

Stereoselective Total Synthesis of (+)-Dodoneine

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Abstract: A total synthesis of the naturally occurring dihydropyranone dodoneine is reported. The combination of a highly catalytic enantioselective allylboration and a highly diastereoselective allylstannation was used for the stereoselective generation of the two stereogenic centers. The pyranone ring was created in two steps through generation of a *Z*-configured α,β -unsaturated ester and lactonization via intramolecular transesterification.

Key words: asymmetric allylation, diastereoselectivity, enantioselectivity, olefination, phenol, total synthesis, lactone

Dodoneine is a naturally occurring dihydropyranone recently isolated from *Tapinanthus dodoneifolius*, a parasitic plant that feeds from the sheanut tree in Burkina Faso (West Africa) (Figure 1).¹ Like many 5,6-dihydropyran-2-ones, dodoneine was expected to exhibit potent biological activities (HIV protease inhibition, apoptosis induction, antileukemic effect). Recent biological studies using (+)-dodoneine revealed a potent relaxing effect on pre-constricted rat aortic rings.² Its structure and absolute configuration were assigned as shown in Figure 1 on the basis of extensive spectroscopic analyses (NMR, HRMS, X-ray).¹

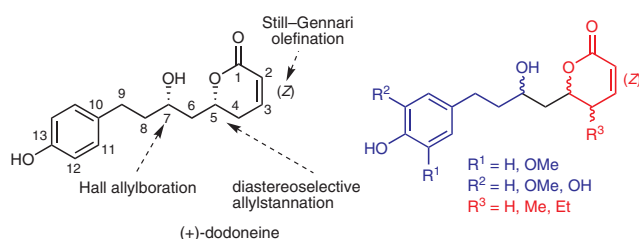
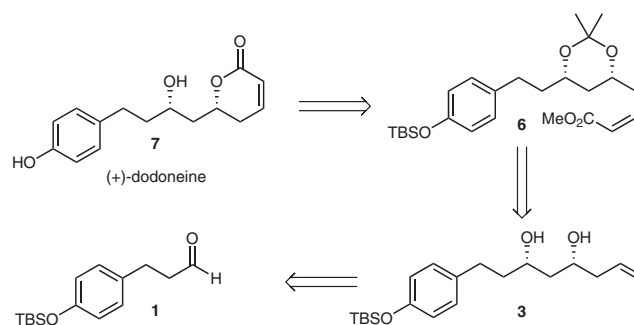


Figure 1

This interesting biological activity has resulted in the recent publication of six total syntheses of dodoneine by Marco,² Srihari,³ Cossy,⁴ Hall,⁵ Das,⁶ and Sabitha⁷ using established aldehyde asymmetric allylation methodologies for introducing the stereogenic centers and either ring-closing metathesis or intramolecular transesterification for pyranone ring closure. Due to our interest in phenylpropanoid related compounds,⁸ we envisaged a design for a new general synthetic methodology for dodoneine and related analogues featuring variously substituted phe-

nylpropanoid and lactone moieties in order to have access to structure–activity relationships (Figure 1).

Herein, we would like to present a short and efficient asymmetric synthesis of dodoneine starting from the known phenylpropanoid aldehyde **1** while limiting the use of expensive catalysts and ligands. In order to limit the cost of the formation of dodoneine, we envisaged initially controlling the chirality of the C7 center by using a highly enantioselective allylboration⁵ followed by a highly diastereoselective allylstannation⁹ to set the configuration at C5. The *Z*-configured unsaturated ester would be thereafter elaborated via a Wadsworth–Horner–Emmons olefination using Still–Gennari phosphonoacetate (Scheme 1).¹⁰



