Asymmetric Synthesis of Antimalarial Alkaloids (+)-Febrifugine and (+)-Isofebrifugine

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Received 13 June 2003

Abstract: Diastereoselective α-amidoalkylation of *N*,*O*-acetal, derivated from controlled regio and diastereoselective reduction of (*S*)-*N*-(4-methoxybenzyl)-3-silyloxyglutarimide provided two diastereomeric 6-allyl-5-silyloxy-2-piperidinones in 76:24 selectivity. The transformation of the major diastereomer into a known advanced intermediate allowed the synthesis of (+)-febrifugine and (+)-isofebrifugine.

Key words: piperidines, alkaloids, allylations, *N*,*O*-acetal, asymmetric synthesis

(+)-Febrifugine (**1**) and (+)-isofebrifugine (**2**)[1] are two alkaloids isolated from Chinese medicinal plants *Dichroa febrifuga* Lour. (Chang Shan)[2,3] and related *hydrangea* arten.[4] The structures of febrifugine and isofebrifugine have puzzled chemists for decades,[4,5] and were unambiguously determined in 1999 by Kobayashi et al via asymmetric total synthesis.[6] The antimalarial activity[2,3,7] exhibits by these two compounds have stimulated intensive chemical and biological studies, which has led to the development of halofuginone (**3**) as an antiparasitic feed additive,[8a] which has recently been shown to inhibit collagen production and is currently under clinical trials for treatment of scleroderma in human.[8b] Recent studies also led to the isolation of hydrachine A (**4**) as a novel alkaloid,[9] and led to the discovery of several febrifugine analogues,[10] which show potent antimalarial activity (Figure 1). In addition, crude drug *Dichroa febrifuga* Lour. also exhibits bioactivity of enhancement of NO production in activated macrophages in vivo.[2c] Although the synthetic activities directed towards febrifugine and isofebrifugine have lasted for decades,[11] not until very recently have their total asymmetric synthesis been achieved.[6,12] In continuation of our ongoing program aimed at the development of a general approach to bioactive 2-substituted 3-piperidinols and 2-substituted 3-aminopiperidines,[13] we now report a new asymmetric synthesis of febrifugine and isofebrifugine.

In previous studies,[13] we showed that *N*-protected 3-hydroxyglutarimide could be served as a valuable chiral building block for the asymmetric synthesis of 3-piperidinols via an intramolecular phenyl migration. In view of the success use of both *cis* and *trans* *N*-carbamoyl 2-allyl-3-piperidinol **5**[12a,d] and **6**[12c] (the later in *O*-benzyl protected form) as the key advanced intermediates in the asymmetric synthesis of febrifugine and isofebrifugine, these diastereomers were chosen as the key intermediates in our approach to febrifugine and isofebrifugine (Scheme 1). Piperidine derivatives **5** and **6** could be accessible from appropriately protected 6-allyl-5-hydroxy-2-piperidinones such as **7** or **8**, which in turn was considered to be prepared from **9** or **10**.

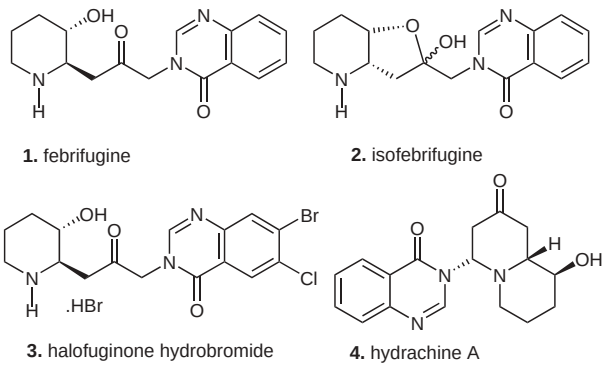
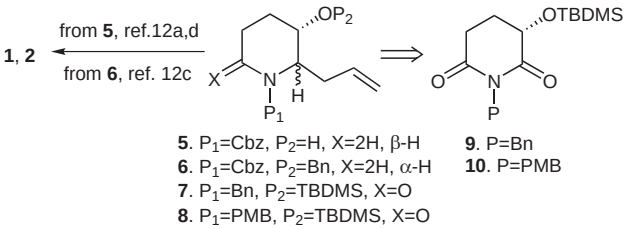


