Toward the Total Syntheses of Pepluanin A and Euphosalicin: Concise Route to a Highly Oxygenated Cyclopentane as a Common Intermediate

Michael W. Gilbert, Anna Galkina, Johann Mulzer*

Institut für Organische Chemie, Währingerstrasse 38, 1090 Wien, Austria
Fax +43(1)427752189; E-mail: johann.mulzer@univie.ac.at

Received 22 September 2004

Abstract: A substrate controlled asymmetric synthesis is described of a highly functionalized cyclopentanyl vinyl triflate which serves as an advanced intermediate in the total synthesis of the novel multidrug resistance reversing jatrophanes pepluanin A and euphosalicin. Key steps are a Claisen–Eschenmoser rearrangement followed by hydroxy-lactonization, intramolecular trans-lactonization, Davis hydroxylation and regioselective enoltriflate formation.

Keywords: oxygenated cyclopentanes, Eschenmoser–Claisen rearrangement, lactonization, Davis oxidation, enol triflate

One of the major problems of cancer chemotherapy is intrinsic or acquired multi-drug resistance (MDR). A primary mechanism of MDR is attributed to the overexpression of P-glycoprotein (P-gp) in the plasma membrane or resistant cells where the P-gp acts as an energy-dependent efflux pump, reducing intracellular accumulation of anticancer drugs.[1] A number of drugs, such as calcium channel blockers, calmodulin inhibitors, and indole alkaloids are known to reverse MDR by competing with anticancer drugs for binding to P-gp. However, they have not been proven clinically useful yet. For example, verapamil, the most extensively studied MDR reversing agent, induces cardiovascular toxicity at the concentration that it reverses MDR.[2] Thus, there remains a need to develop new classes of MDR reversing agents with less toxicity to the host.

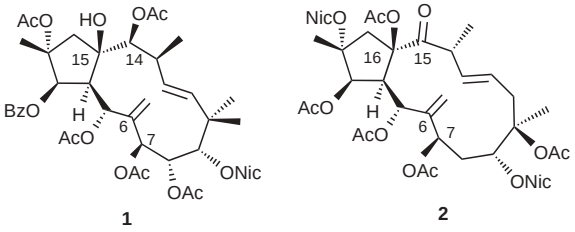
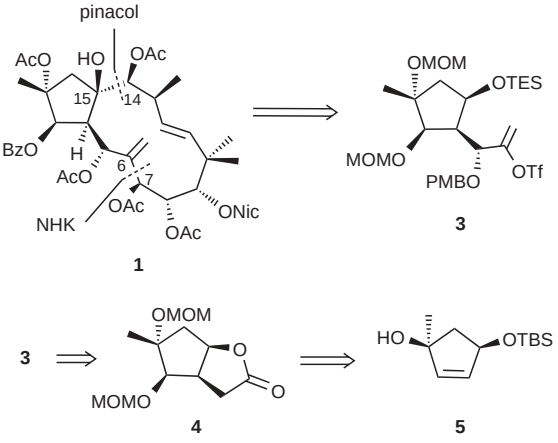


Figure 1 Pepluanin A (**1**) and euphosalicin (**2**).

The *Euphorbiaceae* (spurge) family is known to produce various highly functionalized, structurally unique macrocyclic diterpenes. The MDR-reversing effect of lipophilic extracts of *Euphorbia esula L.*, *E. peplus L.*, *E. salicifolia*, and *E. serrulata* was tested on mouse lymphoma cells.[3] From the active extracts, a series of structurally related compounds with significant P-gp inhibitory activity was isolated, including pepluanin A (**1**) and euphosalicin (**2**, Figure 1).

To allow for a more detailed study of the MDR-related activities and to further analyze the structure activity relationships, it is highly desirable to develop a general synthetic access to pepluanin A (**1**) and euphosalicin (**2**) as well as other structurally related jatrophane natural products.[4] Structural analysis of **1** and **2** revealed that the differences in the oxygenation patterns and carbon skeletons primarily lie in the C7-14 segment of the larger ring. Retrosynthetic analysis suggested that at a late stage formation of bonds C14-15 and C6-7 might be achieved via pinacol and Nozaki–Hiyama–Kishi (NHK) type couplings, respectively (Scheme 1). Triflate **3** could thus serve as a versatile coupling partner and allow synthetic access to several natural products upon preparation of the corresponding C7-14 segments. It was envisaged that triflate **3** should be available from the bicyclic lactone **4** via stereoselective α-hydroxylation and ring-opening of the lactone. We hoped to prepare **4** from alcohol **5** and establish the synthetically challenging oxygenation pattern via a series of transformations including an epoxide-opening step to introduce the *trans*-1,2-diol moiety on the ring.



