First Asymmetric Synthesis and Determination of the Absolute Configuration of a Lignan Isolated from *Virola sebifera*

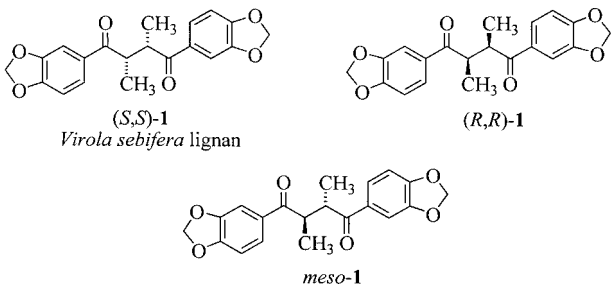
Dieter Enders,*[a] Mile Milovanovic,[a] Elena Voloshina,[a] Gerhard Raabe,[a] and Jörg Fleischhauer[a]

Keywords: Lignans / Nucleophilic acylation / α-Amino nitriles / Michael addition / Circular dichroism

The first asymmetric synthesis of a lignan isolated from the seeds of *Virola sebifera*, one of the most widely spread *Myristicaceae* species in Brazil, in four steps (48 % overall yield) and with excellent stereoselectivity (*de*, *ee* ≥ 96 %) is described. The key step is the asymmetric Michael addition of a lithiated enantiopure α-amino nitrile to an enone, followed by α-methylation and cleavage of the amino nitrile. The absolute configuration of the naturally occurring 1,4-diketone was determined by polarimetry as well as by CD spectroscopy and quantum chemical calculations.

Introduction

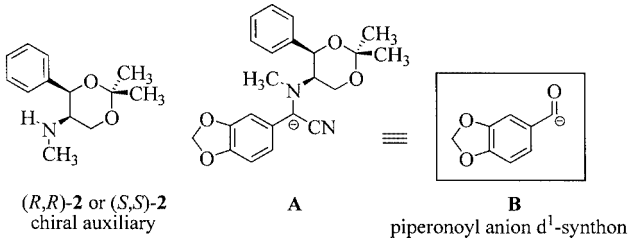
Lignans are important secondary plant metabolites produced in nature by oxidative dimerization of phenylpropenes, such as ferulic acid, coniferyl alcohol or isoeugenol.[1] This large class of natural products has been of great interest to synthetic organic chemists, mainly because its members possess a variety of different biological activities.[2] Recently, Kato and Rezende[3] isolated the 2,3-dipiperonoylbutane lignan **1** from the seed extract of *Virola sebifera* (Aublet.), one of the most widely spread *Myristicaceae* species in Brazil. The absolute configuration of this new lignan remained unknown, but the *meso* compound (*meso*-**1**) could be excluded because of the optical activity of the isolated natural lignan. Interestingly, the racemic diketone *rac*-**1** had already been synthesized much earlier, before its isolation from a natural source, by Stevenson et al.[4] in the course of the synthesis of other lignans. We decided to synthesize both enantiomers of the title lignan by the asymmetric nucleophilic acylation methodology (Umpolung) employing enantiopure lithiated α-amino nitriles developed in our group[5] and to determine the absolute configuration of the natural product.



[a] Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule,
Professor-Pirlet-Straße 1, 52074 Aachen, Germany
Fax: +49-241-8092127
E-mail: enders@rwth-aachen.de

Results and Discussion

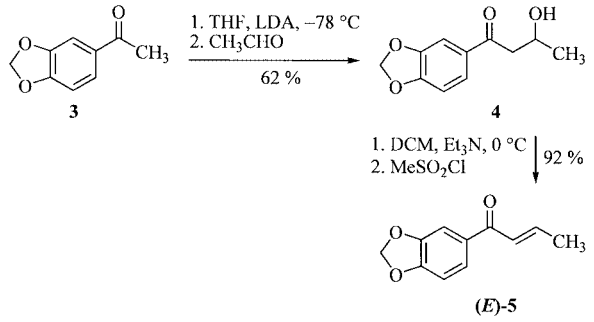
For the asymmetric synthesis of the title 1,4-diketone lignan **1** we had a choice of two synthetic methods developed in our group: oxidative coupling of metallated SAMP-hydrazones[6] and asymmetric nucleophilic acylation with amino nitriles.[5] We choose the latter methodology, which has already been shown to give excellent asymmetric induction with the chiral auxiliaries (*R*,*R*)-**2** or (*S*,*S*)-**2** in Michael additions to enoates,[5c] cyclic enones[5e,5f] and butenolide.[5g–5j] For this approach the methodology needed to be extended to acyclic enones as Michael acceptors, so we planned to use the amino nitrile anion **A** as an enantiopure synthetic equivalent of the piperonoyl anion d^1-synthon **B** in a 1,4-addition to the enone (*E*)-**5**, easily available by aldol condensation.



Starting from acetopiperone **3**, the aldol adduct **4** was obtained in 62% yield after metallation with lithium diisopropylamide (LDA) and trapping of the enolate with acetal-

  DOI: 10.1002/ejoc.200400885

dehyde, followed by condensation with mesyl chloride and triethylamine to afford the enone (*E*)-**5** in 92% yield (Scheme 1).



3 **4** (*E*)-**5**

Scheme 1. Synthesis of the enone Michael acceptor (*E*)-**5**.

The α-amino nitrile (*R*,*R*,*S*/*R*)-**7** was synthesized from the enantiomerically pure secondary amine (*R*,*R*)-**2**, piperonal (**6**) and sodium cyanide in methanol. The product was obtained in 81% yield as a mixture of α-epimers**.** Deprotonation of **7** with LDA in THF and treatment with the enone (*E*)-**5** at –100 °C afforded the Michael adduct (*R*,*R*,*S*,*S*)-**8** in high yield (83%) and with good diastereoselectivity (*de* ≥ 96%). The second stereogenic centre of the natural product was introduced through subsequent metallation of the Michael adduct **8** with potassium diisopropylamide (KDA) in THF at –100 °C and trapping of the enolate with methyl iodide at –78 °C. The resulting amino nitrile (*R*,*R*,*S*,*S*,*S*)-**9** was obtained in excellent yield (90%) and high diastereomeric purity (*de* ≥ 96%). It is important to note that KDA was necessary for the α-methylation of **8**, all attempts to deprotonate **8** with LDA under a variety of conditions having failed. We also tried a tandem Michael addition/methylation process by trapping of the intermediate enolate of **8** after 1,4-addition with methyl iodide in situ, but unfortunately the *de* decreased from 96% to 68% under these conditions. While trying to improve the yield of the final cleavage step we found that (*R*,*R*,*S*,*S*,*S*)-**9** can be converted into (*S*,*S*)-**1** not only with aqueous silver nitrate solution as reported earlier,[5e] but also under acidic conditions. The cleavage of the amino nitrile **9** to provide the ketone **1** with 2 M hydrochloric acid at reflux in THF was complete after 15 min, was epimerization-free and gave a high yield (79%). This method was more reliable than the silver nitrate cleavage, which required longer reaction times (Scheme 2).

