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Stereoselective Synthesis of the Naturally Occurring 2-Pyranone Dodoneine

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The first total synthesis of the naturally occurring dihydropyranone dodoneine is reported. Asymmetric allylation reactions were used for the stereoselective generation of the two stereogenic centers. The pyranone ring was created by ring-closing metathesis.

Introduction

Dodoneine is a compound belonging to the ample group of naturally occurring 5,6-dihydropyran-2-ones, a compound class whose members exhibit many different biological activities. They have been shown, for example, to be cytotoxic, HIV protease inhibitors, apoptosis inductors, and antileukemic agents. Some of these pharmacological effects have been related to the Michael acceptor properties of the conjugated double bond.[1] Dodoneine was very recently isolated from *Tapinanthus dodoneifolius*, a parasitic plant that grows on the sheanut tree in Burkina Faso (West Africa), and was found to exhibit a vasorelaxant effect on preconstricted rat aortic rings.[2] Its structure was assigned as **1** (Figure 1) on the basis of spectroscopic analyses combined with an X-ray diffraction analysis of a crystalline derivative. In the present communication, we report the first synthesis of this natural 2-pyranone.

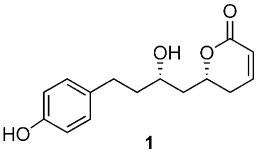
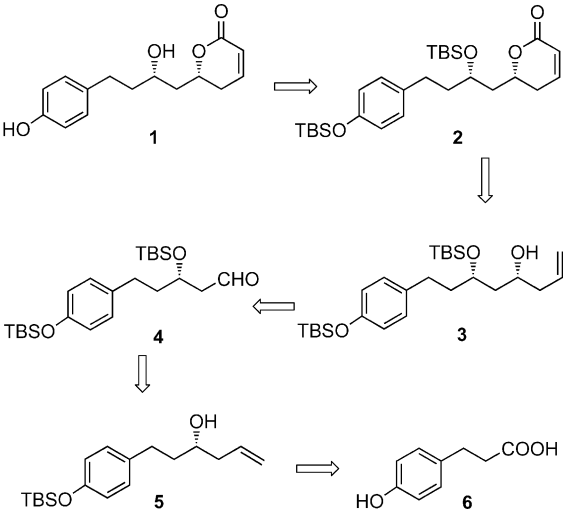


Figure 1. Structure of dodoneine (**1**).

The retrosynthetic scheme for pyranone **1**, based on our previous experience of the syntheses of several members of this compound class,[1] is shown in Scheme 1. Thus, **1** should be available via **2** from homoallyl alcohol **3** through a reaction sequence comprising acylation with acryloyl chloride, olefin metathesis, and deprotection.[3] Likewise, **3** was to be prepared from homoallyl alcohol **5** via aldehyde **4** by alcohol protection, oxidative cleavage of the olefinic bond, and asymmetric allylation. The preparation of **5** from dihydro-*p*-coumaric acid **6** has already been reported.[4,5]



Scheme 1. Retrosynthetic analysis of **1**.

Results and Discussion

Scheme 2 shows the specific details of the synthesis. Homoallyl alcohol **5** (ca. 95% *ee*) was prepared from commercial dihydro-*p*-coumaric acid **6** according to previously

