Atropo-Enantioselective Synthesis of the Natural Bicoumarin (+)-Isokotanin A via a Configurationally Stable Biaryl Lactone[‡]

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The atropo-enantioselective total synthesis of the axially chiral bicoumarin (+)-isokotanin A (**1**) is described. Key steps were the formation of a configurationally stable seven-membered biaryl lactone and its kinetic resolution by atroposelective ring cleavage. The previous assignment of the absolute configuration of (+)-isokotanin A (**1**) (and its synthetic precursors) was confirmed by quantum chemical CD calculations.

Introduction

The isokotanins A (**1**), B (**2**), and C (**3**, see Figure 1) are axially chiral bicoumarins from the sclerotia of the fungus *Aspergillus alliaceus*, first isolated in 1994 by Gloer et al.[1] All of these natural biaryls show antifeedant activity against the fungivorous beetle *Carpophilus hemipterus*.[1] A short time after its discovery, isokotanin B (**2**), now named *O*-demethyl-6,6′-bisiderin, was also isolated from the ascosttromata of the fungus *Petromyces alliaceus* by Udagawa's group.[2] *O*-Methylation of this bicoumarin gave 6,6′-bisiderin (i.e., isokotanin A, **1**).[2]

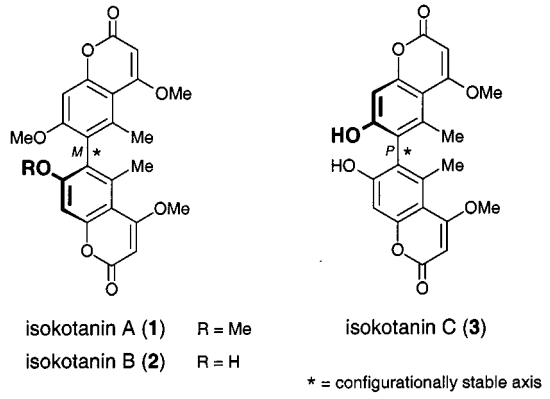

Figure 1. Isokotanins A (**1**), B (**2**), and C (**3**), axially chiral bicoumarins with insect antifeedant activity

Because of their interesting bioactivities and unusual, apparently polyketide-derived,[1] structures, including the axial chirality, the isokotanins are rewarding target molecules for stereoselective total synthesis. In the course of the first, and so far only, reported enantioselective preparation of (+)-isokotanin A (**1**), the naturally occurring atropisomer was assigned the (*M*) configuration.[3] As isokotanin A (**1**) contains two C_1 substituents in its *o*- and *o*′-positions next to the biaryl axis, it seemed profitable to construct this compound in enantiomerically pure form by our "lactone method",[4] using a recently introduced variant, the kinetic resolution of configurationally *stable* biaryl lactones.[5] This total synthesis of (+)-isokotanin A (**1**) is described here.

Results and Discussion

Our synthetic plan was to construct **1** by way of a biphenyl derivative (*M*)-**4** (Scheme 1), which should be available in enantiomerically pure form by kinetic resolution of the − presumably configurationally stable − lactone **5**. It was planned to prepare this bridged biaryl from the bromo ester **6** as a single monoaryl precursor. The (*P*) enantiomer of 4,4′-bisorcinol (biaryl **4** in its deprotected, tetraphenolic form) had already been prepared earlier, via a six-membered lactone, although with only moderate atropo-diastereoselectivity in the ring-cleavage step (up to 48% *de*).[6] Later, (*M*)-**4** was used as an intermediate in Lin's synthesis of (+)-isokotanin A (**1**).[3]

Similar biaryl lactones with two naphthalene components, as in **7** (Figure 2), had previously been prepared in a five-step reaction sequence starting from their monomeric bromonaphthalene precursors.[7] Being configurationally stable at the biaryl axis, they can be reductively transformed

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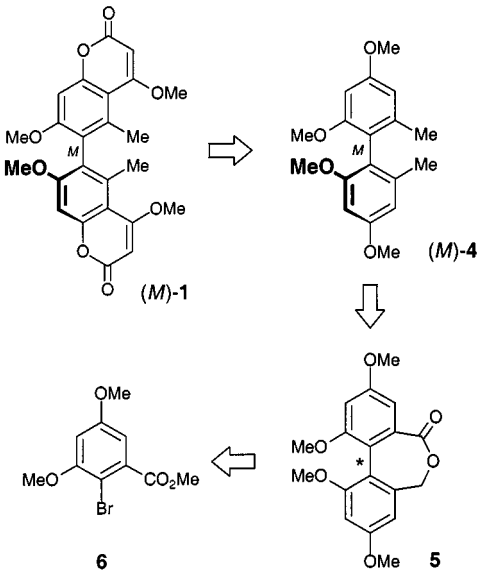


Scheme 1. Retrosynthetic analysis of isokotanin A (**1**)

with high efficiency (with a relative rate constant, k_{rel}, of 50) into the corresponding atropisomerically pure diol by kinetic resolution, with oxazaborolidine-activated borane as a chiral H-nucleophile.[5] Similar reductions with the corresponding biaryldicarbaldehyde or the respective hydroxy aldehyde, in contrast, were found to be essentially nonstereoselective ($k_{rel} \approx 1$).[8]

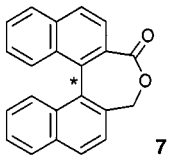
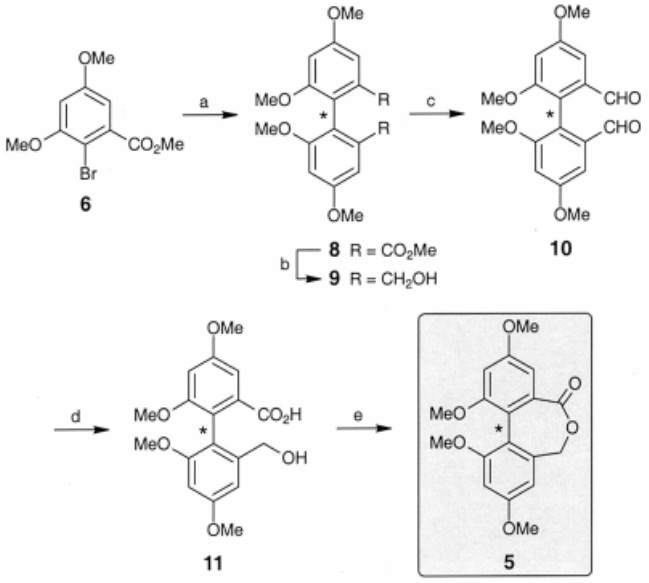


Figure 2. The configurationally stable seven-membered biaryl lactone **7**

For the synthesis of the key lactone **5** required here, bromo ester **6** was prepared from 3,5-dimethoxybenzoic acid by esterification[9] and bromination according to a procedure reported by Danishefsky.[10] Ullmann coupling of **6** gave the corresponding racemic diester **8**[11,12] (Scheme 2), reduction of which with $LiAlH_4$ provided diol **9**,[12] which was then oxidized to the dialdehyde **10**. This known[13] compound can thus now be prepared in a substantially improved overall yield (79%) and without use of toxic reagents such as HgO or benzene, as employed formerly.[13] Under Cannizzaro conditions, **10** underwent an intramolecular disproportionation to the hydroxy acid **11**. The final ring closure was achieved with DCC and DMAP under modified[14] Steglich conditions[15] to give the seven-membered lactone **5** in an overall yield of 39% (7 steps).

Compounds **9** and **5** were obtained in crystalline forms suitable for X-ray structure analysis.[16] As can be seen in Figure 3, the two phenyl rings adopt nearly orthogonal positions, not only in the "open" biaryl **9**, but also in lactone **5**. The ester bridge, as part of the seven-membered lactone, is too long to force the two parts of the molecule into a



Scheme 2. (a) Cu, DMF, 89%; (b) $LiAlH_4$, THF, 97%; (c) MnO_2, CH_2Cl_2, 92%; (d) KOH, EtOH, 94%; (e) DCC, DMAP, CH_2Cl_2, 72%

more coplanar, helical arrangement as observed for similar six-membered lactones.[4] Whilst, for the latter compounds, the bridge drastically lowers the atropisomerization barrier, this is not the case for seven-membered lactones such as **5**. We therefore anticipated that **5** should, like **7**,[5] be configurationally stable at room temperature. This was confirmed by HPLC experiments on a chiral phase, which produced two well-separated peaks (for detailed conditions, see Exp. Sect.).

