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First stereoselective total synthesis of (+)-dodoneine

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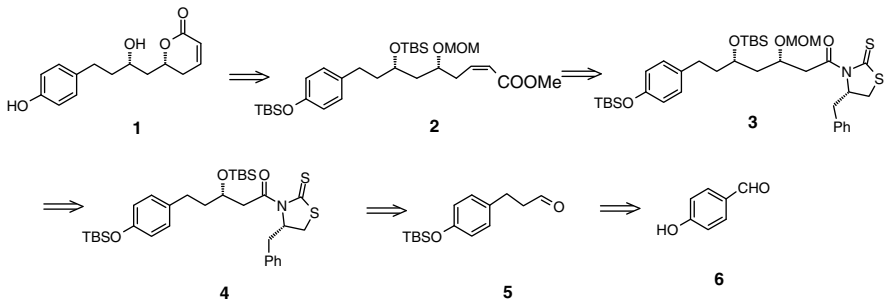
ABSTRACT

The first stereoselective total synthesis of the natural product (+)-dodoneine is described involving a Crimmins aldol reaction and a Horner–Wadsworth–Emmons olefination as the key steps.

α,β-Unsaturated γ- and δ-lactone motif-containing molecules continue to attract the attention of medicinal and organic chemists due to their interesting biological properties.[1] Our own interest in the synthesis of biologically active molecules has led to the total synthesis of several lactone-containing natural products and other analogues.[2] Recently, the dihydropyranone (*R*)-6-[(*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydropyran-2-one **1** was isolated from the methanolic extract of a hemiplant parasite, *Tapinanthus dodoneifolius* DC Danser (known as African mistletoe) found on a sheanut tree in Loumbila, West Africa.[3] *T. dodoneifolius* is known to be used as a remedy to treat cardiovascular and respiratory diseases, and also for cholera, diarrhoea, stomach ache and wounds.[4] The structure of the dihydropyranone **1** was determined from spectroscopic and X-ray crystallographic analysis of the camphorsulfonate derivative of dodoneine. Compound **1** was found to exhibit relaxation effects on preconstricted rat aortic rings with an IC_{50} value of 81.4 ± 0.9 μM.[3] Even though, dodoneine can be extracted in good amounts, to date there is no total synthesis of this molecule. Intrigued by the therapeutic properties associated with *T. dodoneifolius*, in particular by dodoneine, and in continuation of our interest in the total synthesis of biologically active α,β-unsaturated lactone-containing molecules, we chose to synthesize dodoneine. Herein, we report the first total synthesis of (+)-dodoneine.

Retrosynthetic analysis revealed an intermediate **2** which can be synthesized by Horner–Wadsworth–Emmons olefination of the aldehyde obtained by reaction of **3** with DIBAL-H. The two asymmetric centre in compound **3** were realized from double Crimmins aldol reaction starting from the aldehyde **5**, which in turn can be obtained from commercially available 4-hydroxybenzaldehyde (Scheme 1).

Thus, our synthesis started with 2C-Witting homologation of 4-hydroxybenzaldehyde **6** with (carboethoxymethylene)triphenylphosphorane and protection of the resulting product with TBSCl to yield TBS ether **7**. The compound **7** was treated with $LiAlH_4$ and oxidized with PCC to afford aldehyde **5** in 86% overall yield. The aldehyde **5** was treated with (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone[5] in the presence of titanium chloride using the Crimmins protocol[6] to give the easily separable diastereomers of β-hydroxy amide (having the required stereochemistry for the



Scheme 1.

