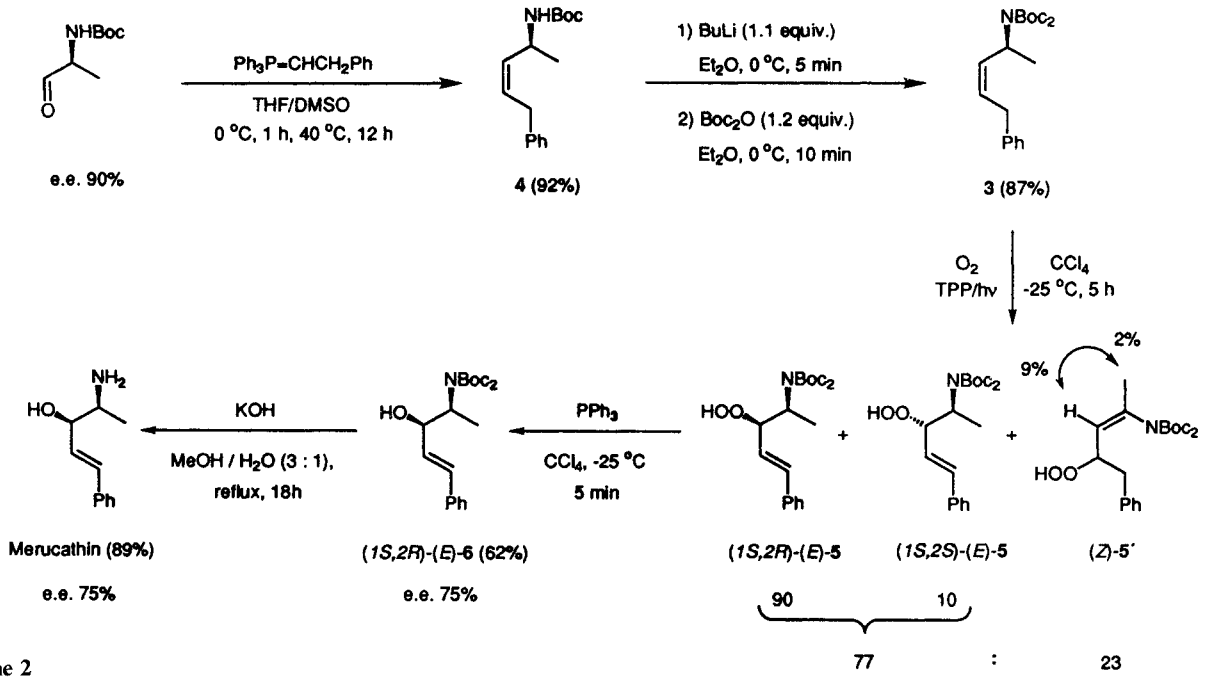
We have employed this *erythro* selectivity for the preparation of the *erythro*- and *E*-configured allylic amino alcohol functionality in merucathin. For this purpose the *Z*-configured allylic amine **3** was required (Scheme 2), which meets all requisites for the desired *erythro* selectivity in the singlet oxygen ene reaction. Thus, it contains the sterically demanding, polar $NBoc_2$ substitutent and high 1,3-allylic strain. Furthermore, this merucathin precursor can be synthesized enantioselectively from the readily available L-alanine as starting material. The latter is first converted into the Boc-protected L-alanine aldehyde according to the literature procedure[15,16] in an enantiomeric excess (ee) of 90%. Wittig reaction of the aldehyde afforded the *Z*-configurated allylic carbamate **4** in 92% yield. The second Boc-group was then introduced by deprotonation of the carbamate **4** with BuLi and subsequent addition of bis(1,1-dimethylethyl) dicarbonate gave the required imidodicarbonate **3** in 87% yield.

Photooxygenation of the optically active merucathin precursor **3** at subambient temperature gave the regioisomeric hydroperoxides **5** and (*Z*)-**5′** in a 77:23 ratio (Scheme 2). As expected, *E*-configured hydroperoxide **5** was exclusively obtained in an *erythro/threo* ratio of 90:10. Furthermore, the minor regioisomeric hydroperoxide **5′** was formed exclusively as the *Z*-configured isomer, whose configuration was determined by NOE experiments (Scheme 2).

