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Total Synthesis of Solandelactone I

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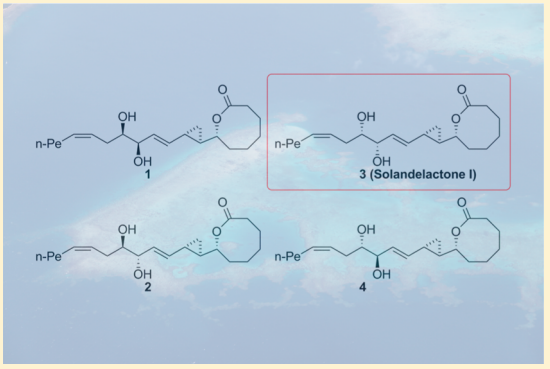
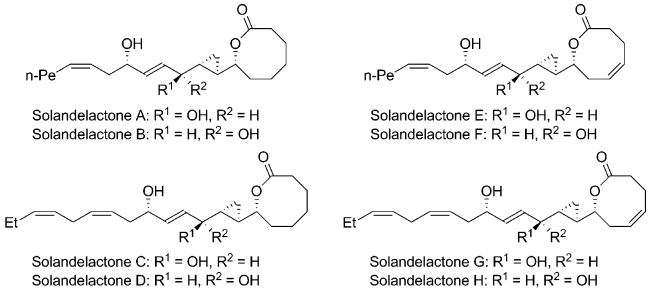
Supporting Information

ABSTRACT: Since the marine natural products solandelactones A−I were isolated from the hydroid *Solanderia secunda* and investigated by Seo et al. in 1996, considerable synthetic efforts toward these marine oxylipins followed. However, the structure elucidation of solandelactone I remained incomplete, and no synthesis has been reported. On the basis of our retrosynthetic analysis, the key building blocks were combined in a Horner−Wadsworth−Emmons reaction to create two common intermediates for the stereodivergent synthesis of all four diastereomers **1**−**4** matching the proposed structure of solandelactone I. Comparison of the published analytical data of natural product solandelactone I and data obtained from the synthetic endeavor toward diastereomers **1**−**4** enabled the structure assignment of isomer **3**; the proposed biosynthetic pathway for marine oxylipins also supports the result.



In 1996 Seo et al. reported the isolation and structure elucidation of marine oxylipins solandelactone A−I.[1] Following this report, chemical synthesis of these natural products showing promising bioactivity gained considerable attention.[2−8] Several total syntheses of solandelactones A−H and of key building blocks therefore were developed, manifesting the correct structures. In contrast to the accomplishments regarding synthesis of solandelactones A−H, no achievements toward the synthesis and structure elucidation of solandelactone I have been reported up to now. This may be explained by the initial report of Seo et al.[1] leaving the configurations of the two stereogenic centers unassigned and by the characterization of solandelactone I as being unstable. Herein, we report the structure assignment of solandelactone I by stereoselective total synthesis of all four diastereomers **1**, **2**, **3**, and **4** matching the proposed structure.



In the retrosynthetic analysis toward the potential solandelactone I **1**−**4**, we assumed that a Horner−Wadsworth−Emmons (HWE) reaction between phosphonates **5**/*ent*-**5** and cyclopropyl aldehyde **6** might be appropriate to enable a late diversification to obtain the desired structures **1**−**4**. Recently, we reported the synthesis of the cyclopropyl lactone **6** as a key intermediate in the syntheses of solandelactones A and B,[9] while enantiomerically pure phosphonates **5** and *ent*-**5** were assumed to be accessible starting from commercially available compounds, alkyne **7** and oxiranes **8**/*ent*-**8** (compounds can also be synthesized from chiral pool compounds D- and L-serine at low cost following a reliable and approved procedure[10,11]) (Scheme 1).

Once the olefination products **10**/*dia*-**10** are formed, all four diastereomers **1**−**4** should be accessible by stereoselective reduction of the keto group in the presence or absence of the TBS protecting group (TBS: *tert*-BuMe_2Si group stemming from **5** or *ent*-**5**) and consequently the TBS protective group cleavage either before or after the reduction step. Because the absolute and relative configurations of solandelactone I were unknown, it was regarded as necessary to synthesize all four diastereomers for determination of the correct configurations of the stereogenic centers and identification of the natural product (Scheme 2).

RESULTS AND DISCUSSION

Synthesis of the Western Part. Starting from alkyne **7**, the desired phosphonates **5** and *ent*-**5** were synthesized in five steps. The starting material 1-heptyne (**7**) was iodinated by

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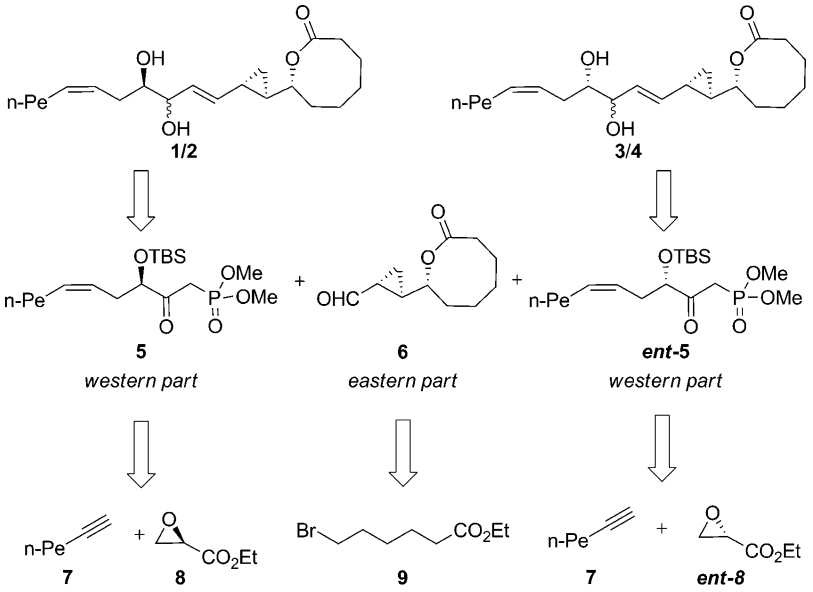
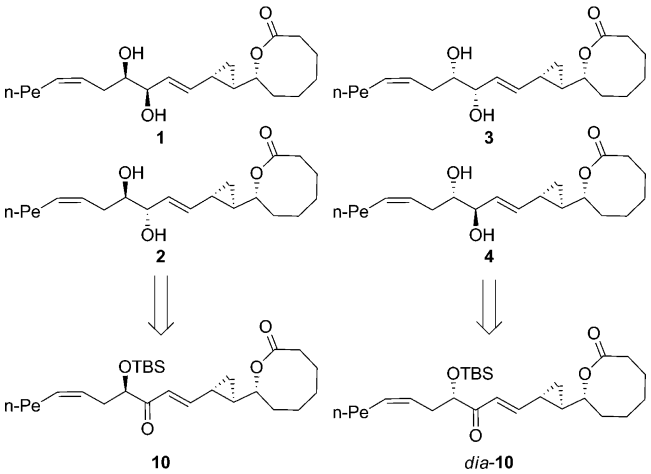
Scheme 1. Retrosynthetic Approach toward All Diastereomers 1−4 of Solandelactone I's Proposed Structure



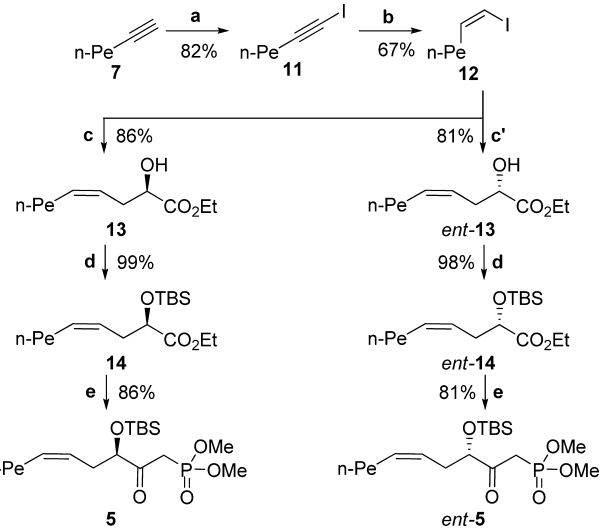
Scheme 2. Synthesis of Four Diastereomers from Two Common Precursors



lithiation followed by quenching with I_2. In the next step iodoalkyne **11** was converted to *Z*-iodoalkene **12** following a hydroboration/protodeboronation procedure.[12] For the synthesis of enantiomerically pure α-hydroxy esters **13** and *ent*-**13** compound **12** was transformed to the corresponding cuprate via Li−I exchange followed by reaction with a Cu(I) salt. Unexpectedly, initial experiments using *tert*-butyllithium[13] for lithiation and copper bromide failed. For this reason, halogen−metal exchange was performed using elemental lithium,[14] while subsequent formation of the required cuprate nucleophile was achieved in analogy with a procedure by Lipshutz and Barton.[14] As exact stoichiometry of reagents is very important in this step, the formed organolithium reagent was titrated according to Plaquevent.[15] After formation of the cuprate reagent, it was applied directly for the ring-opening of oxirane **8** or *ent*-**8**, respectively, to form the two enantiomeric esters **13** and *ent*-**13** with excellent enantioselectivity (ee >98%) in separate reactions. Hydroxy groups of **13** and *ent*-**13** were protected with TBS (*tert*-butyldimethylsilyl) protective groups, and then α-siloxy esters **14** and *ent*-**14** were finally converted to phosphonates **5** and *ent*-**5**.

