JOC The Journal of Organic Chemistry

ARTICLE

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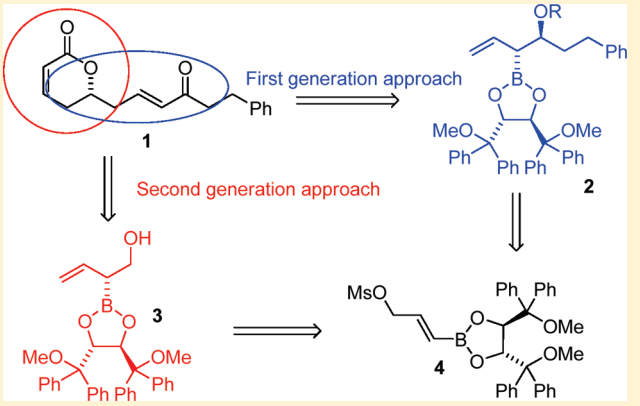
Stereoselective Synthesis of Both Enantiomers of Rugulactone

Dietrich Böse, Enrique Fernández, and Jörg Pietruszka*

Institut für Bioorganische Chemie der Heinrich-Heine-Universität Düsseldorf, Forschungszentrum Jülich, Stetternicher Forst, Geb. 15.8, 52426 Jülich, Germany

Supporting Information

ABSTRACT: The stereoselective total synthesis of both enantiomers of rugulactone **1** has been completed by applying enantioselective allyl additions as key steps. Two different strategies based on highly stable and enantiomerically pure α-substituted allylboronic esters **2** and **3** were performed starting from boronic ester **4**.



INTRODUCTION

Rugulactone (**1**) is a naturally occurring dihydro-α-pyrone isolated for the first time in 2009 from the plant *Cryptocarya rugulosa*.[1] Rugulactone (**1**) has proved to inhibit the nuclear factor NF-kB activation pathway in lymphoma cell lines, which is constitutively active in many types of cancers, and thus a potential therapeutic target.[2] Due to its remarkable inhibition activity,[1,3] some total syntheses have already been reported in the literature.[3,4] The published syntheses of rugulactone are based in cross-coupling reactions or Horner-Wadworth-Emmons (HWE) olefination for the construction of the internal *E*-olefin, and Still-Gennari olefination or Ring-Closing-Metathesis (RCM) for the synthesis of the *Z*-configured α,β-unsaturated lactone. The chirality was induced through different ways: by using a chiral pool,[4c] proline-catalyzed α-aminooxylation of aldehydes,[3] enzymatic resolution of racemic homoallylic alcohols,[4e] Jacobsen's hydrolytic kinetic resolution of epoxides,[4a] or Kecks asymmetric allylation.[4b] A close look at the structure of rugulactone (**1**) shows two chiral 1,5-ene-diol systems, which can be considered as the key targets for its successful enantioselective total synthesis.

As a part of our ongoing project focused on the development of efficient allylboron reagents[5] for allyl additions to obtain enantiopure homoallylic alcohols, we have recently developed a family of new reagents for the stereocontrolled synthesis of 1,5-ene-diols.[5e,f] We have shown that boronic ester **4** is a suitable precursor for palladium-catalyzed allylation of carbonyl compounds with $SnCl_2$ via the formation of an π-allylpaladium(II) complex. The reaction proceeds smoothly to give stereoselectively α-substituted allylboronic esters. The addition of the new reagents to aldehydes proved to be an excellent approach for the construction of enantiomerically pure 1,5-ene-diols. The ease of access of these reagents, their stability, high stereoselectivity, and the mild conditions of the allyl additions make the use of this method appropriate for multistep synthesis.

RESULTS AND DISCUSSION

To prove the viability of our reagents we envisioned two approaches for the enantioselective synthesis of rugulactone (**1**). The first approach, which is summarized in Scheme 1, was based on the synthesis of the open chain 1,5-ene-diol system (*E*-olefin) by means of the allyl addition of allylboronic ester **2** to aldehyde **5** and the subsequent construction of the lactone using RCM after functional group interconversion of acrylate **6**.

The starting α-substituted allylboronic ester **2a** was readily available[5e,f] from methylsulfonate **4** after palladium-catalyzed carbonyl allylation with $SnCl_2$ (60% yield, Scheme 2). Subsequent TES protection of **2a** furnished the protected allylboronic ester **2b** (95% yield). The addition of the resulting allylboronic ester **2b** to aldehyde **5** produced the corresponding 1,5-ene-diols **7b** and **8b** in moderate yield (53%) and with unfavorable diastereomeric ratio (**7b**:**8b** = 40:60). Nevertheless, we were able to separate the two diastereomers by means of MPLC. The observed *Z*-selectivity was somehow expected, since we have already shown that the presence of a protecting group in these reagents results in an enhancement of the *Z*-product in the allyl addition (transition states **B** versus **A**).[5f] Therefore, we

Received: March 2, 2011
Published: March 24, 2011

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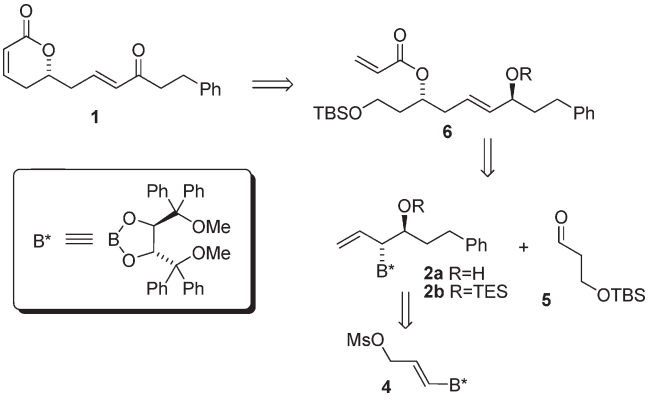
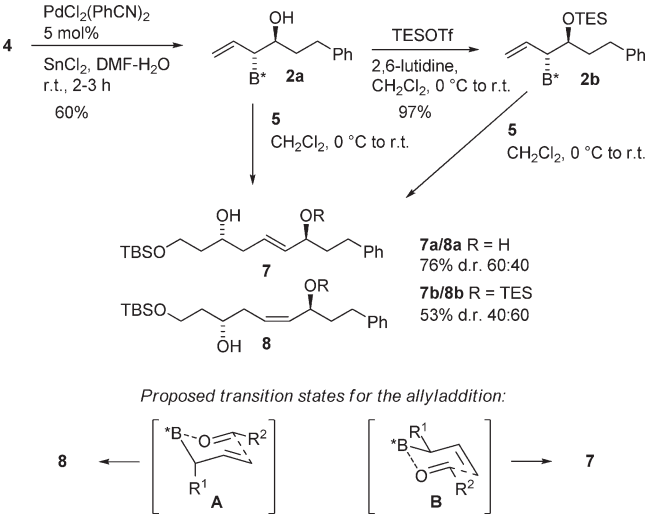
dx.doi.org/10.1021/jo2004583 | *J. Org. Chem.* 2011, 76, 3463–3469

Scheme 1. First Retrosynthetic Approach for the Synthesis of Rugulactone (1)



