31. Model Studies Towards a Novel Fragment Coupling for the Synthesis of Mycalamides and Related Natural Products

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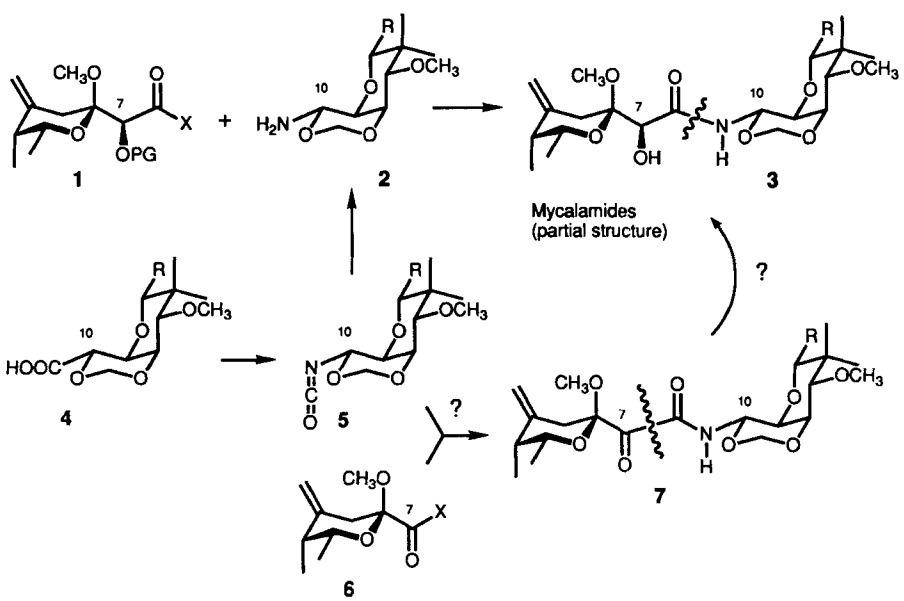
The mycalamides (**3**) and related natural products contain an α-hydroxy acid **1** bound *via* an amide bond to an α-alkoxy amine. The high density of functional groups in the 'coupling region' renders the coupling reactions delicate. Model studies showed that an alternate assembly of the molecular halves is possible using an 'Umpolung' of an α-alkoxy isocyanate, *e.g.* **13**. Thus, combination of the ester **12** with **13** led to the α-keto amide **16**. The further elaboration of **16** to the α-hydroxy-amide structure found in the mycalamides is reported.

Introduction. – The mycalamides **3** [1] [2] and the related natural products pederin [3], onnamide [4] [5], and the theopederins [6] are of high current interest due to their special biological activity. For instance, the mycalamides inhibit both protein and DNA synthesis at subnanomolar levels [7]. Structural features similar to the left-hand part of pederin are found in the antibiotics L156,602 [8], acinothricin [9], and A 83586C [10]. After the pioneering syntheses of pederin [11–15] and the first synthesis of mycalamide [16], there is renewed interest in finding better synthetic routes to these compounds. The approach hitherto used was to form the amide bond between an acid derivative **1** and an α-alkoxy

Scheme 1

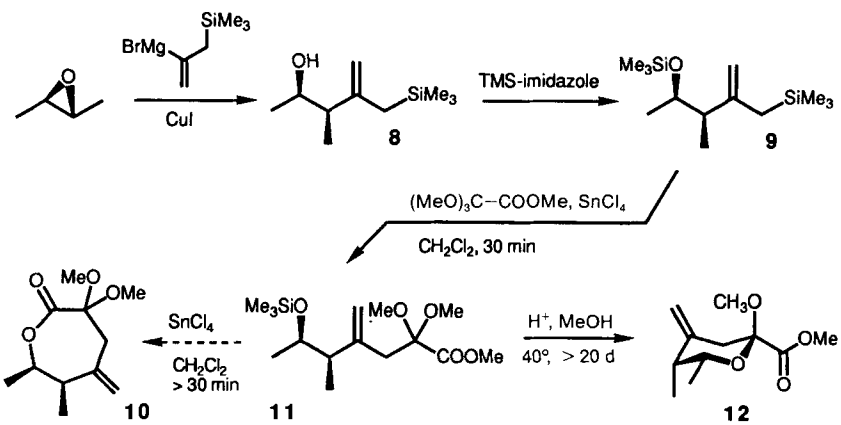


amine **2** [13] [15] [17] [18] (*Scheme 1*). Groups presently interested in this subject[1]) found it preferable to generate the amine **2** from a carboxylic acid **4** *via* a *Curtius* degradation and an isocyanate of type **5** [19]. Unfortunately, the free amine **2** is configurationally labile at C(10) [16], and this limits the possibility to carry over the configuration of C(10) from **4** to **2**. *Marron* and *Roush* have recently devised a protective-group scheme *via* carbamates by which the configuration of C(10) of the amine may be preserved in the coupling with the segment **1** [20].