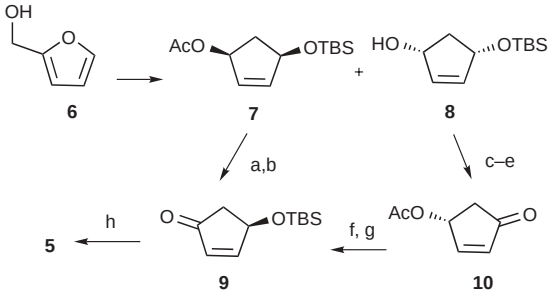
Scheme 1 Retrosynthetic analysis.

Prior to tackling the synthesis of **3**, we first investigated alternative preparations of the known alcohol **5**.[5] Following a protocol by Curran and co-workers,[6] commercially available furfuryl alcohol (**6**) was elaborated into a separable mixture of acetate **7** (13%, 98% ee) and alcohol **8** (13%, 98% ee, Scheme 2). Using well-established chemistry,[7] compounds **7** and **8** were then converted to a

SYNLETT 2004, No. 14, pp 2558–2562
Advanced online publication: 20.10.2004
DOI: 10.1055/s-2004-834822; Art ID: G36704ST

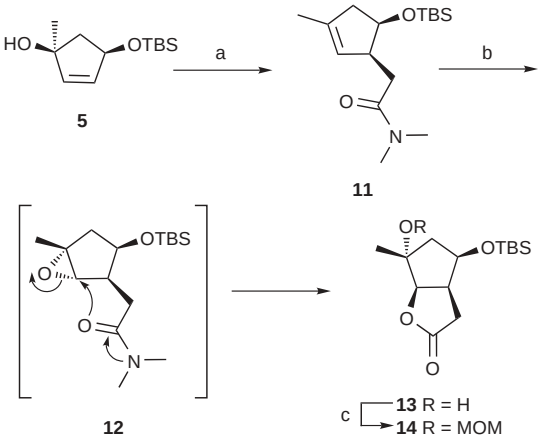
common intermediate, ketone **9**, in two and five steps, respectively.[8,9] Finally, treatment of **9** with MeLi furnished the desired tertiary alcohol **5** in good yield.[5]

With multigram quantities of enantiomerically enriched alcohol **5** in hand, the first steps in the elaboration of the 5-membered ring were investigated. Subjection of the allylic alcohol **5** to the Claisen–Eschenmoser rearrangement protocol[10] afforded *N*,*N*-dimethyl amide **11** in good yield (Scheme 3). A completely stereoselective epoxidation of the double bond in **11** from the less hindered β-face was then accomplished by treatment of **11** with in situ generated DMDO.[11]

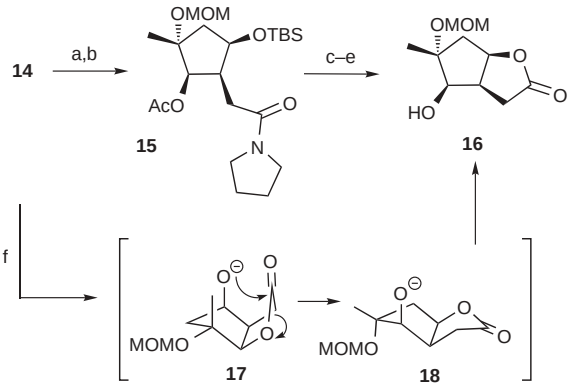


Scheme 2 *Reagents*: (a) K_2CO_3, MeOH (94%); (b) PDC (88%); (c) Ac_2O, Et_3N, DMAP (99%); (d) TBAF (82%); (e) PDC (96%); (f) K_2CO_3, MeOH (99%); (g) TBSCl, Et_3N, DMAP (86%); (h) MeLi (89%).

Fortuitously, the next step in our synthesis, regioselective opening of the epoxide, occurred spontaneously upon flash chromatography of the unstable epoxide **12**. NMR analysis of the product confirmed the bicyclic lactone structure **13**. Thus, the newly formed epoxide had been opened by an internal attack of the neighboring amide carbonyl group, affording the desired *trans*-1,2-diol moiety. The tertiary alcohol in **13** was then protected as the MOM ether (**14**). The next series of steps were intended for the migration of the lactone function in **14** from the oxygenated C2 position on the cyclopentyl ring to the oxygenated C5 position (Scheme 4). The lactone in **14** was opened with pyrrolidine and the resulting alcohol was protected as an acetate **15**. Upon optimization of our synthesis, this five-step sequence was replaced by one simple high yielding step. Removal of the TBS protection group liberated the C5 alcohol in **15**, which was utilized in the desired lactonization. Subsequent deacetylation afforded alcohol **16**. Indeed, treatment of **14** with TBAF for 18 hours at room temperature directly afforded the desired lactone **16** in 88% yield. From a mechanistic point of view, the alkoxide generated upon TBAF-desilylation of **14** apparently adopted conformation **17** suitable for an intramolecular *trans*-lactonization. Protonation of the resulting alkoxide **18** would then directly give alcohol **16**. Upon MOM protection of the sterically hindered free hydroxyl at C2 in **16** to give **4**, the stage was set to introduce the last point of oxygenation (Scheme 5). The topology of the *cis*-fused bicycle **16** exposes a convex face, which appears to be significantly less sterically hindered than the corresponding face.