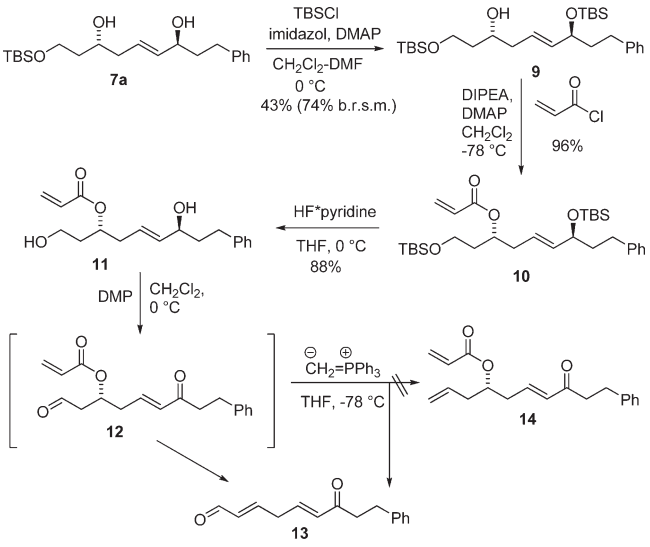
Scheme 2. Synthesis of 1,5-Ene-Diols by Means of Allyl Additions



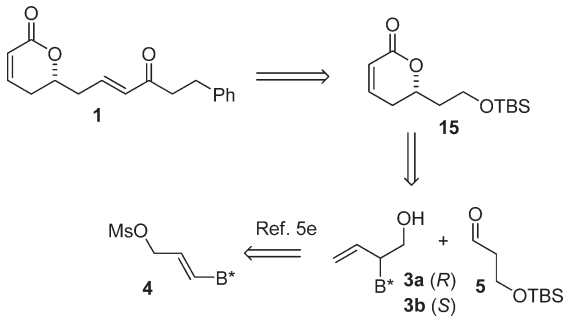
performed the allyl addition with unprotected allylboronic ester **2a**, envisaging an improvement of the *E*-selectivity as well as the yield. Indeed, the *E*-selectivity (**7a**:**8a** = 60:40) and the yield (76%) were increased.

With the improved yield and selectivity, we faced the problem of having two unprotected hydroxy groups in diol **7a**. Consequently, we needed a strategy to distinguish between the homoallylic alcohol and the allylic alcohol. Surprisingly, attempts failed to selectively oxidize the allylic alcohol directly, e.g. with γ-MnO_2. Roush and co-workers showed that upon treatment with imidazole and catalytic DMAP in 1:1 CH_2Cl_2−DMF at −78 °C, silyl-protecting groups can mask one of two hydroxyl groups in similar 1,5-diols chemoselectively (>95:5).[6] Although they described that the selective protection works best with TESCl, in the present example TBSCl proved to be superior: the desired allyl-protected alcohol **9** was obtained in 43% yield [31% of starting material (**7a**) was recovered (Scheme 3)]. Further efforts to increase the yield of the reaction by adding additional equivalents of TBSCl resulted in the doubly protected product.

Scheme 3. Dead End of the First Approach Toward Rugulactone (1)



Scheme 4. Second Retrosynthetic Approach for the Synthesis of Rugulactone (1)

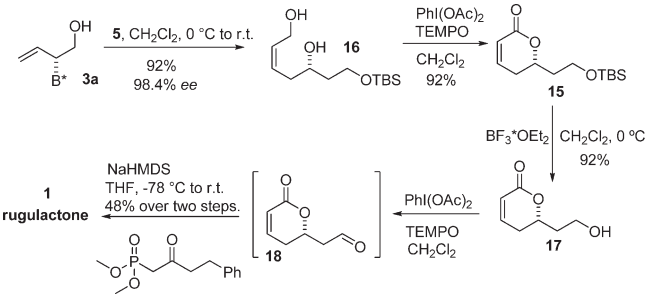


With alcohol **9** in hand, we were able to move on with our strategy by esterification with acryloyl chloride (96% yield) and the simultaneous deprotection of both TBS protected alcohols in acrylate **10** with HF·pyridine (88% yield). The next step was the oxidation of both hydroxyl groups in diol **11** with DMP. However, we were not able to isolate the desired keto-aldehyde **12**. We observed decomposition, most likely by β-elimination, leading to α,β-unsaturated aldehyde **13** (Scheme 3). As expected, aldehyde **12** proved to be very unstable under alkaline conditions. To avoid this, we decided not to isolate the intermediate **12**, but to perform the Wittig-olefination in situ. Unfortunately, no formation of acrylate **14** was detected and aldehyde **13** was again obtained almost quantitatively. The uncontrolled reactivity of **12** and the low selectivity of the original allyl addition led us to focus our efforts in a second approach.

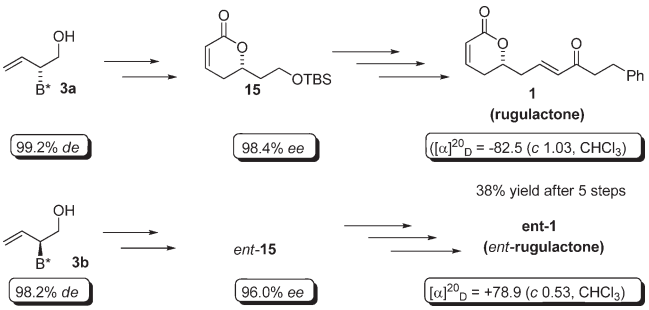
The second route utilizes allylboronic ester **3** to achieve enantioselectively the *Z*-configured α,β-unsaturated lactone of rugulactone (**1**), and a HWE olefination for the synthesis of the *E*-olefin (Scheme 4). We thought that an allyl addition of allylboronic ester **3** to aldehyde **5**, followed by oxidation of the

dx.doi.org/10.1021/jo2004583 |*J. Org. Chem.* 2011, 76, 3463–3469

Scheme 5. Synthesis of Rugulactone (1)



Scheme 6. Enantioselective Total Synthesis of Both Enantiomers of Rugulactone Starting from Allylboronic Esters 3a and 3b



corresponding 1,5-ene-diol to form α,β-unsaturated lactone **15**,[7] should be more effective than our first synthetic approach. We have previously reported that boronic ester **3** adds to aldehydes producing 1,5-ene-diols with complete *Z*-selectivity.[5e] Furthermore, both diastereomers **3a** and **3b** are readily available, which give us access to both enantiomers of rugulactone (**1**).

Allylboronic esters **3a** and **3b** were synthesized starting from methylsulfonate **4** and isolated in 85% yield as a 50:50 mixture of diastereomers, which were completely separated by means of MPLC. The subsequent addition of reagent **3a** to aldehyde **5** via transition state **A** (see Scheme 2) gave 1,5-ene-diol **16** in 93% yield, with almost complete *Z*-selectivity (dr >20:1) and in excellent enantioselectivity (98.4% ee; determined by means of HPLC of the corresponding lactone **15**) (Scheme 5). The regioselective oxidation of diol **16** with $PhI(OAc)_2$ (BAIB) and TEMPO in CH_2Cl_2 produced lactone **15** (92%); the TBS-group was deprotected with $BF_3 \cdot OEt_2$ to obtain lactone **17** in 92% yield. The oxidation of lactone **17** with BAIB led to aldehyde **18**, which was directly subjected to HWE-olefination giving rugulactone (**1**) in 48% yield after two steps (38% yield after 5 steps starting from **3a**). Likewise, allylboronic ester **3b** was used in the same sequence producing *ent*-rugulactone (*ent*-**1**) in 38% yield after 5 steps.