Figure 1

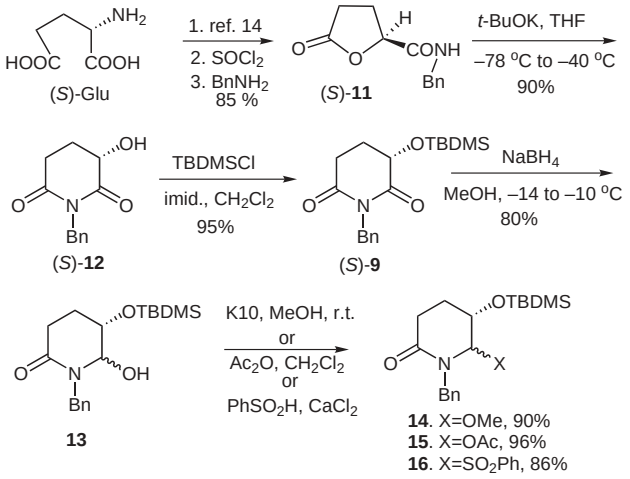


Scheme 1

As a first attempt, we chosen to explore *N*-benzyl protected 2-piperidinone **7** as a ready precursor to **5**/**6**. Thus, lactone-amide **11** was prepared from (*S*)-glutamic acid[13] via the one-pot diazodation – acid chloride formation[14] and amidation in an overall yield of 85% (Scheme 2). Treatment of lactone-amide **11** with *t*-BuOK in THF at –78 °C resulted in the expected ring expansion[13] product (–)-**12** in 90% yield. Protection of the hydroxy group provided the desired *N*-benzyl-3-silyoxyglutarimide **9**. Controlled regioselective C-2 carbonyl reduction of **9** to hydroxy lactam **13** was achieved using sodium borohydride in methanol at low temperature as described previously[13] and as documented for malimides.[15] It is to note that when

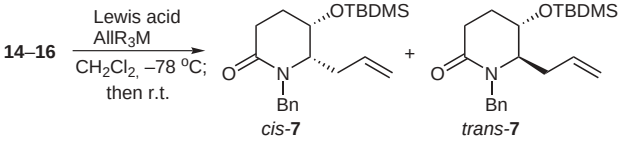
Synlett 2003, No. 11, Print: 02 09 2003. Web: 05 08 2003.
Art Id.1437-2096,E;2003,0,11,1663,1667,ftx,en;U11503ST.pdf.
DOI: 10.1055/s-2003-40988

the reduction was performed at temperature between –14 to –10 °C, a good balance of C-2 regioselectivity (11:1) and chemical yield (80%) was obtained. In all cases, a mixture of two diastereomers was obtained, which without further separation was treated with methanol in the presence of montmorillonite clay (K-10)[16] to give *N*,*O*-acetal **14** as the sole diastereomer (yield, 90%). The stereochemistry of **14** was not determined.[17] Standard acetylation of **13** resulted in an inseparable diastereomeric mixture of **15**. On the other hand, treatment of **13** using Ley's conditions[18] ($CaCl_2$, $PhSO_2H$, CH_2Cl_2, r.t.) yielded sulfone **16** as a separable diastereomeric mixture in 91:9 ratio (combined yield, 86%).