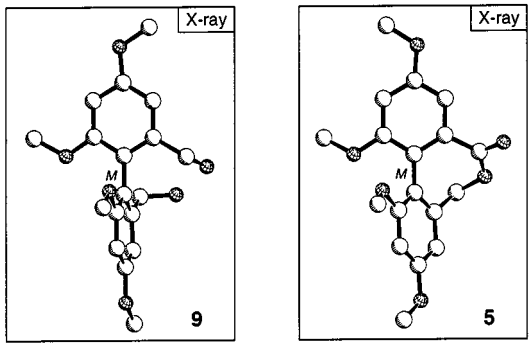
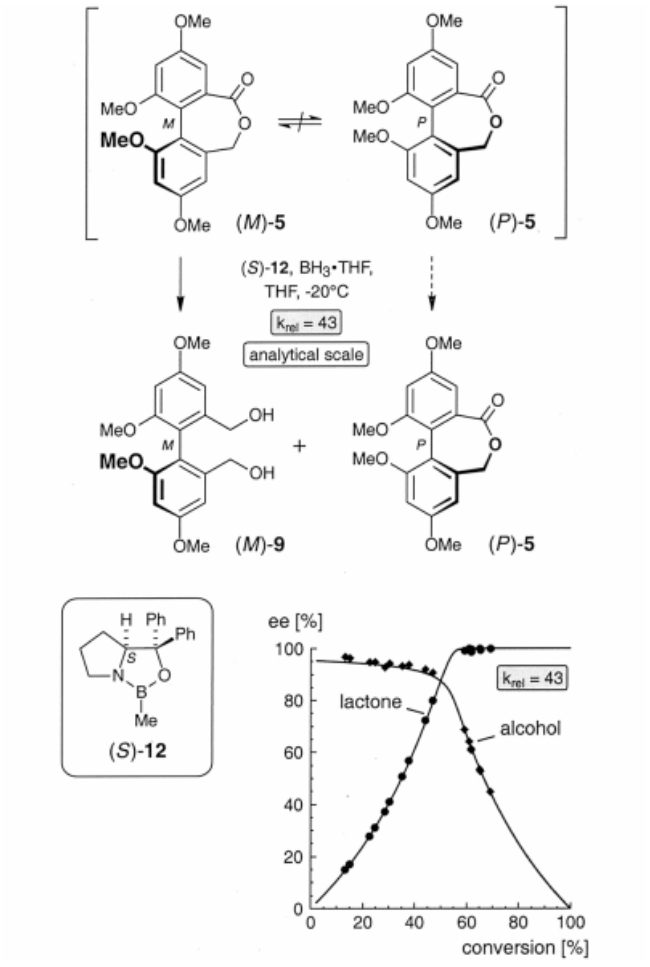


Figure 3. Crystal structures of compounds **5** and **9**

As previously noted for the model lactone **7**,[5] atropo-enantioselective reduction of racemic **5** with oxazaborolidine-activated borane[17] resulted in an efficient kinetic resolution, with a high relative rate constant[18] (k_{rel}) of 43 (Scheme 3, analytical scale). The product alcohol (*M*)-**9** was obtained with up to 96% *ee* at the beginning of the reaction, whilst the less reactive (*P*) enantiomer of the starting material **5** was enriched to optical purity (for the assignment of the absolute configurations, vide infra).



Scheme 3. Kinetic resolution of biaryl lactone **5** (analytical scale)

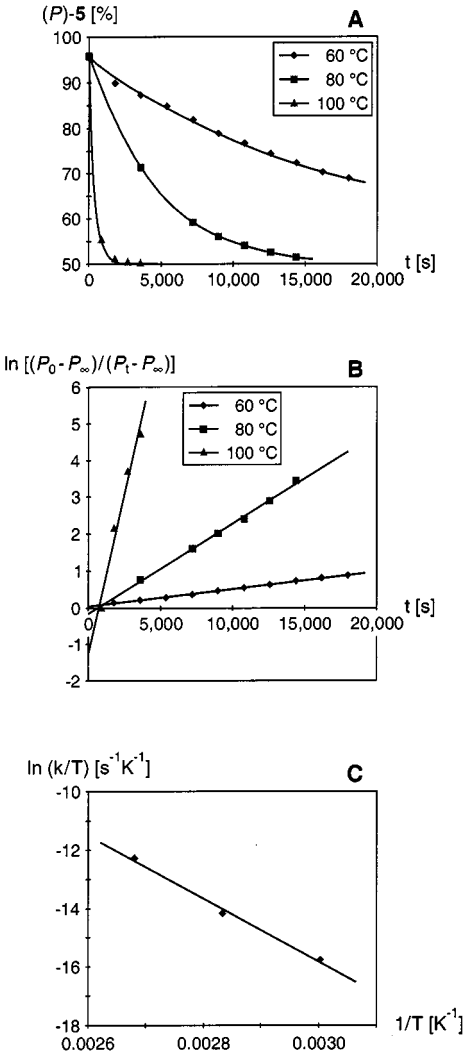


Figure 4. Determination of the atropisomerization barrier of lactone **5**: thermal racemization of (*P*)-**5** in toluene (A), determination of the rate constants *k* (B), and Eyring plot for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (C)

With enantiomerically pure lactone (*P*)-**5** available, its atropisomerization barrier was determined by thermal racemization experiments in toluene. As depicted (A in Figure 4), the isomerization is still very slow at 60 °C, while complete racemization was achieved after 1 h at 100 °C. Although it precludes the possibility of recycling the more slowly reacting substrate atropisomer during the ring-opening reaction in situ, in a *dynamic* kinetic resolution, this option allows a similarly efficient "off-line" recycling of the − still precious − material with the undesired configuration. The activation parameters for the atropisomerization [(*M*)-**5** ⇄ (*P*)-**5**] are summarized in Table 1. As in the case of the calculation of the isomerization barriers of helically twisted six-membered biaryl lactones,[19] the semiempirical AM1 parameterization should similarly give reliable results for the seven-membered lactone **5**. Indeed, the experimental data were in good agreement with the results obtained by quantum chemical calculations ($\Delta H^{\neq}$ = 83.2 kJ/mol, AM1).

For the thermal atropisomerization of the biaryl **13**, also seven-membered but ether-bridged, (see Figure 5, below), an activation enthalpy $\Delta H^{\neq}$ of 120.2 kJ/mol (in cyclohexanone) had been determined earlier.[12,20] The lower isomerization barrier for the lactone **5** is in agreement with decreased activation parameters for lactones versus cyclic ethers in the field of six-membered bridged biaryls[4,21] − but is still not low enough to permit unhindered rotation at the biaryl axis at room temperature.

Table 1. Experimental activation parameters for the atropisomerization [(*M*)-**5** ⇄ (*P*)-**5**]

T [°C]	*k* [s^{-1}]	$t_{1/2}$ [min]	$\Delta G^{\neq}$ [kJ/mol]
60	$4.71 \cdot 10^{-5}$	245.2	109.4
80	$2.44 \cdot 10^{-4}$	47.3	111.4
100	$1.75 \cdot 10^{-3}$	6.6	111.7

$\Delta H^{\neq}$ = 90.1 kJ/mol calcd. (AM1): $\Delta H^{\neq}$ = 83.2 kJ/mol
$\Delta S^{\neq}$ = −58.9 J/K·mol

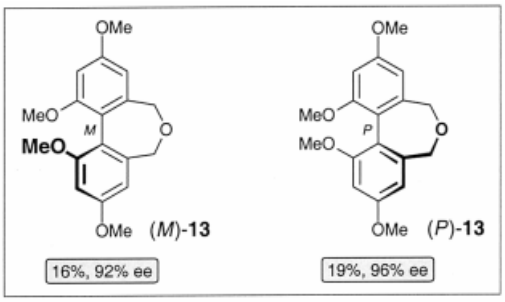


Figure 5. The ether-bridged biaryls (*M*)-**13** and (*P*)-**13**, obtained as by-products

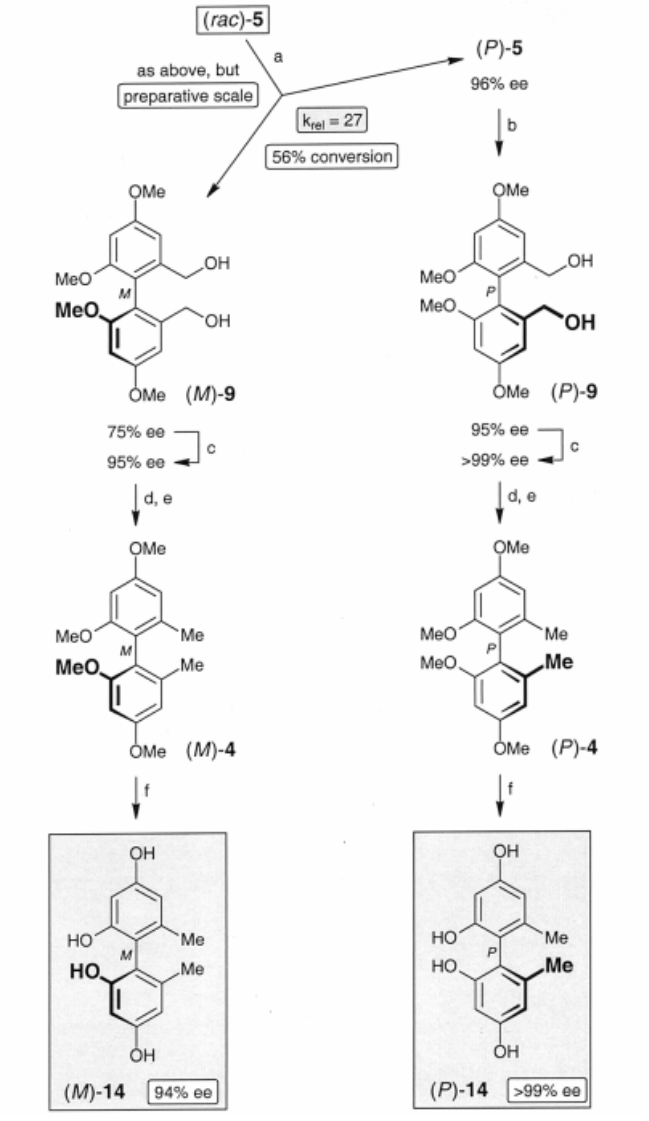
On a preparative scale, the oxazaborolidine-mediated kinetic resolution of **5** (k_{rel} = 27) was stopped at 56% conversion (see Scheme 4). After chromatographic separation, the optical purity of the product alcohol (*M*)-**9** was increased from 75% to 95% *ee* by a single crystallization step, while the remaining lactone (*P*)-**5** was enantiomerically almost pure (96% *ee*) straightaway (Scheme 4). $LiAlH_4$ reduction of (*P*)-**5** gave the diol (*P*)-**9** without significant loss of enantiomeric purity. On recrystallization, (*P*)-**9** was obtained in stereochemically homogeneous form (> 99% *ee*).