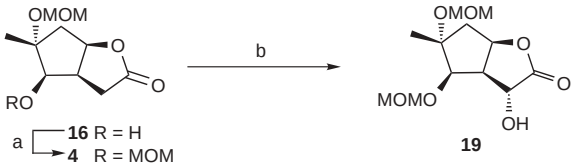


Scheme 3 *Reagents*: (a) $(MeO)_2C(Me)NMe_2$ (85%); (b) oxone, acetone, 18-crown-6, $NaHCO_3$, (80%); (c) MOMCl, Et*N*i-Pr_2 (81%).



Scheme 4 *Reagents*: (a) Pyrrolidine (97%); (b) Ac_2O, pyridine (92%); (c) TBAF (73%); (d) CSA (79%); (e) K_2CO_3, MeOH (89%); (f) TBAF (88%).

This difference was thought to be sufficient to direct the stereoselective introduction of a hydroxyl group next to the carbonyl. Indeed, the hydroxylation step was smoothly achieved by treatment of **4** with KHMDS at –78 °C followed by addition of a cold solution of Davis' oxaziridine[12] yielding the desired alcohol **19**. The relative configuration of the newly introduced hydroxyl group in **19** was confirmed by ^{1}H 2D NOESY experiments. Among the noted cross peaks, strong correlations were detected between the proton adjacent to the newly introduced hydroxyl, H_a, and the ring methyl group, Me_a (Figure 2).



Scheme 5 *Reagents*: (a) MOMCl, NaI, Et*N*i-Pr_2 (86%); (b) KHMDS, Davis' reagent; CSA (74%).

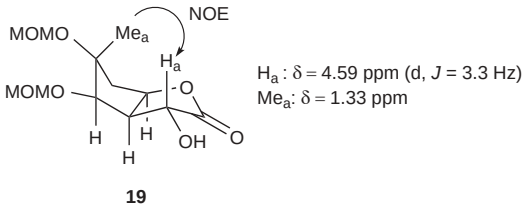


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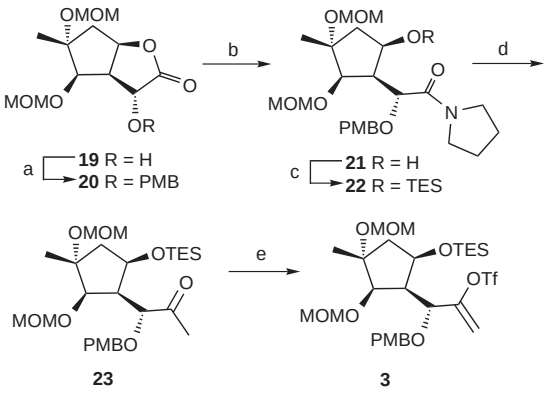
Figure 2

The final steps in the preparation of our target intermediate **3** began with a PMB protection of the newly introduced hydroxyl to give **20** (Scheme 6). The lactone in **20** was then opened with pyrrolidine to give amide **21** and the resulting free hydroxl group was then TES protected to give **22**. The pyrrolidine amide **22** was then converted to the corresponding methyl ketone **23** by addition of two equivalents of methyl lithium at 0 °C. Although more than one equivalent of MeLi was required for this reaction to go to completion, none of the double addition product was detected. The final step in this sequence, regioselective vinyl triflate formation, was accomplished by first deprotonating the methyl ketone **23** under kinetically controlled conditions. The resulting enolate was then quenched with $PhNTf_2$ to give **3** in excellent yield.

In summary, we have prepared the highly functionalized triflate **3** from enantiomerically enriched alcohol **5** via an eleven-step sequence[13] that incorporates highly stereoselective epoxidation and subsequent intramolecular ring-opening reactions, allowing for the establishment of the oxygenation pattern with the desired relative and absolute configuration. The advanced intermediate **3** should allow synthetic access to a multitude of jatrophane natural products and the preparation of the coupling partners required for the synthesis of polyesters pepluanin A (**1**) and euphosalicin (**2**) is currently underway in our laboratory.



Scheme 6 *Reagents*: (a) $PMBOC(NH)CCl_3$, CSA (87%); (b) pyrrolidine (91%); (c) TESCl, pyridine (88%); (d) MeLi (81%); (e) KHMDS, $PhNTf_2$ (91%).

Acknowledgment

Financial support by the Austrian Science Foundation (FWF, project P15929-N03) is gratefully acknowledged. We also thank Hanspeter Kählig for NMR support.