Scheme 1

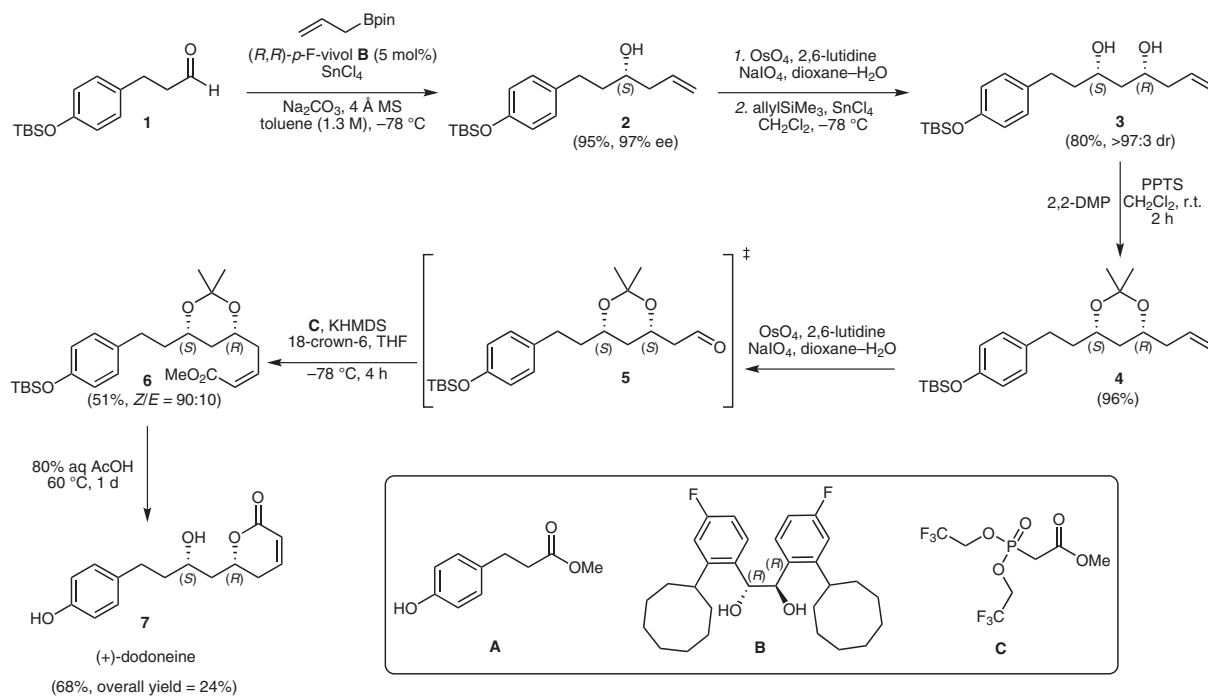
The synthesis starts from known aldehyde **1**, which can be readily obtained from the commercially available ester **A** in two steps: protection of the phenol through the formation of the corresponding *tert*-butyldimethylsilyl ether (TBSCl, imidazole, CH₂Cl₂), followed by controlled reduction of the methyl ester into the aldehyde (DIBAL-H, toluene, –78 °C, 85% overall yield) (Scheme 2). In our quest for an economic synthesis that would be easy to scale up, we focused our efforts on a design of dodoneine synthesis that would minimize the use of expensive catalysts (i.e., metal/ligands). Therefore, any asymmetric allylation process involving stoichiometric amounts of metal–chiral ligand complex (e.g., Brown and Duthaler methodologies) was ruled out. Hall recently developed a potent catalytic enantioselective allylboration using *p*-F-Vivol (**B**) as ligand and applied it to the synthesis of dodoneine and, thereby, efficiently controlled both C5 and C7 chiral centers in a sequence involving two allylboration reactions.⁵ We similarly used this methodology on aldehyde **1** and synthesized optically active homoallylic alcohol **2** in 97% ee and 95% yield, [allylBpin, (*R,R*)-*p*-F-vivol (5

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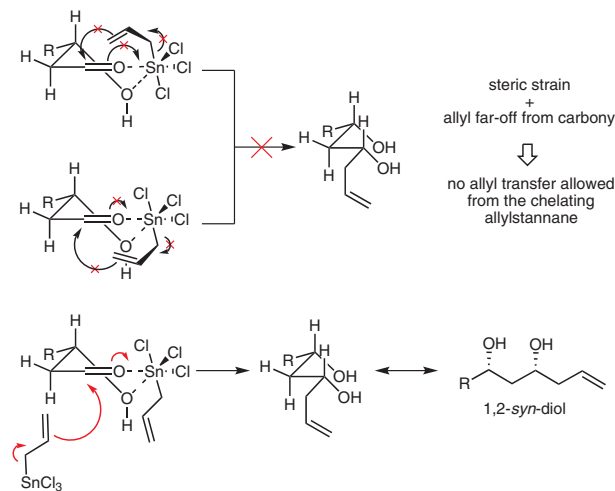
Scheme 2

mol%), SnCl₄ (3.8 mol%), Na₂CO₃, 4 Å MS, toluene (1.3 M), -78 °C].

At this stage of the synthesis, as we had dedicated ourselves to limit catalyst use, a highly diastereoselective allylation was needed to take advantage of the stereogenic center at C7 to control the configuration at C5. Thus, after the one-step oxidative cleavage of the terminal double bond of **2** (OsO₄, 2,6-lutidine, NaIO₄, dioxane-H₂O), the crude corresponding β-hydroxyaldehyde produced was directly treated with a premixed solution of trimethylallylsilane and tin(IV) chloride in dichloromethane at -78 °C and gave the desired homoallylic alcohol **3** in good overall yield (80%, 2 steps) and with excellent diastereoselectivity (dr >97:3) in favor of the *syn*-isomer. The stereochemical assignment was achieved by examination of the ¹H and ¹³C NMR spectra of ketal **4**, obtained from **3** by treatment with 2,2-dimethoxypropane in the presence of pyridinium 4-toluenesulfonate (0.1 equiv) in dichloromethane at room temperature (96% yield). In fact, the stereochemistry of *syn*- and *anti*-1,3-diol acetonides can be assigned from the ¹³C chemical shifts of the acetal methyl groups and from the ¹³C chemical shifts of the acetal carbon. In general, the *syn*-1,3-diol acetonides have diastereotopic acetal methyls shifts at δ = 19 and 30 and the acetal carbon shift at δ = 98.5, while the *anti*-acetonides have enantiotopic acetal methyl shifts at δ = 25 and the acetal carbon shift at δ = 100.5.¹¹