Yet, in starting from the carboxylic acid **4**, the former carboxy C-atom is eventually lost as CO_2. Both the preservation of the stereochemical information at C(10) and the retention of the carboxy C-atom in the synthesis would be possible, if somehow the isocyanate **5** could be directly coupled with a building block such as **6**. This would lead to an α-keto-amide precursor **7** of the mycalamides. Having C(7) at the ketone oxidation level would moreover temporarily reduce the marked acid sensitivity [17] of the homo-allylic acetal moiety present in **3**. Of course then, the task of stereoselective reduction of the C(7) keto function of **7** to **3** would have to be adressed [11] [13] [14]. To evaluate this alternate strategy, we carried out model studies which we report here.

Results and Discussion. – The synthesis of the left-hand building block **6** started from *trans*-2,3-epoxybutane which was transformed into **8** following a procedure developed by *Kocienski* and coworkers [14] (*Scheme 2*). Silylation provided the allylsilane **9**, which could be condensed with $(MeO)_3CCOOMe$ (*cf.* [21]) to give in short reaction times the ester **11** (65%). Longer reaction times led to seven-membered lactone **10**. Treatment of the former with camphor-10-sulfonic acid in MeOH afforded the desired ester **12** in 78% yield.

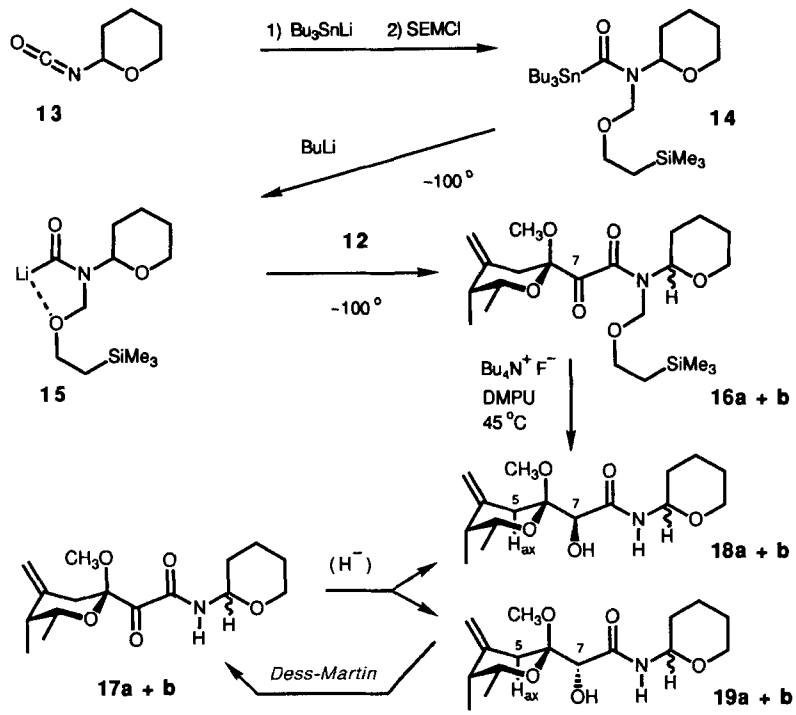
Scheme 2



The model studies for the novel coupling step were carried out with the commercially available isocyanate **13** as a surrogate for the building block **5** (*Scheme 3*). The intended coupling requires an 'Umpolung' step or, its equivalent, a two-electron reduction. We envisaged an 'Umpolung' *via* the acylstannane **14**. Treatment of **13** with Bu_3SnLi fol-

[1]) Including *P. Kocienski* (Southampton) and *V. Raval* (Chicago).

