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Synthesis of (+) and (-)-Streptomyces coelicolor Butanolide 5 (SCB-5)

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Various 1-(1-hydroxyalkyl) paraconyl alcohols are important signaling molecules within antibiotics production in Streptomyces sp. Intending developing a flexible convergent chemical synthesis of such butanolides, a zwitterionic aza-Claisen rearrangement was chosen as reliable strategy generating the central stereotriad. Reaction of enantiopure *N*-allyl pyrrolidines and 4-phenylbutenoic acid fluoride delivered defined configured amides displaying the 2,3,1′ stereotriads. The configuration was determined by the allyl alcohol moiety indicating a complete remote stereo control. Amide removal by iodolactonization and proceeding reductions, halocyclization and elimination gave key alkylidene tetrahydrofuran derivatives. Stepwise degradation of the olefins through ozonolysis, reductive workup and protecting group removal delivered both enantiomers of the target Streptomyces coelicolor butanolide 5.

Introduction

Small molecule hormones are known to trigger the antibiotic production in various bacteria.[1] Focusing on Streptomyces sp., defined 2,3 disubstituted γ-butyrolactones had been identified as a family of compounds characterized by prominent bioactivity.[2] Systematic investigation and structure elucidation had been initiated by the pioneering work of Khokhlov et al. in 1976 isolating and characterizing the so-termed A-factor **1g** from Streptomyces griseus (S. griseus) displaying the only 2-acyl-3-hydroxymethyl γ-butyrolactone natural product found so far (Figure 1).[3] Since then, three series of *trans* 2-(1′-hydroxyalkyl)-3-hydroxymethyl γ-butyrolactones had been isolated successively from Streptomyces sp. such as S. viridochromogenes,[4a] S. bikiniensis,[5a] S. cyaneofuscatus,[5a] S. coelicolor,[4a–d] S. virginiae,[5c,d] S. lavendulae,[4e] S. badius.[6a] Despite of the fact, that the relative and absolute stereochemistry of several γ-butyrolactones (GBL's) remain to be validated,[4a,5a,7] three substitution pattern types predominate. The Streptomyces coelicolor butanolide/IM-2 type **2** (SCB) comprises (2*R*, 3*R*, 1′*R*)-*trans*-2-(1′-hydroxyalkyl)-3-(hydroxymethyl)-γ-butyrolactones SCB-1 (Gräfe SCB-Factor 1) to SCB-8 and IM-2 **2a**–**2k**.[4] In contrast, the Virginiae butanolide (VB) type **3** displays the (2*R*, 3*R*, 1′*S*) diastereomers VB–A (Gräfe VB-Factor I) to VB–E and Gräfe VB-Factors II and III **3a**–**3i**.[5] The SCB-type

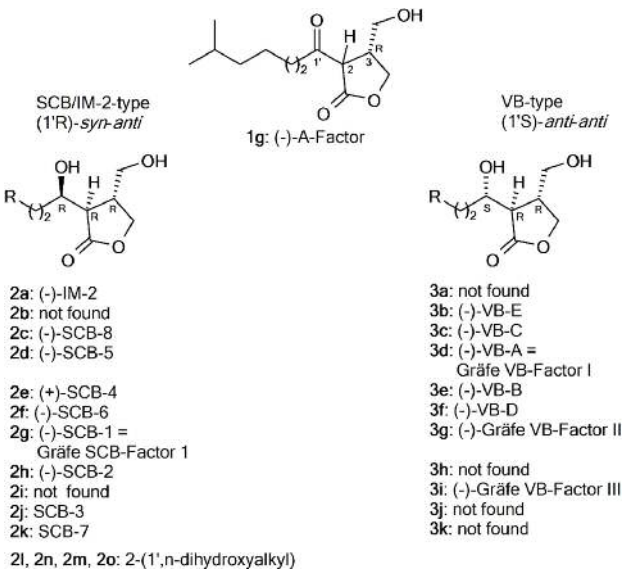

Figure 1. γ-Butyrolactones from natural sources/bioreactors: (C_7)**1g** (−)-A-factor (R = 3-Me–C_4H_8 [*i*C_5H_{11}]). **2** (SCB-type, increasing C2 chain length) (C_4) **2a** (−)-IM-2 (R = Me). (C_6) **2c** (−)-SCB-8 (R = *n*C_3H_7). **2d** (−)-SCB-5 (R = 2-Me–C_3H_6 [*i*C_4H_9]). **2e** (+)-SCB-4 (R = 1-Me–C_3H_6 [*s*C_4H_9], 2 diastereomers), (C_7) **2f** (−)-SCB-6 (R = *n*C_4H_9). **2g** (−)-SCB-1, Gräfe SCB-Factor 1 (R = 3-Me–C_4H_8 [*i*C_5H_{11}]). (C_8) **2h** (−)-SCB-2 (R = *n*C_5H_{11}), **2j** SCB-3 (R = 3-Me–C_5H_{10} [*s*C_6H_{13}], 2 diastereomers). (C_9) **2k** SCB-7 (R = *n*C_6H_{13}). 2-(1,n-dihydroxylalkyl) SCB-series: (C_4) **2l** (R = 3-hydroxy-3-Me–C_4H_7). (C_5) **2m** (R = 3-hydroxy-4-Me–C_5H_9, 2 diastereomers). (C6): **2n** (R = 4-hydroxy-5-Me–C_6H_{11}, 2 diastereomers). **2o** (R = 5-hydroxy-5-Me–C_6H_{11}). **3** (VB-type, increasing C2 chain length) (C_5) **3b** (−)-VB–E (R = 1-Me–C_2C_4 [*i*C_3H_7])., (C_6) **3c** (−)-VB–C (R = *n*C_3H_7). **3d** (−)-VB–A, (−)-Gräfe VB-factor I, (R = 2-Me–C_3H_6 [*i*C_4H_9]). **3e** (−)-VB–B (R = 1-Me–C_3H_6 [*s*C_4H_9], 2 diastereomers). (C_7) **3f** (−)-VB–D (R = *n*C_4H_9), **3g** (−)-Gräfe VB-factor II (R = 3-Me–C_4H_8 [*i*C_5H_{11}])., (C_8) **3i** (−)-Gräfe VB-factor III (R = 4-Me–C_5H_{10} [*i*C_6H_{13}]).

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GBL's incorporating 2-(1',n-dihydroxyalkyl) side chains should be attributed to a third family **2l**–**2o**.[6]

Various defined GBL's have been isolated from different streptomyces strains.[4,5] Obviously, a particular GBL influences biosynthesis pathways depending on the individual bacterium.[2e,4d,8] Analyzing the SCB and the VB diastereomers and enantiomers of the SCB-1 type, Takano et al. found, that the bioactivity of the all (*R*) configured (−)-SCB-1 showed by far the highest activity within a Kanamycin bioassay in comparison to the three analogues pointing out the importance of the defined substituted and configured compound in connection with the bioactivity of a special organism.[4c] Furthermore, investigation of a series of GBL's gave an optimal C2 chain length of 7 to 9 carbon atoms, an additional methyl group at C6 (favored) and C7 (less favored) and a 1' (*R*) OH group. Generally, the corresponding 1'(*S*) VB diastereomers were described to be less active.[4c]

In contrast, VB-bioessays gave different results in respect to bioactivity. Investigations by Y. Yamada et al. gave optimal C2 chain lengths of 6 to 8 carbon atoms,[2e,8] an additional methyl group at C5 (VB–A) and the standard 1' (*S*) configured OH group.[9] In contrast, additional methyl groups at C4 caused a drastic loss of bioactivity.[5d] The corresponding SCB-type diastereomers were described to be about 10-fold less active.[9a] Investigation of the VB–A hyperproducing strain S. antibioticus NF-18 improved the biosynthesis of (−)-VB–A (major) and both enantiomers of SCB-5 (minor).[9d] However, the bioactivity regulating role of the GBL's remains unclear.

Despite of the fact, that modified hyperproducing Streptomyces strains deliver (semi)preparative amounts of suitable GBL derivatives, chemical syntheses of A-factor,[10a–e] SCB-type[4b,10f–i] and VB-type[10j–k] products promised a higher flexibility upon generating defined diastereomers and enantiomers.[4b,5c,10]

Chemical syntheses of GBL's **A** known so far can be subdivided in two strategies (Figure 2). Most attempts described the generation of optically active protected paraconyl alcohol **C** from paraconic acid **B-1** and open chain reactants **B-1**/**B-2**, respectively. The final steps incorporate the butanolide C2 side chain introduction via aldol type reaction (using suitable aldehydes, direct formation of **A**)[10f] or via Claisen condensation (using acid derivatives) affording 2-acyl butanolides **C** and subsequent reduction of the ketone moiety (→**A**).[10f–i] Jørgensen et al.[10k] started with a Michael addition of a suitable β-ketoester (X = OR)/amide (X = NR_2) derivative **D** and nitroalkene **E** to generate a protected 3-nitroallyl alcohol **F**. Ring closure generating the γ-lactone **G**, reduction of the ketone moiety and Nef reaction of the nitro group and a final reduction delivered the target molecules **A**.

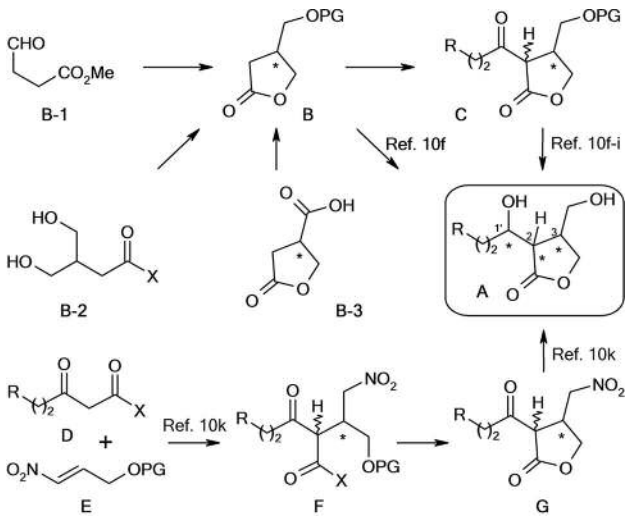


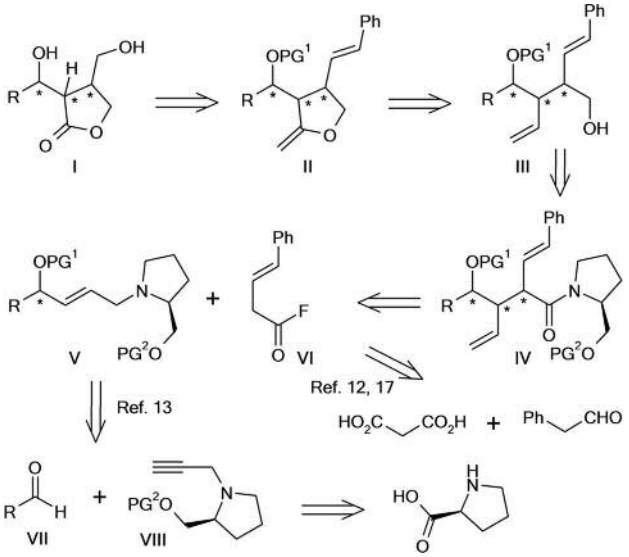
Figure 2. Chemical syntheses of butanolides (X = O-alkyl, NH-alkyl, N-acyl/alkyl; PG = OH, TBS, Bn, Ph, acyl, etc.). For details see Ref 10.

Overall, all attempts incorporated a late-stage introduction of almost two stereogenic centers requiring challenging structure elucidations. Until 1990, the VB-type GBL's had been described as 2,3-*cis* butanolides displaying 2(*S*), 3(*R*), 1'(*R*) configurations (see K. Mori et al. 1990).[10h] In 1991, Y. Yamada et al. published a corrected assignment of the stereocenters of the VB-type GBL's as 2(*R*), 3(*R*), 1'(*S*).[10i] Obviously, the so termed *"trans*-VB-type" diastereomers effectively displayed the SCB-type 2(*R*), 3(*R*), 1'(*R*) configuration.[10h,i] Consequently, synthesis strategies separating the generation of the stereogenic centers and the complete assembly of the β hydroxy lactone moiety occurred advantageous meeting the stereoselectivity challenges.

Results and Discussion

Re-analyzing the substitution patterns of the Streptomyces butanolides, the sequence of three continuous stereogenic centers (2, 3, 1') can be defined as the central segment of all targets. The defined generation of the optically active stereotriad independent of final ring closure and functional group transformations promised developing flexible and reliable syntheses of selected natural products. The retrosynthesis concentrated on assembling the backbone including the stereogenic centers (1', 2, 3) using a kit of building blocks and final functional group variations enabling completion of the syntheses (Scheme 1).

Starting from target butanolide **I**, lactone and hydroxymethyl function should originate from the corresponding olefins in **II** via ozonolytic cleavage and reductive work-up without endangering epimerization of the adjacent C2 and C3 positions. The vinyl ether in **II** must be obtained from unsaturated carbinol **III** via haloether formation and elimination. Carbinol **III** represents the reduction product of amide **IV**, which should be build-up by a zwitterionic aza-Claisen rearrangement from allylamine **V** and styryl acetic acid fluoride **VI**.[11] Acyl fluoride **VI** can be generated in two steps from malonic acid and phenyl acetaldehyde via Knoevenagel condensation and acid fluoride formation.[12] Allylamine **V** should be obtained from aldehyde **VII** and a suitable N-propargyl prolinol derivative **VIII** via alkyne addition reduction and carbinol protection.[13] Prolinol derivative **VIII** can be generated from *L*-(−)-proline via reduction/OH protection and N propargylation adapting literature procedures.[13]

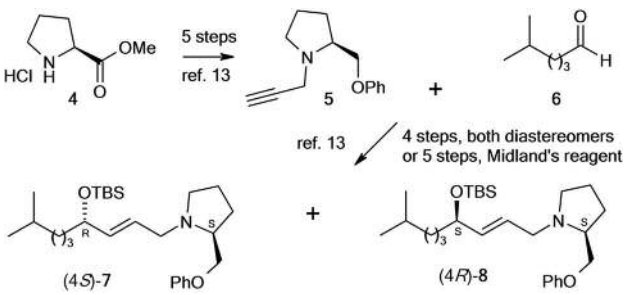


Scheme 1. Retrosynthesis of defined γ-butyrolactones. Streptomyces coelicolor butanolide 5 (SCB-5) **2d** and Virginiae butanolide A (VB–A) **3d** substitution pattern: R = 4-Me–C_5H_{10}/*i*C_6H_{13}.