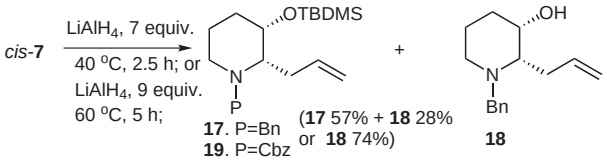
Scheme 2

With synthetic equivalents (**14**–**16**) of *N*-acyliminium[19] in hands, we investigated Lewis acid induced allylation of **14**–**16**. Thus, treatment of *N*,*O*-acetal **14** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ yielded a disappointing 50:50 mixture of *cis*-**7** and *trans*-**7** (combined yield, 96%), which were separable by flash chromatography (Scheme 3). When starting from acetate **15** and using $TiCl_4$ as a Lewis acid the *trans*–*cis* ratio was 34:66. Reaction of sulfone **16** with allyltrimethylsilane or allyltributyl stannane in the presence of anhydrous $ZnCl_2$ gave similar low ratio's of 51:49 and 57:43, respectively, the major isomer was tentatively assigned as *cis* based on the mechanistic considerations.[15c] This was partially confirmed by comparing the silica gel chromatographic behavior of the two diastereomers *cis*-**7** and *trans*-**7** with that of **8** and **23**, *trans*-diastereomers being faster eluting diastereomers.



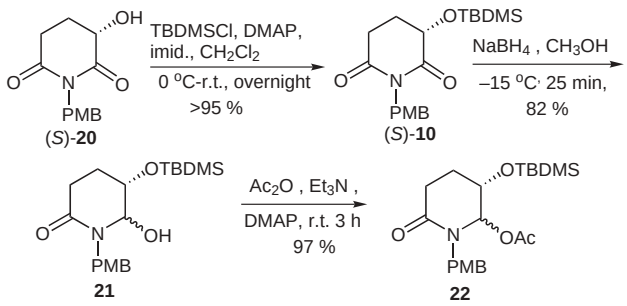
Scheme 3

Attempt reduction of the amide carbonyl of *cis*-**7** with lithium aluminum hydride ($LiAlH_4$, 7 molar equiv., 40 °C, 2.5 h) resulted in the desired piperidine derivative **17** in 57% yield and the concomitant formation of desilylated product **18** in 28% yield (Scheme 4). This observation led us to consider an one-pot carbonyl reduction–desilylation protocol. Indeed, when heating a suspension of *cis*-**7** and 9 molar equivalents of LAH in THF at 60 °C for 5 hours, 3-piperidinol **18** was formed in 74% yield. Unfortunately, after several attempts, we were unable to realize the key one-pot debenzylative–carbamoylation[20] (CbzCl, THF, reflux)[11g] for the conversion of **17** to **19**. At this stage, the change of *N*-protective group from benzyl (in **7** and **9**) to 4-methoxybenzyl (in **8** and **10**) appeared to be an attractive solution to our approach, because PMB is a well-known complementary protective group to benzyl[21] in the sense that the former is removable under mild oxidative conditions.[22]



