Formal Synthesis of (−)-Cyclaradine Using Ring Closing Metathesis

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The stereoselective formal synthesis of (−)-cyclaradine from the inexpensively available starting material L-glutamic acid is described, using *Eschenmoser*'s reagent, and applying *Luche* reduction, *Grignard* reaction, and ring closing metathesis (RCM) as the key steps.

Introduction. – Carbanucleosides contain pseudo-sugars or related cyclitols in place of the sugar moiety of nucleosides. Unlike nucleosides, carbanucleosides are chemically very stable even in the biological systems due to the absence of glycosidic linkage [1]. Therefore, natural carbanucleosides such as (−)-aristeromycin (**1**), and (−)-neplanocins **2** and **3** (*Fig.*) possess various biological properties such as anti-viral, antimicrobial, antitumour, *etc.* [2]. Hence, the synthesis and biological evaluation of carbocyclic analogs of nucleosides are of current interest.

The nucleoside ara-A (9-(β-D-arabinofuranosyl)adenine; **4**) shows excellent activity against DNA virus, particularly herpes simplex virus (HSV) [3]. However, ara-A (**4**) easily undergoes deamination to ara-H (9-(β-D-arabinofuranosyl)hypoxanthine; **5**) by the adenosine deaminase (ADase) enzyme. Nucleoside **5** is about ten fold less active than **4** against HSV [4], thus limiting its clinical use. (+)-Cyclaradine (Sch31172; **6**) [5] was developed by *Vince* and *Daluge* [6] as a novel carbocyclic analog of the clinically effective synthetic antiviral drug ara-A (**4**) to overcome the deamination problem of **4**. In the case of **6**, the presence of a CH_2 group instead of the ring O-atom renders it very resistant to deamination [5][7] in the serum with

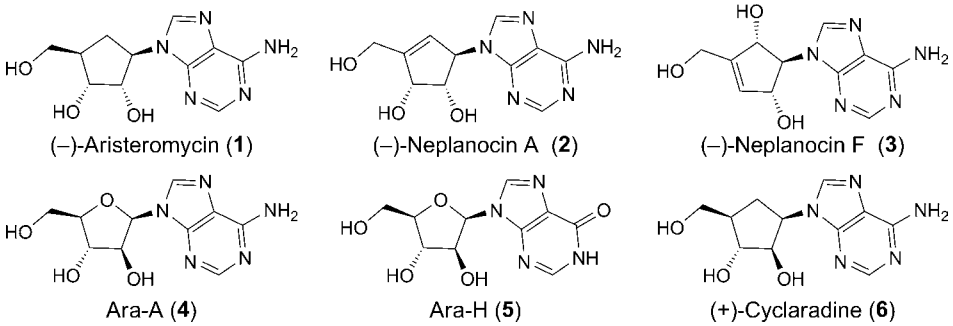


Figure. *Structures of some carbanucleosides and nucleosides*

retention of anti-HSV activity. (+)-Cyclaradine (**6**) also exhibits activity against trifluorothymidine or acycloguanisine (acyclovir)-resistant HSV mutants [7]. Because of these biological properties and interesting structural features, **6** became an interesting synthetic target [8][9].

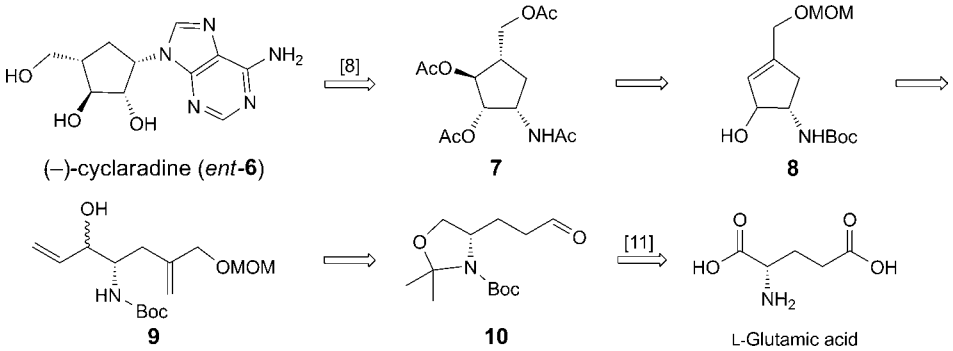
In continuation of our work on the synthesis of cyclitols and amino cyclitols [10], herein we report a simple and efficient strategy for the synthesis of the 'carbasugar' moiety **7** of (−)-cyclaradine (*ent*-**6**). The preparation of (+)-cyclaradine (**6**) from *ent*-**7** in good yield within three steps has been already reported in the literature [8]. Hence, an efficient synthesis of compound **7** would open up an easy approach for the preparation of **6**. Therefore we focused our attention on the synthesis of the key intermediate **7**.