The formation of a *syn*-1,3-diol from unprotected β-hydroxyaldehydes/ketones⁹ suggested that, during the allyltrichlorostannation, tin is chelated to both the free hydroxy group and the aldehyde leading to a 'chair-like' six-membered cyclic transition state (Scheme 3).¹² However, in our case, due to steric strain and the fact that the

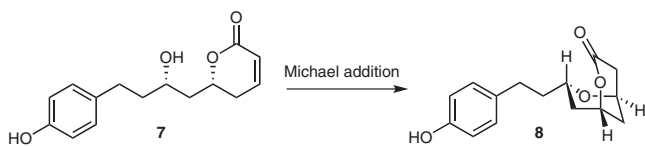
allyl moiety is too far off from the electrophilic carbonyl, we cannot reasonably consider an intramolecular allyl transfer originating from the chelating allyltrichlorostannane. The formation of the *syn*-1,3-diol can only be explained by the attack of a second allyltrichlorostannane on the less hindered face of the carbonyl. This is, in our opinion, the most plausible explanation to account for the formation of the *syn*-1,3-diol. Unlike alkyltin species (e.g., Bu₃SnR), the stannane derivatives issued from the allyltrichlorostannane are water soluble and can be easily removed by a simple methanol/aqueous work-up leading to tin-free *syn*-1,3-diols. The fact that no fluoride ions (TBAF, HF, or KF)¹³ are required in the work-up procedure allows the presence of silyl protecting groups on the substrates. Besides, unlike allylsilylations that often require polar solvents like *N,N*-dimethylformamide, these



Scheme 3

allyltrichlorostannations are performed in nonpolar solvents (such as CH_2Cl_2) thus simplifying the reaction procedure and the work-up.

With the stereogenic centers at C5 and C7 set, the formation of the *Z*-configured unsaturated ester was undertaken. Thus, the double bond of ketal **4** was submitted to an oxidative cleavage (OsO_4 , 2,6-lutidine, NaIO_4 , dioxane- H_2O) to furnish the corresponding aldehyde **5**, which underwent Horner–Wadsworth–Emmons olefination using Still–Gennari fluorinated phosphonoacetate **C** (KHMDS, 18-crown-6, THF, -78°C , 3 h).¹⁰ The *Z*-configured α,β -unsaturated ester **6** was thereby obtained in good yield (51%, 2 steps) and with a *Z/E* ratio of 90:10. Finally, acidic treatment of **6** (80% aq AcOH, 60°C , 1 d) led to an onepot phenol deprotection/ketal removal/lactonization giving pure (+)-dodoneine (**7**) in 68% yield and the bicyclic product **8** (21% yield) likely due to the Michael addition of the C7-hydroxy onto the unsaturated lactone (Scheme 4). The spectral properties of synthetic target **7** and its bicyclic derivative **8** were found similar to those reported in the literature.^{1,3}



Scheme 4

In conclusion, the total asymmetric synthesis of (+)-dodoneine has been realized in seven steps from known aldehyde **1** with an overall yield of 24%. The stereogenic centers were generated via the unique combination of a highly stereoselective allylboration (C7) and a highly diastereoselective allylstannation (C5), while the *Z*-configured lactone was built using a Still–Gennari olefination/intramolecular transesterification sequence. This synthesis proves itself valuable for biological studies and/or scale-up as it limits the use of atom-consuming ligands and avoids the use of expensive catalysts while allowing the formation of appreciable quantities of material as a single isomer and in a timely fashion. Moreover, this synthetic pathway is highly flexible as we can start from readily available substituted cinnamic acids. That will lead to the synthesis of numerous analogues of dodoneine whom potential superior activity will be evaluated through in-depth biological tests. This thorough study will give access to structure–activity relationships, thus allowing the design of potent biological active analogues for therapeutic treatments. This work will be published in due course.