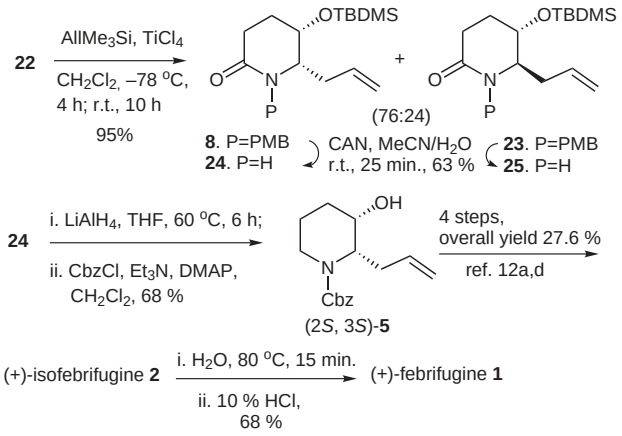
Scheme 4

For this purpose, known *N*-(*p*-methoxybenzyl)-3-hydroxyglutarimide (*S*)-**20**,[13] easily prepared from (*S*)-glutamic acid (Scheme 1) as described previously,[13] was silylated (TBDMSCl, DMAP, imidazole, r.t., overnight) to give *O*-silylated product (*S*)-**10** {colorless solid. Mp 63–64 °C. $[\alpha]_D^{20}$ –19.2 (*c* 1.1, $CHCl_3$)} in 95% yield (Scheme 5). Regio and stereoselective reduction of imide (*S*)-**10** C-2 carbonyl furnished predominantly hydroxy amide **21** in 88:12 regioselectivity and as a diastereomeric mixture (combined yield, 82%). In the light of the above-mentioned studies on *N*-benzyl series, acetate **22** was selected as the substrate for the stereoselective allylation. Thus, acetylation of the diastereomeric mixture of **21** gave acetate **22** as a partially separable diastereomeric mixture. Repeated flash chromatography allowed to obtain a sample of pure major diastereomer, which showed a $J_{5,6}$ = 3.5 Hz.



Scheme 5

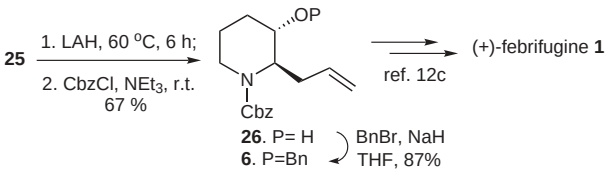
For the allylation of **22**, after several trials, it was found that when the reaction was conducted by very slow addition of a CH_2Cl_2 solution of freshly distillated $TiCl_4$ to a cooled (–78 °C) CH_2Cl_2 solution of **22** and allyltrimethylsilane, and keeping the reaction at –78 °C for 4 hours before warming up, a 76:24 stereoselectivity, in favor of *cis*-isomer **8** was achieved[23] (both the stereoselectivity and the *cis* versus *trans* diastereoisomer attribution were deduced from the followed step, Scheme 6). Although the allylation products **8** and its isomer **23** are only partially separable, we were delight to find that the two diastereomers were easily separable after removal of *N*-protective group (PMB) under oxidative conditions (CAN, MeCN/H_2O, r.t., 25 min., 63%).[22] Moreover, well resolute ^1H NMR spectra of both **24**[24] and its stereoisomer **25**[24] allowed an easy assignment of stereochemistry.[17] Thus, the major isomer (**24**) showing a vicinal coupling constants: $J_{5,6}$ = 2.8 Hz, was assigned as *cis*-isomer (**24**), and the minor isomer with a vicinal coupling constants $J_{5,6}$ = 6.5 Hz, was assigned to *trans*-isomer (**25**).



Scheme 6

The *cis* stereochemistry of **24** was later and unambiguously confirmed by its conversion to known compounds (2*S*,3*S*)-**5**, isofebrifugine (**2**) and febrifugine (**1**) (Scheme 6). The transformation of **24** to (2*S*,3*S*)-**5** was achieved via an one-pot amide reduction-desilylation (*vide infra*) by an excess of lithium aluminum hydride in refluxing tetrahydrofuran for 6 hours, followed by reaction with Cbz-Cl. The overall yield from **24** to **5** was 68%. Compound (2*S*,3*S*)-**5** {colorless oil. $[\alpha]_D^{20}$ +77.1 (*c* 1.0, EtOH); lit.[12a] $[\alpha]_D^{24}$ +76.2 (*c* 1.0, EtOH); lit.[12d] $[\alpha]_D^{20}$ +78.5 (*c* 1.00, EtOH), 97% ee} showed the same spectral data as reported. Chiral HPLC analysis on a chiral column showed that the ee of thus synthesized (2*S*,3*S*)-**5** was 97.18%.[25] Following Takeuchi's four-step procedure,[12a,d] (2*S*,3*S*)-**5** was converted, in an overall yield of 27.6%, into isofebrifugine (+)-**2** {white solid, mp 126–128 °C; lit.[2b,12d] mp 129–130 °C. $[\alpha]_D^{20}$ +123 (*c* 0.30, $CHCl_3$); lit.[12d] $[\alpha]_D^{27}$ +124.3 (*c* 0.5, $CHCl_3$); lit.[12i] $[\alpha]_D^{20}$ +128.9 (*c* 0.319, $CHCl_3$); lit.[2b] $[\alpha]_D^{23}$ +131 (*c* 0.35, $CHCl_3$)}. Finally, heating an aqueous solution of isofebrifugine (+)-**2** at 80 °C for 15 minutes afforded the desired epimerized product febrifugine (+)-**1**, which was characterized as its dihydrochloride {colorless solid, mp 217–219 °C (dec.); lit.[12d] 218–219 °C; lit.[4a] 223–225 °C. $[\alpha]_D^{20}$ +12.5 (*c* 0.2, H_2O); lit.[12d] $[\alpha]_D^{29}$ +13.3 (*c* 1.01, H_2O); lit.[4a] $[\alpha]_D^{31}$ +12.8 (*c* 0.85, H_2O)}.