Both enantiomers of **9** were separately transformed into the respective tetramethyl ethers **4** (Scheme 4) by hydroxy/bromo exchange and subsequent $LiAlH_4$ reduction, as previously used for other biaryl systems.[22] As by-products, the known,[12] stereochemically almost pure, seven-membered biaryl ethers (*M*)-**13** and (*P*)-**13** (Figure 5) were obtained in < 20% yield, presumably due to base-catalyzed ring closure during or after the first hydroxy/halogen exchange on diol **9**.

Crystals of (*M*)-**4** were of suitable quality for X-ray structure analysis.[23] As expected, the two phenyl rings adopt a nearly orthogonal position, due to the space needed by the four *ortho* substituents (Figure 6).

Finally, by treatment of (*M*)-**4** and (*P*)-**4** with boron tribromide (Scheme 4, vide supra), (*M*)-4,4′-bisorcinol [(*M*)-**14**] and (*P*)-4,4′-bisorcinol [(*P*)-**14**] were obtained. By this strategy, both enantiomers of **14** were prepared in good overall yields and (nearly) enantiopure from *one* kinetic resolution experiment. As illustrated for related cases,[5] recycling of the undesired atropisomer [e.g., of the (*P*) products if only (*M*)-configured material is needed] is in principle possible through thermal racemization of the respective "wrong" lactone enantiomer [here (*P*)-**5**], but also by oxidative conversion of (*P*)-**9** back to lactone (*P*)-**5** by the route outlined in Scheme 2, its subsequent racemization, and renewed resolution. If, vice versa, only (*P*)-configured products are required, the same strategies still apply, now with the (*R*) enantiomer of oxazaborolidine **12**.

The assignment of the absolute configurations of (*M*)-**14** and (*P*)-**14** and their precursors was achieved by comparison of their optical rotations with literature data.[3,6,24,25] An additional confirmation of these previous[26] assignments was provided by quantum chemical CD calculations.[27] For this purpose, the configurationally stable biaryl ether (+)-**13** was chosen, since it had already been synthesized previously, but as yet without assignment of its absolute configuration.[12] As clearly shown in Figure 7, the position and intensity of the maxima calculated for (*P*)-**13**



Scheme 4. (a) (*S*)-**12**, BH_3·THF, THF, 46% of (*M*)-**9** and 43% of (*P*)-**5**; (b) $LiAlH_4$, THF, 76%; (c) recrystallization from ethyl acetate/cyclohexane; (d) PPh_3, $(CBrCl_2)_2$,[53] CH_2Cl_2; (e) $LiAlH_4$, Et_2O, 83% for (*M*)-**4** (two steps), 81% for (*P*)-**4** (two steps); (f) BBr_3, CH_2Cl_2, 96% for (*M*)-**14**, 84% for (*P*)-**14**

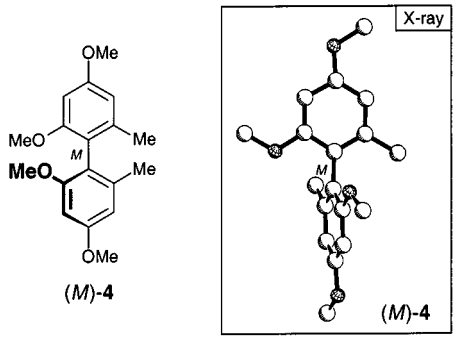


Figure 6. Crystal structure of biaryl (*M*)-**4**

are in good agreement with the CD spectrum experimentally obtained for (+)-**13**, whereas the CD curve calculated for (*M*)-**13** is nearly the mirror image of the experimental one. The biaryl ether (+)-**13** can thus unambiguously be assigned the (*P*) configuration.

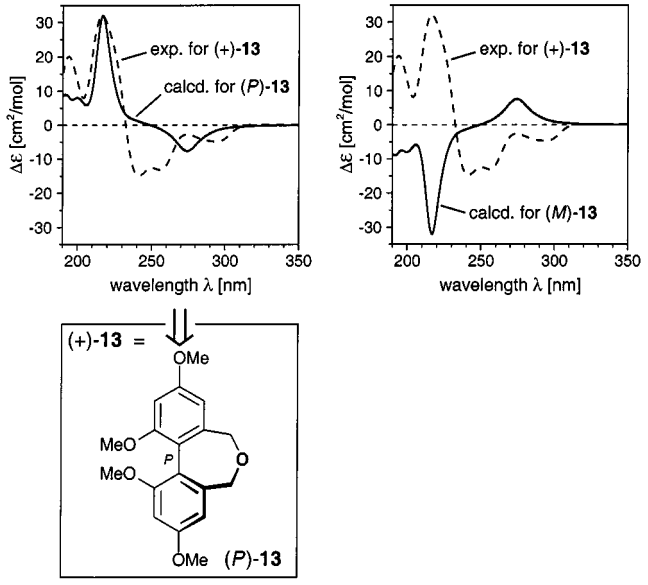
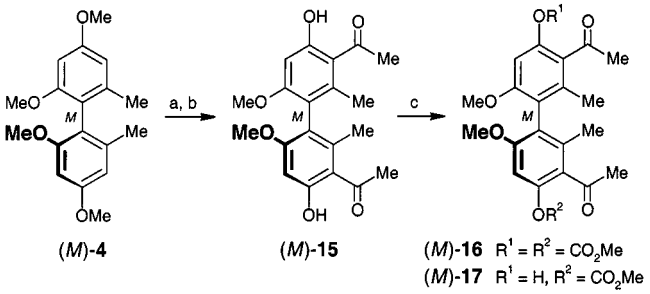


Figure 7. Determination of the absolute configuration of (+)-**13** by comparison of the experimental CD spectrum with the spectra quantum chemically calculated for (*P*)- and (*M*)-**13**

These investigations not only permitted the first attribution of the absolute configuration of compound **13**, but more importantly also established the axial configurations for *all* of the biphenyls of this series. Furthermore, they confirmed the assignments already made for diol **9**,[3] 4,4′-bisorcinol (**14**),[3,6,24,25] and finally for (+)-isokotanin A (**1**, vide infra).[3]

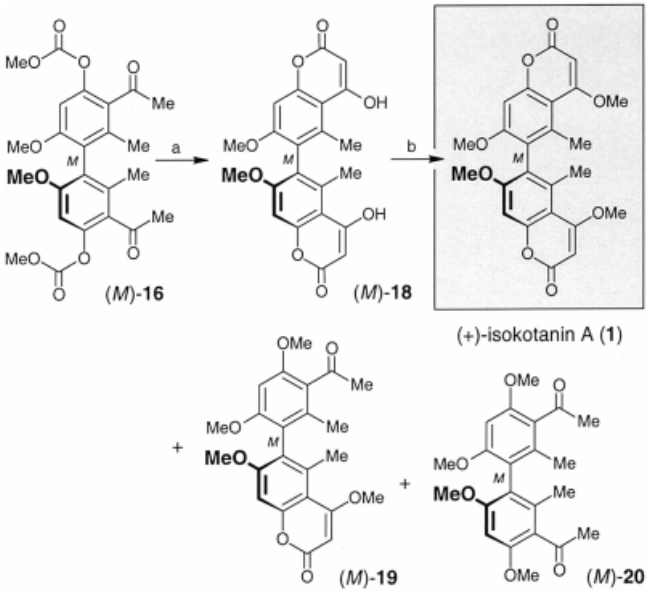
The final steps towards the target molecule (*M*)-**1** were accomplished by use of Lin's procedure,[3,28] according to a sequence already well known for the preparation of dimeric coumarins.[29,30] The tetramethyl ether (*M*)-**4** was acylated in the presence of $TiCl_4$[29] in almost quantitative yield (Scheme 5). In the next step, the methyl ethers *para* to the biaryl axis were cleaved selectively to give the phenol (*M*)-**15** in 82% yield. Treatment of this material with methyl chloroformate gave the carbonate (*M*)-**16**, along with 10% of the (previously[3] undescribed) monoacylated product (*M*)-**17**.

In the presence of KO*t*Bu as a base, (*M*)-**16** cyclized to give the bicoumarin (*M*)-**18** (Scheme 6). This very polar compound contained some impurities, but could not be purified by column chromatography, due to its very low solubility in common organic solvents. Therefore, the crude (*M*)-**18** obtained was directly transformed into (+)-isokotanin A (**1**) by use of the reagent combination NaH, Me_2SO_4, and HMPA.[3,28,31] The spectroscopic data and the optical rotation of (*M*)-**1** were in full accordance both with those of the natural product[1] and with those of material synthesized earlier.[2,3] The melting point of 286−289 °C,



Scheme 5. (a) $(CH_3CO)_2O$, $TiCl_4$, CH_2Cl_2, 94%; (b) $TiCl_4$, benzene, 82%; (c) $ClCO_2Me$, pyridine, 55% of (*M*)-**16** and 10% of (*M*)-**17**

however, was considerably higher than those reported during the initial isolation of (*M*)-**1** (223−226 °C)[1] and its first total synthesis (240−242 °C)[3] − but was in good agreement with the respective value of "6,6′-bisiderin" [= (*M*)-**1**, vide supra] (285−290 °C).[2] The low yield for (+)-isokotanin A (**1**) − only 26% over the last two steps − can be explained by the formation of the by-products (*M*)-**19** and (*M*)-**20**, resulting from the loss of one or two carbonate groups prior to the ring closure of (*M*)-**16**, with subsequent methylation of all hydroxy functions.