For a first total synthesis, the SCB-5/VB–A **2d**/**3d** substitution pattern was chosen. (−)-VB–A is described as the most bioactive compound of the VB family. Including the corrections of Yamada et al.[10i] Mori et al. already published the syntheses of (−)-SCB-5 **2d** and (−)-VB–A **3d** in 1990 as a mixture of diastereomers.[10h,14] Therefore, diastereoselective syntheses aiming for assembling complete data sets of these compounds have been developed in our laboratory.

The synthesis started synthesizing the key *N*-allyl prolinol diastereomers **10** and **11** (retrosynthesis compound **V**) as well as acid fluoride **12** (retrosynthesis compound **VI**) according literature procedures.[15]

For optically active pyrrolidine derivative **7** and **8** syntheses, *L*-(−)-proline methyl ester **4** was used as starting material (Scheme 2). A five-step sequence (N-benzylation, $LiAlH_4$ reduction, Buchwald phenyl ether formation, benzylamine hydrogenolysis and N-propargylation) afforded *N*-propargyl prolinol **5** via five steps with 74% yield overall.[13] Alkynyl anion coupling with aldehyde **6** (two steps from 5-methyl hexanoic acid: $LiAlH_4$ reduction, TEMPO oxidation, 96%), HPLC resolution of the



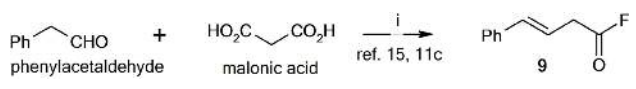
Scheme 2. Syntheses of optically active *N*-allylpyrrolidine diastereomers (4*S*)-**7** and (4*R*)-**8** according ref. 13.

diastereomers of the corresponding *O*-acetyl mandelic esters, $LiAlH_4$ reduction and allylalcohol TBS protection delivered both, *N*-allyl prolinol derivative (4*R*)-**8** with 34% yield and diastereomer (4*S*)-**7** with 37% yield. Alternatively, a five-step sequence of alkynyl anion (from **5**) coupling with aldehyde **6**, MnO_2 oxidation and subsequent Midland's reagent controlled diastereoselective ketone reduction, $LiAlH_4$ reduction and TBS protection allylalcohol moiety selectively afforded *N*-allyl prolinol derivative (4*R*)-**8** with 42% yield.[16]

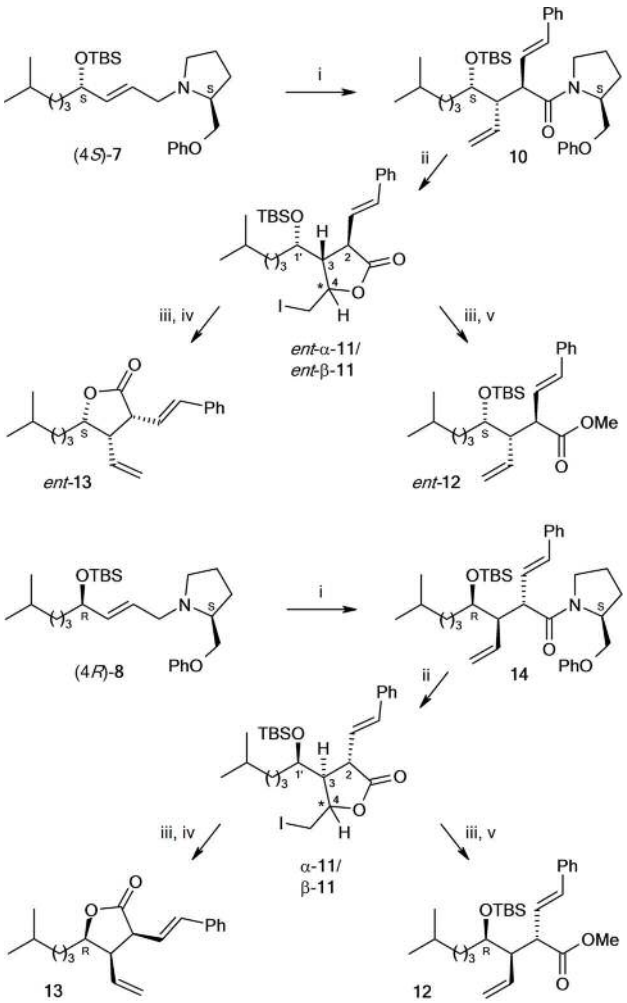
Acid fluoride **9** was obtained from phenylacetaldehyde and malonic acid via two steps (Scheme 3). Literature known Knoevenagel condensation of phenylacetaldehyde and malonic acid delivered 4-phenyl-3-butenoic acid (78% yield),[17] which then was activated with cyanuric fluoride and pyridine to give acid fluoride **9** with quantitative yield.[12c]

The aza-Claisen rearrangement using allylamine diastereomers (4*S*)-**7** and (4*R*)-**8**, respectively, and acid fluoride **9** served as the key step upon generating the stereotriad displaying amides **10** and **11** (Scheme 4).[11] Predictably, the reaction of TBS-ether derived allylamine (4*S*)-**7** and acid fluoride **9** gave product amide **10** with 93% yield as a single diastereomer (matched combination of the stereodirecting factors, see Figure 5 below). First attempts intending for direct reduction of the amide to the corresponding primary alcohol failed despite of wide variation of the reaction conditions.[18] Because of unconvincing results running direct tertiary amide cleavage processes,[19] a reliable two-step sequence was applied. Removal of the pyrrolidine auxiliary moiety succeeded via iodo lactonization.[11g,19,20] Treatment of amide **10** with iodine in DME/H_2O delivered a mixture of C4-α iodolactone *ent*-α-**11** and C4-β iodolactone *ent*-β-**11** as a 0.85:1 mixture of C4-epimers with 91% yield. The relative configuration of the new stereogenic centers (C2/C3 *anti*) was elucidated by means of NOESY analyses. Furthermore, iodolactone *ent*-β-**11** crystallized and the X-ray analysis improved absolute and relative configurations of all stereogenic centers (Figure 3).[21] Reductive opening of the lactones *ent*-**11** with Zn/HOAc gave the intermediate acid (85% yield, not shown), which was treated with diazomethane solution to afford corresponding ester *ent*-**15** with 88% yield (75% yield over 2 steps). Furthermore, reaction of the intermediate acid with $SOCl_2$ in MeOH caused TBS group removal and subsequent cyclization to give lactone *ent*-**13** with 90% yield (77% yield over 2 steps). Careful structure elucidation via NOESY analysis gave the *cis* arrangement of all γ-butyrolactone side chains.

Surprisingly, reaction of allylamine (4*R*)-**8** and acid fluoride **9** delivered amide **14** with 90% yield as a single diastereomer (Scheme 4). No minor compounds had been found after careful analyses (HPLC, NMR). Despite of the fact, that the mismatched combination of the stereodirecting ether and pyrrolidine



Scheme 3. Synthesis of acid fluoride **9**. Conditions and yields: iv) (a) *N*-methyl morpholine, 95 °C, 14 h, 78%. Ref 17. (b) $C_3F_3N_3$, CH_2Cl_2, pyridine, 0 °C to 23 °C, 3 h, > 99%. According Ref. 12c.



Scheme 4. Aza-Claisen rearrangement of allylamines (4*S*)-**7** and (4*R*)-**8**, structure elucidation and auxiliary removal. Conditions and yields: i) **9**, Me_3Al, Na_2CO_3, CH_2Cl_2, 0 °C, 4 d, yields: 93% (**10**), 90% (**14**). (ii) I_2, DME, H_2O, 23 °C, 4 d, yields: 38% β-**11** + 38% α-**11** (from **13**); yields: 49% *ent*-β-**11** + 42% *ent*-α-**11** (from **10**), 21 h. (iii) Zn, HOAc, Et_2O, 23 °C, 2 d, (iv) $SOCl_2$, MeOH, 23 °C, 3 d, yields: 55% **13** (from **11**); 77% *ent*-**13** from *ent*-**11** (two steps each). (v) CH_2N_2, Et_2O, 0 °C, 5 h, yields: 75% **12** (from **11**); 75% *ent*-**12** from *ent*-**11** (two steps each). Remark: Since α and β characterize the relative arrangement of the iodomethyl group within the present drawing, α-**11**/*ent*-β-**11** as well as β-**11**/*ent*-α-**11** represent enantiomers.

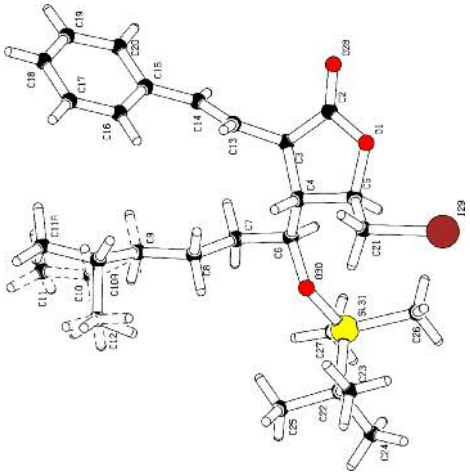


Figure 3. X-ray structure of iodolactone *ent*-β-**11** (only selected hydrogens are shown).

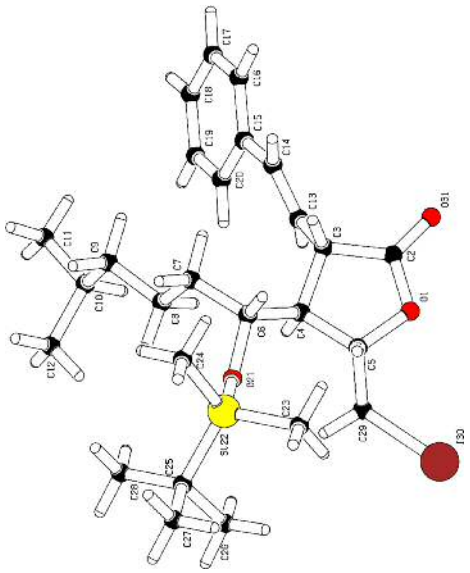
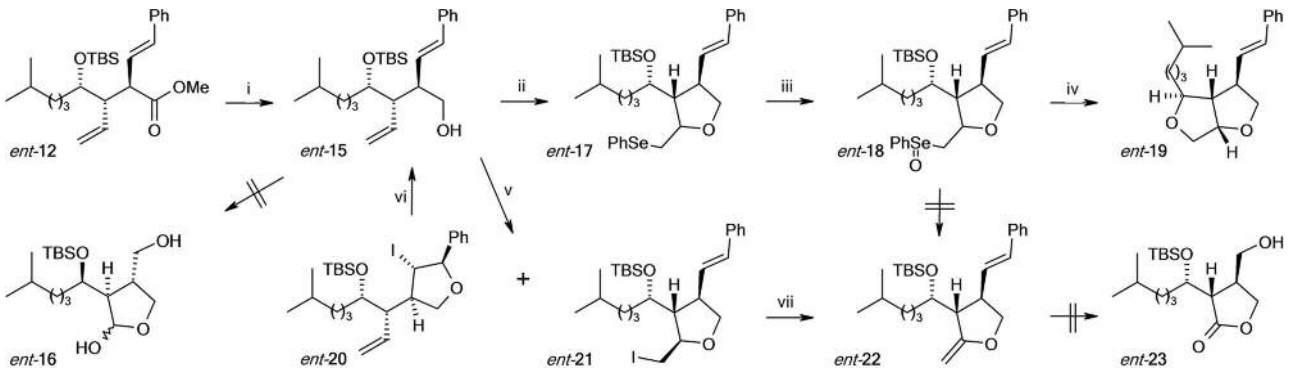


Figure 4. X-ray structure of iodolactone α-**11** (only selected hydrogens are shown).

moieties had been involved, one of these factors completely predominated the diastereoselectivity of the process (see Figure 5 below). Again, removal of the pyrrolidine via iodocyclization delivered lactones α-**11** and β-**11** as a 1:1 mixture of C4-epimers (76% yield). The relative configuration of the new stereogenic centers (C2/C3 *anti*) could be elucidated by means of NOESY analyses. In analogy to the enantiomer series mentioned above, iodolactone α-**11** crystallized and the X-ray analysis improved absolute and relative configurations of all stereogenic centers (Figure 4).[21] Finally, reductive opening of the lactones **11** with Zn/HOAc gave the intermediate acid (81% yield, not shown), which was treated with diazomethane solution to afford corresponding ester **12** with 92% yield (75% yield over 2 steps). Furthermore, reaction of the intermediate acid with $SOCl_2$ in MeOH caused TBS group removal and subsequent cyclization to give lactone **13** with 68% yield (55% yield over 2 steps). Careful structure elucidation via NOESY analysis gave the *cis* arrangement of all γ-butyrolactone side chains.

Methyl esters **12** and *ent*-**12** displaying both enantiomeric stereotriades served as starting key intermediates for SCB/IM-2 butenolide syntheses (2*R*,3*R*,1′*R*) (−)-SCB-5 **2d** (Scheme 6, Scheme 7, Scheme 9) and (2*S*,3*S*,1′*S*) (+)-SCB-5 *ent*-**2d** (Scheme 5, Scheme 8).[22] Reduction of the ester functions with DIBAL–H afforded the carbinols **15** and *ent*-**15** with high yields (99% of **15** and 85% of *ent*-**15**, respectively).