Scheme 3



SEMCl = [2-(Trimethylsilyl)ethoxy]-methyl chloride.

lowed by quenching with [2-(trimethylsilyl)ethoxy]methyl (SEM) chloride furnished **14** in 55% yield. The SEM protection on the N-atom proved to be advantageous for allowing the formation of the lithio derivative **15** in high yield at low temperatures. We were pleasantly surprised that generation of **15** in the presence of the ester **12** proceeded readily to give by *in situ* coupling 87% of a 1:1 mixture of the diastereoisomeric keto amides **16a** + **b**. The diastereoisomers of **16** may be separated by repeated flash chromatography. (Diastereoisomeric mixtures of **16** resulted, because racemates of both **12** and **13** were used.)

The beneficial SEM group was, however, quite refractory to being removed: the best conditions followed a *Lipshutz* procedure [22]: treatment of the keto amides **16** with $Bu_4N^+F^-$ in DMPU, however, did not give the desired keto amide **17**. Rather, the α-hydroxy amides **18** and **19** were obtained in 87% yield by an unexpected *in situ* reduction of **17**. The hydride source for this reduction is unknown. We speculate that it might be an NCH_2O^- or FCH_2O^- entity resulting from the cleavage of the SEM moiety.

Thus, this deprotection protocol serendipitously furnished directly the C(7)–OH moiety present in the mycalamides **3** or the pederins. The C(7)-epimers **18** and **19** were obtained in a 3:1 ratio, either starting from **16a**/**16b** or starting from the separated diastereoisomers **16a** or **16b**. From these experiments, a set of ^{13}C-NMR signals could be assigned to each of the four diastereoisomeric α-hydroxy amides **18** and **19**.

It is, of course, of interest, whether the major product **18** possesses the 'natural' configuration at C(7) (as shown) or not? While the ^{13}C-NMR chemical shifts did not allow an unambiguous assignment, we hoped to get clues from the ^{1}H-NMR spectra. This required highly enriched samples of each of the diastereoisomers **18a**, **18b**, **19a**, and **19b**. Since chromatographic separation could not be attained, the mixture **18a**/**19a** was oxidized with the *Dess-Martin* reagent [23] to give **17a** (83%), and the latter was reduced with $Li^+(s\text{-}Bu)_3BH^-$ at −100° to give **19a** in > 10:1 selectivity. Likewise, a mixture **18b**/**19b** was oxidized to **17b**, which, on reduction with $Li^+(s\text{-}Bu)_3BH^-$ formed **18b** in > 10:1 selectivity. These results allowed the recording of high-quality ^{1}H-NMR data for **18a**, **18b**, and **19a**. The diastereoisomers **18a** and **18b** showed the signal for H_{ax}–C(5) at 2.30 and 2.26 ppm, respectively. This corresponds to the signal position in the mycalamides (δ = 2.20–2.36 ppm) [7]. In pederin (δ = 2.36 ppm) [2], the theopederins [6], and in onnamide [4], this signal occurs around 2.4 ppm. In turn, **19a** showed resonance for H_{ax}–C(5) at 2.55 ppm which corresponds to the position of this signal in 7-epi-mycalamide (δ = 2.50 ppm) [24]. This led us to assign the structure of **18** to the C(7)-'natural' and of **19** to the C(7)-epi series.

The high stereoselectivity that can be attained in the reduction of the α-keto amides **17** is certainly gratifying. Unexpected, though, is the finding that the direction of the reduction is strongly influenced by the relative configuration at the aminal stereogenic center: **17a** is reduced to the 'unnatural' C(7)-epi-alcohol **19a**; **17b**, in turn, is reduced to **18b** with the 'natural' configuration at C(7). Therefore, our model studies give no clue, as to whether an intermediate **7** of a mycalamide synthesis will be reduced to the natural configuration, as hoped for, or to the C(7)-epimer! This model study showed, however, that a convergent synthesis of the mycalamides and pederins by the alternate bond-construction set indicated in **7** is feasible. In fact, the ready availability of the left-hand fragment **12** should allow combination with a larger variety of isocyanates to furnish various pederin analogs. This model study, moreover, opens up an interesting route to α-keto-amide structures of interest in natural-product chemistry.

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Experimental Part

General. All temp. quoted are not corrected. ^{1}H- and ^{13}C-NMR: *Bruker ARX-200, AC-300.* Boiling range of petroleum ether: 40–60°. Flash chromatography (FC): silica gel *Si 60, E. Merck AG,* Darmstadt, 40–63 μm.