The enantiomeric purity of the final rugulactones (**1** and *ent*-**1**) was highly dependent on the diastereomeric purity of the allylboronic esters **3a** and **3b** that were separated by means of MPLC (Scheme 6). Thus, when we employed allylboronic ester **3a** (99.2% de), lactone **15** was obtained after oxidation with 98.4% ee, while allylboronic ester **3b** (98.2% de) led to lactone *ent*-**15** with 96.0% ee. In the literature several different values for the optical rotation of the natural product **1** have been reported. Values range from −46.5 (*c* 0.7, $CHCl_3$)[4e] or −47.0 (*c* 0.3, $CHCl_3$)[4c] to −57.9 (*c* 0.7, $CHCl_3$)[3] or −61.9 (*c* 0.5, $CHCl_3$).[4b] Not surprisingly the values we received {$[\alpha]^{20}_D$ (**1**) −82.5 (*c* 1.03, $CHCl_3$), $[\alpha]^{20}_D$ (*ent*-**1**) +78.9 (*c* 0.53, $CHCl_3$)} are different from the ones mentioned before; however, to exclude a systematic error in our investigation we rigorously proved the analytical purity of the final natural product **1**.

CONCLUSION

We have reported the enantioselective synthesis of both enantiomers of rugulactone (**1**) employing highly stereoselective allyl additions of allylboronic esters as the source of chirality. The synthesis was short (five steps starting from **3**), efficient (38% overall yield), highly selective [98.4% ee for rugulactone (**1**) and 96.0% ee for *ent*-rugulactone (*ent*-**1**)], and provided the product **1** with unprecedented purity. The success of this total synthesis shows the versatility and viability of the family of α-substituted allylboronic esters. Further applications of these reagents in natural product synthesis are currently under investigation in our laboratories.

EXPERIMENTAL SECTION

General Experimental Details. Unless otherwise specified the reactions were carried out by using standard Schlenk techniques under dry N_2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use. All the reagents were used as purchased from commercial suppliers without further purification. Common solvents for chromatography (petroleum ether 40−60 °C, ethyl acetate) were distilled prior to use. Flash column chromatographies were performed on silica gel 60, 0.040−0.063 mm (230−400 mesh). TLC (monitoring the course of the reactions) was performed on precoated plastic sheets with detection by UV (254 nm) and/or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), H_2O (940 mL)]. Preparative medium pressure liquid chromatography (MPLC) was performed with a packed column (25 × 300 mm or 40 × 475 mm; Si 60, 15−25 μm) and a UV detector (254 nm). HPLC was performed on standard devices equipped with a Chiralcel OB or Chiralcel IA column. ^1H and ^{13}C spectra were recorded at room temperature in $CDCl_3$ on a spectrometer at 600 and 151 MHz, respectively. The chemical shifts are given in ppm relative to internal standard TMS (^1H: δ [$Si(CH_3)_4$] 0.00 ppm) or relative to the resonance of the solvent (^{13}C: δ ($CDCl_3$) 77.0 ppm). Coupling constants *J* are given in Hz. Higher order δ and *J* values are not corrected. ^{13}C signals were assigned by means of C, H, COSY, and HSQC or HMBC spectroscopy. Optical rotations were measured at 20 °C, using a quartz cell with 1 mL capacity and a 10 cm path length. Melting points are uncorrected. Synthesis of allyl boronic esters **2a**, **3a**, and **3b**[5f] as well as of aldehyde **5**[8] and dimethyl-(2-oxo-4-phenylbutyl)phosphonate[9] was accomplished according to literature procedures.

(3*S*,4*R*,4′*R*,5′*R*)-Triethylsilyl-4-[4′,5′-bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl)]-1-phenylhex-5-en-3-ol (2b). Allylboronic ester (3*S*,4*R*,4′*R*,5′*R*)-4-[4′,5′-bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-1-phenylhex-5-en-3-ol (**2a**) (200 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. To this solution were added 2,6-lutidine (92 mg, 0.62 mmol, 3.00 equiv) and TESOTf (159 mg, 0.62 mmol, 2.00 equiv) under a atmosphere of dry nitrogen. The reaction mixture was warmed to room temperature and stirred for 12 h. After full conversion (as judged by TLC) 10 mL of sat. aq $NaHCO_3$ was added. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The combined organic

dx.doi.org/10.1021/jo2004583 |*J. Org. Chem.* 2011, 76, 3463–3469

layers were dried with $MgSO_4$ and filtered, then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 90:10) yielding allylboronic ester **2b** (220 mg, 0.29 mmol, 97%) as a colorless foam. R_f 0.81 (petroleum ether/ethyl acetate, 80:20); $[\alpha]^{20}_D$ −85.0 (*c* 1.20, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3060, 3026, 2833, 1629, 1603, 1495, 1368, 1341, 1231, 1200, 1076, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 0.50 (q, *J* = 7.8 Hz, 6 H, CH_3CH_2Si), 0.88 (t, *J* = 7.8 Hz, 9 H, CH_3CH_2Si), 1.20 (dddd, *J* = 13.7, 12.3, 5.5, 4.4 Hz, 1 H, 2-H_a), 1.41 (dddd, *J* = 13.7, 12.2, 4.9, 4.6 Hz, 1 H, 2-H_b), 1.75 (dd, *J* = 10.0, 8.1 Hz, 1 H, 4-H), 2.43 (ddd, *J* = 13.4, 12.3, 4.6 Hz, 1 H, 1-H_a), 2.48 (ddd, *J* = 13.4, 12.2, 5.5 Hz, 1 H, 1-H_b), 2.98 (s, 6 H, OCH_3), 3.58 (ddd, *J* = 8.1, 4.9, 4.4 Hz, 1 H, 3-H), 4.69 (dd, *J* = 17.0, 2.2 Hz, 1 H, 6-H_E), 4.78 (dd, *J* = 10.1, 2.2 Hz, 1 H, 6-H_Z), 5.34 (s, 2 H, 4′-H and 5′-H), 5.47 (ddd, *J* = 17.0, 10.1, 10.0 Hz, 1 H, 5-H), 6.95−7.40 (m, 25 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 5.2 (CH_3CH_2Si), 7.0 (CH_3CH_2Si), 30.2 (C-1), 37.4 (C-4), 37.9 (C-2), 51.8 (OCH_3), 71.5 (C-3), 77.7 (C-4′ and C-5′), 83.6 (CPh_2OMe), 115.1 (C-6), 125.3, 127.3, 127.7, 128.1, 128.3, 129.7 (Ar−C), 136.9 (C-5), 141.1, 141.4 (Ar−C_{ipso}); MS (ESI, positive ion) *m*/*z* (%) 775 (100) $[(M + Na)^+]$, 770 (30) $[(M + NH_4)^+]$. Anal. Calcd (%) for $C_{48}H_{57}BO_5Si$ (752.86): C 76.58, H 7.63. Found: C 76.53; H 7.63.

General Procedure A: Allyl Additions. 3-(*tert*-Butyldimethylsilyloxy)propanal (**5**) (2.00 equiv) was added to a precooled solution of the allylboronic esters **2b**, **2a**, **3a**, or **3b** (1.00 equiv) in dry CH_2Cl_2 (0.5 mL/mmol allylboronic ester) at 0 °C and the mixture was first stirred at 0 °C for 12 h and then at room temperature until full conversion was determined by TLC (3 d). The solvent was removed under reduced pressure and the products were purified via column chromatography, yielding the allylic alcohols as colorless oils. In cases where *E*/*Z*-diastereomers of the 1,5-diols were obtained an additional MPLC was used to separate them.