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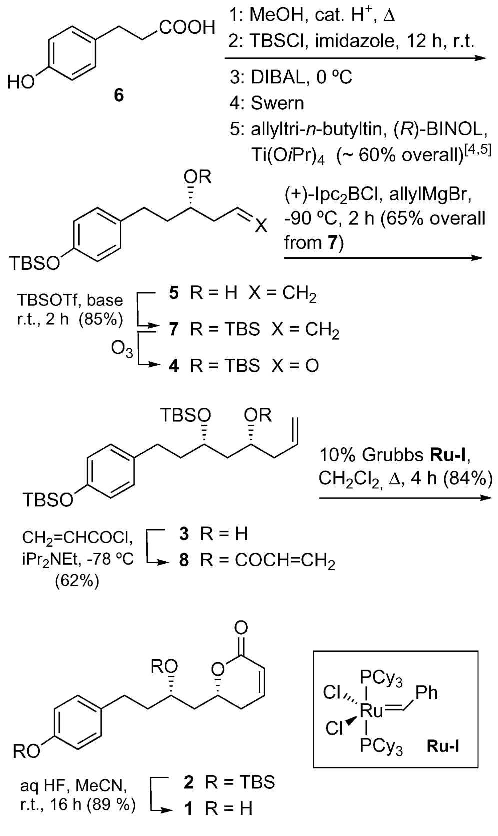
described procedures,[4,5] which included asymmetric Keck allylation[6] of an intermediate silylated dihydro-*p*-coumaraldehyde. We also prepared homoallyl alcohol **5** by Brown's asymmetric allylboration[6b,7] of the same intermediate. However, we could not improve the reported result[5] as the *ee* obtained was only 90%, as determined by chiral HPLC.[8] Silylation of **5** to **7** (TBS = *tert*-butyldimethylsilyl) and ozonolytic cleavage of the olefinic bond in **7** yielded aldehyde **4**, which was then subjected in its crude form to asymmetric allylboration with (+)-Ipc$_2$BCl/allylmagnesium bromide (Ipc = diisopinocampheyl).[7] This provided homoallyl alcohol **3**, which was isolated as a single diastereomer (the minor stereoisomers were lost during chromatographic separation). Sequential acylation of the latter with acryloyl chloride and ring-closing olefin metathesis of the resulting acrylate **8** using Grubbs' first-generation catalyst Ru-I[9] furnished pyranone **2**. Cleavage of the two silyl groups in **2** was achieved with aqueous HF in MeCN to yield a compound with spectroscopic properties coincident with those reported for dodoneine **1**.[2]



Scheme 2. Stereoselective synthesis of **1**.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively, in CDCl$_3$ solution at 25 °C. The signals of the deuteriated solvent CDCl$_3$ were taken as the reference (the singlet at δ = 7.25 for ^{1}H NMR and the triplet centered at δ = 77.00 ppm for ^{13}C NMR). Carbon atom types (C, CH, CH$_2$, CH$_3$) were determined with the DEPT pulse sequence. Mass spectra were recorded using the electron impact (EI-MS, 70 eV) or fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) with a VG AutoSpec mass spectrometer. IR data are given only for compounds with significant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions that required an inert atmosphere were carried out under N$_2$ with flame-dried glassware. Et$_2$O and THF were freshly distilled from sodium/benzophenone ketyl and transferred through a syringe. Dichloromethane was freshly distilled from CaH$_2$. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine followed by extraction with the solvent indicated in parentheses. If the reaction medium was acidic, additional washing with 5% aq. NaHCO$_3$ was performed. If the reaction medium was basic, additional washing with aq. NH$_4$Cl was performed. Further washing with brine, drying with anhydrous Na$_2$SO$_4$, and elimination of the solvent under reduced pressure were followed by chromatography on a silica gel column (60–200 µm) and elution with the indicated solvent mixture. When solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent, and the washings incorporated into the main organic layer.

1-(*tert*-Butyldimethylsilyloxy)-4-[(*R*)-3-(*tert*-butyldimethylsilyloxy)hex-5-enyl]benzene (7): Alcohol **5** (613 mg, 2 mmol) was dissolved under N$_2$ in dry CH$_2$Cl$_2$ (10 mL) and treated sequentially with 2,6-lutidine (350 µL, 3 mmol) and TBSOTf (575 µL, 2.5 mmol). The reaction mixture was then stirred for 2 h at room temp. and worked up (extraction with CH$_2$Cl$_2$). Column chromatography on silica gel (hexanes/EtOAc, 19:1) afforded **7** (715 mg, 85%) as an oil. $[\alpha]_D$ = –2 (c = 1.4, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ = 7.05 (apparent d, J = 8.3 Hz, 2 H), 6.78 (apparent d, J = 8.3 Hz, 2 H), 5.85 (m, 1 H), 5.10–5.00 (m, 2 H), 3.77 (quint., $J \approx$ 6 Hz, 1 H), 2.70–2.60 (m, 1 H), 2.60–2.50 (m, 1 H), 2.30 (m, 2 H), 1.80–1.70 (m, 2 H), 1.00 (s, 9 H), 0.93 (s, 9 H), 0.20 (s, 6 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C): δ = 153.6, 135.3, 18.3, 18.2 (C$_q$), 135.2, 129.2 (2×), 119.9 (2×), 71.6 (CH), 116.8, 41.9, 38.8, 31.0 (CH$_2$), 26.0 (3×), 25.8 (3×), –4.4 (4×) (CH$_3$) ppm. HRMS (EI): m/z (%) = 420.2880 (1) [M]$^+$, 363 (11) [M – tBu]$^+$, 221 (100); calcd. for C$_{24}$H$_{44}$O$_2$Si$_2$: 420.2880.

