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 allylations were used for the stereoselective generation of the two stereogenic centers. The pyranone ring was created by means of a ring-closing metathesis.

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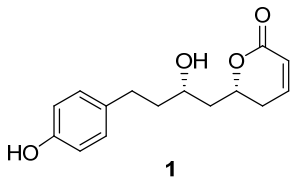
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

Introduction

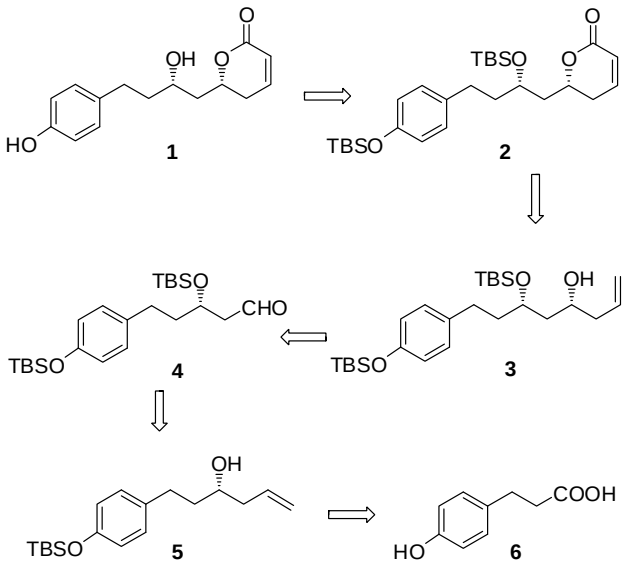
Dodoneine is a compound belonging to the ample group of naturally occurring 5,6-dihydropyran-2-ones, a compound class whose members exhibit many various biological activities. As a matter of fact, they have been shown to be cytotoxic, HIV protease inhibitors, apoptosis inductors, anti-leukemic agents, etc. 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 growing on a sheanut tree in Burkina Faso (West Africa), and was found to exhibit a vasorelaxant efect 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.



1

Figure 1

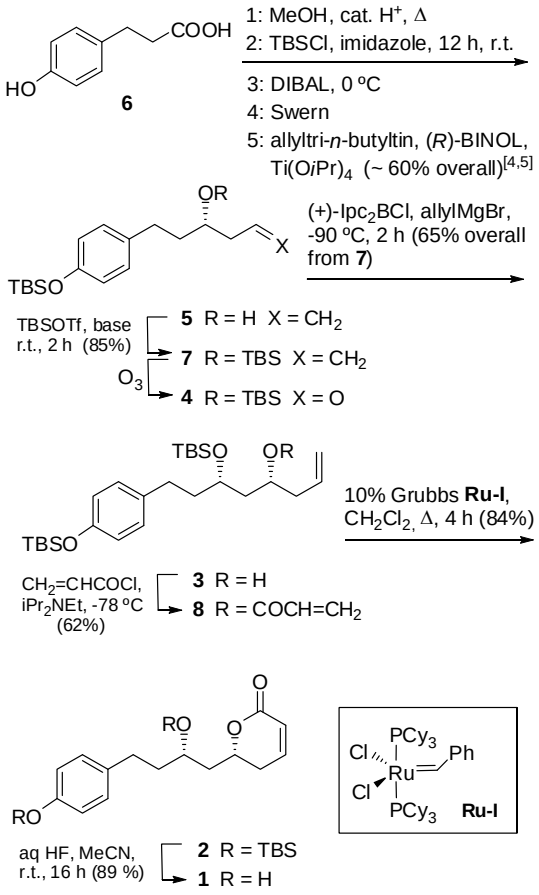
The retrosynthetic plan for pyranone **1**, based on our previous experience with the syntheses of several members of this compound class,[1] is shown in Scheme 1. Thus, **1** should be available via **2** from homoallyl alcohol **3** by means of a reaction sequence comprising acylation with acryloyl chloride, olefin metathesis and deprotection.[3] Likewise, **3** was to be prepared from homoallyl alcohol **5** via aldehyde **4** by means of 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