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(13) **Experimental Details**.
2-[(1*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylcyclopent-2-enyl]-*N*,*N*-dimethylacetamide (11). To a stirred solution of alcohol **4** (13.9 g, 61.0 mmol) in toluene (30 mL) *N*,*N*-dimethlyacetamide dimethoxy acetal (24.6 g, 183.0 mmol) was added dropwise. The mixture was heated to reflux for 48 h, during which time the generated MeOH was allowed to distill out. The volatiles were removed under reduced pressure and the resulting crude material was purified by flash chromatography (5:1 hexane–EtOAc) to give amide **11** (15.5 g, 52.0 mmol, 85% yield) as a clear yellow oil: R_f = 0.31 (hexane–EtOAc = 2:1); $[\alpha]_D^{20}$ +24.4 (*c* 1.1, acetone). IR (thin film): ν = 3035, 2929, 2856, 1652, 1471, 1397 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.68 (s, 3 H), 2.10–2.25 (m, 2 H), 2.43 (dd, *J* = 16.0, 6.7 Hz, 1 H), 2.62 (dd, *J* = 16.0, 6.8 Hz, 1 H), 2.92 (s, 3 H), 2.97 (s, 3 H), 3.09–3.17 (m, 1 H), 4.48–4.54 (m, 1 H), 5.25–5.30 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.1, –4.7, 17.0, 18.1, 25.8, 32.3, 35.3, 37.1, 45.6, 46.1, 73.6, 127.0, 137.7, 172.8 ppm. MS (EI, 70eV): *m/z* (%) = 297 (1) [M^+], 240 (42), 72 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_{31}NO_2Si$ [M^+]: 297.2124; found: 297.2127.
(3a*S*,4*R*,6*R*,6a*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-6-methyl-hexahydrocyclopenta[*b*]furan-2-one (13). To a cool (0 °C), stirred solution of amide **11** (15.0 g, 50.3 mmol) and 18-crown-6 ether (1.0 g, 3.8 mmol) in a mixture of 1:1:1 CH_2Cl_2–acetone–H_2O (450 mL) was added $NaHCO_3$ (32.0 g, 381 mmol) portionwise over 20 min. A solution of oxone (60.0 g, 100 mmol) in H_2O (300 mL) was added dropwise over 1 h. The resulting mixture was allowed to stir for another 2 h at 0 °C, EtOAc (200 mL) was then added and the layers were separated. Usual workup and flash chromatography (2:1 hexane–EtOAc gave lactone **13** (11.5 g, 40.2 mmol, 80% yield) as a clear colorless oil: R_f = 0.17 (hexane–EtOAc = 2:1); $[\alpha]_D^{20}$ –26.6 (*c* 0.95, acetone). IR (thin film): ν = 3440, 2957, 2931, 1778, 1472 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.40 (s, 3 H), 1.53–1.65 (m, 2 H), 1.97 (dd, *J* = 13.6, 6.3 Hz, 1 H), 2.44 (dd, *J* = 18.8, 10.9 Hz, 1 H), 2.98 (dd, *J* = 18.8, 2.9 Hz, 1 H), 3.09–3.18 (m, 1 H), 4.41 (dd, *J* = 6.6, 1.5 Hz, 1 H), 4.52–4.59 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.0, –4.8, 18.0, 23.6, 25.7, 28.0, 41.4, 45.3, 71.1, 78.4, 89.9, 177.6 ppm. MS (EI, 70eV): *m/z* (%) = 229 (41) [M – *t*-Bu]$^+$, 137 (42), 75 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_{17}O_4Si$ [M – *t*-Bu]$^+$: 229.0896; found: 229.0901.

(3a*S*,4*R*,6*R*,6a*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(methoxymethoxy)-6-methyl-hexahydrocyclopenta[*b*]furan-2-one (14). To a cool (0 °C), stirred solution of alcohol **13** (11.2 g, 39.3 mmol) and *i*-Pr_2NEt (25.2 g, 194 mmol) in dry CH_2Cl_2 (100 mL) was added MOMCl (9.5 g, 118 mmol) dropwise over 15 min. The resulting mixture was allowed to warm to r.t. and stirred for 48 h. Sat. aq $NaHCO_3$ (25 mL) was added and usual workup including flash chromatography (3:1 hexane–EtOAc) gave MOM ether **14** (10.5 g, 31.8 mmol, 81% yield) as a clear colorless oil: R_f = 0.39 (2:1 hexane–EtOAc); $[\alpha]_D^{20}$ –21.3 (*c* 1.2, acetone). IR (thin film): ν = 2957, 2823, 1789, 1471 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 1.37 (s, 3 H), 1.50 (dd, *J* = 13.9, 9.3 Hz, 1 H), 2.18 (dd, *J* = 13.9, 6.4 Hz, 1 H), 2.45 (dd, *J* = 18.7, 10.9 Hz, 1 H), 2.98 (dd, *J* = 18.7, 2.9 Hz, 1 H), 3.05–3.08 (m, 1 H), 3.37 (s, 3 H), 4.50 (ddd, *J* = 9.3, 8.3, 6.4 Hz, 1 H), 4.58 (dd, *J* = 6.6, 1.5 Hz, 1 H), 4.65–4.70 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.1, –4.7, 18.0, 18.9, 25.7, 28.0, 41.4, 43.7, 55.7, 71.0, 83.8, 88.5, 91.3, 177.4 ppm. MS (EI, 70eV): *m/z* (%) = 273 (21) [M – *t*-Bu]$^+$, 243 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{21}O_5Si$ [M – *t*-Bu]$^+$: 273.1158; found: 273.1161.

