Tandem β-Elimination-Morita–Baylis–Hillman Reaction in α,β-Unsaturated Sugar Aldehydes

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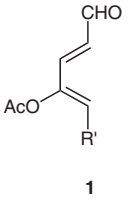
Abstract: The first Morita–Baylis–Hillman reaction of a 1-formylbutadiene derivative is reported. In addition, a convenient synthesis of 2-acetoxy-4-formylbutadiene derivatives starting from easily available D-galactal and D-arabinal is also described.

Key words: DABCO, functionalized dienes, Morita–Baylis–Hillman reaction, unsaturated sugar aldehydes

Functionalized dienes are versatile reagents in organic synthesis,[1] in particular as partner in Diels–Alder reaction.[2] Also their synthetic uses as organometallic (mainly organoiron) complexes are well documented.[3] In this context, diastereomerically pure 4-acetoxypenta-2,4-dienal derivatives **1** (R′ = H, CH_2OAc) (Figure 1) may constitute interesting synthetic building blocks,[4] provided that their synthesis and isolation could be conveniently achieved from inexpensive starting materials.

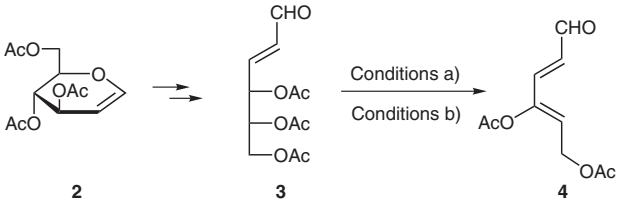


1

Figure 1 4-Acetoxypenta-2,4-dienal **1** (R′ = H, CH_2OAc)

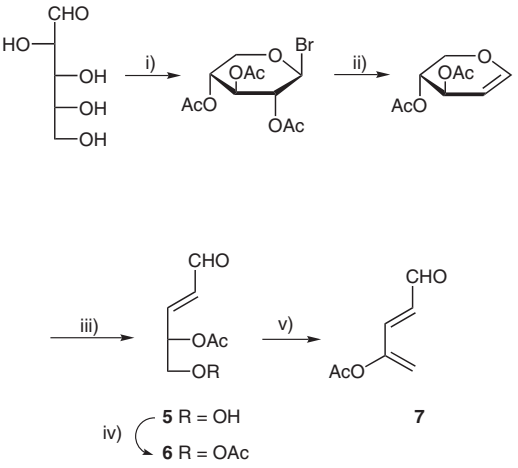
To the best of our knowledge 4,6-diacetoxyhexa-2,4-dienal (**4**) is the only compound with this structure so far described.[5] This compound has been previously synthesized from 3,4,6-tri-*O*-acetyl-D-glucal (**2**) via DBU-induced elimination of the α,β-unsaturated aldehyde **3** (80% isolated yield, 9:1 mixture of 2*E*,4*Z*:2*E*,4*E* diastereomers which were not separated) (Scheme 1, Conditions a). In the search for a total diastereoselective reaction, we decided to use other different basic reagents. In this way the use of DABCO shows to be the most convenient alternative (Scheme 1, Conditions b).[6]

The described protocol has also been applied to the synthesis of the hitherto unknown diene 4-acetoxypenta-2,4-dienal (**7**). The starting aldehyde **6** was synthesized from



2 **3** **4**

Scheme 1 Synthesis of diene **4** from glucal **2**. Conditions a): DBU (1 equiv); r.t.; CH_2Cl_2; 16 h, 56%; ratio 2*E*,4*Z*/2*E*,4*E* = 9:1; Conditions b): DABCO (1.5 equiv); 15 °C; MeCN; 4 h 15 min, 92%; only the 2*E*,4*Z* diastereomer was obtained.



Scheme 2 Synthesis of diene **7** from D-arabinose. *Reagents and conditions*: i) $HClO_4$, Ac_2O, P, Br_2, 41%; ii) Zn, $CuSO_4$, NaOAc, 88%; iii) $HgSO_4$, H_2SO_4, quant; iv) Ac_2O, Py, quant; v) DABCO (1.5 equiv), MeCN, 15 °C, quant.

D-arabinose in four steps and 36% overall yield. Treatment of **6** with DABCO (1.5 equiv, MeCN, 15 °C) afforded diene **7** in quantitative yield (Scheme 2).