CH_2Cl_2 (stabilized with amylene) was purified by distillation from CaH_2 under N_2 immediately before use. THF and Et_2O were purified by distillation from $\text{Na}/\text{benzoquinone}$ under N_2 . Moisture and O_2 -sensitive reactions were carried out in flame-dried glassware under N_2 . Evaporations were conducted under reduced pressure at temperature below 45°C unless otherwise noted. Column chroma-

tography (CC) were carried out under positive N_2 pressure with 40–63 μm silica gel (Merck) and the indicated solvents. Mp: uncorrected. ^1H Spectra of samples in the indicated solvent were recorded at 300 MHz on a MercuryPlus 300 Varian instrument [^1H NMR residual solvent signals: CDCl_3 $\delta = 7.26$; CD_3OD $\delta = 3.31$; acetone- d_6 $\delta = 2.05$]. ^{13}C NMR spectra of samples in the indicated solvent were recorded at 75 MHz on a Varian instrument [^{13}C NMR residual solvent signals: CDCl_3 $\delta = 77.26$; CD_3OD $\delta = 49.00$; acetone- d_6 $\delta = 29.84$]. ^{13}C multiplicities were determined by DEPT₁₃₅ experiments. Assignments are given relatively to Figure 1 labeling. IR analyzes were performed on a Nicolet Avatar 320 FT-IR. Optical rotations were measured on a Bellingham+ ADP410 from Stanley. Electron impact (EI), and LR-MS and HRMS analyses were obtained from the mass spectrometry service of the ICSN-CNRS, Gif-sur-Yvette, Versailles, France. Chemicals were bought from Sigma-Aldrich and Acros Organics and used without further purification. All reported yields are uncorrected and refer to purified products.

3-[4-(*tert*-Butyldimethylsilyloxy)phenyl]propionaldehyde (**1**)

To a soln of commercially available ester **A** (8.0 g, 44.4 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) under argon was added TBSCl (7.4 g, 48.9 mmol, 1.1 equiv) followed by imidazole (4.5 g, 66.7 mmol, 1.5 equiv). The mixture was stirred at r.t. overnight. H_2O (100 mL) was then added and the mixture was extracted with Et_2O (2×200 mL) and the combined organic layers were washed with brine and then dried (anhyd MgSO_4), filtered, and concentrated in vacuo to afford the crude product, which was purified by flash chromatography (cyclohexane– EtOAc , 9:1) to provide methyl 3-[4-(*tert*-butyldimethylsilyloxy)phenyl]propanoate (12.9 g, 99%); $R_f = 0.25$ (cyclohexane– EtOAc , 7:3).

IR (neat): 2955, 2931, 2859, 1743, 1611, 1512, 1473, 1258, 1170, 917, 840, 781 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 7.04$ (d, $J = 8.4$ Hz, 2 H, H11), 6.75 (d, $J = 8.4$ Hz, 2 H, H12), 3.65 (s, 3 H, CO_2CH_3), 2.88 (t, $J = 7.5$ Hz, 2 H, H9), 2.57 (d, $J = 7.5$ Hz, 2 H, H8), 0.97 [s, 9 H, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], 0.18 [s, 6 H, $\text{OSi}(\text{CH}_3)_2\text{-Bu}$].

^{13}C NMR (75 MHz, CDCl_3): $\delta = 173.3$ (s, CO_2Me), 154.3 (s, C13), 133.5 (s, C10), 129.4 (d, C11), 120.2 (d, C12), 51.5 (q, CO_2CH_3), 36.5 (t, C8), 30.5 (t, C9), 25.9 [q, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], 18.5 [s, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], -4.2 [q, $\text{OSi}(\text{CH}_3)_2\text{-Bu}$].

HRMS (EI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{NaO}_3\text{Si}$: 317.1549; found: 317.1552.

Silyl ether (5.13 g, 18.0 mmol, 1.0 equiv) was charged into a flame dried 250-mL round-bottom flask. Anhyd toluene (100 mL) was added and the mixture was cooled to -78°C . 1 M DIBAL-H in toluene (18.0 mL, 18 mmol, 1.0 equiv) was added dropwise and the mixture was stirred until completion. The mixture was then quenched with sat. Rochelle's salts (100 mL) and brought to r.t.. The mixture was stirred for 1 h and filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 (2×250 mL) and the combined organic extracts were washed with brine and then dried (anhyd MgSO_4), filtered, and concentrated in vacuo to afford the crude product which was purified by flash chromatography (cyclohexane– EtOAc , 8:2) to provide aldehyde **1**⁵ (4.12 g, 86%); $R_f = 0.54$ (cyclohexane– EtOAc , 6:4).

IR (neat): 3030, 2956, 2931, 2857, 2716, 1726, 1610, 1512, 1263, 1170, 917, 840, 781 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 9.81$ (t, $J = 1.2$ Hz, 1 H, CHO), 7.04 (d, $J = 8.4$ Hz, 2 H, H11), 6.76 (d, $J = 8.4$ Hz, 2 H, H12), 2.89 (t, $J = 7.2$ Hz, 2 H, H9), 2.74 (t, $J = 7.5$ Hz, 2 H, H8), 0.97 [s, 9 H, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], 0.18 [s, 6 H, $\text{OSi}(\text{CH}_3)_2\text{-Bu}$].

^{13}C NMR (75 MHz, CDCl_3): $\delta = 202.0$ (s, CHO), 154.3 (s, C13), 133.2 (s, C10), 129.4 (d, C11), 120.4 (d, C12), 45.7 (t, C8), 27.6 (t,

C9), 25.9 [q, OSiMe₂C(CH₃)₃], 18.4 [s, OSiMe₂C(CH₃)₃], -4.2 [q, OSi(CH₃)₂*t*-Bu].