A most straight forward process heading for the target butanolide *ent*-**2d** formation was the oxidative cleavage of both double bonds of carbinol *ent*-**15** (Scheme 4). Ozonolysis



Scheme 5. Synthesis of iodo tetrahydrofuranes *ent*-**20** and *ent*-**21**: Conditions and yields: (i) DIBAL–H, CH_2Cl_2, −78 °C, 5 h, yield: 85% *ent*-**15**; (ii) $SnCl_2$, PhSeBr, CH_2Cl_2, 23 °C, 15 min, yield *ent*-**17** 77% overall. HPLC separation gave β (CH_2SePh) *ent*-**17**: 32% (OTBS + 9% (OH), α (CH_2SePh) *ent*-**17**: 26% (OTBS) + 10% (OH). (iii) from *ent*-**15** via crude *ent*-**17**: *m*CPBA, pyridine, DME, −78 °C, 30 min, 23 °C, 1.5 h, yield *ent*-**18** (mixture of diastereomers) 97% (from *ent*-**15**). (iv) pyridine, DME, 80 °C 4 h, yield *ent*-**19**: 19% (from *ent*-**15**). (v) I_2, $NaHCO_3$, Et_2O, H_2O, 23 °C, 9 h yields: 36% *ent*-**20** and 48% *ent*-**21** (d.r. 43:57). (vi) Zn, HOAc, Et_2O, 23 °C, 22 h, yield: > 99%. (vii) tBuOK, THF, 60 °C, 6 d, yield: > 99% *ent*-**22**.

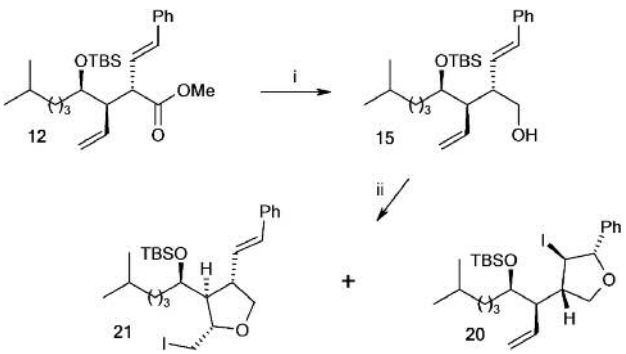
had to generate two aldehyde functions, five-membered ring lactol formation should protect the C1 position. The remaining aldehyde moiety had to be reduced selectively[20] to deliver hydroxymethyl lactol *ent*-**16**. However, various attempts varying reagents and conditions failed because of the rapid destruction of the material under the oxidizing conditions or the competing reduction of the lactol delivering triol side products (stereochemical information of C3 is lost).

The failure of the twofold oxidative cleavage of the double bonds in combination with proceeding chemoselective aldehyde reduction (hydroxymethyl moiety) and oxidation (lactol moiety) motivated to generate an enolether function first (Scheme 5). Now, ozonolysis of olefin and enolether type *ent*-**22** would have generated a lactono aldehyde intermediate, the so formed aldehyde function had to be selectively reduced to build-up hydroxy lactones type *ent*-**23**.

For tetrahydrofuran formation and subsequent β elimination to generate *exo* enol ethers of type *ent*-**22**, a selenocyclization,[24a–c] oxidation, *syn*-elimination cascade[24d,e] had been tested (Scheme 5). Treatment of carbinol *ent*-**15** with PhSeBr and $SnCl_2$ in CH_2Cl_2 smoothly delivered 2-(phenylselanylmethyl) tetrahydrofuran *ent*-**17** with 77% yield as a 41:36 mixture of C1 β and α-epimers.[25] Subsequent oxidation with *m*CPBA afforded the corresponding selenoxide *ent*-**18** diastereomers with nearly quantitative yields (> 97%). However, in contrast to literature precedence describing tetrahydropyran *exo* enolether formation from phenylselenyl methyl precursors,[24d,e] no β elimination generating enolether *ent*-**22** could be enforced. Heating of the material induced decomposition and competing product formation (e.g. furofuran derivative *ent*-**19** after silyl group removal and cyclization). Furthermore, no *exo* enolether *ent*-**22** and hydroxylactones type *ent*-**23** compounds were found upon running selenium oxidation, oxidative cleavage of the olefins and aldehyde reduction as a one pot process.

Ring closure by means of iodocyclization required careful optimization.[26] In contrast to the iodolactonizations using amides **10**/**14** and the selenocyclizations described above, treatment of carbinols **15** and *ent*-**15** with iodine in Et_2O/aq. $NaHCO_3$ afforded two regioisomer tetrahydrofurans **20**/**21** (63% yield, ratio 48:52) and *ent*-**20**/*ent*-**21** (84% yield, ratio 43:57) as single diastereomers, respectively (Scheme 5, Scheme 6). After careful column chromatography and HPLC separation 2-(iodomethyl) tetrahydrofurans **21**/*ent*-**21** displayed the standard 5-*exo*-*trig* substitution pattern in favor of the *trans* C1/C2 arrangement of the side chains.[26a–f] The formation of the regioisomers **20**/*ent*-**20** indicated a competing 5-*endo*-*trig* reaction.[26g,h] Obviously, the attack of the iodo cation at the styryl double bond generated an intermediate benzyl cation, which finally underwent intramolecular five membered ring ether formation affording the 2-phenyl-tetrahydrofurans **20**/*ent*-**20** with *trans* arrangement of all side chain substituents. Wide variation of iodo cation donor and reaction conditions resulted no higher regioselectivity in favor of regioisomers **21**/*ent*-**21**. However, starting from iodo tetrahydrofuran *ent*-**20**, reductive elimination using Zn and HOAc enabled regeneration of carbinol *ent*-**15** with nearly quantitative yield (Scheme 5).

Then, installation of the exo enolether moiety had been investigated (→*ent*-**22**) (Scheme 5).[27] Reactions of iodomethyl derivative *ent*-**21** at room temperature induced substitution



Scheme 6. Synthesis of iodo tetrahydrofuranes **20** and **21**: Conditions and yields: (i) DIBAL–H, CH_2Cl_2, −78 °C, 5 h, yield: > 99% **15**; (ii) I_2, $NaHCO_3$, Et_2O, H_2O, 23 °C, 17 h yields: 32% **21** and 31% **20** (d.r. 52:48).

processes. AgOTf/*t*BuOK, pyridine replacement of iodide only generated carbinols and pyridinium salts, respectively.[28] In contrast, long lasting subjecting of iodomethyl tetrahydrofuran *ent*-**21** to potassium *tert*-butoxide in refluxing THF gave *exo* enolether *ent*-**22** with >99% yield after 9 days of reaction time. Again, simultaneous oxidative cleavage of both double bonds failed (→*ent*-**23**). The intermediately formed lactonoaldeyde might have suffered from proceeding condensation (β-elimination of the lactone carboxyl group) and further oxidation of the nascent acrolein moiety.

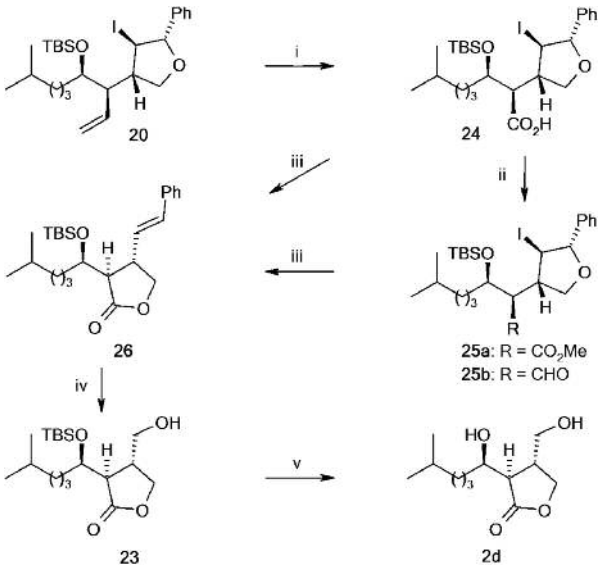
Overall, the simultaneous oxidative cleavage of both olefines failed, enforcing development of a stepwise process. In this connection, the iodoethers **20**/*ent*-**20** and **21**/*ent*-**21** served as appropriate starting materials.

2-Phenyl tetrahydrofuran **20** was chosen to install the carboxyl function first.[29] Ozonolysis of iodoether **20** in MeOH and oxidative work-up with aqueous H_2O_2 afforded acid **24** (Scheme 7). Because of work-up and purification problems, a disappointing yield of 21% was found. For facilitating chromatographic purification and characterization, the crude acid **24** was immediately treated with a solution of freshly prepared diazomethane. Methyl ester **25a** was isolated with moderate 26% yield (3 steps). Remaining aldehyde **25b** (21% yield) indicated an incomplete second H_2O_2 oxidation step. Reductive ring opening with Zn in AcOH/Et_2O induced regeneration of the styrene moiety, the intermediate hydroxy acid underwent γ-lactonization delivering butanolide **26** with 49% yield from acid **24** and 87% yield from ester **25a**. Best results were achieved running a cascade of oxidative degradation of the vinyl group and reductive ring opening of the iodo tetrahydrofuran segment with final lactonization. Stating from iodoether **20**, such a sequence enabled generation of butanolide **26** with 36% yield overall.[30]

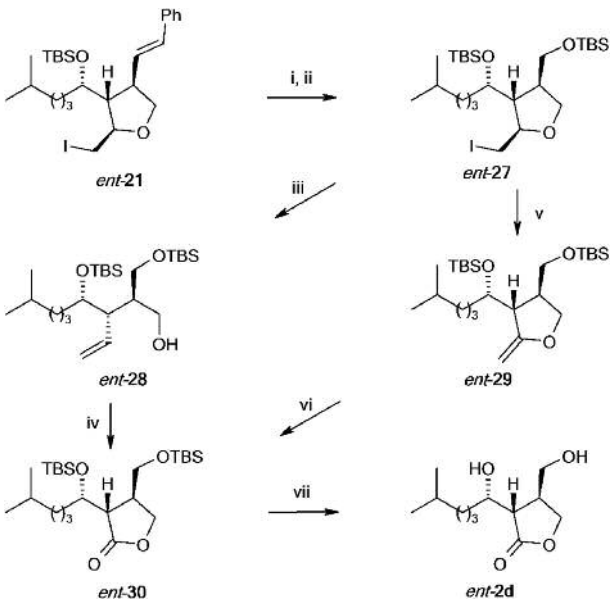
Ozonolytic cleavage of the styryl double bond of lactone **26** in MeOH/CH_2Cl_2 and subsequent reductive work-up using $NaBH_4$ afforded 3-(hydroxymethyl) lactone **23** with 71% yield.[31,11d] Finally, protecting group removal with buffered TBAF- solution in THF/HOAc enabled to complete a first total synthesis of (−) SCB-5 **2d** with 98% yield.[32]

Iodomethyl tetrahydrofuran *ent*-**21** served as key intermediate for a synthesis of (+)-SCB-5 *ent*-**2d**. The starting sequence focused on introduction of the 3-(hydroxymethyl) group first (Scheme 8). Treatment of reactant *ent*-**21** with O_3/O_2 in MeOH, subsequent reduction with $NaBH_4$ and final protection of the carbinol delivered TBS ether *ent*-**27** with >76% yield (2 steps). Reductive ring opening using Zn/HOAc afforded alkenol *ent*-**28** with 79% yield.

For introduction of the lactone carboxyl function, two alternative reaction paths were tested (Scheme 8). In analogy to the oxidative degradation of the vinyl group of tetrahydrofuran **21** delivering lactone **26** (see above, Scheme 7), hydroxyalkene *ent*-**28** was subjected to O_3/O_2 in CH_2Cl_2 and subsequent oxidative work-up with 35% aq. H_2O_2. Surprisingly, a lactol only (82% yield, not shown) was found indicating the failure of the final oxidation. No lactone *ent*-**30** was detected. Consequently, introduction of the carboxyl function required an additional transformation. Reaction of the intermediate lactol with PCC in dry CH_2Cl_2 gave the desired TBS protected SCB-5 derivative *ent*-



Scheme 7. Synthesis of (−)-SCB-5 **2d**. Conditions and yields: (i) O_3/O_2, MeOH, −78 °C, 20 min, then: 35% aq. H_2O_2, MeOH, −78 °C to 23 °C, 15 h. Yield: 21% **24**. (ii) CH_2N_2, Et_2O, 0 °C, 3 h, yield 26% **25a** (from **20**) + 21% of the aldehyde **25b**. (iii) Zn, HOAc, Et_2O, 23 °C, 36 h, yields of **26**: 49% (from **24**), 87% (from **25a**), 36% (from **20**). (iv) O_3/O_2, MeOH/CH_2Cl_2, −78 °C, 1 h, then: MeOH/CH_2Cl_2, $NaBH_4$, −78 °C to 23 °C, 23 h, Yield 71% of **23**. (v) TBAF, HOAc, THF, 23 °C, 19 h, yield: 98% **2d**, (−)-SCB-5.

