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Access to Enantiopure 2,5-Diaryltetrahydrofurans – Application to the Synthesis of (–)-Virgatusin and (+)-Urinaligran

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The diastereoselective Mn^{III}-promoted radical addition of β-oxoesters **1** onto *N*-cinnamoyloxazolidinones **2** afforded 2,3-dihydrofurans **3**. After catalytic hydrogenation of the C=C bond, followed by reductive removal of the chiral auxiliary, the resulting enantiopure tetrahydrofurans **5** were transformed in two steps into naturally occurring (–)-virgatusin and (+)-urinaligran and two other, nonnatural, tetrasubstituted THF lignans.

Introduction

2,5-Diaryltetrahydrofuran (2,5-diaryl-THF) lignans constitute an important subgroup of the extended family of natural lignans.[1] A great number of these THF lignans possess interesting biological and pharmacological properties (antitumor, antibacterial, antifungal, antioxidant).[2] They differ from each other by the substitution pattern on Ar^1 and Ar^2, the nature of R^1 and R^2, and by the stereochemistry (relative and absolute) about the four contiguous stereocenters (Figure 1). To this day, 2,5-diaryl-THF lignans possessing the *trans*,*trans*,*cis* relative stereochemistry have received the most attention and constitute the major group for which a total synthesis has been reported (Figure 1).[3] These syntheses suffer, nevertheless, from one or two major drawbacks: they are somewhat lengthy, as they are rather linear and/or they are not totally diastereoselective, which results in poor overall yield in the desired target.

In order to overcome these shortcomings, we envisioned to prepare enantiopure 2,5-diaryl-THF lignans possessing the *trans*,*trans*,*cis* relative stereochemistry (taking virgatusin as a model compound) by a shorter (more convergent) and highly stereocontrolled route according to the initial retrosynthetic analysis depicted in Scheme 1 (path a). This scheme rested upon our previous works concerning the asymmetric synthesis and utilization of enantiopure tetrasubstituted 2,3-dihydrofurans.[4] The two key steps, each involving the concomitant creation of two stereocenters, are the radical oxidative addition[5] of methyl benzoylacetate **1**[6] to phenyl-substituted cinnamic acid **2** bearing a chiral auxiliary[7] followed by the reduction of the prochiral C=C

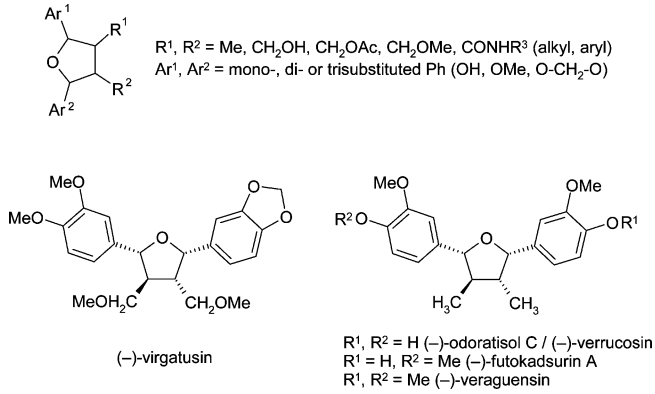

Figure 1. General structure of 2,5-diaryl-THF lignans and structures of previously synthesized *trans*,*trans*,*cis*-2,5-diaryl-THF lignans.

bond of the 2,3-dihydrofuran thus formed, after removal of the chiral auxiliary. As already shown, the absolute configuration at C2 and C3 can be controlled by the chiral auxiliary.[4,8] For this purpose, 4-substituted 1,3-oxazolidin-2-ones have proven their efficacy and their versatility: they can be readily grafted onto the cinnamic moiety, they tolerate the harsh conditions of the oxidative addition step, and they can be smoothly removed from the adduct to furnish at will an acid, an ester, or a primary alcohol. Besides, the absolute configuration at C4 and C5 could be controlled by catalytic hydrogenation performed on an enantiopure dihydrofuran precursor.

A preliminary study conducted on racemic dihydrofurans with a methoxycarbonyl group at C3 (H_2, 10% Pd/C, EtOAc, 1 bar, r.t.) showed that this step was not totally diastereoselective, giving predominantly the expected diastereomer accompanied by a minor one (10–20%, depending on Ar^1 and Ar^2), which could not be separated either at this stage or in a subsequent step. This fact has also been reported, during the course of our work, in the