(3*R*,7*S*,5*E*)-1-(*tert*-Butyldimethylsilyloxy)-9-phenyl-7-(triethylsiloxy)non-5-en-3-ol (7b) and (3*S*,7*S*,5*Z*)-1-(*tert*-Butyldimethylsiloxy)-9-phenyl-7-(triethylsiloxy)non-5-en-3-ol (8b). **7b** and **8b** were synthesized according to general procedure A with allylboronic ester **2b** (1.36 g, 1.80 mmol), yielding a mixture of diastereomers **7b** and **8b** (dr **7b**:**8b** = 40:60; separated by MPLC, petroleum ether/ethyl acetate, 77:23) (347 mg, 0.96 mmol, 53%) as a colorless oil.

7b: R_f 0.71 (petroleum ether/ethyl acetate, 80:20); $[\alpha]^{20}_D$ +2.1 (*c* 0.49, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3461, 2952, 2876, 1462, 1253, 1082, 1004; ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (s, 6 H, CH_3Si), 0.59 (q, *J* = 7.9 Hz, 6 H, CH_3CH_2Si), 0.91 (s, 9 H, *t*-BuSi), 0.95 (t, *J* = 7.9 Hz, 9 H, CH_3CH_2Si), 1.62−1.71 (m, 2 H, 2-H_a and 2-H_b), 1.78 (dddd, *J* = 13.6, 10.4, 5.8, 5.8 Hz, 1 H, 8-H_a), 1.85 (dddd, *J* = 13.6, 10.3, 6.2, 6.2 Hz, 1 H, 8-H_b), 2.19−2.28 (m, 2 H, 4-H_a and 4-H_b), 2.62 (ddd, *J* = 13.7, 10.3, 5.8 Hz, 1 H, 9-H_a), 2.67 (ddd, *J* = 13.7, 10.4, 6.2 Hz, 1 H, 9-H_b), 3.29 (d, *J* = 2.3 Hz, 3-O*H*), 3.80 (ddd, *J* = 10.3, 8.3, 4.4 Hz, 1 H, 1-H_a), 3.84−3.89 (m, 1 H, 3-H), 3.90 (ddd, *J* = 10.3, 4.7, 4.7 Hz, 1 H, 1-H_b), 4.12 (dddd, *J* = 6.7, 6.2, 5.8, 1.0 Hz, 1 H, 7-H), 5.55 (dddd, *J* = 15.4, 6.7, 1.1, 1.1 Hz, 1 H, 6-H), 5.62 (dddd, *J* = 15.4, 6.9, 6.8, 1.0 Hz, 1 H, 5-H), 7.15−7.29 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.3 (CH_3Si), 5.3 (CH_3CH_2Si), 7.1 (CH_3CH_2Si), 18.3 ($(CH_3)_3CSi$), 26.1 ($(CH_3)_3CSi$), 31.9 (C-9), 38.0 (C-2), 40.3 (C-8), 40.5 (C-4), 62.8 (C-1), 71.7 (C-3), 73.2 (C-7), 126.9 (C-5), 125.8, 128.5, 128.6 (Ar−C), 136.4 (C-6), 142.2 (Ar−C_{ipso}); MS (EI, positive ion, 70 eV) *m*/*z* (%) 355 (48), 289 (10), 223 (14), 189 (52) $[(C_9H_{21}O_2Si)^+]$, 131 (100) $[(C_6H_{15}OSi)^+]$. Anal. Calcd (%) for $C_{27}H_{50}O_3Si_2$ (478.86): C 67.72, H 10.52. Found: C 67.53, H 10.44.

8b: R_f 0.71 (petroleum ether/ethyl acetate, 80:20); $[\alpha]^{20}_D$ −43.0 (*c* 0.51, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3480, 2952, 2876, 1462, 1253, 1082, 1004; ^1H NMR (600 MHz, $CDCl_3$) δ 0.09 (s, 6 H, CH_3Si), 0.59 (q, *J* = 7.9 Hz, 6 H, CH_3CH_2Si), 0.91 (s, 9 H, *t*-BuSi), 0.95 (t, *J* = 7.9 Hz, 9 H, CH_3CH_2Si), 1.61−1.68 (m, 2 H, 2-H_a and 2-H_b), 1.74 (dddd, *J* = 13.4 11.1, 5.6, 5.5 Hz, 1 H, 8-H_a), 1.86 (dddd, *J* = 13.4, 11.0, 7.1, 5.3 Hz, 1 H, 8-H_b), 2.20 (dddd, *J* = 14.5, 7.7, 6.2, 1.5 Hz, 1 H, 4-H_a), 2.27 (dddd, *J* = 14.5, 7.0, 7.0, 1.8 Hz, 1 H, 4-H_b), 2.61 (ddd, *J* = 13.8, 11.0, 5.6 Hz, 1 H, 9-H_a), 2.71 (ddd, *J* = 13.8, 11.1, 5.3 Hz, 1 H, 9-H_b), 3.50 (d, *J* = 2.3 Hz, 1 H, 3-O*H*), 3.81 (ddd, *J* = 10.4, 7.8, 5.3 Hz, 1 H, 1-H_a), 3.84−3.89 (m, 1 H, 3-H), 3.91 (ddd, *J* = 10.4, 4.7, 4.5 Hz, 1 H, 1-H_b), 4.46 (dddd, *J* = 7.1, 6.5, 5.5, 1.2 Hz, 1 H, 7-H), 5.42 (dddd, *J* = 11.1, 7.7, 7.1, 1.2 Hz, 1 H, 5-H), 5.55 (dddd, *J* = 11.1, 8.5, 1.8, 1.5 Hz, 1 H, 6-H), 7.15−7.28 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.3 (CH_3Si), 5.2 (CH_3CH_2Si), 7.1 (CH_3CH_2Si), 18.3 ($(CH_3)_3CSi$), 26.1 ($(CH_3)_3CSi$), 31.9 (C-9), 36.1 (C-4), 38.0 (C-2), 40.4 (C-8), 63.0 (C-1), 68.5 (C-7), 72.2 (C-3), 125.2 (C-5), 125.9, 128.5, 128.6 (Ar−C), 136.1 (C-6), 142.2 (Ar−C_{ipso}); MS (EI, positive ion, 70 eV) *m*/*z* (%) 355 (48), 289 (10), 223 (14), 189 (52) $[(C_9H_{21}O_2Si)^+]$, 131 (100) $[(C_6H_{15}OSi)^+]$; HRMS (ESI, positive ion) *m*/*z* calcd for $C_{27}H_{50}O_3Si_2Na$ $[M + Na]^+$ 501.31907, found 501.31906.

(3*R*,7*S*,5*E*)-1-(*tert*-Butyldimethylsilyloxy)-9-phenylnon-5-ene-3,7-diol (7a) and (3*S*,7*S*,5*Z*)-1-(*tert*-Butyldimethylsilyloxy)-9-phenylnon-5-ene-3,7-diol (8a). **7a** and **8a** were prepared according to general procedure A with allyloronic ester **2a** (1.09 g, 1.70 mmol), yielding a mixture of diastereomers **7a** and **8a** (dr **7a**:**8a** = 60:40; separated by MPLC, petroleum ether/ethyl acetate, 70:30) (469 mg, 1.29 mmol, 76%) as a colorless oil.