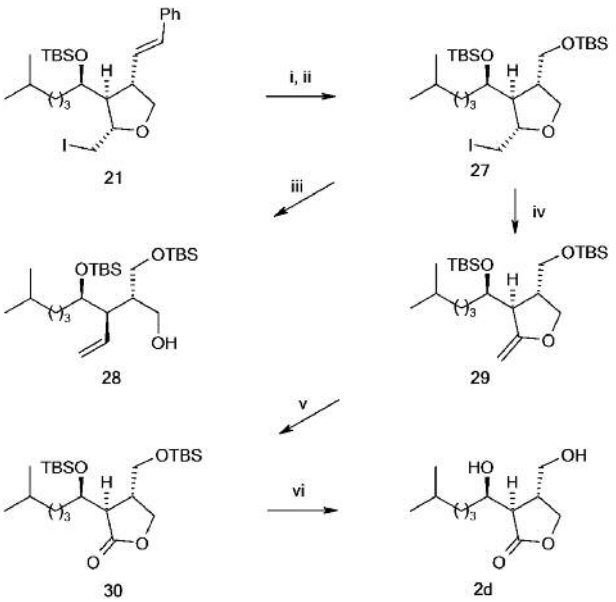


Scheme 8. Synthesis of (+)-SCB-5 *ent*-**2d**. Conditions and yields: (i) O_3/O_2, CH_2Cl_2, −78 °C, 15 min, then: MeOH, $NaBH_4$, −78 °C to 23 °C, 22 h, Yield 99% of carbinol. (ii) TBSOTf, Et_3N, CH_2Cl_2, 23 °C, 20 h, yield 78% silylether *ent*-**27**. (iii) Zn, HOAc, Et_2O, 23 °C, 24 h, yield 79% olefin *ent*-**28**. (iv) (a) O_3/O_2, CH_2Cl_2, −78 °C, 15 min, then: 35% aq. H_2O_2, CH_2Cl_2, 23 °C to reflux, 2 h, yield: 82% of lactol. (b) PCC, 3 Å molsieves, CH_2Cl_2, 23 °C, 1 h, Yield: 34% lactone *ent*-**30** (+ 43% of ketoformiate, see supporting information). (v) *t*BuOK, THF, 50 °C, 3 d, Yield 98% of enolether *ent*-**29**. (vi) O_3/O_2, CH_2Cl_2, −78 °C, 1 h, then: Me_2S, CH_2Cl_2, −78 °C to 23 °C, 4 h, Yield 75% of lactone *ent*-**30**. (vii) TBAF, HOAc, THF, 23 °C, 15 h, yield: 99% of target (+)-SCB-5 *ent*-**2d**.

30 with moderate 34% yield. Competing degradation products could be isolated in up to 43% yield.[33]

The cumbersome oxidative cleavage of alkenol *ent*-**28** advised reactivation of the enol ether pathway (Scheme 8, in analogy to the consideration to generate lactone moiety in *ent*-**23**, Scheme 5). Starting from TBS ether *ent*-**27**, H–I β-elimination succeeded using KO*t*Bu in THF at 50 °C. After 3 d of reaction time *exo* enol ether *ent*-**29** could be isolated with 98% yield. Oxidative cleavage of the double bond with O_3/O_2 in CH_2Cl_2 and standard work-up with Me_2S delivered the desired TBS protected SCB-5 *ent*-***30*** with 75% yield. Finally, global protective group removal with TBAF/HOAc in THF gave the target (+)-SCB-5 derivative *ent*-**2 d** with < 99% yield.[32]

In addition, the synthesis of (−)-SCB-5 **2 d** had been run via the optimized route developed for (+)-SCB-5 *ent*-**2 d** applying slightly varied conditions (Scheme 9). The oxidative cleavage of the styrene subunit starting from tetrahydrofuran **21** with O_3/O_2 in CH_2Cl_2, subsequent reduction with $NaBH_4$ and final protection of the carbinol delivered TBS ether **27** with 70% yield (2 steps). Too, reductive ring opening using Zn/HOAc enabled to generate alkenol **28** with 81% yield. Again, the enol ether route proved successful. Starting from TBS ether **27**, H–I β-elimination was achieved using KO*t*Bu in THF at 50 °C. After 3 d of reaction time *exo*-enol ether **29** could be isolated with nearly quantitative yield. Oxidative cleavage of the double bond with O_3/O_2 in CH_2Cl_2 and standard work-up with Me_2S delivered the desired TBS protected SCB-5 derivative **30** with 63% yield. Finally, global protective group removal with TBAF/HOAc in THF gave the target (−)-SCB-5 **2 d** with < 99% yield.[32]



Scheme 9. Synthesis of (−)-SCB-5 **2 d**. Conditions and yields: (i) O_3/O_2, CH_2Cl_2, −78 °C, 1 h, then: MeOH, $NaBH_4$, −78 °C to 23 °C, 21 h, Yield 82% of carbinol. (ii) TBSOTf, Et_3N, CH_2Cl_2, 23 °C, 20 h, yield 86% silylether **27**. (iii) Zn, HOAc, Et_2O, 23 °C, 21 h, yield 81% olefin **28**. (iv) *t*BuOK, THF, 50 °C, 3 d, Yield 99% of enolether **29**. (v) O_3/O_2, CH_2Cl_2, −78 °C, 1 h, then: Me_2S, CH_2Cl_2, −78 °C to 23 °C, 3 h, Yield 63% of lactone **30**. (vi) TBAF, HOAc, THF, 23 °C, 20 h, yield: > 99% of target (−)-SCB-5 **2 d**.

Comparison of the ^{1}H NMR data of our (−)-SCB-5 with these published by Mori et al. (corrected structure)[10h,i] gave a convincing agreement of both sets. Especially, the lactone protons H-5 and H-5′ were described as two dd systems at 4.41 and 3.97 ppm. The proton attached to C-1′ was found as a m between 4.05 and 4.00 ppm. In contrast, the VB–A protons are found as dd systems at 4.42 and 4.1 ppm, respectively, the proton attached to C-1′ was described as a m between 4.15 and 4.10 ppm. Comparison of the data of further SCB/VB type substitution pattern pairs of several compounds **2**/**3** displayed the same tendency in connection with the protons mentioned above. Unfortunately, no ^{13}C NMR data of SCB-5 have been published in the literature so far.[34]

Generally, the aza-Claisen rearrangement as the central key step offers two options in respect of the stereocontrol building up stereotriads (Figure 5) involving *N*-allylpyrrolidines (4*S*)-**7** and (4*R*)-**8**, respectively and activated intermediate ketene **9 a** (from acid fluoride **9** and Me_3Al, evolution of methane).[11] The addition of the lone pair of the nitrogen at the carbonyl center of the ketene **9 a** was the initiating step in both cases, delivering the central zwitterionic intermediate with high diastereoselectivity. Then, Claisen rearrangement required the passing of a chair-like transition state. In this connection, the stereodirecting factors need to be examined.

1) Starting from *N*-allyl pyrrolidines **7** and **8** bearing a defined ether function in position 4, 1,2 asymmetric induction enables to generate stereotriads with *anti*/*syn* substitution pattern with high diastereoselectivity (minimized repulsive interactions because of *anti*-arrangement of enolate C and bulky TBS ether).[35] 2) Starting from optically active *N*-allyl (*S*)-prolinol derivatives **7** and **8**, auxiliary induced rearrangements deliver 2,3 *anti*-amides with 2 (*R*) configurations (quasi equatorial arrangement of the bulky branched pyrrolidine moiety). The combination of both independently directing stereoinductors in a single molecule should affect matched and mismatched results concerning the amide formation. The matched case is found in reactant (4*S*)-**7**/(*S*)-prolinol derivative delivering the *syn-anti* amide **10** as an intermediate of a (+)-SCB-5 *ent*-**2 d** synthesis. In contrast, the mismatched combination of reactant (4*R*)-**8**/(*S*)-prolinol derivative resulted *syn-anti* amide **14** (via mismatched-s, predominating substrate control, transition state suffering from quasi axial arrangement of the bulky branched pyrrolidine moiety) as a (−)-SCB-5 **2 d** precursor. However, formation of *anti-anti* amide **14 a** (via mismatched-a, predominating auxiliary control, transition state suffering from repulsive interactions because of *syn*-arrangement of enolate C and bulky TBS ether) inducing a (+)-VB–A **3 d** synthesis was not observed.

Conclusion

The stereoselective synthesis of enantiopure Streptomyces coelicolor butanolide hormones required efficient access to the optically active (2,3,1′) stereotriads characterizing the key fragments of this series of natural products. Zwitterionic aza-Claisen rearrangements developed earlier proved to serve as reliable tools to generate such stereotriads with high selectivity.

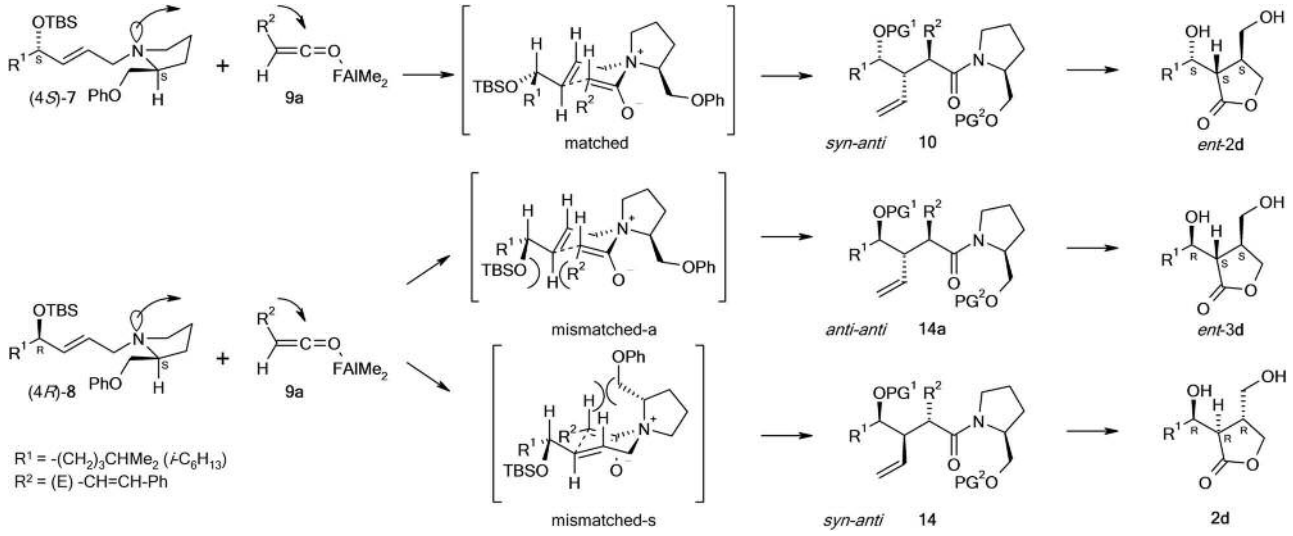


Figure 5. Stereochemical outcome of the zwitterionic aza-Claisen rearrangement key-step: axial N lone pair in (4*S*)-**7** and (4*R*)-**8**, attack at the carbonyl C of ketene **9a**, passing of chair-like transition states with minimized repulsive interactions. "matched" gives *syn anti* **10** (→(+)-SCB-5 *ent*-**2d**), mismatched-a auxiliary control gives *anti anti* **14a** (→(+)-VB-A *ent*-**3d**), mismatched-s substrate control gives *syn anti* **14** (→(−)-SCB-5 **2d**).

Starting from suitably substituted *N*-allylpyrrolidine (4*S*)-**7**, reaction with 4-phenylbutenoyl fluoride **9** delivered the γ,δ-unsaturated amide **10** as a single diastereomer with high yield (93%, matched combination of stereochemistry inducing factors). Despite of involving differently directing stereochemistry inducing factors as present in pyrrolidine (4*R*)-**8**, 1,2 asymmetric induction (remote stereocontrol) of the (4*R*)-TBS ether moiety predominated delivering γ,δ-unsaturated amide **14** only with 90% yield. Two step removal of the amide via iodocyclization, reductive ring opening and subsequent reduction of the carboxyl function afforded carbinols **15** (*R*,*R*,*R* stereotriad, 55% yield) and *ent*-**15** (*S*,*S*,*S* stereotriad, 58% yield). Structure elucidation succeeded by means of NOESY and X-ray analyses of appropriate intermediates in both series.

Chemoselective conversion of the olefins into carboxyl and hydroxymethyl groups required careful elaborated reaction sequences. Despite of several attempts, the simultaneous degradation of both double bonds failed. Iodocyclizaton of carbinols **15**/*ent*-**15** delivered two regioisomeric iodoethers **20**/*ent*-**20** (protected styryl double bond) and **21**/*ent*-**21** (protected vinyl group).[36]

Starting from iodoether **20** allowed introduction of the carboxyl function first. Best results were achieved via ozonolysis/oxidative work-up and reductive iodoether ring opening generating γ lactone **26** with 36% yield. A second ozonolysis/reductive work-up gave protected (−)-SCB-5, a final silyl ether removal enabled completion of the total synthesis of target (−)-**2d** (25% overall from iodoether **20**).

Starting from iodoether *ent*-**21** enabled introduction of the hydroxymethyl function first. Ozonolysis/reductive work-up and silyl ether protection delivered tetrahydrofuran *ent*-**27** (77% yield). Since the carboxyl group introduction with regeneration of the vinyl group (via *ent*-**28**) and subsequent oxidative degradation gave moderate results upon generating protected (+)-SCB-5 *ent*-**30** (6 steps from *ent*-**21**, 17% yield), potassium *tert*-butoxide induced HI elimination gave enol ether *ent*-**29**. Subsequent ozonolysis/standard work-up of the double bond afforded lactone *ent*-**30** with 74% yield (2 steps). Final protecting group removal gave (+)-SCB-5 *ent*-**2d** with nearly quantitative yield (overall: 5 steps from *ent*-**21**, 56% yield). In addition, starting from iodoether **21** enabled completion of the total synthesis of (−)-SCB-5 **2d** with 44% yield (5 steps from **21** applying the enol ether **28** cascade).

The data of the SCB-5 enantiomers synthesized here match with these published by Mori.[10h] In contrast, a VB–A synthesis requires a late-stage inversion of the C1′ OH group.[37] Alternatively, more attractive auxiliary dominated zwitterionic aza-Claisen rearrangement would require a sterically less encumbered C4 carbinol protection group and a suitable auxiliary substituent. Further investigations in our laboratory aim for such Virginiae butanolide total syntheses.

