Efficient Asymmetric Syntheses of (+)-Strictifolione

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 77th birthday

Abstract: The asymmetric synthesis and a formal asymmetric synthesis of (+)-strictifolione are described. As key step in both approaches the Julia–Kocienski olefination to create an *E*-configured alkene was used. The *anti*-1,3-diol moiety was synthesized by employing a SAMP-hydrazone α,α′-bisalkylation/deoxygenation protocol and the stereocentre of the lactone unit is based on an enzymatic reduction with baker's yeast. Alternatively, a lactone precursor could be efficiently synthesized by a (*S*)-proline catalyzed α-oxyamination of pent-4-enal.

Key words: asymmetric synthesis, enzymatic reduction, hydrazones, natural products, organocatalysis

(+)-Strictifolione (**1**, Figure 1) has been isolated by Aimi et al. from the stem bark of *Cryptocaria strictifolia* in West Kalimantan, Indonesia.[1] Later, Takayama et al. were able to determine its absolute configuration by an 'exchiral-pool' synthesis.[2] Shortly thereafter, a formal total synthesis by Shibasaki et al.[3] and an asymmetric total synthesis by BouzBouz and Cossy[4] were reported, which mainly relied on synthetic methods developed by these groups.

The main structural features of (+)-strictifolione (**1**) are an *anti*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone[5] subunit, which are present in various natural products with important biological activities, e.g. the polyene macrolides[6] and the leptomycin family[7] of natural products, respectively. However, not much is known about the biological activity of **1**, a fact which is surprising if one takes into account that structurally similar ω-arylalkyl 6-substituted 5,6-dihydro-α-pyrones like kurzilactone[8] (**2**, cytotoxic) and the lactone diol **3**[9] (antifungal) have been shown to be biologically active. A comparison of **1** and **3** indicates that the absolute configuration of the *anti*-1,3-diol subunit might be crucial in this respect. New flexible and efficient asymmetric syntheses of the title compound are therefore desirable.

Since we have developed efficient asymmetric approaches to both the subunits mentioned above,[10,11] we have chosen **1** as an appropriate target in order to demonstrate their applicability in natural product synthesis. Our retrosynthetic analysis is depicted in Scheme 1 (route I and route II). In route I the olefin **4** has to be constructed from the

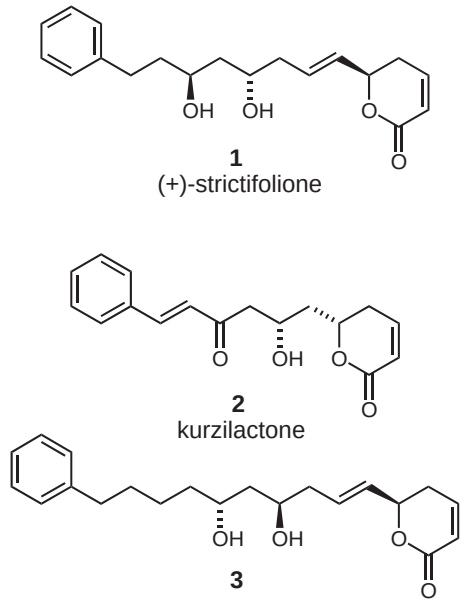

Figure 1 (+)-Strictifolione and related ω-arylalkyl 6-substituted 5,6-dihydro-α-pyrones.

sulfone **6** and the aldehyde **7**. The *anti*-1,3-diol subunit of **6** was planned to be built up starting from 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone (**9**) by an α,α′-double alkylation protocol.

The asymmetric synthesis of sulfone **6** was carried out as shown in Scheme 2. Successive alkylation of hydrazone **9** with (2-bromoethoxy)-*tert*-butyldimethylsilane and (2-iodoethyl)-benzene according to our previously published procedure[12] yielded the SAMP-hydrazone **12**, which was virtually diastereomerically pure according to ^{13}C NMR spectroscopy (de ≥ 96%). Due to the proposed mechanism for the alkylation of SAMP-hydrazones and the order of the electrophiles used we assume the depicted *E*-geometry concerning the C=N double bond.[13] Cleavage of the hydrazone was easily accomplished utilizing sat. oxalic acid.[14] The dioxanone **13** was thus obtained in very good yield over three steps (68%) with de, ee ≥ 96% (^{13}C NMR). As has been shown in previous cases,[10] the most suitable reaction sequence for the removal of the keto group is a radical deoxygenation according to Barton and McCombie, which was also applied to **13**. Its reduction with $NaBH_4$ yielded a diastereomeric mixture of alcohols **14** (de = 6%), which was transformed to the correspond-

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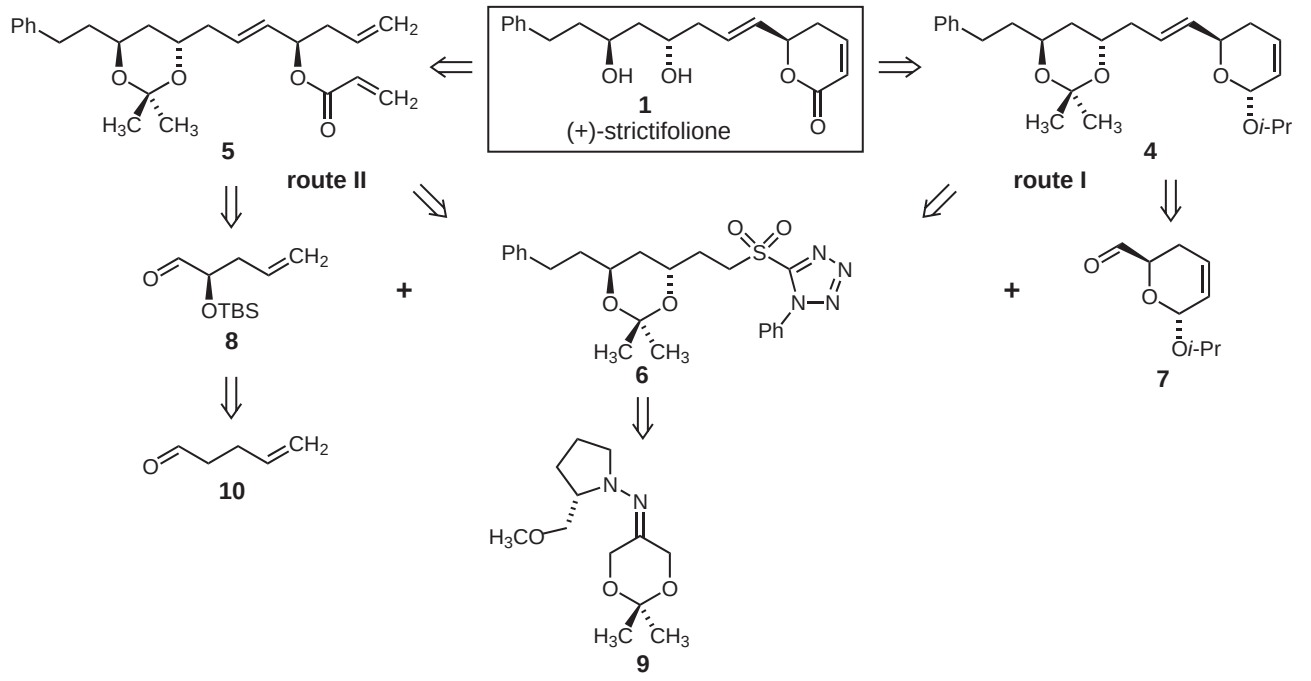
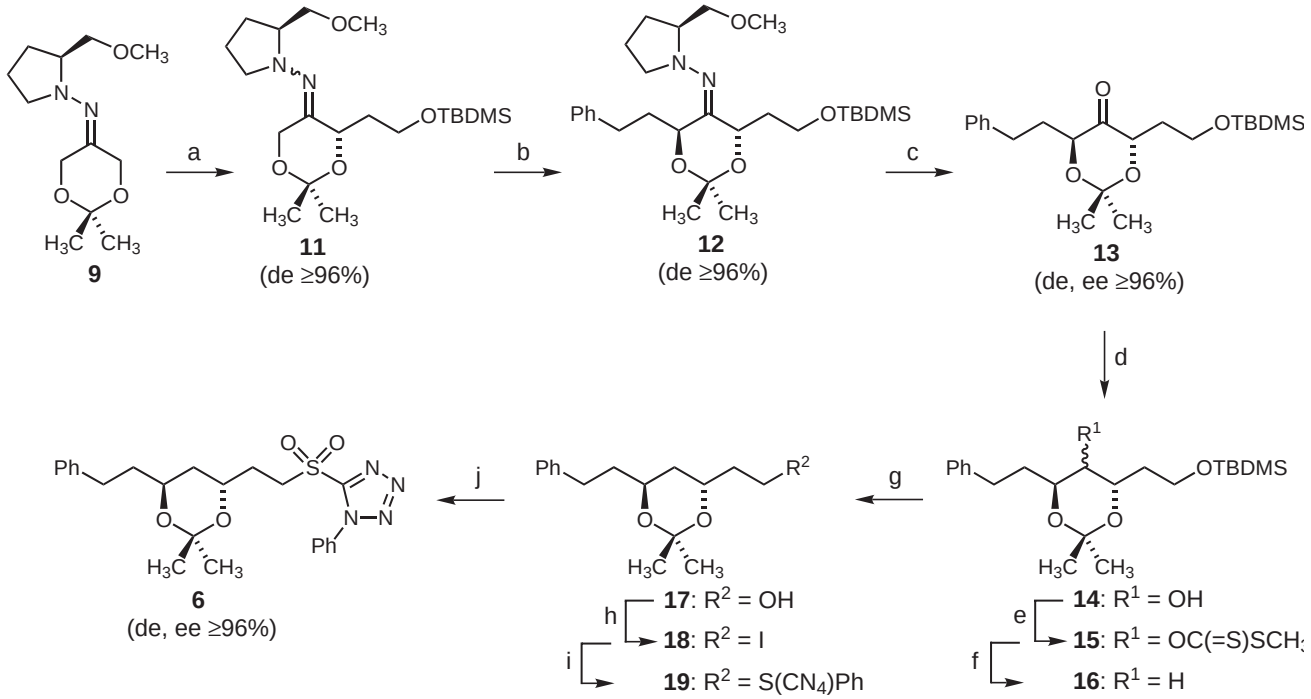


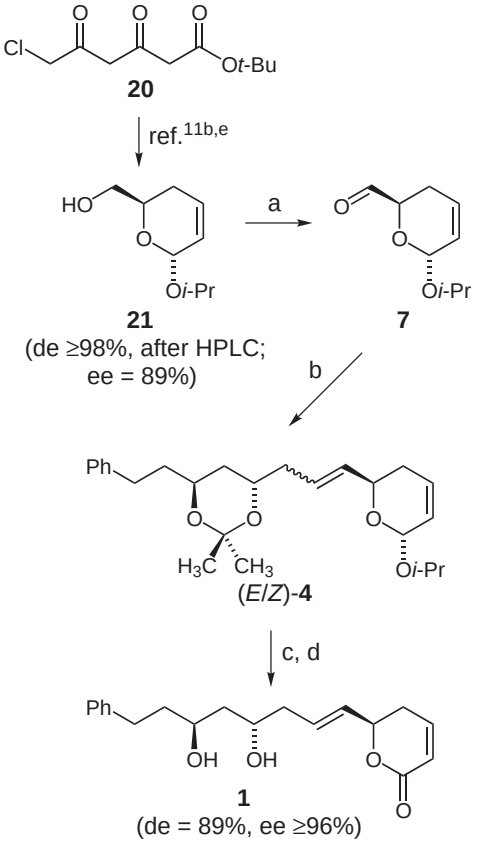
Scheme 1 Retrosynthetic analysis of (+)-strictifolione.

ing xanthates **15** in excellent yield (99% over two steps). Reduction of **15** was then easily accomplished using Bu_3SnH and a catalytic amount of AIBN in refluxing toluene. This yielded the 1,3-dioxane **16** at which stage the relative orientation of both substituents of the 1,3-dioxane ring could be proven to be *trans* according to Rychnovsky's criteria.[15] Cleavage of the TBS-protecting group of **16** with TBAF gave the primary alcohol **17** (93% over two steps), which was converted to the corresponding iodide **18** (84%), followed by a Williamson etherification to give sulfide **19** (99%). Finally, oxidation with MCPBA yielded the desired sulfone **6** (87%).