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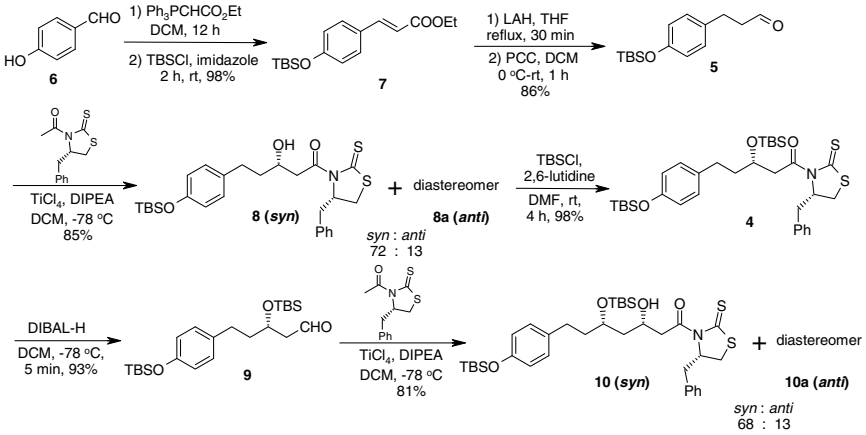
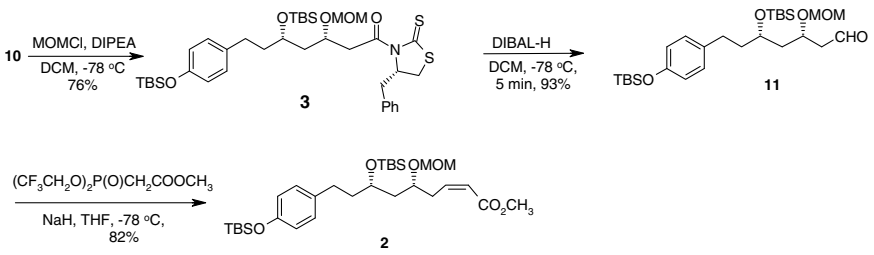
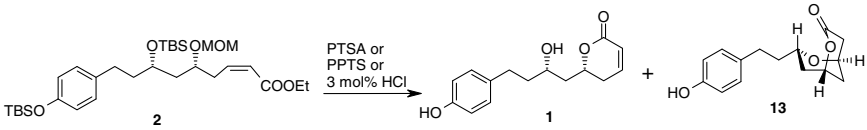


Scheme 2.



Scheme 3.



Scheme 4.

major *syn* product **8** along with the undesired minor *anti* product **8a** (Scheme 2).[7]

The hydroxyl group in **8** was protected to give TBS ether **4**, which was then treated with DIBAL-H to yield aldehyde **9** in 93% yield. The aldehyde **9** was subjected to the Crimmins aldol reaction with (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone following the earlier protocol to afford the easily separable diastereomers **10** and **10a**.

At this stage, based on the prior results of aldol reaction, we proceeded further with the polar major 1,3-diol expecting it to be the required 1,3-*syn* diol. The required geometry was also realized at the later stage by comparing the synthesized target molecule **1** with the natural product. The free hydroxyl group in compound **10** was masked with MOMCl to yield MOM ether **3**. The amide **3** was treated with DIBAL-H to provide aldehyde **11** which was further subjected to a Horner–Wadsworth–Emmons olefination reaction employing bis(2,2,2-trifluoromethyl)(methoxy carbonylmethyl)phosphonate[8] to give the *cis*-olefinic ester **2** (Scheme 3).

With *cis*-olefinic ester **2** in hand, we proceeded further with the one-pot global deprotection of the silyl and MOM groups and simultaneous cyclization of the ester and alcohol functionalities with an acid catalyst to give the target product **1** (Scheme 4). In this end, we started with a catalytic amount of PTSA in methanol and observed the formation of a significant amount of bicyclic lactone **13** which was presumably due to the involvement of the C7-hydroxyl group in the Michael addition reaction.[9] However, after careful investigation (see Table 1) with other acids such as PPTS and 3 mol % HCl solution with respect to time and temperature, we found that 3 mol % HCl solution was the best in terms of yield of the required target. The spectral properties of synthetic target **1**[10] were compared with the natural product and found to be similar.