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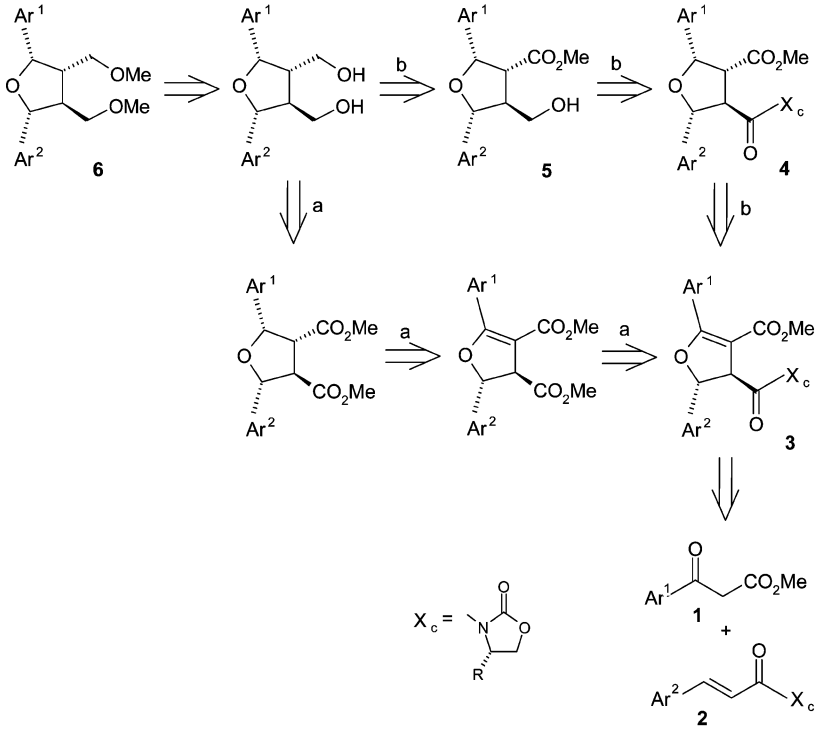
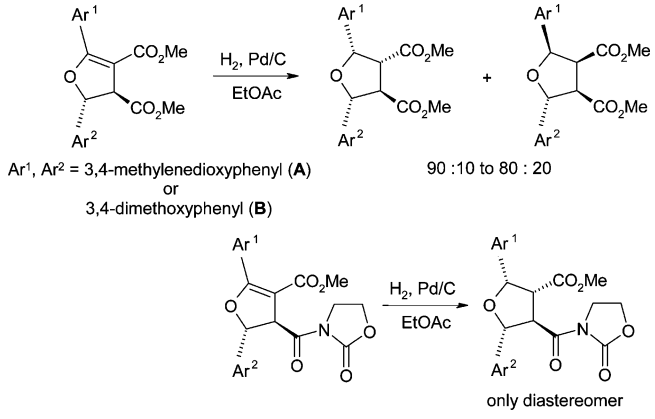


Scheme 1. Initial (a) and modified (b) retrosynthetic analyses of (–)-virgatusin and congeners.

synthesis of a closely related compound.[9] We thus decided to reinvestigate this crucial step. Fortunately, when we performed the catalytic hydrogenation by using the same experimental conditions on a dihydrofuran with an achiral *N*-oxazolidinylcarbonyl substituent at C3, it could be rendered entirely diastereoselective, furnishing quantitatively the single *trans*,*trans*,*cis* diastereomer (Scheme 2).[10]



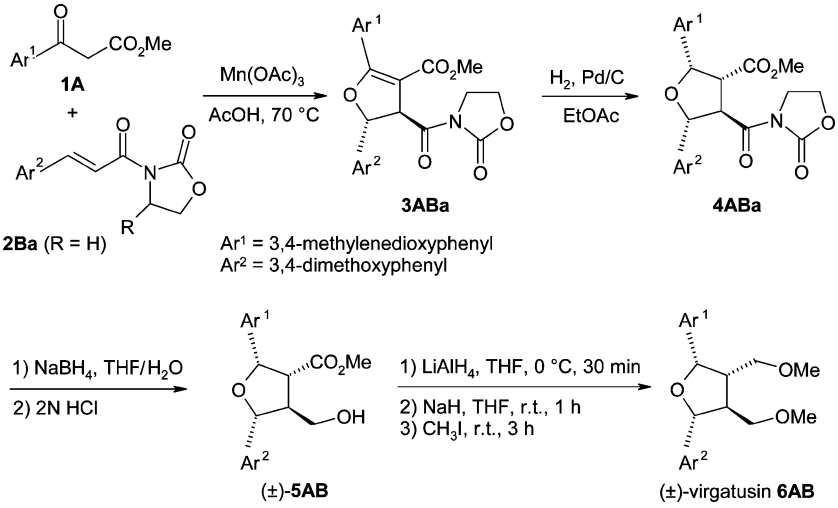
Scheme 2. Diastereoselectivity of the hydrogenation step.

Results and Discussion

At this stage, we could prepare the requisite diol by two possible routes: either simultaneous reduction of the two C=O groups by $LiAlH_4$ or initial reductive removal ($NaBH_4$, THF/H_2O) of the oxazolidinone[11] followed by $LiAlH_4$ reduction of the methyl ester. In all cases, it appeared that the two-step procedure gave consistently a better overall yield of the desired diol. Accordingly, we modified our initial retrosynthetic analysis: to accommodate these new findings, the chiral auxiliary had to be removed after the hydrogenation step and by reductive cleavage (Scheme 1, path b).