Scheme 2 *Reagents and conditions:* (a) *t*-BuLi, THF, –78 °C; $Br(CH_2)_2OTBS$, –100 °C→ r.t.; (b) *t*-BuLi, THF, –78 °C; $Ph(CH_2)_2I$, –100 °C → r.t., 71% over two steps; (c) sat. aq oxalic acid, Et_2O, r.t., 96%; (d) $NaBH_4$, MeOH, 0 °C; (e) NaH, THF, 0 °C; CS_2; MeI, 0 °C → r.t., 99% over two steps; (f) Bu_3SnH, AIBN (cat.), toluene, reflux; (g) TBAF, THF, r.t., 93% over two steps; (h) Ph_3P, imidazole, I_2, Et_2O–CH_3CN, 0 °C, 84%; (i) 1-Phenyl-1*H*-tetrazole-5-thiol, NaH, THF–DMF, 0 °C; **18**, 0 °C → r.t., 99%; (j) MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 87%.

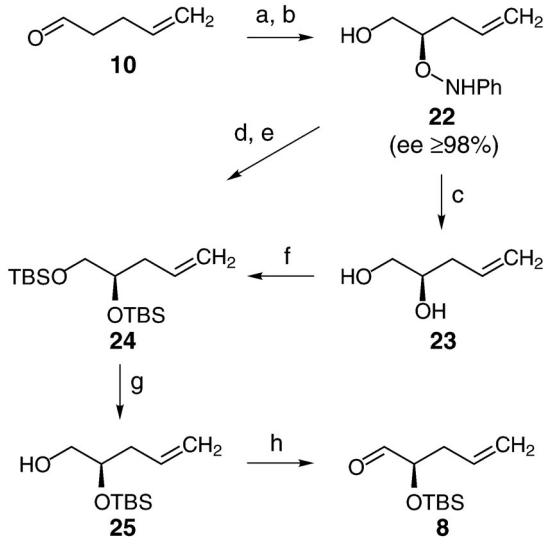
The synthesis of the aldehyde **7** and the final stages of our total synthesis are shown in Scheme 3. Swern oxidation of alcohol **21** (obtained with ee = 89% from the diketoester **20** according to ref.,[11b,e] the crucial step being an enzymatic reduction with baker's yeast) gave **7**, which was coupled with the sulfone **6** under Barbier-type reaction conditions (i.e. addition of the base to a mixture of sulfone and aldehyde). Whereas NaHMDS as base gave (*E*/*Z*)-**4** in 77% yield and with *E*/*Z* = 3.3:1 (according to GC), KHMDS led to a significantly improved *E*/*Z*-selectivity of 8.5:1 but slightly lower yield (61%). These observations parallel those, which had been made by Kocienski et al.[16] Both isomers could be separated by preparative HPLC yielding pure (*E*)-**4** in 52% yield (referring to the coupling reaction). Compound (*E*)-**4** could then be transformed to the final natural product in two further steps. Firstly, both acetal protecting groups where cleaved with PPTS. The resulting lactol was finally oxidized with MnO_2 to (+)-strictifolione (**1**) in good yield (69% over two steps; de = 89% for the C_6-epimers, ee ≥96%).



Scheme 3 *Reagents and conditions:* (a) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; **21**; Et_3N, –78 °C → r.t.; (b) **6**, DME, –(65–60) °C; base (see text), –(65–60) °C → r.t. (yield, see text); (c) PPTS, acetone–H_2O, r.t.; (d) MnO_2, CH_2Cl_2, r.t., 69% over two steps.

Although we had succeeded in an asymmetric total synthesis of the target molecule in quite a convincing manner [16% yield (including HPLC) over 13 linear steps; de = 89% for the C_6-epimers, ee ≥96%], we felt that a further improvement concerning the *E*/*Z*-selectivity in the coupling reaction might be possible. The most obvious variation in this respect would be the employment of an open-chain aldehyde instead of a cyclic one like **7**. This idea is outlined in our second retrosynthesis (Scheme 1, route II) employing the protected α-hydroxy pentenal **8** as the coupling partner of sulfone **6** instead of **7**. We thought that the α-silyloxy substituted aldehyde **8** might be obtainable via an (*S*)-proline catalyzed α-oxyamination of pent-4-enal (**10**). Such enantioselective catalytic α-hydroxylations of aldehydes[17] and ketones[18] have recently been developed.

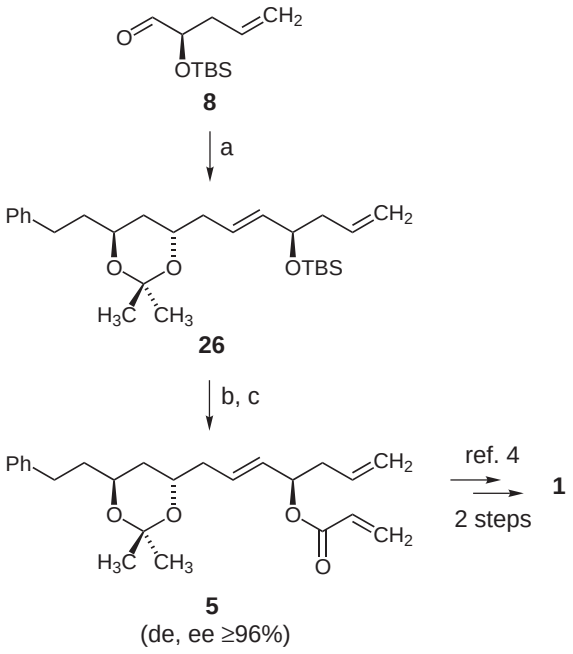
The realization of this concept is shown in Scheme 4. The α-oxyamination of pent-4-enal (**10**) and in situ reduction with $NaBH_4$ gave the primary alcohol **22** with excellent yield (92% over two steps) and enantioselectivity (ee ≥98% according to HPLC).[17a] An enormous advantage in this respect is the fact that the reaction can be scaled up easily, which allows for the synthesis of gram quantities of **22**. Although various conditions for the N-O bond cleavage of **22** were tested, the yields of **23** remained unsatisfactory. An explanation for this might be the high polarity of **23**, which makes its extraction during an aqueous workup quite difficult. In order to avoid an aqueous workup, we finally passed over to an in situ protection of **23**. After SmI_2 mediated N-O bond cleavage[19] (complete according to TLC) the reaction mixture was simply evaporated and subjected to conditions, which had been proven to be satifactory for pure **23** (i.e. TBSCl, imidazole, DMF). This 'one-pot' sequence gave **24** in moderate yield (50% over two steps). The selective deprotection of the primary alcohol in **24** turned out to be the next hurdle. Among the different conditions tested, the HF·pyridine complex served best for this purpose (57%).[20] Swern oxidation finally gave **8** (98%) without a detectable degree of racemisation (vide infra).



Scheme 4 *Reagents and conditions:* (a) (*S*)-proline (10 mol%), PhNO, $CHCl_3$, 0 °C; (b) $NaBH_4$, MeOH, 0 °C, 92% over two steps; (c) $CuSO_4 \cdot 5H_2O$, MeOH, 0 °C → r.t., 28%; (d) SmI_2, THF, r.t.; (e) TBSCl, imidazole, DMF, r.t., 50% over two steps; (f) TBSCl, imidazole, DMF, r.t., 91%; (g) HF·pyridine, pyridine, THF, r.t., 57%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; **25**; Et_3N, 0 °C, 98%.

Coupling of sulfone **6** and aldehyde **8** under the same conditions as described above (Barbier-type reaction conditions; KHMDS, DME, –60 °C → r.t.) gave **26** as a single isomer according to ^{13}C NMR spectroscopy with good yield (69%) (Scheme 5). In contrast to that, Grignard-type reaction conditions (i.e. metalation of the sulfone before the addition of the aldehyde) led to a diminished yield of only 26%, probably due to self-condensation of the metalated sulfone.[16]

The fact that **26** was detected as a single isomer does not only show that the coupling reaction proceeds with a very high degree of *E*-selectivity but also that the Swern oxidation, employed for the synthesis of **8**, was not accompanied by racemization. Cleavage of the TBS-protecting group and esterification with acryloyl chloride gave **5** (91% over two steps), an intermediate that had been described already by BouzBouz and Cossy in their total synthesis of the title compound.[4] Our synthesis of **5** (28% yield over 13 linear steps; de, ee ≥96%) therefore represents a formal synthesis of (+)-strictifolione (**1**).



Scheme 5 *Reagents and conditions:* (a) **6**, DME, –(65–60) °C; KHMDS, –(65–60) °C → r.t., 69%; (b) TBAF, THF, r.t.; (c) acryloyl chloride, Et*i*-Pr_2N, CH_2Cl_2, –78 °C, 91% over two steps.

In summary, we have presented efficient asymmetric syntheses of (+)-strictifolione by employing a SAMP-hydrazone α,α′-bisalkylation/deoxygenation protocol for the synthesis of *anti*-1,3-diols on the one hand and an enzymatic reduction with baker's yeast for the synthesis of the δ-lactone moiety on the other hand. Moreover we have described the application of the recently developed organocatalytic enantioselective α-oxyamination of aldehydes in natural product synthesis.

Reactions were carried out at r.t. under Ar using anhyd solvents unless otherwise stated. Phosphate buffer (pH 7) was a solution of KH_2PO_4 (34.0 g) and NaOH (5.82 g) in H_2O (500 mL). Distilled solvents were used for column chromatography and reaction workup. Column chromatography was carried out under pressure using Merck silica gel 60, particle size 0.040–0.063 mm. Analytical TLC was performed using precoated, glass backed plates (Merck silica gel 60 F_{254}) and visualized by either UV radiation or acidic ammonium molybdate(IV). (2-Bromoethoxy)-*tert*-butyldimethyl-silane,[21] 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydra-zone (**9**)[12] and *tert*-butyl 6-chloro-3,5-dioxohexanoate (**20**)[11b] were prepared according to the published procedures.

Optical rotations were measured with a Perkin-Elmer P 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1760 FT spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300, Mercury 300 and Inova 400 spectrometers using TMS as reference. *J* values are given in Hz. Mass spectra were obtained on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV) and HRMS spectra on a Finnigan MAT 95. Microanalyses were performed on a Heraeus CHN-O-RAPID element analyzer.

General Workup Procedure

Unless stated otherwise, the reaction workup always followed the same procedure: After the reaction had been quenched (typically with sat. aq $NaHCO_3$ or pH 7 buffer), the phases were separated. The aqueous phase was extracted with an organic solvent for several times (typically Et_2O or CH_2Cl_2), after which the combined organic fractions were dried over a drying agent (typically $MgSO_4$). Subsequent filtration through a pad of glass wool and evaporation of the volatiles resulted in a residue, which was either purified by column cromatography or used as such for the next step. This workup procedure is summarized in the form: (quenching agent; solvent used for extraction; drying agent).