After reduction of the crude product mixture with triphenylphosphine and column chromatography, the *erythro/E*-**6** was isolated in 62% yield. Its ee value of 75% was determined by HPLC analysis on a chiral column. Since the aldehyde used for the syntheses had an ee of 90% and since the singlet oxygen ene reaction is strictly stereoselective,[17] some racemization must have taken place during the Wittig reaction. By deprotection of *erythro/E*-**6** with potassium hydroxide in 3:1 methanol/water (acidic conditions must be avoided), merucathin was obtained in 89% yield (ee 75%), i.e. without further epimerization (Scheme 2).

In summary, the present regio- and diastereoselective merucathin synthesis illustrates that *erythro/E*-configured β-amino allylic alcohols can be conveniently and efficiently prepared under mild conditions by the singlet oxygen ene reaction (Schenck reaction) of acylated allylic amines. By the use of starting materials from the chiral pool for the synthesis of the required allylic amines, in the present case L-alanine, the desired β-amino allylic alcohols can be obtained in good enantiomeric excess.

Mps were determined on a Büchi 535 apparatus. The IR spectra were recorded on a Perkin-Elmer spectrophotometer 1420. NMR



Scheme 2

spectra were run on a Bruker AC 200 and a Bruker AC 250 spectrometer with $CDCl_3$ as internal standard [$\delta = 7.26$ (^1H) and 77.0 (^{13}C)]. Elemental analyses were performed by the Analytical Division of the Institute of Inorganic Chemistry, University of Würzburg. Column chromatography was conducted on silica gel (32–63 μm) from Woelm, Erlangen. Commercial reagents and solvents were purified according to literature procedures to match reported physical and spectral data. For the HPLC analysis, a Daicel-Chiracel OD, 250 × 4 mm column and 1:9 *n*-hexane/isopropyl alcohol eluent (flow rate 0.6 mL min^{-1}) were used. The methyl L-alanate hydrochloride,[15] methyl (*S*)-*N*-[(dimethylethoxy)carbonyl]alanate,[15] (*S*)-(dimethylethyl)(1-methyl-2-oxoethyl)carbamate[16] and (phenylethyl)triphenylphosphonium bromide[18] were prepared according to literature procedures. The enantiomeric excess of the carbamate was 90%. For all new compounds statisfactory elemental analyses were obtained: C ± 0.35, H ± 0.38, N ± 0.32.

(*S*,*Z*)-Bis(1,1-dimethylethyl) *N*-(1-Methyl-4-phenylbut-2-enyl)-imidodicarbonate (3):

To **4** (755 mg, 2.89 mmol) in E_2O (20 mL) was added at 0 °C BuLi (3.42 mmol, 1.2 equiv, in hexane 1.53 M). After 5 min stirring, bis(1,1-dimethylethyl) dicarbonate (1.25 g, 5.71 mmol) was added. After stirring for a further 10 min at room temperature, methanol (0.1 mL) was added and the solvent was removed (20 °C/20 Torr). The residue was purified by column chromatography (50 g silica gel; pentane–*t*-BuOMe = 94:4) to afford 910 mg (87%) of **3** as a colorless oil.

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 1.41$ (d, $J = 6.9$ Hz, 3H, CH_3), 1.45 (s, 18H, CH_3), 3.45 (d, $J = 7.3$ Hz, 2H, CH_2), 5.18–5.30 (m, 1H, CH), 5.60 (ddt, $J = 10.6$, 0.9, 7.3 Hz, 1H, HC=), 5.59 (ddt, $J = 10.6$, 8.1, 1.5 Hz, 1H, HC=), 7.16–7.32 (m, 5H, arom).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 19.7$ (q), 28.0 (6q), 33.9 (t), 48.9 (d), 82.0 (2s), 125.9 (d), 128.3 (2d), 128.4 (2d), 130.7 (d), 131.1 (d), 140.3 (s), 152.8 (2s).