1. *(3*RS*,4*RS*)-3-Methyl-2-(trimethylsilylmethyl)-4-(trimethylsilyloxy)pent-4-ene* (**9**). Into a soln. of 5.88 g (31.6 mmol) of *(2*RS*,3*RS*)-3-methyl-4-(trimethylsilylmethyl)pent-4-en-2-ol* (**8**) [14] in 150 ml of Et_2O were added, at 0°, 8.0 ml (55 mmol) of 1-(trimethylsilyl)-1*H*-imidazole. After stirring for 1 d, the mixture was filtered. The filtrate was concentrated *i.v.* and the residue purified by FC with petroleum ether/Et_2O 10:1 to give 7.94 g (97%) of **9** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.01 (*s*, 9 H); 0.08 (*s*, 9 H); 1.01 (*d*, *J* = 6.9, 3 H); 1.12 (*d*, *J* = 6.2, 3 H); 1.48, 1.56 (*AB*, *J* = 13.6, 2 H); 1.89 (*dq*, *J* = 6.9, 6.9, 1 H); 3.63 (*dq*, *J* = 6.3, 6.3, 1 H); 4.59 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −1.17; 0.30; 16.5; 22.2; 27.6; 48.6; 72.2; 107.4; 150.2. Anal. calc. for $C_{13}H_{30}OSi_2$ (258.6): C 60.39, H 11.70; found: C 60.29, H 11.86.

2. *Methyl (5RS,6RS)-2,2-dimethoxy-5-methyl-4-methylidene-6-(trimethylsilyloxy)heptanoate* (**11**). A soln. of 1.08 g (4.18 mmol) of **9** and of 0.68 g (4.1 mmol) of $(MeO)_3CCOOMe$ in 30 ml of CH_2Cl_2 was stirred for 30 min over molecular sieves (4 Å). 2 ml (2 mmol) of a 1M soln. of $SnCl_4$ in CH_2Cl_2 were added over 5 min leading to a deep red color of the soln. After 30 min, 2.0 ml (0.13 mol) of *N,N,N',N'*-tetramethylethylenediamine were added. After 10 min of vigorous stirring, the mixture was hydrolyzed by addition of 10 ml of sat. aq. $NaHCO_3$ soln. The mixture was filtered, and the phases were separated. The aq. phase was extracted with CH_2Cl_2 (4 × 20 ml). The combined org. phases were washed with 10 ml of brine, dried ($MgSO_4$) and concentrated. FC of the residue with petroleum ether/Et_2O 3:1 furnished 0.76 g (65%) of **11** as a slightly yellowish oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.07 (*s*, 9 H); 0.98 (*d*, *J* = 7.0, 3 H); 1.04 (*d*, *J* = 6.1, 3 H); 2.04 (*dq*, *J* = 7.0, 7.0, 1 H); 2.59 (*AB*, *J* = 16.8, 2 H); 3.25 (*s*, 3 H); 3.26 (*s*, 3 H); 3.63 (*dq*, *J* = 6.1, 6.1, 1 H); 3.72 (*s*, 3 H); 4.82 (*s*, 1 H); 5.00 (*d*, *J* = 1.3, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 0.23; 16.4; 21.7; 38.5; 48.1; 49.6; 49.7; 52.2; 71.4; 102.4; 113.2; 145.5; 169.0. Anal. calc. for $C_{15}H_{30}O_5Si$ (318.5): C 56.57, H 9.49; found: C 56.65, H 9.58.

3. *(5RS,6RS)-2,2-Dimethoxy-4-methylidene-5,6-dimethylhexano-6-lactone* (**10**). Into a soln. of 5.10 g (19.7 mmol) of **9** and of 3.57 g (21.7 mmol) of $(MeO)_3CCOOMe$ in 30 ml of CH_2Cl_2 were added, at 0°, 7.8 ml (10.1 mmol) of a 1.3M soln. of $SnCl_4$ in CH_2Cl_2 over 15 min. After stirring the deep-red soln. for 3 h at 0°, 350 ml of sat. aq. $NaHCO_3$ soln. were added. The phases were separated and the aq. phase extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phases were washed with 50 ml of brine, dried ($MgSO_4$), and concentrated. FC of the residue with petroleum ether/Et_2O 5:1 furnished 1.10 g (26%) of **10** as a slightly yellowish oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00 (*d*, *J* = 7.1, 3 H); 1.30 (*d*, *J* = 6.6, 3 H); 2.43 (*q*, *J* = 7.3, 1 H); 2.55, 2.72 (*AB*, *J* = 15.4, 2 H); 3.27 (*s*, 3 H); 3.36 (*s*, 3 H); 4.81 (*s*, 1 H); 4.93 (*s*, 1 H); 5.17 (*q*, *J* = 6.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.7; 19.6; 37.3; 45.9; 49.8; 50.3; 77.6; 99.9; 115.7; 145.9; 168.4. Anal. calc. for $C_{11}H_{18}O_4$ (214.3): C 61.66, H 8.47; found: C 61.54, H 8.58.

