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A Baylis–Hillman/ozonolysis route towards (±) 4,5-dihydroxy-2,3-pentanedione (DPD) and analogues

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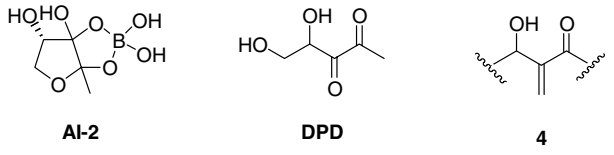
Abstract—The Baylis–Hillman reaction between 2-(*tert*-butyldimethylsilyloxy)ethanal and 3-buten-2-one followed by desilylation gave rise to the corresponding α-methylene-β,γ-dihydroxy ketone further converted by reductive ozonolysis of the carbon–carbon double bond into racemic 4,5-dihydroxy-2,3-pentanedione (**DPD**), a significant molecule in bacterial cell–cell communication systems. The same sequence applied to other substrates allowed the preparation of chain elongated analogues and 5-*O*-acylated derivatives of **DPD**.

Many bacterial species are able to sense their own population size through a cell–cell communication system, named quorum sensing (QS), based on the production and exchange of diffusible extracellular signaling molecules called autoinducers.[1] Since a link between this process and virulence factor production[2] or biofilms formation[3] has been established for a number of pathogenic bacteria, the design of QS inhibitors has recently attracted considerable interest for the development of anti-infection therapies.[4] Among the various autoinducers which have been identified so far, a borate, known as autoinducer-2 (**AI-2**), formed from the metabolic product (*S*) 4,5-dihydroxy-2,3-pentanedione (**DPD**) (Scheme 1), is produced by a large number of both Gram-negative and Gram-positive bacteria.[5]

As part of a programme aimed at obtaining QS inhibitors,[6,7] we recently became interested in designing a new access to **DPD** and analogues. Despite its very simple structure, the synthesis of **DPD** is not an easy task owing, in particular, to its instability at high concentrations.[8] At the time we initiated this work, only two syntheses of the (*S*) enantiomer had been reported in the literature, both involving the oxidation of a triple bond to generate the α-diketone function.[9,10] We imagined an alternative approach in which the α-diketo-β-hydroxy moiety in **DPD** would be generated by the reductive ozonolysis of the carbon–carbon double bond in α-methylene-β-hydroxy ketones of type **4** resulting from a Baylis–Hillman reaction.



AI-2 **DPD** **4**

Scheme 1.

Thus, using dimethyl sulfide as the reducing agent, the byproducts formed during the last step will be formaldehyde and dimethylsulfoxide. The latter compounds being reputed non-toxic, at least at low concentrations, the purification of **DPD** or analogues would become unnecessary before biological assays. In addition, asymmetric Baylis–Hillman reaction being well documented,[11] the preparation of non-racemic compounds could be considered. The very recent report of Vanderleyden and co-workers[12] describing a synthesis of (*S*)-**DPD** by reductive ozonolysis of (*S*)-1,2-dihydroxy-4-methyl-4-penten-3-one (Scheme 2) prompts us to report our preliminary results.

When carried out in THF at 0 °C,[13] the Baylis–Hillman reaction between 2-(*tert*-butyldimethylsilyloxy) ethanal **1a**[14] and 3-buten-2-one **2a** (4 equiv) in the presence of DABCO (0.25 equiv) was completed in 21 h and

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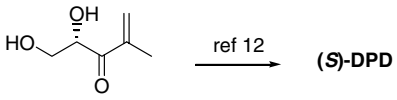


Scheme 2.

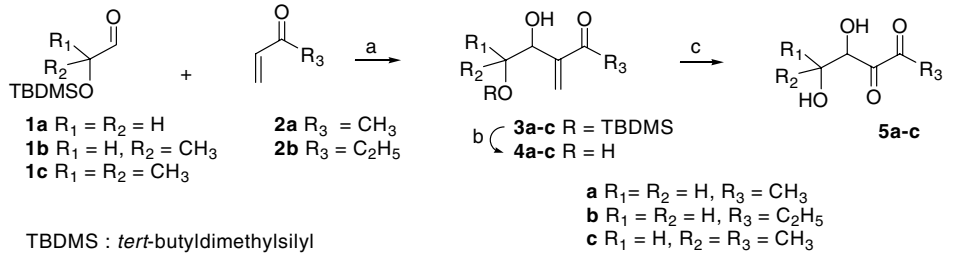
afforded the expected enone **3a** in 74% yield (Scheme 3 and Table 1). Removal of the silyl protecting group led to the corresponding diol **4a** which was subjected to ozonolysis. When conducted on a diluted (≈10 mM) CD_3OD solution,[15] the reaction gave rise to **5a** (**DPD**).