Results and Discussion

Scheme 2 shows the specific details of the synthesis. Homoallyl alcohol **5** (~ 95% ee) was prepared from commercial dihydro-*p*-coumaric acid **6** according to the described procedures,[4,5] which include an asymmetric Keck allylation[6] of an intermediate silylated dihydro-*p*-coumaraldehyde. We also prepared homoallyl alcohol **5** by means of Brown´s asymmetric allylboration[6b,7] of the same intermediate. However, we could not improve the reported results[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 the latter compound yielded aldehyde **4**, which was then subjected in crude form to an asymmetric allylboration with the (+)-Ipc_2BCl/allyl magnesium bromide reagent (Ipc = di*iso*pinocampheyl).[7] This provided homoallyl alcohol **3**, which was isolated as a single diastereomer (the minor stereoisomers went lost during the 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 by treatment with aqueous HF in MeCN to yield a compound with spectroscopic properties coincident with those reported for dodoneine **1**.[2]



Scheme 2

Experimental Section

General experimental procedures: $^{1}H/^{13}C$ NMR spectra were measured at 500/125 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^{1}H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on 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 which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via 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 parenthesis. If the reaction medium was acidic, an additional washing with 5% aq $NaHCO_3$ was performed. If the reaction medium was basic, an additional washing with aq NH_4Cl was performed. New washing with brine, drying over anhydrous Na_2SO_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. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. Nonstandard acronyms are explained in the caption of Scheme 2.

1-(*tert*-Butyldimethylsilyloxy)-4-[(*R*)-3-(*tert*-butyl-dimethylsilyloxy)-hex-5-enyl]benzene (7): Alcohol **5** (613 mg, 2 mmol) was dissolved under N_2 in dry CH_2Cl_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_2Cl_2). Column chromatography on silica gel (hexanes-EtOAc, 19:1) afforded **7** (715 mg, 85%): 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, 2H), 6.78 (apparent d, *J* = 8.3 Hz, 2H), 5.85 (m, 1H), 5.10-5.00 (m, 2H), 3.77 (quint, *J* ~ 6 Hz, 1H), 2.70-2.60 (m, 1H), 2.60-2.50 (m, 1H), 2.30 (m, 2H), 1.80-1.70 (m, 2H), 1.00 (s, 9H), 0.93 (s, 9H), 0.20 (s, 6H), 0.07 (s, 6H); ^{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); HR EIMS *m/z* (% rel. int.) 420.2880 (M^+, 1), 363 (M^+–*t*Bu, 11), 221 (100). Calcd. for $C_{24}H_{44}O_2Si_2$, 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_2Cl_2 (25 mL) and cooled to −78 ºC. 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 a stream of N_2, and the mixture was allowed to reach room temperature, treated with PPh_3 (790 mg, ~ 3 mmol) and allowed to stir for 2 hours. After solvent removal under reduced pressure, the crude residue was stirred for 10 min. under 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 1M solution in Et_2O, 2 mL, 2 mmol) was added dropwise under N_2 via syringe to a cooled solution of (+)-Ipc_2BCl (800 mg, ~ 2.5 mmol) in dry Et_2O (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 via canula. After cooling this flask at −90 °C, a solution of the crude aldehyde **4** from above in dry Et_2O (4 mL) was added dropwise via syringe. The resulting solution was further stirred at −90 °C for 2 h. The reaction mixture was quenched through 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 onto satd. aq $NaHCO_3$ and worked up (extraction with Et_2O). The residue was subjected to a 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**): oil; $[\alpha]_D$ = +19.4 (*c* = 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.04 (apparent d, *J* = 8.2 Hz, 2H), 6.77 (apparent d, *J* = 8.2 Hz, 2H), 5.85 (m, 1H), 5.15-5.10 (m, 2H), 3.96 (m, 1H), 3.83 (m, 1H), 3.00 (br s, 1H, OH), 2.65-2.55 (m, 2H), 2.25 (t, *J* ~ 6.5 Hz, 2H), 1.90-1.60 (br m, 4H), 1.00 (s, 9H), 0.93 (s, 9H), 0.20 (s, 6H), 0.10 (s, 6H); ^{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); IR ν_{max} 3450 (br, OH) cm^{-1}; HR FAB MS *m/z* 465.3236 ($M+H^+$). Calcd. for $C_{26}H_{49}O_3Si_2$, 465.3220.