Scheme 6. (a) KO*t*Bu, *t*BuOH; (b) NaH, Me_2SO_4, HMPA, 26% of (*M*)-**1**, 19% of (*M*)-**19**, and 13% of (*M*)-**20** (two steps)

According to the CD spectrum of (*M*)-**1** (Figure 8), Udagawa's 6,6′-bisiderin,[2] which had been obtained by partial synthesis from *O*-demethyl-6,6′-bisiderin (= isokotanin B, **2**), can now also be assigned to have the (*M*) configuration. Unfortunately, Udagawa et al. did not give the optical rotation of 6,6′-bisiderin, and the CD spectrum was only measured from 225 to 325 nm (the reported maxima are marked in Figure 8). The good agreement in this region, however, is sufficient for unambiguous assignment of the absolute configuration of 6,6′-bisiderin (and the natural *O*-demethyl-6,6′-bisiderin). Gloer et al. showed (+)-isokotanin B (**2**) to have the same axial configuration as (+)-isokotanin A (**1**).[1]

Therefore, isokotanin B (**2**) isolated from *A. alliaceus* is also (*M*)-configured.

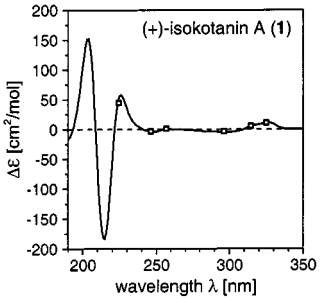


Figure 8. CD spectrum of synthetic isokotanin A (**1**) and comparison with literature data (marked as small squares) for "6,6′-bisiderin"[2]

Conclusion

In summary, an efficient atropo-enantioselective total synthesis of the bicoumarin (+)-isokotanin A (**1**) has been accomplished. In contrast to the first synthesis of the title compound, in which a Meyers-type homocoupling[32] of a bromooxazoline was utilized in the coupling step,[3] the common intermediate (*M*)-**4** has now been prepared by kinetic resolution of the configurationally stable seven-membered biaryl lactone **5**, with the option of recycling the "wrong" atropisomer by thermal racemization. The quantum chemical CD calculation of **13** confirmed the previous assignment of the absolute configuration of (+)-isokotanin A (**1**) and its synthetic precursors.

Computational Section

Conformational Analyses

Conformational analyses of the biaryl lactone **5** and the biaryl ether **13** were performed on Silicon Graphics OCTANE R10000 workstations by AM1[33] parameterization as implemented in the VAMP6.5 program package,[34] starting from preoptimized geometries generated by the TRIPOS[35] force field.

Helimerization Barrier

The potential surface was calculated through variation of two particular dihedral angles that describe the atropisomerization process of **5**. The corresponding transition structures were optimized by initial calculation of the molecular forces, followed by a transition state search by the NS01A[36] algorithm as implemented in VAMP6.5. Force calculations were subsequently applied to characterize transition structures by computation of their normal vibrations. Correspondence to their local minima was determined by IRC calculations.

CD Calculations

The wavefunctions required for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states of compound **13** were obtained by CNDO/S-CI calculations[37] with a CI expansion including 576 singly occupied configurations and the ground state determinant. These calculations were carried out with LinuX Pentium II workstations by use of the BDZDO/MCDSPD[38] program package. All single CD spectra thus obtained were added up by Boltzmann statistics using appropriate heats of formation, to give the calculated overall CD spectrum for the biaryl ether **13**. For better visualization, the rotational strengths were transformed into Δε values and superimposed with a Gaussian band shape function. The assignment of responsible transitions of the relevant calculated CD bands at 217 and 274 nm was performed by comparison of the experimental UV spectrum with the calculated one. For further details concerning quantum chemical calculation of chiroptical properties, see the corresponding section in ref.[39]

Experimental Section

General Remarks: Melting points were determined with a Reichert-Jung Thermovar hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin−Elmer 1420 spectrometer and are reported in wavenumbers (cm^{-1}). Optical rotations were measured with a Perkin−Elmer 241 MC polarimeter. CD spectra were taken with a Jasco J-715 spectropolarimeter, with ethanol (Uvasol®, Merck) as the solvent. ^1H and ^{13}C NMR spectra were recorded with Bruker AC 250 (250 and 63 MHz), AMX 400 (400 and 101 MHz), and DMX 600 (600 and 151 MHz) machines. Chemical shifts δ are reported in ppm, and coupling constants *J* in Hertz (Hz). As the internal reference, the residual solvent signals [^1H: $\delta(CDCl_3)$ = 7.26; $\delta([D_6]DMSO)$ = 2.50; ^{13}C: $\delta(CDCl_3)$ = 77.0; $\delta([D_6]DMSO)$ = 39.4] were used. EI mass spectra (70 eV) were measured with Finnigan MAT 90 and MAT 8200 mass spectrometers; the relative intensities are given in brackets. Microanalyses were performed by the microanalytical laboratory of the Inorganic Institute of the University of Würzburg, Germany (Leco CHNS-932). THF was freshly distilled from potassium, DMF and DMSO from CaH_2, and CH_2Cl_2 from P_2O_5. Et_2O and toluene were distilled from sodium wire. Methanol and ethanol were heated under reflux in the presence of magnesium; the drying agent during the distillation of *tert*-butyl alcohol was KO*t*Bu. Acetone, acetonitrile, 2-propanol, *n*-hexane, cyclohexane, petroleum ether (PE, 50−70 °C), and ethyl acetate were used after distillation. Pyridine was distilled from NaH. All air- or moisture-sensitive reactions were carried out with dry glassware under nitrogen or argon. Reaction solvents were removed in vacuo. Column chromatography was performed on 63−200 μm silica gel (Merck); for preparative TLC, silica gel aluminum foils (60 F_{254}, 20 × 20 cm, Merck) were used. Oxazaborolidine (*S*)-**12** (1 M in toluene, which was removed in vacuo prior to use) and BH_3·THF (1 M in THF) were obtained from Aldrich. HPLC analyses were carried out with a combination of a Waters 510 HPLC pump, a 20-μL injection loop, and Chiralcel OF and OD-H columns (0.46 × 25 cm, Daicel Chem. Ind.) with UV detection at 254 nm (biaryl ether **13**: 280 nm). The atropisomers of lactone **5** were separated on the OD-H column with hexane/2-propanol (70:30; 0.8 mL/min) as the eluent; the retention times for

(*M*)-**5** and (*P*)-**5** were 11 min and 16 min, respectively. For diol **9**, the OF column was used with hexane/2-propanol (50:50; 1.0 mL/min) as the eluent, with retention times of 13 and 19 min for (*P*)-**9** and (*M*)-**9**, respectively. For the chromatographic separation of (*M*)- and (*P*)-**13**, the OD-H column was used with hexane/2-propanol (70:30; 0.5 mL/min); (*M*)-**13**: 15 min, (*P*)-**13**: 21 min. The samples of bisorcinol **14** were analyzed on the OF stationary phase (hexane/2-propanol, 80:20; 0.5 mL/min), with signals for (*P*)-**14** after 44 min and for (*M*)-**14** after 51 min.

Methyl 2-Bromo-3,5-dimethoxybenzoate (6): A solution of 3,5-dimethoxybenzoic acid (10.0 g, 54.9 mmol) in methanol (150 mL) was heated under reflux in the presence of conc. H_2SO_4 (292 μL, 5.49 mmol) for 24 h. The solvent was removed, water (150 mL) was added, and the mixture was extracted with Et_2O (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give methyl 3,5-dimethoxybenzoate[9] (10.3 g, 52.5 mmol, 96%). The purity of this product, which solidified on standing (m.p. 39−41 °C, ref.[9] 41 °C), was sufficient for the next step. According to a known procedure,[10] methyl 3,5-dimethoxybenzoate (10.0 g, 51.0 mmol) in acetonitrile (400 mL) was treated with *N*-bromosuccinimide (10.9 g, 61.2 mmol) at 0 °C and stirred at room temperature for 24 h. After removal of the solvent, the residue was purified by column chromatography (PE/Et_2O, 2:1), yielding the desired compound **6**[10] (10.6 g, 38.4 mmol, 75%) after recrystallization from Et_2O/PE (m.p. 56.5−58.5 °C, ref.[10] 57−59 °C). A chromatographically slower fraction contained methyl 2,6-dibromo-3,5-dimethoxybenzoate[40] (2.51 g, 7.09 mmol, 14%), m.p. 148−149 °C (ref.[40] 149−150 °C).