As already reported,[9,10,12] the ^1H NMR spectrum of **DPD** is rather complicated due to the presence of three isomers in equilibrium: the open diketone, and its two cyclic anomers **6** and **7**, in about a 0.5:1:1 ratio.[16] In order to get structure verification, this mixture was submitted to the action of 1,2-phenylene-diamine (3 equiv)[9,10,12] and we observed that it was totally converted into the quinoxaline **8a** (Scheme 4).[17,18]

We then extended this approach to the preparation of some chain elongated analogues of **DPD** by varying the nature of both the vinyl ketone and the silyloxyaldehyde. A similar sequence was carried out from aldehyde **1a** and 4-penten-3-one **2b** (Scheme 3 and Table 1) to give diketone **5b**. The Baylis–Hillman reaction of α-methyl substituted aldehyde **1b** with **2a** gave **3c** as a mixture (≈ 65:35) of *anti*/*syn* diastereoisomers,[19] which were incompletely separated by column chromatography. The deprotection step was carried out on each pure stereoisomer to give the corresponding *anti* or *syn* diol **4c**,[20] which were submitted to ozonolysis and led to expected dicarbonyl compounds **5c**.[21] As seen above in the case of **5a**, when **5b** and **5c** were reacted with excess 1,2-phenylene-diamine, they were quantitatively transformed into the corresponding quinoxaline **8b** and **8c**.[22] Conversely, when carried out from α-dimethyl substituted aldehydes **1c**[23] and **2a**, the Baylis–Hillman reaction did not take place.[24]

The method was also successfully applied for the preparation of derivatives bearing 5-OH enzymolabile masking groups, which could be used as in vivo precursors of **DPD**. Thus, the Baylis–Hillman reaction between acetoxyacetaldehyde **9a**[13] or pivaloxyacetaldehyde **9b**[25] and **2a** led to the corresponding adducts **10a** and **10b** in very good yields.[26] Further, ozonolysis gave the diketonic compounds **11a** and **11b** (Scheme 5).[27]

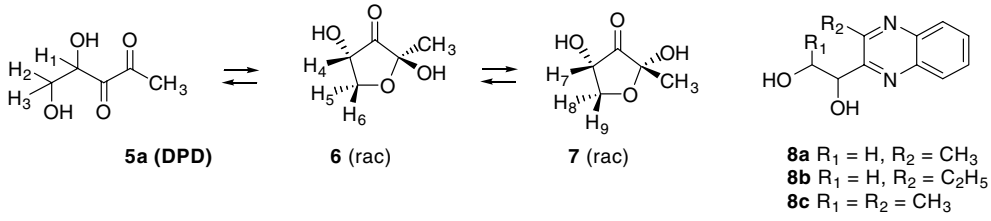
In conclusion, we developed a short reaction sequence leading to racemic **DPD**. The sequence was successfully applied for the preparation of elongated chain analogues or 5-*O*-acylated derivatives. We are presently exploring the possibilities of our method to obtain more elaborated analogues of **DPD** as well as non-racemic compounds.



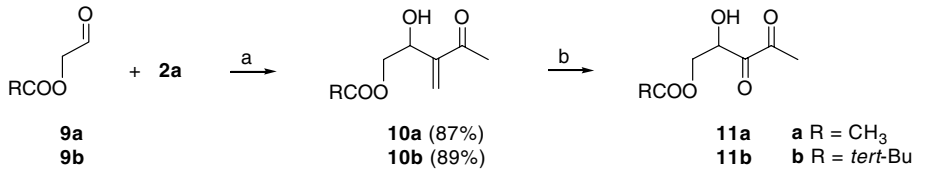
Scheme 3. Synthetic sequence to compounds **5**. Reagents and conditions: (a) THF, DABCO (0.25 equiv), 0 °C. (b) TBAF (1 equiv), THF, rt. (c) O_3, MeOH, −78 °C, then DMS, −78 °C to rt.