Next, the possibility for the conversion of the minor diastereomer (**23**) resulted from the allylation of **22** to another key intermediate for (+)-febrifugine (**1**) was examined. Thus as outlined in Scheme 7, treatment of **25** with an excess of lithium aluminum hydride followed by reaction of the resultant *trans*-2-allyl-3-piperidinol with Cbz-Cl furnished **26** in an overall yield of 67%. *O*-Benzylation of **26** under standard conditions afforded known **6** {$[\alpha]_D^{28}$ –47.8 (*c* 1.0, $CHCl_3$); lit.[12c] $[\alpha]_D^{20}$ –45.1 (*c* 1.0, $CHCl_3$)} in a yield of 87%. Since **6** has previously been converted to (+)-febrifugine (**1**),[12c] the simple transformations showed in Scheme 7 not only allowed to confirm the stereochemistry of **25**, but also constituted a formal synthesis of (+)-febrifugine (**1**), and thus justified the utility of the minor diastereomer **23**.



Scheme 7

In conclusion, we have demonstrated that (*S*)-1-(*p*-methoxybenzyl)-3-silyloxyglutarimide is a valuable chiral building block, which could be used in the asymmetric synthesis of natural enantiomers of (+)-febrifugine and (+)-isofebrifugine. Investigation is in progress for the application of this new chiral 3-piperidinol synthon in the asymmetric synthesis of other 3-piperidinol-based alkaloids.

Acknowledgement

The authors are grateful to the National Science Fund for Distinguished Young Investigators, the NNSF of China, (29832020; 20072031; 20272048; 203900505) and the Fund for doctoral sites of the Ministry of Education for financial support.

