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The formation of novel 1,3-dioxolanes: atypical Baylis–Hillman reaction of a sesquiterpene lactone parthenin

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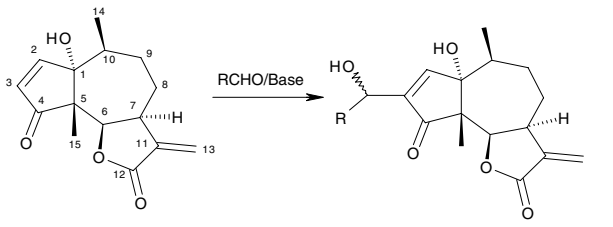
Abstract—The Baylis–Hillman reaction of a sesquiterpene lactone parthenin with various aldehydes gave unexpected products containing a 1,3-dioxolane moiety. Both small aliphatic and aromatic aldehydes produced 1,3-dioxolanes, whereas higher aliphatic aldehydes produced normal Baylis–Hillman products.

The Baylis–Hillman reaction originated from a German Patent[1] in 1972 and is regarded as an important method for carbon–carbon bond formation. During the last three decades, the procedure has been significantly advanced as demonstrated by a number of applications as described in the reviews by Basavaih et al.[2] and Kim and Lee.[3] The Baylis–Hillman reaction essentially involves the coupling of an activated alkene with an electrophile in the presence of a catalyst, to give 2-hydroxyalkyl-enones. It has been applied to cyclic enones as well as noncyclic enones, with aldehydes, using tertiary amines,[4] tertiary phosphines,[5] chalcogenides-$TiCl_4$[6] and $TiCl_4$[7] as catalysts leading to α-functionalization of α,β-unsaturated enones.

Parthenin **1**, the major sesquiterpene lactone of the exotic weed *Parthenium hysterophorus* L. (compositae), has a cyclopentenone ring and an α-methylene-γ-lactone moiety. It has been found to be of interest due to its anticancer,[8] antibacterial,[9] antimalarial[10] and allelopathic properties.[11] It is also reported to be toxic and cause allergic contact dermatitis in humans and animals.[12] During our attempts to modify the structure of parthenin by introducing additional functionalities on the cyclopentenone ring, we explored the Baylis–Hillman reaction. In a normal Baylis–Hillman coupling, an α-functionalized product **1a** would be expected (Scheme 1).

A DBU mediated reaction of parthenin **1** with formaldehyde (30%, 2 equiv) in THF/H_2O (2:1) at room temperature resulted in the formation of three products,[13] which were separated by chromatography and characterized as **2**–**4** on the basis of their spectral data. Compounds **2** (35%) and **3** (22%), identified as abnormal Baylis–Hillman products, were formed in major quantities whereas **4** was isolated as a minor product (13%) (Scheme 2).

In the ^1H NMR spectrum of **2**, the signals for an α,β-unsaturated double bond (δ 7.60 and 6.13, respectively, in parthenin) were absent and two additional proton signals for the dioxolane protons appeared at δ 5.01 and 5.12 (^{13}C NMR signal at δ 94.2). Compound **4**, obtained in low yields, was the anticipated coupling product,



parthenin **1** normal Baylis-Hillman product **1a**

Scheme 1.

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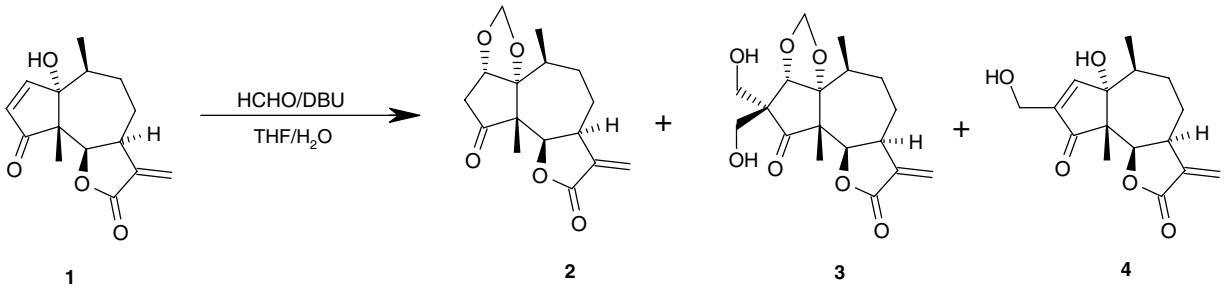


Scheme 2.