4. *Methyl (2RS,5RS,6RS)-2-Methoxy-5,6-dimethyl-4-methylidene-2H-tetrahydropyran-2-acetate* (**12**). Into a soln. of 264 mg (0.83 mmol) of **11** in 20 ml of anh. MeOH were added 13.3 mg (0.04 mmol) of camphor-10-sulfonic acid. After stirring for 6 weeks at r.t., TLC showed little conversion. Therefore, the mixture was stirred for 4 weeks during day time at 40° and overnight at r.t. 5 ml of sat. aq. $NaHCO_3$ soln. were added and the phases separated. The aq. phase was extracted with Et_2O (3 × 20 ml). The combined org. phases were washed with 10 ml of brine, dried ($MgSO_4$), and concentrated. FC of the residue with petroleum ether/Et_2O 3:1 furnished 138 mg (78%) of **12** as a slightly yellowish oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.04 (*d*, *J* = 7.1, 3 H); 1.21 (*d*, *J* = 6.6, 3 H); 2.23 (*qd*, *J* = 7.0, 2.6, 1 H); 2.38 (*d*, *J* = 14.2, 1 H); 2.53 (*ddd*, *J* = 14.2, 1.9, 1.9, 1 H); 3.21 (*s*, 3 H); 3.79 (*s*, 3 H); 3.92 (*dq*, *J* = 6.6, 2.7, 1 H); 4.74 (*dd*, *J* = 1.9, 1.9, 1 H); 4.86 (*dd*, *J* = 1.9, 1.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.8; 17.8; 36.7; 41.2; 50.9; 52.5; 69.4; 98.9; 110.5; 145.4; 169.6. Anal. calc. for $C_{11}H_{18}O_4$ (214.3): C 61.66, H 8.47; found: C 61.90, H 8.31.

5. *Tributyl{N-(tetrahydropyran-2-yl)-N-{[2-(trimethylsilyl)ethoxy]methyl}carbamoyl}stannane* (**14**). To a soln. of 5.8 g (10 mmol) of $Bu_3SnSnBu_3$ in 50 ml of anh. THF were added, at 0°, 6.5 ml (9.8 mmol) of a 1.5M soln. of BuLi in hexane. After stirring for 30 min at 0°, the soln. was cooled to −78°, and a soln. of 0.93 g (7.3 mmol) of tetrahydropyran-2-yl isocyanate in 15 ml of THF was added over 60 min. After stirring for 4 h at −78°, a soln. of 1.7 g (10 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride in 10 ml of THF was added dropwise. The mixture was allowed to reach r.t. overnight. H_2O (10 ml) was added, the phases were separated, and the aq. phase was extracted with Et_2O (5 × 25 ml). The combined org. phases were washed with 10 ml of brine, dried ($MgSO_4$), and concentrated. FC of the residue furnished 2.2 g (55%) of **14** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.00–0.04 (*m*, 9 H); 0.75–1.97 (*m*, 35 H); 3.41–3.62 (*m*, 3 H); 3.95–4.01 (*m*, 1 H); 4.51–4.59 (*m*, 2 H); 5.13 (*d*, *J* = 10.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −1.4; 11.5; 13.6; 18.2; 23.8; 25.0; 27.2; 28.9; 31.3; 65.5; 68.0; 68.5; 87.6; 194.7. Anal. calc. for $C_{24}H_{51}NO_3SiSn$ (548.5): C 52.43, H 9.36, N 2.55; found: C 52.46, H 9.47, N 2.56.