7a: R_f 0.22 (petroleum ether/ethyl acetate, 80:20); $[\alpha]^{20}_D$ +5.5 (*c* 0.52, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3352, 2928, 2857, 1496, 1471, 1253, 1082, 970; ^1H NMR (600 MHz, $CDCl_3$) δ 0.07, 0.08 (s, 3 H, CH_3Si), 0.09 (s, 9 H, *t*-BuSi), 1.64−1.68 (m, 2 H, 2-H_a and 2-H_b), 1.73 (dddd, *J* = 13.6, 9.8, 6.4, 5.7 Hz, 1 H, 8-H_a), 1.80 (dddd, *J* = 13.6, 9.6, 7.3, 6.1 Hz, 1 H, 8-H_b), 2.14 (dddd, *J* = 14.1, 7.0, 5.6, 1.3 Hz, 1 H, 4-H_a), 2.18 (dddd, *J* = 14.1, 7.1, 6.8, 1.2 Hz, 1 H, 4-H_b), 2.58 (ddd, *J* = 13.8, 9.6, 6.4 Hz, 1 H, 9-H_a), 2.65 (ddd, *J* = 13.8, 9.8, 6.1 Hz, 1 H, 9-H_b), 3.70−3.75 (m, 1 H, 1-H_a), 3.42 (s, 1 H, 7-O*H*), 3.78−3.83 (m, 2 H, 1-H_b and 3-H), 4.02 (dddd, *J* = 7.3, 6.7, 5.7, 1.0 Hz, 1 H, 7-H), 5.52 (dddd, *J* = 15.4, 6.7, 1.3, 1.2 Hz, 1 H, 6-H), 5.63 (dddd, *J* = 15.4, 7.1, 7.0, 1.0 Hz, 1 H, 5-H), 7.08−7.21 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.5, −5.6 (2 × CH_3Si), 18.1 ($(CH_3)_3CSi$), 25.8 ($(CH_3)_3CSi$), 31.7 (C-9), 37.7 (C-2), 38.7 (C-8), 40.2 (C-4), 62.6 (C-1), 71.5 (C-7), 72.0 (C-3), 125.7, 128.3, 128.4 (Ar−C), 127.9 (C-6), 135.6 (C-5), 142.0 (Ar−C_{ipso}); MS (EI, positive ion, 70 eV) *m*/*z* (%) 281 (31), 207 (33), 189 (17) $[(C_9H_{21}O_2Si)^+]$, 131 (100) $[C_6H_{15}OSi^+)]$; HRMS (ESI, positive ion) *m*/*z* calcd for $C_{21}H_{36}O_3SiNa$ $[M + Na]^+$ 387.23259, found 387.23226.

8a: R_f 0.31 (petroleum ether/ethyl acetate, 80:20); $[\alpha]_D{}^{20}$ −48.0 (*c* 0.66, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3370, 2928, 2857, 1496, 1471, 1253, 1082, 970; ^1H NMR (600 MHz, $CDCl_3$) δ 0.07, 0.08 (s, 3 H, CH_3Si), 0.89 (s, 9 H, *t*-BuSi), 1.60 (dddd, *J* = 14.3, 4.3, 3.3, 2.2 Hz, 1 H, 2-H_a), 1.73 (dddd, *J* = 14.3, 9.9, 9.7, 4.3 Hz, 1 H, 2-H_b), 1.80 (dddd, *J* = 13.2, 10.2, 6.0, 5.8 Hz, 1 H, 8-H_a), 1.93 (dddd, *J* = 13.2, 10.0, 7.1, 5.9 Hz, 1 H, 8-H_b), 2.21 (dddd, *J* = 14.0, 6.8, 5.6, 1.2 Hz, 1 H, 4-H_b), 2.43 (dddd, *J* = 14.0, 8.8, 5.1, 1.2 Hz, 1 H, 4-H_a), 2.67 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1 H, 9-H_a), 2.74 (ddd, *J* = 13.9, 10.0, 6.0 Hz, 1 H, 9-H_b), 3.81 (ddd, *J* = 10.1, 9.9, 3.3 Hz, 1 H, 1-H_b), 3.87 (ddd, *J* = 10.1, 4.3, 4.3 Hz, 1 H, 1-H_a), 3.97 (dddd, *J* = 9.7, 5.6, 5.1, 2.2 Hz, 1 H, 3-H), 4.40 (dddd, *J* = 8.2, 7.1, 5.8, 1.1 Hz, 1 H, 7-H), 5.60 (dddd, *J* = 11.0, 8.8, 6.8, 1.0 Hz, 1 H, 5-H), 5.67 (dddd, *J* = 11.0, 8.2, 1.2, 1.2 Hz, 1 H, 6-H), 7.15−7.29 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.4, −5.3 (2 × CH_3Si), 18.2 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 32.0 (C-9), 35.1 (C-4), 37.4 (C-2), 38.8 (C-8), 63.4 (C-1), 66.6 (C-7), 71.7 (C-3), 127.7 (C-5), 125.9, 128.5, 128.6 (Ar−C), 136.1 (C-5), 142.3 (Ar−C_{ipso}); MS (EI, positive ion, 70 eV) *m*/*z* (%) 281 (76), 189 (10) $[(C_9H_{21}O_2Si)^+]$, 131 (100) $[C_6H_{15}OSi)^+]$; HRMS (ESI, positive ion) *m*/*z* calcd for $C_{21}H_{36}O_3SiNa$ $[M + Na]^+$ 387.23259, found 387.23221.

(5*S*,2*Z*)-7-(*tert*-Butyldimethylsilyloxy)hept-2-ene-1,5-diol (16). The title compound was synthesized according to general

procedure A with allyloronic ester **3a** (513 mg, 0.96 mmol) yielding diol **16** (226 mg, 0.87 mmol, 93%) as a colorless oil. R_f 0.26 (petroleum ether/ethyl acetate, 75:25); $[\alpha]^{20}_D$ (**16**) −4.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3339, 2929, 2857, 1471, 1253, 1086, 1005, 832, 774; ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (s, 6 H, CH_3Si), 0.89 (s, 9 H, *t*-BuSi), 1.64 (dddd, *J* = 14.4, 4.5, 3.5, 2.3 Hz, 1 H, 6-H_a), 1.73 (dddd, *J* = 14.4, 9.7, 9.4, 4.4 Hz, 1 H, 6-H_b), 2.23 (dddd, *J* = 14.1, 7.4, 4.2, 1.4 Hz, 1 H, 4-H_a), 2.37 (dddd, *J* = 14.1, 8.5, 7.4, 1.2 Hz, 1 H, 4-H_b), 2.58 (s, 1 H, 5-O*H*), 3.83 (ddd, *J* = 10.2, 4.5, 4.4 Hz, 1 H, 7-H_a), 3.88 (dddd, *J* = 9.4, 7.8, 3.2, 2.3 Hz, 1 H, 5-H), 3.91 (ddd, *J* = 10.2, 4.5, 4.4 Hz, 1 H, 7-H_b), 4.06 (ddd, *J* = 12.5, 7.0, 1.4 Hz, 1 H, 1-H_a), 4.18 (ddd, *J* = 12.5, 8.0, 1.4 Hz, 1-H_b), 5.66 (ddddd, *J* = 10.9, 8.0, 7.0, 1.4, 1.2 Hz, 1 H, 2-H), 5.90 (ddddd, *J* = 10.9, 7.4, 7.4, 1.4, 1.4 Hz, 1 H, 3-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.4, −5.5 (2 × CH_3Si), 18.3 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 35.4 (C-4), 38.0 (C-6), 57.7 (C-1), 63.1 (C-7), 71.3 (C-5), 129.5 (C-3), 131.5 (C-2); MS (EI, positive ion, 70 eV) *m*/*z* (%) 189 (40), 131 (100), 105 (50), 75 (70). Anal. Calcd (%) for $C_{13}H_{28}O_3Si$ (260.45): C 59.95, H 10.84. Found: C 59.65, H 10.68.

