Synthesis of New Enantiopure Bicyclic 1,2-Oxazines by Addition of Lithiated Methoxyallene to Chiral Cyclic Nitrones

Robert Pulz,[a] Stefano Cicchi,[b] Alberto Brandi,[b] and Hans-Ulrich Reißig*[a]

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A highly diastereoselective addition of lithiated methoxyallene **3** to chiral cyclic nitrones **1** and **2** provided *N*-hydroxy pyrrolidines **4** and **5**, respectively, which cyclized to bicyclic 1,2-oxazines **6** and **7** by simple stirring in dilute CH_2Cl_2 solution. Storage of **4** in a more concentrated solution led to formation of a 60:40 mixture of 1,2-oxazine **6** and amine oxide **8**. Hydroboration of **7** furnished the hydroxy-substituted bicyclic 1,2-oxazine **9** with excellent diastereoselectivity. Hydrogenolysis of **6** provided the substituted pyrrolidine derivative **10**.

Introduction

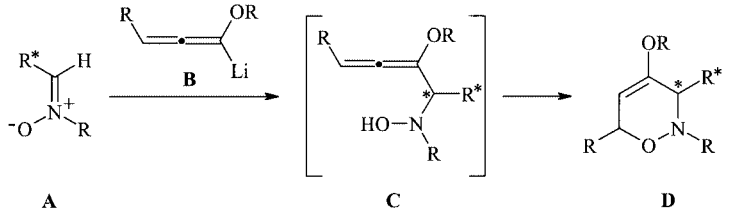
In earlier publications the Berlin group has reported a new route to enantiopure 3,6-dihydro-2*H*-1,2-oxazines **D** by addition of lithiated alkoxyallenes **B** to chiral nitrones **A** and subsequent cyclization of the intermediate allenyl hydroxylamines **C** (Scheme 1).[1−3] The primary adducts **C** could usually not be isolated because they undergo very fast cyclization to 1,2-oxazines **D**. The 1,2-oxazines **D** were obtained in good yields and moderate to excellent diastereoselectivities. The authors also demonstrated that these 1,2-oxazines are valuable intermediates for the synthesis of enantiopure furan and pyran derivatives,[2] amino alcohols[3,4] and pyrrolidines.[3,4]

Results and Discussion

So far the reported syntheses of 1,2-oxazines from alkoxyallenes are based on acyclic chiral nitrones derived from carbohydrates and amino acids.[1−3] Herein we present our first results with enantiopure bicyclic 1,2-oxazines starting from cyclic chiral nitrones **1**[5] and **2**,[6] which are easily accessible from malic acid and tartaric acid, respectively, in a few steps. Compounds **1** and **2** were very successfully employed for diastereoselective 1,3-dipolar cycloadditions, leading to bicyclic isoxazolidines that allow a variety of synthetically important transformations.[7]

In contrast to the acyclic nitrones, where 1,2-oxazines were isolated directly after reaction with alkoxyallenes, the addition of lithiated methoxyallene **3** to nitrone **1** allowed isolation of the allenyl hydroxylamine **4** in high yield (Scheme 2). The second possible diastereomer was not observed. Similar results were obtained by reaction of nitrone **2** with **3**. After workup the diastereomerically pure *N*-hydroxy pyrrolidine **5** was also isolated in very good yield and purity. The diastereoselectivity of these reactions is governed by the steric bulkiness of the *tert*-butoxy group at C-3. Thus, the nucleophile attacks at C-2 on the sterically less-hindered face of the electrophiles **1** and **2**.

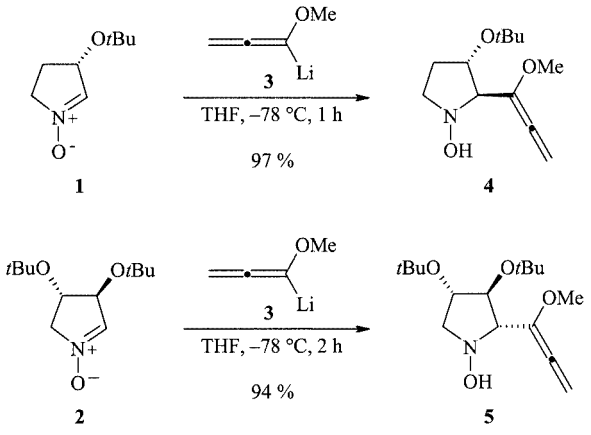
Cyclization of the allenyl hydroxylamines **4** and **5** was easily accomplished by stirring the primary products in dichloromethane at high dilution (approx. 0.05 M). Similar