The retrosynthetic analysis of compound **7** based on ring closing metathesis (RCM) is shown in *Scheme 1*. The key intermediate in our strategy is the diene **9**, which, by RCM, should give the core structure **8**. Compound **9** can be synthesized from the aldehyde **10**.

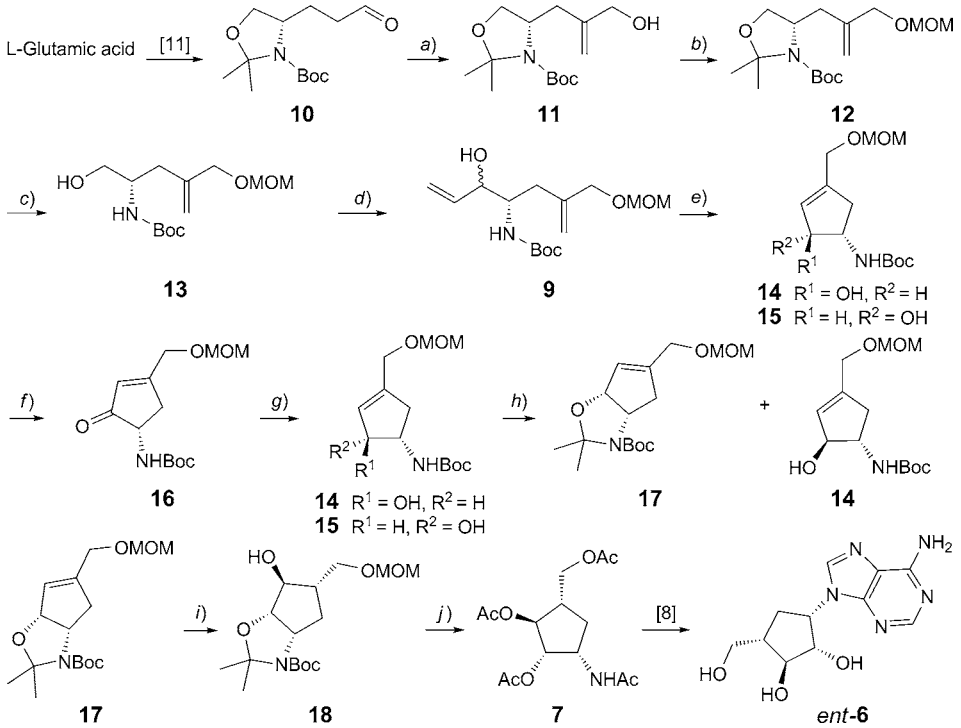
Results and Discussions. – L-Glutamic acid was converted to **10** by a known procedure [11]. The next step was to generate the 1,1-disubstituted alkene part of the diene **9**. We assume that the success of the RCM strategy depends on the efficient preparation of the diene. In this connection, recently we utilized *Eschenmoser*'s salt (=dimethyl(methylidene)ammonium iodide) [12] for the synthesis of a 1,1 disubstituted diene [13]. Accordingly, treatment of aldehyde **10** with *Eschenmoser*'s salt yielded an α,β-unsaturated aldehyde, which, on reduction under *Luche* conditions [14], gave the corresponding allyl alcohol derivative **11** (*Scheme 2*).