The synthesis of (±)-virgatusin **6AB**[12] was then realized uneventfully according to this scheme. It nevertheless allowed us to find out that the overall yield of **6AB** could be optimized by conducting the dimethylation reaction on the crude diol immediately after $LiAlH_4$ reduction and that only two chromatographic purifications were required: one after the first step and one after the last step (Scheme 3).

With our final retrosynthetic analysis thus validated, in order to obtain (–)-virgatusin we had next to focus on the first step and find a chiral auxiliary able to furnish desired adduct **3AB** in optimal yield and diastereoselectivity. We already knew that to access (2*R*,3*S*,4*S*,5*S*)-(–)-virgatusin we had to employ a (*S*)-4-substituted oxazolidinone.[4] We therefore screened three of them that had previously given the best diastereoselectivity in the oxidative addition step (Table 1 and Scheme 4). As expected, the diphenylmethyloxazolidinone chiral auxiliary gives the best result in terms of diastereoselectivity but the two diastereomers **3ABd/3′ABd** could not be efficiently separated by silica-gel chromatography. However, *tert*-butyloxazolidinone as a chiral auxiliary was also efficient, and in this case, major diastereomer **3ABc** could be obtained pure in a significantly better yield (45%) after careful chromatography. The hydrogenation step was then carried out by using the same condi-

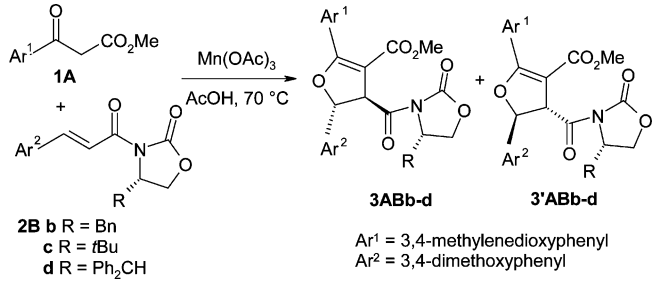


Scheme 3. Synthesis of (±)-virgatusin (**6AB**).

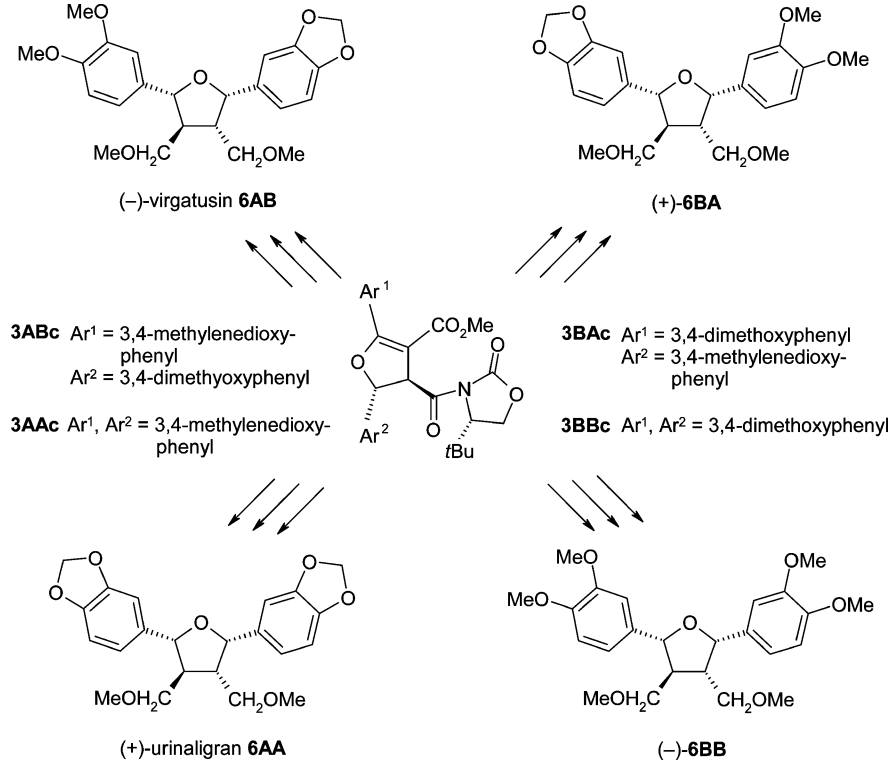
tions employed in the racemic synthesis (Scheme 3) to give quantitatively a single compound (**4ABc**), which was transformed into (–)-virgatusin (**6AB**; Scheme 5).

Table 1. Addition of methyl benzoylacetate **1A** to *N*-cinnamoyloxazolidinones **2Bb–d**.

2B	Time [h]	Unchanged **2B** [%]	**3AB** + **3′AB** [%]	**3AB**/**3′AB**
b (R = Bn)	4	27	58	75:25
c (R = *t*Bu)	3	30	52	88:12
d (R = Ph_2CH)	5	20	40	90:10



Scheme 4. Addition of methyl benzoylacetate **1A** to *N*-cinnamoyloxazolidinones **2Bb–d**.



Scheme 5. Total synthesis of (–)-virgatusin (**6AB**), (+)-urinaligran (**6AA**), (+)-**6BA**, and (–)-**6BB**.