(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 ºC and treated sequentially with N,N-di*iso*propyl ethylamine (1.4 mL, 8 mmol) and acryloyl chloride (570 µL, ~ 7 mmol). The reaction mixture was stirred at −78 ºC 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%): oil; $[\alpha]_D$= −44.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.02 (apparent d, *J* = 8.2 Hz, 2H), 6.74 (apparent d, *J* = 8.2 Hz, 2H), 6.38 (d, *J* = 17.3 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 5.80-5.70 (br m, 1H), 5.15-5.00 (br m, 3H), 3.75 (m, 1H), 2.65-2.50 (br m, 2H), 2.45-2.30 (br m, 2H), 1.90-1.65 (br m, 4H), 0.98 (s, 9H), 0.91 (s, 9H), 0.18 (s, 6H), 0.07 (s, 3H), 0.05 (s, 3H); ^{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); IR ν_{max} 1726 (C=O) cm^{-1}; FAB MS *m/z* 519 ($M+H^+$); HR EIMS *m/z* (% rel. int.) 518.3252 (M^+, 1), 461 (M^+−*t*Bu, 5), 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%): oil; $[\alpha]_D$ = +38.2 (*c* = 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.04 (apparent d, *J* = 8.3 Hz, 2H), 6.88 (m, 1H), 6.75 (apparent d, *J* = 8.3 Hz, 2H), 6.03 (br d, *J* = 9.8 Hz, 1H), 4.60 (m, 1H), 3.96 (apparent quint, *J* ~ 6 Hz, 1H), 2.65-2.55 (m, 2H), 2.40-2.30 (m, 2H), 2.15-2.05 (m, 1H), 1.90-1.70 (br m, 3H), 0.99 (s, 9H), 0.91 (s, 9H), 0.18 (s, 6H), 0.08 (s, 3H), 0.05 (s, 3H); ^{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); IR ν_{max} 1732 (C=O) cm^{-1}; HR FAB MS *m/z* 491.3025 ($M+H^+$). Calcd. for $C_{27}H_{47}O_4Si_2$, 491.3013.

(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 hours. 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%): amorphous solid; $[\alpha]_D$ = +40.2 (*c* = 0.35, $CHCl_3$), lit.[2] $[\alpha]_D$ = +40.2 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.07 (apparent d, *J* = 8.6 Hz, 2H), 6.88 (dt, *J* = 9.7, 4.5 Hz, 1H), 6.76 (apparent d, *J* = 8.6 Hz, 2H), 6.02 (dt, *J* = 9.8, 2 Hz, 1H), 4.65 (qd, *J* = 7.8, 5.4 Hz, 1H), 3.89 (tt, *J* ~ 7.8, 4.4 Hz, 1H), 2.75-2.65 (br m, 2H), 2.40-2.35 (m, 2H), 2.02 (dt, *J* = 14.5, 8 Hz, 1H), 1.85-1.75 (br m, 3H); ^{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); IR ν_{max} 3350 (br, OH), 1698 (C=O), 1515 cm^{-1}; HR EIMS *m/z* (% rel. int.) 262.1206 (M^+, 11), 244 (M^+-H_2O, 6), 159 (40), 107 (100). Calcd. for $C_{15}H_{18}O_4$, 262.1205.

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

Acknowledgments

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((Key Topic))

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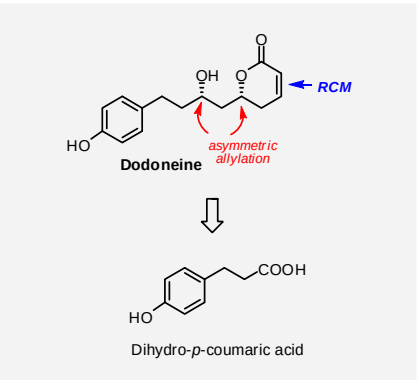

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