The primary OH group of **11** was converted to the MOM (=methoxymethyl) ether by treatment with MOMCl to give compound **12** in good yield. The acetonide group in **12** was deprotected selectively [15] to afford the OH compound **13**. The latter was oxidized under *Swern* conditions to give an aldehyde, which was treated immediately with CH_2=CHMgBr to afford **9** as an inseparable mixture of diastereoisomers in a 5:1 ratio (^{1}H-NMR). The stereochemical outcome of the nucleophile additions to 2-amino aldehydes is well-studied [16] and predictable. Thus, diene mixture **9** was subjected to RCM using *Grubbs*' 2nd-generation catalyst [17] to afford a mixture of stereoisomeric

Scheme 1. *Retrosynthetic Analysis*



Scheme 2. *Synthesis of Compound* **7**



a) 1. Et_3N, *Eschenmoser*'s salt, CH_2Cl_2, 0° to r.t., 3 h; 2. $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH, 0°, 1 h; 70% (over two steps). *b*) Methoxymethyl chloride (MOMCl), EtN^iPr_2, CH_2Cl_2, −5° to r.t., 8 h; 88%. *c*) $CuCl_2 \cdot H_2O$, MeCN, 0°, 30 min; 98%. *d*) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°, 3 h; 2. CH_2=CHMgBr, THF, −78°, 4 h; 70% (over two steps). *e*) *Grubbs*' 2nd-generation catalyst (5 mol-%), CH_2Cl_2, (reflux) 1 h; 88%; **14**/**15** 5:1. *f*) Pyridinium dichromate (PDC), CH_2Cl_2, 3 h; 90%. *g*) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH, 0°, 1 h; 85%; **14**/**15** 1:3. *h*) 2,2-Dimethoxypropane (2,2-DMP), acetone, TsOH, 30 min; **17** (53%) and **14** (10%) from **16**. *i*) $BH_3 \cdot Me_2S$, H_2O_2, NaOH, THF, 0° to r.t., 3 h; 60%. *j*) 1. 10% HCl, MeOH, 1 h; 2. Ac_2O, pyridine, r.t., 7 h; 92% (over two steps).

cyclopentene derivatives **14**/**15** in a 5:1 ratio (*Scheme 2*). Based on this ratio, it is obvious that the *syn*-diastereoisomer is the major diene in mixture **9**, since the nucleophile addition takes place under chelation control [16]. To obtain the required *cis*-isomer **15** as major compound, the mixture **14**/**15** was oxidized with pyridinium dichromate (PDC) to furnish the keto compound **16**, which, on reduction under *Luche* conditions [14], gave **14** and the required *cis*-1-amino-2-hydroxy diastereoisomer **15** as major product in a 1:3 ratio as a result of the facial selectivity of the H^- ion addition. These two diastereoisomers **14** and **15** were separated by chromatography after converting **15** to the isopropylidene derivative **17** by treatment of the mixture **14**/**15** with 2,2-dimethoxypropane in acidic medium. The unreacted **14** was recovered. The hydroboration of **17** with $BH_3 \cdot Me_2S$ gave the hydroxy compound **18** as the exclusive isomer (*Scheme 2*). This stereoselective hydroboration takes place due to the preferential attack of borane from less hindered side. The next step is deprotection

of **18**, followed by peracylation, for the sake of purification leading to compound **7**, whose spectroscopic data were in good agreement with the reported values [18].

Conclusions. – We have developed a stereoselective and good yielding strategy for the synthesis of (−)-cyclaradine carbasugar moiety **7** starting from L-glutamic acid. This strategy is also useful to prepare (+)-cyclaradine by using D- instead of L-glutamic acid as a starting material and also useful to prepare various other amino cyclitols.