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(23) To a cooled (–78 °C) solution of **22** (348 mg, 0.85 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise allyltrimethylsilane (0.270 mL, 1.71 mmol). After being stirred for 5 min, a solution of $TiCl_4$ (0.14 mL, 1.283 mmol) in anhyd CH_2Cl_2 (2 mL) was added over a period of 40 min. The mixture was stirred for 4 h at the same temperature and then allowed to warm to r.t. and stirred for 10 h. After which, a sat. aq $NaHCO_3$ (1 mL) and brine (2 mL) were slowly added. The organic layer was separated and the aq phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated. The crude was purified by chromatography on silica gel (EtOAc/PE) to give pure (5*S*,6*S*)-**8** (86 mg), pure (5*S*, 6*R*)-**23** (38 mg), and a mixture of un-separated (5*S*,6*S*)-**8** and (5*S*,6*R*)-**23** (191 mg) in a combined yield of 95%. Major diastereomer (5*S*,6*S*)-**8**: colorless oil. $[\alpha]_D^{20}$ +56.5 (*c* 1.0, $CHCl_3$). IR(neat): ν_{max} = 3075, 2952, 2929, 1642,1513, 1463, 1248, 1175 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (m, 2 H, Ar-H), 6.83 (m, 2 H, Ar-H), 5.87 (m, 1 H, CH=), 5.40 (d, *J* = 14.6 Hz, 1 H, NCH_2), 5.13 (m, 1 H, =CH_2), 5.09 (m, 1 H, =CH_2), 3.94–3.88 (m, 1 H, H-5), 3.91 (s, 3 H, OCH_3), 3.88 (d, *J* = 14.6 Hz, 1 H, NCH_2), 3.23 (vrt. dt, *J* = 6.6, 4.7 Hz, 1 H, H-6), 2.63 (m, 2 H, =CCH_2) 2.50 (ddd, *J* = 8.0, 8.8, 17.0 Hz, 1 H, H-3), 2.27 (ddd, *J* = 7.4, 8.2, 17.0 Hz, 1 H, H-3), 1.94 (m, 1 H, H-4), 1.81 (m, 1 H, H-4), 0.9 (s, 9 H, *t*-Bu), 0.18 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, Si-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.39 (C=O), 158.99 (Ar), 136.11 (CH=), 129.44 (Ar), 129.37 (2 C, Ar), 117.44 (=CH_2), 114.01 (2 C, Ar), 68.38 (C-6), 59.39 (C-5), 55.32 (OCH_3), 48.23 (N-CH_2), 33.62 (=CH-CH_2), 28.96 (C-3), 25.77 (C-4), 25.68 (3C, *t*-Bu), 17.97 ($SiCMe_3$), –4.90 (Si-CH_3), –5.13 ($SiCH_3$) ppm. MS (ESI): *m/z* (%) = 390(100) [M + H$^+$], 412 (11) [M + Na$^+$]. HRMS calcd for [$C_{22}H_{35}NO_3Si$ + H]$^+$: 390.2464. Found: 390.2463. (5*S*,6*R*)-Minor diastereomer **23**: colorless oil. $[\alpha]_D^{20}$ –51.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (m, 2 H,

Ar-H), 6.80 (m, 2 H, Ar-H), 5.67 (m, 1 H, CH=), 5.44 (d, J = 14.9 Hz, 1 H, NCH_2), 5.12 (m, 1 H, $=CH_2$), 5.09 (m, 1 H, $=CH_2$), 3.95 (m, 1 H, H-5), 3.78 (s, 3 H, OCH_3), 3.77 (d, J = 14.9 Hz, 1 H, NCH_2), 3.21 (vrt. ddt, J = 9.8, 3.4, 2.0 Hz, 1 H, H-6), 2.70 (ddd, J = 7.2, 12.3, 18.5 Hz, 1 H, H-3), 2.52 (m, 1 H, $=CCH_2$), 2.37 (ddd. J = 1.4, 6.5, 18.5 Hz, 1 H, H-3), 2.09 (m, 1 H, $=CCH_2$), 2.01 (m, 1 H, H-4), 1.74 (m, 1 H, H-4), 0.8 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.68 (C=O), 158.79 (Ar), 133.85 (CH=), 129.24 (Ar), 129.20 (2 C, Ar), 118.32 ($=CH_2$), 113.94 (2 C, Ar), 65.78 (C-6), 61.86 (C-5), 55.30 (OCH_3), 46.60 (NCH_2), 36.65 ($=CHCH_2$), 26.89 (C-3), 25.68 (3 C, *t*-BuC), 24.17 (C-4), 17.92 ($SiCMe_3$), –4.94 (2 C, $SiCH_3$) ppm. MS (ESI): *m/z* (%) = 390.1 (100) $[M + H^+]$, 412.2 (19) $[M + Na^+]$. HRMS calcd for $[C_{22}H_{35}NO_3Si + H]^+$: 390.2464. Found: 390.2463.