Experimental Section

General Remarks: Thin film IR spectra were recorded with a Jasco FT/IR-4100 spectrometer with single reflection horizontal ATR (ZnSe window). Melting points were determined with an IA 9100 apparatus, manufactured by Electrothermal Engineering Ltd. Optical rotation was recorded with MC 241 polarimeter (Perkin-Elmer). ^{1}H NMR, ^{13}C NMR and 2D NMR (COSY, HSQC, HMBC, NOESY) spectra were recorded at room temperature with a Bruker Avance III HD 300, Avance II 400 or Avance III HD 400 spectrometer in C_6D_6 or $CDCl_3$, e.g. using the signal of residual $CHCl_3$ (^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm) as internal standard. FD mass spectra were obtained using a Finnigan MAT 95, ESI spectra were measured using a Waters Micromass QTOF Ultima 3. HRMS ESI spectra were recorded using an Agilent G6545A Q-ToF spectrometer. Column chromatography was performed on MN silica gel 60 M from Macherey-Nagel GmbH & Co. KG with a grain size of 0.040–0.063 nm. The analytical HPLC

system was used to analyze the products: Knauer HPLC Pump 64 connected to a HPLC column (see table below), a Knauer Variable Wavelength Monitor at λ = 254 nm or 220 nm and Knauer Differential Refractometer. Preparative HPLC system: Knauer WellChrom Preparative Pump K-1800 connected to the HPLC column, a Knauer Variable Wavelength Monitor at λ = 254 nm or 220 nm and Bischoff RI-detector 8100. A selection of experimental procedures is given in the following. For all procedures and the numbering used in the ^{1}H and ^{13}C NMR spectra, see supporting information.

(2*R*,3*S*,4*S*)-4-((*tert*-Butyldimethylsilyloxy)-8-methyl-1-((*S*)-2-(phenoxymethyl)-pyrrolidin-1-yl)-2-((E)-styryl)-3-vinylnonan-1-one 10: Sodium carbonate (1.446 g, 13.644 mmol, 6.0 eq) was dried and *N*-allyl pyrrolidine (4*S*)-**7** (1.007 g, 2.259 mmol, 1.0 eq.) in DCM (30 mL) was added. Acyl fluoride **9** (0.904 g, 5.507 mmol, 2.4 eq) in DCM (10 mL) was added at 0 °C. Then, trimethylaluminum (2.75 mL, 0.40 g, 5.5 mmol, 2.4 eq, 2 M in toluene) was added dropwise over 30 min. After stirring for 4 d at 0 °C (cryostat), the mixture was warmed-up room temperature. Water (2 mL) and saturated aqueous KNa tartrate (15 mL) were added dropwise and the resulting mixture was stirred for 3 h. The organic layer was washed with saturated aqueous K,Na tartrate (100 mL). The aqueous layer was extracted with DCM (3×100 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:10 to 1:4) to afford amide **10** (1.234 g, 2.091 mmol, 93%) as a yellow oil. R_f = 0.29 (EtOAc/petroleum ether 1:15, ninhydrin, UV). $[\alpha]_D^{22} = -16.87°$ (CH_2Cl_2, *c* = 1.00 g/100 mL). IR (thin film): 2953 (s), 2927 (s), 2853 (m), 1727 (w), 1637 (s), 1600 (m), 1497 (s), 1469 (m), 1415 (s), 1245 (s), 1088 (m), 1038 (w), 1004 (m), 964 (w), 914 (m), 836 (s), 775 (s), 752 (vs), 691 (s), 617 (m). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.41–7.16 (m, 7H, *H*-17, *H*-22, *H*-23, *H*-24), 7.00–6.83 (m, 3H, *H*-16, *H*-18), 6.59 (d, ^{3}J = 16.1 Hz, 0.2H, *H*-20B), 6.49 (d, ^{3}J = 16.0 Hz, 0.8H, *H*-20A), 6.26 (dd, ^{3}J = 16.0 Hz, ^{3}J = 9.2 Hz, 0.8H, *H*-19A), 6.22 (dd, ^{3}J = 16.1 Hz, ^{3}J = 9.3 Hz, 0.2H, *H*-19B), 5.91–5.78 (m, 1H, *H*-25), 5.30–5.20 (m, 0.4H, *H*-26B), 5.21–5.10 (m, 1.6H, *H*-26A), 4.42–4.33 (m, 1H, *H*-10), 4.22 (dd, ^{2}J = 9.7 Hz, ^{3}J = 3.2 Hz, 0.8H, *H*-14Aa), 4.02 (dd, ^{2}J = 9.0 Hz, ^{3}J = 3.8 Hz, 0.2H, *H*-14Ba), 3.89 (dd, ^{2}J = 9.7 Hz, ^{3}J = 7.6 Hz, 0.8H, *H*-14Ab), 3.86–3.79 (m, 1H, *H*-4), 3.78–3.70 (m, 0.2H, *H*-14Bb), 3.70–3.62 (m, 1H, *H*-2), 3.61–3.43 (m, 2H, *H*-13), 2.85–2.75 (m, 0.2H, *H*-3B), 2.71–2.63 (m, 0.8H, *H*-3A), 2.12–2.04 (m, 2H, *H*-11a, *H*-12a), 1.98–1.88 (m, 2H, *H*-11b, *H*-12b), 1.54–1.43 (m, 2H, *H*-5a, *H*-8), 1.43–1.32 (m, 1H, *H*-5b), 1.30–1.16 (m, 1H, *H*-6a), 1.15–1.04 (m, 3H, *H*-6b, *H*-7), 0.96 (s, 7.2H, *H*-29A), 0.83 (d, ^{3}J = 6.6 Hz, 6H, *H*-9, *H*-9′), 0.74 (s, 1.8H, *H*-29B), 0.06 (s, 2.4H, *H*-27A), 0.05 (s, 2.4H, *H*-27A′), −0.02 (s, 1.2H, *H*-27B, *H*-27B′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 172.5 [171.6] (*C*-1), 158.8 [158.6] (*C*-15), 137.0 [136.9] (*C*-21), 134.7 [134.7] (*C*-25), 132.8 [133.0] (*C*-20), 129.5 [129.6] (*C*-17), 128.7 [128.7] (*C*-23), 128.4 [128.2] (*C*-19), 127.6 [127.7] (*C*-24), 126.5 [126.4] (*C*-22), 120.7 [121.2] (*C*-18), 119.1 [119.6] (*C*-26), 114.8 [114.4] (*C*-16), 71.6 [71.7] (*C*-4), 67.1 [68.5] (*C*-14), 56.0 [56.5] (*C*-10), 50.5 [50.3] (*C*-3), 50.1 [49.7] (*C*-2), 47.5 [46.2] (*C*-13), 39.2 [39.3] (*C*-7), 36.1 [36.2] (*C*-5), 28.0 [28.0] (*C*-8), 27.6 [29.0] (*C*-11), 26.3 [26.0] (*C*-29), 24.2 [21.8] (*C*-12), 23.1 [23.1] (*C*-6), 22.8 [22.9] (*C*-9), 22.6 (*C*-9′), 18.4 [18.2] (*C*-28), −3.0 [−3.1] (*C*-27), −4.3 [−4.5] (*C*-27′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{37}H_{56}NO_3Si^+$: 590.4024; found: 590.4003. Because of the slowly reconverting amide rotamers, ^{1}H and ^{13}C NMR spectra display a double set of signals (ratio 4:1). The absolute configuration of new stereogenic centers was elucidated via X-ray analysis of iodolactones.

Iodolactonization: Iodine (3.607 g, 14.231 mmol, 3 eq) was added to amide **14** (2.789 g, 4.727 mmol, 1.0 eq) in dimethoxy ethane (40 mL) and water (10 mL). The reaction mixture was stirred at room temperature for 21 h with exclusion of light. DCM (100 mL) and an aqueous $Na_2S_2O_3$ (30 mL, 10%) were added. The layers were separated and the aqueous layer was extracted with DCM (3× 100 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:30) to afford the iodolactones *ent*-β-**11** and *ent*-α-**11** (2.391 g, 4.296 mmol, 91%) as a yellow oil, 1:0.85 mixture of diastereomers. For characterization, an analytical amount was separated via column chromatography (EtOAc/petroleum ether 1:30).

Analytical data of **(3*R*,4*R*,5*S*)-4-((*S*)-1-(*tert*-butyldimethylsilyloxy)-5-methylhexyl)-5-(iodo-methyl)-3-((*E*)-phenethenyl)-dihydrofuran-2(3*H*)-one *ent*-α-11**: R_f = 0.18 (EtOAc/petroleum ether 1:30, cerium reagent, UV). HPLC: t_0 = 1.28 min, *k* = 4.50 (Nucleosil 50–5; EtOAc/hexane 5:95, 2 mL/min, 102 bar), t_0 = 1.60 min, *k* = 15.60 (*S*,*S*-Whelk-O1; EtOAc/hexane 8:92, 2 mL/min, 50 bar. $[\alpha]_D^{29} = +124.0°$ (CH_2Cl_2, *c* = 0.99 g/100 mL). IR (thin film): 2952 (m), 2931 (m), 2856 (w), 1779 (vs), 1496 (w), 1469 (m), 1385 (w), 1327 (w), 1254 (m), 1169 (w), 1132 (m), 1079 (s), 1006 (m), 962 (m), 888 (w), 835 (s), 805 (m), 775 (s), 745 (s), 692 (s), 614 (w), 602 (w), 586 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.38–7.30 (m, 4H, *H*-15, *H*-16), 7.29–7.24 (m, 1H, *H*-17), 6.61 (d, ^{3}J = 15.8 Hz, 1H, *H*-13), 6.00 (dd, ^{3}J = 15.9 Hz, ^{3}J = 8.0 Hz, 1H, *H*-12), 4.87–4.77 (m, 1H, *H*-5), 4.01–3.92 (m, 1H, *H*-6), 3.66–3.52 (m, 2H, *H*-3, *H*-18a), 3.31 (dd, ^{2}J = 11.3 Hz, ^{3}J = 9.7 Hz, 1H, *H*-18b), 2.75–2.65 (m, 1H, *H*-4), 1.65–1.43 (m, 3H, *H*-7, *H*-10), 1.36–1.22 (m, 2H, *H*-8), 1.20–1.04 (m, 2H, *H*-9), 0.91 (s, 9H, *H*-21), 0.85 (d, ^{3}J = 6.6 Hz, 3H, *H*-11), 0.84 (d, ^{3}J = 6.6 Hz, 3H, *H*-11′), 0.11 (s, 3H, *H*-19), 0.10 (s, 3H, *H*-19′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 175.7 (*C*-2), 136.1 (*C*-14), 135.8 (*C*-13), 128.8 (*C*-15), 128.3 (*C*-17), 126.6 (*C*-16), 122.9 (*C*-12), 80.3 (*C*-5), 69.8 (*C*-6), 49.7 (*C*-4), 44.4 (*C*-3), 39.0 (*C*-9), 35.5 (*C*-7), 28.1 (*C*-10), 26.0 (*C*-21), 23.3 (*C*-8), 22.7 (*C*-11), 22.6 (*C*-11′), 18.1 (*C*-20), 4.3 (*C*-18), −3.7 (*C*-19), −4.4 (*C*-19′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{41}INaO_3Si^+$: 579.1759; found: 579.1762.

Analytical data of **(3*R*,4*R*,5*R*)-4-((*S*)-1-(*tert*-butyldimethylsilyloxy)-5-methylhexyl)-5-(iodomethyl)-3-((*E*)-phenethenyl)-dihydrofuran-2(3*H*)-one *ent*-β-11**: R_f = 0.26 (EtOAc/petroleum ether 1:30, cerium reagent, UV). HPLC: t_0 = 1.70 min, *k* = 3.25 (Nucleosil 50–5; EtOAc/hexane 5:95, 2 mL/min, 102 bar), t_0 = 1.49 min, *k* = 20.42 (*S*,*S*-Whelk-O1; EtOAc/hexane 1:9, 2 mL/min, 50 bar). $[\alpha]_D^{29} = +19.0°$ (CH_2Cl_2, *c* = 1.00 g/100 mL). IR (thin film): 2952 (s), 2926 (s), 2854 (m), 1778 (vs), 1496 (w), 1463 (m), 1412 (w), 1362 (w), 1256 (m), 1163 (s), 1063 (m), 963 (m), 901 (w), 835 (s), 805 (m), 775 (s), 745 (s), 692 (s), 624 (w), 613 (w), 587 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.41–7.36 (m, 2H, *H*-16), 7.36–7.30 (m, 2H, *H*-15), 7.31–7.22 (m, 1H, *H*-17), 6.59 (d, ^{3}J = 15.8 Hz, 1H, *H*-13), 6.17 (dd, ^{3}J = 15.8 Hz, ^{3}J = 8.1 Hz, 1H, *H*-12), 4.37–4.30 (m, 1H, *H*-5), 3.81–3.77 (m, 1H, *H*-6), 3.65 (dd, ^{2}J = 11.1 Hz, ^{3}J = 4.0 Hz, 1H, *H*-18a), 3.42–3.33 (m, 2H, *H*-3, *H*-18b), 2.54–2.46 (m, 1H, *H*-4), 1.64–1.27 (m, 5H, *H*-15, *H*-16, *H*-17), 1.16–1.07 (m, 2H, *H*-9), 0.91 (s, 9H, *H*-21), 0.84 (d, ^{3}J = 6.6 Hz, 3H, *H*-11), 0.83 (d, ^{3}J = 6.6 Hz, 3H, *H*-11′), 0.13 (s, 3H, *H*-19), 0.11 (s, 3H, *H*-19′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 175.3 (*C*-2), 136.2 (*C*-14), 135.1 (*C*-13), 128.7 (*C*-15), 128.2 (*C*-17), 126.7 (*C*-16), 123.9 (*C*-12), 77.3 (*C*-5), 72.2 (*C*-6), 51.0 (*C*-4), 47.5 (*C*-3), 39.1 (*C*-9), 35.6 (*C*-7), 28.0 (*C*-10), 26.0 (*C*-21), 22.7 (*C*-11), 22.6 (*C*-11′), 22.6 (*C*-8), 18.2 (*C*-20), 11.1 (*C*-18), −3.8 (*C*-19), −4.2 (*C*-19′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{41}INaO_3Si^+$: 579.1762; found: 579.1745.