{(*S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-2,2-dimethyl-[1,3]dioxan-(5*E*/*Z*)-ylidene}-[(*S*)-2-methoxymethylpyrrolodin-1-yl]-amine (11)

A solution of **9** (1.504 g, 6.2 mmol, 1 equiv) in THF (25 mL) was cooled to –78 °C. *t*-BuLi (4.6 mL of a 1.6 N solution in pentane, 6.8 mmol, 1.1 equiv) was slowly added and the solution was stirred for 2 h at that temperature. After the solution had been cooled down to –100 °C, (2-bromoethoxy)-*tert*-butyldimethylsilane (1.633 g, 6.8 mmol, 1.1 equiv), dissolved in THF (2 mL), was slowly added. Stirring at –100 °C was continued for 2 h after which the solution was allowed to warm to r.t. overnight. Workup (pH 7 buffer; Et_2O; $MgSO_4$) yielded crude **11** as a mixture of *E*- and *Z*-isomers concerning the C=N double bond. It could be used as such for the next step without further purification. An analytical sample of (*E*)-**11** was obtained after standing at 4 °C for 2 d and flash column chromatography (*n*-pentane–Et_2O, 6:1, 2% Et_3N).; colorless oil; de ≥ 96% by ^{13}C NMR; $[\alpha]_D^{23}$ +98.3 (*c* = 2.10, acetone) {ref.[10c], $[\alpha]_D^{23}$ +78.7 (*c* = 2.0, acetone)}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, CH_3SiCH_3), 0.06 (s, 3 H, CH_3SiCH_3), 0.09 [s, 9 H, C$(CH_3)_3$], 1.38 (s, 3 H, CH_3CCH_3), 1.39 (s, 3 H, CH_3CCH_3), 1.60–1.70 (m, 2 H, C*H*HCH_2OTBS, NCHC*H*H), 1.83 (m, 2 H, NCH_2CH_2), 1.96–2.04 (m, 1 H, NCHCH*H*), 2.20 (m, 1 H, CH*H*CH_2OTBS), 2.40 (q, *J* = 8.4 Hz, 1 H, NC*H*H), 3.03 (m, 1 H, NCH*H*), 3.23 (dd, *J* = 9.1, 7.4 Hz, 1 H, C*H*HOCH_3), 3.28–3.34 (m, 1 H, NCH), 3.35 (s, 3 H, OCH_3), 3.43 (dd, *J* = 9.1, 3.9 Hz, 1 H, CH*H*OCH_3), 3.71–3.80 (m, 2 H, CH_2OTBS), 4.14 (dd, *J* = 15.8, 1.8 Hz, 1 H, C*H*HC=N), 4.50 (d, *J* = 15.7 Hz, 1 H, CH*H*C=N), 4.54 (m, 1 H, CHC=N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 [Si$(CH_3)_2$)], 18.3 [*C*$(CH_3)_3$], 22.7 (NCH_2*C*H_2), 24.1 [C(*C*$H_3)_2$], 25.9 [C(*C*$H_3)_3$], 26.7 (NCH*C*H_2), 35.0 (*C*H_2CH_2OTBS), 55.3 (N*C*H_2), 58.9 (*C*H_2OTBS), 59.1 (O*C*H_3), 59.7 (*C*H_2C=N), 66.6 (NCH), 67.0 (*C*HC=N), 75.5 (*C*H_2O*C*H_3), 100.1 [*C*$(CH_3)_2$], 162.7 (C=N).

MS (EI): *m*/*z* (%) = 400 (5) [M^+], 356 (16), 355 (65) [$M^+ - CH_2OCH_3$], 342 (16) [$M^+ - CH_3COCH_3$], 297 (34) [$M^+ - CH_2OCH_3 - CH_3COCH_3$], 184 (58), 139 (44), 131 (22), 105 (20), 101 (25), 98 (100), 89 (16), 75 (17), 73 (27), 71 (12), 70 (60), 59 (12), 45 (12).

Other spectroscopic data are in accordance with previously published data.[10c]

{(4*S*,6*S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-2,2-dimethyl-6-phenethyl-[1,3]dioxan-(5*E*)-ylidene}-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-amine (12)

Crude **11** thus obtained was dissolved in THF (25 mL) and cooled to –78 °C. *t*-BuLi (4.6 mL of a 1.6 N solution in pentane, 6.8 mmol, 1.1 equiv) was slowly added and the solution was stirred for 2 h at that temperature. After the solution had been cooled to –100 °C, (2-iodoethyl)-benzene (1.584 g, 6.8 mmol, 1.1 equiv), dissolved in THF (2 mL), was slowly added. Stirring at –100 °C was continued for 2 h after which the solution was allowed to warm to r.t. overnight. Workup (pH 7 buffer; Et_2O; $MgSO_4$) and column chromatography (*n*-pentane–Et_2O, 30:1, 2% Et_3N) provided **12**; yield: 2.217 g (71% over two steps); colorless oil; de ≥ 96% by ^{13}C NMR; $[\alpha]_D^{27}$ +43.9 (*c* = 1.02, $CHCl_3$).

IR (film): 3062 (w), 3026 (m), 2931 (vs), 2860 (vs), 2736 (w), 1603 (w), 1497 (w), 1460 (s), 1376 (s), 1330 (w), 1251 (s), 1221 (s), 1163 (m), 1106 (vs), 1052 (s), 1008 (m), 954 (m), 837 (vs), 777 (s), 748 (m), 701 (m), 662 (w), 528 (w), 495 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 6 H, $Si(CH_3)_3$], 0.90 [s, 9 H, $C(CH_3)_3$], 1.33 (s, 3 H, CH_3CCH_3), 1.42 (s, 3 H, CH_3CCH_3), 1.51–1.63 (m, 2 H, $CHHCH_2OTBS$, $NCHCHH$), 1.71 (m, 2 H, NCH_2CH_2), 1.99 (m, 2 H, $CHHCH_2OTBS$, $PhCH_2CHH$), 2.10 (m, 1 H, $NCHCHHCH_2$), 2.22 (q, *J* = 8.3 Hz, 1 H, $NCHH$), 2.42 (m, 1 H, $PhCH_2CHH$), 2.67–2.72 (m, 2 H, $PhCH_2$), 2.77 (m, 1 H, $NCHH$), 3.19 (dd, *J* = 8.8, 8.0 Hz, 1 H, $CHHOCH_3$), 3.27 (m, 1 H, NCH), 3.33 (s, 3 H, OCH_3), 3.47 (dd, *J* = 8.8, 3.8 Hz, 1 H, $CHHOCH_3$), 3.69–3.80 (m, 2 H, CH_2OTBS), 4.36 [br d, *J* = 7.4 Hz, 1 H, $Ph(CH_2)_2CH$)], 4.54 [ddd, *J* = 8.0, 4.5, 1.3 Hz, 1 H, $CH(CH_2)_2OTBS$], 7.15–7.22 (m, 3 H, PhH), 7.25– 7.29 (m, 2 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (CH_3SiCH_3), –5.2 (CH_3SiCH_3), 18.3 [$C(CH_3)_3$], 22.6 (NCH_2CH_2), 24.5 (CH_3CCH_3), 26.0 [$C(CH_3)_3$], 26.5 (CH_3CCH_3), 27.0 (CH_2CH_2OTBS), 29.1 ($PhCH_2CH_2$), 31.1 ($PhCH_2$), 33.6 ($NCHCH_2CH_2$), 52.6 (NCH_2), 59.0 (OCH_3), 59.3 (CH_2OTBS), 66.6, 66.7 [NCH, $CH(CH_2)_2OTBS$], 69.6 [$Ph(CH_2)_2CH$], 76.0 (CH_2OCH_3), 100.0 [$C(CH_3)_2$], 125.6 (*p*-Ph*C*), 128.0, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 141.8 (*i*-Ph*C*), 161.3 (C=N).

MS (EI): *m*/*z* (%) = 504 (20) [M^+], 460 (34), 459 (100) [$M^+ - CH_2OCH_3$], 447 (26), 446 (76) [$M^+ - CH_3COCH_3$], 402 (23), 401 (72) [$M^+ - CH_2OCH_3 - CH_3COCH_3$], 342 (11), 332 (21), 313 (10), 297 (18), 288 (32), 259 (11), 243 (30), 202 (18), 198 (35), 144 (13), 131 (21), 117 (21), 116 (13), 115 (13), 114 (20), 101 (14), 91 (52) [$C_7H_7^+$], 89 (22), 73 (31), 70 (55), 59 (25), 45 (16).

Anal. Calcd for $C_{28}H_{48}N_2O_4Si$ (504.78): C, 66.62; H, 9.58; N, 5.55. Found C, 66.76; H, 9.58; N, 6.00.

(4*S*,6*S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2,2-dimethyl-6-phenethyl-[1,3]dioxan-5-one (13)

SAMP-hydrazone **12** (2.217 g, 4.4 mmol) was dissolved in Et_2O (50 mL) and stirred vigorously with a sat. aq solution of oxalic acid (20 mL) for 4 h (TLC control; no Ar). The aqueous layer was separated, extracted with Et_2O and the organic extracts were combined and washed with pH 7 buffer. After re-extraction of the buffer solution with Et_2O all ethereal portions were combined and dried over $MgSO_4$. The mixture was filtered through a pad of glass wool and the crude product obtained after evaporation of the solvent was purified by column chromatography (*n*-pentane–Et_2O, 45:1 → 40:1) to give **13**; yield: 1.652 g (96%); colorless oil which solidifies upon standing at –20 °C; de, ee ≥ 96% by ^{13}C NMR; $[\alpha]_D^{28}$ –154.8 (*c* = 1.07, $CHCl_3$).

IR (film): 3063 (w), 3028 (m), 2987 (s), 2931 (vs), 2859 (vs), 2741 (w), 1745 (vs), 1604 (w), 1497 (w), 1466 (m), 1379 (s), 1322 (w), 1253 (vs), 1230 (vs), 1176 (s), 1096 (vs, br), 1048 (m), 1009 (w), 955 (m), 836 (vs), 778 (s), 747 (m), 700 (s), 662 (w), 555 (w), 524 (w), 494 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.87 [s, 9 H, $C(CH_3)_3$], 1.41 (s, 3 H, CH_3CCH_3), 1.46 (s, 3 H, CH_3CCH_3), 1.65 (m, 1 H, $CHHCH_2OTBS$), 1.86 (m, 1 H, $PhCH_2CHH$), 2.09 (m, 1 H, $CHHCH_2OTBS$), 2.20 (m, 1 H, $PhCH_2CHH$), 2.68 (dt, *J* = 13.7, 8.2 Hz, 1 H, $PhCHH$), 2.80 (ddd, *J* = 13.7, 8.8, 5.0 Hz, 1 H, $PhCHH$), 3.65–3.74 (m, 2 H, CH_2OTBS), 4.14 [ddd, *J* = 9.3, 3.4, 1.2 Hz, 1 H, $Ph(CH_2)_2CH$], 4.42 [ddd, *J* = 7.7, 3.8, 1.1 Hz, 1 H, $CH(CH_2)_2OTBS$], 7.16–7.21 (m, 3 H, PhH), 7.25–7.30 (m, 2 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 [$Si(CH_3)_2$)], 18.2 [$C(CH_3)_3$], 24.0 (CH_3CCH_3), 24.2 (CH_3CCH_3), 25.9 [$C(CH_3)_3$], 30.3 ($PhCH_2CH_2$), 31.0 ($PhCH_2$), 32.0 (CH_2CH_2OTBS), 58.3 (CH_2CH_2OTBS), 70.8 [$CH(CH_2)_2OTBS$], 73.0 [$Ph(CH_2)_2CH$], 101.0 [$C(CH_3)_2$], 125.8 (*p*-Ph*C*), 128.2, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 141.0 (*i*-Ph*C*), 211.6 (C=O).

MS (EI): *m*/*z* (%) = 335 (10) [M^+ – *t*-Bu], 278 (17), 277 (82) [M^+ – TBS], 259 (18), 247 (31), 207 (12), 201 (17), 185 (26), 157 (16), 147 (40), 146 (12), 145 (13), 144 (13), 143 (37), 134 (11), 133 (100) [$Ph(CH_2)_2CO^+$], 131 (66), 129 (15), 118 (31), 117 (40), 115 (11), 105 (82) [$Ph(CH_2)_2^+$], 101 (26), 91 (76) [$C_7H_7^+$], 85 (30), 75 (33), 73 (24), 59 (26), 57 (10), 55 (21).

MS (CI, *iso*-butane): *m*/*z* (%) = 394 (28), 393 (100) [MH^+], 376 (10), 375 (33), 335 (28) [$MH^+ - CH_3COCH_3$].

Anal. Calcd for $C_{22}H_{36}O_4Si$ (392.60): C, 67.30; H, 9.24. Found C, 67.24; H, 9.25.

(4*S*,6*S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2,2-dimethyl-6-phenethyl-[1,3]dioxan-5-ol (14)

Ketone **13** (1.652 g, 4.2 mmol, 1 equiv) was dissolved in MeOH (40 mL) and cooled to 0 °C (no Ar). $NaBH_4$ (0.318 g, 8.4 mmol, 2 equiv) was added in one portion and stirring was continued for 2 h after which TLC revealed complete consumption of the starting material. The solvent was evaporated and the residue taken up in a mixture of CH_2Cl_2 and pH 7 buffer. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$. The mixture was filtered through a pad of glass wool and the solvent evaporated. The crude product thus obtained could be used for the next step without further purification. An analytical sample of the mixture of diastereomeric alcohols **14** was obtained by column chromatography (*n*-pentane–Et_2O, 3:1); colorless oil; de 6% by GC.