Dimethyl *rac*-4,4′,6,6′-Tetramethoxy-1,1′-biphenyl-2,2′-dicarboxylate (8): Under dry argon, bromo ester **6** (3.83 g, 13.9 mmol) and activated copper[41] (9.56 g, 150 mmol) in dry DMF (12 mL) were heated to 165 °C for 24 h. After the mixture had cooled to room temperature, the copper was filtered off and washed thoroughly with CH_2Cl_2. The solvents were evaporated, and the residue was subjected to column chromatography (PE/Et_2O, 2:1), to yield colorless crystals of **8**[42] (2.41 g, 6.17 mmol, 89%) after recrystallization from CH_2Cl_2/PE. M.p. 162 °C (ref.[11] 160−161 °C, ref.[12] 161−163 °C). IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1} (m, Ar-H), 2970, 2925, 2815 (m, s, m, C−H), 1705 (s, C=O), 1580 (s, C=C), 1440, 1325, 1195, 1055, 840 (s, s, s, s, m). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.60 (s, 6 H, CO_2CH_3), 3.66 (s, 6 H, 6- and 6′-OCH_3), 3.87 (s, 6 H, 4- and 4′-OCH_3), 6.65 (d, ^4J = 2.4 Hz, 2 H, 5- and 5′-H), 7.08 (d, ^4J = 2.4 Hz, 2 H, 3- and 3′-H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.8 (CO_2CH_3), 55.4, 56.0 (4-, 4′-, 6- and 6′-OCH_3), 102.4, 105.1, 120.1, 132.0, 158.1, 159.3 (Ar-C), 167.6 (C=O). MS (70 eV): *m*/*z* (%) = 390 (100) [M^+], 375 (1) [$M^+ - CH_3$], 359 (6) [$M^+ - CH_3O$], 329 (13) [359 − CH_2O], 300 (21) [329 − CHO], 299 (16) [329 − CH_2O], 209 (66). $C_{20}H_{22}O_8$ (390.39): calcd. C 61.53, H 5.68; found C 61.63, H 5.70. In addition, a small quantity of methyl 3,5-dimethoxybenzoate[9] (180 mg, 917 μmol, 7%), the hydro-dehalogenation product of ester **6**, was obtained.

***rac*-2,2′-Dihydroxymethyl-4,4′,6,6′-tetramethoxy-1,1′-biphenyl (9):** A solution of diester **8** (3.98 g, 10.2 mmol) in THF (150 mL) was slowly added to a suspension of $LiAlH_4$ (582 mg, 15.3 mmol) in THF (50 mL). After stirring for 2 h at room temperature, the mixture was hydrolyzed by careful addition of water (25 mL) and acidified with 2 N HCl. The organic solvent was evaporated, and the aqueous residue was diluted with water (100 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the crude product was crystallized from CH_2Cl_2 to yield pure **9**[42] (3.30 g, 9.87 mmol, 97%) as colorless crystals. An analytical sample was recrystallized from ethyl acetate/cyclohexane, affording crystals suitable for X-ray structure analysis. M.p. 174−176 °C (ref.[12] 174−175.5 °C). IR (KBr): $\tilde{\nu}$ = 3360 cm^{-1} (br. s, OH), 3070 (m, Ar-H), 2970, 2930, 2910, 2860, 2815 (w, w, w, w, m, C−H), 1585, 1565 (s, s, C=C), 1305, 1145, 830 (s, s, s). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.68 (s, 6 H, 6- and 6′-OCH_3), 3.86 (s, 6 H, 4- and 4′-OCH_3), 4.18 and 4.24 (AB system, ^2J = 11.6 Hz, 4 H, CH_2OH), 6.52 (d, ^4J = 2.4 Hz, 2 H, Ar-H), 6.70 (d, ^4J = 2.4 Hz, 2 H, Ar-H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.3, 55.9 (OCH_3), 63.7 (CH_2OH), 98.7, 105.3, 116.3, 142.0, 158.1, 160.4 (Ar-C). MS (70 eV): *m*/*z* (%) = 334 (85) [M^+], 317 (18) [335 − H_2O], 316 (100) [$M^+ - H_2O$], 301 (15) [316 − CH_3], 285 (9) [316 − CH_3O], 273 (70) [316 − C_2H_3O], 168 (84) [$C_9H_{12}O_3^+$]. $C_{18}H_{22}O_6$ (334.37): calcd. C 64.66, H 6.63; found C 64.35, H 6.73.

***rac*-4,4′,6,6′-Tetramethoxy-1,1′-biphenyl-2,2′-dicarbaldehyde (10):** Diol **9** (3.22 g, 9.63 mmol) and MnO_2 (8.37 g, 96.3 mmol) were added to CH_2Cl_2 (300 mL) and heated under reflux for 12 h. After filtration and evaporation of the solvent, the crude product was obtained as a colorless solid. This material was crystallized from 2-propanol to give pure dialdehyde **10**[42] (2.94 g, 8.90 mmol, 92%). M.p. 164−165 °C (ref.[13] 159−160 °C). IR (KBr): $\tilde{\nu}$ = 3045 cm^{-1} (w, Ar-H), 2980, 2945, 2920, 2825 (w, w, w, m, C−H), 1670 (s, C=O), 1580 (s, C=C), 1310, 1145, 830 (s, s, m). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 6 H, 6- and 6′-OCH_3), 3.91 (s, 6 H, 4- and 4′-OCH_3), 6.76 (d, ^4J = 2.4 Hz, 2 H, Ar-H), 7.16 (d, ^4J = 2.4 Hz, 2 H, Ar-H), 9.63 (s, 2 H, CHO). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.7, 56.0 (OCH_3), 101.4, 104.6, 118.7, 136.7, 158.6, 160.9 (Ar-C), 191.7 (C=O). MS (70 eV): *m*/*z* (%) = 330 (100) [M^+], 315 (7) [$M^+ - CH_3$], 302 (15) [M^+ − CO], 301 (34) [M^+ − CHO], 299 (14) [$M^+ - CH_3O$], 286 (23) [$M^+ - C_2H_4O$], 271 (49) [286 − CH_3]. $C_{18}H_{18}O_6$ (330.34): calcd. C 65.45, H 5.49; found C 65.47, H 5.47.

***rac*-2′-Hydroxymethyl-4,4′,6,6′-tetramethoxy-1,1′-biphenyl-2-carboxylic Acid (11):** Dialdehyde **10** (2.87 g, 8.69 mmol) was dissolved in ethanol (200 mL), treated with KOH (8.10 g, 144 mmol), and heated to reflux for 1.5 h. The solvent was removed in vacuo, water (50 mL) was added to the oily residue, and the pH value was carefully adjusted to 1−2 with conc. HCl. This mixture was then extracted with CH_2Cl_2 (500 mL altogether), and the combined organic fractions were washed with water (2 × 100 mL). During this workup procedure, the hydroxy acid **11** precipitated in the form of a very pure colorless powder, which was collected by filtration (1.71 g). Concentration of the organic solution yielded a second batch of the desired product; the combined yield was 2.86 g (8.21 mmol, 94%). M.p. 210−211 °C. IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (br. s, OH), 3000 (w, Ar-H), 2940, 2835 (m, m, C−H), 1685 (s, C=O), 1585 (s, C=C), 1445, 1315, 1150, 1070, 825 (s, s, s, s, m). ^1H NMR (250 MHz, [D_6]DMSO): δ = 3.54 (s, 3 H, 4-OCH_3), 3.62 (s, 3 H, 6-OCH_3), 3.78 (s, 3 H, 4′-OCH_3), 3.83 (s, 3 H, 6′-OCH_3), 4.04 (br. s, 2 H, CH_2), 6.40 (d, ^4J = 2.4 Hz, 1 H, 5-H), 6.69 (d, ^4J = 2.4 Hz, 1 H, 3-H), 6.75 (d, ^4J = 2.4 Hz, 1 H, 5′-H), 6.87 (d, ^4J = 2.8 Hz, 1 H, 3′-H). ^{13}C NMR (63 MHz, [D_6]DMSO): δ = 54.8 (4′-OCH_3), 55.2 (6′-OCH_3), 55.3 (4-OCH_3), 55.7 (6-OCH_3), 60.5 (CH_2), 96.2 (C-5), 101.2 (C-5′), 102.0 (C-3), 105.1 (C-3′), 114.9, 117.0, 134.7, 142.7, 157.2, 157.9, 159.0, 159.2 (Ar-C), 168.3 (C=O). MS (70 eV): *m*/*z* (%) = 348 (29) [M^+], 330 (90) [$M^+ - H_2O$], 315 (5) [330 − CH_3], 301 (17) [330 − CHO], 299 (9) [330 − CH_3O], 286 (15) [301 − CH_3], 271 (36) [299 − CO], 182 (100) [$C_9H_{10}O_4^+$], 166 (46) [$C_9H_{10}O_3^+$]. $C_{18}H_{20}O_7$ (348.35): calcd. C 62.06, H 5.79; found C 61.77, H 5.54.

***rac*-1,3,9,11-Tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (5):** A solution of DMAP (192 mg, 1.57 mmol) in CH_2Cl_2 (250 mL) was saturated with gaseous HCl (5 min) and then added to a mixture of

hydroxy acid **11** (1.04 g, 2.99 mmol) and DCC (975 mg, 4.73 mmol). The resulting slurry was heated to reflux for 4 h under argon. After this had cooled to room temperature, excess reagent was destroyed by addition of glacial HOAc (ca. 250 μL). The clear solution obtained by filtration was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. Column chromatography (PE/Et_2O, 1:1 → 1:10) gave crude lactone **5**, which could be further purified by a second chromatographic step (cyclohexane/ethyl acetate, 4:1 → 2:1) and crystallization from Et_2O/PE (colorless cubes, suitable for X-ray structure analysis, 707 mg, 2.14 mmol, 72%). M.p. 124−126 °C. IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1} (w, Ar-H), 2975, 2920, 2820 (m, m, m, C−H), 1700 (s, C=O), 1585, 1550 (s, m, C=C), 1450, 1325, 1150, 1045, 830 (s, s, s, s, m). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, 1-OCH_3 or 3-OCH_3), 3.82 (s, 3 H, 9-OCH_3), 3.85 (s, 3 H, 11-OCH_3), 3.88 (s, 3 H, 1-OCH_3 or 3-OCH_3), 4.81 and 4.99 (AB system, ^2J = 11.7 Hz, 2 H, CH_2), 6.57 (d, ^4J = 2.1 Hz, 1 H, 2-H or 4-H), 6.59 (d, ^4J = 2.4 Hz, 1 H, 2-H or 4-H), 6.71 (d, ^4J = 2.4 Hz, 1 H, 10-H), 6.96 (d, ^4J = 2.4 Hz, 1 H, 8-H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.5 (11-OCH_3), 55.7, 55.8 (1-OCH_3 and 3-OCH_3), 56.1 (9-OCH_3), 70.0 (CH_2), 99.8 (C-2 or C-4), 102.9 (C-10), 104.5 (C-2 or C-4), 105.1 (C-8), 116.3, 116.8, 132.9, 137.7, 157.8, 159.1, 160.0, 160.5 (Ar-C), 170.0 (C=O). MS (70 eV): *m/z* (%) = 330 (100) [M^+], 315 (5) [$M^+ - CH_3$], 301 (7) [$M^+ - CHO$], 299 (6) [$M^+ - CH_3O$], 287 (9) [315 − CO], 271 (26) [299 − CO]. $C_{18}H_{18}O_6$ (330.34): calcd. C 65.45, H 5.49; found C 65.05, H 5.52.