6. *2-[(2RS,5RS,6RS)-2-Methoxy-4-methylidene-5,6-dimethyltetrahydropyran-2-yl]-2-oxo-N-(tetrahydropyran-2-yl)-N-{[2-(trimethylsilyl)ethoxy]methyl}acetamide* (**16**). A soln. of 321 mg (1.5 mmol) of **12** and of 821 mg (1.5 mmol) of **14** in 10 ml of anh. THF was stirred for 30 min over molecular sieves (3 Å). The soln. was cooled to −105°, and 1.2 ml (2.3 mmol) of a 1.9M soln. of BuLi in hexane were added over 45 min with a motor-driven syringe in such a manner, that the soln. of the BuLi contacted the cold wall of the reaction vessel before being mixed with the reactants. After stirring for 15 min at −105°, the mixture was stirred for 30 min at −78° and hydrolyzed by addition of a mixture of 5 ml of sat. aq. $NaHCO_3$ soln. and 5 ml of sat. aq. NH_4Cl soln. After reaching r.t., 20 ml of *t*-BuOMe and 2 ml of Et_3N were added, the phases were separated, and the aq. phase was extracted with *t*-BuOMe (3 × 25 ml). The combined org. phases were washed with 10 ml of brine, dried (Na_2SO_4), and concentrated. FC of the residue with petroleum ether/*t*-BuOMe 7:1 containing 0.5% of Et_3N furnished 565 mg (85%) of **16** as a 1:1 mixture of diastereoisomers. Anal. calc. for $C_{22}H_{39}NO_6Si$ (441.6): C 59.83, H 8.90, N 3.17; found: C 60.13, H 8.87, N 3.16.

By repeated FC, it was possible to obtain fractions which contained only one diastereoisomer.

Data of **16a**: TLC (petroleum ether/*t*-BuOMe 7:1): R_f 0.19. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.04 (*s*, 9 H); 0.81–0.94 (*m*, 2 H); 1.00 (*d*, *J* = 7.0, 3 H); 1.11 (*d*, *J* = 6.6, 3 H); 1.42–1.91 (*m*, 5 H); 2.19–2.25 (*m*, 2 H); 2.34, 2.98 (*AB*, *J* = 14.2, 2 H); 3.27 (*s*, 3 H); 3.31–3.67 (*m*, 3 H); 3.91–4.02 (*m*, 2 H); 4.70–4.84 (*m*, 4 H); 5.10 (*d*, *J* = 11.0, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −1.4; 11.7; 17.6; 18.1; 23.2; 24.7; 30.2; 36.1; 41.2; 50.7; 66.0; 68.2; 69.7; 69.9; 85.2; 100.6; 110.5; 145.1; 168.8; 198.9.

Data of **16b**: TLC (petroleum ether/*t*-BuOMe 7:1): R_f 0.15. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.04 (*s*, 9 H); 0.81–0.91 (*m*, 2 H); 0.99 (*d*, *J* = 7.1, 3 H); 1.12 (*d*, *J* = 6.5, 3 H); 1.34–1.94 (*m*, 5 H); 2.17–2.24 (*m*, 2 H), overlayed with 2.25 (*d*, *J* = 14.3, 1 H); 2.98 (*ddd*, *J* = 14.3, 2.0, 2.0, 1 H); 3.27 (*s*, 3 H); 3.32–3.76 (*m*, 3 H); 3.88–4.02 (*m*, 2 H); 4.68–4.90 (*m*, 4 H); 5.06 (*d*, *J* = 11.1, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −1.4; 11.6; 17.7; 18.2; 23.5; 24.7; 30.6; 36.2; 41.2; 50.4; 66.4; 68.2; 69.8; 70.2; 85.1; 101.1; 110.4; 144.7; 168.7; 197.9.

7. *2-Hydroxy-2-[(2*RS,*5*RS,*6*RS*)-2-methoxy-4-methylidene-5,6-dimethyltetrahydropyran-2-yl]*-N-*(tetrahydropyran-2-yl)acetamide* (**18a**/**18b** and **19a**/**19b**). To 438 mg (0.99 mmol) of **16** were added 5 ml (5 mmol) of a 1M soln. of $Bu_4N^+F^-$ in THF. The solvent was removed *i.v.* and the solid residue taken up in 2 ml of 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU). Powdered molecular sieves (400 mg; 4 Å) were added, and the mixture was stirred for 30 min at 45°. H_2O (10 ml) and *t*-BuOMe (10 ml) were added, the phases separated, and the aq. phase was extracted with *t*-BuOMe (3 × 10 ml). The combined org. phases were washed with 5 ml of brine, dried (Na_2SO_4), and concentrated. FC of the residue with *t*-BuOMe containing 0.5% of Et_3N furnished 262 mg (83%) of a mixture **18a**/**18b**/**19a**/**19b** in a 3:3:1:1 ratio. Anal. calc. for $C_{16}H_{27}NO_5$ (313.4): C 61.32, H 8.68, N 4.47; found: C 61.18, H 8.94, N 4.46.