(4*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-[4-(*tert*-butyldimethylsilyloxy)phenyl]oct-1-en-4-ol (3): Olefin **7** (631 mg, 1.5 mmol) was dissolved in CH$_2$Cl$_2$ (25 mL) and cooled to –78 °C. A stream of ozone-containing air was then bubbled through the solution until complete consumption of the starting material (TLC monitoring). Ozone residues were then eliminated by bubbling through the solution a stream of N$_2$, and the mixture was allowed to reach room temperature, treated with PPh$_3$ (790 mg, ca. 3 mmol) and stirred for 2 h. After solvent removal under reduced pressure, the crude residue was stirred for 10 min in cold pentane (10 mL) and filtered. The solution was then concentrated under reduced pressure and the crude residue containing **4** was used directly in the next step.

Allylmagnesium bromide (commercial 1 M solution in Et$_2$O, 2 mL, 2 mmol) was added dropwise under N$_2$ through a syringe to a cooled solution of (+)-Ipc$_2$BCl (800 mg, ca. 2.5 mmol) in dry Et$_2$O (12 mL; dry ice–acetone bath). After finishing the addition, the dry ice–acetone bath was replaced by an ice bath and the mixture was stirred for 1 h. The solution was allowed to stand, whereby precipitation of magnesium chloride took place. The supernatant solution was carefully transferred to another flask through a cannula. After cooling this flask at –90 °C, a solution of the crude aldehyde **4** from above in dry Et$_2$O (4 mL) was added dropwise through a syringe.

The resulting solution was further stirred at –90 °C for 2 h. The reaction mixture was quenched by the addition of phosphate pH 7 buffer solution (10 mL), MeOH (10 mL), and 30% H_2O_2 (5 mL). After stirring for 30 min, the mixture was poured into saturated aq. $NaHCO_3$ and worked up (extraction with Et_2O). The residue was subjected to careful column chromatography on silica gel (hexanes, then hexanes/EtOAc, 19:1 and 9:1) to afford pure **3** (453 mg, 65% overall from **7**) as an oil. $[\alpha]_D$ = +19.4 (*c* = 1.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.04 (apparent d, *J* = 8.2 Hz, 2 H), 6.77 (apparent d, *J* = 8.2 Hz, 2 H), 5.85 (m, 1 H), 5.15–5.10 (m, 2 H), 3.96 (m, 1 H), 3.83 (m, 1 H), 3.00 (br. s, 1 H, OH), 2.65–2.55 (m, 2 H), 2.25 (t, *J* ≈ 6.5 Hz, 2 H), 1.90–1.60 (br. m, 4 H), 1.00 (s, 9 H), 0.93 (s, 9 H), 0.20 (s, 6 H), 0.10 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 153.7, 134.7, 18.2, 18.0 (C_q), 134.9, 129.1 (2×), 120.0 (2×), 72.2, 70.0 (CH), 117.6, 42.4, 42.2, 39.8, 30.3 (CH_2), 25.9 (3×), 25.7 (3×), –4.1, –4.4 (2×), –4.6 (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 3450 (br., OH) cm^{-1}. HRMS (FAB): calcd. for $C_{26}H_{49}O_3Si_2$, 465.3220; found 465.3236 $[M + H]^+$.