(3a*S*,4*R*,5*R*,6a*R*)-4-Hydroxy-5-(methoxymethoxy)-5-methyl-hexahydrocyclopenta[*b*]furan-2-one (16). To a stirred solution of silyl ether **14** (9.50 g, 28.8 mmol) in dry THF (40 mL) was added a solution of TBAF (1 M in THF, 43.2 mL, 43.2 mmol). The mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure and the resulting crude material was subjected to flash chromatography (1:1 hexane–EtOAc) to give alcohol **16** (5.47 g, 25.3 mmol, 88% yield) as a clear colorless oil: R_f = 0.3 (100% EtOAc); $[\alpha]_D^{20}$ –15.1 (*c* 1.2, $CHCl_3$). IR (thin film): ν = 3443, 2940, 2825, 1769, 1644, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 2.03 (dd, *J* = 14.8, 3.5 Hz, 1 H), 2.39 (dd, *J* = 14.8, 6.8 Hz, 1 H), 2.56 (dd, *J* = 18.4, 11.1 Hz, 1 H), 2.60 (br s, 1 H), 2.81 (dd, *J* = 18.4, 2.8 Hz, 1 H), 3.18–3.26 (m, 1 H), 3.38 (s, 3 H), 3.97 (dd, *J* = 6.5, 2.6 Hz, 1 H), 4.63 (d, *J* = 7.6 Hz, 1 H), 4.75 (d, *J* = 7.6 Hz, 1 H), 4.99 (ddd, *J* = 7.5, 6.8, 3.5 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.8, 28.7, 41.3, 42.4, 55.8, 77.9, 83.2, 86.7, 91.3, 177.9 ppm. MS (EI, 70eV): *m/z* (%) = 216 (1) [M$^+$], 171 (46), 153 (65), 57 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_{16}O_5$ [M$^+$]: 216.0998; found: 216.0993.

(3a*R*,4*R*,5*R*,6a*R*)-4,5-*Bis*(methoxymethoxy)-5-methyl-hexahydrocyclopenta[*b*]furan-2-one (4). To a cool (0 °C), stirred solution of alcohol **16** (950 mg, 4.40 mmol) and *i*-Pr_2NEt (2.84 g, 22.00 mmol) in dry CH_2Cl_2 (20 mL) was added MOMCl (1.06 g, 13.20 mmol) dropwise over 15 min. NaI (20 mg, 0.13 mmol) was added and the resulting mixture was heated to reflux for 18 h. The mixture was allowed to cool to r.t., sat. aq $NaHCO_3$ (10 mL) was added. Usual workup and flash chromatography (1:1 hexane–EtOAc) gave MOM ether **4** (984 mg, 3.79 mmol, 86% yield) as a clear colorless oil: R_f = 0.38 (100% EtOAc); $[\alpha]_D^{20}$ +28.5 (*c* 1.1, $CHCl_3$). IR (thin film): ν = 2947, 2896, 1772, 1451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.93 (dd, *J* = 14.8, 4.2 Hz, 1 H), 2.44 (ddd, *J* = 14.8, 7.2, 1.3 Hz, 1 H), 2.58 (dd, *J* = 18.0, 10.1 Hz, 1 H), 2.68 (dd, *J* = 18.0, 2.8 Hz, 1 H), 3.10–3.25 (m, 1 H), 3.33 (s, 3 H), 3.41 (s, 3 H), 3.86 (d, *J* = 5.8 Hz, 1 H), 4.55–4,70 (m, 4 H), 4.97 (dd, *J* = 7.5, 7.5, 4.3 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.4, 29.5, 41.6, 42.7, 55.7, 56.6, 83.7, 85.3, 87.3, 91.4, 98.2, 177.5 ppm. MS (EI, 70eV): *m/z* (%) = 260 (2) [M$^+$], 240 (25), 215 (74), 198 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{20}O6$ [M$^+$]: 260.1260; found: 260.1264.