Scheme 1

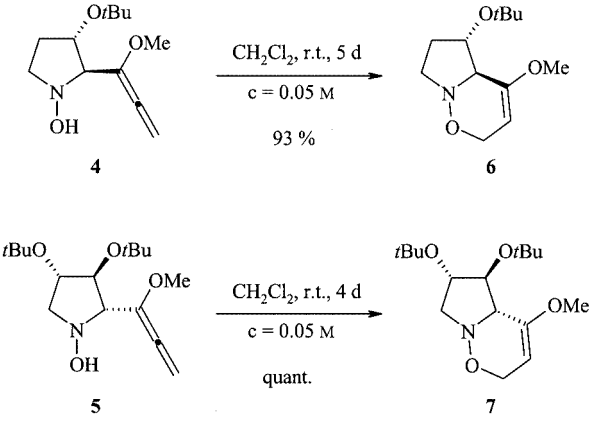
results were obtained by Dulcere et al., who observed cyclization of other allenyl hydroxylamines in chloroform.[8] Thus, the reaction of **4** provided the corresponding bicyclic 1,2-oxazine **6** in high yield and cyclization of **5** led quantitatively to the bicyclic derivative **7** (Scheme 3). Both products were obtained spectroscopically pure and no chromatography was required. Starting from **1** and **2** we obtained

[a] Institut für Chemie − Organische Chemie, Freie Universität Berlin,
Takustrasse 3, 14195 Berlin, Germany
Fax: (internat.) +49-30/8385-5367
E-mail: hans.reissig@chemie.fu-berlin.de
[b] Dipartimento di Chimica Organica "U. Schiff", Università degli Studi di Firenze − Polo Scientifico,
Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy



Scheme 2

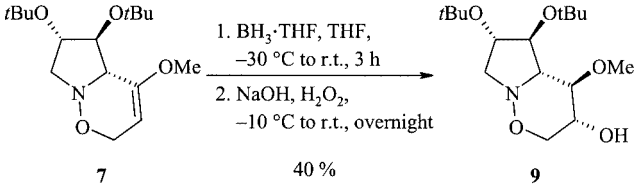
1,2-oxazines **6** and **7** without any purification in 90% and 94% overall yield, respectively. The relative configuration of the stereogenic centers of **6** and **7**, and therefore that of **4** and **5**, was proved by 2D-NOESY experiments.



Scheme 3

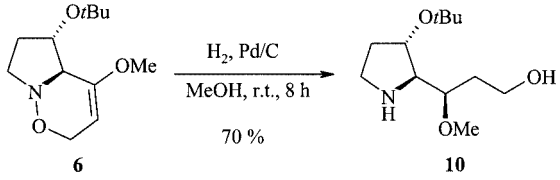
Interestingly, cyclization of **4** in a solution of higher concentration (NMR tube, 0.8 M in $CDCl_3$) led to 1,2-oxazine **6** and the amine oxide **8** in a 60:40 ratio (Scheme 4). It was possible to separate **8** by chromatography in 26% yield. A comparison of the ^{13}C NMR spectroscopic data of 1,2-oxazine **6** and amine oxide **8** indicated a remarkable downfield shift of C-2, C-4a and C-7. Furthermore, the mass spectrum of **8** displays a strong signal for $[M - O]^+$ which is missing in the mass spectrum of compound **6**. The competition between cyclizations involving the nitrogen (leading to amine oxide **8**) and the oxygen (furnishing **6**) apparently depends on the concentration of the solution. Although a full mechanistic discussion of this and other aspects of the allenyl hydroxylamine cyclizations[8] cannot be provided here, we interpret this observation as a result of the considerably higher polarity of the more concentrated solution, which favours the more polar product **8**.

As described in the literature, enantiopure 1,2-oxazines are useful building blocks for the synthesis of a variety of interesting compounds with potential biological activity.[2–4,9] Thus, the functionalization of the enol ether double bond and the cleavage of the N–O bond are versatile tools for subsequent synthetic transformations. In previous experiments with 1,2-oxazines, stereoselective hydroboration has proved to be a very useful method to functionalize the enol ether double bond.[3] Application of this procedure to bicyclic 1,2-oxazine **7** furnished the expected hydroxy-substituted compound **9** in excellent diastereoselectivity ($dr > 95:5$) and good yield for the crude product (Scheme 5). However, after chromatography pure **9** was isolated in only 40% yield.