IR ($CHCl_3$): 3464 (br s), 3063 (m), 3027 (m), 2987 (s), 2932 (vs), 2859 (vs), 2740 (w), 1604 (w), 1497 (m), 1464 (s), 1380 (s), 1252 (vs), 1228 (vs), 1167 (s), 1091 (vs, br), 1036 (s), 959 (s), 837 (vs), 778 (s), 750 (s), 701 (s), 664 (w), 527 (w), 495 (w) cm^{-1}.

Diastereomer 1

^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 [s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $C(CH_3)_3$], 1.32 (s, 3 H, CH_3CCH_3), 1.40 (s, 3 H, CH_3CCH_3), 1.75–2.05 (m, 4 H, $PhCH_2CH_2$, CH_2CH_2OTBS), 2.63 (d, *J* = 5.4 Hz, 1 H, OH), 2.64–2.71 (m, 1 H, $PhCHH$), 2.76–2.87 (m, 1 H, $PhCHH$), 3.55 (m, 1 H), 3.64 (m, 1 H), 3.74–3.83 [m, 3 H, $Ph(CH_2)_2CH$, $CHOH$, $CH(CH_2)_2OTBS$, CH_2OTBS], 7.16–7.31 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 [$Si(CH_3)_2$)], 18.2 [$C(CH_3)_3$], 24.2 (CH_3CCH_3), 24.6 (CH_3CCH_3), 25.9 [$C(CH_3)_3$], 30.4, 31.9,

37.0 ($PhCH_2CH_2$, $PhCH_2$, CH_2CH_2OTBS), 60.0 (CH_2OTBS), 69.9, 73.0, 74.7 [$CH(CH_2)_2OTBS$, $Ph(CH_2)_2CH$, $CHOH$], 100.9 [$C(CH_3)_2$], 125.8 (*p*-Ph*C*), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 142.1 (*i*-Ph*C*).

Diastereomer 2

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.35 (s, 3 H, CH_3CCH_3), 1.37 (s, 3 H, CH_3CCH_3), 1.70–1.91 (m, 2 H), 1.95–2.14 (m, 2 H) ($PhCH_2CH_2$, CH_2CH_2OTBS), 2.60–2.71 (m, 1 H, $CHHCH_2OTBS$), 2.80–2.91 (m, 1 H, $CHHCH_2OTBS$), 3.13 (d, *J* = 4.2 Hz, 1 H, OH), 3.50–3.57 (m, 2 H), 3.64 (dt, *J* = 1.9, 10.3 Hz, 1 H), 3.79–3.85 (m, 1 H), 3.90 [m, 1 H, $Ph(CH_2)_2CH$, $CHOH$, $CH(CH_2)_2OTBS$, CH_2OTBS], 7.15–7.30 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 24.1 (CH_3CCH_3), 24.6 (CH_3CCH_3), 25.8 [$C(CH_3)_3$], 31.8, 32.1, 35.6 ($PhCH_2CH_2$, $PhCH_2$, CH_2CH_2OTBS), 60.1 (CH_2OTBS), 70.6, 72.7, 74.3 [$CH(CH_2)_2OTBS$, $Ph(CH_2)_2CH$, $CHOH$], 100.7 [$C(CH_3)_2$], 125.7 (*p*-Ph*C*), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 142.2 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 394 (1) [M^+], 379 (8) [$M^+ - CH_3$], 336 (15) [$M^+ - CH_3COCH_3$], 279 (18) [M^+ – TBS], 262 (26), 261 (61) [M^+ – TBS – H_2O], 202 (20), 189 (45), 187 (20), 169 (22), 157 (10), 146 (12), 145 (100), 131 (63), 117 (33), 115 (21), 105 (27), 101 (11), 92 (25), 91 (30), 89 (16), 75 (31), 73 (14), 59 (31).

Anal. Calcd for $C_{22}H_{38}O_4Si$ (394.62): C, 66.96; H, 9.71. Found C, 66.85; H, 9.64.

Dithiocarbonic Acid {(4*S*,6*S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2,2-dimethyl-6-phenethyl-[1,3]di-oxan-5-yl} Ester Methyl Ester (15)

The crude alcohol **14** thus obtained was dissolved in THF (10 mL) and added to a suspension of NaH (0.337 g of a 60% suspension in mineral oil, 8.4 mmol, 2 equiv) in THF (30 mL) at 0 °C. After 30 min CS_2 (0.89 mL, 14.7 mmol, 3.5 equiv) was added and 30 min later MeI (0.79 mL, 12.7 mmol, 3 equiv) was added to the reaction mixture. From this moment stirring was continued at r.t. until TLC indicated complete conversion of the starting material (about 2 h). Workup (pH 7 buffer; Et_2O; $MgSO_4$) and column chromatography (*n*-pentane–Et_2O = 50:1 → 45:1 → 40:1) gave **15**; yield: 2.033 g (99% over two steps); yellow oil.

IR ($CHCl_3$): 3062 (w), 3026 (w), 2987 (m), 2952 (s), 2931 (s), 2858 (s), 1496 (w), 1463 (m), 1427 (w), 1381 (m), 1252 (s), 1208 (vs), 1132 (m), 1091 (s), 1057 (vs), 1009 (m), 962 (m), 884 (m), 837 (s), 777 (m), 700 (w), 664 (w) cm^{-1}.

Diastereomer 1

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.32 (s, 3 H, CH_3CCH_3), 1.44 (s, 3 H, CH_3CCH_3), 1.64–1.88 (m, 4 H, $PhCH_2CH_2$, CH_2CH_2OTBS), 2.56 (s, 3 H, SCH_3), 2.57–2.65 (m, 1 H, PhC*H*H), 2.76–2.85 (m, 1 H, PhH*H*), 3.65 (dd, *J* = 7.4, 4.7 Hz, 2 H, CH_2OTBS), 3.91–4.01 [m, 2 H, $Ph(CH_2)_2CH$, $CH(CH_2)_2OTBS$], 5.88 (dd, *J* = 7.2, 4.0 Hz, 1 H, C*H*OC=S), 7.16–7.30 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 19.0 (SCH_3), 24.1 (CH_3CCH_3), 24.7 (CH_3CCH_3), 25.9 [$C(CH_3)_3$], 30.4, 31.6, 36.2 ($PhCH_2CH_2$, $PhCH_2$, CH_2CH_2OTBS), 58.6 (CH_2OTBS), 67.4, 69.3 [$CH(CH_2)_2OTBS$, $Ph(CH_2)_2CH$], 84.5 ($CHOC=S$), 101.2 [$C(CH_3)_2$], 125.9 (*p*-Ph*C*), 128.4, 128.6 (*o*-Ph*C*, *m*-Ph*C*), 141.5 (*i*-Ph*C*).

Diastereomer 2

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.37 (s, 3 H, CH_3CCH_3), 1.40 (s, 3 H, CH_3CCH_3), 1.61–1.67 (m, 2 H, CH_2CH_2OTBS), 1.89–1.99 (m, 2 H, $PhCH_2CH_2$), 2.54 (s, 3 H, SCH_3), 2.59–2.68 (m, 1 H, PhC*H*H), 2.77–2.87 (m, 1 H, PhH*H*), 3.65 (m, 2 H, CH_2OTBS), 3.75 [m, 1 H, $Ph(CH_2)_2CH$], 4.27 [m, 1 H, $CH(CH_2)_2OTBS$], 5.90 (dd, *J* = 6.9, 3.7 Hz, 1 H, C*H*OC=S), 7.16–7.29 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 19.1 (SCH_3), 24.1 (CH_3CCH_3), 24.6 (CH_3CCH_3), 25.9 [$C(CH_3)_3$], 31.4, 32.1, 34.7 ($PhCH_2CH_2$, $PhCH_2$, CH_2CH_2OTBS), 58.6 (CH_2OTBS), 66.5, 70.2 [$CH(CH_2)_2OTBS$, $Ph(CH_2)_2CH$], 84.8 ($CHOC=S$), 101.2 [$C(CH_3)_2$], 125.9 (*p*-Ph*C*), 128.4, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 141.6 (*i*-Ph*C*), 216.6 (CS_2).

MS (EI): *m*/*z* (%) = 469 (0.5) [$M^+ - CH_3$], 427 (1.5) [M^+ – *t*-Bu], 369 (18) [M^+ – TBS], 262 (20), 261 (100) [M^+ – TBS – COS – CH_3SH], 244 (20), 165 (14), 157 (14), 131 (13), 117 (17), 105 (18), 91 (44), 89 (12), 75 (18), 73 (17).

MS (CI, *iso*-butane): *m*/*z* (%) = 485 (31) [MH^+], 429 (17), 428 (28), 427 (100) [$MH^+ - CH_3COCH_3$], 395 (21), 379 (10), 377 (32) [MH^+ – COS – CH_3SH], 320 (12), 319 (44) [MH^+ – COS – CH_3SH – CH_3COCH_3].

Anal. Calcd for $C_{24}H_{40}O_4S_2Si$ (484.79): C, 59.46; H, 8.32. Found C, 59.59; H, 8.28.

tert-Butyl-{2-[(4*S*,6*S*)-2,2-dimethyl-6-phenethyl-[1,3]dioxan-4-yl]-ethoxy}-dimethylsilane (16)

Bu_3SnH (5.6 mL, 21.1 mmol, 5 equiv) was dissolved in toluene (130 mL) and heated to reflux. Then, a solution of xanthate **15** (2.033 g, 4.2 mmol, 1 equiv) in toluene (13 mL) and a sat. solution of AIBN in toluene (0.8 mL) were added to the reaction mixture over a time period of 2 h. After complete addition of both solutions stirring was continued under reflux for 1 h. All volatiles were removed in vacuo and the residue was directly subjected to column chromatography: The excess of Bu_3SnH was first eluted with *n*-pentane (the tin compound was easily detected by UV radiation) after which the column was flushed with Et_2O. Evaporation of the ethereal fractions gave crude **16**, which could be used for the next step without further purification. An analytical sample of **16** was obtained by column chromatography (*n*-pentane–Et_2O = 25:1); colorless oil; $[\alpha]_D^{23}$ +10.1 (*c* = 1.04, $CHCl_3$).

IR ($CHCl_3$): 3063 (w), 3027 (m), 2986 (s), 2934 (vs), 2859 (vs), 2739 (w), 1604 (w), 1496 (m), 1464 (s), 1380 (s), 1252 (vs), 1225 (vs), 1171 (s), 1096 (vs), 1035 (m), 1010 (m), 960 (s), 837 (vs), 777 (s), 753 (m), 700 (m), 662 (w), 526 (w), 496 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 [s, 6 H, $Si(CH_3)_2$)], 0.89 [s, 9 H, $C(CH_3)_3$], 1.33 (s, 3 H, CH_3CCH_3), 1.36 (s, 3 H, CH_3CCH_3), 1.56–1.92 (m, 6 H, CH_2CH_2OTBS, $OCHCH_2CH$, $PhCH_2CH_2$), 2.56–2.66 (m, 1 H, PhC*H*H), 2.72–2.81 (m, 1 H, PhCH*H*), 3.66 (m, 2 H, CH_2OTBS), 3.77 [m, 1 H, $Ph(CH_2)_2CH$], 3.99 [m, 1 H, $CH(CH_2)_2OTBS$], 7.15–7.29 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 [$Si(CH_3)_2$], 18.3 [$C(CH_3)_3$], 24.9 [$C(CH_3)_2$], 25.9 [$C(CH_3)_3$], 31.7, 37.5, 38.8, 39.0 ($OCHCH_2CH$, CH_2CH_2OTBS, $PhCH_2CH_2$, $PhCH_2$), 59.3 (CH_2OTBS), 63.4, 65.8 [$CH(CH_2)_2OTBS$, $Ph(CH_2)_2CH$], 100.3 [$C(CH_3)_2$], 125.8 (*p*-Ph*C*), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 142.1 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 363 (20) [$M^+ - CH_3$], 264 (14), 263 (84) [M^+ – TBS], 171 (71), 143 (14), 131 (100), 129 (64), 117 (46), 115 (12), 105 (45), 101 (30), 91 (71), 89 (32), 75 (41), 73 (29), 59 (32), 57 (19), 45 (12).

MS (CI, *iso*-butane): *m*/*z* (%) = 380 (29), 379 (100) [MH^+], 322 (13), 321 (56) [$MH^+ - CH_3COCH_3$], 303 (13), 263 (11).

Anal. Calcd for $C_{22}H_{38}O_3Si$ (378.62): C, 69.79; H, 10.12. Found C, 69.64; H, 9.91.