(3*R*,3a*R*,4*R*,5*R*,6a*R*)-3-Hydroxy-4,5-*bis*(methoxymethoxy)-5-methyl-hexahydrocyclopenta[*b*]furan-2-one (19). To a cold (–78 ºC), stirred solution of lactone **4** (850 mg, 3.27 mmol) in dry THF (40 mL) was added a solution of KHMDS (0.5 M in toluene, 9.80 mL, 4.90 mmol). The mixture was stirred for 1 h at –78 ºC and a cold (–78 ºC) solution of Davis' reagent [2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine] (1.28 g, 4.90 mmol) in dry THF (5 mL) was added via a cannula. The mixture was stirred for an additional 30 min at –78 ºC and a solution of CSA (1.14 g, 4.90 mmol) in dry THF (5 mL) was added via a cannula. The resulting mixture was allowed to warm to r.t. over 1 h and sat. aq NH_4Cl (15 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). Usual workup including flash chromatography (1:1 hexane–EtOAc) gave alcohol **19** (665 mg, 2.41 mmol, 74% yield) as a clear colorless oil: R_f = 0.36 (100% EtOAc); $[\alpha]_D^{20}$ +21.6 (*c* 1.1, $CHCl_3$). IR (thin film): ν = 3385, 2948, 1770, 1640, 1567, 1447 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.86 (dd, *J* = 14.5, 5.2 Hz, 1 H), 2.42 (ddd, *J* = 14.5, 7.2, 1.3 Hz, 1 H), 2.88 (br s, 1 H), 3.16 (ddd, *J* = 7.9, 6.6, 3.3 Hz, 1 H), 3.35 (s, 3 H), 3.42 (s, 3 H), 4.08 (dd, *J* = 6.6, 1.3, 1 H), 4.59 (d, *J* = 3.3 Hz, 1 H), 4.65–4.72 (m, 4 H), 5.10 (ddd, *J* = 7.9, 7.2, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.4, 42.2, 49.7, 55.8, 56.5, 68.9, 82.1, 83.4, 87.0, 91.4, 97.9, 177.6 ppm. MS (EI, 70eV): *m/z* (%) = 276 (2) [M$^+$], 231 (25), 214 (51), 77 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{20}O_7$ [M$^+$]: 276.1209; found: 276.1217.

(3*R*,3a*R*,4*R*,5*R*,6a*R*)-3-(4-Methoxybenzyloxy)-4,5-*bis*(methoxymethoxy)-5-methyl-hexahydrocyclopenta[*b*]furan-2-one (20). To a stirred solution of alcohol **19** (505 mg, 1.83 mmol) in dry CH_2Cl_2 (25 mL) was added $PMBOC(=N)CCl_3$ (780 mg, 2.74 mmol) and CSA (42 mg, 0.18 mmol). The resulting mixture was stirred for 18 h at r.t. Sat. aq $NaHCO_3$ (10 mL) was then added and the resulting layers were separated. Usual workup including flash chromatography (2:1 hexane–EtOAc) gave PMB ether **20** (630 mg, 1.59 mmol, 87% yield) as a clear colorless oil: R_f = 0.16 (2:1 hexane–EtOAc); $[\alpha]^{20}_D$ +48.6 (*c* 1.1, $CHCl_3$). IR (thin film): ν = 3277, 2948, 1769, 1731, 1613, 1586, 1447 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.90 (dd, *J* = 14.9, 4.3 Hz, 1 H), 2.44 (ddd, *J* = 14.9, 7.3, 1.2 Hz, 1 H), 3.12 (ddd, *J* = 7.4, 5.9, 1.5 Hz, 1 H), 3.30 (s, 3 H), 3.32 (s, 3 H), 3.80 (s, 3 H), 3.97 (d, *J* = 6.3 Hz, 1 H), 4.20 (d, *J* = 1.5 Hz, 1 H), 4.40–4.80 (m, 6 H), 5.10 (ddd, *J* = 7.4, 7.4, 4.2 Hz, 1 H), 6.9 (d, *J* = 8.6 Hz, 2 H), 7.30 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 42.4, 49.5, 55.3, 55.8, 56.6, 71.7, 74.4, 82.9, 84.3, 87.4, 91.4, 98.0, 113.9, 129.2, 130.1, 159.5, 175.0 ppm. MS (EI, 70eV): *m/z* (%) = 396 (1) [M$^+$], 275 (3), 137 (24), 121 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{28}O_8$ [M$^+$]: 396.1786; found: 396.1775.