Kinetic Resolution of *rac*-1,3,9,11-Tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one (5) (Analytical Scale): BH_3·THF (1 M in THF, 129 μL, 129 μmol) was added at 0 °C under argon to a solution of oxazaborolidine (*S*)-**12** (26.8 mg, 96.6 μmol) in THF (1.5 mL). After stirring for 30 min at room temperature, the solution was added dropwise over 5 min to a solution of racemic lactone **5** (10.6 mg, 32.1 μmol) in THF (1.5 mL) at −20 °C. Stirring was continued at this temperature. At intervals, 100-μL portions of the reaction mixture were quenched with 2 N HCl and extracted with diethyl ether. The organic solutions were purified by TLC (cyclohexane/ethyl acetate, 1:5) to yield samples of lactone **5** and diol **9**, which were analyzed by HPLC.[18]

(*M*)-2,2′-Dihydroxymethyl-4,4′,6,6′-tetramethoxy-1,1′-biphenyl [(*M*)-9] and (*P*)-1,3,9,11-Tetramethoxydibenzo[*c*,*e*]oxepin-5(7*H*)-one [(*P*)-5]: The oxazaborolidine/borane system used for the kinetic resolution of **5** on a preparative scale was prepared from (*S*)-**12** (503 mg, 1.82 mmol) and BH_3·THF (2.42 mL, 2.42 mmol) in THF (15 mL) as outlined above, cooled to −20 °C, and added dropwise over 10 min to a solution of racemic lactone **5** (200 mg, 605 μmol) in THF (15 mL) at −20 °C under argon. The course of the reaction was monitored by HPLC. After 2 h of stirring at −20 °C (56% conversion, k_{rel} = 27), the reaction mixture was carefully hydrolyzed with water (8 mL) and 2 N HCl (6 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), the solvent was evaporated, and the residue was subjected to column chromatography (cyclohexane/ethyl acetate, 1:5). Lactone (*P*)-**5** (86.3 mg, 261 μmol, 43%) was obtained as a colorless oil with 96% *ee*, while the alcohol (*M*)-**9** (93.2 mg, 279 μmol, 46%) had an *ee* of 75% and was recrystallized from ethyl acetate/cyclohexane to give colorless crystals (50% *ee*, 36.3 mg, 109 μmol, 18%) and enantiomerically enriched mother liquor (95% *ee*, 56.9 mg, 170 μmol, 28%). **(*M*)-9 (95% *ee*):** M.p. 141−142 °C (ref.[12] 144−145 °C, ref.[3] 144−145 °C). $[\alpha]_D^{23}$ = +58.6 (*c* = 1.03, acetone) {ref.[12,43] $[\alpha]_D^{18}$ = +54.9 (*c* = 0.51, acetone), ref.[3] $[\alpha]_D^{24}$ = +62.5 (*c* = 1.10, $CHCl_3$)}. CD (EtOH): $\Delta\varepsilon_{208}$ = +59.5, $\Delta\varepsilon_{228}$ = +11.8, $\Delta\varepsilon_{246}$ = −9.7, $\Delta\varepsilon_{288}$ = +4.1. **(*P*)-5 (96% *ee*):** $[\alpha]_D^{23}$ = −8.4 (*c* = 0.94, CH_2Cl_2). CD (EtOH): $\Delta\varepsilon_{194}$ = +25.6, $\Delta\varepsilon_{213}$ = −16.3, $\Delta\varepsilon_{232}$ = +29.7, $\Delta\varepsilon_{261}$ = −15.3.

Determination of the Atropisomerization Barrier of Lactone 5 by Thermal Racemization Experiments: A solution of enantiomerically almost pure (92% *ee*) lactone (*P*)-**5** (2.00 mg, 6.05 μmol) in toluene (2 mL) was heated with stirring at the respective temperature under argon. At defined times, samples (200 μL) were taken, concentrated, and stored at −20 °C until HPLC examination. The racemization data thus obtained are summarized (see A in Figure 4 and the section Results and Discussion); from these data, the activation parameters for the atropisomerization [(*M*)-**5** ⇄ (*P*)-**5**] were calculated.[44]

(*M*)-2,2′,4,4′-Tetramethoxy-6,6′-dimethyl-1,1′-biphenyl [(*M*)-4]: 1,2-Dibromotetrachloroethane [$(CBrCl_2)_2$, 98.3 mg, 302 μmol] and PPh_3 (79.2 mg, 302 μmol) were added to a solution of (*M*)-**9** (95% *ee*, 36.2 mg, 108 μmol) in CH_2Cl_2 (3 mL). After stirring for 4 h at room temperature, the mixture was cooled to 0 °C, Et_2O (1 mL) and $LiAlH_4$ (17.2 mg, 453 μmol) were added, and stirring was continued at room temperature for 5 h. Water (4 mL) and 2 N HCl (4 mL) were used to stop the reaction. The mixture was then extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and purified by column chromatography (PE/Et_2O, 3:1 → 1:1). The two colorless products were crystallized from Et_2O/PE, providing crystals suitable for an X-ray structure analysis in the case of the main product (*M*)-**4**. The spectroscopic data of (*M*)-**4** (27.1 mg, 89.6 μmol, 83%) were in accordance with those previously obtained for racemic material.[28,29,45] **(*M*)-4:** M.p. 127 °C. $[\alpha]_D^{23}$ = +33.9 (*c* = 0.83, $CHCl_3$). CD (EtOH): $\Delta\varepsilon_{208}$ = +12.5, $\Delta\varepsilon_{230}$ = +5.7, $\Delta\varepsilon_{243}$ = −4.5, $\Delta\varepsilon_{285}$ = +0.8. The biaryl ether (*M*)-**13** (92% *ee*, 5.40 mg, 17.1 μmol, 16%) was obtained as a by-product, whose spectroscopic data were identical with literature values.[12,46] **(*M*)-13:** M.p. 140−141 °C (ref.[12] 137.5−139 °C). $[\alpha]_D^{23}$ = −7.5 (*c* = 0.17, acetone) {ref.[12] $[\alpha]_D^{20}$ = −16.0 (*c* = 2.12, acetone)}. CD (EtOH): $\Delta\varepsilon_{194}$ = −18.9, $\Delta\varepsilon_{204}$ = −8.3, $\Delta\varepsilon_{217}$ = −31.0, $\Delta\varepsilon_{242}$ = +13.9, $\Delta\varepsilon_{256}$ = +12.7, $\Delta\varepsilon_{274}$ = +2.8, $\Delta\varepsilon_{291}$ = +4.7; calculated for (*M*)-**13**: $\Delta\varepsilon_{192}$ = −9.1, $\Delta\varepsilon_{200}$ = −7.9, $\Delta\varepsilon_{206}$ = −5.8, $\Delta\varepsilon_{217}$ = −32.2, $\Delta\varepsilon_{274}$ = +7.4.

(*M*)-2,2′,4,4′-Tetrahydroxy-6,6′-dimethyl-1,1′-biphenyl [(*M*)-14]: At 0 °C, a solution of biaryl (*M*)-**4** (26.5 mg, 87.6 μmol) in CH_2Cl_2 (5 mL) was treated with a BBr_3 solution (1.0 M in CH_2Cl_2, 420 μL, 420 μmol). After 5 h of stirring at room temperature, more BBr_3 (105 μL, 105 μmol) was added. Complete conversion was reached after 20 h, and excessive reagent was destroyed with methanol (1 mL). After removal of the solvent, the crude product was purified by two consecutive chromatographic steps (each with cyclohexane/ethyl acetate, 1:5), providing (*M*)-**14** (94% *ee*, 20.7 mg, 84.1 μmol, 96%) as a colorless oil. The spectroscopic data of (*M*)-**14** agreed with those reported for the racemic compound.[47] $[\alpha]_D^{23}$ = +35.8 (*c* = 1.01, ethanol) {ref.[48,49] $[\alpha]_D^{25}$ = +36.2 (*c* = 0.50, ethanol), ref.[24] $[\alpha]_D^{25}$ = +39.4 (*c* = 0.50, ethanol), ref.[25] $[\alpha]_D^{20}$ = +40.0 (*c* = 3.00, ethanol), ref.[3] $[\alpha]_D^{24}$ = +38.7 (*c* = 0.90, ethanol)}. CD (EtOH): $\Delta\varepsilon_{195}$ = −2.9, $\Delta\varepsilon_{209}$ = +9.5, $\Delta\varepsilon_{229}$ = +1.7, $\Delta\varepsilon_{246}$ = −1.3, $\Delta\varepsilon_{270}$ = −1.0, $\Delta\varepsilon_{288}$ = +1.6.