3-hydroxymethyl parthenin. In compound **3**, besides the formation of a 1,3-dioxolane moiety, double hydroxymethylation at C-3 had also occurred. Under the experimental conditions, it was possible that the reaction of formaldehyde with **2** via an aldol type addition led to the formation of **3**.

The predominant formation of 1,3-dioxolane products prompted us to study the reaction of parthenin **1** with other aldehydes. Therefore, **1** was subjected to Baylis–Hillman reaction conditions with a series of aliphatic and aromatic aldehydes. The reactions were effected by stirring a mixture, comprising three components, that is, the aldehyde (2 equiv), parthenin **1** and DBU in aqueous THF at room temperature, and separating the products formed after 24–72 h. The results of these reactions are summarized in Table 1.

The formation of 1,3-dioxolanes was observed in the majority of the reactions. The lower chain aliphatic aldehydes in general produced more 1,3-dioxolanes, whereas the higher homologues, for example, butyraldehyde to heptaldehyde, gave dehydrated Baylis–Hillman products. With lower aliphatic aldehydes the yield of the atypical product varied between 35% and 60%. Aromatic aldehydes including cinnamaldehyde, on the other

Table 1.

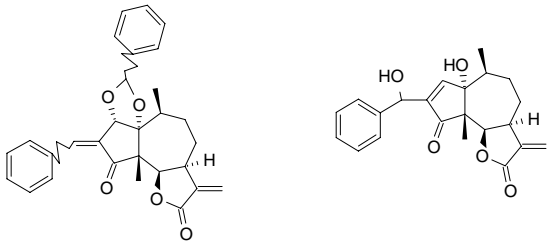
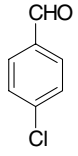
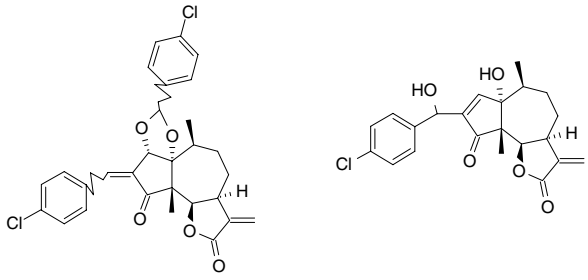
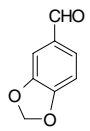
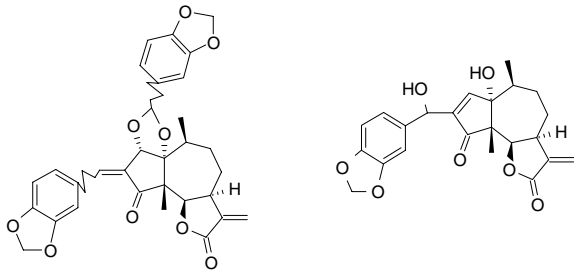
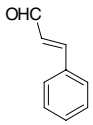
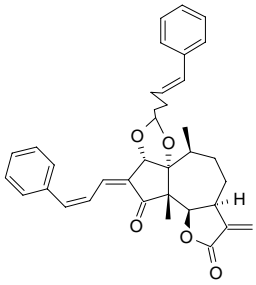
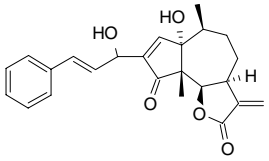
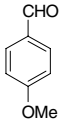
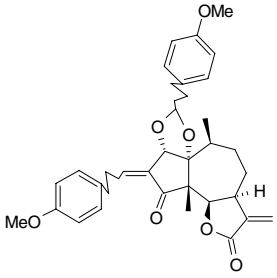
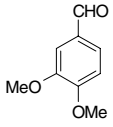
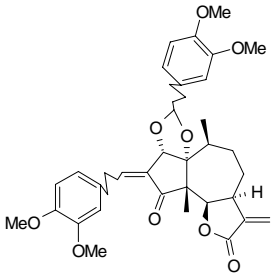
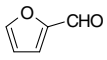
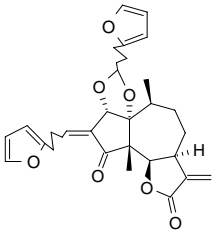
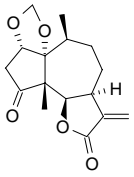
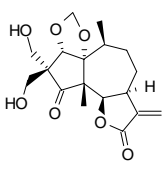
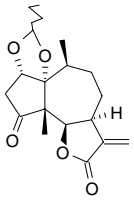
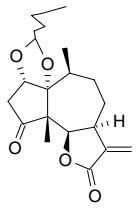
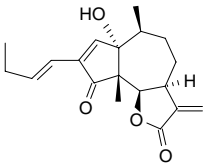
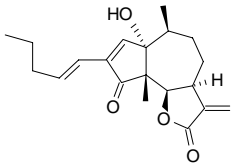
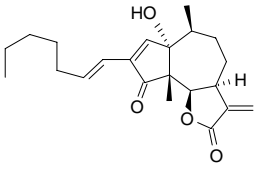
Entry	Aldehyde	Product types	Time (h)	Yield (%)
1			24	60/12
2			24	65/6
3			24	65/6