The oxiranes **8** and *ent*-**8** required for the previously described ester synthesis (**13**/*ent*-**13**, Scheme 3) were obtained

Scheme 3. Synthesis of the Western Part of Solandelactone I[a]



[a]Conditions: (a) 1.00 equiv of 2.5 M *n*-butyllithium (in hexanes), 1.00 equiv of I_2, Et_2O; (b) i: 1.00 equiv of 10 M $BH_3{\cdot}Me_2S$, Et_2O, 2.00 equiv of cyclohexene; ii: 0.50 mL/mmol acetic acid (conc); (c) i: 4.50 equiv of Li, Et_2O, ii: 0.50 equiv of CuCN, THF, iii: 0.55 equiv of oxirane **8**; (c′) i: 4.50 equiv of Li, Et_2O, ii: 0.50 equiv of CuCN, THF, iii: 0.55 equiv of oxirane *ent*-**8**, (d) CH_2Cl_2, 1.30 equiv of imidazole, 1.30 equiv of TBSCl; (e) 2.00 equiv of methyl dimethylphosphonate, THF, 2.5 M *n*-butyllithium (in hexanes).

in a three-step procedure from moderately priced chiral pool compounds L- and D-serine following a perfectly reliable procedure (Scheme 4).[10,11] In our hands **8** and *ent*-**8** were obtained in 28% and 38% yield over three steps, respectively.

Synthesis of Solandelactone I Diastereomers. For joining the cyclopropyl lactone **6** and phosphonates **5** and *ent*-**5**, respectively, HWE reactions were performed, resulting in isolation of diastereomerically pure compounds **10** and *dia*-**10**.

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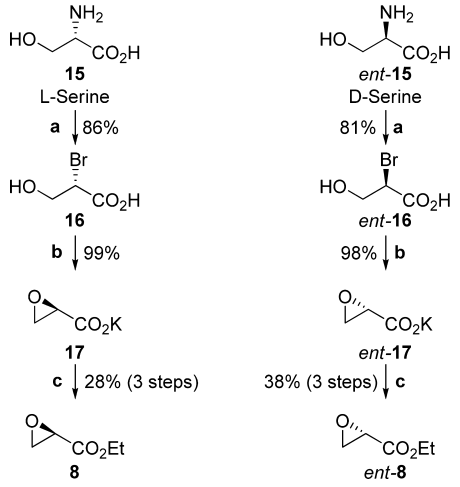
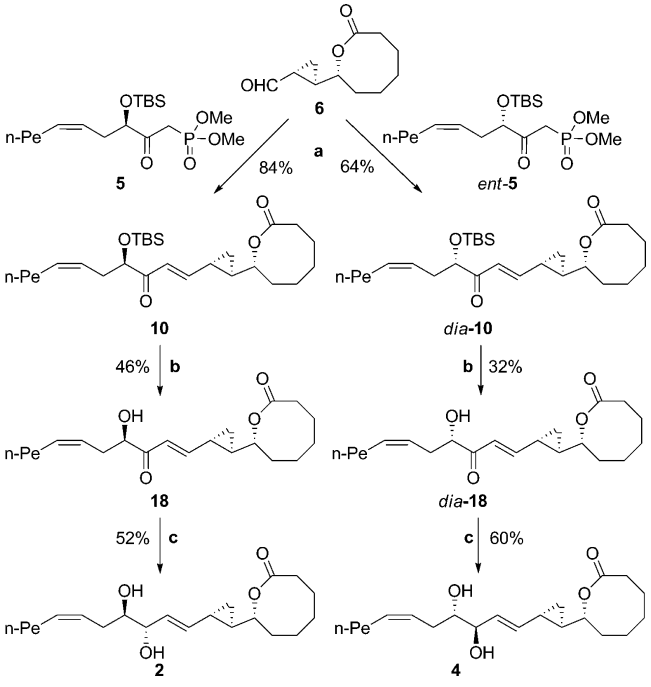
Scheme 4. Synthesis of Oxiranes 8/*ent*-8 from Serine[a]



[a]Conditions: (a) 3.40 equiv of KBr, H_2O, HBr, 1.25 equiv of $NaNO_2$; (b) 2.46 equiv of KOH, EtOH; (c) 1.00 equiv of benzyl triethylammonium chloride, 3.75 equiv of EtBr, CH_2Cl_2.

These two diastereomers constitute common precursors for the four diastereomers **1**–**4**, of which one is assumed to be the structure of solandelactone I. To obtain the *anti*-configured isomers **2** and **4**, compounds **10** and *dia*-**10** were deprotected by silyl group cleavage with TBAF, resulting in isolation of compounds **18** and *dia*-**18**. Finally the carbonyl groups of α-hydroxy ketones **18** and *ent*-**18** were reduced stereoselectively with zinc borohydride to obtain the *anti*-configured isomers for solandelactone I assignment (Scheme 5).

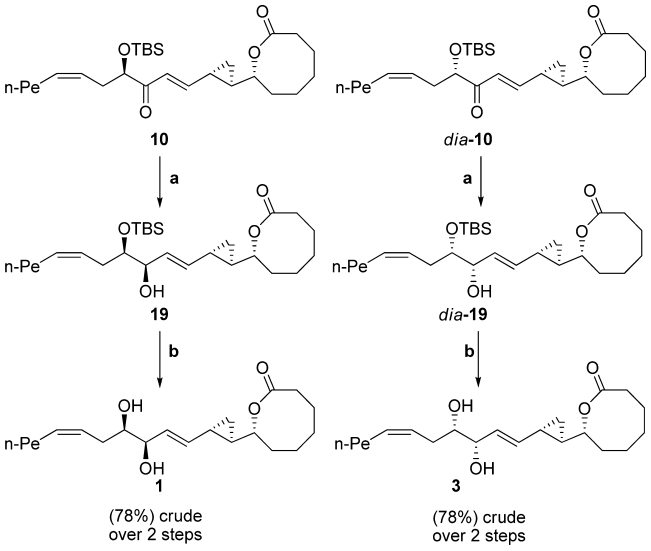
Scheme 5. Preparation of *anti*-Diastereomers 2 and 4[a]



[a]Conditions: (a) 3 equiv of Cs_2CO_3, CH_3CN, 1.10 equiv of of **5** (for the synthesis of compound **10**)/*ent*-**5** (for the synthesis of compound *dia*-**10**), THF; (b) 1.25 equiv of TBAF·$3H_2O$, THF; (c) 8.00 equiv of 0.25 M $Zn(BH_4)_2$ solution in THF, THF.

In contrast, synthesis of the *syn*-configured isomers (**1** and **3**) commenced with the reduction of the carbonyl functionality applying modified Luche conditions.[16] The desired vicinal *syn*-diols **1** and **3** were obtained by cleavage of TBS protective groups (Scheme 6). Purification difficulties due to separation

Scheme 6. Preparation of the *syn*-Diastereomer 1 and 3[a]



[a]Conditions: (a) 1.30 equiv of $CeCl_3$, 1.30 equiv of $NaBH_4$, THF; (b) 1.00 equiv of TBAF, THF.

problems and presumably low stability on the normal silica columns and the alternatively applied preparative HPLC resulted in a loss of yield, but did increase purity in the final step.

Structure Assignment. As a first step toward identification of solandelactone I NMR data published by Seo et al.[1] and NMR data obtained from the four diastereomers synthesized were compared. By this, the *anti*-configured isomers **2** and **4** were ruled out as possible structures. While the ^{1}H NMR spectra of solandelactone I and both *syn*-diastereomers **1** and **3** show two distinct peaks for H-7 and H-13 ($\Delta\delta$ = 0.21 ppm), these proton signals of the *anti*-diastereomers **2**/**4** partially overlap in the 600 MHz spectra (Figure 1). Apart from this, no further conclusions were drawn from the interpretation of ^{1}H NMR spectra, as the spectra of *syn*-isomers **1** and **3** are very similar and both match the data given for solandelactone I; unfortunately no sample of the natural product was available for direct comparison.

Turning to ^{13}C NMR spectroscopy, a general shift of approximately 0.2 ppm was found when ^{13}C NMR spectra of *syn*-diastereomers **1**/**3** and data from solandelactone I were compared, which is assumed to be a systematic deviation from the measurement of solandelactones by Seo et al. and our NMR experiments.[8,9] To facilitate comparison, $\Delta\delta$ of the ^{13}C NMR shifts were calculated. In particular the data for C-11 and C-13 were assumed to be significant, with diastereomer **3** showing a better match with the reported data (Table 1 and Supporting Information for the complete list).

In order to get evidence for structure **3** being identical with solandelactone I, the specific rotation was determined. Again, no complete congruence of obtained data and literature data was observed, but the value obtained from compound **3** was clearly closer to published specific rotation of solandelactone I

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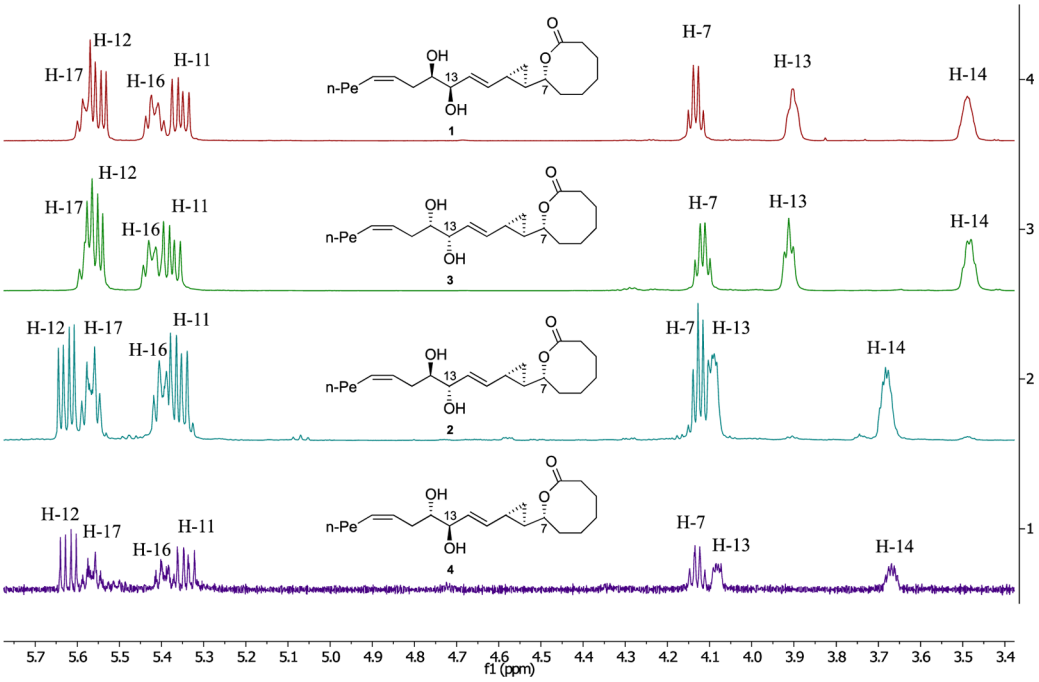

Figure 1. Comparison of the ^{1}H NMR spectra of the two *syn*- and *anti*-configured diastereomers **1**−**4** representing the proposed structure for solandelactone I.