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Experimental Part

General. The moisture- and O_2-sensitive reactions were carried out under N_2 in flame- or oven-dried glassware with magnetic stirring. The solvents were distilled under standard procedures. THF used was freshly distilled over Na and benzophenone prior to use. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Before concentration of the solvent, the org. layer was dried (Na_2SO_4). Column chromatography (CC): silica gel (SiO_2; 60–120 mesh) with AcOEt hexane mixtures as eluent. M.p.: *Fisher John*'s melting-point apparatus; uncorrected. Optical rotations: *JASCO* digital polarimeter. IR Spectra: *PerkinElmer RX-1 FT-IR* system; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Varian Gemini-200*, *Bruker Avance-300*, and *Inova-500* spectrometer; δ in ppm rel. to Me_4Si as internal standard; *J* in Hz. MS: *QSTAR* mass spectrometer (*Applied Biosystems*, USA); in *m*/*z*.

tert-*Butyl (4*S*)-4-[2-(Hydroxymethyl)prop-2-en-1-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate* (**11**). To an ice-cooled, stirred soln. of aldehyde **10** (6 g, 23.34 mmol) in CH_2Cl_2 (50 ml), Et_3N (9.74 ml, 70.03 mmol) and *Eschenmoser*'s salt (8.63 g, 46.69 mmol) were added, and the mixture was stirred for 3 h at r.t. and extracted with CH_2Cl_2. The combined org. extracts were washed with H_2O, $NaHCO_3$, and brine, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the crude product was added to an ice-cooled, stirred soln. of $CeCl_3 \cdot 7\ H_2O$ (16.62 g, 44.60 mmol) and $NaBH_4$ (2.53 g, 66.91 mmol) in MeOH. The mixture was stirred for 30 min at 0°, sat. $NaHCO_3$ soln. was added. and the solvent was removed under reduced pressure. The residue was taken in AcOEt (250 ml), filtered through a *Celite* pad, and the filtrate was washed with H_2O and brine. The solvent was removed on a rotary evaporator, and the residue was purified by CC (AcOEt/hexane 2:3) to give pure **11** (4.43 g, 70%). Colorless liquid. $[\alpha]_D^{30} = +47.1$ ($c = 1.46$, $CHCl_3$). IR (neat): 3019, 2934, 1692, 1514, 1214, 751. ^1H-NMR (300 MHz, $CDCl_3$; major rotamer): 5.01 (*s*, 1 H); 4.85 (*s*, 1 H); 4.26–4.17 (*m*, 1 H); 4.12 (*s*, 2 H); 4.0–3.84 (*m*, 1 H); 3.83–3.26 (*m*, 1 H); 3.61 (br. *s*, 1 H); 2.52 (*dd*, $J = 7.3, 13.2$, 1 H); 2.27 (*dd*, $J =$ 7.3, 12.8, 1 H); 1.59 (*s*, 3 H); 1.47 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major rotamer): 152.9, 145.8; 113.2; 93.5; 80.5; 67.3; 66.8; 56.4; 38.7; 28.3; 27.7; 24.4. HR-ESI-MS: 294.167 ($[M + Na]^+$, $C_{14}H_{25}NNaO_4^+$; calc. 294.166).

tert-*Butyl (4*S*)-4-{2-[(Methoxymethoxy)methyl]prop-2-en-1-yl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate* (**12**). To an ice-cooled, stirred soln. of **11** (4.30 g, 15.86 mmol) in CH_2Cl_2 (40 ml) were added EtN^iPr_2 (15.54 ml, 95.20 mmol), MOMCl (3.8 ml, 47.6 mmol) and 4-(dimethylamino)pyridine (DMAP; 5 mg). The mixture was allowed to warm to r.t., then stirred for 12 h, and finally extracted with CH_2Cl_2 (3×30 ml) and H_2O (30 ml). The combined org. layers were washed with brine (20 ml) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:4) to afford **12** (4.40 g, 88 %). Liquid. $[\alpha]_D^{30} = -3.783$ ($c = 2.0$, $CHCl_3$). IR (neat): 3018, 2979, 2934, 2885, 1692, 1514, 1391, 1367, 1214, 1169, 1151, 1048, 751, 667. ^1H-NMR (300 MHz, $CDCl_3$): 5.12 (*s*, 1 H); 4.94 (*s*, 1 H); 4.59 (*d*, $J = 4.9$, 2 H); 4.12–3.74 (*m*, 5 H); 3.35 (*s*, 3 H); 2.63–2.43 (*m*, 1 H); 2.26–2.09 (*m*, 1 H); 1.60 (*s*, 3 H); 1.48 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major rotamer): 151.9; 142.4; 114.5; 95.5; 93.7; 79.5; 70.3; 69.6; 66.2; 55.9; 37.5; 28.3; 26.8; 23.1. HR-ESI-MS: 338.19379 ($[M + Na]^+$, $C_{16}H_{29}NNaO_5^+$; calc. 338.19409).