Scheme 5

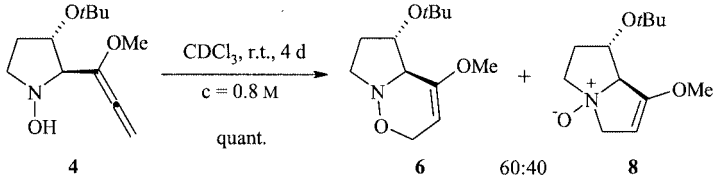
1,2-Oxazines are prone to hydrogenolysis[10] since the relatively weak N–O bond is easily cleaved. Reaction of **6** with hydrogen and palladium on charcoal as catalyst furnished the expected pyrrolidine **10** in moderate yield (Scheme 6).[11] The assignment of the new stereogenic center was determined in analogy to previous results obtained with other 1,2-oxazines.[4] Conversion of **10** into pyrrolizidines has so far not been successful.



Scheme 6

Conclusion

We have demonstrated that the addition of lithiated methoxyallene to chiral cyclic nitrones furnishes *N*-hydroxy pyrrolidines in excellent diastereoselectivity.[12] They can be



Scheme 4

easily transformed into the corresponding bicyclic 1,2-oxazines by simply stirring under high dilution. Starting from the chiral nitrone and methoxyallene, the 1,2-oxazines are available in high yields and purity without any purification. The 1,2-oxazines prepared can be regarded as oxygen-incorporating novel analogs of polyhydroxylated indolizidines, but they may also be transformed into enantiopure pyrrolidines and pyrrolizidines. All these compounds are of high interest because of their potential biological activity (e.g. as glycosidase inhibitors).

Experimental Section

For general information see ref.[10a]

(2*S*,3*S*)-3-*tert*-Butoxy-2-(1-methoxypropa-1,2-dienyl)pyrrolidin-1-ol (4): A solution of methoxyallene (0.223 g, 3.18 mmol) in dry THF (6 mL) was treated with *n*-butyllithium (2.5 M in *n*-hexane; 1.2 mL, 2.8 mmol) at −40 °C. After 5 min, the resulting mixture was cooled to −78 °C, and a solution of nitrone **1** (0.250 g, 1.59 mmol) in dry THF (2 mL) was added. The mixture was stirred for 1 h at −78 °C and then quenched with water. Warming up to room temperature was followed by extraction with diethyl ether. The combined extracts were dried with $MgSO_4$ and the solvents were removed in vacuo. Spectroscopically pure *N*-hydroxy pyrrolidine **4** (0.350 g, 97%) was isolated as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.48 (s, 2 H, 3′-H), 4.10 (m_c, 1 H, 2-H), 3.45 (s, 3 H, OMe), 3.35−3.24 (m, 2 H, 3-H, 5-H_A), 3.03 (td, *J* = 9.0, 9.9 Hz, 1 H, 5-H_B), 2.05, 1.73 (2 m_c, 1 H each, 4-H), 1.63 (br. s, 1 H, OH), 1.13 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 199.9 (s, C-2′), 131.2 (s, C-1′), 90.1 (t, C-3′), 76.6 (d, C-3), 73.6, 28.1 (s, q, *t*Bu), 71.0 (d, C-2), 56.2 (t, C-5), 56.0 (q, OMe), 31.2 (t, C-4) ppm.