On the basis of this facile synthesis of 4-acetoxypenta-2,4-dienal (**7**) induced by DABCO and considering that DABCO is the most used basic reagent for the Morita–Baylis–Hillman (MBH) reaction,[7] the direct transformation of aldehyde **6** in MBH adducts appears to be a reasonable possibility. In this way, the reaction of **6** with some activated alkenes in the presence of DABCO gave the expected adducts **8** in reasonable yields and according with our previous assumption (Table 1).

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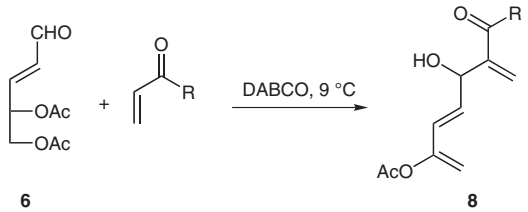
Table 1 Tandem β-Elimination-MBH Reactions of Compound **6** and Activated Alkenes



6 **8**

Entry	R	Reaction time (d)	Product	Yield (%)[a]
1	Me	5.5	**8a**	68
2	Et	6	**8b**	50
3	OMe	27	**8c**	48

[a] Isolated yield.

It should be pointed out that, to the best of our knowledge, *this is the first example of a MBH reaction using a masked formylbutadiene derivative.*[8] Isolated diene **7** gave similar results as those obtained starting from aldehyde **6**.

In summary, in this report the first MBH adducts derived from a formylbutadiene derivative have been synthesized in a tandem sequence base-induced elimination-MBH reaction. In addition, a simple and straightforward synthesis of 4-acetoxypenta-2,4-dienal derivatives, conveniently functionalized diene systems, was carried out.

Analytical TLC was performed on Merck 60 GF_{254} silica gel with monitoring by UV irradiation at 254 and 360 nm or by exposure to I_2 vapor. Flash chromatography was performed on Merck 60 silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were obtained on a Bruker AM 400 instrument at 400 MHz and 100 MHz, respectively in $CDCl_3$ (Me_4Si as internal standard) unless otherwise specified. Mass spectra (HRMS/CI$^+$ or FAB+) were recorded on a VG Autospec spectrometer; only significant fragment ions are reported.

(2*E*,4*Z*)-4,6-Diacetoxyhexa-2,4-dienal (4)

Conditions b): To a solution of DABCO (2.24 g, 19.9 mmol) in freshly distilled MeCN (84 mL) under argon and at r.t. was added a solution of aldehyde **3**[5] (2.28 g, 8.39 mmol) in MeCN (84 mL) and the mixture was stirred for 4 h 15 min. Then the mixture was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were washed successively with 0.1 N HCl (2 × 50 mL), aq sat. solution of $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL), dried ($MgSO_4$), and filtered. Evaporation of the solvent (reduced pressure) afforded **4** as an oil; yield: 1.54 g (92%). If necessary, **4** can be purified by flash chromatography (hexane–EtOAc, 2:1). Compound **4** was identified by comparison with an authentic sample.[5]

(2*E*)-4,5-Di-*O*-acetyl-2,3-dideoxy-*aldehyde*-D-pent-2-enose (6)

(2*E*)-4-*O*-Acetyl-2,3-dideoxy-*aldehyde*-D-pent-2-enose (**5**;[9] 2.35 g, 14.86 mmol) was dissolved in a mixture of pyridine (9.6 mL) and Ac_2O (9.6 mL) at 0 °C. The mixture was stirred and kept at r.t. for 4 h, then poured onto a slurry of ice and 2 N HCl (120 mL), and extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ extracts were combined, successively washed with 2 N HCl (3 × 50 mL), aq $NaHCO_3$ solution (3 × 50 mL) and H_2O, dried and evaporated to an oil; yield: 2.94 g (99%).

IR (film): 1744 s, 1688 s, 1220 cm^{-1} s.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 6.73 (dd, 1 H, $J_{3,2}$ = 15.6 Hz, $J_{3,4}$ 4.4 Hz, H-3), 6.29 (ddd, 1 H, $J_{2,1}$ = 8 Hz, $J_{2,3}$ = 16 Hz, $J_{2,4}$ = 2.0 Hz, H-2), 5.74 (m, 1 H, H-4), 4.35 (dd, 1 H, $J_{5,4}$ = 4.4 Hz, $J_{5,5'}$ = 12 Hz, H-5), 4.21 (dd, 1 H, $J_{5',4}$ = 6.4 Hz, $J_{5,5'}$ = 12.0 Hz, H-5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5 (C-1), 170.4, 169.6 (2 O*C*OCH$_3$), 149.0 (C-3), 133.0 (C-2), 70.0 (C-4), 63.5 (C-5), 20.6 and 20.5 (2 OCO*C*H$_3$).