tert-*Butyl {(2*S*)-1-Hydroxy-4-[(methoxymethoxy)methyl]pent-4-en-2-yl}carbamate* (**13**). To a soln. of **12** (5.9 g, 10.35 mmol) in MeCN (40 ml), $CuCl_2 \cdot 2\,H_2O$ was added at 0°, and the mixture was stirred for 1 h. The reaction was quenched with sat. $NaHCO_3$ soln., and the mixture was filtered through a *Celite* pad. The filtrate was extracted with AcOEt (3 × 30 ml) and H_2O (30 ml). The combined org. layers were washed with brine (20 ml) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:1.5) to afford **13** (5.05 g, 98%). Syrup. $[\alpha]_D^{30}$ − 24.5 ($c = 0.60$, $CHCl_3$). IR (neat). 3019, 1708, 1515, 1214, 1045, 928, 743, 667, 626. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.15 (*s*, 1 H); 5.01 (*s*, 1 H); 4.89 (*d*, $J = 7.1$, 1 H); 4.61 (*s*, 2 H); 4.0 (*s*, 2 H); 3.79–3.69 (*m*, 1 H); 3.60 (*d*, $J = 3.7$, 2 H); 3.36 (*s*, 3 H); 2.38–2.19 (*m*, 2 H); 1.43 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.3; 141.7; 115.6; 95.7; 79.6; 70.4; 65.4; 55.4; 51.5; 34.9; 28.3. HR-ESI-MS: 298.1625 ($[M + Na]^+$, $C_{13}H_{25}NNaO_5^+$; calc. 298.1631).

tert-*Butyl {(4*S*)-5-Hydroxy-2-[(methoxymethoxy)methyl]hepta-1,6-dien-4-yl}carbamate* (**9**). To a stirred soln. of oxalyl chloride (2.22 ml, 25.45 mmol) in dry CH_2Cl_2 (10 ml) under N_2 was added DMSO (1.80 ml, 50.90 mmol) slowly at − 78°, and the mixture was stirred further for 30 min at − 78°. Then **13** (3.5 g, 12.72 mmol) in dry CH_2Cl_2 (20 ml) was added slowly over 10 min, and the mixture was stirred further for 2 h, and then Et_3N (10.62 ml, 76.3 mmol) was added. The temp. was slowly raised to r.t. over 20 min, and then the mixture was diluted with CH_2Cl_2 (50 ml). The org. layer was sequentially washed with sat. aq. NH_4Cl soln. and brine, and dried (Na_2SO_4). The solvent was removed with a rotary evaporator.

To the soln. of crude aldehyde in THF, at − 78° under N_2, 1M CH_2=CHMgBr (102.12 ml, 102.12 mmol) was added. After stirring for 3 h at − 78°, the mixture was poured on sat. NH_4Cl (50 ml) and extracted with AcOEt (3 × 50 ml). The collected org. layers were combined, washed with H_2O and brine, then dried (Na_2SO_4), concentrated under reduced pressure and purified by CC (AcOEt/hexane 4:1) to afford the mixture **9** (3:1; 2.69 g, 70% for two steps). Yellow oil. $[\alpha]_D^{30}$ − 4.39 ($c = 5.5$, $CHCl_3$). IR (neat): 3434, 3349, 3015, 2977, 2930, 1693, 1505, 1451, 1392, 1367, 1214, 1168, 1106, 1046, 921, 856, 751, 667, 626. ^{1}H-NMR (300 MHz, $CDCl_3$; major diastereoisomer): 5.97–5.81 (*m*, 1 H); 5.40–5.12 (*m*, 3 H); 5.07–4.98 (*s*, 1 H); 4.89–4.77 (br. *s*, 1 H); 4.65 (*s*, 2 H); 4.28–4.16 (*m*, 1 H); 4.04 (*s*, 2 H); 3.96–3.70 (*m*, 1 H); 3.38 (*s*, 3 H); 2.46–2.06 (*m*, 2 H); 1.43 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major diastereoisomer): 156.2; 142.0; 137.9; 116.6; 115.2; 95.6; 79.3; 73.5; 69.9; 55.3; 53.3; 33.5; 28.2. HR-ESI-MS: 324.1781 ($[M + Na]^+$, $C_{15}H_{27}NNaO_5^+$; calc. 324.1782).