(*P*)-2,2′-Dihydroxymethyl-4,4′,6,6′-tetramethoxy-1,1′-biphenyl [(*P*)-9]: A solution of lactone (*P*)-**5** (96% *ee*, 74.8 mg, 226 μmol) in THF (8 mL) was treated with $LiAlH_4$ (17.2 mg, 453 μmol) at 0 °C. After stirring for 4 h at room temperature, the reaction was stopped by addition of water and the mixture was acidified with 2 N HCl. Extraction with CH_2Cl_2, drying of the organic phase (Na_2SO_4), and column chromatography (cyclohexane/ethyl acetate, 1:5) of the residue obtained by evaporation of the solvent gave (*P*)-**9** (95% *ee*,

57.7 mg, 173 μmol, 76%). Crystallization from ethyl acetate/cyclohexane provided enantiomerically pure diol (*P*)-**9** (99.9% *ee*, 42.0 mg, 126 μmol, 56%), while the mother liquor (15.2 mg, 45.5 μmol, 20%) had 85% *ee*. **(*P*)-9 (99.9% *ee*):** M.p. 143.5−144 °C (ref.[12] 143.5−145 °C). $[\alpha]_D^{23} = -60.4$ (*c* = 0.97, acetone) {ref.[12,50] $[\alpha]_D^{24} = -55.0$ (*c* = 1.04, acetone), ref.[3] $[\alpha]_D^{24} = -62.8$ (*c* = 0.97, $CHCl_3$)}. CD (EtOH): $\Delta\varepsilon_{209} = -69.2$, $\Delta\varepsilon_{227} = -13.8$, $\Delta\varepsilon_{246} = +10.4$, $\Delta\varepsilon_{287} = -5.0$.

(*P*)-2,2′,4,4′-Tetramethoxy-6,6′-dimethyl-1,1′-biphenyl [(*P*)-4]: $(CBrCl_2)_2$ (115 mg, 353 μmol) and PPh_3 (92.6 mg, 353 μmol) were added to a solution of (*P*)-**9** (99.9% *ee*, 42.0 mg, 126 μmol) in CH_2Cl_2 (4 mL). After 4 h of stirring at room temperature, the mixture was cooled to 0 °C, diluted with Et_2O (1 mL), and treated with $LiAlH_4$ (20.1 mg, 530 μmol). Stirring was continued at room temperature (6 h), after which water (6 mL) and 2 N HCl (6 mL) were added. Extraction with CH_2Cl_2, drying of the combined organic phases with Na_2SO_4, and evaporation of the solvents gave a crude product, from which pure (*P*)-**4** was obtained by column chromatography (PE/Et_2O, 3:1 → 1:1) and crystallization from Et_2O/PE. The spectroscopic data of (*P*)-**4** (colorless crystals, 30.9 mg, 102 μmol, 81%) were in accordance with those previously obtained for racemic material.[28,29,45] **(*P*)-4:** M.p. 125−126 °C. $[\alpha]_D^{23} = -35.1$ (*c* = 0.75, $CHCl_3$). CD (EtOH): $\Delta\varepsilon_{208} = -15.6$, $\Delta\varepsilon_{228} = -9.5$, $\Delta\varepsilon_{243} = +6.9$, $\Delta\varepsilon_{285} = -3.0$. The biaryl ether (*P*)-**13**[12,46] (96% *ee*, 7.50 mg, 23.7 μmol, 19%) was obtained as a by-product. **(*P*)-13:** $[\alpha]_D^{23} = +8.5$ (*c* = 0.38, acetone) {ref.[12] $[\alpha]_D^{20} = +15.5$ (*c* = 2.03, acetone)}. CD (EtOH): $\Delta\varepsilon_{194} = +20.1$, $\Delta\varepsilon_{204} = +8.0$, $\Delta\varepsilon_{217} = +32.1$, $\Delta\varepsilon_{241} = -15.0$, $\Delta\varepsilon_{256} = -13.2$, $\Delta\varepsilon_{274} = -2.8$, $\Delta\varepsilon_{293} = -4.9$; calculated for (*M*)-**13**: $\Delta\varepsilon_{192} = -9.1$, $\Delta\varepsilon_{200} = -7.9$, $\Delta\varepsilon_{206} = -5.8$, $\Delta\varepsilon_{217} = -32.2$, $\Delta\varepsilon_{274} = +7.4$.

(*P*)-2,2′,4,4′-Tetrahydroxy-6,6′-dimethyl-1,1′-biphenyl [(*P*)-14]: At 0 °C, BBr_3 (neat, 60.0 μL, 635 μmol) was added to a solution of biaryl (*P*)-**4** (24.0 mg, 79.4 μmol) in CH_2Cl_2 (4 mL). After 2 h at room temperature, the reaction mixture was quenched with methanol (1 mL), concentrated, and purified by column chromatography (cyclohexane/ethyl acetate, 1:5) to yield a slightly yellow oil, from which the desired product (*P*)-**14** was obtained as a colorless solid by crystallization from ethyl acetate/cyclohexane (> 99% *ee*, 17.2 mg, 69.8 μmol, 88%). Compound (*P*)-**14** gave spectroscopic data identical with literature values for the racemic compound.[47] M.p. 129−131 °C (ref.[25] < 130 °C).[51] $[\alpha]_D^{23} = -35.9$ (*c* = 0.97, ethanol) {ref.[48,49] $[\alpha]_D^{25} = -36.7$ (*c* = 0.50, ethanol), ref.[25] $[\alpha]_D^{20} = -41.3$ (*c* = 3.00, ethanol), ref.[6] $[\alpha]_D^{25} = -38.6$ (*c* = 0.28, ethanol)}. CD (EtOH): $\Delta\varepsilon_{194} = +4.0$, $\Delta\varepsilon_{209} = -11.9$, $\Delta\varepsilon_{229} = -1.6$, $\Delta\varepsilon_{242} = +0.9$, $\Delta\varepsilon_{272} = +0.7$, $\Delta\varepsilon_{287} = -1.7$.

(*M*)-3,3′-Diacetyl-4,4′-dihydroxy-6,6′-dimethoxy-2,2′-dimethyl-1,1′-biphenyl [(*M*)-15]: According to literature precedence,[3,28,29] tetramethyl ether (*M*)-**4** (95% *ee*, 25.1 mg, 83.0 μmol) in CH_2Cl_2 (8 mL) was stirred with Ac_2O (24.3 μL, 258 μmol) and $TiCl_4$ (77.5 μL, 706 μmol) at room temperature for 1 h. After addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the crude product was purified by column filtration (PE/ethyl acetate, 1:2). Evaporation of the solvent gave (*M*)-3,3′-diacetyl-4,4′,6,6′-tetramethoxy-2,2′-dimethyl-1,1′-biphenyl (30.2 mg, 78.1 μmol, 94%) as a colorless solid, spectroscopically identical with racemic material obtained earlier.[28,29] This product was immediately dissolved in benzene (8 mL), treated with $TiCl_4$ [3,28] (68.8 μL, 627 μmol), and heated under reflux for 75 min. After this had cooled to room temperature, water (10 mL) was added carefully. The organic phase was separated, the aqueous component was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. From the brownish residue, the pure product (*M*)-**15**[3] was obtained by column chromatography (PE/ethyl acetate, 1:2) in the form of a colorless oil (22.9 mg, 63.9 μmol, 82%). $[\alpha]_D^{23} = +35.2$ (*c* = 0.76, $CHCl_3$) {ref.[3] $[\alpha]_D^{24} = +29.3$ (*c* = 0.50, $CHCl_3$)}. CD (EtOH): $\Delta\varepsilon_{211} = +4.3$, $\Delta\varepsilon_{241} = -1.5$, $\Delta\varepsilon_{267} = +1.0$, $\Delta\varepsilon_{310} = -0.6$.