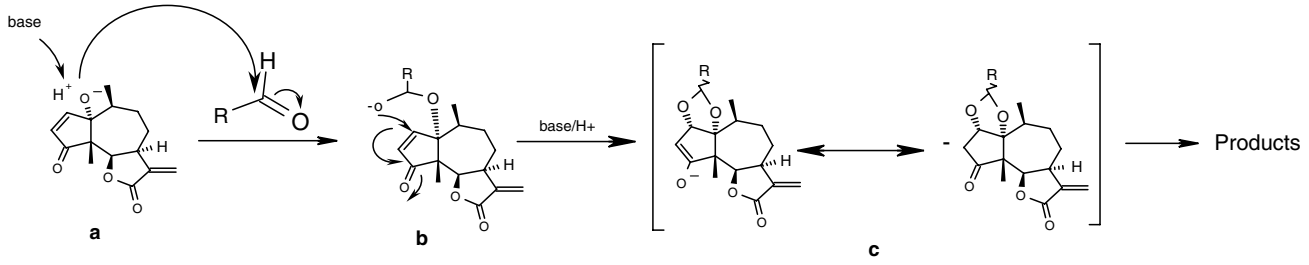
Table 1 (*continued*)

Entry	Aldehyde	Product types		Time (h)	Yield (%)
4				24	65/5
5				24	65
6				24	65
7				24	70
8	HCHO			72	35/22/13
9	CH_3CHO			72	60

(*continued on next page*)

Table 1 (*continued*)

Entry	Aldehyde	Product types	Time (h)	Yield (%)
10	C_2H_5CHO		72	55
11	C_3H_7CHO		72	55
12	C_4H_9CHO		72	50
13	$C_6H_{13}CHO$		72	50



Scheme 3.

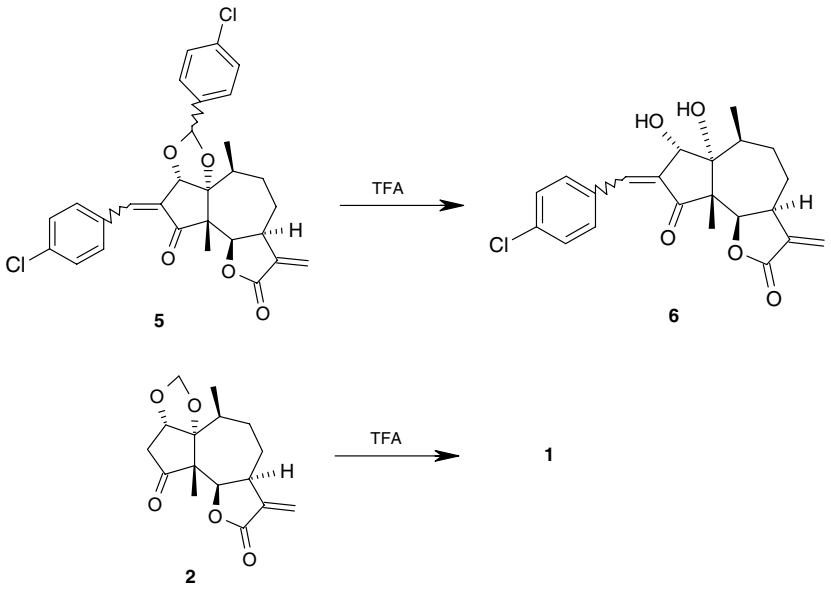
hand, produced 1,3-dioxolanes along with minor amounts of the normal condensation products. The yields of 1,3-dioxolanes with aromatic aldehydes varied between 60% and 70%. All the aromatic aldehydes underwent further base catalyzed condensation at C-3 to produce arylidene derivatives.