(5*R*,2*Z*)-7-(*tert*-Butyldimethylsilyloxy)hept-2-ene-1,5-diol (*ent*-16) (151 mg, 0.57 mmol, 93%): $[\alpha]^{20}_D$ (*ent*-**16**) +3.1 (*c* 0.81, $CHCl_3$); the spectroscopic data are identical with those of compound **16**.

(3*R*,7*S*,5*E*)-1,7-di(*tert*-Butyldimethylsiloxy)-9-phenylnon-5-en-3-ol (9). 3,7-Diol **7a** (100 mg, 0.27 mmol) was dissolved in 2 mL of a mixture of dry CH_2Cl_2 and dry DMF (1:1). To this solution were added imidazole (30 mg, 0.43 mmol, 1.59 equiv) and DMAP (4 mg, 0.03 mmol, 0.11 equiv) under an atmosphere of dry nitrogen before the mixture was cooled to 0 °C. At this temperature a solution of TBSCl (64 mg, 0.42 mmol, 1.56 equiv) in 1 mL of dry CH_2Cl_2 and dry DMF (1:1) was added dropwise over a period of 20 min. The reaction mixture was slowly warmed to room temperature and was stirred for an additional 12 h. After dilution with 10 mL of Et_2O the reaction was quenched by addition of 5 mL of saturated NH_4Cl solution. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford a mixture of the desired alcohol **9** and the starting material **7a**. The mixture was separated by chromatography on silica gel (petroleum ether/ethyl acetate, 97:3 to 60:40) to afford alcohol **9** (56 mg 0.12 mmol, 43%) and the starting material **7a** (31 mg 0.09 mmol, 31%) as colorless oils. R_f 0.61 (petroleum ether/ethyl acetate, 90:10); $[\alpha]^{20}_D$ +4.3 (*c* 0.48, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3459, 2952, 2929, 2857, 1472, 1252, 1081, 970; ^1H NMR (600 MHz, $CDCl_3$) δ 0.02, 0.05, 0.07, 0.08 (s, 3 H, 4 × CH_3Si), 0.89, 0.90 (s, 9 H, 2 × *t*-BuSi), 1.64 (dddd, *J* = 14.4, 8.5, 8.4, 4.6 Hz, 1 H, 2-H_a), 1.68 (dddd, *J* = 14.4, 5.1, 4.3, 3.0 Hz, 1 H, 2-H_b), 1.77 (dddd, *J* = 13.5, 10.6, 5.7, 5.6 Hz, 1 H, 8-H_a), 1.82 (dddd, *J* = 13.5, 10.6, 6.6, 5.9 Hz, 1 H, 8-H_b), 2.21 (dddd, *J* = 13.8, 9.6, 6.7, 1.1 Hz, 1 H, 4-H_a), 2.25 (dddd, *J* = 13.8, 9.8, 6.5, 1.1 Hz, 1 H, 4-H_b), 2.60 (ddd, *J* = 13.8, 10.6, 5.7 Hz, 1 H, 9-H_a), 2.67 (ddd, *J* = 13.8, 10.6, 5.9 Hz, 1 H, 9-H_b), 3.28 (d, *J* = 2.5 Hz, 1 H, 3-O*H*), 3.80 (ddd, *J* = 10.2, 8.4, 4.3 Hz, 1 H, 1-H_a), 3.83−3.87 (m, 1 H, 3-H), 3.89 (ddd, *J* = 10.2, 5.1, 4.6 Hz, 1 H, 1-H_b), 4.12 (dddd, *J* = 6.6, 6.5, 5.6, 1.0 Hz, 1 H, 7-H), 5.53 (dddd, *J* = 15.4, 6.5, 1.1, 1.1 Hz, 1 H, 6-H), 5.60 (dddd, *J* = 15.4, 6.7, 6.5, 1.0 Hz, 1 H, 5-H), 7.15−7.28 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.1, −5.0, −4.5, −4.1 (4 × CH_3Si), 18.3, 18.5 (2 × $(CH_3)_3CSi$), 26.1, 26.2 (2 × $(CH_3)_3CSi$)), 32.0 (C-9), 39.0 (C-8), 40.0 (C-2), 40.6 (C-4), 60.0 (C-1), 69.1 (C-3), 72.6 (C-7), 126.0, 128.6, 128.7 (Ar−C), 128.6 (C-5), 135.4 (C-6), 142.2 (Ar−C_{ipso}); MS (EI, positive ion, 70 eV) *m*/*z* (%) (22), 281 (25), 263 (27), 197 (81), 131 (100). Anal. Calcd (%) for $C_{27}H_{50}O_3Si_2$ (478.86): C 67.72, H 10.52. Found: C 67.74, H 10.53.

(3*R*,7*S*,5*E*)-1,7-di(*tert*-Butyldimethylsiloxy)-9-phenylnon-5-en-3-yl acrylate (10). A solution of alcohol **9** (134 mg, 0.28 mmol) and DMAP (4.2 mg, 0.03 mmol, 0.09 equiv) in 3 mL of dry CH_2Cl_2 was cooled to −78 °C before freshly distilled *N*,*N*-diisopropylethylamine (120 μL, 0.71 mmol, 2.54 equiv) and freshly distilled acryloyl chloride (50 μL, 0.59 mmol, 2.11 equiv) were added successively. The reaction was monitored by TLC and quenched immediately after full conversion was detected (2 h) by addition of 10 mL of Et_2O and 10 mL of saturated NH_4Cl solution. The layers were separated and the organic layer was washed with 10 mL of a saturated $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and concentrated in vacuo, then purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) to afford acrylate **10** as a colorless oil (142 mg, 0.27 mmol, 96%). R_f 0.39 (petroleum ether/ethyl acetate, 95:5); $[\alpha]^{20}_D$ −24.0 (*c* 0.51, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 2954, 2929, 2857, 1725, 1472, 1405, 1253, 1085; ^1H NMR (600 MHz, $CDCl_3$) δ 0.01, 0.02, 0.04, 0.05 (s, 3 H, 4 × CH_3Si), 0.88, 0.89 (s, 9 H, 2 × *t*-BuSi), 1.73 (dddd, *J* = 13.4, 10.6, 5.8, 5.6 Hz, 1 H, 8-H_a), 1.78 (dddd, *J* = 13.4, 10.6, 6.4, 6.0 Hz, 1 H, 8-H_b), 1.84 (ddd, *J* = 6.7, 6.3, 6.0 Hz, 2 H, 2-H), 2.31 (dddd, *J* = 14.0, 6.5, 6.3, 1.1 Hz, 1 H, 4-H_a), 2.42 (dddd, *J* = 14.0, 6.0, 5.5, 1.1 Hz, 1 H, 4-H_b), 2.57 (ddd, *J* = 13.9, 10.6, 5.8 Hz, 1 H, 9-H_a), 2.63 (ddd, *J* = 13.9, 10.6, 6.0 Hz, 1 H, 9-H_b), 3.64 (dt, *J* = 10.3, 6.7 Hz, 1 H, 1-H_a), 3.66 (dt, *J* = 10.3, 6.3 Hz, 1 H, 1-H_b), 4.10 (dddd, *J* = 6.4, 5.6, 5.5, 1.1 Hz, 1 H, 7-H), 5.11 (ddt, *J* = 6.3, 6.0, 6.0 Hz, 1 H, 3-H), 5.50−5.55 (m, 2 H, 5-H and 6-H), 5.76 (dd, *J* = 10.4, 1.5 Hz, 1 H, 12-H_Z), 6.08 (dd, *J* = 17.3, 10.4 Hz, 1 H, 11-H), 6.38 (dd, *J* = 17.3, 1.5 Hz, 1 H, 12-H_E), 7.15−7.28 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.3, −4.6, −4.3, −4.0 (4 × CH_3Si), 18.4, 18.5 (2 × $(CH_3)_3CSi$), 26.1, 26.2 (2 × $(CH_3)_3CSi$), 31.8 (C-9), 36.8 (C-2), 37.4 (C-4), 40.3 (C-8), 59.6 (C-1), 71.3 (C-3), 73.2 (C-7),125.2 (C-5), 125.8, 128.5, 128.6 (Ar−C), 129.0 (OCO*C*HCH$_2$), 130.6 (OCO*C*HCH$_2$), 137.0 (C-6), 142.7 (Ar−C_{ipso}.), 165.9 (O*C*OCHCH$_2$); (EI, positive ion, 70 eV) *m*/*z* (%) 355 (10), 289 (32), 197 (37), 171 (15), 129 (100). Anal. Calcd (%) for $C_{30}H_{52}O_4Si_2$ (532.90): C, 67.61; H, 9.84. Found: C, 67.65; H. 10.00.