Repeated FC with petroleum ether/*t*-BuOMe 3:1 containing 0.5% of Et_3N furnished a mixture **18a**/**18b** free of **19**.

By the same procedure, **16a** was converted into a mixture **18a**/**19a**. Likewise, **16b** furnished a mixture **18b**/**19b**. With the aid of the material obtained under *Exper. 9*, the following data were obtained.

Data of **18a**: TLC (*t*-BuOMe): R_f 0.27. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, *J* = 7.1, 3 H); 1.15 (*d*, *J* = 6.6, 3 H); 1.22–1.89 (*m*, 6 H); 2.20–2.25 (*m*, 1 H); 2.03 (*ddd*, *J* = 14.2, 2.0, 2.0, 1 H); 2.30 (*d*, *J* = 14.2, 1 H); 3.28 (*s*, 3 H); 3.55–3.64 (*m*, 1 H); 3.84–4.05 (*m*, 3 H); 4.20 (*s*, 1 H); 4.72 (*dd*, *J* = 1.9, 1.9, 1 H); 4.83 (*dd*, *J* = 1.8, 1.8, 1 H); 5.14–5.20 (*m*, 1 H); 7.30 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.3; 17.9; 22.6; 24.9; 31.4; 32.7; 41.3; 48.2; 67.2; 69.3; 70.4; 77.8; 100.0; 110.9; 145.5; 171.0.

Data of **18b**: TLC (*t*-BuOMe): R_f 0.43. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.02 (*d*, *J* = 7.1, 3 H); 1.15 (*d*, *J* = 6.6, 3 H); 1.18–1.88 (*m*, 6 H); 2.10–2.28 (*m*, 1 H), overlayed with 2.13 (*ddd*, *J* = 14.2, 2.0, 2.0, 1 H) and 2.26 (*d*, *J* = 14.2, 1 H); 3.29 (*s*, 3 H); 3.49–3.58 (*m*, 1 H); 3.87–4.04 (*m*, 2 H), overlayed with 3.96 (*d*, *J* = 3.6, 1 H); 4.16 (*d*, *J* = 3.4, 1 H); 4.70 (*dd*, *J* = 1.9, 1.9, 1 H); 4.82 (*dd*, *J* = 1.9, 1.9, 1 H); 5.00–5.07 (*m*, 1 H); 7.33 (*d*, *J* = 8.8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.8; 17.9; 22.7; 25.0; 31.7; 32.8; 41.4; 48.2; 67.1; 69.5; 70.2; 78.0; 100.0; 110.5; 145.5; 171.3.

Data of **19a**: TLC (*t*-BuOMe): R_f 0.33. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.01 (*d*, *J* = 7.0, 3 H); 1.17 (*d*, *J* = 6.5, 3 H); 1.36–1.84 (*m*, 6 H); 2.07–2.22 (*m*, 1 H); 2.23 (*d*, *J* = 14.2, 1 H); 2.55 (*d*, *J* = 14.2, 1 H); 3.31 (*s*, 3 H); 3.50–3.64 (*m*, 1 H); 3.92–4.04 (*m*, 3 H); 4.12 (*s*, 1 H); 4.71 (*s*, 1 H); 4.83 (*s*, 1 H); 5.09–5.16 (*m*, 1 H); 7.34 (*d*, *J* = 8.8, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.7; 17.9; 22.4; 25.1; 31.4; 33.2; 41.2; 49.7; 66.9; 69.5; 72.0; 77.8; 100.4; 110.2; 146.2; 170.0.

Data of **19b**: TLC (*t*-BuOMe): R_f 0.29. ^{13}C-NMR (75 MHz, $CDCl_3$): 11.7; 17.8; 22.4; 25.0; 31.4; 32.2; 41.2; 49.6; 66.9; 69.4; 72.0; 77.7; 100.4; 110.2; 146.1; 170.0.