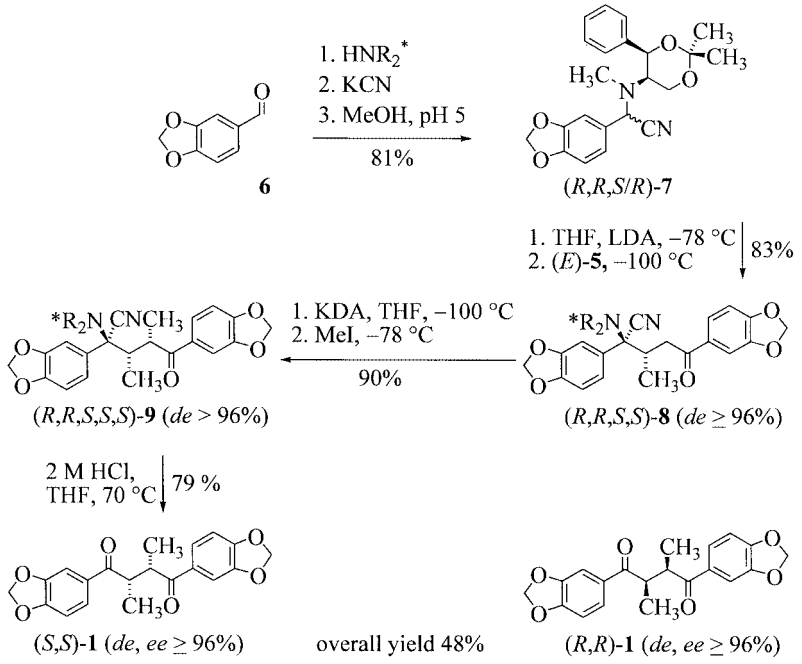
The diastereomeric excesses were determined by ^{1}H and ^{13}C NMR spectroscopy. The *ee* value of the title lignan (*S*,*S*)-**1** is based on the *de* value of the precursor **9**, because no epimerization and racemization occurred during the amino nitrile cleavage. The enantiomeric lignan (*R*,*R*)-**1** was prepared in the same manner by employing the chiral amine auxiliary (*S*,*S*)-**2**, and a similar overall yield and stereoselectivity was achieved (*de*, *ee* ≥ 96%).

Determination of the Absolute Configuration by CD Spectroscopy and Quantum Chemical Calculations

The experimentally measured spectra of the two enantiomers of **1** [(*R*,*R*) and (*S*,*S*)] are shown in Figure 1. For the assignment of the absolute configuration we performed quantum chemical calculations.

Conformational Search

Starting with the arbitrarily chosen (*R*,*R*) enantiomer of **1**, we performed a Monte-Carlo conformational search using the semiempirical AM1[7] parametrization and the program SPARTAN.[8]



6 (*R*,*R*,*S*/*R*)-**7** (*R*,*R*,*S*,*S*,*S*)-**9** (*de* > 96%) (*R*,*R*,*S*,*S*)-**8** (*de* ≥ 96%) (*S*,*S*)-**1** (*de*, *ee* ≥ 96%) (*R*,*R*)-**1** (*de*, *ee* ≥ 96%)

Scheme 2. First asymmetric synthesis of the *Virola sebifera* lignan (*S*,*S*)-**1**.

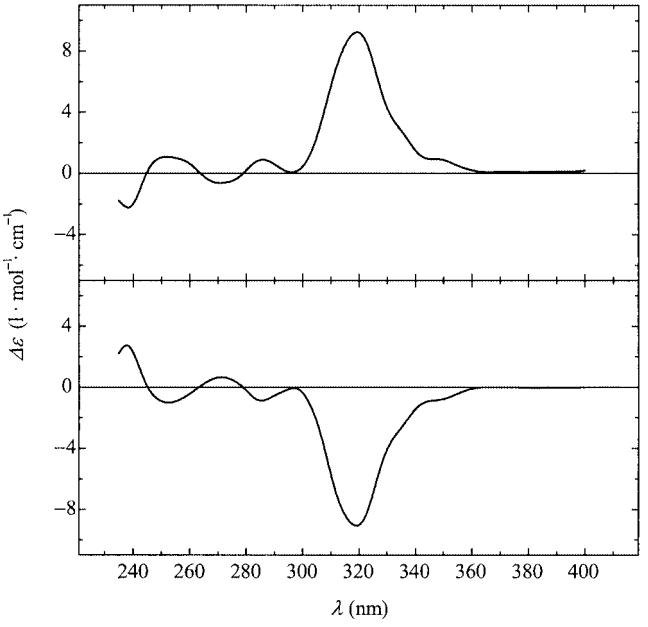
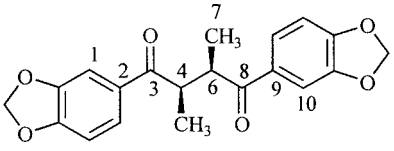


Figure 1. CD spectra of the two enantiomers [(*R*,*R*) and (*S*,*S*)] of **1**. For the assignment of the absolute configuration see text.



(*R*,*R*)-**1**

The following five dihedral angels were included in the search: θ_1 = ∠C^4–C^3–C^2–C^1 and θ_5 = ∠C^6–C^8–C^9–C^{10}, since the C^2–C^3(=O)C^4– and the C^9–C^8(=O)C^6 segment might occur in two different orientations with values of θ_1 and θ_5 close to 0° or 180°, θ_2 = ∠C^5–C^4–C^3–C^2 and θ_4 = ∠C^7–C^6–C^8–C^9, because the methyl groups at C^4 and C^6 might be rotated around the C^3–C^4 and C^6–C^8 bonds, respectively, and θ_3 = ∠C^3–C^4–C^6–C^8, because the two halves of the molecule can be rotated relative to each other about the C^4–C^6 bond. The initial geometry was defined by use of the following values: θ_1 = 0, θ_5 = 180, θ_2 = 0, θ_4 = 120 and θ_3 = 240°. The energetically lowest 66 stable conformers lying within an energy range of 6 kcal mol^{-1} were reoptimized at the DFT level by use of the B3LYP combination of functionals[9] and the 6–31+G* basis set. Only those conformers with energies not more than about 3 kcal mol^{-1} above that of the energetically lowest structure should contribute significantly to the overall CD spectrum. By this criterion, only the 20 energetically lowest structures for (*R*,*R*)-**1** were considered further in the calculation of the chiroptical properties.[10]