tert-*Butyl {(1*S*)-2-Hydroxy-4-[(methoxymethoxy)methyl]cyclopent-3-en-1-yl}carbamates* (**14**/**15**). To the soln. of **9** (2.5 g, 8.3 mmol) in CH_2Cl_2 (332 ml), *Grubbs*' 2nd-generation catalyst (0.14 g, 0.16 mmol) was added at r.t. After stirring the mixture at 48° for 2 h, CH_2Cl_2 was removed under vacuum, and the residue was submitted for CC (AcOEt/hexane 1:1) to provide the inseparable mixture **14**/**15** (5:1; 1.99 g, 88%). $[\alpha]_D^{30} = -10.17$ ($c = 1.53$, $CHCl_3$). IR (neat): 3019, 1692, 1480, 1214, 1047, 928, 742, 667, 626. ^{1}H-NMR (300 MHz, $CDCl_3$; major diastereoisomer **14**): 5.70 (*s*, 1 H); 4.99–4.92 (*m*, 1 H); 4.72–4.66 (*m*, 1 H); 4.62 (*s*, 2 H); 4.11 (*d*, $J = 13.2$, 1 H); 4.03 (*d*, $J = 13.2$, 1 H); 4.0–3.87 (*m*, 1 H); 3.37 (*s*, 3 H); 2.79 (*dd*, $J = 8.3$, 7.1, 1 H); 2.14 (*dd*, $J = 8.3$, 7.1, 1 H); 1.45 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major diastereoisomer **14**): 156.9; 140.8; 128.1; 95.7; 83.5; 80.0; 65.5; 60.8; 55.2; 37.5; 28.3. HR-ESI-MS: 296.1468 ($[M + Na]^+$, $C_{13}H_{23}NNaO_5^+$; calc. 296.1468).

tert-*Butyl {(1*S*)-4-[(Methoxymethoxy)methyl]-2-oxocyclopent-3-en-1-yl}carbamate* (**16**). To the soln. of **14**/**15** (1.8 g, 6.59 mmol) in CH_2Cl_2 (15 ml), pyridinium dichromate (PDC; 4.96 g, 13.18 mmol) was added at 0°. After stirring at r.t. for 24 h, the mixture was filtered through a *Celite* pad and washed with CH_2Cl_2. Filtrate and washings were combined, concentrated to a syrup and purified by CC (AcOEt / hexane 2:3) to give **16** (1.61 g, 90%). Colorless liquid. $[\alpha]_D^{30} = -53.33$ ($c = 0.2$, $CHCl_3$). IR (neat): 3338, 2975, 1705, 1623, 1520, 1367, 1251, 1150, 1046, 922, 771, 721. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.20 (*s*, 1 H); 5.21 (*s*, 1 H); 4.68 (*s*, 2 H); 4.34 (*s*, 2 H); 4.05 (*s*, 1 H); 3.37 (*s*, 3 H); 3.05 (*d*, $J = 18$, 1 H); 2.55 (*d*, $J = 18$, 1 H); 1.41 (*s*, 9 H). ^{13}C-NMR (300 MHz, $CDCl_3$): 204.9; 175.3; 155.8; 126.3; 96.2; 80.0; 66.5; 55.5; 55.2; 36.7; 28.2. HR-ESI-MS: 294.1312 ($[M + Na]^+$, $C_{13}H_{21}NNaO_5^+$; calc. 294.1319).