HRMS (EI): *m/z*[M + Na]⁺ calcd for C₁₅H₂₄NaO₂Si: 287.1443; found: 264.1438.

(*R*)-1-[4-(*tert*-Butyldimethylsiloxy)phenyl]hex-5-en-3-ol (2)⁵

To a flame-dried 50-mL round-bottom flask equipped with a stirrer bar was added (*R,R*)-*p*-F-vivol (**B**, 213 mg, 0.454 mmol, 0.05 equiv), anhyd Na₂CO₃ (74 mg, 0.70 mmol, 0.08 equiv), and 4 Å molecular sieves (50 mg, previously dried under high vacuum at 100 °C and stored in an oven). The flask was capped with a rubber septum and placed under argon followed by the addition of freshly distilled toluene (7.0 mL). The mixture was stirred for 2 min followed by addition of 1.0 M SnCl₄ in CH₂Cl₂ (349 μL, 0.349 mmol, 0.038 equiv). This mixture was stirred at r.t. for 5 min, cooled to -78 °C, and maintained at this temperature for 15 min, which was followed by the addition of allylboronic acid pinacol ester (1.91 mL, 9.98 mmol, 1.10 equiv). This mixture was then stirred for an additional 30 min after which, aldehyde **1** (2.4 g, 9.08 mmol, 1 equiv) was added to the mixture. The mixture was stirred at -78 °C for 12 h after which, 1.5 M DIBAL-H in toluene (10.0 mL) was added to quench any unreacted aldehyde. The mixture stirred at -78 °C for an additional 15 min, after which time 1 M HCl (25 mL) was added. The mixture was then allowed to warm to r.t. and stirred for 30 min. The resulting mixture was extracted with Et₂O (3 × 50 mL) and the combined organic extracts were washed with brine (30 mL), dried (anhyd Na₂SO₄), filtered, and concentrated in vacuo to give an oily residue that was purified by flash chromatography (cyclohexane-EtOAc, 95:5) to provide the requisite homoallylic alcohol product **2** in quantitative yield. The ee of the product was determined by formation of diastereomeric esters by condensation with (*S*)-Mosher acid chloride (97% ee).

[α]_D²⁵ -13.2 (*c* 0.68, CHCl₃) [Lit.⁵ [α]_D²⁵ -11.96 (*c* 1.02, CHCl₃)].

IR (neat): 3367, 2956, 2930, 2859, 1610, 1472, 1259, 917, 780 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.05 (d, *J* = 8.2 Hz, 2 H, H11), 6.76 (d, *J* = 8.2 Hz, 2 H, H12), 5.88–5.77 (m, 1 H, H5), 5.17–5.12 (m, 2 H, H4), 3.64 (tt, *J* = 4.4, 7.6 Hz, 1 H, H7), 2.70–2.78 (m, 1 H, H9), 2.66–2.59 (m, 1 H, H9), 2.35–2.29 (m, 1 H, H6), 2.22–2.15 (m, 1 H, H6), 1.73–1.79 (m, 2 H, H8), 1.65 (s, 1 H, OH), 0.99 [s, 9 H, OSiMe₂C(CH₃)₃], 0.19 (s, 6 H, OSi(CH₃)₂*t*-Bu).

¹³C NMR (100 MHz, CDCl₃): δ = 153.7 (s, C13), 134.7 (s, C10), 134.6 (d, C5), 129.4 (d, C11), 119.9 (d, C12), 118.2 (t, C4), 70.0 (d, C7), 42.0 (t, C6), 38.6 (t, C8), 31.2 (t, C9), 25.7 [q, OSiMe₂C(CH₃)₃], 18.2 [s, OSiMe₂C(CH₃)₃], -4.4 [q, OSi(CH₃)₂*t*-Bu].

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₈H₃₀NaO₂Si: 329.1913; found: 329.1918.

(4-{2-[[(4*S*,6*R*)-6-Allyl-2,2-dimethyl-1,3-dioxan-4-yl]ethoxy]phenoxy}-*tert*-butyldimethylsilane (4)

To a soln of **2** (200 mg, 0.65 mmol, 1 equiv) in dioxane-H₂O (3:1, 5.4 mL:1.8 mL) at r.t. was successively added OsO₄ (0.013 mmol, 0.02 equiv), 2,6-lutidine (0.15 mL, 1.29 mmol, 2 equiv), and NaIO₄ (554.6 mg, 2.59 mmol, 4 equiv). The soln was stirred at r.t. until completion then quenched by addition of H₂O (10 mL) followed by the addition of CH₂Cl₂ (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic layers were dried (anhyd MgSO₄), filtered, and concentrated in vacuo. The crude *b*-hydroxyaldehyde was used directly without further purification.