2-{(4*S*,6*S*)-2,2-Dimethyl-6-phenethyl-[1,3]dioxan-4-yl}-ethanol (17)

The crude TBS-ether **16** thus obtained was dissolved in THF (20 mL; no Ar). TBAF (8 mL of a 1 M solution in THF, 8.0 mmol, 1.9 equiv) was added and the solution was stirred until complete consumption of starting material (about 5 h). Workup of the reaction (pH 7 buffer; Et_2O; $MgSO_4$) and column chromatography (*n*-pentane–Et_2O, 1:1) gave **17**; yield: 1.035 g (93% over two steps); colorless oil; $[\alpha]_D^{23}$ +23.1 (*c* = 0.70, $CHCl_3$) {ref.[2], $[\alpha]_D^{25}$ +24.9 (*c* = 1.7, $CHCl_3$)}.

IR ($CHCl_3$): 3416 (s), 3061 (m), 3026 (m), 2986 (s), 2938 (vs), 2878 (s), 1603 (w), 1496 (m), 1454 (m), 1379 (s), 1226 (vs), 1166 (s), 1123 (s), 1059 (s), 1030 (s), 969 (m), 903 (w), 877 (w), 813 (w), 749 (s), 701 (s), 580 (w), 526 (w), 501 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, C*H*$_3$CCH$_3$), 1.41 (s, 3 H, CH$_3$CC*H*$_3$), 1.55–1.92 (m, 6 H, OCHC*H*$_2$CH, C*H*$_2$CH$_2$OH, PhCH$_2$C*H*$_2$), 2.51 (br s, 1 H, OH), 2.57–2.67 (m, 1 H, PhC*H*H), 2.73–2.82 (m, 1 H, PhCH*H*), 3.74–3.84 [m, 3 H, Ph(CH$_2$)$_2$C*H*, C*H*$_2$OH], 4.07 [m, 1 H, C*H*(CH$_2$)$_2$OTBS], 7.16–7.31 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (*C*H$_3$CCH$_3$), 25.0 (CH$_3$*C*CH$_3$), 31.6 (Ph*C*H$_2$), 37.5, 37.6, 38.4 (OCH*C*H$_2$CH, *C*H$_2$CH$_2$OTBS, PhCH$_2$*C*H$_2$), 61.4 (*C*H$_2$OTBS), 65.8 [Ph(CH$_2$)$_2$*C*H], 67.1 [*C*H(CH$_2$)$_2$OTBS], 100.5 [*C*(CH$_3$)$_2$], 125.8 [*p*-Ph*C*], 128.4, 128.5 [*o*-Ph*C*, *m*-Ph*C*], 141.9 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 264 (2) [M$^+$], 250 (11), 249 (73) [M$^+$ – CH$_3$], 246 (8) [M$^+$ – H$_2$O], 204 (11), 171 (30), 143 (18), 129 (42), 117 (35), 105 (13), 92 (21), 91 (100) [C$_7$H$_7^+$], 59 (41), 55 (11), 45 (14).

Anal. Calcd for $C_{16}H_{24}O_3$ (264.36): C, 72.69; H, 9.15. Found C, 72.28; H, 9.46.

(4*R*,6*S*)-4-(2-Iodoethyl)-2,2-dimethyl-6-phenethyl-[1,3]dioxane (18)

Alcohol **17** (0.969 g, 3.7 mmol, 1 equiv), Ph_3P (2.884 g, 11.0 mmol, 3 equiv) and imidazole (1.497 g, 22.0 mmol, 6 equiv) were dissolved in a mixture of Et_2O (9 mL) and CH_3CN (6 mL) at 0 °C. Iodine was added in small portions until a brown color persisted. After stirring for 1 h the reaction was quenched by the addition of pH 7 buffer. The mixture was diluted with Et_2O and Na_2SO_3 was added until both phases appeared colorless. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and filtered through a pad of glass wool. Evaporation of the solvents and column chromatography (*n*-pentane–Et_2O, 30:1) afforded **18**; yield: 1.156 g (84%); colorless oil; $[\alpha]_D^{23}$ –8.3 (*c* = 0.39, $CHCl_3$).

IR ($CHCl_3$): 3083 (w), 3061 (m), 3026 (m), 2986 (s), 2935 (vs), 1603 (w), 1496 (m), 1453 (s), 1379 (vs), 1226 (vs), 1176 (s), 1116 (s), 1062 (m), 1022 (s), 943 (w), 894 (w), 842 (w), 748 (s), 701 (s), 603 (w), 579 (w), 529 (w), 509 (m), 484 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, C*H*$_3$CCH$_3$), 1.40 (s, 3 H, CH$_3$CC*H*$_3$), 1.61 (m, 2 H, OCHC*H*$_2$CH), 1.65–1.89 (m, 2 H, PhCH$_2$C*H*$_2$), 1.93 (m, 2 H, C*H*$_2$CH$_2$I), 2.57–2.66 (m, 1 H, PhC*H*H), 2.72–2.82 (m, 1 H, PhCH*H*), 3.19–3.27 (m, 2 H, C*H*$_2$I), 3.76 [m, 1 H, Ph(CH$_2$)$_2$C*H*], 3.92 [m, 1 H, C*H*(CH$_2$)$_2$I], 7.15–7.30 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 2.5 (CH$_2$I), 24.7 (*C*H$_3$CCH$_3$), 25.1 (CH$_3$*C*CH$_3$), 31.7 (Ph*C*H$_2$), 37.4, 38.0, 39.2 (OCH*C*H$_2$CH, *C*H$_2$CH$_2$I, PhCH$_2$*C*H$_2$), 65.8 [Ph(CH$_2$)$_2$*C*H], 66.4 [*C*H(CH$_2$)$_2$I], 100.5 [*C*(CH$_3$)$_2$], 125.8 (*p*-Ph*C*), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 141.9 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 374 (11) [M$^+$], 360 (17), 359 (100) [M$^+$ – CH$_3$], 316 (40) [M$^+$ – CH$_3$COCH$_3$], 314 (13), 299 (20), 298 (23) [M$^+$ – CH$_3$COCH$_3$ – H$_2$O], 171 (32), 143 (11), 129 (15), 117 (30), 105 (12), 92 (18), 91 (87), 59 (31), 55 (20).

Anal. Calcd for $C_{16}H_{23}IO_2$ (374.26): C, 51.35; H, 6.19. Found C, 51.68; H, 6.39.

5-{2-[(4*R*,6*S*)-2,2-Dimethyl-6-phenethyl-[1,3]dioxan-4-yl]-ethylsulfanyl}-1-phenyl-1*H*-tetrazole (19)

NaH (0.222 g of a 60% suspension in mineral oil, 5.6 mmol, 1.8 equiv) was suspended in a mixture of THF (30 mL) and DMF (5 mL) and cooled to 0 °C. 1-Phenyl-1*H*-tetrazole-5-thiol (1.101 g, 6.2 mmol, 2 equiv), dissolved in THF (15 mL), was slowly added. After complete addition, the ice-bath was removed and the solution stirred for 30 min at r.t. Iodide **18** was taken up in THF (5 mL) and added. Stirring overnight, workup (sat. aq $NaHCO_3$; Et_2O; $MgSO_4$) and column chromatography (*n*-pentane–Et_2O = 2:1) afforded sulfide **19**; yield: 1.299 g (99%); colorless oil; $[\alpha]_D^{25}$ +5.9 (*c* = 1.27, $CHCl_3$).

IR ($CHCl_3$): 2990 (m), 2938 (m), 2860 (w), 1599 (w), 1500 (s), 1456 (w), 1383 (s), 1284 (w), 1223 (s), 1158 (w), 1120 (w), 1023 (m), 954 (w), 913 (w), 757 (vs), 698 (m), 667 (w), 553 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, C*H*$_3$CCH$_3$), 1.35 (s, 3 H, CH$_3$CC*H*$_3$), 1.62 (t, *J* = 7.7 Hz, 2 H, OCHC*H*$_2$CH), 1.67–2.12 (m, 4 H, C*H*$_2$CH$_2$S, PhCH$_2$C*H*$_2$), 2.56–2.66 (m, 1 H, PhC*H*H), 2.71–2.81 (m, 1 H, PhCH*H*), 3.36–3.55 (m, 2 H, CH$_2$S), 3.77 [m, 1 H, Ph(CH$_2$)$_2$C*H*], 3.96 (m, 1 H, C*H*(CH$_2$)$_2$S), 7.14–7.30 (m, 5 H, PhH), 7.51–7.59 (m, 5 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (*C*H$_3$CCH$_3$), 24.9 (CH$_3$*C*CH$_3$), 29.6 (*C*H$_2$S), 31.6 (Ph*C*H$_2$), 35.0, 37.4 (*C*H$_2$CH$_2$S, PhCH$_2$*C*H$_2$), 38.3 (OCH*C*H$_2$CH), 65.0 [*C*H(CH$_2$)$_2$S], 65.7 [Ph(CH$_2$)$_2$*C*H)], 100.5 [*C*(CH$_3$)$_2$], 123.8, 125.8, 128.3, 128.4, 129.8, 130.1, 133.7, 141.9, 154.3 (Ph*C*, *C*N$_2$).

MS (EI): *m*/*z* (%) = 424 (2), 409 (20) [M$^+$ – CH$_3$], 366 (21) [M$^+$ – CH$_3$COCH$_3$], 275 (17), 233 (16), 189 (24), 179 (35), 178 (12), 151 (18), 129 (12), 118 (14), 117 (43), 105 (13), 92 (13), 91 (100) [C$_7$H$_7^+$], 89 (12), 87 (12), 77 (16), 67 (10), 59 (19), 55 (12).

HRMS (EI): *m*/*z* [M$^+$ – CH$_3$] calcd for $C_{22}H_{25}N_4O_2S$: 409.1698; found: 409.1698.

Anal. Calcd for $C_{23}H_{28}N_4O_2S$ (424.56): C, 65.07; H, 6.65; N, 13.20. Found C, 65.54; H, 6.95; N, 13.20.

5-{2-[(4*R*,6*S*)-2,2-Dimethyl-6-phenethyl-[1,3]dioxan-4-yl]-ethylsulfonyl}-1-phenyl-1*H*-tetrazole (6)

Sulfide **19** (0.219 g, 0.52 mmol, 1 equiv) was dissolved in CH_2Cl_2 (11 mL). $NaHCO_3$ (0.426 g, 5.1 mmol, 9.8 equiv) and a solution of MCPBA (0.430 g, 2.5 mmol, 4.8 equiv) in CH_2Cl_2 (3 mL) were added. After stirring for 48 h the reaction was worked up (sat. aq $NaHCO_3$; CH_2Cl_2; $MgSO_4$) and the residue subjected to column chromatography (*n*-pentane–Et_2O = 2:1) to give sulfone **6**; yield: 0.204 g (87%); colorless, very sticky oil; $[\alpha]_D^{25}$ +9.7 (*c* = 0.60, $CHCl_3$).

IR ($CHCl_3$): 3063 (w), 3026 (m), 2988 (s), 2938 (s), 1598 (m), 1498 (s), 1456 (m), 1380 (s), 1345 (vs), 1292 (w), 1226 (vs), 1189 (m), 1154 (vs), 1119 (s), 1066 (w), 1025 (m), 955 (w), 901 (w), 760 (vs), 695 (s), 625 (m), 576 (w), 547 (m), 525 (m), 457 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, C*H*$_3$CCH$_3$), 1.35 (s, 3 H, CH$_3$CC*H*$_3$), 1.56–1.89 (m, 4 H, PhCH$_2$C*H*$_2$, OCHC*H*$_2$CH), 1.97–2.07 (m, 1 H, C*H*HCH$_2$S), 2.12–2.21 (m, 1 H, CH*H*CH$_2$S), 2.57–2.64 (m, 1 H, Ph*H*H), 2.72–2.79 (m, 1 H, PhH*H*), 3.91–3.99 (2 m, 4 H, CH$_2$S, OC*H*CH$_2$C*H*), 7.15–7.29 (m, 5 H, PhH), 7.55–7.69 (m, 5 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (*C*H$_3$CCH$_3$), 24.8 (CH$_3$*C*CH$_3$), 28.1 (*C*H$_2$CH$_2$S), 31.5 (Ph*C*H$_2$), 37.3, 38.0 (OCH*C*H$_2$CH, PhCH$_2$*C*H$_2$), 52.8 (*C*H$_2$S), 64.5, 65.5 [Ph(CH$_2$)$_2$*C*H, *C*H(CH$_2$)$_2$S], 100.5 [*C*(CH$_3$)$_2$], 124.9, 125.6, 128.1, 128.2, 129.5, 131.2, 132.8, 141.5, 153.2 (Ph*C*, *C*N$_2$).