(2*R*,3*S*,4*S*)-4-((*tert*-Butyldimethylsilyloxy)-8-methyl-2-((*E*)-styryl)-3-vinyl-nonanoic acid: Zinc powder (1.658 g) and acetic acid (10 drops) were added to iodolactone *ent*-**11** (43.3 mg, 0.078 mmol, 1.0 eq, mixture of diastereomers) in Et_2O (5 mL). The reaction mixture was stirred for 2 d. After filtration through a silica gel pad and careful rinsing with DCM, the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:20 to 1:10 + 0.1% AcOH) to afford the acid (28.5 mg, 66.2 µmol, 85%) as yellow oil. R_f = 0.25 (EtOAc/petroleum ether 1:10 + 0,1% AcOH, ninhydrin, UV). For data see supporting information.

Methyl (2*R*,3*S*,4*S*)-4-((*tert*-butyldimethylsilyloxy)-8-methyl-2-((*E*)-2-phenylethenyl)-3-vinyl-nonanoate *ent*-12: *N*-Methyl-*N*-nitroso urea (139.6 mg, 1.354 mmol, 20.5 eq) was dissolved in Et_2O (20 mL) and aqueous KOH (20 mL, 40%) was added in a beaker at 0 °C. After stirring for 10 min the bright yellow color of diazomethane within the organic layer occurred. In a second beaker the crude acid (28.5 mg, 0.066 mmol, 1.0 eq) in Et_2O (5 mL) was treated with diazomethane in ether until the yellow color of surplus diazomethane remained. Stirring was continued at 0 °C for 5 h. Then acetic acid (5 mL, 2 M) in Et_2O was added dropwise to quench the excess of diazomethane and stirring was continued for further 30 min. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with Et_2O (3× 30 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:50) to afford ester *ent*-**12** (25.8 mg, 0.058 mmol, 88%) as a colorless oil. R_f = 0.25 (EtOAc/petroleum ether 1:50, cerium reagent, UV). $[\alpha]_D^{23} = +28.4°$ (CH_2Cl_2, c = 1.01 g/100 mL). IR (thin film): 2954 (s), 2931 (s), 2858 (m), 1740 (vs), 1471 (m), 1434 (m), 1363 (w), 1256 (s), 1155 (s), 1090 (s), 1002 (w), 969 (m), 919 (m), 836 (vs), 774 (s), 751 (m), 690 (m), 605 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.39–7.29 (m, 4H, *H*-13, *H*-14), 7.27–7.22 (m, 1H, *H*-15), 6.56 (d, ^3J = 15.9 Hz, 1H, *H*-11), 6.12 (dd, ^3J = 15.9 Hz, ^3J = 9.6 Hz, 1H, *H*-10), 5.85 (ddd, ^3J = 17.3 Hz, ^3J = 10.3 Hz, ^3J = 10.1 Hz 1H, *H*-16), 5.13 (dd, ^3J = 10.3 Hz, ^2J = 2.2 Hz, 1H, *H*-17a), 5.07 (dd, ^3J = 17.3 Hz, ^2J = 2.2 Hz, 1H, *H*-17b), 3.76 (ddd, ^3J = 9.5 Hz, ^3J = 4.6 Hz, ^3J = 1.7 Hz, 1H, *H*-4), 3.62 (s, 3H, *H*-21), 3.49–3.40 (m, 1H, *H*-2), 2.49 (ddd, ^3J = 11.0 Hz, ^3J = 10.1 Hz, ^3J = 1.7 Hz, 1H, *H*-3), 1.55–1.47 (m, 1H, *H*-8), 1.49–1.25 (m, 2H, *H*-5), 1.25–1.16 (m, 1H, *H*-6a), 1.19–1.05 (m, 3H, *H*-6b, *H*-7), 0.93 (s, 9H, *H*-20), 0.85 (d, ^3J = 6.6 Hz, 6H, *H*-9, *H*-9′), 0.03 (s, 3H, *H*-18), 0.02 (s, 3H, *H*-18′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 173.8 (*C*-1), 136.8 (*C*-12), 135.3 (*C*-16), 134.0 (*C*-11), 128.7 (*C*-14), 127.8 (*C*-15), 126.5 (*C*-13), 126.4 (*C*-10), 118.4 (*C*-17), 71.2 (*C*-4), 52.1 (*C*-2), 51.7 (*C*-21), 50.8 (*C*-3), 39.2 (*C*-7), 36.0 (*C*-5), 28.0 (*C*-8), 26.2 (*C*-20), 23.1 (*C*-6), 22.9 (*C*-9), 22.6 (*C*-9′), 18.4 (*C*-19), −3.2 (*C*-18), −4.2 (*C*-18′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{45}O_3Si^+$: 445.3132; found: 445.3135.

(2*R*,3*S*,4*S*)-4-((*tert*-Butyldimethylsilyloxy)-8-methyl-2-((*E*)-2-phenylethenyl)-3-vinylnonan-1-ol *ent*-15: DIBAL–H (0.82 mL, 0.82 mmol, 2.7 eq, 1.0 M in toluene) was added dropwise to ester *ent*-**12** (133.1 mg, 0.299 mmol, 1.0 eq) in DCM (2 mL) at −78 °C. After stirring at this temperature for 3 h, the reaction mixture was warmed to 0 °C. Saturated aqueous KNa tartrate (15 mL) was added dropwise and the resulting mixture was stirred for 1.5 h at room temperature. The layers were separated and the aqueous phase was extracted with DCM (5×10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:20) to afford alcohol *ent*-**15** (106.0 mg, 0.254 mmol, 85%) as a colorless oil. R_f = 0.29 (EtOAc/petroleum ether 1:10, vanillin, UV). $[\alpha]_D^{25} = +0.6°$ (CH_2Cl_2, c = 0.99 g/100 mL). IR (thin film): 3393 (br, m), 2954 (s), 2929 (s), 2857 (m), 1638 (w), 1494 (m), 1471 (m), 1386 (m), 1365 (m), 1254 (m), 1089 (s), 1057 (s), 1004 (m), 970 (m), 913 (m), 834 (vs), 807 (m), 773 (s), 748 (s), 692 (s), 665 (m), 614 (w), 601 (w), 592 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.40–7.30 (m, 4H, *H*-13, *H*-14), 7.27–7.22 (m, 1H, *H*-15), 6.55 (d, ^3J = 16.0 Hz, 1H, *H*-11), 6.00 (dd, ^3J = 16.0 Hz, ^3J = 9.3 Hz, 1H, *H*-10), 5.85 (ddd, ^3J = 17.4 Hz, ^3J = 10.1 Hz, ^3J = 10.1 Hz, 1H, *H*-16), 5.19 (dd, ^3J = 10.1 Hz, ^2J = 2.2 Hz, 1H, *H*-17a), 5.08 (dd, ^3J = 17.4 Hz, ^2J = 2.2 Hz, 1H, *H*-17b), 3.77 (ddd, ^3J = 9.4 Hz, ^3J = 4.7 Hz, ^3J = 1.6 Hz, 1H, *H*-4), 3.74–3.68 (m, 1H, *H*-1a), 3.45 (dd, ^2J = 11.0 Hz, ^3J = 8.0 Hz, 1H, *H*-1b), 2.69–2.58 (m, 1H, *H*-2), 2.14 (ddd, ^3J = 10.2 Hz, ^3J = 10.1 Hz, ^3J = 1.6 Hz, 1H, *H*-3), 1.60 (s, 1H, *H*-21), 1.56–1.43 (m, 2H, *H*-5a, *H*-8), 1.40–1.31 (m, 1H, *H*-5b), 1.29–1.16 (m, 1H, *H*-6a), 1.15–1.06 (m, 3H, *H*-6b, *H*-7), 0.91 (s, 9H, *H*-20), 0.85 (d, ^3J = 6.6 Hz, 6H, *H*-9, *H*-9′), 0.03 (s, 3H, *H*-18), 0.01 (s, 3H, *H*-18′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 137.1 (*C*-12), 136.9 (*C*-16), 133.8 (*C*-11), 130.9 (*C*-10), 128.7 (*C*-14), 127.6 (*C*-15), 126.3 (*C*-13), 117.8 (*C*-17), 72.8 (*C*-4), 65.1 (*C*-1), 50.2 (*C*-3), 46.3 (*C*-2), 39.2 (*C*-7), 35.9 (*C*-5), 28.0 (*C*-8), 26.2 (*C*-20), 23.3 (*C*-6), 22.9 (*C*-9), 22.6 (*C*-9′), 18.4 (*C*-19), −3.3 (*C*-18), −4.2 (*C*-18′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{45}O_2Si^+$: 417.3184; found: 417.3184.

Iodocyclization: Iodine (997.4 mg, 3.93 mmol, 3.03 eq) was added to alcohol *ent*-**15** (540.9 mg, 1.298 mmol, 1.0 eq) in Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (18 mL). The reaction mixture was stirred at room temperature for 9 h with exclusion of light. Et_2O (20 mL) and an aqueous $Na_2S_2O_3$ (20 mL, 10%) were added. The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was filtered through a silica gel pad (careful rinsing with DCM). The solvent was removed in vacuo and the residue was purified via HPLC (Gemini NX C18, MeCN, 40 mL/min, 37 bar) to afford iodoether *ent*-**21** (334.9 mg, 0.617 mmol, 48%) and iodoether *ent*-**20** (250.5 mg, 0.462 mmol, 36%) as colorless oils. For data of minor *cis* alkene *ent*-**21 a** see supporting information.

Analytical data of **(2*R*,3*R*,4*R*)-3-(((1*S*)-*tert*-butyldimethylsilyloxy)-5-methylhexyl)-2-(iodomethyl)-4-((*E*)-styryl)-tetrahydrofuran *ent*-21**: R_f = 0.19 (EtOAc/ petroleum ether 1:100, cerium reagent, UV). HPLC: t_0 = 1.33 min, k = 2.09 (Gemini NX C18, MeCN, 2 mL/min, 73 bar). $[\alpha]_D^{23} = +12.2°$ (CH_2Cl_2, c = 0.99 g/100 mL). IR (thin film): 3027 (w), 2954 (s), 2929 (s), 2899 (m), 2857 (s), 1740 (m), 1600 (w), 1493 (w), 1471 (m), 1411 (w), 1385 (w), 1364 (w), 1255 (s), 1075 (s), 1051 (s), 1006 (w), 967 (s), 938 (w), 835 (vs), 807 (m), 774 (vs), 747 (s), 693 (s), 615 (w), 597 (w), 585 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.38–7.26 (m, 4H, *H*-15, *H*-16), 7.27–7.18 (m, 1H, *H*-17), 6.42 (d, ^3J = 15.8 Hz, 1H, *H*-13), 6.13 (dd, ^3J = 15.8 Hz, ^3J = 9.1 Hz, 1H, *H*-12), 3.99 (dd, ^2J = 8.8 Hz, ^3J = 7.5 Hz, 1H, *H*-5a), 3.94 (ddd, ^3J = 6.6 Hz, ^3J = 6.4 Hz, ^3J = 3.1 Hz, 1H, *H*-2), 3.85–3.75 (m, 2H, *H*-5b, *H*-6), 3.56 (dd, ^2J = 10.5 Hz, ^3J = 3.1 Hz, 1H, *H*-21a), 3.32 (dd, ^2J = 10.5 Hz, ^3J = 6.4 Hz, 1H, *H*-21b), 3.00–2.88 (m, 1H, *H*-4), 2.08–1.99 (m, 1H, *H*-3), 1.63–1.42 (m, 3H, *H*-7, *H*-10), 1.42–1.16 (m, 2H, *H*-8), 1.13–1.01 (m, 2H, *H*-9), 0.91 (s, 9H, *H*-20), 0.81 (d, ^3J = 6.6 Hz, 3H, *H*-11), 0.79 (d, ^3J = 6.6 Hz, 3H, *H*-11′), 0.11 (s, 3H, *H*-18), 0.08 (s, 3H, *H*-18′). ^{1}H NMR (C_6D_6, 600 MHz): δ [ppm] = 7.26–7.22 (m, 2H, *H*-16), 7.16–7.10 (m, 2H, *H*-15), 7.08–7.02 (m, 1H, *H*-17), 6.34 (d, ^3J = 15.8 Hz, 1H, *H*-13), 6.06 (dd, ^3J = 15.8 Hz, ^3J = 9.2 Hz, 1H, *H*-12), 4.00–3.94 (m, 1H, *H*-2), 3.89 (dd, ^2J = 8.7 Hz, ^3J = 7.5 Hz, 1H, *H*-5a), 3.78–3.73 (m, 1H, *H*-5b), 3.73–3.67 (m, 1H, *H*-6), 3.47 (dd, ^2J = 10.4 Hz, ^3J = 3.4 Hz, 1H, *H*-21a), 3.18 (dd, ^2J = 10.4 Hz, ^3J = 5.9 Hz, 1H, *H*-21b), 2.80–2.72 (m, 1H, *H*-4), 2.08 (ddd, ^3J = 7.9 Hz, ^3J = 6.3 Hz, ^3J = 6.3 Hz, 1H, *H*-3), 1.55–1.45 (m, 1H, *H*-7a), 1.47–1.39 (m, 1H, *H*-10), 1.41–1.31 (m, 2H, *H*-7b, *H*-8a), 1.33–1.23 (m, 1H, *H*-8b), 1.10–1.01 (m, 2H, *H*-9), 0.97 (s, 9H, *H*-20), 0.83 (d, ^3J = 6.6 Hz, 3H, *H*-11), 0.81 (d, ^3J = 6.6 Hz, 3H, *H*-11′), 0.10 (s, 3H, *H*-18), 0.06 (s, 3H, *H*-18′).^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 137.1 (*C*-14), 131.6 (*C*-13), 129.9 (*C*-12), 128.7 (*C*-15), 127.6 (*C*-17), 126.3 (*C*-16), 80.9 (*C*-2), 72.8 (*C*-6), 72.8 (*C*-5), 55.3 (*C*-3), 47.9 (*C*-4), 39.2 (*C*-9), 36.0 (*C*-7), 28.1 (*C*-10), 26.1 (*C*-20), 22.7 (*C*-11), 22.7 (*C*-11′), 22.0 (*C*-8), 18.2 (*C*-19), 13.0 (*C*-21), −3.9 (*C*-18), −4.1 (*C*-18′). ^{13}C NMR (C_6D_6, 151 MHz): δ [ppm] = 137.4 (*C*-14), 131.9 (*C*-13), 130.3 (*C*-12), 128.9 (*C*-16), 127.7(*C*-17), 126.5 (*C*-15), 81.2 (*C*-2), 73.4 (*C*-6), 72.8 (*C*-5), 55.7 (*C*-3), 48.1 (*C*-4), 39.5 (*C*-9), 35.9 (*C*-7), 28.3 (*C*-10), 26.2 (*C*-20), 22.8 (*C*-11), 22.7 (*C*-11′), 22.2 (*C*-8), 18.3 (*C*-19), 13.1 (*C*-21), −3.9 (*C*-18), −4.1 (*C*-18′). HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{26}H_{43}INaO_2Si^+$: 565.1969; found: 565.1970.

