Total Synthesis of (+)-Dodoneine

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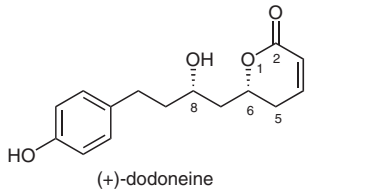
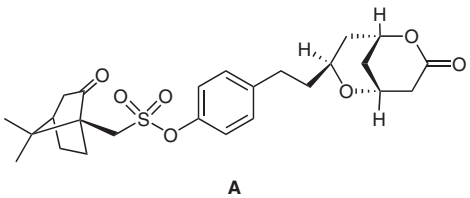
Abstract: An eight-step synthesis of (+)-dodoneine was achieved from methyl 3-(4-hydroxyphenyl)propionate.

Key words: total synthesis, dodoneine, allyltitanation, cross-metathesis, 1,4-addition

Recently, a new dihydropyranone, (+)-dodoneine, was isolated from *Tapinanthus dodoneifolius* which was collected on a sheanut tree in Loumbila (West Africa).[1] The structure of (+)-dodoneine was established through careful NMR and HRMS (ESI) studies. The relative configuration was determined by chemical transformations and NMR studies, and the absolute configuration by X-ray crystallographic analysis of dodoneine derivative **A**. (+)-Dodoneine was identified as a *para*-substituted phenolic ring bearing an alcohol *syn* to the hydroxyl group involved in a substituted 5,6-dihydropyran-2-one moiety[1] (Figure 1). Biological assays of (+)-dodoneine revealed a potent relaxing effect on preconstricted rat aortic rings (IC_{50} = 81.4 ± 0.9 μM).

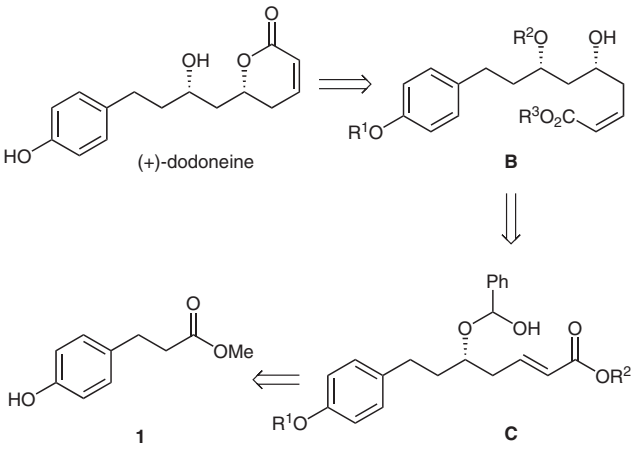
Herein, we would like to report a short and efficient synthesis of (+)-dodoneine. The synthesis was envisioned to begin with the commercially available methyl ester **1**. The construction of the lactone would be elaborated by using a lactonization of the unsaturated hydroxy ester **B**. An enantioselective allyltitanation and an intramolecular diastereoselective 1,4-addition of a hemiacetal of type **C** would install the two stereogenic centers (Scheme 1).





A

Figure 1



Scheme 1

The synthesis of (+)-dodoneine started with the commercially available ester **1**. After protection of the phenol (TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 12 h, 98% yield) followed by a DIBAL-H reduction (toluene, –78 °C, 1 h, 90% yield), the desired aldehyde **2** was obtained. This aldehyde was treated directly with the highly face-selective allyltitanium complex (*S*,*S*)-Ti-**I**[2] (Et_2O, –78 °C, 3 h) to furnish the optically active homoallylic alcohol **3** in 97% yield with an enantiomeric excess superior to 96%.[3] As the introduction and the stereocontrol of the second hydroxyl group was planned to require a 1,4-addition of a hemiacetal onto an unsaturated ester,[4] homoallylic alcohol **3** was transformed to the unsaturated ester **4** by using a cross-metathesis.[5] Thus, when **3** (1 equiv) was treated with ethyl acrylate (3 equiv) in the presence of the Grubbs–Hoveyda second generation catalyst HG-**II**[6] (5 mol%) (CH_2Cl_2, r.t., 2.5 d), the unsaturated ester **4** was isolated in 80% yield. Unsaturated ester **4** was then transformed to the protected 1,3-diol **5** in 68% yield with a *syn*/*anti* ratio of 98:2 after treatment with benzaldehyde under basic conditions (*t*-BuOK, THF, 0 °C, 2 h). At this stage, two additional steps were necessary to obtain the homologated unsaturated ester **8**, precursor of (+)-dodoneine. First, compound **5** was reduced to the corresponding aldehyde **6** (DIBAL-H, toluene, –78 °C, 1.5 h, 94% yield), and this latter compound was involved in a Horner–Wadsworth–Emmons reaction by using the Still–Gennari reagent **7**[7] (KHMDS, 18-C-6, THF, –78 °C, 2 h) to furnish the desired unsaturated ester **8** with a *Z*/*E* ratio of 90:10 and in 70% yield. In order to perform a three-step one-pot reaction to access (+)-dodoneine (deprotection of the phenol, deprotection of the diol and lactonization) compound