MS (EI): *m*/*z* (%) = 441 (19) [$M^+ - CH_3$], 173 (26), 171 (14), 169 (29), 147 (13), 143 (11), 131 (12), 129 (24), 119 (14), 118 (27), 117 (76), 105 (13), 104 (12), 92 (15), 91 (100) [$C_7H_7^+$], 65 (12), 59 (20), 57 (13), 55 (21).

MS (CI, methane): *m*/*z* (%) = 485 (9), 457 (4) [MH^+], 400 (21), 399 (100) [$MH^+ - CH_3COCH_3$], 381 (28), 265 (15), 157 (17), 119 (14).

HRMS (EI): *m*/*z* [$M^+ - CH_3$] calcd for $C_{22}H_{25}N_4O_4S$: 441.1679; found: 441.1677.

[(2*R*,6*R*)-6-Isopropoxy-3,6-dihydro-2*H*-pyran-2-yl]-methanol (21)

Starting from *tert*-butyl 6-chloro-3,5-dioxohexanoate (**20**) (2.373 g, 10.1 mmol) the alcohol (2*R*,6*S*/*R*)-**21** (0.429 g, 2.5 mmol) was obtained according to the literature (25% yield over 7 steps) with de = 85%, ee = 89%.[11b,11e] Separation of the minor diastereomer, (2*R*,6*S*)-**21**, by preparative HPLC (LiChrosorb, *n*-pentane–Et_2O, 1:4) gave alcohol **21** with de ≥ 98%, ee = 89%; yield: 0.336 g (19% over 7 steps and HPLC); colorless solid; $[\alpha]_D^{20}$ +38.7 (*c* = 0.66, $CHCl_3$) {ref.[11e], $[\alpha]_D^{22}$ +36.5 (*c* = 0.26, $CHCl_3$; de = 83%, ee = 94%)}.

The other spectroscopic data were in full agreement with the literature.[11e]

(4*S*,6*S*)-4-{(*E*/*Z*)-3-[(2*R*,6*R*)-6-Isopropoxy-3,6-dihydro-2*H*-pyran-2-yl]-allyl}-2,2-dimethyl-6-phenethyl-[1,3]dioxane [(*E*/*Z*)-4]

Firstly, alcohol **21** was oxidized to aldehyde **7** under Swern conditions: A solution of oxalyl chloride (0.10 mL, 1.2 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was cooled to –78 °C. DMSO (0.18 mL, 2.5 mmol, 3.1 equiv) was added in one portion and after stirring for 15 min the alcohol **21** (0.140 g, 0.8 mmol, 1 equiv), dissolved in CH_2Cl_2 (2 mL), was slowly added. After 30 min Et_3N (0.57 mL, 4.1 mmol, 5 equiv) was added after which stirring was continued for 15 min. The cooling bath was removed and the solution was allowed to warm to r.t. The reaction mixture was carefully evaporated (aldehyde **7** is volatile) and the remaining slurry directly subjected to column chromatography (*n*-pentane–Et_2O, 3:1). Evaporation of the solvents yielded aldehyde **7**, which was directly used for the next step: It was dissolved in DME (6.5 mL) and cooled to –(65–60) °C. Sulfone **6** (8.5 mL of a 0.106 M solution of **6** in DME, 0.90 mmol, 1.1 equiv) was then added and the solution allowed to reach its original temperature again. NaHMDS (0.44 ml of a 2 M solution in THF, 0.88 mmol, 1.08 equiv) was added dropwise and the solution was warmed to r.t. overnight. Workup (sat. aq $NaHCO_3$; Et_2O, $MgSO_4$) and column chromatography (*n*-pentane–Et_2O, 7:1) afforded 0.249 g (77% over two steps) of a 3.3:1-mixture of (*E*)-**4**/(*Z*)-**4**. Both isomers could be separated by preparative HPLC (LiChrosorb, *n*-pentane–Et_2O, 9:1).

(*E*)-4

Yield: 0.170 g (52% over two steps and HPLC); colorless oil; $[\alpha]_D^{20}$ +49.4 (*c* = 0.67, $CHCl_3$).

IR ($CHCl_3$): 3027 (m), 2980 (s), 2933 (s), 1658 (w), 1603 (w), 1496 (w), 1455 (m), 1379 (s), 1316 (m), 1225 (s), 1183 (m), 1122 (s), 1102 (s), 1058 (s), 1027 (vs), 1001 (s), 971 (s), 750 (m), 719 (m), 701 (m), 527 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.23 (d, *J* = 6.3 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.34 (s, 3 H, C*H*$_3$CCH$_3$), 1.36 (s, 3 H, CH$_3$CC*H*$_3$), 1.59 (m, 2 H, OCHC*H*$_2$CHO), 1.67–1.77 (m, 1 H, PhCH$_2$C*H*H), 1.79–1.88 (m, 1 H, PhCH$_2$CH*H*), 1.95–2.02 (m, 1 H, CH=CHCHC*H*H), 2.04–2.13 (m, 1 H, CH=CHCHCH*H*), 2.14–2.21 [m, 1 H, Ph(CH$_2$)$_2$CHCH$_2$CHC*H*H], 2.25–2.32 [m, 1 H, Ph(CH$_2$)$_2$CHCH$_2$CHCH*H*], 2.57–2.65 (m, 1 H, PhC*H*H), 2.72–2.80 (m, 1 H, PhCH*H*), 3.76 [m, 1 H, Ph(CH$_2$)$_2$C*H*], 3.85 [m, 1 H, Ph(CH$_2$)$_2$CHCH$_2$C*H*], 3.98 (sep, *J* = 6.2 Hz, 1 H, CH$_3$C*H*CH$_3$), 4.39 (ddd, *J* = 10.3, 6.1, 4.3 Hz, 1 H, CH=CHC*H*CH$_2$), 5.09 (br s, 1 H, *i*-PrOC*H*), 5.56–5.62 (m, 1 H, *i*-PrOCHOCHCH=C*H*), 5.67–5.75 (m, 2 H, *i*-PrOCHOCHC*H*, *i*-PrOCHC*H*), 5.99 (m, 1 H, *i*-PrOCHCH=C*H*), 7.15–7.20 (m, 3 H, PhH), 7.24–7.29 (m, 2 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (*C*H$_3$CHCH$_3$), 23.8 (CH$_3$CH*C*H$_3$), 24.78 (*C*H$_3$CCH$_3$), 24.84 (CH$_3$C*C*H$_3$), 30.6 (CH=CHCH*C*H$_2$), 31.6 (Ph*C*H$_2$), 37.4 (PhCH$_2$*C*H$_2$), 38.1 (OCH*C*H$_2$CHO), 38.6 [Ph(CH$_2$)$_2$CHCH$_2$CH*C*H$_2$], 65.7 [Ph(CH$_2$)$_2$*C*H], 66.3 [Ph(CH$_2$)$_2$CHCH$_2$*C*H], 66.6 (CH=CH*C*HCH$_2$), 69.7 (CH$_3$*C*HCH$_3$), 93.3 (*i*-PrO*C*H), 100.2 (CH$_3$*C*CH$_3$), 125.6 (*p*-Ph*C*), 125.9 (*i*-PrOCH*C*H), 128.0 (*i*-PrOCHCH=*C*H), 128.1, 128.25 (*o*-Ph*C*/*m*-Ph*C*), 128.33 (CH=*C*HCHCH$_2$), 132.2 (*C*H=CHCHCH$_2$), 141.8 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 400 (0.4) [M^+], 385 (10) [$M^+ - CH_3$], 283 (11), 220 (14), 219 (100), 161 (72), 133 (11), 117 (40), 112 (60), 105 (11), 91 (46), 70 (58), 59 (27).

HRMS (EI): *m*/*z* [$M^+ - CH_3$] calcd for $C_{24}H_{33}O_4$: 385.2379; found: 385.2378.

Anal. Calcd for $C_{25}H_{36}O_4$ (400.55): C, 74.96; H, 9.06. Found C, 74.73; H, 9.35.

(*Z*)-4

Yield: 0.027 g (9% over two steps and HPLC); colorless oil; $[\alpha]_D^{20}$ –6.3 (*c* = 0.34, $CHCl_3$).

IR ($CHCl_3$): 3026 (m), 2977 (s), 2932 (vs), 1659 (w), 1603 (w), 1496 (m), 1455 (m), 1423 (w), 1378 (s), 1317 (m), 1225 (s), 1182 (s), 1124 (s), 1102 (s), 1057 (s), 1029 (vs), 1003 (vs), 949 (m), 893 (w), 861 (w), 794 (w) 745 (s), 701 (s), 634 (w), 528 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.22 (d, *J* = 6.0 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.33 (s, 3 H, C*H*$_3$CCH$_3$), 1.35 (s, 3 H, CH$_3$CC*H*$_3$), 1.59 (t, *J* = 7.8 Hz, 2 H, OCHC*H*$_2$CHO), 1.68–1.76 (m, 1 H, PhCH$_2$C*H*H), 1.79–1.88 (m, 1 H, PhCH$_2$CH*H*), 1.89–1.97 (m, 1 H, CH=CHCHC*H*H), 2.04–2.13 (m, 1 H, CH=CHCHCH*H*), 2.31 [m, 2 H, Ph(CH$_2$)$_2$CHCH$_2$CHC*H*$_2$], 2.57–2.64 (m, 1 H, PhC*H*H), 2.73–2.80 (m, 1 H, PhCH*H*), 3.75 [m, 1 H, Ph(CH$_2$)$_2$C*H*], 3.82 [m, 1 H, Ph(CH$_2$)$_2$CHCH$_2$C*H*], 4.00 (sep, *J* = 6.2 Hz, 1 H, CH$_3$C*H*CH$_3$), 4.72 (ddd, *J* = 11.1, 7.7, 3.4 Hz, 1 H, CH=CHC*H*CH$_2$), 5.08 (br s, 1 H, *i*-PrOC*H*), 5.50–5.62 (m, 2 H, *i*-PrOCHOCHC*H*, *i*-PrOCHOCHCH=C*H*), 5.71 (m, 1 H, *i*-PrOCHC*H*), 6.00 (m, 1 H, *i*-PrOCHCH=C*H*), 7.15–7.20 (m, 3 H, PhH), 7.25–7.30 (m, 2 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (*C*H$_3$CHCH$_3$), 23.9 (CH$_3$CH*C*H$_3$), 24.8 [C(*C*H$_3$)$_2$], 30.6 (CH=CHCH*C*H$_2$), 31.6 (Ph*C*H$_2$), 34.0 [Ph(CH$_2$)$_2$CHCH$_2$CH*C*H$_2$], 37.5 (PhCH$_2$*C*H$_2$), 38.0 (OCH*C*H$_2$CHO), 62.5 (CH=CH*C*HCH$_2$), 65.7, 66.2 [Ph(CH$_2$)$_2$*C*H, Ph(CH$_2$)$_2$CHCH$_2$*C*H], 69.2 (CH$_3$*C*HCH$_3$), 92.6 (*i*-PrO*C*H), 100.2 (CH$_3$*C*CH$_3$), 125.6 (*p*-Ph*C*), 125.9 (*i*-PrOCH*C*H), 128.06 (*i*-PrOCHCH=*C*H), 128.11, 128.25 (*o*-Ph*C*, *m*-Ph*C*), 128.29 (CH=*C*HCHCH$_2$), 131.4 (*C*H=CHCHCH$_2$), 141.8 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 400 (0.3) [M^+], 385 (3) [$M^+ - CH_3$], 325 (14), 283 (12), 273 (10), 220 (14), 219 (100), 213 (14), 161 (84), 150 (10), 142 (10), 133 (16), 131 (11), 117 (54), 112 (82), 105 (18), 91 (74), 81 (28), 70 (90), 59 (37).

HRMS (EI): *m*/*z* [$M^+ - CH_3$] calcd for $C_{24}H_{33}O_4$: 385.2379; found: 385.2378.