Having successfully achieved the total synthesis of (–)-virgatusin (**6AB**)[13] in five steps and 20% overall yield from **1A** and **2Bc**, we extended this approach to the preparation of three of its congeners by employing consistently (*S*)-4-*tert*-butyl-1,3-oxazolidin-2-one as the chiral auxiliary for the oxidative addition step (Table 2). We thus obtained enantiopure (+)-urinaligran (**6AA**),[14] (+)-**6BA**, and (–)-**6BB** in 8.2, 12.4, and 25.4% overall yield, respectively, over five steps (Scheme 5).

Table 2. Addition of methyl benzoylacetate **1A** or **1B** to *N*-cinnamoyloxazolidinone **2Ac** or **2Bc**.

1/2c	Time [h]	Unchanged **2c** [%]	**3c** + **3′c** [%]	**3c/3′c**
1A/2Ac	4.5	**2Ac** [25]	**3AAc** + **3′AAc** [30]	**3AAc/3′AAc** 88:12
1B/2Ac	4	**2Ac** [13]	**3BAc** + **3′BAc** [31]	**3BAc/3′BAc** 77:23
1B/2Bc	4	**2Bc** [23]	**3BBc** + **3′BBc** [45]	**3BBc/3′BBc** 87:13

Conclusions

We have devised a short synthesis of enantiopure 2,5-diaryl-THF lignans possessing the *trans,trans,cis* relative stereochemistry. We have thus prepared in five steps two natural, (–)-virgatusin and (+)-urinaligran, and two nonnatural THF lignans from readily available starting compounds. This convergent, modular, and versatile strategy could be extended to the synthesis of other enantiopure 2,5-diaryl-THF lignans endowed with the same stereochemistry or of other diastereomers provided that the C=C bond could be reduced by a means other than the catalytic hydrogenation employed in this work, which we are currently investigating.

Experimental Section

General Remarks: All NMR spectra were recorded with a Bruker AC 250 spectrometer (^{1}H 250 MHz; ^{13}C 62 MHz). Chemical shifts are reported in ppm. The following abbreviations are used in reporting spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, br. s = broad singlet. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1-dm cell.

Materials: All experiments were conducted under an atmosphere of nitrogen unless indicated otherwise, and the reaction mixtures were stirred magnetically. $Mn(OAc)_3{\cdot}2H_2O$ (Aldrich) and 10% Pd/C (Aldrich) were used as received. THF was distilled from sodium benzophenone–ketyl immediately prior to use. Flash chromatography was performed with Merck silica-gel 60 H. Thin-layer chromatography (TLC) was carried out on Merck silica-gel 60 F_{254} aluminum-backed-plates. TLC visualization was done with a 254 nm UV lamp and phosphomolybdic acid staining solution.

General Procedure for the Oxidative Addition: A mixture of methyl benzoylacetate **1A** or **1B** (1 mmol), *N*-cinnamoyloxazolidinone **2A** or **2B** (1 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (590 mg, 2.2 mmol) in AcOH (10 mL) was heated at 70 °C until complete discoloration. After cooling, H_2O (5 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and dried with $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by flash chromatography.

Dihydrofuran 3ABb: The general procedure was applied starting from **1A** (222 mg, 1 mmol) and **2Bb** (367 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3ABb** (190 mg, 0.32 mmol, 32% yield) then a mixture of **3ABb** and **3′ABb** (82 mg, 0.14 mmol, 14% yield), and finally pure **3′ABb** (71 mg, 0.12 mmol, 12% yield). Data for **3ABb**: $[\alpha]_D^{25}$ = –43.5 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.81 (dd, *J* = 13.3, 9.0 Hz, 1 H), 3.20 (dd, *J* = 13.3, 3.4 Hz, 1 H), 3.56 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.10–4.30 (m, 2 H), 4.85 (m, 1 H), 5.65 (d, *J* = 6.9 Hz, 1 H), 5.78 (d, *J* = 6.9 Hz, 1 H), 5.95 (s, 2 H), 6.80 (m, 2 H), 6.96 (m, 3 H), 7.10 (m, 4 H), 7.40 (m, 2 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 38.15, 51.31, 53.90, 54.33, 55.96, 56.03, 66.38, 86.21, 101.53, 102.12, 107.77, 109.53, 110.04, 111.02, 119.02, 122.74, 124.95, 127.48, 128.98 (2 C), 129.49 (2 C), 130.97, 134.94, 147.12, 149.21, 149.47, 149.92, 153.32, 164.62, 166.67, 173.42 ppm. $C_{32}H_{29}NO_{10}$ (587.58): calcd. C 65.41, H 4.97, N 2.38; found C 65.48, H 4.92, N 2.44. Data for **3′ABb**: $[\alpha]_D^{25}$ = +131.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.66 (dd, *J* = 13.3, 10.3 Hz, 1 H), 3.28 (dd, *J* = 13.3, 2.7 Hz, 1 H), 3.61 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.12 (d, *J* = 4.7 Hz, 2 H), 4.65 (m, 1 H), 5.63 (d, *J* = 6.8 Hz, 1 H), 5.83 (d, *J* = 6.8 Hz, 1 H), 5.95 (s, 2 H), 6.80 (m, 3 H), 6.96 (m, 2 H), 7.10 (m, 4 H), 7.40 (m, 2 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 37.41, 51.27, 54.16, 54.35, 55.99, 56.03, 66.00, 86.20, 101.51, 102.18, 107.77, 109.62, 110.01, 111.02, 119.10, 122.68, 124.93, 127.38, 129.04 (2 C), 129.44 (2 C), 130.92, 135.41, 147.13, 149.22, 149.53, 149.91, 153.32, 164.51, 166.69, 173.54 ppm. $C_{32}H_{29}NO_{10}$ (587.58): calcd. C 65.41, H 4.97, N 2.38; found C 65.27, H 5.02, N 2.35.