Anal. Calcd for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found: C, 54.06; H, 6.28.

(2*E*)-4-*O*-Acetoxypenta-2,4-dienal (7)

To a solution of DABCO (0.840 g, 7,53 mmol) in freshly distilled MeCN (75 mL) under argon and at r.t. was added a solution of aldehyde **6** (1.003 g, 5.02 mmol) in MeCN (75 mL) and the mixture was stirred for 1 h 40 min. Then the mixture was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were rinsed successively with 0.1 N HCl (2 × 50 mL), aq sat. solution of $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL), dried ($MgSO_4$), and filtered. Evaporation of the solvent (reduced pressure) afforded **7** as an oil; yield: 0.69 g (99%). If necessary, **7** can be purified by flash chromatography (hexane–EtOAc).

IR (film): 1682 s, 1764 s, 1640 m, 1598 m, 1200 cm^{-1} s.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1), 7.01 (d, 1 H, $J_{3,2}$ = 15.2 Hz, H-3). 6.18 (dd, 1 H, $J_{2,1}$ = 7.6 Hz, $J_{2,3}$ = 15 Hz, H-2) 5.52 (d, 1 H, $J_{5,5'}$ = 1.6 Hz, H-5), 5.41 (d, 1 H, $J_{5,5'}$ = 2 Hz, H-5′), 2.26 (s, 3 H, CH_3COO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8 (C-1), 162.8 (CH_3COO), 145.1 (C-4), 129.1 (C-2), 114.8 (C-5), 20.6 (*C*H$_3$COO).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.04; H, 5.94.

(2*E*)-2-Acetoxy-6-acetyl-5-hydroxyhepta-1,3,6-triene (8a); Typical Procedures

Method A: To a solution of DABCO (0.84 g, 7.5 mmol) in freshly distilled MeCN (37 mL) under argon and at r.t. was added a solution of aldehyde **6** (0.75 g, 3.75 mmol) in MeCN (37 mL). After 5 min, methyl vinyl ketone was added (3.1 mL, 37.5 mmol) and the mixture was kept at 9 °C for 5.5 days. Then, the mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic layers were washed successively with 0.1 N HCl (2 × 25 mL), aq sat. solution of $NaHCO_3$ (2 × 25 mL) and H_2O (2 × 25 mL), dried ($MgSO_4$), and filtered. Evaporation of the solvent (reduced pressure) afforded **8a** as an oil (1.54 g, 92%), which was purified by flash chromatography (hexane–EtOAc, 1.5:1); yield: 0.53 g (65%).

Method B: To a solution of DABCO (0.41 g, 3.62 mmol) in freshly distilled MeCN (24 mL) under argon and at r.t. was added a solution of diene **7** (0.34 g, 2.41 mmol) in MeCN (24 mL). After 5 min, methyl vinyl ketone was added (2.0 mL, 24.1 mmol) and the mixture was kept at 9 °C for 5.5 days. Similar work up as in Method A afforded **8a** as an oil; yield: 0.50 g (68%).

IR (film): 3475 m, 3020 w, 1760 s, 1672 s, 1205 cm^{-1} s.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.26 (dd, 1 H, $J_{3,5}$ = 1.6 Hz, $J_{3,4}$ = 16 Hz, H-3), 6.16 (s, 1 H, H-1b), 6.05 (s, 1 H, H-1a), 5.81 (dd, 1 H, $J_{4,3}$ = 16 Hz, $J_{4,5}$ = 6 Hz, H-4), 5.10 (t, 1 H, $J_{5,4}$ = $J_{5,OH}$ = 6 Hz, H-5), 5.04 (d, 1 H, $J_{7a,7b}$ = 1,6 Hz, H-7a), 4.93 (d, 1 H, $J_{7a,7b}$ = 1.6 Hz, H-7b), 2.92 (d, 1 H, $J_{OH,4}$ = 5.2 Hz, OH), 2.38 (s, 3 H, $COCH_3$), 2.23 (s, 3 H, $OCOCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1 (CH_3CO), 168.8 (CH_3COO), 151.0 (C-6), 148.5 (C-2), 131.1 (C-4), 126.9 (C-1), 124.7 (C-3), 106.2 (C-7), 70.1 (C-5), 26.3 (*C*H$_3$CO), 20.8 (*C*H$_3$COO).