tert-*Butyl {(1*S*)-2-Hydroxy-4-[(methoxymethoxy)methyl]cyclopent-3-en-1-yl}carbamates* (**14**/**15**). To an ice-cooled soln. of $CeCl_3 \cdot 7\,H_2O$ (4.39 g, 11.80 mmol) in MeOH (10 ml), $NaBH_4$ (0.67 g, 17.71 mmol) was added under stirring portion wise. After stirring at 0° for 10 min, **16** (1.6 g, 5.90 mmol) in MeOH (16 ml) was added. The mixture was stirred for 30 min at 0°, sat. NH_4Cl soln. was added, and

solvent was removed under reduced pressure. The residue was taken in AcOEt (75 ml), filtered through a *Celite* pad and the filtrate was washed with H_2O and brine. The solvent was evaporated on a rotary evaporator and the residue was purified by CC (AcOEt/hexane 1:1) to give compounds **14**/**15** (1:3; 1.37 g, 85%) Colorless liquid. $[\alpha]_D^{30} = -162.3$ ($c = 0.1$, $CHCl_3$). IR (neat): 3424, 2975, 1689, 1504, 1366, 1249, 1039, 920, 752, 665. ^{1}H-NMR (500 MHz, $CDCl_3$; major diastereoisomer **15**): 5.79 (*s*, 1 H); 5.26 (br. *s*, 1 H); 4.72–4.56 (*m*, 3 H); 4.24–383 (*m*, 3 H); 3.35 (*s*, 3 H); 2.65 (*dd*, $J = 7.9$ 7.5, 1 H); 2.25 (*dd*, $J =$ 7.9, 7.5, 1 H); 1.42 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major diastereoisomer **15**): 155.9; 145.4; 126.7; 95.8; 83.4; 79.9; 65.7; 60.6; 55.2; 37.6; 28.3. HR-ESI-MS: 296.1468 ($[M + Na]^+$, $C_{13}H_{23}NNaO_5^+$; calc. 296.1468).

tert-*Butyl (3a*S,*6a*R*)-4,6a-Dihydro-5-[(methoxymethoxy)methyl]-2,2-dimethyl-2*H*-cyclopenta[*d*]-[1,3]oxazole-3(3a*H*)-carboxylate* (**17**). To a soln. **14** and **15** (1.2 g, 4.39 mmol) in acetone (10 ml) was added 2,2-dimethoxypropane (2,2-DMP; 1.59 ml, 13.18 mmol) and TsOH (cat.), and the mixture was stirred for 1 h at r.t. After evaporation of the solvents, H_2O was added (15 ml), and the mixture extracted with AcOEt (2×10 ml). The combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), and concentrated in vacuum. Purification by CC (AcOEt/hexane 1:4) afforded unreacted **14** (10% starting from **16**) and **17** (0.98 g, 53% starting from **16**). Colorless liquid. $[\alpha]_D^{30} = -2.53$ ($c = 1.04$, $CHCl_3$). IR (neat): 3018, 2977, 2926, 2852, 1697, 1514, 1454, 1390, 1368, 1253, 1214, 1168, 1101, 1045, 926, 867, 751, 667, 626. ^{1}H-NMR (300 MHz, $CDCl_3$; * = doubling of signals may be due to rotamers): 5.75 (*s*, 1 H); 5.08 (*s*, 1 H); 4.63 (*s*, 2 H); 4.57–4.37 (*m*, 1 H); 4.18–4.02 (*m*, 2 H); 3.37 (*s*, 3 H); 2.84–2.64* (*m*, 1 H); 2.59–2.38* (*m*, 1 H); 1.62 (*s*, 3 H); 1.50 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major rotamer): 151.9; 145.4; 125.1; 95.8; 95.0; 83.2; 80.2; 65.5; 59.2; 55.2; 41.2; 28.4; 27.3; 24.9. HR-ESI-MS: 336.1781 ($[M + Na]^+$, $C_{16}H_{27}NNaO_5^+$; calc. 336.1781).