In conclusion, we have achieved the stereoselective total synthesis of the natural product (+)-dodoneine **1** starting from 4-hydroxybenzaldehyde employing a Horner–Wadsworth–

Table 1

Entry	Acid, solvent, conditions	Yield[b] of **1** + **13** (%)	Ratio of **1**:**13**
1	PTSA, MeOH, 12 h, rt[a]	—	
2	PPTS, MeOH, 12 h, rt[a]	—	
3	PTSA, MeOH, 1 h reflux	80	25/75
4	PPTS, MeOH, 2 h, reflux	85	30/70
5	3 M HCl, THF (1:1), 3 h, rt	70	70/30
6	3 M HCl, THF (1:1), 18 h, rt	70	20/80

[a] Only TBS deprotection was observed even after 12 h.
[b] Isolated combined yield.

Emmons olefination and Crimmins aldol approach as the key steps to obtain the required stereochemistry of the target molecule in twelve steps with an overall yield of 14.7%. Application of this strategy to obtain other isomers for evaluation of their biological properties is currently being investigated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.027.

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7. Based on the polarity difference, we expected the major isomer with high polarity to be the required *syn* product. This product **8** was further characterized by ^{1}H NMR chemical shift signals for the alpha-protons at 3.66 ppm (dd, J = 17.9, 2.3 Hz) for the less shielded proton and at 3.23 ppm (dd, J = 17.9, 9.4 Hz, merged with thioxothiozolidine moiety) for the more shielded proton. The *anti* product **8a** gave chemical shift signals for the alpha-protons at 3.50 ppm (dd, J = 17.7, 9.3 Hz) for the less shielded proton and at 3.30 ppm (dd, J = 17.7, 2.7 Hz) for the more shielded proton. These data were comparable with the known *syn* and *anti* products whose structure was determined by X-ray crystallographic analysis. See Ref. 6b.
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9. The bicyclic lactone obtained was compared with the product obtained by treatment of dodoneine with K_2CO_3 as reported in Ref. 3 and was found to be identical.
10. Spectral data for selected compounds: *(S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-5-(4-tert-butyldimethylsilyloxy)phenyl)-3-hydroxypentan-1-one* (**8**): Yellow oil; $[\alpha]_D^{25}$ +109.2 (*c* 0.60, $CHCl_3$); IR (neat): 3400, 2929, 2856, 1688, 1607, 1508, 1463, 1258, 1163, 1138, 1040, 914, 839, 780, 746, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.97 (s, 9H), 1.70–1.91 (m, 2H), 2.60–2.80 (m, 3H), 2.84 (d, J = 11.3 Hz, 1H), 2.99–3.23 (m, 3H), 3.40 (dd, J = 12.0, 7.5 Hz, 1H), 3.66 (dd, J = 17.9, 2.3 Hz, 1H), 4.09–4.17 (br multiplet, 1H), 5.35–5.42 (m, 1H), 6.75 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 7.26–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.4, 18.1, 25.6, 29.6, 30.9, 31.9, 36.8, 38.0, 40.2, 45.8, 67.1, 68.2, 119.9, 127.2, 128.9, 129.2, 129.4, 134.2, 136.3, 153.6, 173.1, 201.3. *(R)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(4-(tert-butyldimethylsilyloxy)phenyl)-3-hydroxypentan-1-one* (**8a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.97 (s, 9H), 1.67–1.95 (m, 2H), 2.58–2.83 (m, 2H), 2.89 (d, J = 11.7 Hz, 1H), 3.03 (dd, J = 14.2, 11.4 Hz, 1H), 