Table 1. Comparison of the NMR Shifts of Both *syn*-Configured Diastereomers and Data Reported by Seo et al.[1]

	diastereomer **3**[a]		diastereomer **1**[a]		solandelactone I[b] (according to Seo et al.)	
position	δ_C, type; $\Delta\delta$ [ppm]	δ_H (J in Hz)	δ_C, type; $\Delta\delta$ [ppm]	δ_H (J in Hz)	δ_C, type	δ_H (J in Hz)
7	81.43, CH; + 0.14	4.12, m$_c$	81.32, CH; + 0.03	4.13, m$_c$	81.29, CH	4.12, dt (6.3, 7.6)
11	136.04, CH; + 0.42	5.38, dd (8.7, 15.4)	136.35, CH; + 0.73	5.37, dd (8.7, 15.4)	135.62, CH	5.37, dd (8.3, 15.1)
12	127.76, CH; + 0.16	5.56, dd (7.0, 15.3)	127.71, CH; + 0.11	5.56, dd (7.1, 15.4)	127.60, CH	5.56, dd (6.3, 15.1)
13	75.27, CH; + 0.17	3.91, m$_c$	75.49, CH; + 0.39	3.91, m$_c$	75.10, CH	3.92, dd (6.3, 6.3)
14	74.43, CH; + 0.14	3.48, m$_c$	74.42, CH; + 0.13	3.49, m$_c$	74.29, CH	3.49, ddd (4.8, 6.3, 7.8)
16	124.55, CH; + 0.13	5.42, m$_c$	124.50, CH; + 0.08	5.42, m$_c$	124.42, CH	5.42, dtt (1.5, 7.8, 9.8)
17	133.85, CH; + 0.30	5.54−5.60, m (overlapped)	133.96, CH; + 0.41	5.53−5.60, m (overlapped)	133.55, CH	5.57, dtt (1.5, 7.3, 9.8)

[a]Compound measured in $CDCl_3$ with a 600 MHz NMR device (m$_c$ = centered multiplet). [b]Compound measured in $CDCl_3$ with a 500 MHz NMR device.

Table 2. Specific Rotation Values ($[\alpha]_D^{25}$) of All Four Diastereomers (1−4) of Solandelactone I

	anti		*syn*		
	2	**4**	**1**	**3**	Seo et al.
$CHCl_3$	−12.2 (c = 0.18)	−20.8 (c = 0.66)	−9.3 (c = 1.00)	−30.6 (c = 1.00)	
MeOH			−13.3 (c = 0.33)	−48.6 (c = 0.50)	−37.0 (c = 0.50)

(Table 2). Furthermore, the assumption that the structure of compound **3** matches the structure of solandelactone I is also supported by the assumed biosynthesis (Scheme 7). With respect to the postulated biosynthesis of the structurally related constanolactones by the Gerwick group,[17−19] Shin et al.[1] adopted it also for the group of solandelactones. The primary step, the lipoxygenase-catalyzed oxidation of the corresponding fatty acid **20** or **21**, respectively, ultimately decides the configuration of this stereogenic center at position C-12 (and C-14 in the case of the solandelactones). It is not changed in any of the assumed intermediates **22**−**25**. The diversity with respect to the formation of different diastereomeric natural products stems from the unselective hydroxylation of the allyl systems **24** and **25** leading on one hand to the structurally unambiguously assigned solandelactones A + B (**26**) + (**27**) as well as constanolactones A + B (**28**) + (**29**), but also to the regioisomeric constanolactone F (**30**). Obviously, this relates to diastereomer **3**, and it hence can be assumed that the natural product solandelactone I possesses this (13*S*,14*S*)-configuration. An interesting side aspect is the fact that in the constanolactone series the corresponding *anti*-isomer (constanolactone E) is also known; one could speculate that another solandelactone J (matching the structure of diastereomer **4**) that was not isolated from natural sources yet is a likely natural extension within this series of marine oxylipins.

SUMMARY

In summary we established a stereodivergent synthesis (eight linear steps to lactone **6**[9] and five linear steps to phosphonates **5**/*ent*-**5** starting from known or commercially available

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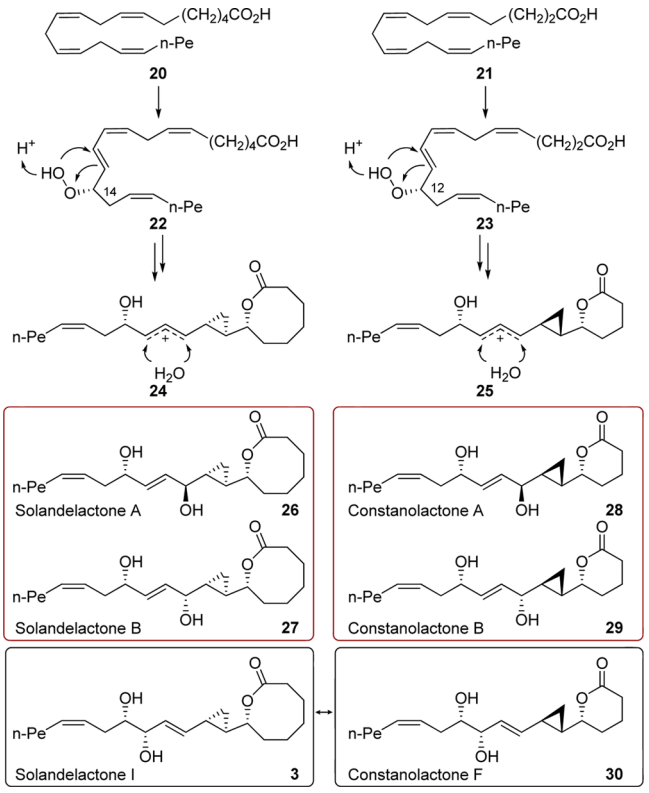
Scheme 7. Proposed Biosynthesis of Constanolactones[17−19] (Right) and Solandelactones[1] (Left)



compounds; the final sequence required three additional steps) of all four diastereomers of the structure proposed for solandelactone I. As the source of the enantiomerically pure building blocks, low cost amino acids D- and L-serine were used. All four diastereomers **1**−**4** were synthesized from HWE products **10** and *dia*-**10**. Two of these compounds (*anti*-configured isomers **2**/**4**) were excluded from being the natural product according to the comparison of the obtained NMR data and literature data.[1] Compound **3** was finally found to best match the data given for marine oxylipin solandelactone I. This assignment is supported by the proposed biosynthesis.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotation values were measured (at 20 or 25 °C) in $CHCl_3$ and in case of the proposed natural product in MeOH. Infrared measurements were performed using an FT-IR spectrometer (Spectrum One) from PerkinElmer. ^1H NMR spectra were measured with a 600 MHz and ^{13}C NMR spectra with a 151 MHz spectrometer (Ultra Shield; Bruker). For structure elucidation and assignments, DEPT135, COSY, HSQC, and HMBC were measured. All spectra were assigned to the appropriate signals of the deuterated solvents ($CDCl_3$: 7.26 ppm; D_2O: 4.79 ppm). GC/MS measurements were carried out using a Hewlett-Packard HP 6890 Series GC System/Hewlett-Packard 5973 mass selective detector. Therefore, aliquots of the reaction were quenched with NH_4Cl and extracted with EtOAc. HPLC measurements (Dionex UltiMate 3006) with different chiral stationary-phase columns were always performed using the solvent system heptane/2-propanol at 25 °C (for further information see the Supporting Information).

Chemicals. All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, VWR International, or Fischer Scientific. The applied solvents have been purchased as H_2O-free agents or, as in case of THF, toluene, CH_2Cl_2, and diethyl ether, were dried via a solvent purification system (Braun MB SPS 800).

1-Iodohept-1-yne (11). In a flame-dried Schlenk flask equipped with a magnetic stirring bar under a N_2 atmosphere 51.1 mL of 2.5 M *n*-butyl lithium solution in hexanes (124.7 mmol, 1.00 equiv) was added to a solution of 1-heptyne (**7**) (16.4 mL, 12.0 g, 124.8 mmol) in 60 mL of Et_2O at −50 °C over 30 min. Stirring was continued for 30 min at the same temperature. The solution was cooled to −70 °C (formation of white solid was observed); then a solution of iodine (31.70 g, 124.7 mmol, 1.00 equiv) in 170 mL of Et_2O performed under inert conditions was added dropwise over 1 h. Upon completion of addition, the cooling bath was removed and the reaction was allowed to reach room temperature (rt) while stirring.[12] The reaction mixture was washed three times with 150 mL of H_2O, then dried over $MgSO_4$ and filtered. After evaporation of the solvent the product **11** (22.40 g, 100.8 mmol, 81%) was isolated as a colorless oil (under storage it turned slightly red) by vacuum distillation (bp 69−70 °C; 7 mbar). Analytical data are in agreement with those previously reported.[12]

(*Z*)-1-Iodohept-1-ene (12). A solution of 10 M $BH_3{\cdot}Me_2S$ (9.00 mL, 90.1 mmol, 1.00 equiv) in 90 mL of Et_2O at 0 °C was placed in a flame-dried Schlenk flask. Freshly distilled cyclohexene (18.24 mL, 180.1 mmol, 2.00 equiv) was added while stirring with a magnetic stirring bar. After 10 min the ice bath was removed and the reaction mixture was stirred for a further 50 min at rt (formation of a precipitate). Then the mixture was cooled to 0 °C again, 1-iodoheptyne (**11**) (20.00 g, 90.06 mmol, 1.00 equiv) was added within 10 min, and the mixture was stirred for a further 30 min at this temperature. Upon removal of the cooling bath, the reaction mixture was stirred for another hour, leading to full consumption of the previously observed precipitate. The solution was cooled to 0 °C again, and 45 mL of glacial acetic acid was added within 15 min. After 2 h of stirring, 50 mL of Et_2O was added, and the solution was washed four times with 40 mL of H_2O and dried over $MgSO_4$. After evaporation of the solvents, alkene **12** (13.32 g, 59.5 mmol, 66%) was obtained by distillation under reduced pressure (bp: 63−64 °C, 6−7 mbar). Analytical data are in agreement with those previously reported.[12]

(*S*)-(−)-2-Bromo-3-hydroxypropanoic acid (16). L-Serine (24.00 g, 228.0 mmol, 1.00 equiv) and KBr (92.40 g, 776.5 mmol, 3.40 equiv) were dissolved in 185 mL of H_2O in a three-necked-flask equipped with a magnetic stirring bar, gas inlet tube, and a washing bottle (KOH solution). At room temperature, 56.3 mL of 48% hydrobromic acid was added, and the reaction was cooled to −15 °C afterward. Subsequently seven portions of sodium nitrite (19.70 g, 285.5 mmol, 1.25 equiv; ∼2.80 g every 15 min) were added to the reaction mixture while bubbling N_2 gently. After addition of sodium nitrite was complete, N_2 bubbling was stopped after 1.5 h and the reaction was stirred for a further 6 h at 0 °C. The reaction was then stirred while bubbling N_2 for 40 min before it was extracted six times with 200 mL of Et_2O and dried over $MgSO_4$. Solvent was removed at 25 °C under reduced pressure using a rotary evaporator. The obtained almost pure product **16** (31.00 g, 183.5 mmol, 80%) was used without further purification in the next step.