Analytical data of **(2*R*,3*S*,4*R*)-4-(((2*S*)-*tert*-butyldimethylsilyloxy)-(1*S*)-ethenyl-6-methylheptyl)-3-iodo-2-phenyl-tetrahydrofuran *ent*-20**: R_f = 0.15 (EtOAc/ petroleum ether 1:100, cerium reagent, UV). HPLC: t_0 = 1.33 min, k = 3.01 (Gemini NX C18, MeCN, 2 mL/min, 73 bar). $[\alpha]_D^{23} = -43.3°$ (CH_2Cl_2, c = 0.98 g/100 mL). IR (thin film): 3068 (w), 2954 (s), 2929 (s), 2895 (m), 2860 (s), 1741 (m), 1636 (w), 1492 (w), 1471 (m), 1382 (w), 1365 (w), 1255 (s), 1086 (s), 1050 (s),

1027 (s), 1005 (m), 922 (m), 874 (w), 836 (vs), 807 (m), 774 (vs), 759 (s), 733 (w), 698 (s), 61w (w), 597 (w), 586 (w). ^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.43–7.39 (m, 2H, *H*-15), 7.37–7.30 (m, 3H, *H*-14, *H*-16), 5.79 (ddd, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^3J = 9.9 Hz, 1H, *H*-17), 5.26 (dd, ^3J = 10.2 Hz, ^2J = 2.1 Hz, 1H, *H*-18a), 5.14 (dd, ^3J = 17.2 Hz, ^2J = 2.1 Hz, 1H, *H*-18b), 4.96 (d, ^3J = 9.0 Hz, 1H, *H*-2), 4.07 (dd, ^2J = 8.8 Hz, ^3J = 8.7 Hz, 1H, *H*-5a), 4.00 (dd, ^2J = 8.8 Hz, ^3J = 7.5 Hz, 1H, *H*-5b), 3.78–3.67 (m, 2H, *H*-3, *H*-7), 2.81–2.71 (m, 1H, *H*-4), 2.55 (ddd, ^3J = 9.9 Hz, ^3J = 3.8 Hz, ^3J = 3.8 Hz, 1H, *H*-6), 1.59–1.52 (m, 1H, *H*-11), 1.51–1.42 (m, 1H, *H*-8a), 1.43–1.30 (m, 1H, *H*-8b), 1.29–1.18 (m, 2H, *H*-9), 1.18–1.10 (m, 2H, *H*-10), 0.91 (s, 9H, *H*-21), 0.88 (d, ^3J = 6.6 Hz, 3H, *H*-12), 0.88 (d, ^3J = 6.6 Hz, 3H, *H*-12′), 0.11 (s, 3H, *H*-19), 0.08 (s, 3H, *H*-19′). ^{1}H NMR (C_6D_6, 600 MHz): δ [ppm] = 7.58–7.54 (m, 2H, *H*-14), 7.19–7.15 (m, 2H, *H*-15), 7.11–7.08 (m, 1H, *H*-16), 5.74–5.66 (m, 1H, *H*-17), 5.07 (d, ^3J = 8.8 Hz, 1H, *H*-2), 5.06–4.99 (m, 2H, *H*-18), 4.05–3.98 (m, 2H, *H*-5), 3.89 (dd, ^3J = 8.8 Hz, ^3J = 8.8 Hz, 1H, *H*-3), 3.68 (ddd, ^3J = 6.1 Hz, ^3J = 6.1 Hz, ^3J = 3.8 Hz, 1H, *H*-7), 2.86–2.80 (m, 1H, *H*-4), 2.63 (ddd, ^3J = 9.8 Hz, ^3J = 4.0 Hz, ^3J = 3.8 Hz, 1H, *H*-6), 1.54–1.44 (m, 2H, *H*-8a, *H*-11), 1.41–1.20 (m, 3H, *H*-8b, *H*-9), 1.17–1.10 (m, 2H, *H*-10), 1.00 (s, 9H, *H*-21), 0.90 (d, ^3J = 6.7 Hz, 3H, *H*-12), 0.90 (d, ^3J = 6.7 Hz, 3H, *H*-12′), 0.14 (s, 3H, *H*-19), 0.08 (s, 3H, *H*-19′). ^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm] = 138.9 (*C*-13), 133.9 (*C*-17), 128.6 (*C*-14), 128.5 (*C*-16), 126.9 (*C*-15), 120.1 (*C*-18), 88.0 (*C*-2), 75.0 (*C*-7), 69.0 (*C*-5), 51.8 (*C*-4), 48.6 (*C*-6), 39.2 (*C*-10), 35.4 (*C*-8), 34.8 (*C*-3), 28.0 (*C*-11), 26.2 (*C*-21), 23.1 (*C*-9), 22.8 (*C*-12), 22.7 (*C*-12′), 18.3 (*C*-20), −3.8 (*C*-19), −3.8 (*C*-19′). ^{13}C NMR (C_6D_6, 151 MHz): δ [ppm] = 139.6 (*C*-13), 134.2 (*C*-17), 128.6 (*C*-15), 128.3 (*C*-16), 126.9 (*C*-14), 119.7 (*C*-18), 88.2 (*C*-2), 74.9 (*C*-7), 68.7 (*C*-5), 51.8 (*C*-4), 49.2 (*C*-6), 39.2 (*C*-10), 35.4 (*C*-8), 35.3 (*C*-3), 28.1 (*C*-11), 26.1 (*C*-21), 23.2 (*C*-9), 22.7 (*C*-12), 22.6 (*C*-12′), 18.2 (*C*-20), −3.9 (*C*-19), −4.0 (*C*-19′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{44}IO_3Si^+$: 543.2150; found: 543.2156.

((2*R*,3*R*,4*S*)-3-((1*S*)-((*tert*-Butyldimethylsilyloxy)-5-methylhexyl)-4-(hydroxymethyl)-2-(iodomethyl)-tetrahydrofuran: Alkene *ent*-**21** (85.1 mg, 0.157 mmol, 1.0 eq) in DCM (10 mL) was cooled to −78 °C. Oxygen was bubbled through the solution for 10 min. Then, ozone was bubbled through the solution for 1 h until the blue color of unreacted ozone occurred. The ozone was displaced by oxygen (10 min) and argon (15 min). Then, sodium borohydride (68.6 mg, 1.81 mmol, 11.6 eq) in MeOH (4 mL, cooled to −78 °C) was added dropwise. The mixture was stirred for 21 h, the temperature was allowed to warm-up to 23. After washing with semi-saturated aqueous NH_4Cl (20 mL), the aqueous layer was extracted with DCM (4×10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:6) to afford the *ent*-alcohol (72.8 mg, 0.155 mmol, 99%) as a colorless oil. R_f = 0.25 (EtOAc/petroleum ether 1:5, vanillin, UV). For analytical data see supporting information.

(2*R*,3*R*,4*R*)-3-((1*S*)-1-(*tert*-Butyldimethylsilyloxy)-5-methylhexyl)-4-*tert*-butyldimethylsilyloxymethyl-1-(iodomethyl)-tetrahydrofuran *ent*-27: Triethylamine (0.12 mL, 0.87 mmol, 7.4 eq) and TBSOTf (0.14 mL, 0.61 mmol, 5.2 eq) were added dropwise to *ent*-alcohol (55.3 mg, 0.118 mmol, 1.0 eq) in DCM (3 mL) at 0 °C. The mixture was stirred at room temperature for 20 h. After dilution with DCM (10 mL) and washing with saturated aqueous $NaHCO_3$ (8 mL), the resulting aqueous layer was extracted with DCM (4×6 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:100) to afford silyl ether *ent*-**27** (53.8 mg, 0.092 mmol, 78%) as a colorless oil. R_f = 0.20 (EtOAc/petroleum ether 1:50, cerium reagent). $[\alpha]_D^{23} = -1.2°$ (CH_2Cl_2, c = 1.00 g/100 mL). IR (thin film): 2954 (s), 2929 (s), 2857 (s), 1471 (m), 1411 (w), 1386 (m), 1362 (m), 1255 (s), 1176 (w), 1093 (s), 1073 (s), 1006 (m), 938 (w), 915 (w), 835 (vs), 774 (vs), 726 (w), 666 (m), 630 (w), 617 (w), 607 (w), 588 (w). ^{1}H NMR (C_6D_6, 400 MHz): δ [ppm] = 3.89 (dd, ^2J = 8.9 Hz, ^3J = 4.9 Hz, 1H, *H*-5a), 3.86–3.77 (m, 2H, *H*-2, *H*-5b), 3.75–3.69 (m, 1H, *H*-6), 3.64–3.58 (m, 2H, *H*-12), 3.42 (dd, ^2J = 10.2 Hz, ^3J = 4.6 Hz, 1H, *H*-19a), 3.14 (dd, ^2J = 10.2 Hz, ^3J = 5.3 Hz, 1H, *H*-19b), 2.36–2.26 (m, 1H, *H*-4), 2.01–1.94 (m, 1H, *H*-3), 1.61–1.48 (m, 1H, *H*-10), 1.48–1.32 (m, 4H, *H*-7, *H*-8), 1.19–1.10 (m, 2H, *H*-9), 0.97 (s, 9H, *H*-18), 0.96 (s, 9H, *H*-15), 0.92 (d, ^3J = 6.6 Hz, 6H, *H*-11, *H*-11′), 0.11 (s, 3H, *H*-16), 0.08 (s, 3H, *H*-16′), 0.07 (s, 6H, *H*-13, *H*-13′). ^{13}C NMR (C_6D_6, 101 MHz): δ [ppm] = 80.4 (*C*-2), 74.0 (*C*-6), 70.3 (*C*-5), 64.9 (*C*-12), 52.1 (*C*-3), 46.0 (*C*-4), 39.6 (*C*-9), 35.6 (*C*-7), 28.4 (*C*-10), 26.2 (*C*-15), 26.2 (*C*-18), 23.3 (*C*-8), 22.9 (*C*-11), 22.8 (*C*-11′), 18.5 (*C*-17), 18.3 (*C*-14), 12.2 (*C*-19), −3.9 (*C*-16), −4.0 (*C*-16′), −5.2 (*C*-13), −5.2 (*C*-13′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{54}IO_3Si_2^+$: 585.2651; found: 585.2654.