Table 1.

Aldehyde	Vinyl-ketone	Baylis–Hillman adduct	Reaction time (h)	Yield (%)	Deprotected product	Yield (%)
1a	**2a**	**3a**	21	74	**4a**	78
1a	**2b**	**3b**	30	80	**4b**	90
1b	**2a**	**3c** (*anti*/*syn* 65:35)	24	70	**4c** *anti*	71
					4c *syn*	78



Scheme 4. Structures of **DPD**, its two cyclic anomers **6** and **7**, and quinoxalines **8**.



Scheme 5. Synthetic sequence to compounds **11**. Reagents and conditions: (a) THF, DABCO (0.25 equiv), 0 °C, 20 h. (b) O_3, MeOH, −78 °C, then DMS, −78 °C to rt.

Acknowledgements

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15. A solution of **4a** (8 mg, 62 μmol) in CD_3OD (6 mL) was cooled to −78 °C and ozone was bubbled through the solution. The reaction mixture first turned light yellow and after about 30 min, became light green. At this time, the solution was purged with oxygen until the green colour disappeared and Me_2S (45 μL, 10 equiv) was added. The mixture was then allowed to warm at rt and stirred for 16 h. To 1 mL of the colourless reaction mixture, D_2O (1 mL) was added and the resulting solution was concentrated under vacuum to a residual volume of about 1 mL.
16. ^{1}H NMR (500 MHz, D_2O). **5a** (20%) + **6** (40%) + **7** (40%). δ 4.35 (dd, $J = 6.9$, $J = 5.7$ Hz, H-4), 4.16 (m, 2H, H-5, H-8), 4.03 (dd, $J = 6.0$, $J = 3.5$ Hz, H-7), 3.95 (dd, $J = 7.4$, $J = 3.5$ Hz, H-1), 3.80 (m, 2H, H-3, H-9), 3.63 (dd, $J = 11.9$, $J = 7.4$ Hz, H-2) 3.56 (dd, $J = 9.4$, $J = 5.7$ Hz, H-6), 2.35 (s, CH_3), 1.42 (s, CH_3), 1.39 (s, CH_3). Assignments are based on published data and 2D-COSY experiments.
17. ^{1}H NMR (300 MHz, D_2O). **8a** δ 8.04 (m, 1H), 7.92 (m, 1H), 7.80 (m, 2H), 5.30 (dd, $J = 6.7$, $J = 4.5$ Hz, 1H), 3.99 (dd, $J = 12$, $J = 4.5$ Hz 1H), 3.90 (dd, $J = 12$, $J = 6.7$ Hz, 1H), 2.77 (s, 3H) in agreement with published data.
18. Minor signals were observed in the ^{1}H NMR spectra of **DPD** (three singulets in the 2.0–2.2 ppm area and a multiplet at 3.95 ppm) and of **8a** (multiplet at 7.49 and 7.70 ppm).
19. The *anti* stereochemistry was temporarily assigned to the major isomer by analogy with the results reported in the literature for Baylis–Hillman reactions between α-alkoxyaldehydes and vinyl ketones or esters: Drewes, S. E.; Manickum, T.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1065–1070.
20. In these cases, compounds **4c** are in equilibrium with small amounts (25% for **4c** *anti*, 5% for **4c** *syn*) of isomeric cyclic anomers.
21. ^{1}H NMR (500 MHz, D_2O). **5b** δ 4.38 (dd, $J = 7.3$, $J = 6.0$ Hz, 1H), 4.16 (dd, $J = 10.1$, $J = 6.0$ Hz, 1H), 4.15 (dd, $J = 9.5$, $J = 7.3$ Hz, 1H), 4.02 (dd, $J = 6.0$, $J = 3.2$ Hz, 1H), 3.94 (dd, $J = 7.3$, $J = 4.0$ Hz, 1H), 3.79 (dd, $J = 10.1$, $J = 3.2$ Hz, 1H), 3.77 (dd, $J = 12.0$, $J = 4.0$ Hz, 1H), 3.62 (dd, $J = 12.0$, $J = 7.3$ Hz, 1H), 3.53 (dd, $J = 9.5$, $J = 6.0$ Hz, 1H) 2.77 (m, 2H), 1.75 (m, 4H), 1.03 (t, $J = 7.1$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H), 0.97 (t, $J = 7.5$ Hz, 3H). (300 MHz, D_2O) **5c** *anti* δ 3.97 (m, 1H), 3.93 (d, $J = 7.9$ Hz, 1H), 3.76 (m, 1H), 3.56 (d, $J = 6.0$ Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H). **5c** *syn* δ 4.37 (m, 1H), 4.30 (m, 1H), 4.05 (d, $J = 5.3$ Hz, 1H), 3.86 (d, $J = 4.5$ Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H).
22. ^{1}H NMR (300 MHz, D_2O). **8b** δ 8.06 (m, 1H), 7.98 (m, 1H), 7.83 (m, 2H), 5.33 (dd, $J = 6.8$, $J = 4.9$ Hz, 1H), 3.99 (dd, $J = 11.7$, $J = 4.9$ Hz, 1H), 3.93 (dd, $J = 11.7$, $J = 6.8$ Hz, 1H), 3.11 (m, 2H), 1.36 (t, $J = 7.5$ Hz, 3H). **8c** *anti* δ 8.10 (m, 1H), 7.98 (m, 1H), 7.83 (m, 2H), 5.06 (d, $J = 6.8$ Hz, 1H), 4.26 (m, 1H), 2.81 (s, 3H), 1.33 (d, $J = 6.4$ Hz, 3H). **8c** *syn* δ 8.05 (m, 1H), 7.95 (m, 1H), 7.83 (m, 2H), 5.04 (d, $J = 5.7$ Hz, 1H), 4.32 (m, 1H), 2.78 (s, 3H), 1.19 (d, $J = 6.4$ Hz, 3H).
23. The aldehydes **1b** and **1c** were prepared by the reductive ozonolysis of known *tert*-butyldimethylsilyl protected 3-buten-2-ol and 2-methyl-3-buten-2-ol, respectively.
24. The starting aldehyde **1c** was recovered unchanged after 30 h of stirring at 0 °C. This failure was probably due to the sterically hindered carbonyl function of the neopentylic type aldehyde **1c**.