Dihydrofuran 3ABc: The general procedure was applied starting from **1A** (222 mg, 1 mmol) and **2Bc** (333 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3ABc** (249 mg, 0.45 mmol, 45% yield) then a mixture of **3ABc** and **3′ABc** (38.7 mg, 0.07 mmol, 7% yield). Data for **3ABc**: $[\alpha]_D^{25}$ = –35.1 (*c* = 1.13, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (s, 9 H), 3.55 (s, 3 H), 3.81 (s, 6 H), 4.24 (d, *J* = 5.0 Hz, 2 H), 4.82 (d, *J* = 5.0 Hz, 1 H), 5.72 (d, *J* = 8.0 Hz, 1 H), 5.86 (d, *J* = 8.0 Hz, 1 H), 5.93 (s, 2 H), 6.75 (m, 2 H), 6.96 (m, 2 H), 7.29 (d, *J* = 1.6 Hz, 1 H), 7.38 (dd, *J* = 8.2, 1.6 Hz, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 25.64 (3 C), 35.60, 51.28, 53.61, 55.95 (2 C), 61.68, 65.42, 86.95, 101.52, 102.53, 107.73, 109.30, 109.98, 111.03, 118.94, 122.75, 124.87, 130.86, 147.07, 149.18, 149.41, 149.84, 154.80, 164.62, 166.45, 173.63 ppm. $C_{29}H_{31}NO_{10}$ (553.56): calcd. C 62.92, H 5.64, N 2.53; found C 62.78, H 5.72, N 2.55.

Dihydrofuran 3ABd: The general procedure was applied starting from **1A** (222 mg, 1 mmol) and **2Bd** (443 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3ABd** (133 mg, 0.20 mmol, 20% yield) then a mixture of **3ABd** and **3′ABd** (132 mg, 0.20 mmol, 20% yield). Data for **3ABd**: $[\alpha]_D^{25}$ = +10.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.55 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.30–4.40 (m, 2 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 5.14 (d, *J* = 6.5 Hz, 1 H), 5.40 (m, 1 H), 5.64 (d, *J* = 6.8 Hz, 1 H), 5.93 (s, 2 H), 6.70–7.40 (m, 16 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 51.28, 51.64, 53.54, 55.96, 56.03, 60.44, 65.53, 85.91, 101.51, 101.87, 107.73, 109.47,

109.99, 110.99, 118.95, 122.74, 124.89 (2 C), 127.17, 127.92 (2 C), 128.47 (2 C), 128.69 (2 C), 129.04, 129.25, 131.14, 138.05, 139.30, 147.09, 149.12, 149.36, 149.86, 153.39, 164.64, 166.63, 172.97 ppm. $C_{38}H_{33}NO_{10}$ (663.68): calcd. C 68.77, H 5.01, N 2.11; found C 68.88, H 4.96, N 2.03.

Dihydrofuran 3AAc: The general procedure was applied starting from **1A** (222 mg, 1 mmol) and **2Ac** (317 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3AAc** (129 mg, 0.24 mmol, 24% yield) then a mixture of **3AAc** and **3′AAc** (32 mg, 0.06 mmol, 6% yield). Data for **3AAc**: $[\alpha]_D^{26}$ = –38.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (s, 9 H), 3.55 (s, 3 H), 4.25 (m, 2 H), 4.44 (m, 1 H), 5.63 (d, J = 7.5 Hz, 1 H), 5.73 (d, J = 7.5 Hz, 1 H), 5.91 (s, 2 H), 5.94 (s, 2 H), 6.65–6.85 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 25.68 (3 C), 36.63, 51.30, 54.07, 61.71, 65.45, 86.75, 101.32, 101.52, 102.23, 106.58, 107.73, 108.31, 110.01, 120.09, 122.67, 124.92, 132.71, 147.05, 148.11, 148.19, 149.86, 154.73, 164.61, 166.50, 173.56 ppm. $C_{28}H_{27}NO_{10}$ (537.58): calcd. C 62.56, H 5.06, N 2.62; found C 62.42, H 5.13, N 2.65.