(*R*)-2-(4-Methoxybenzyloxy)-2-[(1*R*,2*R*,3*R*,5*R*)-5-hydroxy-2,3-*bis*(methoxymethoxy)-3-methylcyclopentyl]-1-(pyrrolidin-1-yl)ethanone (21). To a stirred solution of lactone **20** (504 mg, 1.27 mmol) in dry toluene (5 mL) was added pyrrolidine (524 μL, 6.40 mmol). The resulting mixture was heated to reflux for 18 h. The mixture

was allowed to cool to r.t. and the volatiles were removed under reduced pressure. The resulting crude material was subjected to flash chromatography (EtOAc) to give amide **21** (541 mg, 1.16 mmol, 91% yield) with traces amount of pyrrolidine as a clear orange oil: R_f = 0.9 (EtOAc); $[\alpha]_D^{20}$ –13.3 (*c* 1.0, $CHCl_3$). IR (thin film): ν = 3450, 2957, 2882, 1774, 1631, 1514, 1449 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.72–1.95 (m, 5 H), 2.44 (dd, *J* = 14.6, 7.1 Hz, 1 H), 2.77 (m, 1 H), 3.31 (s, 3 H), 3.32–3.38 (m, 1 H), 3.40 (s, 3 H), 3.45–3.60 (m, 4 H), 3.79 (s, 3 H), 4.03 (d, *J* = 3.8 Hz, 1 H), 4.12–4.20 (m, 1 H), 4.40 (d, *J* = 10.9 Hz, 1 H), 4.48 (d, *J* = 10.9 Hz, 1 H), 4.53 (d, *J* = 11.1 Hz, 1 H), 4.62 and 4.69 (m, 3 H), 4.76 (d, *J* = 6.6 Hz, 1 H), 6.86 (br d, *J* = 8.8 Hz, 2 H), 7.24 (br d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.0, 23.9, 26.8, 46.7, 46.9, 48.2, 50.0, 55.7, 55.9, 57.0, 71.2, 72.9, 76.9, 86.8, 86.9, 91.9, 99.0, 114.2, 129.7, 130.0, 159.7, 171.2 ppm. MS (EI, 70eV): *m/z* (%) = 422 (1) $[M – MOM]^+$, 210 (13), 137 (27), 121 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{22}H_{32}O_7N$ $[M – MOM]^+$: 422.2179; found: 422.2191.

(*R*)-2-[(1*R*,2*R*,3*R*,5*R*)-2,3-*Bis*(methoxymethoxy)-3-methyl-5-(triethylsilyloxy)cyclopentyl]-2-(4-methoxybenzyloxy)-1-(pyrrolidin-1-yl)ethanone (22). To a stirred solution of alcohol **21** (392 mg, 0.84 mmol) in dry CH_2Cl_2 (10 mL) was added pyridine (200 μL, 2.5 mmol). TESCl (212 μL, 1.26 mmol) was added and the resulting mixture was stirred at r.t. for 1 h. Sat. aq NH_4Cl (5 mL) was added. Usual workup including flash chromatography (2:1 hexane–EtOAc) gave TES ether **22** (430 mg, 0.74 mmol, 88% yield) as a clear colorless oil: R_f = 0.21 (hexane–EtOAc = 2:1); $[\alpha]_D^{20}$ –34.0 (*c* 0.6, $CHCl_3$). IR (thin film): ν = 3854, 3822, 1646, 1613, 1586, 1441 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.51 (q, *J* = 7.9 Hz, 6 H), 0.91 (t, *J* = 7.9 Hz, 9 H), 1.40 (s, 3 H), 1.73 (dd, *J* = 13.8, 5.4 Hz, 1 H), 1.75–1.95 (m, 4 H), 2.38 (dd, *J* = 13.8, 6.8 Hz, 1 H), 3.28–3.35 (m, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.40–3.55 (m, 3 H), 3.58–3.68 (m, 1 H), 3.78 (s, 3 H), 3.85 (d, *J* = 4.3 Hz, 1 H), 4.29 (d, *J* = 10.8 Hz, 1 H), 4.49 (d, *J* = 10.8 Hz, 1 H), 4.51–4.58 (m, 1 H), 4.61–4.72 (m, 4 H), 4.83 (d, *J* = 6.3 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 4.8, 6.8, 19.7, 24.2, 26.1, 45.3, 45.5, 45.8, 47.6, 55.2, 55.7, 56.4, 66.6, 72.6, 73.7, 85.2, 86.3, 91.4, 98.44, 113.6, 129.3, 130.9, 158.9, 168.3 ppm. MS (EI, 70eV): *m/z* (%) = 582 (2) $[M^+]$, 552 (9) $[M – Et]^+$, 324 (34), 121 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{28}H_{46}O_8NSi$ $[M – Et]^+$: 552.2883; found: 552. 2881.