(*R*)-(+)-2-Bromo-3-hydroxypropanoic acid (*ent*-16). Compound *ent*-**16** was prepared in full analogy with the synthesis of **16** using D-serine instead of L-serine. The almost pure product *ent*-**16** (82%, 186.4 mmol, 31.50 g) was used without further purification in the following step. The analytical data correspond to those of compound **16**.

Potassium (*R*)-(+)-2,3-Epoxypropanoate (17). Crude **16** was dissolved in 120 mL of freshly distilled absolute EtOH and cooled to −20 °C. A solution of KOH (<86%, 25.40 g, 452.70 mmol, 2.46 equiv) in 130 mL of freshly distilled absolute EtOH was filtered and added to a previously formed solution of **16**. After 1.5 h the temperature was set to 0 °C, and the reaction mixture was stirred for 17 h. The formed precipitate was collected by filtration; the filtrate was reduced to half of its volume and cooled to 0 °C. The precipitate was filtered off again, and the combined solids were dried under vacuum. The obtained solids were split into three portions. Each portion was dissolved in 224 mL of EtOH and 6 mL of H_2O and heated to reflux for 30 min; then the solution was directly filtered hot. The precipitate formed upon cooling the filtrate was collected, and the mother liquor was used for the next extraction. After extraction of all three portions the filtration

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residues of all three approaches were also extracted using the mother liquor a fourth time. All collected precipitates of the cooled filtrates were combined and dried under vacuum. The fluffy solid (12.30 g, max. 97.50 mmol, max. 53%) was applied in the next reaction step without titrimetric determination of residual KBr content.[11]

Potassium (*S*)-(−)-2,3-Epoxypropanoate (*ent*-17). *ent*-**17** was prepared in full analogy with the synthesis of compound **17**. Also the analytical data correspond to those mentioned in the synthesis of **17**.

Ethyl (*R*)-(+)-2,3-Epoxypropanoate (8). In a round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser with drying tube potassium salt **17** (12.30 g, max. 97.50 mmol, 1.00 equiv), benzyltriethylammonium chloride (22.20 g, 97.50 mmol, 1.00 equiv), and bromoethane (27.30 mL, 365.6 mmol, 3.75 equiv) were dissolved in 150 mL of CH_2Cl_2. The reaction mixture was heated to reflux for 5 h, and then it was stirred at rt for 17 h and finally heated to reflux for 6 h. The solvent and excess bromoethane were removed on a rotary evaporator (22 °C; 560−120 mbar). The remaining solid was triturated with 4 × 60 mL of Et_2O. The ethereal solution was then dried over $MgSO_4$ and filtered. After evaporation (22 °C), the obtained crude **8** was purified via vacuum distillation (44−47 °C; 3.8 mbar). Compound **8** (7.58 g, 65.30 mmol, 67%; 28% over three steps) was obtained as an analytically pure and clear liquid and stored in a refrigerator. Analytical data are in agreement with those previously reported.[11]

Ethyl (*S*)-(−)-2,3-Epoxypropanoate (*ent*-8). *ent*-**8** (10.05 g, 86.50 mmol, 38% over three steps) has been synthesized in full analogy with compound **8**.

Ethyl (*R,Z*)-2-Hydroxydec-4-enoate (13). *i. Preparation of Organolithium Reagent Solution.* In analogy with a procedure by Whitesides and co-workers[20] lithium beads (846 mg, 106 mmol, 4.50 equiv) and 28 mL of Et_2O were cooled to −30 °C in a flame-dried and argon-purged Schlenk flask while stirring. (*Z*)-Iodoheptene (**12**) (5.30 g, 23.7 mmol, 1.00 equiv) was dissolved in 7 mL of Et_2O and added to the lithium beads via cannula through a septum. The reaction mixture was stirred vigorously for 1.5 h. The completion of conversion was determined by hydrolysis of an aliquot using a 0.5 M aqueous HCl solution and extraction with EtOAc followed by GC/MS analysis. Thus, the obtained solution of the organolithium reagent was titrated according to a procedure by Duhamel and Plaquevent[15] and found to be 0.59 M. Stirring was stopped and the solids were allowed to settle, enabling withdrawal of the formed solution by syringe needle.

ii. Preparation of Cyano Diorganocopper Reagent Solution/ Ring-Opening Reaction. In a separate Schlenk flask CuCN (866.00 mg, 9.67 mmol, 1.00 equiv) was dried for 2 h at 120 °C under high vacuum. In analogy with a procedure by Lipshutz and Barton[14] the Cu(I) salt was suspended in 12 mL of THF and cooled to −78 °C. A previously prepared 0.59 M heptenyl lithium solution in Et_2O (33.0 mL, 19.3 mmol, 2.00 equiv) was added to the CuCN suspension; then the acetone/dry ice cooling bath was removed. The stirred reaction mixture was allowed to warm while stirring until the mixture became clear; then it was immediately cooled again to −78 °C. In the next step, a solution of oxirane **8** (1.20 g, 10.6 mmol, 1.10 equiv) in 8 mL of THF was added via syringe. The cooling bath was removed, and the reaction was allowed to reach room temperature. The reaction mixture was hydrolyzed by addition of 20 mL of saturated aqueous NH_4Cl and 2 mL of 25% aqueous NH_3 solution. The aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organic layers were washed with 50 mL of H_2O and 50 mL of brine. The organic layer was dried over $MgSO_4$ and filtered, and then the solvent was evaporated under reduced pressure. The desired product **13** (1.80 g, 8.30 mmol, 86%) was isolated by column chromatography on silica (85/15 PE/EtOAc) as a colorless oil. Analytical data are in agreement with those previously reported.[21]

Ethyl (*S,Z*)-2-Hydroxydec-4-enoate (*ent*-13). Compound *ent*-**13** was prepared in full analogy with the synthesis of the enantiomeric compound **13** using a 0.55 M (*Z*)-hept-1-en-1-yllithium solution (35.00 mL, 19.14 mmol, 2.00 equiv), 857.00 mg of CuCN (9.57 mmol, 1.00 equiv), and oxirane *ent*-**8** (1.22 g, 10.5 mmol, 1.10 equiv). The desired product could be isolated as a pure and colorless oil in 81% yield (1.67 g, 7.79 mmol).

Ethyl (*R,Z*)-2-((*tert*-Butyldimethylsilyl)oxy)dec-4-enoate (14). Ester **13** (902 mg, 4.21 mmol, 1.00 equiv) was dissolved in 5 mL of CH_2Cl_2 under a N_2 atmosphere. At 0 °C imidazole (373 mg, 5.47 mmol, 1.30 equiv) was added while stirring. When dissolution of imidazole was complete, TBSCl (825 mg, 5.47 mmol, 1.30 equiv) was added, and the resulting mixture was stirred for 24 h; then 20 mL of H_2O was added. The aqueous layer was extracted with 3 × 30 mL of EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was purified by column chromatography on silica (90/10 PE/EtOAc). Title compound **14** (1.37 g, 4.15 mmol, 99%) was obtained as a clear oil: R_f (80/20 PE/EtOAc) 0.81; $[\alpha]_D^{20}$ +11.9 (*c* 1.00, $CHCl_3$); FT-IR ν_{max} 2957, 2929, 2858, 1755, 1734, 1464, 1251, 1184, 1136, 1034, 947, 835, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.05 [3H, s, $Si(CH_3)_a$], 0.08 [3H, s, $Si(CH_3)_b$], 0.88 (3H, t, $^3J_{10,9}$ = 7.1 Hz, H-10), 0.9 [9H, s, $SiC(CH_3)_3$], 1.27 (3H, t, $^3J_{2',1'}$ = 7.2 Hz, H-2′), 1.22−1.39 (6H, m, H-10, H-9, H-8), 1.96−2.07 (2H, m, H-6), 2.46 (2H, m, H-3), 4.10−4.22 (3H, m, H-1′, H-2), 5.40 (1H, m, H-4), 5.50 (1H, m, H-5); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −5.1 [$Si(CH_3)_a$], −4.8 [$Si(CH_3)_b$], 14.2 (C-10), 14.4 (C-2′), 18.5 [$SiC(CH_3)_3$], 22.7 (C-7, C-8 or C-9), 25.9 [$SiC(CH_3)_3$], 27.5 (C-6), 29.4 (C-7, C-8 or C-9), 31.7 (C-7, C-8 or C-9), 33.4 (C-3), 60.9 (C-1′), 72.6 (C-2), 124.1 (C-4), 133.0 (C-5), 173.5 (C-1); HPLC [Chiralpak IC, 250 × 10 mm, Fa. Diacel; 100% heptane; 0.5 mL/min, 202 nm] 37.8 min; ee > 95%; HRMS *m/z* 351.2324 $[M + Na]^+$ (calcd for $C_{18}H_{36}O_3SiNa$, 351.2329).