Calculation of the CD Spectra

The CD spectra of all twenty conformers of (*R*,*R*)-**1** were calculated by the time-dependent DFT method (TDDFT)[11] as implemented in the program TURBOMOLE[12] with use of the same functional (B3LYP) as in the ground state geometry optimizations and a TZVP (triple-ζ valence plus polarization functions)[13] basis set. The rotational strengths were calculated by use of the origin-independent dipole-velocity formalism.[14] The CD spectra of all 20 conformers[10] were obtained as sums of Gaussians, each centred at the calculated wavelength of the corresponding transition and multiplied with its rotational strength.[15] The Gaussians were generated by use of the empirical formula $\Gamma = k{\cdot}\lambda^{1.5}$ for the half bandwidth Γ at $\Delta\varepsilon_{max}$/e with k = 0.00375 nm$^{-1/2}$.[16] The total CD curve shown in Figure 2 was then obtained as a Boltzmann-weighted superposition of the individual CD spectra.

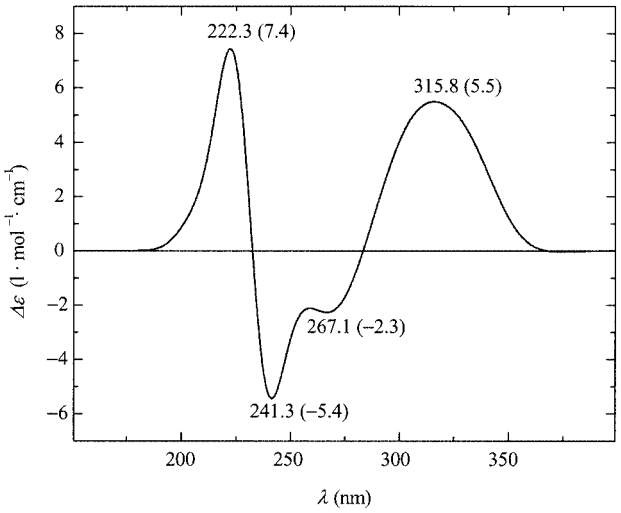


Figure 2. CD spectrum of (*R*,*R*)-**1** calculated at the B3LYP/TZVP level of time-dependent density functional theory (TDDFT).

The four highest occupied and the two lowest unoccupied *Kohn–Sham* orbitals (KSOs) of the most stable conformer (Ψ_{90}–Ψ_{95}) are shown in Figure 3 (see part b). Our TDDFT calculations predict 20 transitions in the range between 210 and 340 nm. The relevant configurations for these states obtained for the most stable conformer are listed in Table 1, together with the calculated rotational strengths. In addition we list the angle Θ between the electrical and the magnetic transition dipole moments. Note that in cases in which this angle is close to 90° the sign of the corresponding Cotton effect is not very reliable because the cosine changes its sign at 90°.

Both the spectrum calculated for (*R*,*R*)-**1** and the experimentally obtained one in the upper part of Figure 1 show a positive first Cotton effect. The first calculated CD band, with λ_{max} = 315.8 nm, is relatively broad (~275–350 nm) with a tail in the long-wavelength region. It is governed by two $n\rightarrow\pi^*$ transitions with rotational strengths of 14 and 35·10^{-40} erg cm^3 at 329 and 325 nm for the most stable conformer. At 20.8 and 50.9° the corresponding angles Θ are sufficiently different from 90°, so their signs can be considered reliable. The first measured Cotton effect in the upper spectrum in Figure 1 is a relatively weak positive band with a maximum at 350 nm, followed by a shoulder at 340 nm. We assign these two absorptions to the transitions calcu-

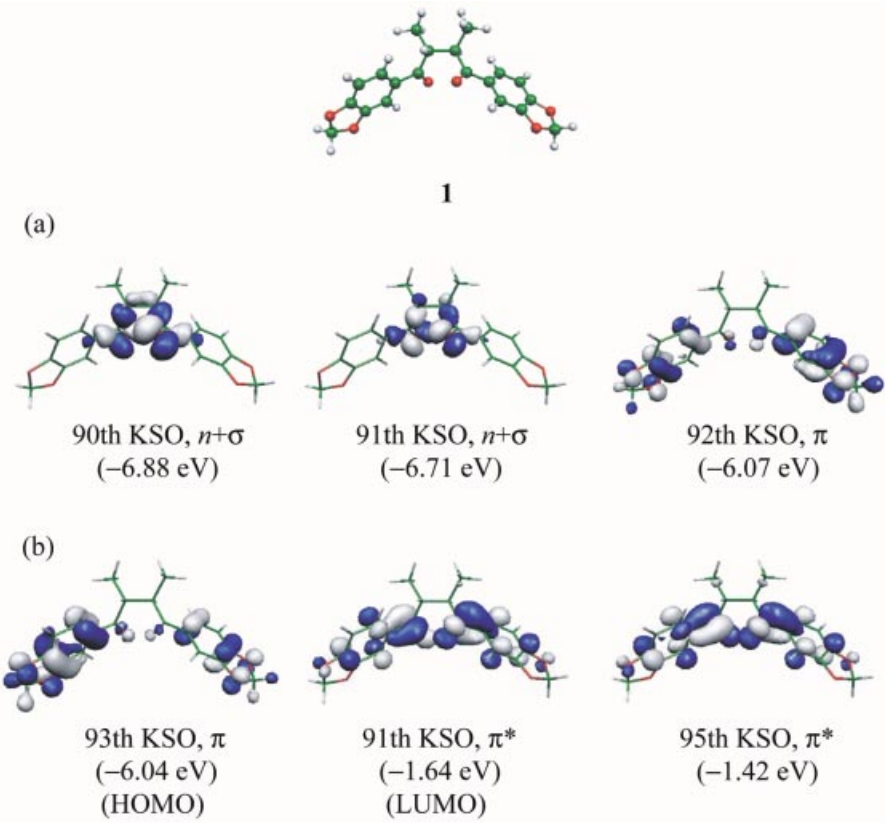


Figure 3. a) Structure of the most stable conformer of **1** calculated at the B3LYP/6-31+G* level of density functional theory. b) Kohn–Sham orbitals ψ_{90}–ψ_{95}.[10]

Table 1. The electronic configurations and rotational strengths for the exited states of the most stable conformer of **1** (Boltzmann factor: 0.198) calculated at the B3LYP/TZVP level of DFT. Θ is the angle between the electrical and the magnetic dipole moment.