3.21 (dd, J = 13.5, 2.4 Hz, 1H), 3.31 (dd, J = 17.4, 2.7 Hz, 1H), 3.39 (dd, J = 11.4, 7.4 Hz, 1H), 3.50 (dd, J = 17.7, 9.3 Hz, 1H), 3.98–4.11 (m, 1H), 5.34–5.43 (m, 1H), 6.74 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.23–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): −4.2, 18.4, 25.9, 31.0, 32.3, 37.0, 38.5, 45.7, 67.8, 68.4, 120.1, 127.5, 129.1, 129.5, 129.6, 134.5, 136.5, 153.9, 173.9, 201.6. MS-ESIMS: m/z 538 (M+Na)$^+$; HRMS calcd for $C_{27}H_{37}NO_3NaS_2Si$: 538.1889, found 538.1881. *(3S,5S)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(tert-butyldimethylsilyloxy)-7-(4-(tert-butyldimethylsilyloxy)phenyl)-3-hydroxyheptan-1-one* (**10**): Yellow semi-solid; $[\alpha]_D^{25}$ +77.8 (*c* 0.80, $CHCl_3$); IR (neat): 3435, 2926, 2855, 1683, 1609, 1508, 1258, 1164, 1041, 915, 839, 771, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.18 (s, 6H), 0.90 (s, 9H), 0.97 (s, 9H), 1.68–1.90 (m, 4H), 2.58 (t, J = 9.0, 7.5 Hz, 2H), 2.88 (d, J = 12.0 Hz, 1H), 3.04 (dd, J = 12.8, 9.8 Hz, 1H), 3.20-3.30 (m, 3H), 3.39 (dd, J = 12.0, 7.5 Hz, 1H), 3.55 (dd, J = 17.3, 3.0 Hz, 1H), 3.98 (m, 1H), 4.27–4.40 (br multiplet, 1H), 5.35–5.46 (m, 1H), 6.75 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 7.23–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.2, −4.1, −3.9, 1.2, 18.2, 18.4, 25.9, 26.1, 29.9, 30.6, 32.2, 37.0, 39.6,42.9, 46.4, 66.7, 68.5, 71.1, 120.1, 127.4, 129.1, 129.3, 129.6, 135.0, 136.6, 153.8, 172.7, 201.5; MS-ESIMS: m/z 674 (M+H)$^+$; HRMS calcd for $C_{35}H_{56}NO_4S_2Si_2$: 674.31897, found 674.31838. *(+)-Dodoneine or (R)-6-((S)-2-hydroxy-4-(4-hydroxyphenyl)butyl-5,6-dihydropyran-2-one* (**1**): Colorless solid, mp 57–59 °C; $[\alpha]_D^{25}$ +41.2 (*c* 0.35, $CHCl_3$), Lit[3] $[\alpha]_D^{25}$ +40.2 (*c* 0.4, $CHCl_3$); IR (neat): 3417, 2924, 2853, 1715, 1607, 1511, 1461, 1381, 1257, 1217, 915, 837, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.85 (m, 4H), 1.97–2.07 (m, 1H), 2.33–2.42 (br multiplet, 3H), 2.59–2.77 (m, 2H), 3.83–3.93 (br multiplet, 1H), 4.65 (dddd, J = 7.7, 7.7, 7.7, 5.3 Hz, 1H), 5.62-5.80 (br s, 1H, OH), 6.04 (dt, J = 9.8, 1.7 Hz, 1H), 6.78 (dt, J = 8.4, 2.6 Hz, 2H), 6.91 (dt, J = 9.6, 4.5 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 29.6, 31.0, 39.5, 42.2, 68.8, 77.4, 115.5, 121.3, 129.6, 133.6, 145.7, 154.2, 164.5; MS-ESIMS: m/z 285 (M+Na)$^+$; HRMS calcd for $C_{15}H_{18}NaO_4$: 285.10986, found 285.10973. *Bicyclic lactone* (**13**): White solid, mp 173–175 °C; $[\alpha]_D^{25}$ −32.9 (*c* 0.50, $CHCl_3$); IR (neat): 3338, 2924, 2856, 1685, 1517, 1451, 1382, 1347, 1230, 1076, 1004, 821, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53–1.86 (m, 4H), 1.90–2.05 (m, 2H), 2.49–2.59 (m, 1H), 2.64–2.74 (m, 1H), 2.79–2.82 (m, 2H), 3.67–3.76 (m, 1H), 4.38–4.43 (br multiplet, 1H), 4.88–4.93 (br multiplet, 1H), 5.21–5.52 (bs, 1H), 6.75 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 29.9, 30.7, 36.5, 37.1, 38.0, 65.0, 66.0, 73.3, 115.5, 129.5, 133.6, 154.1, 170.3; MS-ESIMS: m/z 263 (M+H)$^+$; HRMS calcd for $C_{15}H_{19}O_4$: 263.12771, found 263.12779.