(4*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-[4-(*tert*-butyldimethylsilyloxy)phenyl]oct-1-en-4-yl Acrylate (8): Compound **3** (325 mg, 0.7 mmol) was dissolved under N_2 in dry CH_2Cl_2 (20 mL), cooled to –78 °C and treated sequentially with *N*,*N*-diisopropylethylamine (1.4 mL, 8 mmol) and acryloyl chloride (570 µL, ca. 7 mmol). The reaction mixture was stirred at –78 °C until consumption of the starting material (TLC monitoring). Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 19:1) provided **8** (225 mg, 62%) as an oil. $[\alpha]_D$ = –44.6 (*c* = 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.02 (apparent d, *J* = 8.2 Hz, 2 H), 6.74 (apparent d, *J* = 8.2 Hz, 2 H), 6.38 (d, *J* = 17.3 Hz, 1 H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1 H), 5.80 (d, *J* = 10.4 Hz, 1 H), 5.80–5.70 (br. m, 1 H), 5.15–5.00 (br. m, 3 H), 3.75 (m, 1 H), 2.65–2.50 (br. m, 2 H), 2.45–2.30 (br. m, 2 H), 1.90–1.65 (br. m, 4 H), 0.98 (s, 9 H), 0.91 (s, 9 H), 0.18 (s, 6 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 165.6, 153.6, 134.9, 18.2, 18.1 (C_q), 133.4, 130.4, 129.2 (2×), 119.9 (2×), 71.0, 68.9 (CH), 118.0, 117.3, 41.1, 39.0, 38.7, 30.7 (CH_2), 25.9 (3×), 25.8 (3×), –4.4 (4×) (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 1726 (C=O) cm^{-1}. FAB MS *m*/*z* 519 $[M + H^+]$. HRMS (EI): *m*/*z* (%) = 518.3252 (1) $[M]^+$, 461 (5) $[M - tBu]^+$, 315 (100), 221 (76), 129 (38); calcd. for $C_{29}H_{50}O_4Si_2$: 518.3247.

(6*R*)-{(*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-[4-(*tert*-butyldimethylsilyloxy)phenyl]butyl}-5,6-dihydropyran-2-one (2): Diolefin **8** (130 mg, 0.25 mmol) was dissolved under N_2 in dry, degassed CH_2Cl_2 (25 mL) and treated with Grubbs' catalyst, $[PhCH{=}RuCl_2(PCy_3)_2]$ (20 mg, ca. 0.025 mmol). The mixture was heated at reflux until consumption of the starting material (ca. 4 h). Solvent removal under reduced pressure and column chromatography on silica gel (hexane/EtOAc, 19:1) yielded pyranone **2** (103 mg, 84%) as an oil. $[\alpha]_D$ = +38.2 (*c* = 2.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.04 (apparent d, *J* = 8.3 Hz, 2 H), 6.88 (m, 1 H), 6.75 (apparent d, *J* = 8.3 Hz, 2 H), 6.03 (br. d, *J* = 9.8 Hz, 1 H), 4.60 (m, 1 H), 3.96 (apparent quint., *J* ≈ 6 Hz, 1 H), 2.65–2.55 (m, 2 H), 2.40–2.30 (m, 2 H), 2.15–2.05 (m, 1 H), 1.90–1.70 (br. m, 3 H), 0.99 (s, 9 H), 0.91 (s, 9 H), 0.18 (s, 6 H), 0.08 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 164.3, 153.7, 134.7, 18.2, 18.0 (C_q), 144.8, 129.1 (×2), 121.5, 120.0 (×2), 75.2, 68.2 (CH), 41.9, 38.6, 30.7, 29.9 (CH_2), 25.9 (×3), 25.7 (×3), –4.5 (×4) (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 1732 (C=O) cm^{-1}. HRMS (FAB): calcd. for $C_{27}H_{47}O_4Si_2$ 491.3013; found 491.3025 $[M + H]^+$.