Wavelength (nm)	Transition weight (%)	Θ (°)	Rotational strength ($\times 10^{-40}$ erg cm^3)
329.3	91 → 94 (65.3), 90 → 95 (24.3)	20.8	14.12
325.4	90 → 94 (48.5), 91 → 95 (41.9)	50.9	34.89
311.7	93 → 94 (91.9)	92.9	–24.37
307.3	92 → 94 (88.8)	121.2	–21.31
295.4	93 → 95 (87.8)	113.4	–11.89
294.4	92 → 95 (87.6)	82.8	31.28
272.9	91 → 95 (47.6), 90 → 94 (37.9)	119.3	–12.71
270.7	90 → 95 (66.4), 91 → 94 (23.4)	116.0	–2.03
262.6	89 → 94 (35.5), 88 → 94 (14.3), 92 → 96 (11.6), 93 → 97 (10.5)	91.6	–8.80
261.7	88 → 94 (32.8), 89 → 94 (12.8), 93 → 97 (9.6), 89 → 95 (9.2)	75.3	6.28
246.1	89 → 95 (49.2), 89 → 94 (33.1)	119.8	–1.92
245.0	88 → 95 (51.5), 88 → 94 (31.0)	99.1	–5.60
233.4	93 → 96 (62.6), 92 → 96 (32.8)	78.4	0.38
232.5	92 → 97 (60.7), 93 → 97 (34.4)	76.7	0.40
229.5	88 → 95 (25.8), 92 → 96 (21.2), 93 → 97 (19.3), 89 → 95 (7.7)	108.5	–347.95
227.4	89 → 95 (24.9), 92 → 97 (13.6), 92 → 96 (11.3), 93 → 96 (11.2)	60.1	339.82
222.8	91 → 97 (39.1), 91 → 96 (33.3)	111.1	–5.68
222.7	91 → 96 (35.0), 91 → 97 (33.6)	75.8	6.43
210.9	90 → 96 (70.5)	175.4	–1.18
210.2	90 → 97 (76.4)	144.9	–1.25

lated at 329 and 325 nm. The next transition calculated at 311.7 nm is a π→π* excitation with a rotational strength of $-24 \cdot 10^{-40}$ erg cm^3. Since the angle between the corresponding electrical and magnetic transition dipole moment is 92.9° its sign is uncertain. An incorrect sign calculated for this transition will certainly influence the rest of the spectrum, so we omit further discussion of its lower-wavelengths part. However, since the sign of the first calculated

Cotton effect agrees with that of the observed CD spectrum in the upper part of Figure 1 we conclude that this is the spectrum of (*R*,*R*)-**1**, while that in the lower part is that of the (*S*,*S*) isomer. This assignment correlates well with the relative topicity observed in our previous amino nitrile Michael additions.[5] Thus, from the CD data, calculations and the polarimetric data of the synthetic and natural lignan we can unambiguously assign the (*S*,*S*) configuration to the *Virola sebifera* lignan.

Conclusions

In summary, a very efficient and straightforward four-step asymmetric synthesis (*de*, *ee* ≥ 96%) of both enantiomers of the dibenzylbutane-type lignan of *Virola sebifera* has been developed, and the absolute configuration of the natural product was determined as (*S*,*S*). In addition, the new approach demonstrates that acyclic enones can be employed as Michael acceptors in conjugate additions with our metallated enantiopure amino nitriles as well. The title compounds may be used as starting building block in the asymmetric synthesis of other related lignans.[17]

Experimental Section

General Remarks: All moisture-sensitive reactions were carried out by use of standard Schlenk techniques. All reagents were of commercial quality from freshly opened containers or were purified by common methods. The chiral auxiliaries (*S*,*S*)-**2** and (*R*,*R*)-**2** were prepared by the literature procedure.[5b] THF was freshly distilled from sodium/lead alloy, CH_2Cl_2 from CaH_2 under argon. *n*BuLi (1.6 M in hexane) was purchased from Merck, Darmstadt. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh). Analytical TLC: silica gel 60 F_{254} plates from Merck, Darmstadt. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter; solvents used were of Merck UVASOL quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID or a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ 7000 (CI, 100 eV. EI 70 eV) spectrometer. High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer. IR spectra were recorded on a Perkin–Elmer FT/IR 1760. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded on Gemini 300 or Varian Inova 400 spectrometers with $CDCl_3$ as solvent and TMS as internal standard. The CD spectra were recorded at room temperature with an AVIV circular dichroism spectrometer (Model 62DS). The solvent was $CHCl_3$ and for both spectra the concentration was $2.12 \cdot 10^{-3}$ mol L^{-1}.

1-(Benzo[*d*][1,3]dioxol-6-yl)-3-hydroxybutan-1-one (4): Diisopropylamine (21.35 mL, 151.49 mmol) was placed in a dry Schlenk flask and abs. THF (1 mL per mmol diisopropylamine) was added. The reaction mixture was cooled to –78 °C and *n*BuLi (1.6 M, 72.58 mL, 116.13 mmol) was added dropwise. The mixture was stirred for 30 min and acetopiperone (**3**) (15.0 g, 91.37 mmol) was then added. After a further 30 min, freshly distilled acetaldehyde (6.83 mL, 120.96 mmol) in THF (47 mL) was added by syringe pump. The reaction mixture was stirred at –78 °C for 3 h, allowed to warm up to –10 °C and was quenched by addition of sat. NH_4Cl solution with vigorous stirring. After addition of water the organic phase was separated. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with water and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, pentane/diethyl ether, 1:1) to give the aldol product **4** as a colourless solid (11.86 g, 62%), m.p. 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 2.95 (dd, *J* = 17.6, 8.8 Hz, 1 H, COC*H*H), 3.10 (dd, *J* = 17.6, 2.8 Hz, 1 H, COCH*H*), 3.45 (br s, 1 H, O*H*), 4.37 (m, 1 H, C*H*OH), 6.05 (s, 2 H, OCH_2O), 6.85 (d, *J* = 8.2 Hz, 1 H, CH_{arom}), 7.42 (d, *J* = 1.7 Hz, 1 H, CH_{arom}), 7.55 (dd, *J* = 8.2, 1.7 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4 (CH*C*H$_3$), 46.2 (O*C*H$_2$), 64.1 (*C*HOH), 102.0 (O*C*H$_2$O), 107.7, 107.9, 124.6 (Ar-*C*H), 131.6, 148.3, 152.2 (Ar-C_q), 198.8 (*C*O) ppm. IR (KBr): $\tilde{\nu}$ = 3469 (s), 3084 (w), 2991 (w), 2970 (m), 2898 (m), 2788 (w), 2723 (w), 2675 (w), 2346 (w), 2216 (w), 2046 (w), 2000 (w), 1853 (w), 1791 (w), 1671 (s), 1600 (s), 1501 (s),1447 (s), 1410 (w), 1381 (m), 1323 (m), 1253 (s), 1207 (m), 1148 (m), 1110 (s), 1037 (s), 931 (m), 892 (m), 852 (w), 804 (s), 780 (m), 723 (w), 655 (w), 627 (m), 587 (w), 539 (w), 512 (87), 477 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 208 [*M*]$^+$ (32), 164 (17), 151 (27), 150 (16), 149 (100), 122 (11), 121 (23), 65 (8) 63 (7). $C_{11}H_{12}O_4$ (208.21): calcd. C 63.45, H 5.81; found C 63.88, H 6.06.