Dihydrofuran 3BAc: The general procedure was applied starting from **1B** (238 mg, 1 mmol) and **2Ac** (317 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3BAc** (120 mg, 0.22 mmol, 22% yield) then a mixture of **3BAc** and **3′BAc** (50 mg, 0.09 mmol, 9% yield). Data for **3BAc**: $[\alpha]_D^{23}$ = –46.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (s, 9 H), 3.56 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.10 (m, 2 H), 4.40 (m, 1 H), 5.62 (d, J = 7.5 Hz, 1 H), 5.80 (d, J = 7.5 Hz, 1 H), 5.90 (s, 2 H), 6.65–6.85 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 25.68 (3 C), 35.63, 51.23, 54.24, 55.94, 56.00, 61.71, 65.43, 86.73, 101.32, 102.08, 106.64, 108.30, 110.07, 112.80, 120.12, 121.44, 123.44, 132.77, 147.96, 148.11, 148.20, 151.33, 154.73, 164.67, 166.69, 173.69 ppm. $C_{29}H_{31}NO_{10}$ (553.56): calcd. C 62.92, H 5.64, N 2.53; found C 63.01, H 5.68, N 2.48.

Dihydrofuran 3BBc: The general procedure was applied starting from **1B** (238 mg, 1 mmol) and **2Bc** (333 mg, 1 mmol). The crude product was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give first **3BBc** (210 mg, 0.37 mmol, 37% yield) then a mixture of **3BBc** and **3′BBc** (45 mg, 0.08 mmol, 8% yield). Data for **3BBc**: $[\alpha]_D^{26}$ = –18.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (s, 9 H), 3.56 (s, 3 H), 3.81 (s, 6 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.20 (m, 2 H), 4.40 (m, 1 H), 5.73 (d, J = 8.1 Hz, 1 H), 5.89 (d, J = 8.1 Hz, 1 H), 6.78–6.84 (m, 2 H), 6.94–7.00 (m, 2 H), 7.44–7.50 (m, 2 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.62 (3 C), 36.63, 51.23, 52.76, 54.91 (2 C), 54.96 (2 C), 60.64, 64.38, 85.90, 101.31, 108.32, 109.00, 110.00, 111.71, 117.99, 120.48, 122.38, 129.88, 146.91, 148.15, 148.38, 150.25, 153.78, 163.70, 165.66, 172.73 ppm. $C_{30}H_{35}NO_{10}$ (569.67): calcd. C 63.25, H 6.19, N 2.46; found C 63.31, H 6.11, N 2.51.

General Procedure for the Hydrogenation Step: A solution of **3c** (0.10 mmol) in EtOAc (5 mL) was stirred with 10% Pd on charcoal (60 mg). The mixture was thoroughly deoxygenated by bubbling H_2 for 10 min and kept under H_2 (1 bar) at room temperature for 48 h. Pd was filtered through Celite, which was then rinsed with EtOAc (3 × 10 mL). Evaporation of the solvent afforded crude tetrahydrofuran **4c** in quantitative yield and of sufficient purity to be directly used in the next step.

Tetrahydrofuran 4ABc: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70 (s, 9 H), 3.27 (s, 3 H), 3.61 (dd, J = 7.6, 5.4 Hz, 1 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 4.10 (m, 2 H), 4.20 (m, 1 H), 4.39 (dd, J = 7.8, 5.4 Hz, 1 H), 5.05 (d, J = 7.6 Hz, 1 H), 5.10 (d, J = 7.8 Hz, 1 H), 5.89 (s, 2 H), 6.65–7.05 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.46 (3 C), 34.66, 50.82, 52.00, 54.77, 54.84, 54.87, 60.00, 63.94, 81.12, 84.14, 100.02, 106.49, 106.92, 109.70, 109.79, 119.21, 119.46, 129.16, 130.12, 146.28, 146.40, 147.98, 148.35, 152.62, 171.26, 172.38 ppm.

Tetrahydrofuran 4AAc: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.75 (s, 9 H), 3.27 (s, 3 H), 3.60 (dd, J = 8.2, 5.0 Hz, 1 H), 4.11 (m, 2 H), 4.24 (m, 1 H), 4.39 (dd, J = 8.0, 5.6 Hz, 1 H), 5.10 (d, J = 8.2 Hz, 1 H), 5.20 (d, J = 7.8 Hz, 1 H), 5.87 (s, 2 H), 5.90 (s, 2 H), 6.65–6.95 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.50 (3 C), 34.70, 50.87, 51.83, 54.83, 60.06, 64.03, 81.27, 83.82, 100.02, 100.10, 106.12, 106.81, 106.95, 107.04, 119.10, 120.19, 129.78, 131.05, 146.28, 146.40, 146.91, 146.96, 152.64, 170.32, 171.34 ppm.