A plausible mechanism for the formation of 1,3-dioxolanes is depicted in Scheme 3. The homoallylic tertiary hydroxyl at C-1 may play a key role. The formation of oxyanion **a** in the presence of a base could trigger attack on the aldehyde and lead to the generation of anion **b**. Carbanion **b** would then undergo cyclization via oxy-Michael type addition at the β carbon (C-2) to give **c**, which would protonate to give products of type **2**. A normal aldol type condensation would lead to products of type **3**.

To the best of our knowledge, the formation of 1,3-dioxolanes via Baylis–Hillman reaction of cyclic enones comprising a tertiary hydroxyl group at the γ-position is novel. The formation of acetals (1,3-dioxolanes) is generally catalyzed by an acid, but in this situation the formation of the acetal has been triggered by a base.

The abnormal Baylis–Hillman reaction has an important application in the formation of 2-α-hydroxylated analogues. 1,3-Dioxolane **5** underwent a facile TFA catalyzed cleavage to give 2-α-hydroxylated product **6** in almost quantitative yield.[14] The aliphatic 1,3-dioxolane **2**, on the other hand, produced the parent molecule on acid catalyzed cleavage (Scheme 4).

In conclusion, we have established the formation of novel 1,3-dioxolanes, that is, 1,2-(2-aryl substituted-1, 3-dioxolanes), during DBU-catalyzed Baylis–Hillman coupling of the sesquiterpene lactone parthenin with aromatic and aliphatic aldehydes wherein a suitably placed hydroxyl group facilitates the reaction. The 1,3-



Scheme 4.

dioxolanes may also be easily converted to 2-α-hydroxy derivatives, which are otherwise difficult to obtain.

References and notes

1. Baylis, A. B., Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
2. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (b) Basavaiah, D.; Rao, J. A.; Satyanarayna, T. *Chem. Rev.* **2003**, *103*, 811–891.
3. Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645.
4. (a) Hwu, J. R.; Hakimelahi, G. H.; Chou, C. T. *Tetrahedron Lett.* **1992**, *33*, 6469–6472; (b) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965–5966; (c) Basavaiah, D.; Krishnamacharyulu, M.; Rao, A. J. *Synth. Commun.* **2000**, *30*, 2061–2069; (d) Gatri, R.; El Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835–7836.
5. (a) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521–1522; (b) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271–1272.
6. (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813–11824; (b) Iwama, T.; Kinoshita, H.; Kataoka, T. *Tetrahedron Lett.* **1999**, *40*, 3741–3744.
7. Li, G.; Wei, H.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5.
8. Rodriguez, E.; Dillon, M. O.; Mabry, T. J.; Towers, G. H. N.; Mitchell, J. C. *Experientia* **1976**, *32*, 236–237.
9. (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147–1152; (b) Mew, D.; Balza, F.; Towers, G. H. N.; Levy, J. G. *Planta Med.* **1982**, *45*, 23–27.
10. Picman, A. K.; Towers, G. H. N. *Biochem. Syst. Ecol.* **1983**, *11*, 321–327.
11. Hopper, M.; Kirby, G. C.; Kulkarni, M. M.; Kulkarni, S. N.; Nagasampagi, B. A.; O'Neill, M. J.; Philipson, J. D.; Rojatkar, S. R.; Warhurs, D. C. *Eur. J. Med. Chem.* **1990**, *25*, 717–723.
12. (a) Kanchan, S. D. *Curr. Sci.* **1975**, *44*, 358; (b) Patil, T. M.; Hedge, B. A. *Curr. Sci.* **1988**, *57*, 1178–1181.
13. A representative experimental procedure for the preparation of compounds **2**–**4**. A mixture of parthenin **1** (1 g, 3.8 mmol), 30% aqueous formaldehyde (0.8 ml, 8 mmol), 2 ml of THF and DBU (60 mg, 0.39 mmol) was stirred at room temperature. After 72 h, the mixture was acidified by dropwise addition of 1.5 N aqueous HCl. Extraction with methylene chloride, washing with water, removal of the solvent and chromatography of the crude product on a silica gel column using chloroform/acetone (99:1 to 95:5) as eluant gave **2** (yield 35%), **3** (yield 22%) and **4** (yield 13%) all as white powders. Compound **2**: $[\alpha]_D$ −131 (*c* 1.0 $CHCl_3$). Mp 184 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 6.26 (d, $J = 2.5$ Hz, 1H, H_a-13), 5.61 (d, $J = 2.5$ Hz, 1H, H_b-13), 5.12 and 5.01 (2 × s, 2H, O–CH_2–O), 4.87 (d, $J = 8$ Hz, 1H, H-6), 4.85 (t, $J = 5.4$ Hz, 1H, H-2), 3.23 (d, $J = 6.7$ Hz, 1H, H_a-3), 3.10 (d, $J = 6.7$ Hz, 1H, H_b-3), 2.86 (m, 1H, H-7), 1.66–2.38 (m, 5H), 1.31 (s, 3H, H-15); 1.20 (d, $J = 7.6$ Hz, 3H, H-14). ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.4, 170.0, 140.5, 122.0, 94.2, 94.0, 78.7, 75.5, 59.8, 44.6, 39.4, 34.3, 29.5, 27.7, 17.3, 16.5. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.65; H, 7.01. ESI-MS (*m*/*z*): 292. Compound **3**: $[\alpha]_D$ −13 (*c* 1.0 $CHCl_3$). Mp 151 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 6.26 (d, $J = 2$ Hz, 1H, H_a-13), 5.61 (d, $J = 2$ Hz, 1H, H_b-13), 5.16 and 5.11 (2 × s, 2H, O–CH_2–O), 4.99 (s, 1H, H-2), 4.81 (d, $J = 8$ Hz, 1H, H-6), 3.84 and 4.01 (2 × d, 2H, $J = 11.2$ Hz, –CH_2OH), 3.66 and 3.75 (2 × d, 2H, $J = 12$ Hz, –CH_2OH), 2.44 (m, 1H, H-7), 1.69–2.22 (m, 5H), 1.31 (s, 3H, H-15), 1.23 (d, $J = 7.6$ Hz, 3H, H-14). ^{13}C NMR (50 MHz, $CDCl_3$): δ 217.5, 170.2, 140.2, 122.3, 94.9, 93.8, 81.4, 79.1, 66.2, 64.7, 59.2, 57.3, 44.8, 32.0, 29.1, 27.8, 17.2, 16.0. Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.41; H, 6.77. ESI-MS (*m*/*z*): 352. Compound **4**: $[\alpha]_D$ −24.3 (*c* 1.0 $CHCl_3$). Mp 218 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.34 (s, 1H, H-2), 6.22 (d, $J = 2.5$ Hz, 1H, H_a-13), 5.70 (d, $J = 2.5$ Hz, 1H, H_b-13), 4.98 (d, $J = 8$ Hz, 1H, H-6), 4.24 (s, 2H, –CH_2OH), 2.29 (m, 1H, H-7), 1.90–1.60 (m, 5H), 1.25 (s, 3H, H-15), 1.11 (d, $J = 7.5$ Hz, 3H, H-14). ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.9, 171.9, 157.4, 142.9, 140.4, 122.1, 83.8, 82.2, 60.01, 56.0, 44.1, 40.2, 29.6, 28.2, 18.0, 16.9. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.67; H, 6.99. ESI-MS (*m*/*z*): 292.