(*E*)-1-(Benzo[*d*][1,3]dioxol-6-yl)but-2-en-1-one [(*E*)-5]: The aldol adduct **4** (7.50 g, 36.02 mmol) was dissolved in dry CH_2Cl_2 (180 mL) and the solution was cooled to 0 °C. Triethylamine (10.12 mL, 72.04 mmol) was added quickly, and the reaction mixture was stirred for 10 min. Methanesulfonyl chloride (5.58 mL, 72.04 mmol) was added dropwise, and the resulting solution was stirred at 0 °C for 30 min. The reaction mixture was diluted with water, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with HCl (1 M) and saturated aqueous $NaHCO_3$ and were dried over $MgSO_4$, and the solvents were evaporated in vacuo. The resulting crude product was purified by flash chromatography (silica gel, pentane/diethyl ether, 1:3) to give (*E*)-**5** (6.31 g, 92%) as a colourless solid. M.p. 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (dd, *J* = 6.9, 1.6 Hz, 3 H, CH_3), 6.03 (s, 2 H, OCH_2O), 6.84 (d, *J* = 8.2 Hz, 1 H, CH_{arom}), 6.86 (dq, *J* = 15.1, 1.7 Hz, 1 H, COC*H*), 7.05 (dq, *J* = 15.1, 6.9 Hz, 1 H, C*H*CH$_3$), 7.45 (d, *J* = 1.7 Hz, 1 H, CH_{arom}), 7.55 (dd, *J* = 8.2, 1.7 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (*C*H$_3$), 101.8 (O*C*H$_2$O), 107.8, 108.4, 124.6 (Ar-*C*H), 127.0 (CO*C*H), 132.6 (Ar-C_q), 144.3 (CH$_3$*C*H), 148.2, 151.5 (Ar-C_q), 188.5 (*C*O) ppm. IR (KBr): $\tilde{\nu}$ = 3459 (w), 3061 (w), 2978 (w), 2908 (w), 2790 (w), 2720 (w), 2681 (w), 2608 (w), 1839 (w), 1755 (w), 1663 (s), 1617 (s), 1597 (s), 1505 (m), 1486 (s), 1442 (s), 1362 (w), 1327 (m), 1299 (s), 1251 (s), 1141 (w), 1113 (m), 1036 (s), 969 (m), 933 (s), 885 (m), 833 (w), 794 (s), 724 (w), 687 (m), 662 (w), 583 (w), 514 (w) cm^{-1}. MS (EI); *m*/*z* (%) = 192 (0.9), 191 (9), 190 [*M*]$^+$ (80), 175 (22), 149 (8), 148 (100), 121 (20), 91 (5), 69 (13), 63 (7). $C_{11}H_{10}O_3$ (190.20): calcd. C 69.46, H 5.30; found C 69.44, H 5.48.

(*SR*)-2-(Benzo[*d*][1,3]dioxol-6-yl)-2-{methyl[(4*R*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}acetonitrile [(*R*,*R*,*S*/*R*)-7]: NaCN (1.35 g, 27.55 mmol) was stirred for 20 min at room temperature in methanol (50 mL) according to the general procedure described by Weinges.[18] Compound (*R*,*R*)-**2** (5.53 g, 24.98 mmol) and piperonal (3.75 g, 24.98 mmol) were added, and the reaction mixture was cooled to 0 °C. Glacial acetic acid (2.25 mL, 38.97 mmol) was then added, and the reaction mixture was cooled to –5 °C with an ice/NaCl mixture and then allowed to warm to room temperature. The reaction was finished after 3 days and the precipitated crude product was filtered off, washed with water and dried over $MgSO_4$. The amino nitrile (*R*,*R*,*SR*)-**7** was obtained as a colourless solid (7.69 g, 81% yield), m.p. 113 °C, *de* = 58%. $[\alpha]_D^{26}$ = –104.8 (*c* = 1.1,

$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) mixture of epimers: δ = 1.53/1.57 (s, 3 H, CCH_3), 1.58/1.57 (s, 3 H, CCH_3), 2.29/2.41 (s, 3 H, NCH_3), 2.86/2,89 (td, J = 3.3, 1.4 Hz, 1 H, NCHCH$_2$), 4.20/4.32 (dd, J = 13.0, 3.3 Hz, 1 H, OCHHCH), 4.40/5.50 (s, 1 H, CHCN), 4.53/4.60 (dd, J = 13.0, 1.4 Hz, OCHHCH), 5.25/5.28 (d, J = 3.3 Hz, 1 H, OCHPh), 5.87–5,95 (m, 2 H, OCH_2O and 1 H, CH_{arom}), 6.47 (m, 1 H, CH_{arom}), 6.55–6.61 (m, 1 H, CH_{arom}), 7.28–7.43 (5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4/18.8 (CCH_3), 29.4/29.6 (CCH_3), 33.2/37.5 (NCH_3), 57.0/60.6 (NCH), 59.0/60.2 (CHCH_2O), 57.3/62.5 (CHCN), 73.4/74.5 (CHPh), 98.9/99.2 (CCH$_3$), 101.0/101.1 (OCH_2O), 107.2/107.4, 107.5/107.6 (Ar-CH), 117.4/117.7 (CN), 120.3/120.4, 125.3/125.5, 126.9/127.0, 127.7/128.0 (Ar-CH), 128.0/128.6, 139.89/139.93, 147.2/147.4, 147.5/147.7 (Ar-C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3464 (w), 3078 (w), 3031 (w), 2993 (s), 2973 (m), 2937 (s), 2863 (s), 2794 (m), 2703 (w), 2670 (w), 2376 (w), 2343 (w), 2228 (w), 2043 (w), 1956 (w), 1842 (w), 1810 (w), 1725 (w), 1607 (w), 1485 (s), 1439 (s), 1378 (s), 1316 (w), 1263 (s), 1236 (s), 1202 (s), 1152 (m), 1123 (m), 1086 (s), 1041 (s), 997 (m), 957 (m), 936 (s), 894 (w), 858 (m), 829 (m), 809 (w), 782 (m), 733 (s), 697 (m), 657 (w), 595 (w), 556 (m), 528 (w), 466 (w) cm^{-1}. MS (EI): m/z (%) = 354 (3) [M – CN]$^+$, 217 (10), 216 (73), 215 (22), 185 (5), 176 (37), 175 (35), 161 (11), 160 (100), 91 (7), 77 (5). MS (CI, methane): m/z (%) = 380 (1.8) [M]$^+$, 355 (19), 354 (100) [M – CN]$^+$, 323 (10), 217 (10), 216 (57), 215 (5), 160 (31). $C_{22}H_{24}N_2O_4$ (380.44): calcd. C 69.46, H 6.36, N 7.36; found C 69.93, H 6.31, N 7.44.