Tetrahydrofuran 4BAc: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.75 (s, 9 H), 3.22 (s, 3 H), 3.61 (dd, J = 7.6, 5.6 Hz, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.10 (m, 2 H), 4.20 (m, 1 H), 4.39 (dd, J = 8.0, 5.6 Hz, 1 H), 5.05 (d, J = 7.6 Hz, 1 H), 5.25 (d, J = 8.0 Hz, 1 H), 5.90 (s, 2 H), 6.70–6.95 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.48 (3 C), 34.68, 50.83, 52.15, 54.79, 54.85, 54.90, 60.03, 63.99, 81.23, 82.42, 100.06, 106.63, 107.00, 108.86, 109.67, 118.80, 120.04, 127.36, 131.48, 146.31, 147.20, 148.14, 148.25, 152.63, 170.40, 172.29 ppm.

Tetrahydrofuran 4BBc: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70 (s, 9 H), 3.23 (s, 3 H), 3.60 (dd, J = 6.7, 5.1 Hz, 1 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.15 (m, 1 H), 4.22 (m, 2 H), 4.38 (dd, J = 8.5, 5.1 Hz, 1 H), 5.22 (d, J = 6.7 Hz, 1 H), 5.45 (d, J = 8.5 Hz, 1 H), 6.25 (dd, J = 8.6, 2.8 Hz, 1 H), 6.70–7.00 (m, 5 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.48 (3 C), 34.68, 50.82, 52.23, 54.72, 54.80, 54.85, 54.88, 54.91, 60.03, 63.99, 81.16, 83.86, 108.54, 109.58, 109.67, 109.73, 119.12 (2 C), 127.36, 130.18, 147.52, 147.59, 148.13, 148.25, 152.63, 170.55, 171.18 ppm.

General Procedure for the Reductive Removal of the Oxazolidinone: A mixture of compound **4c** (0.50 mmol) and $NaBH_4$ (76 mg, 2 mmol) in THF (2 mL) and H_2O (0.5 mL) was stirred at room temperature for 6 h. Aqueous HCl (2 N, 5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with saturated aqueous NaCl and dried with $MgSO_4$. Evaporation of the solvent afforded crude tetrahydrofuran **5** in quantitative yield and of sufficient purity to be directly used in the next step.

Tetrahydrofuran 5AB: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.55 (br. s, 1 H), 2.85 (m, 1 H), 3.23 (s, 3 H), 3.40 (dd, J = 8.7, 7.0 Hz, 1 H), 3.50 (m, 2 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 4.60 (d, J = 9.0 Hz, 1 H), 5.10 (d, J = 8.7 Hz, 1 H), 5.87 (s, 2 H), 6.70–6.90 (m, 4 H), 7.00 (dd, J = 8.2, 1.8 Hz, 1 H), 7.15 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 51.63, 52.21, 53.72, 55.92 (2 C), 61.50, 81.65, 82.90, 100.98, 107.24, 107.81, 110.28, 110.93, 119.64, 120.14, 132.19 (2 C), 147.11, 147.33, 149.00, 150.01, 172.82 ppm.

Tetrahydrofuran 5AA: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (br. s, 1 H), 2.78 (m, 1 H), 3.21 (s, 3 H), 3.40 (m, 1 H), 3.65 (m, 2 H), 4.58 (d, J = 9.0 Hz, 1 H), 5.10 (d, J = 8.7 Hz, 1 H), 5.87 (s, 2 H), 5.90 (s, 2 H), 6.66–6.84 (m, 4 H), 6.90 (dd, J = 8.0, 1.6 Hz, 1 H), 7.08 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 50.65, 51.39, 52.63, 60.14, 80.56, 81.73, 99.99, 100.09, 106.21, 106.46, 106.82, 107.09, 119.11, 119.79, 130.99, 132.62, 146.09, 146.29, 146.56, 146.94, 171.87 ppm.

Tetrahydrofuran 5BA: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.63 (br. s, 1 H), 2.80 (m, 1 H), 3.17 (s, 3 H), 3.40 (m, 1 H), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.15 (d, J = 5.8 Hz, 2 H), 4.60 (d, J = 9.0 Hz, 1 H), 5.15 (d, J = 8.6 Hz, 1 H), 5.90 (s, 2 H), 6.65–6.95 (m, 5 H), 7.10 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 50.62, 51.44, 52.67, 54.84, 54.87, 60.46, 80.70, 81.79, 100.08, 106.49,

107.08, 108.81, 109.56, 118.07, 119.82, 129.74, 132.83, 146.56, 146.96, 147.44, 147.53, 171.94 ppm.

Tetrahydrofuran 5BB: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.58 (br. s, 1 H), 2.80 (m, 1 H), 3.16 (s, 3 H), 3.40 (dd, J = 8.5, 6.7 Hz, 1 H), 3.50 (m, 2 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 4.65 (d, J = 8.9 Hz, 1 H), 5.15 (d, J = 8.5 Hz, 1 H), 6.65–6.90 (m, 4 H), 7.00 (dd, J = 8.2, 1.8 Hz, 1 H), 7.18 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 50.58, 51.37, 52.73, 54.75, 54.82, 54.90 (2 C), 59.45, 80.68, 81.83, 108.74, 109.25, 109.51, 109.83, 118.02, 118.58, 129.77, 131.57, 147.39, 147.49, 147.96, 148.03, 172.00 ppm.