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26. Compounds **4a**–**c** and **10a**,**b** gave ^{1}H, ^{13}C NMR and HRMS data in agreement with the proposed structures. Data for **4b** and **10a** are given as examples. **4b** ^{1}H NMR (300 MHz, CD_3OD) δ 6.29 (s, 1H), 6.14 (d, $J = 1.1$ Hz, 1H), 4.63 (m, 1H), 3.60 (dd, $J = 3.8$, 11.3 Hz, 1H), 3.36 (dd, $J = 6.8$, 11.3 Hz, 1H), 2.78 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 203.95, 149.60, 125.86, 71.31, 66.93, 32.16, 8.56; HRMS-CI MH^+ calcd for $C_7H_{13}O_3$: 145.0865; found: 145.0866. **10a** H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.18 (d, $J = 1.1$ Hz, 1H), 4.75 (m, 1H), 4.24 (dd, $J = 3.4$, 11.3 Hz, 1H), 4.13 (dd, $J = 6.8$, 11.3 Hz, 1H), 3.00 (d, $J = 5.7$ Hz, 1H), 2.35 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.64, 171.42, 146.60, 127.61, 69.33, 67.61, 26.21, 20.86. HRMS-CI MH^+ calcd for $C_8H_{13}O_4$: 173.0736; found: 173.0817.
27. **11a** ^{1}H NMR (300 MHz, D_2O) δ 4.32 (m, 1H), 4.13 (m, 2H), 2.38 (s, 3H), 2.09 (s, 3H); HRMS-CI MH^+ calcd for $C_7H_{11}O_5$: 175.0606; found: 175.0607. **11b** ^{1}H NMR (300 MHz, D_2O) δ 4.33 (m, 1H), 4.12 (m, 2H), 2.37 (s, 3H), 1.19 (s, 9H).