IR ($CDCl_3$): $\nu = 3020$, 2950, 1760, 1710, 1460, 1390, 1370, 1260, 1190, 1150, 850 cm^{-1}.

(*S*,*Z*)-(1,1-Dimethylethyl) *N*-(1-Methyl-4-phenylbut-2-enyl)-carbamate (4):

To NaH [328 mg, 8.20 mmol; dispersion in paraffin (60%)], washed with pentane (3 × 10 mL), was added DMSO (5 mL). The mixture was heated to 70 °C for 2 h, cooled to 0 °C, and added under argon gas to (2-phenylethyl)triphenylphosphonium bromide (3.50 g, 7.83 mmol) in a mixture of DMSO (4 mL) and THF (30 mL). After stirring for 1 h, (*S*)-*N*-(1,1-dimethylethyl) (1-methyl-2-oxoethyl)-carbamate (ee 90%) (677 mg, 3.91 mmol) in THF (10 mL) was added to the dark red solution at 0 °C. After stirring for 1 h at 0 °C and 12 h at 40 °C, the solvent was removed (40 °C/20 Torr), and to the residue were added water (50 mL) and EtOAc (100 mL). The layers were separated, and the organic layer was washed with brine (2 × 20 mL), and dried (Na_2SO_4). Solvent removal (40 °C/20 Torr) and column chromatography (70 g silica gel; CH_2Cl_2) afforded 937 mg (92%) of **4** as a colorless oil.

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 1.23$ (d, $J = 6.5$ Hz, 3H, CH_3), 1.46 (s, 9H, CH_3), 3.51 (d, $J = 7.4$ Hz, 2H, CH_2), 4.50 (s, 1H, NH), 4.51–4.65 (m, 1H, CH), 5.36 (ddt, $J = 10.7$, 8.7, 1.5 Hz, 1H, HC=), 5.59 (ddt, $J = 10.7$, 7.4, 0.8 Hz, 1H, HC=), 7.12–7.33 (m, 5H, arom).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 22.0$ (q), 28.4 (3q), 33.8 (t), 43.8 (d), 79.2 (s), 125.9 (d), 128.4 (2d), 128.5 (2d), 129.5 (d), 132.5 (d), 140.4 (s), 155.0 (s).

IR ($CDCl_3$): $\nu = 3460$, 3060, 3000, 2940, 1730, 1510, 1470, 1380, 1250, 1200, 1070, 850 cm^{-1}.

(*E*)-Bis(1,1-dimethylethyl) *N*-(2-Hydroperoxy-1-methyl-4-phenylbut-3-enyl)imidodicarbonate (5), (*Z*)-Bis(1,1-dimethylethyl) *N*-(3-hydroperoxy-1-methyl-4-phenylbut-1-enyl)imidodicarbonate [(*Z*)-5]:

A solution of **3** (572 mg, 1.58 mmol) and tetraphenylporphyrin (1.00 mg, 1.17 μmol) in CCl_4 (15 mL) was irradiated for 5 h at −25 °C by two 400 W sodium lamps (Osram NAV V 400 W), while a gentle stream of dried ($CaCl_2$, P_4O_{10}) oxygen gas was allowed to pass through the reaction mixture. For this purpose a 25 mL Schlenk tube with a disposable pipette for the passage of the gas stream, was placed into a transparent Dewar vessel, connected to a Cryostat (HGW Lauda). The entire apparatus was surrounded by an aluminum reflector to optimize the light intensity. Since the hydroperoxides **5** and **5'** were not stable under the conditions of column chromatography, they were identified by their NMR spectra. The relative product ratio was determined from the characteristic signals in the crude product ^1H NMR spectrum. The crude reaction mixture was subsequently reduced with triphenylphosphine.