(6*R*)-[(*S*)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one (1): A solution of **2** (49 mg, 0.1 mmol) in acetonitrile (2.5 mL) was treated at room temperature with aqueous HF (125 µL, 48% in water, 30 equiv.). The mixture was stirred for 16 h. After removal of all volatiles under reduced pressure, column chromatography of the residue on silica gel (hexanes/EtOAc, 1:1, then EtOAc) afforded dodoneine (**1**) (23 mg, 89%) as an amorphous solid. $[\alpha]_D$ = +40.2 (*c* = 0.35, $CHCl_3$) {ref.[2] $[\alpha]_D$ = +40.2 (*c* = 0.4, $CHCl_3$)}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.07 (apparent d, *J* = 8.6 Hz, 2 H), 6.88 (dt, *J* = 9.7, 4.5 Hz, 1 H), 6.76 (apparent d, *J* = 8.6 Hz, 2 H), 6.02 (dt, *J* = 9.8, 2 Hz, 1 H), 4.65 (qd, *J* = 7.8, 5.4 Hz, 1 H), 3.89 (tt, *J* ≈ 7.8, 4.4 Hz, 1 H), 2.75–2.65 (br. m, 2 H), 2.40–2.35 (m, 2 H), 2.02 (dt, *J* = 14.5, 8 Hz, 1 H), 1.85–1.75 (br. m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 164.2, 154.1, 133.7 (C_q), 145.4, 129.6 (2×), 121.4, 115.5 (2×), 77.1, 68.8 (CH), 42.2, 39.5, 31.0, 29.7 (CH_2) ppm. IR: $\tilde{\nu}_{max}$ = 3350 (br., OH), 1698 (C=O), 1515 cm^{-1}. HRMS (EI): *m*/*z* (%) = 262.1206 (11) $[M]^+$, 244 (6) $[M - H_2O]^+$, 159 (40), 107 (100); calcd. for $C_{15}H_{18}O_4$: 262.1205.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **7**, and **8**.

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[1] a) For a recent review on the synthesis of naturally occurring representatives of this compound class, see: J. A. Marco, M. Carda, J. Murga, E. Falomir, *Tetrahedron* **2007**, *63*, 2929–2958; b) see also: V. Boucard, G. Broustal, J. M. Campagne, *Eur. J. Org. Chem.* **2007**, 225–236.

[2] M. Ouedraogo, H. Carreyre, C. Vandebrouck, J. Bescond, G. Raymond, I. P. Guissou, C. Cognard, F. Becq, D. Potreau, A. Cousson, J. Marrot, J. M. Coustard, *J. Nat. Prod.* **2007**, *70*, 2006–2009.

[3] Ref.[1a] gives numerous examples of the synthesis of naturally occurring 5,6-dihydropyran-2-ones by this methodology. For a more recent example, see: J. D. Umarye, T. Leßmann, A. B. García, V. Mamane, S. Sommer, H. Waldmann, *Chem. Eur. J.* **2007**, *13*, 3305–3319.

[4] a) The conversion of **6** into silylated dihydro-*p*-coumaraldehyde has been reported earlier albeit without experimental details: G. B. Jones, S. B. Heaton, *Tetrahedron: Asymmetry* **1993**, *4*, 261–272; b) A. S. K. Hashmi, L. Schwarz, J. W. Bats, *J. Prakt. Chem.* **2000**, *342*, 40–51; c) S. Iimura, K. Manabe, S. Kobayashi, *J. Org. Chem.* **2003**, *68*, 8723–8725; d) D. Boschi, G. C. Tron, L. Lazzarato, K. Chegaev, C. Cena, A. Di Stilo, M. Giorgis, M. Bertinaria, R. Fruttero, A. Gasco, *J. Med. Chem.* **2006**, *49*, 2886–2897; e) A. B. Smith III, J. B. Sperry, Q. Han, *J. Org. Chem.* **2007**, *72*, 6891–6900.

[5] Alcohol **5** has been obtained earlier in 95% enantiomeric excess by Keck's asymmetric allylation of the silylated dihydro-*p*-coumaraldehyde: P. A. Evans, J. Cui, S. J. Gharpure, *Org. Lett.* **2003**, *5*, 3883–3885.

[6] For some reviews on the asymmetric allylations of carbonyl compounds, see: a) R. O. Duthaler, A. Hafner, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 43–45; b) P. V. Ramachandran, *Aldrichim. Acta* **2002**, *35*, 23–35; c) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793; d) D. G. Hall, *Synlett* **2007**, 1644–1655.

[7] P. V. Ramachandran, G.-M. Chen, H. C. Brown, *Tetrahedron Lett.* **1997**, *38*, 2417–2420.

[8] P. Álvarez-Bercedo, Ph. D. Thesis, Universitat Jaume I, Castellón, Spain, in preparation.

[9] a) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; b) L. Jafarpour, S. P. Nolan, *Adv. Organomet. Chem.* **2000**, *46*, 181–222; c) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; d) J. A. Love in *Handbook of Metathesis* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, vol. 2, pp. 296–322; e) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; f) for uses of RCM in the synthesis of 5,6-dihydropyran-2-ones see ref.[1a]

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