(2*R*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-2-(1-methoxypropa-1,2-dienyl)-pyrrolidin-1-ol (5): According to the procedure leading to **4**, a solution of nitrone **2** (0.485 g, 2.11 mmol) in dry THF (6 mL) was added to a solution of methoxyallene (0.296 g, 4.23 mmol) and *n*-butyllithium (2.5 M in *n*-hexane; 1.5 mL, 3.8 mmol). After 2 h product **5** (0.592 g, 94%) was isolated as a spectroscopically pure yellow oil. ^{1}H NMR ($CDCl_3$, 270 MHz): δ = AB system (δ_A = 5.50, δ_B = 5.47, J_{AB} = 8.0 Hz, 2 H, 3′-H), 5.35 (br. s, 1 H, OH), 4.02 (dd, *J* = 3.6, 7.2 Hz, 1 H, 3-H), 3.93 (ddd, *J* = 3.2, 3.6, 7.0 Hz, 1 H, 4-H), 3.45 (s, 3 H, OMe), 3.26 (dd, *J* = 3.2, 10.4 Hz, 1 H, 5-H_A), 3.25 (d, *J* = 7.1 Hz, 1 H, 2-H), 3.12 (dd, *J* = 7.0, 10.4 Hz, 1 H, 5-H_B), 1.173, 1.166 (2 s, 9 H each, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 200.3 (s, C-2′), 130.6 (s, C-1′), 89.9 (t, C-3′), 77.9, 75.2, 75.2 (3 d, C-2, C-3, C-4), 74.0, 73.5, 28.8, 28.4 (2 s, 2 q, *t*Bu), 63.6 (t, C-5), 55.9 (q, OMe) ppm.

(4a*S*,5*S*)-5-*tert*-Butoxy-4-methoxy-4a,5,6,7-tetrahydro-2*H*-pyrrolo-[1,2-*b*][1,2]oxazine (6): A solution of **4** (0.730 g, 3.21 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 5 days. After removal of the solvent 1,2-oxazine **6** (0.678 g, 93%) was obtained as a spectroscopically pure (>95%) pale brown oil. $[\alpha]_D^{20}$ = +92.9 (*c* = 0.72, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.64 (d, *J* = 4.0 Hz, 1 H, 3-H), 4.44 (td, *J* = 1.5, 14.3 Hz, 1 H, 2-H_A), 4.20 (ddd, *J* = 2.2, 6.2, 8.3 Hz, 1 H, 5-H), 4.11 (dd, *J* = 4.0, 14.3 Hz, 1 H, 2-H_B), 3.53 (s, 3 H, OMe), 3.32 (ddd, *J* = 2.2, 8.3, 13.7 Hz, 1 H, 7-H_A), 3.28 (dd, *J* = 1.5, 6.2 Hz, 1 H, 4a-H), 3.21 (ddd, *J* = 8.3, 11.0, 13.7 Hz, 1 H, 7-H_B), 2.43 (tdd, *J* = 8.3, 11.0, 13.0 Hz, 1 H, 6-H_A), 1.65 (tdd, *J* = 2.2, 8.3, 13.0 Hz, 1 H, 6-H_B), 1.29 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.3 (s, C-4), 90.3 (d, C-3), 76.5 (d, C-5), 73.9, 28.3 (s, q, *t*Bu), 71.7 (d, C-4a), 66.0 (t, C-2), 55.6 (t, C-7), 54.2 (q, OMe), 35.0 (t, C-6) ppm. IR (film): $\tilde{\nu}$ = 2970−2850 cm^{-1} (C−H), 1670 (C=C). MS (EI, 80 eV): *m*/*z* (%) = 227 (82) [M^+], 171 (99) [$M^+ - C_4H_8$], 170 (90) [M^+ − *t*Bu], 156 (38) [$M^+ - C_4H_8$ − Me], 154 (65) [M^+ − O*t*Bu], 142 (30) [$M^+ - C_4H_5O_2$], 57 (100) [tBu$^+$]. HRMS (80 eV): calcd. for $C_{12}H_{21}NO_3$ 227.15214, found 227.15586.