(1S,2R)-**5**:

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 1.42$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.44 (s, 18H, CH_3), 4.59 (quint, $J = 6.8$ Hz, 1H, CH), 4.75 (ddd, $J = 8.1$, 6.8, 0.8 Hz, 1H, CH), 6.20 (dd, $J = 16.0$, 8.1 Hz, 1H,

HC=), 6.69 (d, J = 16.0 Hz, 1 H, HC=), 7.10–7.40 (m, 5H, arom), 9.18 (s, 1 H, OOH).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.9 (q), 27.7 (6q), 52.2 (d), 82.4 (2s), 88.8 (d), 124.8 (d), 126.5 (2d), 127.6 (d), 128.2 (2d), 135.3 (d), 136.4 (s), 153.4 (2s).

(1S,2S)-**5**:

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35–1.47 (m, 3H, CH_3, overlapping), 1.55 (s, 18H, CH_3), 4.50–4.64 (m, 1H, CH), 4.70–4.81 (m, 1H, CH, overlapping), 6.40 (dd, J = 16.0, 8.2 Hz, 1H, HC=), 6.69 (d, J = 16.0 Hz, 1H, HC=), 7.10–7.40 (m, 5H, arom), 9.40 (s, 1H, OOH).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.3 (q), 27.8 (6q), 52.4 (d), 82.9 (2s), 86.8 (d), 125.0 (d), 126.5 (2d), 127.8 (d), 128.3 (2d), 135.6 (d), 136.2 (s), 153.8 (2s).

(Z)-**5**':

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.48 (s, 18H, CH_3), 1.95 (d, J = 1.3 Hz, 3H, CH_3), 2.90 (d, J = 5.5 Hz, 1H, CH_2), 2.93 (d, J = 7.6 Hz, 1H, CH_2), 4.60–4.80 (m, 1H, CH), 5.43 (dq, J = 7.9, 1.3 Hz, 1H, HC=), 7.10–7.40 (m, 5H, arom), 9.37 (s, 1H, OOH).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 21.4 (q), 27.8 (6q), 38.4 (t), 81.3 (d), 82.9 (2s), 126.2 (d), 126.3 (d), 128.2 (2d), 129.3 (2d), 137.2 (d), 138.4 (s), 150.8 (2s).

(1*S*,2*R*,*E*)-Bis(1,1-dimethylethyl) *N*-(2-Hydroxy-1-methyl-4-phenylbut-3-enyl)imidodicarbonate [(1*S*,2*R*,*E*-6]:

To the crude product mixture, obtained by the photooxygenation of 572 mg (1.58 mmol) of the imidodicarbonate **3**, was added PPh_3 (445 mg, 1.70 mmol) in CCl_4 (1 mL) at 0 °C. Solvent removal (20 °C/20 Torr) and column chromatography (70 g silica gel; pentane–*t*-BuOMe, 80:20) afforded 370 mg (62%) of (1*S*,2*R*,*E*)-**6** as a colorless oil. The ee was determined by HPLC analysis as 75%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.29 (d, J = 7.1 Hz, 3H, CH_3), 1.49 (s, 18H, CH_3), 4.13 (d, J = 1.6 Hz, 1H, OH), 4.38 (dq, J = 3.8, 7.1 Hz, 1H, CH), 4.54–4.63 (m 1H, CH), 6.18 (dd, J = 15.9, 5.8 Hz, 1H, HC=), 6.70 (dd, J = 15.9, 1.3 Hz, 1H, HC=), 7.17–7.42 (m, 5H, arom).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 11.2 (q), 27.6 (6q), 56. 9 (d), 74.8 (d), 83.0 (2s), 126.4 (2d), 127.4 (d), 128.4 (2d), 129.4 (d), 130.9 (d), 136.8 (s), 153.9 (2s).