tert-*Butyl (3a*S,*5*S,*6*S,*6a*S*)-3,3a,4,5-Tetrahydro-6-hydroxy-5-[(methoxymethoxy)methyl]-2,2-dimethyl-2*H*-cyclopenta[*d*][1,3]oxazole-3(3a*H*)-carboxylate* (**18**). To the stirred soln. of **17** (1.0 g, 3.19 mmol) in THF (4 ml), $BH_3 \cdot Me_2S$ (0.60 ml, 6.38 mmol) was added dropwise at $-10°$. Stirring was continued for 3 h at r.t. The reaction was quenched by the addition of 10% NaOH (1 ml), followed by 30% H_2O_2 (2 ml) at 0°, and the mixture was allowed to warm to r.t., and stirring was continued for another 2 h. The mixture was extracted with AcOEt (3×50 ml), and combined org. extracts were washed with H_2O and brine, and dried (Na_2SO_4). The solvent was evaporated on a rotary evaporator, and the residue was purified by CC (AcOEt/hexane 3:7) to give pure **18** (0.64 g, 60%). Colorless liquid. $[\alpha]_D^{30} = -6.8$ ($c = 0.5$, $CHCl_3$). IR (neat): 3019, 1549, 1515, 1447, 1214, 1044, 928, 876, 742, 667, 626. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.62 (*s*, 2 H); 4.44–4.15 (*m*, 2 H); 4.05 (*dd*, $J = 2.2$, 5.6, 1 H); 3.67 (*dd*, $J = 5.6$, 9.4, 1 H); 3.63–3.53 (*m*, 1 H); 3.36 (*s*, 3 H); 2.44–2.15 (*m*, 3 H); 1.68–1.55 (*s*, 3 H); 1.45 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$; major rotamer): 151.9; 96.5; 96.1; 85.8; 80.3; 79.5; 69.7; 59.5; 55.2; 47.1; 34.9; 28.4; 27.1; 23.7. HR-ESI-MS: 354.1887 ($[M + Na]^+$, $C_{16}H_{29}NNaO_6^+$; calc. 354.1883).

*(1*S,*2*S,*3*S,*5*S*)-3-(Acetylamino)-5-[(acetyloxy)methyl]cyclopentane-1,2-diyl Diacetate* (**7**). To a soln. of **18** (0.5 g, 1.51 mmol) in MeOH was added 6N HCl (4 ml) at 0°, and the mixture was stirred at reflux for 24 h. Then, the soln. was concentrated under reduced pressure. The crude was dissolved in pyridine (2 ml), and Ac_2O was added at 0°, and the mixture was stirred for 12 h. Pyridine was evaporated, and the residue was extracted with AcOEt and H_2O, and the combined org. extracts were washed with H_2O and brine, and dried (Na_2SO_4). The solvent was removed with a rotary evaporator, and the residue was purified by CC (AcOEt/hexane 3:1) to give pure **7** (0.44 g, 92%). White solid. M.p. 125–126°. (*ent*-**7**: 124–125°) [18]. $[\alpha]_D^{30} = -31.0$ ($c = 0.2$, $CHCl_3$), (*ent*-**7**: $[\alpha]_D^{29} = +31.3$) [18]. IR (neat): 3292, 2924, 2853, 1738, 1654, 1545, 1369, 1224, 1045, 932, 771, 603. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.60 (*d*, $J = 7.7$, NH); 5.08 (*dd*, $J = 2.2$, 5.1, 1 H); 4.91 (*dd*, $J = 2.2$, 4.6, 1 H); 4.62–4.55 (*m*, 1 H); 4.16 (*dd*, $J = 6.4$, 11.1, 1 H); 4.09 (*dd*, $J = 6.5$, 11.1, 1 H); 2.39–2.31 (*m*, 1 H); 2.29–2.26 (*m*, 1 H); 2.12 (*s*, 3 H); 2.06 (*s* 6 H); 1.99 (*s*, 3 H); 1.48–1.40 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.8; 169.8; 169.7; 169.5; 77.5; 64.9; 49.4; 41.5; 32.0; 23.1; 20.8; 20.8, 20.8, 20.8. HR-ESI-MS: 338.1206 ($[M + Na]^+$, $C_{14}H_{21}NNaO_7^+$; 338.1207).

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