(4a*R*,5*S*,6*S*)-5,6-Di-*tert*-butoxy-4-methoxy-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazine (7): A solution of **5** (0.610 g, 2.04 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 4 days. After removal of the solvent 1,2-oxazine **7** (0.610 g, quant.) was obtained as a spectroscopically pure (>95%) pale brown oil. $[\alpha]_D^{20}$ = +17.3 (*c* = 0.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.66 (dd, *J* = 1.8, 3.7 Hz, 1 H, 3-H), 4.44 (td, *J* = 1.8, 14.5 Hz, 1 H, 2-H_A), 4.36 (dd, *J* = 4.4, 8.2 Hz, 1 H, 5-H), 4.32 (dd, *J* = 3.7, 14.5 Hz, 1 H, 2-H_B), 4.04 (td, *J* = 4.4, 7.5 Hz, 1 H, 6-H), 3.53 (s, 3 H, OMe), 3.49 (dd, *J* = 7.5, 14.1 Hz, 1 H, 7-H_A), 3.30 (br. d, *J* = 8.2 Hz, 1 H, 4a-H), 3.17 (dd, *J* = 4.4, 14.1 Hz, 1 H, 7-H_B), 1.20, 1.19 (2 s, 9 H each, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.0 (s, C-4), 90.8 (d, C-3), 82.2 (d, C-5), 79.4 (d, C-6), 74.5, 73.7, 28.7, 28.7 (2 s, 2 q, *t*Bu), 66.7 (d, C-4a), 65.5 (t, C-2), 61.4 (t, C-7), 53.8 (q, OMe) ppm. IR (film): $\tilde{\nu}$ = 2975−2835 cm^{-1} (C−H), 1675 (C=C). MS (EI, 80 eV): *m*/*z* (%) = 299 (15) [M^+], 243 (3) [$M^+ - C_4H_8$], 242 (3) [M^+ − *t*Bu], 187 (13) [$M^+ - 2C_4H_8$], 186 (8) [M^+ − *t*Bu − C_4H_8], 170 (8) [M^+ − 2*t*Bu − Me], 128 (35), 57 (100) [tBu$^+$], 41 (23). $C_{16}H_{29}NO_4$ (299.1): calcd. C 64.19, H 9.76, N 4.68; found C 63.53, H 9.32, N 4.73.

(4a*S*,5*S*)-5-*tert*-Butoxy-4-methoxy-4a,5,6,7-tetrahydro-2*H*-pyrrolizin *N*-oxide (8): Allenyl hydroxylamine **4** (0.135 g, 0.594 mmol) was dissolved in $CDCl_3$ (0.7 mL, NMR tube) and stored for 4 days at room temperature. After removal of the solvent a mixture of **6** and **8** (0.135 g; **6**:**8** = 60:40) was obtained, which was separated by filtration through a short silica-gel column. The 1,2-oxazine **6** was obtained by elution with ethyl acetate, whereas crude **8** was eluted with methanol. *N*-oxide **8** was further purified by HPLC (CH_2Cl_2/methanol 85:15) yielding pure **8** (0.035 g, 26%) as pale brown crystals. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.47 (br. s, 1 H, 3-H), 4.39 (br. d, *J* = 13.9 Hz, 1 H, 2-H_A), 4.35 (br. s, 1 H, 4a-H), 4.25 (br. d, *J* = 13.9 Hz, 1 H, 2-H_B), 4.14. (br. s, 1 H, 5-H), 3.79 (br. q, *J* ≈ 8.6 Hz, 1 H, 7-H_A), 3.66 (s, 3 H, OMe), 3.54 (m_c, 1 H, 7-H_B), 2.32 (m_c, 1 H, 6-H_A), 2.07 (m_c, 1 H, 6-H_B), 1.17 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 152.9 (s, C-4), 92.5 (d, C-3), 88.0 (d, C-4a), 75.6 (t, C-2), 75.0, 28.1 (s, q, *t*Bu), 71.7 (d, C-5), 69.0 (t, C-7), 57.1 (q, OMe), 33.9 (t, C-6) ppm. MS (EI, 80 eV): *m*/*z* (%) = 227 (4) [M^+], 212 (12) [M^+ − Me], 211 (28) [M^+ − O], 210 (23) [M^+ − OH], 209 (16) [$M^+ - H_2O$], 171 (14) [$M^+ - C_4H_8$], 170 (10) [M^+ − *t*Bu], 156 (10) [$M^+ - C_4H_8$ − Me], 154 (100) [M^+ − O*t*Bu], 136 (54) [M^+ − O*t*Bu − H_2O], 57 (49) [tBu$^+$].