(*RS*)-2-(Benzo[*d*][1,3]dioxol-6-yl)-2-{methyl[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}acetonitrile [(*S*,*S*,*R*/*S*)-7]: The amino nitrile (*S*,*S*,*RS*)-**7** was synthesized by the same procedure as described for (*R*,*R*,*SR*)-**6** with use of the amine (*S*,*S*)-**2** (*ee* < 99%) as chiral auxiliary. The product was obtained as a colourless solid, m.p. 114 °C, *de* = 63%. $[\alpha]_D^{26}$ = +105.0 (c = 1.1, $CHCl_3$). The spectroscopic data (^1H, ^{13}C NMR, MS) were identical with those given for (*R*,*R*,*SR*)-7.

(2*S*,3*S*)-2,5-Bis(benzo[*d*][1,3]dioxol-6-yl)-2-{methyl[(4*R*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}-3-methyl-5-oxopentanenitrile [(*R*,*R*,*S*,*S*)-8]: Diisopropylamine (1.77 mL, 12.59 mmol) was placed in a dry Schlenk flask, and abs. THF (10 mL per mmol diisopropylamine) was added. The reaction mixture was cooled to –78 °C and *n*BuLi (1.6 M, 7.88 mL, 12.61 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and cooled to –78 °C, and the amino nitrile (*R*,*R*,*SR*)-**7** (4.0 g, 10.51 mmol) was then added. After 1.5 h at –78 °C the reaction mixture was cooled to –100 °C, followed by addition of the Michael acceptor (*E*)-**5** (2.0 g, 10.51 mmol) in THF (1 mL per mmol) by syringe pump. The reaction mixture was stirred overnight and allowed to warm up to –10 °C. After quenching by addition of sat. NH_4Cl solution with vigorous stirring, H_2O was added and the organic phase was separated. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, pentane/diethyl ether, 1:1 with 3% triethylamine) to give amino nitrile (*R*,*R*,*S*,*S*)-**8** (5.00 g, 83% yield), m.p. 115 °C. *de* ≥ 96%. $[\alpha]_D^{26}$ = +49.7 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.57 (d, J = 6.4 Hz, 3 H, CHCH_3), 1.45 (s, 3 H, CCH_3), 1.52 (s, 3 H, CCH_3), 1.83 (dd, J = 16.1, 10.9 Hz, 1 H, COCHH), 2.77 (m, 1 H, NCH), 2.83 (m, 1 H, COCHH), 2.92–3.01 (m, 1H, CHCH$_3$), 3.05 (s, 3 H, NCH_3), 3.99 (dd, J = 13.2, 4.2 Hz, 1 H, OCHHCH), 4.66 (dd, J = 13.2, 2.2 Hz, 1 H, OCHHCH), 5.00 (d, J = 4.2 Hz, 1 H, PhCH), 5.96–6.02 (m, 1 H, CH_{arom}), 6.00 (s, 4 H, OCH_2O), 6.65 (d(br), J = 7.7 Hz, 1 H, CH_{arom}), 6.77 (d, J = 8.2 Hz, 1 H, Ar-CH), 7.25–7.45 (m, 7 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CHCH_3), 19.3 (CCH_3), 28.8 (CCH_3), 35.4 (NCH_3), 36.5 (CHCH$_3$), 42.5 (COCH_2), 54.4 (NCH), 58.8 (OCH_2CH), 73.1 (CCN), 76.0 (PhCH), 99.4 (OCCH$_3$), 101.5 (OCH_2O), 101.8 (OCH_2O), 107.7, 107.8, 108.6 (Ar-CH), 121.1 (CCN), 121.8, 124.3 (Ar-CH), 127.6 (Ar-C_q), 127.7, 127.8, 127.9 (Ar-CH), 131.6, 138.9, 147.6, 147.9, 148.1, 151.7 (Ar-C_q), 195.9 (CO) ppm IR (KBr): $\tilde{\nu}$ = 3774 (w), 3450 (m), 3070 (w), 2987 (m), 2899 (m), 2813 (w), 2611 (w), 2370 (w), 2345 (w), 2216 (w), 2047 (w), 1676 (s), 1609 (m), 1489 (s), 1442 (s), 1380 (m), 1298 (m), 1248 (s), 1202 (m), 1169 (w), 1100 (m), 1037 (s), 935 (m), 895 (w), 854 (w), 813 (m), 746 (m), 701 (m), 669 (w), 642 (w), 574 (w), 533 (w) cm^{-1}. MS (EI): m/z (%) = 543 (3) [M– HCN]$^{+\cdot}$, 406 (6), 395 (13), 394 (34), 355 (11), 354 (45), 350 (10), 336 (7), 322 (8), 243 (5), 232 (7), 231 (21), 230 (100). MS (CI, methane): m/z (%) = 570 (0.6) [M]$^{+\cdot}$, 546 (6), 545 (32), 544 (100) [M – CN]$^+$, 543 (28), 542 (11), 487 (7), 486 (27), 395 (9), 394 (20), 355 (9). $C_{33}H_{34}N_2O_7$ (570.24): calcd. C 69.46, H 6.01, N 4.91; found C 69.38, H 6.04, N 4.58.

(2*R*,3*R*)-2,5-Bis(benzo[*d*][1,3]dioxol-6-yl)-2-{methyl[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}-3-methyl-5-oxopentanenitrile [(*S*,*S*,*R*,*R*)-8]: The Michael adduct (*S*,*S*,*R*,*R*)-**8** was synthesized by the same procedure as described for (*R*,*R*,*S*,*S*)-**8** with use of the amino nitrile (*S*,*S*,*RS*)-**7**. The product was obtained as a colourless solid, m.p. 115 °C, *de* ≥ 96%. $[\alpha]_D^{24}$ = –43.7 (c = 1.0, $CHCl_3$). The spectroscopic data were identical with those of (*R*,*R*,*S*,*S*)-**8**.