(3*S*,4*R*)-3-((1*S*)-*tert*-butyldimethylsilyloxy-5-methylhexyl)-4-(*tert*-butyldimethylsilyloxymethyl)-2-(methylene)-tetrahydrofuran *ent*-29: Potassium *tert*-butoxide (50.0 mg, 0.446 mmol, 14.6 eq) was added to iodoether *ent*-**27** (17.9 mg, 30.6 μmol, 1.0 eq) in THF (10 mL). The reaction mixture was heated for 3 d to 50 °C. Then, the solvent was removed in vacuo. The residue was dissolved in Et_2O (10 mL) and washed with water (10 mL). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to afford olefine *ent*-**29** (13.7 mg, 30.0 μmol, 98%) as a yellow oil. R_f = 0.19 (EtOAc/petroleum ether 1:20, cerium reagent). $[\alpha]_D^{25} = -1.4°$ (CH_2Cl_2, c = 1.00 g/100 mL). IR (thin film): 2954 (s), 2929 (s), 2896 (m), 2857 (m), 1732 (w), 1667 (m), 1602 (w), 1471 (m), 1386 (m),1363 (m), 1256 (s), 1092 (s), 1066 (s), 1006 (m), 939 (w), 889 (w), 837 (vs), 798 (m), 775 (vs), 713 (w), 666 (w), 625 (w), 613 (w), 605 (w), 594 (w). ^{1}H NMR (C_6D_6, 400 MHz): δ [ppm] = 4.63 (dd, ^4J = 1.6 Hz, ^2J = 1.5 Hz, 1H, *H*-19a), 4.15 (dd, ^2J = 8.8 Hz, ^3J = 6.9 Hz, 1H, *H*-5a), 4.07 (dd, ^2J = 8.8 Hz, ^3J = 4.2 Hz, 1H, *H*-5b), 3.90 (dd, ^2J = 1.5 Hz, ^4J = 1.4 Hz, 1H, *H*-19b), 3.89–3.85 (m, 1H, *H*-6), 3.71 (dd, ^2J = 9.8 Hz, ^3J = 5.1 Hz, 1H, *H*-12a), 3.45 (dd, ^2J = 9.8 Hz, ^3J = 8.8 Hz, 1H, *H*-12b), 2.73–2.69 (m, 1H, *H*-3), 2.68–2.59 (m, 1H, *H*-4), 1.68–1.60 (m, 1H, *H*-7a), 1.60–1.54 (m, 1H, *H*-8a), 1.54–1.46 (m, 1H, *H*-10), 1.45–1.34 (m, 1H, *H*-7b), 1.33–1.24 (m, 1H, *H*-8b), 1.24–1.05 (m, 2H, *H*-9), 0.99 (s, 9H, *H*-18), 0.94 (s, 9H, *H*-15), 0.90 (d, ^3J = 6.7 Hz, 3H, *H*-11), 0.90 (d, ^3J = 6.7 Hz, 3H, *H*-11′), 0.09 (s, 3H, *H*-16), 0.07 (s, 3H, *H*-16′), 0.04 (s, 6H, *H*-13, *H*-13′). ^{13}C NMR (C_6D_6, 101 MHz): δ [ppm] = 164.3 (*C*-2), 80.9 (*C*-19), 75.1 (*C*-6), 73.0 (*C*-5), 65.7 (*C*-12), 51.1 (*C*-3), 41.9 (*C*-4), 39.2 (*C*-9), 33.2 (*C*-7), 28.4 (*C*-10), 26.1 (*C*-18), 26.1 (*C*-15), 24.9 (*C*-8), 22.8 (*C*-11), 22.8 (*C*-11′), 18.5 (*C*-14), 18.3 (*C*-17), −4.0 (*C*-16), −4.5 (*C*-16′), −5.3 (*C*-13), −5.3 (*C*-13′). HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{25}H_{52}O_3Si_2Na^+$: 479.3347; found: 479.3359.

(3*S*,4*R*)-3-((1*S*)-1-((*tert*-Butyldimethylsilyloxy)-5-methylhexyl)-4-((*tert*-butyldimethylsilyloxy)-methyl)-dihydrofuran-2(3*H*)-one *ent*-30: Alkene *ent*-**29** (13.7 mg, 30 μmol, 1.0 eq) was dissolved in DCM (10 mL) and cooled to −78 °C. Then, ozone was bubbled through the solution for 1 h until the blue color of unreacted ozone occurred. The ozone was displaced by oxygen (10 min) and argon (15 min). Dimethyl sulfide (0.33 mL, 280.5 mg, 4.73 mmol, 145.8 eq) was added dropwise and the reaction mixture was stirred for 2 h at −78 °C and 1 h at room temperature. The solvent and the excess dimethyl sulfide were removed in vacuo. The residue was purified via column chromatography (EtOAc/petroleum ether 1:50) to afford lactone *ent*-**30** (10.3 mg, 22.5 μmol, 75%) as a colorless oil. R_f = 0.13 (EtOAc/petroleum ether 1:50, cerium reagent). $[\alpha]_D^{23} = +30.5°$ (CH_2Cl_2, c = 0.21 g/100 mL). IR (thin film): 2954 (s), 2929 (s), 2902 (m), 2857 (s), 1775 (s), 1736 (m), 1605 (w), 1514 (w), 1471 (m), 1389 (m), 1363 (m), 1255 (s), 1172 (m), 1094 (s), 1071 (s), 1006 (m), 938 (w), 837 (vs), 776 (vs), 713 (w), 667 (w), 627 (w), 598 (w). ^{1}H NMR ($CDCl_3$, 600 MHz): δ [ppm] = 4.34 (dd, ^2J = 9.0 Hz, ^3J = 8.2 Hz, 1H, *H*-5a), 4.09 (dd, ^2J = 9.0 Hz, ^3J = 5.9 Hz, 1H, *H*-5b), 4.05 (ddd, ^3J = 8.4 Hz, ^3J = 5.2 Hz, ^3J = 3.5 Hz, 1H, *H*-6), 3.73 (dd, ^2J = 10.0 Hz, ^3J = 4.6 Hz, 1H, *H*-12a), 3.58 (dd, ^2J = 10.0 Hz, ^3J = 6.5 Hz, 1H, *H*-12b), 2.75–2.69 (m,

1H, *H*-4), 2.61 (dd, $^3J=6.4$ Hz, $^3J=3.5$ Hz, 1H, *H*-3), 1.60–1.53 (m, 1H, *H*-7a), 1.55–1.49 (m, 1H, *H*-10), 1.49–1.42 (m, 1H, *H*-7b), 1.42–1.33 (m, 1H, *H*-8a), 1.32–1.26 (m, 1H, *H*-8b), 1.24–1.17 (m, 1H, *H*-9a), 1.17–1.09 (m, 1H, *H*-9b), 0.88 (s, 9H, *H*-18), 0.88 (s, 9H, *H*-15), 0.86 (d, $^3J=6.6$ Hz, 3H, *H*-11), 0.86 (d, $^3J=6.6$ Hz, 3H, *H*-11′), 0.09 (s, 3H, *H*-16), 0.07 (s, 3H, *H*-16′), 0.05 (s, 3H, *H*-13), 0.05 (s, 3H, *H*-13′). ^{1}H NMR (C_6D_6, 600 MHz): δ [ppm] = 4.20 (ddd, $^3J=7.9$ Hz, $^3J=4.8$ Hz, $^3J=2.8$, 1H, *H*-6), 4.08–4.03 (m, 1H, *H*-5a), 3.77 (dd, $^2J=9.1$ Hz, $^3J=5.6$ Hz, 1H, *H*-5b), 3.52–3.48 (m, 1H, *H*-12a), 3.33–3.28 (m, 1H, *H*-12b), 2.59–2.52 (m, 2H, *H*-3, *H*-4), 1.77–1.69 (m, 1H, *H*-7a), 1.54–1.42 (m, 3H, *H*-7b, *H*-8a, *H*-10), 1.39–1.25 (m, 1H, *H*-8b), 1.21–1.14 (m, 1H, *H*-9a), 1.14–1.06 (m, 1H, *H*-9b), 0.94 (s, 9H, *H*-18), 0.92 (s, 9H, *H*-15), 0.90 (d, $^3J=6.3$ Hz, 3H, *H*-11), 0.89 (d, $^3J=6.3$ Hz, 3H, *H*-11′), 0.05 (s, 3H, *H*-16), 0.02 (s, 3H, *H*-16′), 0.00 (s, 3H, *H*-13), −0.01 (s, 3H, *H*-13′). ^{13}C NMR ($CDCl_3$, 151 MHz): δ [ppm] = 177.0 (*C*-2), 72.5 (*C*-6), 69.9 (*C*-5), 64.3 (*C*-12), 47.8 (*C*-3), 39.5 (*C*-4), 39.0 (*C*-9), 34.2 (*C*-7), 28.1 (*C*-10), 25.9 (*C*-15, *C*-18), 24.2 (*C*-8), 22.7 (*C*-11), 22.6 (*C*-11′), 18.3 (*C*-14), 18.1 (*C*-17), −4.2 (*C*-16), −4.4 (*C*-16′), −5.4 (*C*-13), −5.4 (*C*-13′). ^{13}C NMR (C_6D_6, 151 MHz): δ [ppm] = 175.7 (*C*-2), 72.8 (*C*-6), 69.5 (*C*-5), 64.8 (*C*-12), 48.3 (*C*-3), 39.5 (*C*-4), 39.1 (*C*-9), 34.4 (*C*-7), 28.3 (*C*-10), 26.0 (*C*-18), 26.0 (*C*-15), 24.6 (*C*-8), 22.8 (*C*-11), 22.7 (*C*-11′), 18.4 (*C*-14), 18.2 (*C*-17), −4.3 (*C*-16), −4.5 (*C*-16′), −5.4 (*C*-13), −5.4 (*C*-13′). HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{50}O_4Si_2Na^+$: 481.3140; found: 481.3140.

(3*S*,4*S*)-3-((*S*)-1-Hydroxy-5-methylhexyl)-4-(hydroxymethyl)-dihydrofuran-2(3*H*)-one *ent*-2 d (+)-SCB-5: Acetic acid (16.8 mg, 0.280 mmol, 12.5 eq) and TBAF (0.23 mL, 0.23 mmol, 10.3 eq, 1.0 M in THF) were added dropwise to a solution of silyl ether *ent*-**30** (10.3 mg, 22.5 μmol, 1.0 eq) in THF (4 mL). The reaction mixture was stirred at room temperature for 20 h. After dilution with Et_2O (10 mL) and washing with an aqueous $NaHCO_3$ (10 mL), the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether 1:10 to 1:1) to afford (+)-SCB-5 *ent*-**2 d** (5.1 mg, 22 μmol, 99%) as a colorless oil. $R_f=0.20$ (EtOAc/petroleum ether 1:1, vanillin). $[\alpha]_D^{19}=+13.5^\circ$ (CH_2Cl_2, $c=0.50$ g/100 mL). IR (thin film): 3421 (s, br), 2953 (s), 2923 (s), 2869 (s), 1767 (s), 1666 (w), 1467 (m), 1388 (m), 1260 (m), 1222 (w), 1179 (s), 1132 (m), 1027 (vs), 906 (w), 846 (w), 804 (w), 680 (w), 651 (w), 625 (w), 613 (w), 597 (w), 583 (w). ^{1}H NMR (C_6D_6, 600 MHz): δ [ppm] = 3.80–3.74 (m, 1H, *H*-6), 3.73 (dd, $^2J=8.6$ Hz, $^3J=7.8$ Hz, *H*-5a), 3.28 (dd, $^2J=8.6$ Hz, $^3J=8.6$ Hz, 1H, *H*-5b), 3.00 (dd, $^2J=10.6$ Hz, $^3J=4.8$ Hz, 1H, *H*-12a), 2.90 (dd, $^2J=10.6$ Hz, $^3J=6.2$ Hz, 1H, *H*-12b), 2.81 (s, 1H, *H*-13), 2.16–2.07 (m, 2H, *H*-3, *H*-4), 1.95 (s, 1H, *H*-14), 1.53–1.45 (m, 2H, *H*-8a, *H*-10), 1.45–1.39 (m, 1H, *H*-7a), 1.38–1.24 (m, 2H, *H*-7b, *H*-8b), 1.18–1.05 (m, 2H, *H*-9), 0.90 (d, $^3J=6.7$ Hz, 3H, *H*-11), 0.90 (d, $^3J=6.7$ Hz, 3H, *H*-11′). ^{13}C NMR (C_6D_6, 151 MHz): δ [ppm] = 176.9 (*C*-2), 70.9 (*C*-6), 67.9 (*C*-5), 62.9 (*C*-12), 49.4 (*C*-3), 40.1 (*C*-4), 39.1 (*C*-9), 34.4 (*C*-7), 28.3 (*C*-10), 24.1 (*C*-8), 22.8 (*C*-11), 22.8 (*C*-11′). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{23}O_4^+$: 231.1592; found: 231.1591.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Bioactive γ-butyrolactone · Diastereoselective synthesis · Iodocyclization · Ozonolysis · Zwitterionic aza-Claisen rearrangement

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[15] For testing purpose, a racemic sequence had been conducted. Starting from racemic *N*-(4-benzyloxy-8-methyl-2-nonenyl)-pyrrolidine (ref. 13, supporting information), aza-Claisen rearrangement, amide cleavage and reduction delivered racemic key intermediate *rac*-**15** analog with high diastereoselectivity. For procedures and data see supporting information.

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[22] The zwitterionic aza-Claisen rearrangement led to the syntheses of both enantiomers of ester **12** and carbinol **15**, respectively. For completion of both, (−)-SCB-5 and (+)-SCB-5 total synthesis, several strategies had been tested involving only one of the enantiomer series. For clarification, all intermediates heading for (−)-SCB-5 **2 d**, the simple molecule numbers are used. All intermediates leading to (+)-SCB-5 *ent*-**2 d** are presented using the prefix "*ent*".

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[30] Sequence tetrahydrofurane **20** to lactone **26**: via isolation/purification of acid **24**: 10% yield, via isolation/purification of ester **25 a**: 23% yield, sequence without purification of the intermediates. 36% yield. Higher yields might be achievable optimizing the intermediate aldehyde **25 b** oxidation. However, such oxidation hampered from several competing processes in analogy to the formation of *ent*-**30** (see below).

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[32] For a final removal of the TBS ether strong basic conditions should be avoided. Any intramolecular transesterification incorporating the C3

hydroxymethyl group would have caused a C3 epimerization potentially leading to competing 2,3 *cis* configured GBL side products.

[33] Furthermore, a ketoformate was isolated indicating some over oxidation within this last Cr(VI) reaction. Presumably, the lactol suffered from H_2O elimination and subsequent dihydrofuran oxidative cleavage. For details and data see supporting information.

[34] For details and data lists see supporting information (NMR data measured in $CDCl_3$ and C_6D_6, respectively. Mori: NMR data in $CDCl_3$ published, ref. 10 h).

[35] Furthermore, orientation of the electron rich enolate terminus in the proximity of the empty *anti* bonding orbital of the C–OTBS bond, might be rated as an attractive interaction, too.

[36] Always, starting from both iodoethers **20**/**21**, reductive ring opening allowed regeneration of carbinols **15** with nearly quantitative yield. Thus, the likewise generation of iodoethers **20** and **21**, respectively, could be optimized by recycling the undesired isomer.

[37] First experiments introducing an ester group at the 1′ OH function gave small amounts of the ester. The major product displayed an *exo* double bond indicating a rapid condensation destroying the stereogenic centers at C2 an C1′. However, OH group inversion requires the absence of the lactone carbonyl function. For details see supporting information.

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