(3*R*,4*R*,4a*S*,5*S*,6*S*)-5,6-Di-*tert*-butoxy-4-methoxy-3,4,4a,5,6,7-hexahydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazin-3-ol (9): BH_3·THF (1 M in THF; 2.7 mL, 2.7 mmol) was added at −30 °C to a solution of **7** (0.200 g, 0.668 mmol) in dry THF (13 mL). The solution was warmed to room temperature and stirred for 3 h, then cooled to −10 °C and NaOH solution (2 M; 4 mL) and H_2O_2 (30%; 2 mL) were added. Stirring was continued overnight at room temp. After addition of sat. $Na_2S_2O_3$ solution the layers were separated and the aqueous layer was extracted with Et_2O. The combined extracts were dried with $MgSO_4$ and the solvents were removed in vacuo. The crude product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 1:3) to yield **9** as pale brown oil (0.085 g, 40%). $[\alpha]_D^{20}$ = +51.3 (*c* = 0.39, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 4.20 (dd, *J* = 3.0, 8.0 Hz, 1 H, 5-H), 4.05 (dd, *J* =

2.4, 10.7 Hz, 1 H, 2-H_A), 3.94 (ddd, J = 2.3, 3.0, 6.8 Hz, 1 H, 6-H), 3.79−3.73 (m, 2 H, 2-H_B, 3-H), 3.50 (t, J = 5.6 Hz, 1 H, 4-H), 3.48 (s, 3 H, OMe), 3.29 (dd, J = 2.3, 12.3 Hz, 1 H, 7-H_A), 3.16 (dd, J = 6.8, 12.3 Hz, 1 H, 7-H_B), 2.83 (dd, J = 5.6, 8.0 Hz, 1 H, 4a-H), 2.33 (br. s, 1 H, OH), 1.25, 1.19 (2 s, 9 H each, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 80.1 (d, C-5), 78.8 (d, C-6), 78.3 (d, C-4), 74.5, 74.1, 29.1, 28.7 (2 s, 2 q, *t*Bu), 70.1 (t, C-2), 69.5 (d, C-4a), 67.7 (d, C-3), 61.5 (t, C-7), 57.5 (q, OMe) ppm. IR (film): $\tilde{\nu}$ = 3435 cm^{-1} (OH), 2975−2930 (C−H). MS (EI, 80 eV): *m*/*z* (%) = 317 (33) [M^+], 260 (39) [$M^+ - t$Bu], 214 (19), 132 (17), 102 (23), 87 (23), 57 (100) [tBu$^+$]. $C_{16}H_{31}NO_5$ (317.4): calcd. C 60.54, H 9.84, N 4.41; found C 60.38, H 9.71, N 4.15.

(2′*S*,3′*S*,3*R*)-3-(3-*tert*-Butoxypyrrolidin-2-yl)-3-methoxypropan-1-ol (10): A stirred suspension of palladium on charcoal (10% Pd; 0.400 g, 0.377 mmol) in dry methanol (24 mL) was saturated with hydrogen for 1 h. Then, a solution of **6** (0.227 g, 1.00 mmol) in dry methanol (5 mL) was added and the mixture was stirred under hydrogen atmosphere at normal pressure for 8 h at room temperature. Filtration through a pad of celite and removal of the solvent in vacuo yielded a pale brown oil of **10** and an unknown side product (0.263 g, 70%) in a ratio of 83:17. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.40 (br. s, 2 H, NH, OH), 3.97 (ddd, J = 5.4, 7.5, 8.2 Hz, 1 H, 3′-H), 3.74 (ddd, J = 1.7, 10.1, 11.9 Hz, 1 H, 1-H_A), 3.61 (td, J = 1.9, 5.9 Hz, 1 H, 3-H), 3.52 (ddd, J = 3.0, 5.4, 11.9 Hz, 1 H, 1-H_B), 3.34 (s, 3 H, OMe), 3.07−2.99 (m, 2 H, 5′-H), 2.82 (dd, J = 1.9, 7.5 Hz, 1 H, 2′-H), 2.20−1.97, 1.79−1.60 (2 m, 2 H each, 4′-H, 2-H), 1.19 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 75.1, 72.7 (2 d, C-3′, C-3), 73.3, 28.3 (s, q, *t*Bu), 67.6 (d, C-2′), 56.6 (q, OMe), 56.0 (t, C-1), 44.3 (t, C-5′), 34.7, 33.3 (2 t, C-4′, C-2) ppm.

Typical signals of the unknown side product: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.74 (d, J = 7.4 Hz, 1 H), 4.09 (d, J = 8.1 Hz, 1 H), 3.38 (s, 3 H), 2.66 (m_c, 1 H) ppm; all other signals are overlaid by the signals of **10**. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 84.1 (t), 77.2 (s), 73.8 (d), 72.3 (d), 63.1 (t), 48.6 (t), 33.8 (t), 31.6 (t), 28.1 (q) ppm.

Acknowledgments

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