Ethyl (*S,Z*)-2-((*tert*-Butyldimethylsilyl)oxy)dec-4-enoate (*ent*-14). Compound *ent*-**14** was prepared in full analogy with the synthesis of compound **14**. By the use of alcohol *ent*-**13** (1.00 g, 4.67 mmol, 1.00 equiv), imidazole (349.00 mg, 5.13 mmol, 1.10 equiv), and TBSCl (703.00 mg, 4.67 mmol, 1.00 equiv) in 8 mL of CH_2Cl_2, compound *ent*-**14** could be isolated as a colorless oil in 98% yield (1.50 g, 4.57 mmol): $[\alpha]_D^{20}$ −10.1 (*c* 1.03, $CHCl_3$); HPLC [Chiralpak IC, 250 × 10 mm, Fa. Diacel; 100% heptane; 0.5 mL/min, 202 nm]: 45.6 min; ee > 99%. All further analytical data correspond to the enantiomeric compound **14**.

Dimethyl (*R,Z*)-(3-((*tert*-Butyldimethylsilyl)oxy)-2-oxoundec-5-en-1-yl)phosphonate (5). A solution of dimethyl methylphosphonate (651 μL, 756 mg, 6.09 mmol, 2.00 equiv) in 12 mL of THF was cooled to −78 °C, and 2.44 mL of a 2.5 M solution of *n*-BuLi (in hexanes) (6.09 mmol, 2.00 equiv) was added dropwise. After 1 h of stirring at this temperature, a solution of α-siloxy ester **14** (1.00 g, 3.05 mmol, 1.00 equiv) in 5.2 mL of THF was added slowly to the solution. The acetone/dry ice cooling bath was removed after 1 h, and the reaction mixture was quenched by addition of 20 mL of a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with 4 × 30 mL of Et_2O, and the combined organic layers were washed with 25 mL of H_2O and 25 mL of brine. The combined organic layers were dried over $MgSO_4$ and filtered; then solvents were removed on a rotary evaporator. The residue was submitted to purification by column chromatography on silica (100% Et_2O). Phosphonate **5** (1.06 g, 2.61 mmol, 86%) was isolated as a slightly yellow oil: R_f (100% Et_2O) 0.27; $[\alpha]_D^{20}$ −11.3 (*c* 1.12, $CHCl_3$); FT-IR ν_{max} 2955, 2929, 2857, 1726, 1463, 1365, 1253, 1029, 835, 810, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.07 [3H, s, $Si(CH_3)_a$], 0.08 [3H, s, $Si(CH_3)_b$], 0.88 (3H, t, $^3J_{10,9}$ = 7.1 Hz, H-11), 0.92 [9H, s, $SiC(CH_3)_3$], 1.21−1.39 (6H, m, H-10, H-9, H-8), 2.00 (2H, m H-7), 2.31−2.38 (1H, m, H-4a), 2.47 (1H, m, H-4b), 3.23 (1H, dd, $^2J_{1a,P}$ = 21.3 Hz, $^2J_{1a,1b}$ = 15.4 Hz, H-1a), 3.27 (1H, dd, $^2J_{1b,P}$ = 20.9 Hz, $^2J_{1b,1a}$ = 15.4 Hz, H-1b), 3.79 (6H, d, $^3J_{H,P}$ = 11.2 Hz, OCH_3), 4.15 (1H, dd, $^3J_{3,4a}$ = 6.4 Hz, $^3J_{3,4b}$ = 5.7 Hz, H-3), 5.34 (1H, dtt, $^3J_{5,6}$ = 10.6 Hz, $^3J_{5,4}$ = 8.2 Hz, $^4J_{5,7}$ = 1.6 Hz, H-5), 5.51 (1H, dtt, $^3J_{6,5}$ = 10.6 Hz, $^3J_{6,7}$ = 7.3 Hz, $^4J_{6,4}$ = 1.4 Hz, H-6); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −4.8 [$Si(CH_3)_a$], −4.6 [$Si(CH_3)_b$], 14.2 (C-11), 18.2 [$SiC(CH_3)_3$], 22.7 (C-8 or C-9), 25.9 [$SiC(CH_3)_3$], 27.5 (C-7), 29.3 (C-8 or C-9), 31.7 (C-10), 32.5 (C-4), 35.4 (d, $^1J_{1,P}$ = 136.5 Hz, C-1), 53.0 (d, $^2J_{OCH3,P}$ = 6.3 Hz, $(OCH_3)_a$), 53.1 (d, $^2J_{OCH3,P}$ = 6.4 Hz, $(OCH_3)_b$), 78.8 (C-3), 123.3 (C-5), 133.5 (C-6), 204.7 (d, $^2J_{2,P}$ = 6.8 Hz, C-2); HPLC [Chiralcel OD-H, 250 × 10 mm, Fa. Diacel; heptane/2-propanol 95/5, 0.5 mL/min, 202 nm] 10.7 min; ee > 99%; HRMS *m/z* 429.2194 $[M + Na]^+$ (calcd for $C_{19}H_{39}O_5PNa$, 429.2197); anal. found C 56.07, H 9.69, calcd for $C_{19}H_{39}O_5PSi$ C 56.13, H 9.67.

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Dimethyl (*S,Z*)-(3-((*tert*-Butyldimethylsilyl)oxy)-2-oxoundec-5-en-1-yl)phosphonate (*ent*-5). *ent*-**5** was prepared in full analogy with the synthesis procedure of compound **5** using α-siloxy ether *ent*-**14** (1.00 g, 3.04 mmol, 1.00 equiv) diluted in 5.5 mL of THF for the conversion with dimethyl methylphosphonate (651 μL, 755 mg, 6.09 mmol, 2.00 equiv) in 12 mL of THF and a 2.5 M solution of *n*-BuLi (in hexanes) (2.44 mL, 6.09 mmol, 2.00 equiv). Product could be isolated in 81% yield (1.00 g, 2.47 mmol): $[\alpha]_D^{20}$ +13.5 (*c* 0.51, $CHCl_3$); HPLC [Chiralcel OD-H, 250 × 10 mm, Fa. Diacel; heptane/2-propanol 95/5, 0.5 mL/min, 202 nm] 12.1 min; ee = 98%; anal. found C 56.15, H 9.70, calcd for $C_{19}H_{39}O_5PSi$ C 56.13, H 9.67.

Fragment Coupling Product *dia*-10. To a solution of phosphonate *ent*-**5** (137 mg, 0.34 mmol, 1.20 equiv) in 0.5 mL of CH_3CN under a N_2 atmosphere was added $CsCO_3$ (274 mg, 0.84 mmol, 3.00 equiv). Cs_2CO_3 itself was dried for 3 h under vacuum before usage. The mixture was stirred for 1 h at rt; then it was cooled to −15 °C, and a solution of the aldehyde[9] **6** (55 mg, 0.28 mmol, 1.00 equiv) in 0.5 mL of THF was added dropwise. The reaction mixture was allowed to reach rt. Stirring was continued for 4 days; then the reaction was hydrolyzed by addition of a saturated aqueous NH_4Cl solution. It was extracted with 4 × 15 mL of Et_2O, and the combined organic layers were washed twice with 15 mL of brine before it was dried over $MgSO_4$. Evaporation of the solvent and purification via silica chromatography (80/20 PE/EtOAc) resulted in isolation of the desired product *ent*-**10** (85.5 mg, 0.18 mmol, 64%) as a colorless oil: R_f (80/20 PE/EtOAc) 0.41, R_f (100 Et_2O) 0.85; $[\alpha]_D^{20}$ −64.6(*c* 1.12; $CHCl_3$); FT-IR ν_{max} 2928, 2857, 1733, 1691, 1614, 1463, 1327, 1252, 1228, 1136, 1095, 1046, 984, 939, 835, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.03 [3H, s, Si(CH_3)], 0.05 [3H, s, Si(CH_3)], 0.88 (3H, t, $^3J_{22,21}$ = 7.1 Hz, H-22), 0.90 [9H, s, SiC(CH_3)$_3$], 0.94 (1H, ddd, $^3J_{9a,10}$ = 8.65 Hz, $^3J_{9a,8}$ = 4.95 Hz, $^2J_{9a,9b}$ = 5.00 Hz, H-9a), 1.14 (1H, ddd, $^3J_{9b,10}$ = 8.40 Hz, $^3J_{9b,8}$ = 6.00 Hz, $^2J_{9b,9a}$ = 5.00 Hz, H-9b), 1.21−1.33 (6H, m, H-21, H-20, H-19), 1.35−1.38 (1H, m, H-8), 1.48−1.61 (4H, m, H-4, H-5a, H-10), 1.67−1.73 (1H, m, H-5b), 1.78−1.83 (2H, m, H-6), 1.86−1.89 (2H, m, H-3), 1.96−2.02 (2H, m, H-18), 2.30−2.40 (2H, m, H-15), 2.41−2.47 (2H, m, H-2), 4.09 (1H, dd, $^3J_{14,15a}$ = 7.4 Hz, $^3J_{14,15b}$ = 5.6 Hz, H-14), 4.24 (1H, m$_c$, H-7), 5.35 (1H, dtt, $^3J_{16,17}$= 10.8 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,18}$ = 1.6 Hz, H-16), 5.48 (1H, dtt, $^3J_{16,17}$ = 10.8 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,18}$ = 1.6 Hz, H-17), 6.51 (1H, dd, $^3J_{11,12}$ = 15.5 Hz, $^3J_{11,10}$ = 9.8 Hz, H-11), 6.64 (1H, d, $^3J_{12,11}$ = 15.5 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −4.7 [Si(CH_3)], −4.7 [Si(CH_3)], 14.1 (C-9), 14.2 (C-22), 18.4 [SiC(CH_3)$_3$], 20.4 (C-10), 22.7 (C-20), 24.4 (C-4), 25.9 [Si(CH_3)$_3$], 26.8 (C-8), 27.0 (C-5), 27.5 (C-18), 29.4 (C-19), 29.4 (C-3), 31.7 (C-21), 33.1 (C-2, 33.4 (C-15), 37.3 (C-6), 78.5 (C-14), 80.4 (C-7), 122.7 (C-12), 123.9 (C-16), 133.0 (C-17), 151.1 (C-11), 176.7 (C-1), 200.7 (C-13); HRMS *m/z* 499.3212 [M + Na]$^+$ (calcd for $C_{28}H_{48}O_4SiNa$, 499.3214).