(2*S*,3*S*,4*S*)-2,5-Bis(benzo[*d*][1,3]dioxol-6-yl)-2-{methyl[(4*R*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}-3,4-dimethyl-5-oxopentanenitrile [(*R*,*R*,*S*,*S*,*S*)-9]: Potassium *tert*-butoxide (0.51 g, 4.53 mmol) was placed in a dry Schlenk flask and carefully heated under vacuum to avoid sublimation. After cooling to room temperature and addition of abs. THF (4.5 mL) and diisopropylamine (0.63 mL, 4.53 mmol) the mixture was cooled to –78 °C and *n*BuLi (1.6 M, 2.83 mL, 4.53 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, followed by addition of the Michael adduct (*R*,*R*,*S*,*S*)-**8** (2.35 g, 4.53 mmol) in THF (4.5 mL). After 4 h at –78 °C the reaction mixture was cooled to –100 °C and methyl iodide (0.51 mL, 8.24 mmol) was added. The reaction mixture was stirred overnight, allowed to warm to –10 °C, and was then quenched by addition of sat. NH_4Cl solution and H_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. Purification of the residue by flash chromatography (silica gel, pentane/diethyl ether, 1:1 with 3% triethylamine) afforded (*R*,*R*,*S*,*S*,*S*)-**9** (2.19 g, 90%), m.p. 120 °C, *de* = 96%. $[\alpha]_D^{26}$ = +85.2 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.20 (d, J = 6.9 Hz, 3 H, COCHCH_3), 0.60 (d, J = 6.9 Hz, 3 H, CHCH_3), 1.44 (s, 3 H, CCH_3), 1.50 (s, 3 H, CCH_3), 2.75–2.85 (m, 2 H, NCH, CHCH$_3$), 2.97 (s, 3 H, NCH_3), 3.33 (qd, 1 H, J = 6.9, 2.5 Hz, COCHCH$_3$), 3.96 (dd, J = 13.1, 4.5 Hz, 1 H, OCHHCH), 4.73 (dd, J = 13.1, 2.2 Hz, 1 H, OCHHCH), 4.97 (d, J = 4.2 Hz, 1 H, PhCH), 5.96–6.02 (m, 1 H, CH_{arom}) 6.03 (s, 4 H, 2×OCH_2O), 6.64 (d(br), J = 7.1 Hz, 1 H, CH_{arom}), 6.85 (d, J = 8.2 Hz, 1 H, CH_{arom}), 7.25–7.46 (m, 7 H, CH_{arom}), 7.58 (dd, J = 8.2, 1.7 Hz, 1 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.0 (CHCH_3), 12.3 (COCHCH_3), 19.4 (CCH_3), 28.7 (CCH_3), 35.1 (NCH_3), 39.8 (CHCH$_3$), 40.5 (COCHCH$_3$), 54.2 (NCH), 58.6 (OCH_2CH), 73.2 (NCC), 76.0 (PhCH) 99.4 (OCO), 101.5 (OCH_2O), 101.8 (OCH_2O), 107.8, 107.9, 108.5, 109.0 (Ar-CH), 121.6 (CN), 122.0, 124.7, 127.7, 127.9 (Ar-CH), 130.5, 138.9, 147.6, 148.1, 148.3, 151.8 (Ar-C_q), 201.1 (CO) ppm, MS (EI): m/z (%) = 558 (1.2) [M – CN]$^+$, 436 (9), 420 (12), 409 (26), 408 (100), 379 (15), 368 (14), 365 (18), 364 (89), 338 (6), 337 (5), 336 (9), 245 (6), 244 (45), 243 (51), 218 (5), 216 (18), 215 (25), 214 (5), 205 (21), 187 (8) ppm. IR (KBr):

$\tilde{\nu}$ = 3452 (w), 3071 (w), 3988 (m), 3940 (m), 3881 (m), 2814 (w), 2603 (w), 2216 (w), 2032 (w), 1956 (w), 1674 (m), 1609 (m), 1488 (s), 1440 (s), 1380 (m), 1246 (s), 1202 (m), 1168 (w), 1101 (m), 1076 (w), 813 (w), 782 (w), 744 (w), 701 (w), 669 (w), 645 (w), 612 (w), 577 (w), 533 (w) cm^{-1} MS (CI, methane): *m*/*z* (%) = 585 (2.7) $[M+1]^{+}$, 559 (18), 558 (63), 557 (16), 500 (8), 420 (12), 500 (17), 409 (16), 408 (57), 379 (15), 365 (6), 379 (15), 368 (13), 365 (21), 364 (100), 337 (8), 336 (9), 244 (15), 243 (14), 215 (7), 205 (14), 164 (8), 149 (24), 114 (6), 105 (6) $C_{34}H_{36}N_2O_7$: (584.25): calcd. C 69.85, H 6.21, N 4.79; found C 69.46, H 6.52, N 4.94.

(2*R*,3*R*,4*R*)-2,5-Bis(benzo[*d*][1,3]dioxol-6-yl)2-{methyl[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]amino}-3,4-dimethyl-5-oxopentanenitrile [(*S*,*S*,*R*,*R*,*R*)-9]: Compound (*S*,*S*,*R*,*R*,*R*)-**9** was synthesized by the same procedure as described for (*R*,*R*,*S*,*S*,*S*)-**9**. The product was obtained as a colourless solid, m.p. 120 °C, *de* = 96%. $[\alpha]_D^{26}$ = –83.3 (*c* = 1.0, $CHCl_3$). The spectroscopic data were identical with those of (*R*,*R*,*S*,*S*,*S*)-**9**.

(2*S*,3*S*)-1,4-Bis(benzo[*d*][1,3]dioxol-6-yl)-2,3-dimethylbutane-1,4-dione [(*S*,*S*)-1]: Compound (*R*,*R*,*S*,*S*,*S*)-**9** (150 mg, 0.26 mmol) was dissolved in THF (10 mL), hydrochloric acid (2 M, 15 mL) was added, and the reaction mixture was heated at reflux for 30 min. The phases were separated and the water phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with CH_2Cl_2 as eluent to afford (*S*,*S*)-**1** (72 mg, 79%). The product was obtained as a colourless solid, m.p. 212 °C, *de* = 96%. $[\alpha]_D^{24}$ = –149.0 (*c* = 0.1, $CHCl_3$), ref.[3] $[\alpha]_D^{25}$ = –125.0 (*c* = 0.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 6 H, CH_3), 3.84 (m, 2 H, $CHCH_3$), 6.02 (s, 4 H, OCH_2O), 6.87 (d, *J* = 8.2 Hz, 2 H, CH_{arom}), 7.43 (d, *J* = 1.7 Hz, 2 H, CH_{arom}), 7.63 (dd, *J* = 8.2 Hz, 1.7 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 ($CHCH_3$), 43.6 ($CHCH_3$), 101.8 (OCH_2O), 107.9, 108.4, 124.7 (Ar-CH), 130.8, 148.2, 151.7 (Ar-C_q), 202.4 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3949 (w), 3884 (w), 3818 (w), 3777 (w), 3676 (w), 3465 (m), 3060 (w), 2980 (m), 2917 (m) 2786 (w), 2700 (w), 2609 (w), 2376 (w), 2345 (w), 2066 (w), 1910 (w), 1787 (w), 1670 (s), 1610 (s), 1503 (s), 1441 (s), 1380 (m), 1357 (s), 1264 (s), 1208 (m), 1165 (w), 1143 (w), 1095 (s), 1038 (s), 977 (s), 931 (m), 890 (w), 868 (m), 835 (m), 812 (w), 749 (m), 718 (w), 670 (w), 611 (w), 577 (w), 535 (w), 501 (w), 460 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 354 (16) $[M]^{+}$, 150 (9), 149 (100), 121 (9), 65 (5) HRMS: $C_{20}H_{18}O_6$: calcd. 354.1103; found 354.1103.