MS (IQ): *m/z* (%) = 151 (M – OAc, 24), 41 (99), 29 (100).

HMRS (FAB+): *m/z* calcd for $C_{11}H_{14}O_4$ + H: 211.097034; found: 211.097057 $(M + H)^+$.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.56; H, 6.97.

(2*E*)-2-Acetoxy-5-hydroxy-6-propanoylhepta-1,3,6-triene (8b)

Method A: Treatment of aldehyde **6** (0.75 g, 3.75 mmol) with ethyl vinyl ketone (3.7 mL, 37.5 mmol) in the presence of DABCO was carried out by following Method A as described above for **8a**, except that the process lasted 6 days. Purification by flash chromatography (hexane–EtOAc, 3:1) gave **8b** as an oil; yield: 0.82 g (50%).

Method B: By using Method B as described above for **8a**, compound **7** was converted into **8b** by treatment with ethyl vinyl ketone, except that the process lasted 6 days; yield: 50%.

IR (film): 3500 m, 2980 m, 2980 m, 1760 s, 1678 s, 1205 cm^{-1} s.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.25 (dd, 1 H, $J_{3,5}$ = 1.6 Hz, $J_{3,4}$ = 16 Hz, H-3), 6.14 (s, 1 H, H-1b), 5.99 (s, 1 H, H-1a), 5.80 (dd, 1 H, $J_{4,3}$ = 16 Hz, $J_{4,5}$ = 1.6 Hz, H-4), 5.10 (d, 1 H, $J_{5,OH}$ = 6 Hz, OH), 5.03 (d, 1 H, $J_{7a,7b}$ = 1.6 Hz, H-7a), 4.92 (d, 1 H, $J_{7a,7b}$ = 1.6 Hz, H-7b), 2.98 (br s, 1 H, OH), 2.74 (q, 2 H, $J_{2',3'}$ = 7.6 Hz, H-2′), 2.22 (s, 3 H, $OCOCH_3$), 1,11 (t, 3 H, $J_{2',3'}$ = 7.2 Hz, H-3′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7 (CH_3CO), 168.7 (CH_3COO), 151.0 (C-6), 148.0 (C-2), 131.2 (C-4), 125.3 (C-1), 124.6 (C-3), 106.0 (C-7), 70.2 (C-5), 31.3 (C-2′), 20.7 (CH_3COO), 7.9 (CH_3CH_2).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.14; H, 6.98.

(2*E*)-2-Acetoxy-5-hydroxy-6-methoxycarbonylhepta-1,3,6-triene (8c)

Method A: Treatment of aldehyde **6** (0.75 g, 3.75 mmol) with methyl acrylate (3.4 mL, 37.5 mmol) in the presence of DABCO was carried out by following Method A as described above for **8a**, except that the process lasted 27 days. Purification by flash chromatography (hexane–EtOAc, 3:1) allowed the isolation of starting material **6** (0.13 g) and **8c** as an oil; yield: 0.51 g (48%).

Method B: By using Method B as described above for **8a**, compound **7** was converted into **8c** by treatment with methyl acrylate, except that the process lasted 27 days; yield: 0.16 g (31%).

IR (film): 3500 m, 3020 m, 1760 s, 1720 s, 1200 cm^{-1} s.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1 H, H-1b), 6.28 (dd, 1 H, $J_{3,5}$ = 1.2 Hz, $J_{3,4}$ = 15.6 Hz, H-3), 5.91 (s, 1 H, H-1a), 5.84 (dd, 1 H, $J_{4,3}$ = 16 Hz, $J_{4,5}$ = 6 Hz, H-4), 5.10 (br s, 1 H, H-5), 5.06 (d, 1 H, $J_{7a,7b}$ = 0.8 Hz, H-7a), 4.95 (d, 1 H, $J_{7a,7b}$ = 0.8 Hz, H-7b), 3.80 (s, 3 H, OCH_3), 3.48 (d, 1 H, $J_{OH,5}$ = 3.6 Hz, OH), 2.24 (s, 3 H, CH_3COO).

^{13}C NMR (100 MHz, $CDCl_3$): 168.6 ($OCOCH_3$), 166.3 ($COOCH_3$), 150.9 (C-6), 140.7 (C-2), 130.8 (C-4), 125.9 (C-1), 124.8 (C-3), 106.1 (C-7), 70.1 (C-5), 51.8 ($OCOCH_3$), 20.6 (CH_3COO).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.01; H, 6.62.

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