(*R*)-1-[(1*R*,2*R*,3*R*,5*R*)-2,3-*Bis*(methoxymethoxy)-3-methyl-5-(triethylsilyloxy)cyclopentyl]-1-(4-methoxybenzyloxy)propan-2-one (23). To a cool (0 ºC), stirred solution of amide **22** (362 mg, 0.623 mmol) in dry THF (10 mL) was added a solution of MeLi (1.6 M in Et_2O, 0.780 mL, 1.240 mmol) dropwise over 30 min. The mixture was stirred for an additional 15 min at 0 ºC and sat. aq NH_4Cl (5 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL). Usual workup and flash chromato-graphy (5:1 hexane–EtOAc) gave methyl ketone **23** (265 mg, 0.503 mmol, 81% yield) as a clear colorless oil: R_f = 0.42 (2:1 hexane–EtOAc); $[\alpha]_D^{20}$ –5.5 (*c* 1.7, $CHCl_3$). IR (thin film): ν = 2955, 2878, 1715, 1613, 1586, 1515, 1458 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.58 (q, *J* = 8.0 Hz, 6 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 1.34 (s, 3 H), 1.82 (dd, *J* = 13.6, 7.6 Hz, 1 H), 2.20–2.29 (m, 4 H), 3.00 (m, 1 H), 3.33 (s, 3 H), 3.35 (s, 3 H), 3.80 (s, 3 H), 3.98 (d, *J* = 5.8 Hz, 1 H), 4.18 (d, *J* = 7.8 Hz, 1 H), 4.38 (ddd, *J* = 7.6, 7.5, 7.3 Hz, 1 H), 4.42 (s, 2 H), 4.52–4.72 (m, 4 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 4.8, 6.7, 20.0, 26.9, 47.0, 49.0, 55.2, 55.4, 56.3, 70.8, 71.1, 81.4, 85.1, 86.0, 91.5, 97.8, 113.8, 129.5, 130.1, 159.2, 210.0 ppm. MS (EI, 70eV): *m/z* (%) = 497 (0.5) $[M – MeO]^+$, 465 (1), 390 (3), 121 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{25}H_{41}O_8Si$ $[M – MeO]^+$: 497.2571; found: 497.2559.

(*R*)-1-[(1*S*,2*R*,3*R*,5*R*)-2,3-*Bis*(methoxymethoxy)-3-methyl-5-(triethylsilyloxy)cyclopentyl]-1-(4-methoxybenzyloxy)prop-2-en-2-yl Trifluoro-methanesulfonate (3). To a cold (–78 ºC), stirred solution of methyl ketone **23** (201 mg, 0.381 mmol) in dry THF (10 mL) was added a solution of KHMDS (0.5 M in toluene, 0.84 mL, 0.42 mmol). The mixture was stirred for 1 h at –78 ºC and a cold (–78 ºC) solution of $PhNTf_2$ (204 mg, 0.57 mmol) in dry THF (1 mL) was added via a cannula. The mixture was stirred for an additional 10 min at –78 ºC and then allowed to warm to r.t. over 1 h. Sat. aq NH_4Cl (5 mL) was added and the resulting layers were separated. Usual workup and flash chromatography (50:10:1 hexane–EtOAc–Et_3N) gave vinyltriflate **3** (229 mg, 0.348 mmol, 91% yield) as a clear colorless oil: R_f = 0.55 (2:1 hexane–EtOAc); $[\alpha]_D^{20}$ –3.3 (*c* 0.9, $CHCl_3$). IR (thin film): ν = 2956, 1664, 1613, 1515, 1443, 1417 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (q, *J* = 7.9 Hz, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.39 (s, 3 H), 1.77 (dd, *J* = 14.2, 4.2 Hz, 1 H), 2.39 (dd, *J* = 14.2, 6.4 Hz, 1 H), 2.71–2.78 (m, 1 H), 3.31 (s, 3 H), 3.38 (s, 3 H), 3.79 (s, 3 H), 3.89 (d, *J* = 4.5 Hz, 1 H), 4.18 (d, *J* = 10.1 Hz, 1 H), 4.32 (d, *J* = 10.4 Hz, 1 H), 4.37 (ddd, *J* = 6.9, 6.4, 4.2 Hz, 1 H), 4.59–4.71 (m, 5 H), 5.24 (d, *J* = 3.4 Hz, 1 H), 5.39 (d, *J* = 3.4 Hz, 1 H), 6.86 (br d, *J* = 8.6 Hz, 2 H), 7.28 (br d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 4.9, 6.8, 20.0, 48.3, 48.5, 55.2, 55.5, 56.3, 69.9, 71.6, 76.6, 85.9, 86.7, 91.4, 98.9, 108.5, 113.7, 118.4 (q, CF_3), 129.5, 129.9, 152.7, 159.1 ppm. MS (EI, 70eV): *m/z* (%) = 613 (1) $[M – MOM]^+$, 283 (3), 181 (5), 135 (8), 121 (100). HRMS (EI, 70 eV): *m/z* calcd for $C_{26}H_{40}O_9F_3SSi$ $[M – MOM]^+$: 613.2114; found: 613.2097.