(*M*)-3,3′-Diacetyl-6,6′-dimethoxy-4,4′-bis(methoxycarbonyloxy)-2,2′-dimethyl-1,1′-biphenyl [(*M*)-16]: According to the literature,[3,28] methyl chloroformate (94.0 μL, 1.22 mmol) was added dropwise at 0 °C to a solution of (*M*)-**15** (21.8 mg, 60.8 μmol) in dry pyridine (3 mL). After this mixture had been stirred for 25 h at 60 °C, 2 N HCl (15 mL) was added at room temperature. The combined organic phases from the extraction with CH_2Cl_2 were washed with 2 N HCl and water and dried with Na_2SO_4. The solvent was removed, and the residue was chromatographed (cyclohexane/ethyl acetate, 1:2) to give, besides the desired compound (*M*)-**16** (16.0 mg, 33.7 μmol, 55%), whose spectroscopic data were in accordance with values for the racemic material,[28] a small quantity of (*M*)-3,3′-diacetyl-4-hydroxy-6,6′-dimethoxy-2,2′-dimethyl-4′-methylcarbonate-1,1′-biphenyl [(*M*)-**17**] (2.51 mg, 6.03 μmol, 10%) as a by-product. Both compounds were oils. **(*M*)-17:** $[\alpha]_D^{23} = +33.8$ (*c* = 0.32, $CHCl_3$). CD (EtOH): $\Delta\varepsilon_{200} = +15.1$, $\Delta\varepsilon_{220} = -2.5$, $\Delta\varepsilon_{230} = +1.2$, $\Delta\varepsilon_{241} = -2.5$, $\Delta\varepsilon_{264} = +2.5$, $\Delta\varepsilon_{280} = -0.5$, $\Delta\varepsilon_{297} = +0.8$, $\Delta\varepsilon_{315} = -0.4$. IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1} (br. m, OH), 3070 (w, Ar-H), 2985, 2950, 2930, 2825 (w, m, w, w, C−H), 1755, 1680, 1670 (s, m, m, C=O), 1580 (s, C=C), 1245, 1195 (s, s). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3 H, 2′-CH_3), 2.15 (s, 3 H, 2-CH_3), 2.51 (s, 3 H, 3′-$COCH_3$), 2.63 (s, 3 H, 3-$COCH_3$), 3.71 (s, 6 H, 6-OCH_3 and 6′-OCH_3), 3.93 (s, 3 H, 4′-OCO_2CH_3), 6.41 (s, 1 H, 5-H), 6.72 (s, 1 H, 5′-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.7 (2-CH_3), 20.4 (2′-CH_3), 32.4, 33.2 (3-CO*C*H_3 and 3′-CO*C*H_3), 55.7, 55.8, 56.0 (6-OCH_3, 6′-OCH_3 and 4′-OCO_2CH_3), 97.9 (C-5), 102.6 (C-5′), 116.3, 118.3, 124.5, 127.4, 136.4, 139.9, 147.8 (Ar-C), 153.8 (4′-OCO_2CH_3), 158.4, 162.3, 165.5 (Ar-C), 202.8, 204.7 (3-*C*OCH_3 and 3′-*C*OCH_3). MS (70 eV): *m*/*z* (%) = 416 (5) [M^+], 401 (6) [$M^+ - CH_3$], 388 (9) [M^+ − CO], 373 (4) [$M^+ - C_2H_3O$], 357 (5) [388 − CH_3O], 344 (41) [373 − CHO], 343 (5) [373 − CH_2O], 330 (24) [373 − C_2H_3O], 329 (100) [388 − $C_2H_3O_2$], 315 (9) [330 − CH_3]. $C_{22}H_{24}O_8$ (416.43): calcd. 416.1471; found 416.1472 (HRMS).

(*M*)-4,4′-Dihydroxy-7,7′-dimethoxy-5,5′-dimethyl-6,6′-bicoumarin [(*M*)-18]: According to Lin's procedure,[3,28] KO*t*Bu (30.3 mg, 270 μmol) and *tert*-butyl alcohol (4 mL) were added to (*M*)-**16** (16.0 mg, 33.7 μmol). This mixture was stirred at exactly 60 °C for 2 h. After this had cooled to room temperature, water (10 mL) was added, the pH value was adjusted to 6 with 2 N HCl, and the solution was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated. The crude product was spectroscopically identical to *rac*-**18**.[28] It still contained impurities, but could not be purified chromatographically, due to its high polarity and very low solubility in common organic solvents. Therefore, (*M*)-**18** was directly used in the next step.

(*M*)-4,4′,7,7′-Tetramethoxy-5,5′-dimethyl-6,6′-bicoumarin (1): By the known procedure,[3,28] crude bicoumarin (*M*)-**18** was dissolved in HMPA (2 mL) and treated with NaH (55−65%, in mineral oil, 3.23 mg, 80.8 μmol). After this had been stirred at room temperature for 15 min, Me_2SO_4 (9.60 μL, 101 μmol) was added and stirring was continued at the same temperature for a further 90 min. Water (5 mL) was added, and the mixture was acidified with 2 N HCl and extracted with ethyl acetate. The organic phases were combined and washed several times with brine, and then dried with Na_2SO_4. The solvent was removed, and the residue was purified in two portions by preparative TLC (cyclohexane/ethyl acetate, 1:2).

The products were recovered from the silica gel with ethyl acetate. The desired final product, (+)-isokotanin A (**1**), was obtained as a colorless solid, which upon recrystallization from ethyl acetate formed colorless crystals (3.90 mg, 8.90 μmol, 26% over two steps), spectroscopically fully identical with the data reported for the isolated natural product[1] and for material already synthesized.[2,3] **(*M*)-1:** M.p. 286−289 °C [ref.[1] 223−226 °C (decomp.), ref.[3] 240−242 °C (decomp.), ref.[2] 285−290 °C (decomp.)]. $[\alpha]_D^{23}$ = +21.6 (*c* = 0.26, $CHCl_3$) {ref.[1] $[\alpha]_D^{23}$ = +21.4 (*c* = 0.22, $CHCl_3$), ref.[3] $[\alpha]_D^{24}$ = +22.4 (*c* = 0.30, $CHCl_3$)}. CD (EtOH): $\Delta\varepsilon_{204}$ = +151.5, $\Delta\varepsilon_{215}$ = −182.0, $\Delta\varepsilon_{226}$ = +57.6, $\Delta\varepsilon_{249}$ = −3.9, $\Delta\varepsilon_{297}$ = −4.7, $\Delta\varepsilon_{327}$ = +11.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 6 H, 5- and 5′-CH_3), 3.72 (s, 6 H, 7- and 7′-OCH_3), 3.94 (s, 6 H, 4- and 4′-OCH_3), 5.59 (s, 2 H, 3- and 3′-H), 6.78 (s, 2 H, 8- and 8′-H).[52] ^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.7 (5- and 5′-CH_3), 55.97, 56.00 (4-, 4′-, 7- and 7′-OCH_3), 87.9 (C-3 and C-3′), 97.4 (C-8 and C-8′), 108.1 (C-4a and C-4a′), 123.4 (C-6 and C-6′), 137.2 (C-5 and C-5′), 156.3 (C-8a and C-8a′), 160.1 (C-7 and C-7′), 163.0 (C=O), 170.1 (C-4 and C-4′).[52] In addition, (*M*)-6-(3′-acetyl-4′,6′-dimethoxy-2′-methylphenyl)-4,7-dimethoxy-5-methylcoumarin [(*M*)-**19**] (colorless crystals from ethyl acetate, 2.69 mg, 6.52 μmol, 19% over two steps) and (*M*)-3,3′-diacetyl-4,4′,6,6′-tetramethoxy-2,2′-dimethyl-1,1′-biphenyl [(*M*)-**20**, compare preparation of compound (*M*)-**15**] (colorless oil, 1.72 mg, 4.45 μmol, 13% over two steps) were isolated as by-products. **(*M*)-19:** M.p. 198−199 °C. $[\alpha]_D^{23}$ = +16.2 (*c* = 0.36, $CHCl_3$). CD (EtOH): $\Delta\varepsilon_{205}$ = +18.1, $\Delta\varepsilon_{217}$ = −17.2, $\Delta\varepsilon_{229}$ = +7.3, $\Delta\varepsilon_{253}$ = −1.4, $\Delta\varepsilon_{305}$ = +1.0. IR (KBr): $\tilde{\nu}$ = 3065 cm^{-1} (w, Ar-H), 2975, 2905, 2825 (w, m, m, C−H), 1705, 1675 (s, s, C=O), 1570 (s, C=C), 1355, 1195, 1080 (s, s, m). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H, 2′-CH_3), 2.25 (s, 3 H, 5-CH_3), 2.52 (s, 3 H, 3′-$COCH_3$), 3.71, 3.73 (s, s, je 3 H, 6′-OCH_3 and 7-OCH_3), 3.89 (s, 3 H, 4′-OCH_3), 3.93 (s, 3 H, 4-OCH_3), 5.57 (s, 1 H, 3-H), 6.42 (s, 1 H, 5′-H), 6.76 (s, 1 H, 8-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.4 (2′-CH_3), 18.8 (5-CH_3), 32.7 (3′-$CO\mathit{C}H_3$), 55.6, 55.8, 55.9, 56.0 (4-, 4′-, 6′- and 7-OCH_3), 87.8 (C-3), 92.8 (C-5′), 97.3 (C-8), 108.0 (C-4a), 118.2 (C-3′), 123.7 (C-6), 124.5 (C-1′), 136.0 (C-2′), 137.4 (C-5), 156.1 (C-8a), 157.2 (C-4′), 158.4 (C-6′), 160.4 (C-7), 163.2 (C-2), 170.2 (C-4), 205.4 (3′-*C*OCH_3). MS (70 eV): *m*/*z* (%) = 412 (33) [M^+], 398 (32) [413 − CH_3], 397 (100) [$M^+ - CH_3$], 382 (2) [$M^+ - CH_2O$], 381 (2) [$M^+ - CH_3O$], 369 (2) [$M^+ - C_2H_3O$], 367 (8) [397 − CH_2O]. $C_{23}H_{24}O_7$ (412.44): calcd. 412.1522; found 412.1523 (HRMS).

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[16] In the crystals of **5** and **9**, both enantiomeric forms are found; for reasons of clarity, only the respective (*M*)-configured atropisomers are shown. Crystal data for **5**: $C_{18}H_{18}O_6$, triclinic, space group $P\bar{1}$; unit cell parameters: *a* = 702.83(6), *b* = 895.83(6), *c* = 1283.36(8) pm; α = 78.685(6), β = 83.700(5), γ = 83.460(5)°; *V* = 783.99(8)·10^6 pm^3. Crystal data for **9**: $C_{18}H_{22}O_6$, monoclinic, space group $P2_1/c$; unit cell parameters: *a* = 835.44(8), *b* = 2521.5(2), *c* = 862.99(8) pm; β = 99.864(7)°; *V* = 1716.4(3)·10^6 pm^3. CCDC-171441 (**5**), -171442 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
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