Fragment Coupling Product 10. HWE olefination product **10** (28 mg, 60 μmol, 84%) was prepared in full analogy with its diastereomer *dia*-**10** in a reaction of aldehyde **6** (13 mg, 70 μmol, 1.0 equiv) in 0.2 mL of THF and phosphonate **5** (31 mg, 80 μmol, 1.10 equiv) with Cs_2CO_3 (66.7 mg, 0.20 mmol, 3.00 equiv) in 0.2 mL of CH_3CN: R_f (80/20 PE/EtOAc) 0.41; $[\alpha]_D^{20}$ −37.3 (*c* 1.01; $CHCl_3$); FT-IR ν_{max} 2928, 2857, 1733, 1690, 1613, 1463, 1328, 1252, 1228, 1183, 1160, 1136, 1094, 1047, 1004, 984, 939, 901, 835, 778, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.03 [3H, s, Si(CH_3)], 0.05 [3H, s, Si(CH_3)], 0.88 (3H, t, $^3J_{22,21}$ = 7.1 Hz, H-22), 0.91 [9H, s, SiC(CH_3)$_3$], 0.94 (1H, ddd, $^3J_{9a,10}$ = 8.65 Hz, $^3J_{9a,8}$ = 4.95 Hz, $^2J_{9a,9b}$ = 5.00 Hz, H-9a), 1.15 (1H, ddd, $^3J_{9b,10}$ = 8.40 Hz, $^3J_{9b,8}$ = 6.00 Hz, $^2J_{9b,9a}$ = 5.00 Hz, H-9b), 1.21−1.33 (6H, m, H-21, H-20, H-19), 1.34−1.37 (1H, m, H-8), 1.48−1.61 (4H, m, H-4, H-5a, H-10), 1.67−1.73 (1H, m, H-5b), 1.79−1.84 (2H, m, H-6), 1.85−1.90 (2H, m, H-3), 1.96−2.02 (2H, m, H-18), 2.30−2.40 (2H, m, H-15), 2.41−2.47 (2H, m, H-2), 4.09 (1H, dd, $^3J_{14,15a}$ = 7.4 Hz, $^3J_{14,15b}$ = 5.6 Hz, H-14), 4.27 (1H, m$_c$, H-7), 5.35 (1H, dtt, $^3J_{16,17}$ = 10.8 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,18}$ = 1.6 Hz, H-16), 5.48 (1H, dtt, $^3J_{16,17}$ = 10.8 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,18}$ = 1.6 Hz, H-17), 6.51 (1H, dd, $^3J_{11,12}$ = 15.4 Hz, $^3J_{11,10}$ = 9.9 Hz, H-11), 6.65 (1H, d, $^3J_{12,11}$ = 15.5 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −4.7 [Si(CH_3)], −4.8 [Si(CH_3)], 13.9 (C-9), 14.2 (C-22), 18.4 [SiC(CH_3)$_3$)], 20.4 (C-10), 22.7 (C-20), 24.4 (C-4), 25.9 [Si(CH_3)$_3$], 26.7 (C-8), 27.0 (C-5), 27.5 (C-18), 29.4 (C-19), 29.4 (C-3), 31.7 (C-21), 33.1 (C-2), 33.4 (C-15), 37.4 (C-6), 78.6 (C-14), 80.1 (C-7), 122.5 (C-12), 122.5 (C-12), 124.0 (C-16), 133.0 (C-17), 151.2 (C-11), 176.6 (C-1), 200.8 (C-13); HRMS *m/z* 499.3212 [M + Na]$^+$ (calcd for $C_{28}H_{48}O_4SiNa$, 499.3219).

(14*S*)-Alcohol *dia*-18. In a 10 mL Schlenk flask 44.5 mg of HWE product *dia*-**10** (90 μmol, 1.0 equiv) was dissolved in 4 mL of THF and cooled to 0 °C. After the addition of TBAF·3H_2O (37 mg, 0.12 mmol, 1.25 equiv) the reaction mixture was stirred for 1 h at rt. After addition of saturated aqueous NH_4Cl the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration the solvents were evaporated under reduced pressure. After purification by column chromatography on silica (50/50−20/80 pentane/Et_2O, for application to column crude product, was dissolved in a minimal amount of EtOAc) the title compound *dia*-**18** (10 mg, 30 μmol, 32%) was obtained as a colorless oil: R_f (Et_2O) 0.56; $[\alpha]_D^{20}$ −28.7 (*c* 0.54; $CHCl_3$); FT-IR ν_{max} 3462, 3013, 2927, 2858, 1723, 1687, 1615, 1456, 1230, 1137, 1035, 985, 946, 935, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (3H, t, $^3J_{22,21}$ = 7.0 Hz, H-22), 0.96 (1H, ddd, $^3J_{9a,10}$ = 8.9 Hz, $^3J_{9a,8}$ = 5.0 Hz, $^2J_{9a,9b}$ = 5.0 Hz, H-9a), 1.21 (1H, d, $^3J_{9b,10}$ = 8.3 Hz, H-9b), 1.23−1.37 (6H, m, H-21, H-20, H-19), 1.40 (1H, m$_c$, H-8), 1.45−1.65 (4H, m, H-4, H-5a, H-10), 1.65−1.75 (1H, m, H-5b), 1.82 (2H, m, H-6), 1.83−1.94 (2H, m, H-3), 2.02 (2H, d, $^3J_{18,17}$ = 7.3 Hz, H-18), 2.31−2.40 (1H, m, H-15a), 2.44 (2H, m$_c$, H-2), 2.53−2.61 (1H, m, H-15b), 3.52 (1H, d, $^3J_{OH,14}$ = 5.6 Hz, OH), 4.28−4.40 (2H, m, H-7, H-14), 5.35 (1H, dtt, $^3J_{16,17}$ = 10.9 Hz, $^3J_{16,15}$ = 7.3 Hz, $^4J_{16,18}$ = 1.5 Hz, H-16), 5.54 (1H, dtt, $^3J_{17,16}$ = 10.9 Hz, $^3J_{17,18}$ = 7.3 Hz, $^4J_{17,15}$ = 1.4 Hz, H-17), 6.33 (1H, d, $^3J_{12,11}$ = 15.4 Hz, H-12), 6.55 (1H, dd, $^3J_{11,12}$ = 15.4 Hz, $^3J_{11,10}$ = 10.1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.9 (C-9), 14.2 (C-22), 20.3 (C-10), 22.7 (C-19 or C-20), 24.4 (C-4), 26.8 (C-5), 27.2 (C-8), 27.6 (C-18), 29.4 (C-19 or C-20), 29.4 (C-3), 31.7 (C-21), 32.4 (C-15), 33.2 (C-2), 37.4 (C-6), 75.1 (C-14), 79.6 (C-7), 122.5 (C-12), 123.1 (C-16), 133.8 (C-17), 152.6 (C-11), 176.6 (C-1), 199.3 (C-13); HRMS *m/z* 385.2350 [M + Na]$^+$ (calcd for $C_{22}H_{34}O_4Na$, 385.2349).

(14*R*)-Alcohol 18. In a 10 mL Schlenk flask 28 mg of HWE product **10** (60 μmol, 1.00 equiv) was dissolved in 4 mL of THF and cooled to 0 °C. After the addition of TBAF·3H_2O (23 mg, 70 μmol, 1.25 equiv) the reaction mixture was stirred for 1.5 h at rt. A 20 mL amount of saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with Et_2O (20 mL) three times. The combined organic layers were washed with brine, then dried over $MgSO_4$ and filtered. After removal of solvents on a rotary evaporator, product **18** (10 mg, 30 μmol, 46%) was isolated by column chromatography on silica (50/50−20/80 pentane/Et_2O, crude product **18** was dissolved in a minimal amount of EtOAc for application) as a colorless oil: R_f (Et_2O) 0.55; $[\alpha]_D^{20}$ −55.3 (*c* 1.43; $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (3H, t, $^3J_{22,21}$ = 7.0 Hz, H-22), 0.97 (1H, ddd, $^3J_{9a,10}$ = 8.7 Hz, ^3J $_{9a,8}$ = 5.0 Hz, $^2J_{9a,9b}$ = 5.0 Hz, H-9a), 1.21 (1H, ddd, $^3J_{9b,10}$ = 8.4 Hz, 3J9b,8 = 6.0 Hz, $^2J_{9b,9a}$ = 5.0 Hz, H-9b), 1.23−1.36 (6H, m, H-21, H-20, H-19), 1.40 (1H, m$_c$, H-8), 1.46−1.66 (4H, m, H-4, H-5a, H-10), 1.66−1.73 (1H, m, H-5b), 1.79−1.83 (2H, m, H-6), 1.85−1.91 (2H, m, H-3), 2.01 (2H, dm, $^3J_{18,17}$ = 7.3 Hz, H-18), 2.8 (1H, dm, $^2J_{15a,15b}$ = 14.5 Hz, H-15a), 2.41−2.48 (2H, m, H-2), 2.56 (1H, dm, $^2J_{15b,15a}$ = 14.5 Hz, H-15b), 3.54 (1H, d, $^3J_{OH,14}$ = 5.6 Hz, OH), 4.32−4.37 (2H, m, H-7, H-14), 5.35 (1H, dtt, $^3J_{16,17}$ = 10.9 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,18}$ = 1.6 Hz, H-16), 5.54 (1H, dtt, $^3J_{17,16}$ = 10.9 Hz, $^3J_{17,18}$ = 7.3 Hz, $^4J_{17,15}$ = 1.5 Hz, H-17), 6.34 (1H, d, $^3J_{12,11}$ = 15.3 Hz, H-12), 6.56 (1H, dd, $^3J_{11,12}$ = 15.3 Hz, $^3J_{11,10}$ = 10.1 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.9 (C-9), 14.2 (C-22), 20.4 (C-10), 22.7 (C-19 or C-20), 24.4 (C-4), 26.8 (C-5), 27.2 (C-8), 27.6 (C-18), 29.4 (C-19 or C-20), 29.4 (C-3), 31.7 (C-21), 32.3 (C-15), 33.2 (C-2), 37.3 (C-6), 75.3 (C-14), 79.5 (C-7), 122.5 (C-12), 123.1 (C-16), 133.8 (C-17), 152.6 (C-11), 176.6 (C-1), 199.3 (C-13); HRMS *m/z* 385.2349 [M + Na]$^+$ (calcd for $C_{22}H_{34}O_4Na$, 385.2349).