(3*R*,4*S*,*E*)-4-Amino-1-phenylpent-1-en-3-ol (Merucathin):[7]

A sample of (1*S*,2*R*,*E*)-**6** (116 mg, 307 μmol) in MeOH (15 mL) (75:25) and KOH (140 mg, 2.45 mmol) were heated for 18 h under reflux. After solvent removal (30 °C/20 Torr), water (5 mL) was added, the mixture was acidified to pH 2 with 1 M aq H_3PO_4 and washed with Et_2O (3 × 20 mL). Subsequently the aqueous layer was made alkaline (pH 10) by addition of 2 N aq NaOH and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (1 × 20 mL) and dried (Na_2SO_4). Solvent removal (20 °C/20 Torr) afforded 48.4 mg (89%) of a colorless powder, the ee was 75%, $[\alpha]_D^{20}$ = + 22.1° (c = 0.6, CH_3OH) {Lit.[7] $[\alpha]_D^{20}$ = + 29.6° (c = 0.6, CH_3OH)}. The spectral data matched those described in the literature.[7]

We are grateful for generous financial support by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm "Peroxidchemie: mechanistische und präparative Aspekte des Sauerstofftransfers") and the Fonds der Chemischen Industrie for a doctoral fellowship (1993–1995) for H.-G. B.

(1) Collins, P.M. *Carbohydrates*; Chapman and Hall: London, 1987.
(2) Barrett, G.C. *Amino Acids*; Chapman and Hall: London, 1985.
(3) Nuhn, P. *Naturstoffchemie*, 2nd ed.; Hirzel: Stuttgart, 1990.
(4) Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1992**, *33*, 1051.
(5) Tucker, H. *J. Org. Chem.* **1979**, *44*, 2943.
Overman, L.E.; Flippin, L.A. *Tetrahedron Lett.* **1981**, *22*, 195.
Tramontini, M. *Synthesis* **1982**, 605.
Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.
Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
Atsuumi, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Chem. Pharm. Bull.* **1990**, *38*, 3460.
Evans, P.A.; Holmes, A.B.; Russel, K. *Tetrahedron: Asymmetry* **1990**, *1*, 593–596.
Reetz, M.T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967.
van Benthem, R.A.T.M.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1992**, *57*, 6083.
(6) Brenneisen, R.; Geisshüsler, S.; Schorno, X. *Planta Med.* **1984**, *50*, 531.
(7) Wolf, J.-P.; Pfander, H. *Helv. Chim. Acta.* **1986**, *69*, 918.
(8) Vogt, H.-H. *Deutsche Lebensmittel-Rundschau* **1989**, *85*, 290.
Schorno, X.; Brenneisen, R.; Steinegger, E. *Pharm. Acta Helv.* **1982**, *57*, 168.
(9) Schenck, G.O.; Eggert, H.; Denk, W. *Liebigs Ann. Chem.* **1953**, *584*, 177.
(10) Adam, W.; Brünker, H.-G. *J. Am. Chem. Soc.* **1993**, *115*, 3008.
(11) Brünker, H.-G.; Adam, W. *J. Am. Chem. Soc.* **1995**, *117*, 3976.
(12) Schulte-Elte, K.H.; Müller, B.L.; Rautenstrauch, V. *Helv. Chim. Acta* **1978**, *61*, 2777.
Schulte-Elte, K.H.; Rautenstrauch, V. *J. Am. Chem. Soc.* **1980**, *102*, 1738.
Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* **1986**, *69*, 1638.
(13) Orfanopoulos, M.; Grdina, M.B.; Stephenson, L.M. *J. Am. Chem. Soc.* **1979**, *101*, 275.
Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.
(14) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549.
Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 5041.
Adam, W.; Gevert, O.; Klug, P. *Tetrahedron Lett.* **1994**, *35*, 1681.
(15) Fujii, T.; Itaya, T.; Matsubara, S. *Chem. Pharm. Bull.* **1989**, *37*, 1758.
(16) Miles, N.J.; Sammes, P.G.; Kennewell, P.D.; Westwood, R. *J. Chem. Soc., Perkin, Trans. 1* **1985**, 2299.
(17) Orfanopoulos, M.; Stephenson, L.M. *J. Am. Chem. Soc.* **1980**, *102*, 1417.
(18) Deutsche Gold- und Silber-Scheideanstalt, vorm. Roessler. Brit. Patent 888958, 1962; *Chem. Abstr.* **1962**, *57*, P13988d.