The analogous reaction sequence starting from **21** (0.070 g, 0.41 mmol, 1 equiv) but using KHMDS as base (0.5 M in toluene) yielded 0.100 g (61% over two steps) of a 8.5:1 mixture of (*E*)-**4**/(*Z*)-**4**.

(+)-Strictifolione, (*R*)-6-[(*E*)-(4*S*,6*S*)-4,6-Dihydroxy-8-phenyl-oct-1-enyl]-5,6-dihydropyran-2-one (1)

Pure (*E*)-**4** (57.6 mg, 0.14 mmol, 1 equiv) was dissolved in a mixture of acetone (6 mL) and water (1 mL; no Ar). PPTS (17.3 mg, 0.08 mmol, 0.5 equiv) was added and the reaction mixture was stirred for 5 h after which TLC control indicated the absence of starting material. Saturated aq $NaHCO_3$ (0.4 mL) was added to the solution. The reaction mixture was diluted with Et_2O, dried over $MgSO_4$ and filtered through a pad of glass wool. The crude product, obtained after evaporation of the solvent, was dissolved in CH_2Cl_2 (7 mL) and stirred with MnO_2 (170 mg, 2.0 mmol, 14 equiv) for 14 h (no Ar). The slurry was filtered through a pad of celite and the solvent evaporated. Column chromatography (*n*-pentane–EtOAc = 1:4) afforded **1**; yield: 31.2 mg (69% over two steps); colorless solid; de = 89% (C_6-epimer), ee ≥ 96% by ^{13}C NMR; $[\alpha]_D^{24}$ +54.1 (*c* = 0.33, $CHCl_3$) {ref.[1], $[\alpha]_D^{24}$ +81.5 (*c* = 0.52, $CHCl_3$; natural source)}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (t, *J* = 5.6 Hz, 2 H, HOCHC*H*$_2$CHOH), 1.74–1.92 (m, 2 H, PhCH$_2$C*H*$_2$), 2.29 (t, *J* = 6.6 Hz, 2 H, C*H*$_2$CH=CHCH), 2.42–2.46 (m, 2 H, C*H*$_2$CH=CHC=O), 2.54 (d, *J* = 4.4 Hz, 1 H, O*H*), 2.64–2.84 (m, 2 H, PhC*H*$_2$), 2.71 (d, *J* = 4.4 Hz, 1 H, OH), 3.98 [m, 1 H, Ph(CH$_2$)$_2$C*H*], 4.03 [m, 1 H, Ph(CH$_2$)$_2$CHCH$_2$C*H*], 4.90 (m, 1 H, CH$_2$CH=CHC*H*), 5.69 (dd, *J* = 15.5, 6.5 Hz, 1 H, CH$_2$CH=C*H*CH), 5.88 (ddt, *J* = 15.5, 1.0, 7.3 Hz, 1 H, CH$_2$C*H*=CHCH), 6.05 (dt, *J* = 9.9, 1.8 Hz, 1 H, C*H*C=O), 6.89 (ddd, *J* = 9.6, 4.9, 3.6 Hz, 1 H, C*H*=CHC=O), 7.18–7.22 (m, 3 H, PhH), 7.27–7.31 (m, 2 H, PhH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7 (*C*H$_2$CH=CHC=O), 32.1 (PhC*H*$_2$), 38.9 (PhCH$_2$*C*H$_2$), 40.3 (*C*H$_2$CH=CHCH), 42.1 (HOCH*C*H$_2$CHOH), 68.2, 68.7 [Ph(CH$_2$)$_2$*C*H, Ph(CH$_2$)$_2$CHCH$_2$*C*H], 77.7 (CH$_2$CH=CH*C*H), 121.4 (*C*HC=O), 125.7 (*p*-Ph*C*), 128.2, 128.3 (*o*-Ph*C*, *m*-Ph*C*), 129.7 (CH$_2$CH=*C*HCH), 131.0 (CH$_2$*C*H=CHCH), 141.7 (*i*-Ph*C*), 144.5 (*C*H=CHC=O), 163.8 (C=O).

The other spectroscopic data were in full agreement with the literature.[1]

***(R)*-2-(*N*-Phenylaminooxy)-pent-4-en-1-ol (22)[17a]**

A suspension of (*S*)-proline (57 mg, 0.5 mmol, 0.1 equiv) in $CHCl_3$ (2.5 mL) was cooled to 0 °C (no Ar). Nitrosobenzene (0.535 g, 5.0 mmol, 1 equiv) and then **10** (1.251 g, 14.9 mmol, 3.0 equiv) were added, each of them in one portion. The green heterogeneous mixture was stirred until it had turned into a yellow homogeneous one (about 25 min). This solution was then transferred with a pipette to a suspension of $NaBH_4$ (0.596 g, 15.8 mmol, 3.2 equiv) in MeOH (14 mL), which had been cooled to 0 °C before. After stirring for 20 min, sat. aq $NaHCO_3$ (30 mL) was added and stirring was continued for 40 min. The solution was extracted with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$. After filtration through a pad of glass wool and evaporation of the solvent the obtained orange oil was purified by column chromatography (*n*-pentane–Et_2O, 4:1) to give **22**; yield: 0.883 g (92% over two steps); orange oil; ee ≥ 98% by HPLC (Chiralpack AD, *n*-heptane–EtOH, 95:5); $[\alpha]_D^{24}$ +12.3 (*c* = 0.83, $CHCl_3$) {ref.[17a], $[\alpha]_D$ +8.0 (*c* = 0.83, $CHCl_3$)}.

MS (EI): *m*/*z* (%) = 193 (14) [M^+], 109 (100) [$PhNHOH^+$], 93 (12), 92 (50) [$PhNH^+$], 65 (14).

The other spectroscopic data were in full agreement with the literature.[17a]

(*R*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-pent-1-ene (24)

*Starting from **22***: The α-oxyamination product **22** (0.202 g, 1.0 mmol, 1 equiv) was dissolved in THF (4 mL) and SmI_2 (20 mL of a 0.1 M solution in THF, 2 mmol, 2 equiv) was added dropwise over a time period of 20 min. After addition and stirring for 2.25 h the reaction was judged to be complete according to TLC. The solvent was evaporated and the remaining yellow residue was dissolved in DMF (4 mL). Imidazole (0.569 g, 8.4 mmol, 8 equiv) and TBS-Cl (0.630 g, 4.2 mmol, 4 equiv) were added and the reaction was stirred overnight. The solution was diluted with Et_2O. Water was added as well as a minimum amount of 1 N HCl (to dissolve the precipitate and to facilitate separation of the phases). The phases were separated and the aq phase was extracted with Et_2O. The combined ethereal extracts were washed with pH 7 buffer, dried over $MgSO_4$ and filtered through a pad of glass wool. Evaporation of the solvent and column chromatography (*n*-pentane–Et_2O, 100:1 → 50:1) yielded **24**; yield: 0.171 g (50% over two steps); colorless liquid.

*Starting from **23** (after $CuSO_4 \cdot 5H_2O$-Mediated Cleavage)*: Diol **23** (0.143 g, 1.4 mmol, 1 equiv) was dissolved in DMF (4 mL). Imidazole (0.290, 4.3 mmol, 3 equiv) and TBS-Cl (0.542 g, 3.6 mmol, 2.6 equiv) were added and the reaction was stirred overnight. After dilution with Et_2O and workup (H_2O; Et_2O; $MgSO_4$), the obtained crude product was purified by column chromatography (*n*-pentane–Et_2O, 50:1) to give **24**.; yield: 0.421 g (91%); colorless liquid; $[\alpha]_D^{24}$ +3.6 (*c* = 1.13, $CHCl_3$).

IR (film): 3079 (w), 2955 (vs), 2932 (vs), 2859 (vs), 1642 (w), 1470 (s), 1436 (w), 1388 (m), 1362 (m), 1255 (s), 1113 (vs), 1003 (s), 937 (m), 915 (m), 837 (vs), 777 (vs), 734 (w), 668 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, Si(CH$_3$)$_2$], 0.06 [s, 6 H, Si(CH$_3$)$_2$], 0.88 [s, 9 H, C(CH$_3$)$_3$], 0.90 [s, 9 H, C(CH$_3$)$_3$], 2.11–2.21 (m, 1 H, CH$_2$=CHC*H*H), 2.30–2.39 (m, 1 H, CH$_2$=CHCH*H*), 3.43 (dd, *J* = 9.9, 6.4 Hz, 1 H, OC*H*H), 3.51 (dd, *J* = 9.9, 5.4 Hz, 1 H, OCH*H*), 3.71 (quint, *J* = 5.8 Hz, 1 H, OC*H*), 5.00–5.09 (m, 2 H, C*H*$_2$=CH), 5.84 (m, 1 H, CH$_2$=C*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 (SiCH$_3$), –5.3 (SiCH$_3$), –4.7 (SiCH$_3$), –4.4 (SiCH$_3$), 18.2 [*C*(CH$_3$)$_3$], 18.4 [*C*(CH$_3$)$_3$], 25.9 [C(*C*H$_3$)$_3$], 26.0 [C(*C*H$_3$)$_3$], 39.0 (CH$_2$=CH*C*H$_2$), 66.9 (OCH$_2$), 72.9 (O*C*H), 116.8 (*C*H$_2$=CH), 135.3 (CH$_2$=*C*H).

MS (EI): *m*/*z* (%) = 289 (7) [M^+ – CH$_2$=CHCH$_2$], 273 (21) [M^+ – *t*-Bu], 189 (13), 149 (10), 148 (16), 147 (100), 73 (27), 67 (15).

Anal. Calcd for $C_{17}H_{38}O_2Si_2$ (330.65): C, 61.75; H, 11.58. Found C, 61.64; H, 11.69.

(*R*)-Pent-4-ene-1,2-diol (23)

*Starting from **22***: The α-oxyamination product **22** (0.552 g, 2.9 mmol, 1 equiv) was dissolved in MeOH (9 mL) at 0 °C and $CuSO_4 \cdot 5H_2O$ (0.217 g, 0.87 mmol, 0.3 equiv) was added (no Ar). After warming to r.t overnight the solvent was evaporated and the residue was directly subjected to column chromatography (*n*-pentane–Et_2O, 1:1 → Et_2O) to give **23**; yield: 0.081 g (28%); red oil.

*Starting from **24**:* For obtaining an analytical sample, it turned out to be much easier to step backwards from **24**. The bis-TBS ether **24** (0.177 g, 0.54 mmol, 1 equiv) was dissolved in a mixture of MeOH (5 mL) and CH_2Cl_2 (3 mL; no Ar). HCl (1 N, 1 mL) was added and the reaction was stirred for 2.5 h. After dilution with Et_2O and drying over $MgSO_4$ the mixture was filtered through a pad of glass wool. Evaporation of the solvent and column chromatography (*n*-pentane–EtOAC, 1:1 → EtOAc) afforded an analytically pure sample of **23**; yield: 0.046 g (84%); colorless oil; $[\alpha]_D^{23}$ –9.0 (*c* = 0.56, $CHCl_3$), $[\alpha]_D^{23}$ +11.4 (*c* = 0.63, MeOH) {ref.[22], $[\alpha]_D^{25}$ +3.3 (*c* = 0.25, $CHCl_3$)}.

The other spectroscopic data were in agreement with the literature.[22]

(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-pent-4-en-1-ol (25)

In a plastic vial the bis-TBS-ether **24** (0.365 g, 1.1 mmol, 1 equiv) was dissolved in THF (3.4 mL). After the addition of pyridine (0.58 mL) and HF·pyridine (0.1 mL of a 65–70% solution of HF in pyridine) the solution was stirred for 24 h. The solution was diluted with Et_2O and washed with 0.5 M HCl (3 × 5 mL) and sat. aq $CuSO_4 \cdot 5H_2O$ (1 × 5 mL, the aqueous solutions were reextracted with Et_2O each time). All ethereal extracts were combined, dried

over $MgSO_4$, filtered through a pad of glass wool and evaporated. Column chromatography (*n*-pentane–Et_2O = 10:1) afforded **25**; yield: 0.136 g (57%); colorless liquid; $[\alpha]_D^{24}$ –15.3 (*c* = 1.04, $CHCl_3$).