(13*R*,14*S*)-Diastereomer 4. *i. Preparation of a 0.25 M $Zn(BH_4)_2$ Solution in THF.* In a Schlenk flask under an Ar atmosphere 2 mL of a 0.5 M $ZnCl_2$ solution in THF (1.0 mmol) and 76 mg of $NaBH_4$ (2.0

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mmol) were stirred overnight at rt. By dilution with 2 mL of THF a 0.25 M solution of $Zn(BH_4)_2$ was obtained.

ii. Preparation of Title Compound ***4***. In a separate flask compound *dia*-**18** (9.7 mg, 30 μmol, 1.00 equiv) was dissolved in 1 mL of THF and cooled to 0 °C. After the addition of 0.82 mL of a preformed 0.25 M $Zn(BH_4)_2$ solution (0.21 mmol, 8.00 equiv) the ice bath was removed and the mixture was stirred for 1 h at rt. After addition of saturated aqueous NH_4Cl the layers were separated and the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed with a saturated solution of NaCl. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Product **4** (6.6 mg, 18 μmol, 60%) was isolated by column chromatography on silica (20/80 pentane/Et_2O) as slight traces of a white solid: R_f (EtOAc) 0.35; $[\alpha]_D^{20}$ −20.8 (*c* 0.66; $CHCl_3$); FT-IR ν_{max} 3444, 3008, 2927, 2858, 1737, 1724, 1456, 1366, 1353, 1231, 1218, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.71 (1H, ddd, $^3J_{9a,10}$ = 8.5 Hz, $^3J_{9a,8}$ = 5.1 Hz, $^2J_{9a,9b}$ = 5.1 Hz, H-9a), 0.88 (3H, t, $^3J_{22,21}$ = 6.9 Hz, H-22), 0.89 (1H, m, H-9b, overlapped), 1.14 (1H, m꜀, H-8), 122−1.38 (6H, m, H-19, H-20, H-21), 1.43 (1H, m꜀, H-10), 1.49−1.59 (3H, m, H-5, H-4a), 1.70 (1H, m꜀, H-4b), 1,83 (2H, m꜀, H-6), 1.85 (2H, m꜀, H-3), 2.00−2.06 (2H, m, H-18), 2.14−2.22 (1H, m, H-15a), 2.23−2.31 (1H, m, H-15b), 2.40−2.47 (2H, m, H-2), 3.67 (1H, m꜀, H-14), 4.08 (1H, m꜀, H-13), 4.13 (1H, m꜀, H-7), 5.34 (1H, ddd, $^3J_{11,12}$ = 15.5 Hz, $^3J_{11,10}$ = 8.8 Hz, $^4J_{11,13}$ = 0.9 Hz, H-11), 5.39 (1H, dt, $^3J_{16,17}$ = 10.7 Hz, $^3J_{16,15}$ = 7.6 Hz, H-16), 5.56 (1H, dt, $^3J_{17,16}$ = 10.7 Hz, $^3J_{17,18}$ 7.3 Hz, H-17), 5.62 (1H, dd, $^3J_{12,11}$ = 15.4 Hz, $^3J_{12,13}$ = 7.3 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.3 (C-9), 14.2 (C-22), 19.5 (C-10), 22.7 (C-20 or C-21), 24.3 (C-5), 25.1 (C-8), 26.7 (C-4), 27.6 (C-18), 29.3 (C-3), 29.4 (C-19), 30.2 (C-15), 31.7 (C-20 or C-21), 32.9 (C-2), 37.3 (C-6), 74.0 (C-14), 75.2 (C-13), 81.4 (C-7), 124.8 (C-16), 126.3 (C-12), 133.9 (C-17), 136.5 (C-11), 176.7 (C-1); HRMS *m*/*z* 387.2506 $[M + Na]^+$ (calcd for $C_{22}H_{36}O_4Na$, 387.2506)].

(13*S*,14*R*)-Diastereomer 2. Compound **18** (10 mg, 30 μmol, 1.0 equiv) was dissolved in 1 mL of THF and cooled to 0 °C. After the addition of 0.82 mL of a 0.25 M $Zn(BH_4)_2$ solution (0.21 mmol, 8.00 equiv) the ice bath was removed. The mixture was stirred for 1 h at rt; then saturated aqueous NH_4Cl was added. The aqueous layer was extracted four times with EtOAc, and the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Product **2** (5.2 mg, 14 μmol, 52%) was isolated after chromatography on silica (20/80 pentane/Et_2O) as slight traces of a white solid: R_f (EtOAc) 0.35, R_f (Et_2O) 0.20, R_f (50/50 PE/EtOAc) 0.25; $[\alpha]_D^{20}$ −12.2 (*c* 0.18; $CHCl_3$); FT-IR ν_{max} 3433, 3003, 2963, 2927, 2860, 1717, 1464, 1449, 1350, 1328, 1237, 1135, 1052, 1044, 1001, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.71 (1H, ddd, $^3J_{9a,10}$ = 8.5 Hz, $^3J_{9a,8}$ = 5.1 Hz, $^2J_{9a,9b}$ = 5.1 Hz, H-9a), 0.89 (3H, t, $^3J_{22,21}$ = 7.1 Hz, H-22), 0.90 (1H, m, H-9b, overlapped), 1.14 (1H, m꜀, H-8), 1.21−1.40 (6H, m, H-19, H-20, H-21), 1.43 (1H, m꜀, H-10), 1.50−1.56 (3H, m, H-5, H-4a), 1.70 (1H, m꜀, H-4b), 1.83 (2H, m꜀, H-6), 1.87 (2H, m꜀, H-3), 2.00−2.07 (2H, m, H-18), 2.17−2.21 (1H, m, H-15a), 2.23−2.31 (1H, m, H-15b), 2.41−2.47 (2H, m, H-2), 3.67 (1H, m꜀, H-14), 4.08 (1H, m꜀, H-13), 4.13 (1H, m꜀, H-7), 5.34 (1H, ddd, $^3J_{11,12}$ = 15.5 Hz, $^3J_{11,10}$ = 8.7 Hz, $^4J_{11,13}$ = 1.0 Hz, H-11), 5.39 (1H, d, $^3J_{16,17}$ = 10.8 Hz, H-16), 5.57 (1H, dt, $^3J_{17,16}$ = 10.8 Hz, $^3J_{17,18}$ 7.3 Hz, H-17), 5.62 (1H, ddd, $^3J_{12,11}$ = 15.5 Hz, $^3J_{12,13}$ = 7.3 Hz, $^4J_{12,10}$ = 0.6 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.4 (C-9), 14.2 (C-22), 19.5 (C-10), 22.7 (C-20 or C-21), 24.4 (C-5), 25.1 (C-8), 26.7 (C-4), 27.6 (C-18), 29.3 (C-3), 29.4 (C-19), 30.2 (C-15), 31.7 (C-20 or C-21), 32.9 (C-2), 37.4 (C-6), 74.0 (C-14), 75.1 (C-13), 81.4 (C-7), 124.8 (C-16), 126.2 (C-12), 133.8 (C-17), 136.4 (C-11), 176.7 (C-1); HRMS *m*/*z* 387.2507 $[M + Na]^+$ (calcd for $C_{22}H_{36}O_4Na$, 387.2506).

(13*S*)-Alcohol *dia*-19. Under inert conditions, $CeCl_3$ (80 μmoL, 19 mg, 1.4 equiv) was added to a solution of HWE reaction product *dia*-**10** (50 μmoL, 26 mg, 1.0 equiv) in 0.26 mL of THF. The suspension was stirred for 1 h at rt. Afterward the suspension was cooled to −78 °C and 80 μmoL of $NaBH_4$ (3.0 mg, 1.4 equiv) and a further 0.1 mL of THF were added. After further stirring of the reaction mixture for 3 h at −78 °C 0.2 mL of H_2O was added, the acetone/dry ice cooling bath was removed, and the mixture was stirred until it reached rt. After 30 min at rt the mixture was diluted with 5 mL of H_2O and extracted with 4 × 5 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure at 30 °C, and then crude *dia*-**19** (23 mg) was first filtered via column chromatography (PE/EtOAc, 95/5); the slightly impure isomer ***dia*-19** was obtained (1.7 mg, 4.0 μmoL) after preparative HPLC as a colorless oil: R_f (80/20 PE/EtOAc) 0.33; R_f (90/10 PE/EtOAc) 0.09; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.07 [3H, s, $Si(CH_3)$], 0.09 [3H, s, $Si(CH_3)$], 0.68 (1H, m꜀, H-9a), 0.82−0.87 (1H, m, H-9b), 0.89 (3H, t, $^3J_{22,21}$ = 7.22 Hz, H-22), 0.90 [9H, s, $SiC(CH_3)_3$], 1.12 (1H, m꜀, H-8), 1.24−1.27 (4H, m, H-20, H-21), 1.28−1.40 (3H, m, H-19, H-10), 1.53−1.55 (3H, m, H-4a, H-5), 1.67−1.74 (1H, m, H-4b), 1.81−1.84 (2H, m, H-6), 1.85−1.87 (2H, m, H-3), 2.02 (2H, m꜀, H-18), 2.17−2.22 (2H, m, H-15), 2.41−2.46 (2H, m, H-2), 3.55 (1H, m꜀, H-14), 3.91 (1H, m꜀, H-13), 4.07 (1H, m꜀, H-7), 5.30 (1H, dd, $^3J_{11,10}$ = 8.52 Hz, $^3J_{11,12}$ = 14.78 Hz, H-11), 5.36−5.40 (1H, m, H-16), 5.45−5.48 (1H, m, H-17), 5.49 (1H, dd, $^3J_{12,13}$ = 6.14 Hz, $^3J_{12,11}$ = 15.21 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −4.4 [$Si(CH_3)$], −4.0 [$Si(CH_3)$], 12.3 (C-9), 14.2 (C-22), 18.3 [$SiC(CH_3)_3$], 19.5 (C-10), 22.7 (C-21), 24.4 (C-5), 24.8 (C-8), 26.0 [$SiC(CH_3)_3$], 26.7 (C-4), 27.6 (C-18), 29.3 (C-19), 29.4 (C-3), 31.8 (C-15), 31.9 (C-20), 32.9 (C-2), 37.4 (C-6), 73.3 (C-13), 75.5 (C-14), 81.8 (C-7), 124.6 (C-16), 129.2 (C-12), 132.7 (C-17), 133.9 (C-11), 176.8 (C-1); HPLC [Chiralpak IC, 250 × 10 mm, Fa. Daicel; heptane/2-propanol 90/10; 2.5 mL/min; 25 bar (const.), 205 nm], t_R = 18.01 min.