To a round-bottom flask under argon was added anhyd CH₂Cl₂ (2 mL), SnCl₄ (91 μL, 0.78 mmol, 1 equiv), and allyltrimethylsilane (0.12 mL, 0.78 mmol, 1 equiv) and the mixture was stirred at r.t. for 12 h. The soln was transferred by cannula to a round-bottom flask containing a soln of *b*-hydroxyaldehyde (0.62 mmol, 0.8 equiv) in

anhyd CH₂Cl₂ (2 mL) at -78 °C under argon. The mixture was allowed to stir at this temperature overnight to ensure completion. Workup entailed addition of MeOH (0.16 mL) and sat. aq NH₄Cl soln (0.4 mL) and extraction with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried (anhyd MgSO₄), filtered, and concentrated in vacuo to give the crude diol **3** as a yellow oil; *R*_f = 0.51 (cyclohexane-EtOAc, 5:5).

¹H NMR (300 MHz, CDCl₃): δ = 7.02 (d, *J* = 8.2 Hz, 2 H, H11), 6.74 (d, *J* = 8.2 Hz, 2 H, H12), 5.79 (ddt, *J* = 6.9, 7.2, 13.9 Hz, 1 H, H3), 5.06 (m, 2 H, H1), 3.85–3.70 (m, 2 H, H7, H5), 2.62 (m, 2 H, H9), 2.29 (dt_{app}, *J* = 6.9, 13.8 Hz, 1 H, H4), 2.14 (dt_{app}, *J* = 6.9, 13.8 Hz, 1 H, H4), 1.86–1.57 (m, 2 H, H8), 1.52–1.10 (m, 2 H, H6), 0.98 [s, 9 H, OSiMe₂C(CH₃)₃], 0.18 [s, 6 H, OSi(CH₃)₂*t*-Bu].

¹³C NMR (75 MHz, acetone-*d*₆): δ = 154.4 (s, C13), 136.4 (s, C10) and (d, C3), 130.2 (d, C11), 120.6 (d, C12), 116.9 (t, C2), 71.9 (d, C5), 71.5 (d, C7), 43.8 (t, C4), 43.5 (t, C8), 41.0 (t, C6), 31.6 (t, C9), 26.1 [q, OSiMe₂C(CH₃)₃], 18.8 [s, OSiMe₂C(CH₃)₃], -4.2 [q, OSi(CH₃)₂*t*-Bu].

The crude diol **3** (0.5 mmol, 1 equiv) was dissolved in CH₂Cl₂ (1 mL) at r.t. and 2,2-dimethoxypropane (0.6 mL, 5 mmol, 10 equiv) and PPTS (6.6 mg, 0.05 mmol, 0.1 equiv) were added to the soln. When the reaction was complete, sat. aq NaHCO₃ soln (1 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 6 mL). The combined organic layers were dried (anhyd MgSO₄), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane-EtOAc, 95:5) to afford pure **4** (195.5 mg, 77% yield from **2**, *dr* >97:3); *R*_f = 0.61 (cyclohexane-EtOAc, 9:1).

[α]_D²² -17.0 (*c* 0.1, CHCl₃).

IR (neat): 2930, 2857, 1609, 1507, 1379, 1249, 911, 782 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.02 (d, *J* = 8.2 Hz, 2 H, H11), 6.74 (d, *J* = 8.2 Hz, 2 H, H12), 5.79 (ddt, *J* = 6.6, 7.5, 13.6 Hz, 1 H, H3), 5.06 (m, 2 H, H2), 3.85–3.70 (m, 2 H, H5, H7), 2.62 (m, 2 H, H9), 2.30 (dt_{app}, *J* = 6.6, 13.6 Hz, 1 H, H4), 2.13 (dt_{app}, *J* = 6.6, 13.6 Hz, 1 H, H4), 1.86–1.57 (m, 2 H, H8), 1.52–1.10 (m, 2 H, H6), 1.42 [s, 3 H, OC(CH₃)₂O], 1.40 [s, 3 H, OC(CH₃)₂O], 0.98 [s, 9 H, OSiMe₂C(CH₃)₃], 0.18 [s, 6 H, OSi(CH₃)₂*t*-Bu].

¹³C NMR (75 MHz, CDCl₃): δ = 153.8 (s, C13), 134.9 (s, C10), 134.5 (d, C3), 129.6 (d, C11), 120.0 (d, C12), 117.2 (t, C2), 98.8 [s, OC(CH₃)₂O], 68.9 (d, C5), 68.0 (d, C7), 41.1 (t, C6), 38.3 (t, C4), 36.8 (t, C8), 30.6 (t, C9), 30.5 [q, OC(CH₃)₂O], 26.0 [q, OSiMe₂C(CH₃)₃], 20.1 [q, OC(CH₃)₂O], 18.4 [s, OSiMe₂C(CH₃)₃], -4.2 [q, OSi(CH₃)₂*t*-Bu].

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₂₃H₃₈NaO₃Si: 413.2488; found: 413.2458.