14. A solution of compound **5** (0.524 g, 1 mmol) in 5 ml TFA/H_2O (1:1.5) was stirred at 55 °C for 10 h. Extraction with methylene chloride, work-up and chromatography of the crude product on silica gel column using chloroform/acetone (99:1 to 92:8) as eluant gave **6** (yield 90%) as a white powder. Compound **6**: $[\alpha]_D$ +17.8 (*c* 1.0 $CHCl_3$). Mp 123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, $J = 8.5$ Hz, $2H_{arom}$), 7.61 (d, $J = 2.5$ Hz, 1H, –CH), 7.39 (d, $J = 8.5$ Hz, $2H_{arom}$), 6.28 (d, $J = 2.5$ Hz, 1H, H_a-13), 5.61 (d, $J = 2.5$ Hz, 1H, H_b-13), 5.47 (s, 1H, H-2), 5.04 (d, $J = 8$ Hz, 1H, H-6), 2.29 (m, 1H, H-7), 1.90–1.60 (m, 5H), 1.25 (s, 3H, H-15), 1.15 (d, $J =$ 7.1 Hz, 3H, H-14). ^{13}C NMR (50 MHz, $CDCl_3$): δ 205.5, 171.9, 141.9, 138.9, 136.5, 134.1, 133.0, 133.0, 129.5, 129.5, 128.1, 122.4, 82.8, 80.0, 70.9, 58.6, 45.2, 37.2, 30.4, 28.2, 17.2, 15.4. Anal. Calcd for $C_{22}H_{23}ClO_5$: C, 65.59; H, 5.75. Found: C, 65.67; H, 5.68. ESI-MS (*m*/*z*): 402.