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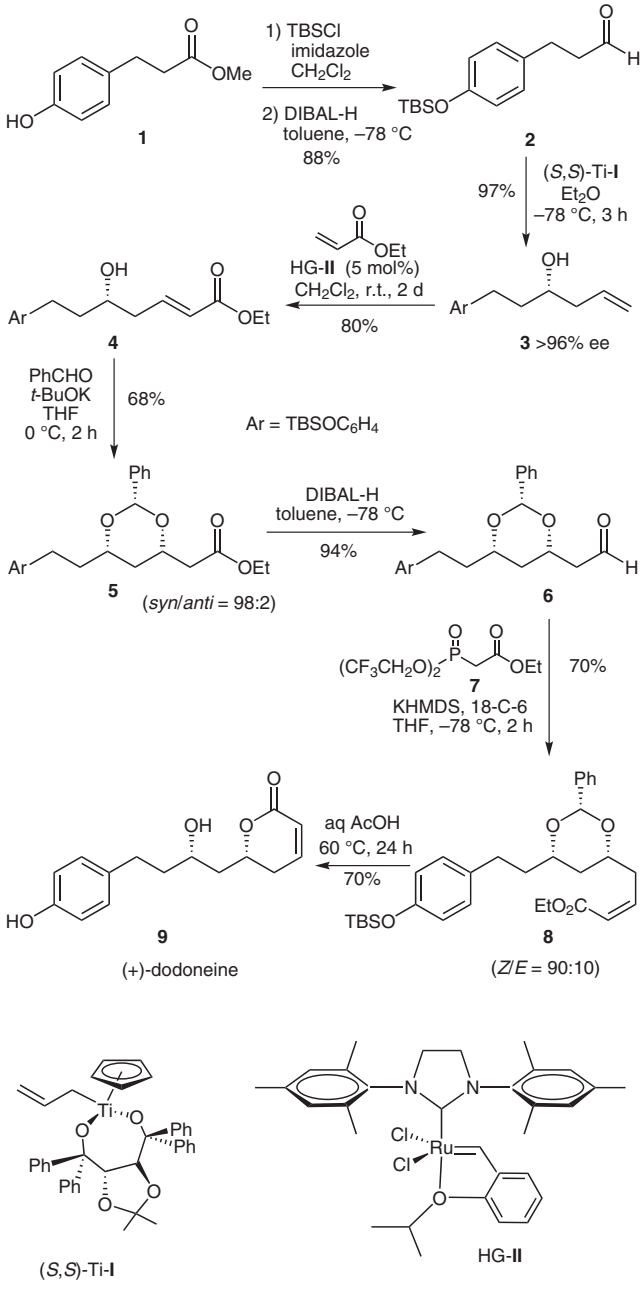
8 was treated under acidic conditions. Thus, when **8** was treated with 80% aqueous AcOH, at 60 °C for 24 hours, (+)-dodoneine **9** was isolated in 70% yield (Scheme 2).[8] Gratifyingly, the ^{1}H and ^{13}C NMR spectra of **9** are in total agreement with those of the natural (+)-dodoneine. The HRMS and optical rotation confirmed that compound **9** is indeed (+)-dodoneine.



Scheme 2

In conclusion, the total synthesis of (+)-dodoneine has been accomplished in eight steps from commercially available ester **1** with an overall yield of 21.4%. The key bond-forming event involves an enantioselective allyltitanation, a 1,4-addition of a hemiacetal to an unsaturated ester, a cross-metathesis reaction, and a Still–Gennari-modified Horner–Wadsworth–Emmons reaction. The route detailed herein is flexible and can be used to synthesize isomers for SAR studies.

Acknowledgment

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References and Notes

(1) Ouedraogo, M.; Carreyre, H.; Vandebrouck, C.; Bescond, J.; Raymond, G.; Guissou, I.-P.; Cognard, C.; Becq, F.; Potreau, D.; Cousson, A.; Marrot, J.; Coustard, J.-M. *J. Nat. Prod.* **2007**, *70*, 2006.

(2) The allyltitanium complex (*S*,*S*)-Ti-**I** was prepared according to: Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(3) The ee of **3** and its *S* absolute configuration were determined by ^{1}H NMR after derivatization with (*S*)- and (*R*)-methoxyphenylacetic acids. See: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (c) Seco, J. M.; Quiñoà, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915.

(4) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

(5) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327.

(6) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(7) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(8) Compound **9**: R_f = 0.23 (PE–EtOAc, 2:8); $[\alpha]_D^{20}$ +48.1 (*c* = 0.34, $CHCl_3$) {Lit.[1] $[\alpha]_D^{20}$ +40.2 (*c* = 0.40, $CHCl_3$)}. IR (neat): 3311, 2920, 1698, 1515 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (app dt, *J* = 8.5, 2.5 Hz, 2 H), 6.88 (app dt, *J* = 9.5, 4.1 Hz, 1 H), 6.76 (app dt, *J* = 8.5, 2.5 Hz, 2 H), 6.02 (dt, *J* = 9.8, 1.9 Hz, 1 H), 5.32 (br s, 1 H), 4.65 (dddd, *J* = 7.7, 7.7, 7.7, 5.3 Hz, 1 H), 3.87 (m, 1 H), 2.67 (m, 2 H), 2.38 (m, 2 H), 2.00 (dt, *J* = 15.7, 8.2 Hz, 1 H), 1.90 (br s, 1 H, OH), 1.79 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (s), 154.3 (s), 145.8 (d), 133.9 (s), 129.8 (2 × d), 121.5 (d), 115.7 (2 × d), 77.4 (d), 69.0(d), 42.4 (t), 39.7 (t), 31.2 (t), 29.8 (t). MS (EI, 70 eV): *m*/*z* (%) = 262 (5), 150 (2), 133 (10), 120 (9), 108 (27), 107 (100), 94 (14), 77 (49), 67 (23), 53 (22). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{18}O_4Na$: 285.10987; found: 285.10973.