(3*R*,7*S*,5*E*)-1,7-Dihydroxy-9-phenylnon-5-en-3-yl acrylate (11). Silyl protected diol **10** (17 mg, 0.03 mmol) was dissolved in 0.5 mL of dry THF and charged with HF·pyridine (20 μL, 0.16 mmol, 5.33 equiv, 70% HF in pyridine) under an atmosphere of dry nitrogen. After full conversion (judged by TLC, 5 h) the reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution (2 × 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo then purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 50:50) to afford alcohol **11** as a colorless oil (8 mg, 0.03 mmol, 88%). R_f 0.25 (petroleum ether/ethyl acetate, 60:40), $[\alpha]^{20}_D$ −35.7 (*c* 0.49, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3371, 2924, 1718, 1405, 1295, 1193, 1047; ^1H NMR (600 MHz, $CDCl_3$) δ 1.60 (d, *J* = 3.7 Hz, 1 H, 7-O*H*), 1.74 (dddd, *J* = 14.1, 9.6, 4.4, 4.2 Hz, 1 H, 2-H_a), 1.78 (dddd, *J* = 13.9, 9.7, 6.5, 5.5 Hz, 1 H, 8-H_a), 1.85 (dddd, *J* = 13.9, 9.5, 7.3, 6.2 Hz, 1 H, 8-H_b), 1.89 (dddd, *J* = 14.1, 9.2, 5.7, 3.3 Hz, 1 H, 2-H_b), 2.28 (dd, *J* = 7.6, 4.9 Hz, 1 H, 1-O*H*), 2.39 (ddd, *J* = 6.3, 4.1, 1.5 Hz, 2 H, 4-H), 2.64 (ddd, *J* = 14.0, 9.5, 6.5 Hz, 1 H, 9-H_a), 2.69 (ddd, *J* = 14.0, 9.7, 6.2 Hz, 1 H, 9-H_b), 3.56 (dddd, *J* = 11.5, 9.2, 4.9, 4.4 Hz, 1 H, 1-H_a), 3.66 (dddd, *J* = 11.5, 7.6, 5.7, 4.2 Hz, 1 H, 1-H_b), 4.08 (dddd, *J* = 7.3, 5.5, 5.4, 3.6 Hz, 1 H, 7-H), 5.17 (dtd, *J* = 9.6, 6.3, 3.3 Hz, 1 H, 3-H), 5.57−5.65 (m, 2 H, 5-H and 6-H), 5.84 (dd, *J* = 10.4, 1.3 Hz, 1 H, 12-H_Z), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1 H, 11-H), 6.35 (dd, *J* = 17.3, 10.4 Hz, 1 H, 12-H_E), 7.16−7.29 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.9 (C-9), 37.2 (C-2), 37.7 (C-4), 38.8 (C-8), 58.7 (C-1), 71.1 (C-3), 72.2 (C-7), 126.6 (C-5), 126.0, 128.6, 128.6 (Ar−C), 128.5 (C-11), 131.7 (C-12), 142.0 (Ar−C_{ipso}), 166.9 (C-10); (EI, positive ion, 70 eV) *m*/*z* (%) 405 (11), 355 (12), 281 (92), 253 (20), 207 (100), 133 (27). Anal. Calcd (%) for $C_{18}H_{24}O_4$ (304.38): C 71.03, H 7.95. Found: C 71.32, H 7.95.

(6*S*)-6-(2′-(*tert*-Butyldimethylsilyloxy)ethyl)-5,6-dihydro-2*H*-pyran-2-one (15). To a solution of alcohol **11** (75 mg, 0.29 mmol) in 4 mL of CH_2Cl_2 were added [bis(acetoxy)iodo]benzene (BAIB) (388 mg, 1.20 mmol, 4 equiv) and TEMPO (9 mg, 0.06 mmol, 0.05 equiv). The solution was stirred for 4 h at room temperature and quenched with a mixture of saturated aqueous $NaHCO_3$ (5 mL) and aqueous $Na_2S_2O_3$ (5 mL, 10%). The layers were separated and the

aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo then purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 90:10) to afford lactone **15** as a colorless oil (68 mg, 0.27 mmol, 92%). R_f 0.54 (petroleum ether/ethyl acetate, 90:10); $[\alpha]^{20}_D$ (**15**) −47.3 (*c* 1.24, $CHCl_3$), ee 98%; HPLC (Chiralcel IA, heptane/*i*PrOH 97:3, flow = 0.5 mL/min, λ = 205 nm) t_R (**15**) = 12.9 min, t_R (*ent*-**15**) = 13.7 min; IR (film) ν_{max} (cm^{-1}) 2954, 2929, 1723, 1388, 1251, 1088, 836, 777, 662; ^1H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 6 H, CH_3Si), 0.88 (s, 9 H, *t*-BuSi), 1.84 (dddd, *J* = 10.1, 8.2, 5.5, 4.7 Hz, 1 H, 1′-H_a), 1.99 (dddd, *J* = 10.1, 7.8, 5.4, 4.6 Hz, 1 H, 1′-H_b), 2.33−2.43 (m, 2 H, 5-H_a and 5-H_b), 3.76 (ddd, *J* = 10.5, = 5.5, 5.4 Hz, 1 H, 2′-H_a), 3.82 (ddd, *J* = 10.5, 8.2, 4.6 Hz, 1 H, 2′-H_b), 4.59−4.61 (m, 1 H, 6-H), 6.02 (ddd, *J* = 9.8, 2.3, 1.5 Hz, 1 H, 3-H), 6.87−6.89 (m, 1 H, 4-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.3, −5.2 (2 × CH_3Si), 18.4 ($(CH_3)_3$CSi), 26.0 ($(CH_3)_3$CSi), 29.8 (C-5), 38.0 (C-1′), 58.6 (C-2′), 76.3 (C-6), 121.6 (C-3), 145.6 (C-4), 164.7 (C-2); MS (EI, positive ion, 70 eV) *m*/*z* (%) 204 (100), 127 (10), 77 (50), 51 (20). Anal. Calcd (%) for $C_{13}H_{24}O_3Si$ (256.41): C 60.89, H 11.1. Found: C 60.56, H 9.56.