Methyl (*Z*)-4-[(4*R*,6*S*)-6-[4-(*tert*-Butyldimethylsiloxy)phenethyl]-2,2-dimethyl-1,3-dioxan-4-yl]but-2-enoate (6)

To a soln of **4** (100 mg, 0.26 mmol, 1 equiv) in dioxane-H₂O (3:1, 2.1 mL:0.7 mL) at r.t. was successively added OsO₄ (0.005 mmol, 0.02 equiv), 2,6-lutidine (0.06 mL, 0.51 mmol, 2 equiv), and NaIO₄ (219 mg, 1 mmol, 4 equiv). The soln was stirred at r.t. until completion then quenched by addition of H₂O (3 mL) followed by the addition of CH₂Cl₂ (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were dried (anhyd MgSO₄), filtered, and concentrated in vacuo. The crude *b*-hydroxyaldehyde was used directly without further purification.

To a stirred soln of 18-crown-6 (169.2 mg, 0.61 mmol) in anhyd THF (2.6 mL) at -40 °C under argon was added methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (**C**, 195.4 mg, 1.2 mmol) and 0.5 M KHMDS in toluene (1.22 mL, 0.61 mmol), successively. After 15 min, the mixture was cooled to -78 °C and stirred for an additional 30 min. Crude aldehyde **5** (0.26 mmol) in anhyd THF (2.6 mL) was added and the resulting mixture was

stirred at $-78\text{ }^{\circ}\text{C}$ for 4 h. The starting material **5** was completely consumed by TLC analysis, and the reaction was quenched by sat. NaHCO_3 (5 mL) at $-78\text{ }^{\circ}\text{C}$. The cooling bath was removed and then the mixture was extracted with Et_2O ($3 \times 15\text{ mL}$). The combined Et_2O extracts were washed with brine (5 mL), dried (MgSO_4), filtered, and concentrated in vacuo. Flash chromatography (cyclohexane– EtOAc , 7:3) afforded the desired ester **6** (59.5 mg, 51% isolated yield from **4**); $R_f = 0.67$ (cyclohexane– EtOAc , 5:5).

$[\alpha]_{\text{D}}^{20} -44.2$ (c 0.1, acetone).

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.02$ (d, $J = 8.2\text{ Hz}$, 2 H, H11), 6.74 (d, $J = 8.2\text{ Hz}$, 2 H, H12), 6.36 (dd, $J = 11.4, 7.5\text{ Hz}$, 1 H, H2), 5.85 (dt, $J = 11.4, 1.6\text{ Hz}$, 1 H, H3), 3.90–3.59 (m, 2 H, H5, H7), 3.77 (s, 3 H, CO_2CH_3), 2.95–2.64 (m, 4 H, H9, H4), 1.82–1.10 (m, 4 H, H8, H6), 1.42 [s, 3 H, $\text{OC}(\text{CH}_3)_2\text{O}$], 1.40 [s, 3 H, $\text{OC}(\text{CH}_3)_2\text{O}$], 0.98 [s, 9 H, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], 0.18 [s, 6 H, $\text{OSi}(\text{CH}_3)_2\text{t-Bu}$].

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 166.5$ (s, C1), 153.6 (s, C13), 145.6 (d, C3), 134.9 (s, C10), 122.9 (d, C2), 129.6 (d, C11), 119.7 (d, C12), 98.8 [s, $\text{OC}(\text{CH}_3)_2\text{O}$], 68.7 (d, C5), 68.0 (d, C7), 41.1 (t, C6), 38.3 (t, C4), 36.9 (t, C8), 30.5 (t, C9), 30.5 [q, $\text{OC}(\text{CH}_3)_2\text{O}$], 26.0 [q, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], 20.1 [q, $\text{OC}(\text{CH}_3)_2\text{O}$], 18.4 [s, $\text{OSiMe}_2\text{C}(\text{CH}_3)_3$], -4.3 (q, $\text{OSi}(\text{CH}_3)_2\text{t-Bu}$).

HRMS (EI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{25}\text{H}_{40}\text{NaO}_5\text{Si}$: 471.2543; found: 471.2539.

(+)-Dodoneine (7)

Compound **6** (51 mg, 0.11 mmol, 1 equiv) was dissolved in 80% AcOH (0.5 mL) and stirred at $60\text{ }^{\circ}\text{C}$ for 24 h. The reaction was quenched with sat. aq. NaHCO_3 and extracted with EtOAc ($3 \times 5\text{ mL}$). The organic layer was washed with brine and dried (anhydrous MgSO_4). After filtration of the mixture and concentration in vacuo, the crude product was purified by flash chromatography (cyclohexane– EtOAc , 3:7) and afforded (+)-dodoneine (**7**, 19.6 mg, 68% isolated yield) and its bicyclic derivative **8** (6.0 mg, 21% yield).

Compound 7

$R_f = 0.36$ (cyclohexane– EtOAc , 1:9).