(2*R*,3*R*)-1,4-Bis(benzo[*d*][1,3]dioxol-6-yl)-2,3-dimethylbutane-1,4-dione [(*R*,*R*)-1]: Diketone (*R*,*R*,)-**1** was synthesized in the same way as (*S*,*S*)-**1**. The product was obtained as a colourless solid. m.p. 212 °C, *de* = 96%. $[\alpha]_D^{23}$ = +151.0 (*c* = 0.1, $CHCl_3$). The spectroscopic data were identical with those of (*S*,*S*)-**1.**

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie. We thank BASF AG, Bayer AG and the former Boehringer Mannheim GmbH for the donation of chemicals.

[1] D. C. Ayres, J. D. Loike, in: *Lignans*: *Chemical, Biological and Clinical Properties*, Cambridge University Press, Cambridge, **1990**.
[2] a) R. S. Ward, *Nat. Prod. Rep.* **1993**, *10*, 1–28; b) R. S. Ward, *Nat. Prod. Rep.* **1995**, *12*, 183–205; c) R. S. Ward, *Nat. Prod. Rep.* **1997**, *14*, 43–74; d) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75–96. For a review on neolignan synthesis, see: e) M. Sefkow, *Synthesis* **2003**, 2595–2625.
[3] K. R. Rezende, M. J. Kato, *Phytochemistry* **2002**, *61*, 427–432.
[4] T. Biftu, B. G. Hazara, R. Stevenson, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1147–1150.
[5] a) For a review on α-amino nitrile chemistry, see: D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359–373; b) D. Enders, H. Lotter, *Nouv. J. Chim.* **1984**, *8*, 747–750; c) D. Enders, P. Gerdes, H. Kipphardt, *Angew. Chem.* **1990**, *102*, 226–228, *Angew. Chem. Int. Ed.* **1990**, *29*, 179–181; d) G. Raabe, E. Zobel, J. Fleischhauer, P. Gerdes, D. Mannes, E. Müller, D. Enders, *Z. Naturforsch., Teil A* **1991**, *46*, 275–288; e) D. Enders, D. Mannes, G. Raabe, *Synlett* **1992**, 837–839; f) D. Enders, J. Kirchhoff, D. Mannes, G. Raabe, *Synthesis* **1995**, 659–666; g) D. Enders, J. Kirchhoff, V. Lausberg, *Liebigs Ann.* **1996**, 1361–1366; h) D. Enders, J. Kirchhoff, P. Gerdes, D. Mannes, G. Raabe, J. Runsink, G. Boche, M. Marsch, H. Ahlbrecht, H. Sommer, *Eur. J. Org. Chem.* **1998**, 63–72. For previous lignan syntheses from our group, see: i) D. Enders, V. Lausberg, G. Del Signore, O. M. Berner, *Synthesis* **2002**, 512–522; j) D. Enders, G. Del Signore, O. M. Berner, *Chirality* **2003**, *15*, 510–513.
[6] D. Enders, P. Müller, D. Klein, *Synlett* **1998**, 43–44.
[7] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
[8] Spartan (Version 5.0), Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612, USA (**1997**).
[9] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; c) B. Miehlich, A. Savin, H. Stoll, H. Preuss, *Chem. Phys. Lett.* **1989**, *157*, 200–206.
[10] A table containing the total and the relative energies and selected structural parameters of the twenty most stable conformers, as well as plots of the individual CD spectra of these structures and a complete figure with all Kohn–Sham orbitals mentioned in Table 1, are available free of charge from the authors upon request.
[11] R. Bauernschmitt, R. Ahlrichs, *Chem. Phys. Lett.* **1996**, *256*, 454–464.
[12] a) R. Ahlrichs, in: *Encyclopedia of Computational Chemistry* (Ed.: P. v. R. Schleyer) *TURBOMOLE.* Wiley: Chichester, **1998**; vol. 5, pp. 3123–3129; b) *TURBOMOLE* (Version 5): R. Ahlrichs, M. Bär, H. P. Baron, R. Bauernschmitt, S. Böcker, M. Ehrig, K. Eichkorn, S. Elliot, F. Furche, F. Haase, M. Häser, H. Horn, C. Huber, U. Huniar, M. Kattannek, C. Kölmel, M. Kollwitz, K. May, C. Ochsenfeld, H. Öhm, A. Schäfer, U. Schneider, O. Treutler, M. von Arnim, F. Weigend, P. Weis, H. Weis, Quantum Chemistry Group: University of Karlsruhe, Germany, **2004**.
[13] A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829–5835.
[14] A. Moscowitz, in: *Modern Quantum Chemistry* (Ed.: O. Sinanoglu), John Wiley & Sons, Inc.: New York, **1965**, *3*, 21.
[15] J. A. Schellman, *Chem. Rev.* **1975**, *75*, 323–331.
[16] a) R. W. Woody, private communication. b) E. N. Voloshina, G. Raabe, M. Estermeier, B. Steffan, J. Fleischhauer, *Int. J. Quantum Chem.* **2004**, *100*, 1104–1113; c) In the present case the band at 320 nm in the experimental spectrum has a half bandwidth of approximately 28 nm at $\Delta\varepsilon_{max}$/e while this formula give a result of a value of about 22 nm at the same wavelength.
[17] T. Biftu, B. G. Hazara, R. Stevenson, *J. Chem. Soc., Perkin Trans. 1* **1979**, 2276–81.
[18] K. Weinges, H. Brachmann, P. Stahnecker, H. Rodewald, M. Nixdorf, H. Irngatinger, *Liebigs Ann. Chem.* **1985**, 566–578.

Received: December 16, 2004