8. *2-[(2*RS,*5*RS,*6*RS*)-2-Methoxy-4-methylidene-5,6-dimethyltetrahydropyran-2-yl]-2-oxo-*N-*(tetrahydropyran-2-yl)acetamide* (**17**). To a soln. of 127 mg (0.40 mmol) of **18**/**19** in 5 ml of CH_2Cl_2 were added 0.32 ml (4.0 mmol) of pyridine and 338 mg (0.8 mmol) of the *Dess-Martin* periodinane [23]. After stirring for 2 d, the mixture was poured into a mixture of 20 ml of *t*-BuOMe, 5 ml of sat. aq. $NaHCO_3$ soln., 5 ml of H_2O, and 1.3 g (8.2 mmol) of sodium thiosulfate. After stirring vigorously for 2 h, the phases were separated, and the aq. phase was extracted with *t*-BuOMe (3 × 15 ml). The combined org. phases were washed with 10 ml of brine, dried (Na_2SO_4), and concentrated. FC of the residue with petroleum ether/*t*-BuOMe 5:2, containing 0.5% of Et_3N furnished 104 mg (83%) of **17** as a yellowish oil. Anal. calc. for $C_{16}H_{25}NO_5$ (311.4): C 61.72, H 8.09, N 4.50; found: C 61.90, H 8.14, N 4.30.

By the same procedure, a mixutre **18a**/**19a** was oxidized to give **17a**. Likewise, a mixture **18b**/**19b** furnished **17b**.

Data of **17a**: ^{1}H-NMR (200 MHz, $CDCl_3$): 1.10 (*d*, *J* = 7.1, 3 H); 1.18 (*d*, *J* = 6.5, 3 H); 1.39–1.96 (*m*, 6 H); 2.17–2.30 (*m*, 1 H); 2.42 (*d*, *J* = 14.1, 1 H); 2.80 (*ddd*, *J* = 14.1, 1.9, 1.9, 1 H); 3.19 (*s*, 3 H); 3.49–3.60 (*m*, 1 H); 3.92–4.07 (*m*, 2 H); 4.74 (*dd*, *J* = 1.9, 1.9, 1 H); 4.87 (*dd*, *J* = 1.9, 1.9, 1 H); 5.04–5.14 (*m*, 1 H); 7.32 (*d*, *J* = 8.6,

1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.9; 17.8; 22.5; 24.9; 31.3; 35.2; 41.4; 50.9; 67.4; 70.1; 77.8; 101.2; 110.8; 144.9; 158.9; 193.1.

Data of **17b**: ^{1}H-NMR (300 MHz, $CDCl_3$): 1.07 (*d*, *J* = 7.1, 3 H); 1.15 (*d*, *J* = 6.5, 3 H); 1.36–1.90 (*m*, 6 H); 2.14–2.24 (*m*, 1 H); 2.46 (*d*, *J* = 14.1, 1 H); 2.77 (*ddd*, *J* = 14.1, 1.9, 1.9, 1 H); 3.13 (*s*, 3 H); 3.49–3.59 (*m*, 1 H); 3.88–4.00 (*m*, 2 H); 4.71 (*dd*, *J* = 1.9, 1.9, 1 H); 4.83 (*dd*, *J* = 1.9, 1.9, 1 H); 5.02–5.15 (*m*, 1 H); 7.30 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.8; 17.6; 22.4; 24.9; 31.3; 35.3; 41.3; 50.7; 67.3; 69.9; 77.8; 100.9; 110.6; 144.9; 158.9; 193.2.

9. *Reduction of* **17** *to* **18**/**19**. A soln. of 35 mg (0.11 mmol) of **17** in 15 ml of THF was stirred over molecular sieves (4 Å) in the lower compartment of a two-compartment low-temperature reaction vessel [25]. The top compartment of the reaction vessel was charged with a soln. of 120 µl (0.12 mmol) of a 1M soln. of *L-Selectride* in THF, diluted to 15 ml with THF. The reactor was cooled to −100°. The *L-Selectride* soln. was slowly added to the lower compartment over 30 min. After stirring further 30 min at −100°, a mixture of 10 ml of sat. aq. $NaHCO_3$ soln. and 10 ml of sat. aq. NH_4Cl soln. was added. After reaching r.t., the phases were separated, and the aq. phase was extracted with *t*-BuOMe (4 × 20 ml). The combined org. phases were washed with 10 ml of brine, dried (Na_2SO_4), and concentrated. FC of the residue with *t*-BuOMe containing 0.5% of Et_3N furnished 33 mg (94%) of **18**/**19**.

Following this procedure, **17a** was reduced to furnish diastereoisomerically pure **19a**, and, likewise **17b** was reduced to give diastereoisomerically pure **18b**.

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