$[\alpha]_{\text{D}}^{25} +42.2$ (c 0.2, CHCl_3) [Lit.⁵ $[\alpha]_{\text{D}}^{25} +41.03$ (c 1.37, CHCl_3)].

IR (neat): 3360, 3018, 2926, 2858, 1703, 1614, 1515, 1393, 1264, 1061, 1037, 815, 756 cm^{-1} .

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.04$ (d, $J = 8.2\text{ Hz}$, 2 H, H11), 6.89 (dt, $J = 4.2, 9.7\text{ Hz}$, 1 H, H3), 6.76 (d, $J = 8.2\text{ Hz}$, 2 H, H12), 6.02 (dt, $J = 1.5, 9.6\text{ Hz}$, 1 H, H2), 5.08 (br s, 1 H, OH), 4.65 (qd, $J = 5.1, 7.4\text{ Hz}$, 1 H, H5), 3.88 (tt, $J = 4.7, 7.4\text{ Hz}$, 1 H, H7), 2.74–2.61 (m, 2 H, H9), 2.40–2.37 (m, 2 H, H4), 2.34 (br s, 1 H, OH), 2.01–1.68 (m, 4 H, H6, H8).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 164.2$ (s, C1), 154.1 (s, C13), 145.4 (d, C3), 134.0 (s, C10), 129.7 (d, C11), 121.6 (d, C2), 115.6 (d, C12), 77.3 (d, C5), 68.9 (d, C7), 42.4 (t, C6), 39.7 (t, C8), 31.1 (t, C9), 29.8 (t, C4).

HRMS (ESI): m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{18}\text{NaO}_4$: 285.1103; found: 285.1089.

Compound 8

$R_f = 0.44$ (cyclohexane– EtOAc , 1:9); mp $173\text{--}174\text{ }^{\circ}\text{C}$.

$[\alpha]_{\text{D}}^{25} -33.5$ (c 0.45, CHCl_3).

IR (neat): 3338, 2924, 2856, 1685, 1517, 1451, 1382, 1347, 1230, 1076, 1004, 821, 759 cm^{-1} .

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.02$ (d, $J = 8.2\text{ Hz}$, 2 H, H11), 6.75 (d, $J = 8.2\text{ Hz}$, 2 H, H12), 5.38 (br s, 1 H, OH), 4.92–4.85 (m, 1 H, H5), 4.45–4.32 (m, 1 H, H7), 3.76–3.66 (m, 1 H, H3), 2.83–2.78 (m, 2 H, H9), 2.74–2.63 (m, 1 H, H2), 2.60–2.48 (m, 1 H, H2), 2.05–1.90 (m, 2 H, H4), 1.86–1.53 (m, 4 H, H8, H6).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 170.3$ (s, C1), 154.1 (s, C13), 133.6 (s, C10), 129.5 (d, C11), 115.6 (d, C12), 73.4 (d, C3), 66.1 (d, C7), 65.1 (d, C5), 38.1 (t, C6), 37.2 (t, C4), 36.7 (t, C8), 30.8 (t, C2), 30.1 (t, C9).

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4$: 263.1277; found: 263.1278.

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References

- Quedraogo, M.; Carreyre, H.; Vanderbrouck, C.; Bescond, J.; Raymond, G.; Guissou, A.; Cognard, C.; Beca, F.; Potreau, D.; Cousson, A.; Marrot, J.; Coustard, J.-M. *J. Nat. Prod.* **2007**, *70*, 2006.
- Àlvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Eur. J. Org. Chem.* **2008**, 4015.
- Srihari, P.; Rajendar, G.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 5590.
- Dittoo, A.; Bellosta, V.; Cossy, J. *Synlett* **2008**, 2459.
- Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.
- Das, B.; Sunnel, K.; Satyalakshmi, G.; Nandan Kumar, D. *Tetrahedron: Asymmetry* **2009**, *20*, 1536.
- Sabitha, G.; Bhaskar, V.; Reddy, S. S.; Yadav, J. S. *Synthesis* **2009**, 3285.
- (a) Allais, F.; Martinet, S.; Ducrot, P.-H. *Synthesis* **2009**, 3571. (b) Quentin, M.; Allasia, V.; Pegard, A.; Allais, F.; Ducrot, P.-H.; Favery, B.; Levis, C.; Martinet, S.; Masur, C.; Ponchet, M.; Roby, D.; Schlaich, N.-L.; Jouanin, L.; Keller, H. *PLoS Pathogens* **2009**, *5* (1), doi:10.1371/journal.ppat.1000264.
- (a) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655. (b) Allais, F.; Louvel, M.-C.; Cossy, J. *Synlett* **2007**, 451. (c) Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864. (d) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461.
- Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
- (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9. (b) Rychnovsky, S. D.; Rogers, B. N.; Guang, Y. O. *J. Org. Chem.* **1993**, *58*, 3511.
- McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, 322.
- Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442.