(6*R*)-6-(2′-(*tert*-Butyldimethylsilyloxy)ethyl)-5,6-dihydro-2*H*-pyran-2-one (*ent*-15) (72 mg, 0.28 mmol, 92%): $[\alpha]^{20}_D$ (*ent*-**15**) +44.9 (*c* 0.98, $CHCl_3$), ee 96%; the spectroscopic data are identical with those of compound **15**.

(6*S*)-6-(2′-Hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-one (17). A solution of TBS-protected lactone **15** (101 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C before $BF_3 \cdot OEt_2$ (124 μL, 0.98 mmol, 2.51 equiv) was added. The reaction mixture was stirred at this temperature for 30 min, quenched with saturated $NaHCO_3$ solution (1 mL), and extracted with CH_2Cl_2 (10 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo then purified by column chromatography on silica gel (CH_2Cl_2/MeOH; 98:2) to afford alcohol **17** as a colorless oil (52 mg, 0.36 mmol, 92%). R_f 0.33 (petroleum ether/ethyl acetate, 90:10); $[\alpha]^{20}_D$ (**17**) −118.0 (*c* 1.29, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3425, 2927, 1699, 1393, 1255, 1056, 818; ^1H NMR (600 MHz, $CDCl_3$) δ 1.91 (dddd, *J* = 14.5, 8.2, 5.2, 4.2 Hz, 1 H, 1′-H_a), 2.03 (dddd, *J* = 14.5, 8.5, 5.6, 4.6 Hz, 1 H, 1′-H_b), 2.39−2.42 (m, 2 H, 5-H_a and 5-H_b), 3.83 (ddd, *J* = 10.9, 5.6, 5.2 Hz, 1 H, 1′-H_a), 3.90 (ddd, *J* = 10.9, 5.2, 4.6 Hz, 1 H, 2′-H_b), 4.67 (dddd, *J* = 8.5, 8.5, 7.5, 4.2 Hz, 1 H, 6-H), 6.03 (ddd, *J* = 9.8, 1.8, 1.8 Hz, 1 H, 3-H), 6.90 (ddd, *J* = 9.8, 4.3, 4.3 Hz, 1 H, 4-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.8 (C-5), 37.1 (C-1′), 58.7 (C-1′), 75.8 (C-6), 121.6 (C-3), 145.7 (C-4), 164.2 (C-2); MS (ESI, positive ion) 159.8 (100) $[(M + NH_4)^+]$, 142.9 (40), $[(M)^+]$. Anal. Calcd (%) for $C_7H_{10}O_3$ (142.15): C 59.14, H 7.09. Found: C 59.10, H 7.03.

(6*R*)-6-(2′-Hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-one (*ent*-17) (40 mg, 0.28 mmol, 93%): $[\alpha]^{20}_D$ (*ent*-**17**) +119.6 (*c* 0.54, $CHCl_3$); the spectroscopic data are identical with those of compound **17**.

(6*S*)-6-(2′-Oxoethyl)-5,6-dihydro-2*H*-pyran-2-one (18). Alcohol **17** (25 mg, 0.18 mmol) was dissolved in 3 mL of CH_2Cl_2 at room temperature, before BAIB (210 mg, 0.65 mmol, 3.61 equiv) and TEMPO (4 mg, 0.03 mmol, 0.09 equiv) were added. The reaction mixture was stirred for 12 h at this temperature, quenched with a mixture of saturated aqueous $NaHCO_3$ (0.5 mL) and aqueous $Na_2S_2O_3$ (0.5 mL, 10%), and extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in dry THF and was used for HWE olefination reaction without further purification. R_f 0.31 (CH_2Cl_2/MeOH, 94:6).

Rugulactone (1). To a solution of dimethyl-(2-oxo-4-phenylbutyl)phosphonate (186 mg, 0.73 mmol) in dry tetrahydrofuran (4 mL) was added 1 M NaHMDS in tetrahydrofuran (0.72 mL, 0.72 mmol) at room temperature under an atmosphere of dry nitrogen. Aldehyde **18** was dissolved in dry tetrahydrofuran (3 mL), cooled to −78 °C, and added via canula to the cooled mixture of phosphonate. After 1 h at this temperature the resulting mixture was warmed to room temperature and quenched by addition of brine (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined extracts were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified twice by column chromatography (first column CH_2Cl_2, second column petroleum ether/ethyl acetate, 60:40) to afford rugulactone **1** as a colorless oil (22 mg, 0.08 mmol, 48% over two steps). R_f 0.21 (petroleum ether/ethyl acetate, 50:50); $[\alpha]^{20}_D$ (**1**) −82.5 (*c* 1.03, $CHCl_3$); IR (film) ν_{max} (cm^{-1}) 2924, 1722, 1674, 1387, 1246, 1043, 816; ^1H NMR (600 MHz, $CDCl_3$) δ 2.32−2.34 (m, 2 H, 5-H_a, 5-H_b), 2.61 (dddd, *J* = 14.9, 7.3, 5.5, 1.4 Hz, 1 H, 1′-H_a), 2.67 (dddd, *J* = 14.9, 7.0, 6.8, 1.5 Hz, 1 H and 1′-H_b), 2.88−2.94 (m, 2 H, 6′-H), 2.93−2.96 (m, 2 H, 5′-H), 4.55 (dddd, *J* = 8.2, 7.6, 6.8, 5.5 Hz, 1 H, 6-H), 6.05 (ddd, *J* = 9.8, 1.9, 1.9 Hz, 1 H, 3-H), 6.20 (ddd, *J* = 15.9, 1.5, 1.5 Hz, 1 H, 9-H), 6.80 (ddd, *J* = 15.9, 7.3, 7.0 Hz, 1 H, 2′-H), 6.88 (ddd, *J* = 9.8, 4.8, 3.6 Hz, 1 H, 4-H), 7.17−7.29 (m, 5 H, Ar−H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.1 (C-5), 30.1 (C-6′), 37.7 (C-1′), 41.9 (C-5′), 76.2 (C-6), 121.7 (C-3), 126.3, 128.5, 128.7 (Ar−C), 133.7 (C-2′), 140.1 (C-4), 141.2 (Ar−C_{ipso}), 144.7 (C-3′), 163.8 (C-2), 199.1 (C-4′); HRMS (ESI, positive ion) *m*/*z* calcd for $C_{17}H_{18}O_3Na$ $[M + Na]^+$ 293.11482, found 293.11472. Anal. Calcd (%) for $C_{17}H_{18}O_3$ (270.32): C 75.53, H 6.71. Found: C 75.50, H 6.69.

(*S*)-Rugulactone (*ent*-1) (10 mg, 0.04 mmol, 47% over two steps): $[\alpha]^{20}_D$ (*ent*-**1**) +78.9 (*c* 0.53, $CHCl_3$); the spectroscopic data are identical with those of (*R*)-rugulactone (**1**).

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of all new products and HPLC chromatograms for **3a**/**3b** and **15**/*ent*-**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: j.pietruszka@fz-juelich.de.

■ ACKNOWLEDGMENT

We gratefully acknowledge the Fonds der Chemischen Industrie (scholarship to D.B.), the Deutsche Forschungsgemeinschaft (DFG PI 263/5-1), the Ministry of Innovation, Science, and Research of the German federal state of North Rhine-Westphalia, the Heinrich-Heine-Universität Düsseldorf, and the Forschungszentrum Jülich GmbH for their generous support of our projects. Furthermore, we thank the analytical departments of the Forschungszentrum Jülich as well as Dennis Weidener, Monika Gehsing, Rainer Goldbaum, Birgit Henssen, Erik Kranz, Vera Ophoven, Bea Paschold, Truc Pham, and Saskia Schuback for their ongoing support.

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