IR ($CHCl_3$): 3395 (s), 3352 (s), 3076 (m), 2932 (vs), 2889 (s), 2859 (vs), 1642 (m), 1469 (s), 1436 (m), 1388 (m), 1363 (m), 1255 (s), 1106 (br vs), 1046 (s), 1001 (m), 966 (w), 916 (s), 836 (vs), 777 (s), 671 (m), 521 (w), 463 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.09 [s, 6 H, $Si(CH_3)_2$], 0.91 [s, 9 H, $C(CH_3)_3$], 1.88 (br t, *J* = 6.2 Hz, 1 H, O*H*), 2.28 (m, 2 H, CH_2=CHCH_2), 3.44–3.50 (m, 1 H, OC*H*H), 3.54–3.59 (m, 1 H, OCH*H*), 3.79 (m, 1 H, OC*H*), 5.03–5.11 (m, 2 H, CH_2=CH), 5.78 (m, 1 H, CH_2=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 (CH_3SiCH_3), –4.4 (CH_3SiCH_3), 18.1 [$C(CH_3)_3$], 25.8 [$C(CH_3)_3$], 38.7 (CH_2=CHCH_2), 65.9 (OCH_2), 72.3 (O*C*H), 117.3 (CH_2=CH), 134.1 (CH_2=*C*H).

MS (EI): *m*/*z* (%) = 185 (14), 175 (13), 117 (47), 75 (100), 73 (42), 67 (21).

Anal. Calcd for $C_{11}H_{24}O_2Si$ (216.39): C, 61.05; H, 11.18. Found C, 60.82; H, 11.30.

(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-pent-4-enal (8)

A solution of oxalyl chloride (0.08 mL, 0.95 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) was cooled to –78 °C. DMSO (0.15 mL, 2.1 mmol, 3.3 equiv) was added in one portion and after stirring for 15 min the alcohol **25** (0.137 g, 0.63 mmol, 1 equiv), dissolved in CH_2Cl_2 (3 mL), was slowly added. After 30 min Et_3N (0.45 mL, 3.2 mmol, 5.1 equiv) was added after which the cooling bath was replaced by an ice bath (0 °C). Stirring was continued for 10 min after which workup (H_2O; CH_2Cl_2; $MgSO_4$) followed immediately. Column chromatography (*n*-pentane–Et_2O, 20:1) gave **8**; yield: 0.133 g (98%); colorless liquid; $[\alpha]_D^{23}$ +33.0 (*c* = 0.98, $CHCl_3$).

IR (film): 3081 (m), 2933 (vs), 2893 (s), 2859 (vs), 2802 (m), 2713 (w), 1740 (vs), 1643 (m), 1470 (s), 1435 (w), 1413 (w), 1365 (m), 1327 (w), 1257 (vs), 1113 (vs), 1000 (m), 919 (s), 839 (vs), 780 (s), 675 (m), 577 (w), 509 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, CH_3SiCH_3), 0.09 (s, 3 H, CH_3SiCH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 2.31–2.50 (m, 2 H, CH_2=CHCH_2), 4.02 (ddd, *J* = 6.9, 5.3, 1.5 Hz, 1 H, C*H*CHO), 5.08–5.16 (m, 2 H, CH_2=CH), 5.80 (m, 1 H, CH_2=C*H*), 9.61 (d, *J* = 1.5 Hz, 1 H, C*H*O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8 (CH_3SiCH_3), –4.7 (CH_3SiCH_3), 18.2 [$C(CH_3)_3$], 25.7 [$C(CH_3)_3$], 37.5 (CH_2=CHCH_2), 77.3 (OCH), 118.4 (CH_2=CH), 132.8 (CH_2=*C*H), 203.7 (CHO).

MS (EI): *m*/*z* (%) = 199 (2) [$M^+ - CH_3$], 185 (32) [M^+ – CHO], 158 (12) [M^+ – *t*-Bu], 157 (100), 129 (11), 127 (64), 115 (10), 101 (23), 75 (57), 73 (61), 59 (11).

HRMS (EI): *m*/*z* [M^+ – CHO] calcd for $C_{10}H_{21}OSi$: 185.1362; found: 185.1362.

{(*E*)-(*R*)-1-Allyl-4-[(4*S*,6*S*)-2,2-dimethyl-6-phenethyl-[1,3]dioxan-4-yl]-but-2-enyloxy}-*tert*-butyldimethylsilane (26)

Sulfone **6** (4.8 mL of a 0.041 M solution of **6** in DME, 0.20 mmol, 1 equiv) and aldehyde **8** (57 mg, 0.27 mmol, 1.3 equiv), dissolved in DME (2.5 mL), were cooled to –(65–60) °C. KHMDS (0.44 mL of a 0.5 M solution in toluene, 0.22 mmol, 1.1 equiv) was added dropwise and the solution was warmed to r.t. overnight. Workup (sat. aq $NaHCO_3$; Et_2O, $MgSO_4$) and column chromatography (*n*-pentane–Et_2O, 35:1) afforded **26**; yield: 61 mg (69%); colorless oil; de, ee ≥ 96% by ^{13}C NMR; $[\alpha]_D^{23}$ +19.9 (*c* = 0.57, $CHCl_3$).

IR ($CHCl_3$): 3079 (w), 3027 (w), 2986 (s), 2932 (vs), 2857 (s), 1739 (w), 1641 (w), 1603 (w), 1497 (w), 1462 (m), 1378 (s), 1252 (s), 1225 (vs), 1165 (m), 1118 (s), 1069 (s), 1026 (w), 972 (m), 941 (w), 913 (s), 835 (vs), 776 (s), 746 (m), 699 (s), 576 (w), 530 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, CH_3SiCH_3), 0.04 (s, 3 H, CH_3SiCH_3), 0.88 [s, 9 H, $C(CH_3)_3$], 1.33 (s, 3 H, CH_3CCH_3), 1.36 (s, 3 H, CH_3CCH_3), 1.59 (t, *J* = 7.8 Hz, 2 H, OCHCH_2CHO), 1.63–1.90 (m, 2 H, PhCH_2CH_2), 2.10–2.31 (m, 4 H, CH_2CH=CHCHCH_2), 2.56–2.66 (m, 1 H, PhC*H*H), 2.71–2.81 (m, 1 H, PhCH*H*), 3.75 (m, 1 H), 3.83 [m, 1 H, $Ph(CH_2)_2$C*H*, $Ph(CH_2)_2CHCH_2$C*H*], 4.10 (q, *J* = 5.9 Hz, 1 H, TBSOC*H*), 4.97–5.06 (m, 2 H, CH_2=CH), 5.44–5.60 (m, 2 H, C*H*=CH, CH=C*H*), 5.77 (m, 1 H, CH_2=C*H*), 7.14–7.20 (m, 3 H, *o*-PhH, *p*-PhH), 7.24–7.30 (m, 2 H, *m*-PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7 (CH_3SiCH_3), –4.3 (CH_3SiCH_3), 18.3 [$C(CH_3)_3$], 24.87 (CH_3CCH_3), 24.91 (CH_3CCH_3), 25.9 [$C(CH_3)_3$], 31.7 (PhCH_2), 37.5, 38.2, 38.6, 43.1 (Ph$CH_2CH_2CHCH_2CHCH_2CH$=CHCHCH_2), 65.8, 66.4 [$Ph(CH_2)_2CH$, $Ph(CH_2)_2CHCH_2CH$], 73.2 (TBSO*C*H), 100.3 [$C(CH_3)_2$], 116.6 (CH_2=CH), 125.76, 125.80 (*p*-Ph*C*, CH=*C*HCH), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 135.2, 135.5 (CH_2=*C*H, *C*H=CHCH), 142.0 (*i*-Ph*C*).

MS (EI): *m*/*z* (%) = 271 (15), 220 (11), 219 (80), 171 (13), 162 (12), 161 (100), 133 (14), 117 (56), 105 (12), 91 (54), 75 (27), 73 (26), 59 (69).

HRMS (EI): *m*/*z* [$M^+ - C_3H_5$] calcd for $C_{24}H_{39}O_3Si$: 403.2669; found: 403.2669.

Acrylic Acid (*E*)-(*R*)-1-Allyl-4-{(4*S*,6*S*)-2,2-dimethyl-6-phenethyl-[1,3]dioxan-4-yl}-but-2-enyl Ester (5)

TBS ether **26** (23 mg, 0.05 mmol, 1 equiv) was dissolved in THF (4 mL; no Ar). TBAF was added (0.3 mL of a 1 M solution in THF, 0.3 mmol, 5.8 equiv) and the solution was stirred for 2 h. The crude product, obtained after workup (pH 7 buffer; Et_2O; $MgSO_4$), was directly used for the next step. It was dissolved in CH_2Cl_2 (4 mL) and cooled to –78 °C. Et*i*-Pr_2N (0.05 mL, 0.3 mmol, 5.9 equiv) and then acryloyl chloride (30 mg, 0.33 mmol, 6.4 equiv) were added. After stirring for 1 h at that temperature the reaction was worked up (pH 7 buffer; CH_2Cl_2; $MgSO_4$). Column chromatography (*n*-pentane–Et_2O, 10:1) gave **5**.

Yield: 18 mg (91%); colorless oil; $[\alpha]_D^{22}$ +37.6 (*c* = 0.48, $CHCl_3$) {ref.[4], $[\alpha]_D^{20}$ +22.9 (*c* = 4.85, $CHCl_3$)}.

IR ($CHCl_3$): 3064 (m), 3026 (m), 2986 (s), 2936 (s), 1725 (vs), 1638 (m), 1496 (m), 1454 (m), 1405 (s), 1378 (s), 1296 (w), 1267 (m), 1224 (s), 1191 (vs), 1117 (m), 1041 (m), 971 (s), 917 (m), 810 (m), 750 (m), 701 (m), 500 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3CCH_3), 1.35 (s, 3 H, CH_3CCH_3), 1.57 (m, 2 H, OCHCH_2CHO), 1.67–1.76 (m, 1 H, PhCH_2C*H*H), 1.79–1.88 (m, 1 H, PhCH_2CH*H*), 2.21 (m, 2 H, CH_2CH=CH), 2.41 (m, 2 H, CH_2=CHCH_2), 2.57–2.64 (m, 1 H, PhC*H*H), 2.72–2.79 (m, 1 H, PhCH*H*), 3.74 [m, 1 H, $Ph(CH_2)_2$C*H*], 3.83 [quint, *J* = 7.1 Hz, 1 H, $Ph(CH_2)_2CHCH_2$C*H*], 5.03–5.12 (m, 2 H, CH_2=CHCH$_2$), 5.34 (q, *J* = 6.7 Hz, 1 H, CH=CHC*H*), 5.52 (dd, *J* = 15.4, 7.1 Hz, 1 H, CH_2CH=C*H*), 5.68–5.77 (m, 2 H, CH_2C*H*=CH, CH_2C*H*=CH_2), 5.80 (dd, *J* = 10.3, 1.5 Hz, 1 H, CH_EH=CHC=O), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1 H, CH_2=C*H*C=O), 6.39 (dd, *J* = 17.3, 1.4 Hz, 1 H, CHH_Z=CHC=O), 7.15–7.20 (m, 3 H, PhH), 7.25–7.30 (m, 2 H, PhH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 [$C(CH_3)_2$], 31.7 (PhCH_2), 37.5, 38.1, 38.5, 39.0 (Ph$CH_2CH_2CHCH_2CHCH_2CH$=CHCHCH_2), 65.8, 66.1 [$Ph(CH_2)_2CH$, $Ph(CH_2)_2CHCH_2CH$], 73.9 (CH=CH*C*H), 100.4 [$C(CH_3)_2$], 117.9 (CH_2=CHCH_2), 125.8 (*p*-Ph*C*), 128.3, 128.5 (*o*-Ph*C*, *m*-Ph*C*), 128.8, 130.1 (2 × C), 130.5 (CH_2=CHC=O), 133.3 (*C*H=CH, CH=*C*H, CH_2=*C*HCH_2, CH_2=*C*HC=O), 142.0 (*i*-Ph*C*), 165.4 (C=O).

MS (EI): *m*/*z* (%) = 369 (29) [$M^+ - CH_3$], 220 (16), 219 (100), 195 (10), 162 (11), 161 (92), 143 (17), 133 (27), 131 (14), 117 (74), 105 (25), 92 (12), 91 (98), 79 (18), 59 (56), 55 (82).

HRMS (EI): *m*/*z* [$M^+ - CH_3$] calcd for $C_{23}H_{29}O_4$; 369.2066; found: 369.2066.

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