(24) Major diastereomer (5*S*, 6*S*)-**24**: white solid. Mp 67–68 °C. $[\alpha]_D^{20}$ –4.5 (*c* 1.05, $CHCl_3$). IR(film): ν_{max} = 3222, 1669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.73 (m, 1 H, =CH), 5.61 (brs, 1 H, NH), 5.22 (m, 1 H, $=CH_2$), 5.19 (m, 1 H, $=CH_2$), 4.0 (m, 1 H, H-5), 3.36 (ddd, J = 2.8, 3.6, 9.7 Hz, 1 H, H-6, decoupling H-5, J = 3.6, 9.7 Hz), 2.57 (ddd, 6.4, 12.1, 18.6 Hz, 1 H, H-3), 2.32 (m, 2 H, $=CH-CH_2$), 2.20 (ddd, J = 9.0, 9.8, 18.6 Hz, 1 H, H-3), 1.97 (m, 1 H, H-4), 1.84 (m, 1 H, H-4), 0.90 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.54 (C=O), 133.63 (CH=), 119.54 (CH_2=), 65.96 (C-5), 56.43 (C-6), 36.96 (C-4), 28.15 (CH_2-CH=), 26.37 (C-3), 25.76 (3 C, *t*-Bu), 18.11 ($SiCMe_3$), –4.39 ($SiCH_3$), –4.94 ($SiCH_3$) ppm. MS (ESI): *m/z* (%) = 270, (100) $[M + H^+]$, 292 (20) $[M + Na^+]$. HR-ESI-MS calcd for $[C_{14}H_{27}NO_2Si + H]^+$: 270.1889. Found: 270.1907. Minor diastereomer (5*S*, 6*R*)-**25**: white solid. Mp 67–68 °C. $[\alpha]_D^{20}$ +15.3 (*c* 0.98, $CHCl_3$). IR(film): ν_{max} = 3190, 1682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.74 (m, 1 H, CH=), 5.70 (m, 1 H, NH), 5.21 (dd, J = 0.8, 14.7 Hz, 1 H, $=CH_2$), 5.18 (dd, J = 0.8, 14.7 Hz, 1 H, $=CH_2$), 3.66 (ddd, J = 3.3, 6.5, 9.3 Hz, 1 H, H-5, irradiation at H-6 gave dd, J = 3.3, 9.3 Hz), 3.23 (ddd, J = 9.5, 6.5, 4.5 Hz, 1 H, H-6), 2.53 (ddd, J = 5.8, 6.2, 17.8 Hz, 1 H, H-3), 2.34 (ddd, J = 6.5, 9.4, 17.8 Hz, 1 H, H-3), 2.12–1.92 (m, 1 H, CH_2CH=), 1.84–1.78 (m, 2 H, H-4), 0.9 (s, 9 H, *t*-Bu), 0.56 (s, 3 H, $SiCH_3$), 0.50 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.28 (C=O), 133.41 (CH=), 119.67 (CH_2=), 69.11 (C-5), 58.11 (C-6), 38.55 (C-4), 28.46 (C-3), 28.30 (CH_2-CH=), 25.71 (3 C, *t*-Bu), 17.95 ($SiCMe_3$), –4.27 ($SiCH_3$), –4.75 ($SiCH_3$) ppm. MS (ESI): *m/z* (%) = 270 (100) $[M + H^+]$, 292 (3) $[M + Na^+]$. HR-ESI-MS calcd for $[C_{14}H_{27}NO_2Si + H]^+$: 270.1889. Found: 270.1890.

(25) The ee was determined by HPLC analysis using a Chiracel® OJ-H column (0.46 cm × 25 cm; column temperature: r.t.; eluent: hexane/isopropyl alcohol = 37:3; flow rate = 1.0 mL/min; wavelength: 240 and 260 nm, t_R = 11.50 and 16.39 min).