General Procedure for the Transformation 5 → 6: A solution of **5** (0.25 mmol) in dry THF (6 mL) was added dropwise to a suspension of $LiAlH_4$ (19 mg, 0.50 mmol) in dry THF at 0 °C. After 30 min at 0 °C, H_2O (27 μL), 15% aqueous NaOH (27 μL), and H_2O (54 μL) were successively added. The resulting cloudy suspension was filtered through Celite, which was then rinsed with CH_2Cl_2 (3 × 5 mL). The filtrate was concentrated to afford quantitatively the diol, which was immediately dimethylated without further purification. A suspension of oil-free NaH (67 mg, 1.4 mmol) in dry THF (5 mL) containing the diol (0.14 mmol) was stirred at room temperature for 1 h. CH_3I (0.087 mL, 1.4 mmol) was added. After stirring for another 3 h, the reaction mixture was cooled to 5 °C and quenched with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with H_2O (3 × 5 mL) and dried with $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by flash chromatography (hexane/EtOAc, 9:1 to 1:1) to give pure **6**.

(–)-Virgatusin (6AB): Yield 63 mg (0.15 mmol, 60% over two steps). $[\alpha]_D^{25}$ = –12.2 (c = 1.10, $CHCl_3$) {ref.[13] $[\alpha]_D^{25}$ = –12.7 (c = 0.50, CH_2Cl_2)}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (m, 1 H), 2.55 (m, 1 H), 2.92 (m, 2 H), 3.02 (s, 3 H), 3.28 (s, 3 H), 3.45 (m, 2 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.65 (d, J = 8.0 Hz, 1 H), 5.00 (d, J = 7.2 Hz, 1 H), 5.88 (s, 2 H), 6.68–7.02 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 45.50, 49.85, 54.82, 54.89, 57.66, 58.05, 71.98, 72.00, 80.42, 81.58, 99.88, 106.03, 106.84, 108.85, 109.88, 117.74, 118.60, 131.73, 133.00, 145.52, 146.34, 147.45, 147.86 ppm. $C_{23}H_{28}O_7$ (416.47): calcd. C 66.33, H 6.78; found C 66.23, H 6.84.

(+)-Urinaligran (6AA): Yield: 41 mg (0.10 mmol, 40% over two steps). $[\alpha]_D^{25}$ = +18.2 (c = 1.10, $CHCl_3$) {ref.[14] $[\alpha]_D^{25}$ = +19.0 (c = 1.00, $CHCl_3$)}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (m, 1 H), 2.50 (m, 1 H), 2.90 (m, 2 H), 3.00 (s, 3 H), 3.30 (s, 3 H), 3.40 (m, 2 H), 4.60 (d, J = 8.0 Hz, 1 H), 5.00 (d, J = 7.3 Hz, 1 H), 5.85 (s, 4 H), 6.60–6.95 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 45.44, 50.37, 57.63, 58.03, 71.90, 72.17, 80.37, 81.57, 99.88, 99.95, 105.94, 106.03, 106.85, 107.04, 118.57, 119.00, 131.64, 134.54, 145.56, 145.98, 146.38, 146.76 ppm. $C_{22}H_{24}O_7$ (400.43): calcd. C 65.99, H 6.04; found C 66.08, H 5.99.

(+)-6BA: Yield: 75 mg (0.18 mmol, 72% over two steps). $[\alpha]_D^{25}$ = +2.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (m, 1 H), 2.48 (m, 1 H), 2.90 (m, 2 H), 3.00 (s, 3 H), 3.30 (s, 3 H), 3.40 (m, 2 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 4.60 (d, J = 8.0 Hz, 1 H), 5.00 (d, J = 7.2 Hz, 1 H), 5.85 (s, 2 H), 6.60–6.96 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 46.57, 51.14, 55.88 (2 C), 58.63, 59.03, 72.93, 73.13, 81.44, 82.63, 100.96, 106.96, 108.03, 109.80, 110.75, 118.58, 120.05, 131.39, 135.63, 147.00, 147.77, 148.08, 148.58 ppm. $C_{23}H_{28}O_7$ (416.47): calcd. C 66.33, H 6.78; found C 66.10, H 6.76.

(–)-6BB: Yield: 78 mg (0.18 mmol, 72% over two steps). $[\alpha]_D^{25}$ = –4.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 (m, 1 H), 2.55 (m, 1 H), 3.05 (m, 2 H), 3.00 (s, 3 H), 3.30 (s, 3 H), 3.49 (m, 2 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.68 (d, J = 8.0 Hz, 1 H), 5.06 (d, J = 7.2 Hz, 1 H), 6.70–7.05 (m, 6 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 45.66, 49.67, 54.74, 54.81, 54.87, 56.97, 57.53, 57.78, 72.07, 72.18, 81.58, 81.65, 106.85, 107.04, 108.00, 108.71, 118.57, 119.00, 131.64, 134.54, 145.56, 145.98, 146.38, 146.74 ppm. $C_{24}H_{32}O_7$ (432.51): calcd. C 66.65, H 7.46; found C 66.54, H 7.52.

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