(13*R*)-Alcohol 19. Compound **19** (11 mg, 23 μmol, 38%) was prepared in analogy with preparation of diastereomeric compound *dia*-**19** using 60 μmol (30 mg, 1.0 equiv) of the HWE compound **10** and 90 μmol (23 mg, 1.5 equiv) of $CeCl_3$ diluted in 0.3 mL of THF. For the reduction, 3.7 mg of $NaBH_4$ (98 μmol, 1.6 equiv) was used: R_f (80/20 PE/EtOAc) 0.36; ^1H NMR (600 MHz, $CDCl_3$) δ 0.07 [3H, s, $Si(CH_3)$], 0.09 [3H, s, $Si(CH_3)$], 0.68 (1H, m꜀, H-9a), 0.83−0.86 (1H, m, overlapped, H-9b), 0.88 (3H, t, $^3J_{22,21}$ = 7.16 Hz, H-22), 0.90 [9H, s, $SiC(CH_3)_3$], 1.11 (1H, m꜀, H-8), 1.24−1.27 (4H, m, overlapped, H-20, H-21), 1.28−1.40 (3H, m, H-19, H-10), 1.51−1.56 (3H, m, H-4a, H-5), 1.68−1.72 (1H, m, H-4b), 1.81−1.84 (2H, m, H-6), 1.85−1.87 (2H, m, H-3), 2.01 (2H, m꜀, H-18), 2.17−2.21 (2H, m, H-15), 2.41−2.46 (2H, m, H-2), 3.55 (1H, m꜀, H-14), 3.89 (1H, m꜀, H-13), 4.07 (1H, m꜀, H-7), 5.27 (1H, dd, $^3J_{11,10}$ = 8.40 Hz, $^3J_{11,12}$ = 15.33 Hz, H-11), 5.37 (1H, dtt, $^3J_{16,17}$ = 10.7 Hz, $^3J_{16,15}$ = 7.4 Hz, $^4J_{16,14}$ = 1.6 Hz, H-16), 5.45−5.49 (1H, m, H-17), 5.48 (1H, dd, $^3J_{12,13}$ = 6.41 Hz, $^3J_{12,11}$ = 15.59 Hz, H-12); ^{13}C NMR ($CDCl_3$, 151 MHz) δ −4.4 [$Si(CH_3)$], −4.0 [$Si(CH_3)$], 12.1 (C-9), 14.2 (C-22), 18.3 [$SiC(CH_3)_3$], 19.6 (C-10), 22.7 (C-21), 24.4 (C-5), 24.9 (C-8), 26.0 [$SiC(CH_3)_3$], 26.7 (C-4), 27.6 (C-18), 29.3 (C-19), 29.4 (C-3), 31.7 (C-15), 31.9 (C-20), 32.9 (C-2), 37.4 (C-6), 73.4 (C-14), 75.5 (C-13), 81.8 (C-7), 124.6 (C-16), 129.2 (C-12), 132.8 (C-17), 134.3 (C-11), 176.7 (C-1).

(13*S*,14*S*)-Diastereomer 3 (Solandelactone I). Crude compound *dia*-**19** (39 mg, 80 μmol, 1.0 equiv) was dissolved in 1.0 mL of THF and cooled to 0 °C. After the addition of TBAF (26 mg, 80 μmol, 1.0 equiv) the reaction was stirred for 4.5 h at rt; then 10 mL of H_2O was added. The aqueous layer was extracted with 5 × 10 mL of Et_2O, and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated at 30 °C using a rotary evaporator; then crude **3** (22 mg, 78%) was purified by preparative HPLC. Solandelactone I (**3**) (11 mg, 30 μmol, 38%) was obtained as a colorless oil: R_f (Et_2O) 0.46; R_f (PE/EtOAc 80/20) 0.03; R_f (EtOAc) 0.68; $[\alpha]_D^{25}$ −30.6 (*c* 1.00; $CHCl_3$), $[\alpha]_D^{25}$ −48.6 (*c* 1.00; MeOH); FT-IR ν_{max} 3405, 3007, 2925, 2857, 1717, 1453, 1350, 1328, 1235, 1184, 1162, 1138, 1050, 1003, 985, 964, 869, 755, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.71 (1H, m꜀, H-9a), 0.89 (3H, t, $^3J_{22,21}$ = 6.6 Hz, H-22), 0.87−0.90 (1H, m, H-9b), 1.14 (1H, m꜀, H-8), 1.25−1.31 (4H, m, H-21, H-20), 1.32−1.37 (2H, m, H-19), 1.38−1.44 (1H, m, H-10), 1.51−1.54 (2H, m, H-5), 1.56 (1H, m, H-4a), 1.68−1.72 (1H, m, H-4b), 1.80−1.84 (2H, m, H-6), 1.85−1.88 (2H, m, H-3), 2.04 (2H, m꜀, 18-H), 2.21−2.30 (2H, m, 15-H), 2.40−2.47 (2H, m, 2-H), 3.48 (1H, m꜀, H-14), 3.91 (1H, m꜀, H-13), 4.12 (1H, m꜀, H-7), 5.38 (1H, dd, $^3J_{11,10}$ = 8.80 Hz, $^3J_{11,12}$ = 15.63 Hz, H-11), 5.42 (1H, m꜀, H-

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16), 5.56 (1H, dd, $^3J_{12,13}$ = 7.07 Hz, $^3J_{12,11}$ = 15.60 Hz, H-12), 5.57−5.60 (1H, m, overlapped, H-17); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.4 (C-9), 14.2 (C-22), 19.4 (C-10), 22.7 (C-21), 24.4 (C-5), 25.1 (C-8), 26.7 (C-4), 27.6 (C-18), 29.3 (C-19), 29.4 (C-3), 31.3 (C-15), 31.7 (C-20), 32.9 (C-2), 37.3 (C-6), 74.4 (C-14), 75.3 (C-13), 81.4 (C-7), 124.5 (C-16), 127.8 (C-12), 133.9 (C-17), 136.1 (C-11), 176.7 (C-1); HPLC [Chiralpak IC, 250 × 10 mm, Fa. Daicel; heptane/2-propanol 80/20; 2.5 mL/min; 205 nm] 61.2 min; HRMS *m/z* 387.2504 $[M + Na]^+$ (calcd for $C_{22}H_{36}O_4Na$, 387.2506).

(13*R*,14*R*)-Diastereomer 1. Product **1** was obtained following the procedure for diastereomeric compound solandelactone I (**3**). Therefore, 50 mg of the crude product **19** (0.10 mmol, 1.00 equiv) was diluted in 1.30 mL of THF followed by the addition of 33.40 mg (0.11 mmol, 1.10 equiv) of TBAF. Purification and isolation were performed using preparative HPLC. The desired product **1** could be isolated in 14% yield (5.0 mg, 14 μmol): R_f (EtOAc) 0.65; $[\alpha]_D^{25}$ −9.3 (*c* 1.00; $CHCl_3$); $[\alpha]_D^{25}$ −13.3 (*c* 0.33; MeOH); FT-IR ν_{max} 3417, 3007, 2926, 2857, 1721, 1456, 1329, 1329, 1236, 1139, 1051, 1000, 963, 897, 867, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.70 (1H, m$_c$, H-9a), 0.89 (3H, t, $^3J_{22,21}$ = 7.02 Hz, H-22), 0.87−0.90 (1H, m, H-9b; overlapped), 1.13 (1H, m$_c$, H-8), 1.25−1.31 (4H, m, H-21, H-20), 1.32−1.37 (2H, m, H-19), 1.38−1.44 (1H, m, H-10), 1.51−1.54 (2H, m, H-5), 1.56 (1H, m, H-4a), 1.68−1.72 (1H, m, H-4b), 1.80−1.84 (2H, m, H-6), 1.85−1.88 (2H, m, 3-H), 2.04 (2H, m$_c$, 18-H), 2.21−2.30 (2H, m, 15-H), 2.40−2.47 (2H, m, 2-H), 3.49 (1H, m$_c$, H-14), 3.90 (1H, m$_c$, H-13), 4.14 (1H, m$_c$, H-7), 5.36 (1H, dd, $^3J_{11,10}$ = 8.7 Hz, $^3J_{11,12}$ = 15.4 Hz, H-11), 5.42 (1H,m$_c$, H-16), 5.55 (1H, dd, $^3J_{12,13}$ = 7.19 Hz, $^3J_{12,11}$ = 15.30 Hz, H-12), 5.57−5.60 (1H, m, overlapped, H-17); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 12.2 (C-9), 14.2 (C-22), 19.4 (C-10), 22.7 (C-21), 24.3 (C-5), 25.1 (C-8), 26.7 (C-4), 27.5 (C-18), 29.3 (C-19), 29.4 (C-3), 31.3 (C-15), 31.7 (C-20), 32.9 (C-2), 37.3 (C-6), 74.4 (C-14), 75.5 (C-13), 81.3 (C-7), 124.5 (C-16), 127.7 (C-12), 134.0 (C-17), 136.4 (C-11), 176.7 (C-1); HPLC [Chiralpak IC, 250*10 mm, Fa. Daicel; heptane/2-propanol 80/20; 2.5 mL/min; 205 nm] 60.6 min; HRMS *m/z* 387.25058 $[M + Na]^+$ (calcd for $C_{22}H_{36}O_4Na$, 387.25058).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00757.

General numbering of the natural compound, NMR data, general procedure and sample preparation for HPLC measurements, HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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