In situ Generation and Nucleophilic Capture of 1,n-Dial Equivalents from 1,n-Dioates (α,ω-Diesters)

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Abstract: A procedure is described for the in situ generation of functional equivalents of glutaric, succinic, and malonic dialdehydes. DIBAL-H reduction of the corresponding 1,n-dioates followed by in situ addition of a nucleophilic trapping agent allows for one-pot, bidirectional homologation. Olefination and Grignard addition classes of reactions are specifically demonstrated.

Key words: nucleophilic additions, hydrides, reductions, tandem reactions, Wittig reactions

The two aldehyde groups in 1,n-dials, especially those of the succinic and glutaric families (**1**, Figure 1), are notorious for their tendencies to engage one another through intramolecular reaction. This phenomenon influences reactivity at the second aldehyde, a requirement for symmetrical chain elongation. Internal hydrate formation (see **2**, Figure 1) or addition of a nucleophilic species (Nu⁻) to one of the free aldehydes and subsequent intramolecular adduct formation with the second (cf., **3**, Figure 1) are common examples of this situation. One strategy for circumventing these problems is to expose the two aldehyde functional groups sequentially, rather than in parallel. While this is cumbersome and inefficient if it requires protecting group or oxidation-state differentiation of the two termini (i.e., multiple manipulations), a viable in situ release of each aldehyde in the presence of a suitable trapping nucleophile would not suffer from these drawbacks.
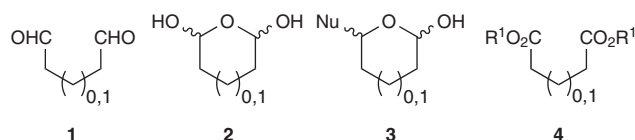

Figure 1

We recently encountered the need to chain extend, in a symmetrical fashion, various 3-oxygenated glutaraldehydes. With that and the above issues in mind, we considered whether a one-pot reduction–addition reaction sequence would provide a solution. In particular, we planned for an α,ω-diester **4** to be treated sequentially and at low temperature first, with two equivalents of diisobutylaluminum hydride (DIBAL-H) and second, with an ex-

cess of a compatible trapping nucleophile (Nu-Met). Species **5** (Scheme 1) contains a pair of tetrahedral intermediates, which we envisioned collapsing to aldehydes, upon warming, at different moments in time. If each reactive aldehyde, once exposed, was rapidly trapped by Nu-Met, then species **7** would arise via **6** without the intervention of **1** or **2** (and the associated issues). Previous reports in which simple monoesters have been subjected to DIBAL-H/Horner–Emmons,[1] DIBAL-H/Mukaiyama aldol,[2] DIBAL-H/Grignard,[3] and LiBH₄/Grignard[4] tandem reactions, provided precedent. Here we report results that demonstrate this strategy.
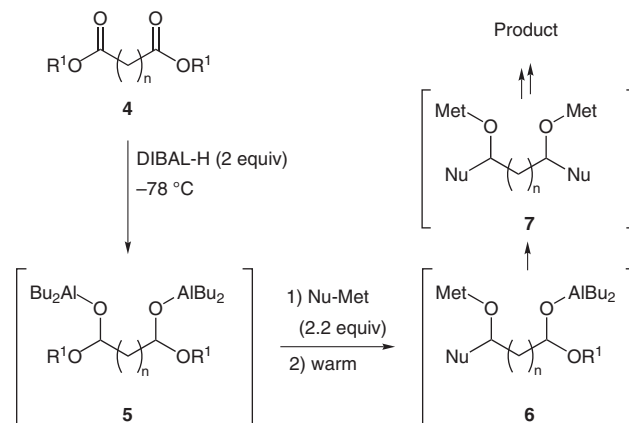
Scheme 1

We chose to study (Scheme 2) double Horner–Emmons (**4** → **10**) and double Grignard additions (**4** → **11**) using phosphonates **8** and allylmagnesium chloride (**9**) as representative trapping nucleophiles, Nu-Met.
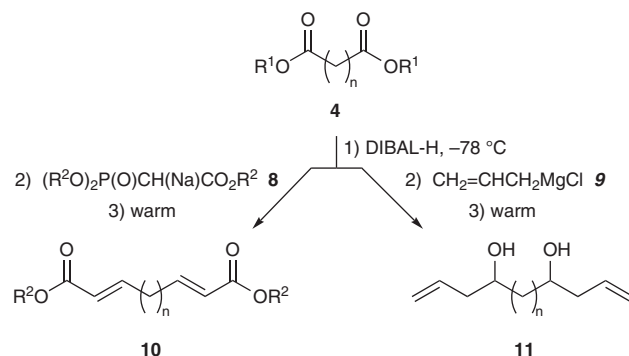
Scheme 2

The essential results are summarized in Table 1. Succinate (entries 1 and 2) and glutarate (entries 3–5) esters were excellent substrates and gave the corresponding dienoate esters **10** or 1,n-diols **11** in very good to excellent yields. Of particular interest because of our more specific motivation, the 3-triethylsilyloxyglutarate ester shown in entry 5 was also well tolerated, without complication from elimination reactions. Finally, the strategy is applicable to malonate esters (entries 6 and 7), but not without competition from other events (see Table 1, note c). Thus, the procedure is even applicable to the particularly challenging malonaldehyde case (i.e., for rapid preparation of 1,3-dienes and -diols like those shown for products in entries 6 or 7), as long as lower efficiencies are acceptable. We did not attempt to optimize this dimethyl malonate reaction.

In conclusion, we have provided a convenient way to symmetrically elongate 1,n-dial equivalents via sequential reduction of the corresponding 1,n-dioates and addition of an appropriate nucleophile.

(2E,7E)-Diethyl Nona-2,7-dienedioate (Entry 3); Typical Procedure

A solution of DIBAL-H in toluene (10.0 mL, 15 mmol) was slowly added (over ca. 15 min) to a solution of dimethyl glutarate (1.0 mL, 6.8 mmol) in Et$_2$O (27 mL) at –78 °C under N$_2$. The internal temperature was maintained below –70 °C (internal temperature probe). The mixture was stirred for 30 min at –78 °C. A solution of the phosphonoacetate anion (20 mmol, preparation described below) was added via cannula at –78 °C. The reaction mixture was then warmed to r.t. and stirred for 2 h. Water (ca. 30 mL) and a saturated solution of Rochelle's salt (ca. 30 mL) were added and the resulting mixture was stirred until the two layers were homogeneous. The aqueous layer was extracted with EtOAc (3 ×). The combined organic layers were dried over Na$_2$SO$_4$. The solvent was removed in vacuo, and the resulting material was purified via flash chromatography (25% EtOAc–75% hexanes) to provide the dienoate product (1.48 g, 6.16 mmol, 91%).

Triethyl Phosphonoacetate Sodium Salt (8-Et); Typical Procedure

Triethyl phosphonoacetate (4.1 mL, 20 mmol) was added to a suspension of NaH (0.46 g, 19 mmol) in THF (40 mL) at 0 °C. The mixture was stirred until the evolution of H$_2$ gas ceased (≤10 min). At this time the solution had become homogeneous. No-D ^{1}H NMR analysis[5] confirmed that a small amount of starting, non-deprotonated triethyl phosphonoacetate remained. In the case of entry 5, excess NaH remaining after sodiophosphonoacetate generation led to decomposition of the desired product. It therefore was necessary to use a slight excess (0.05 equiv) of phosphonoacetate relative to NaH.

Undeca-1,10-diene-4,8-diol (Entry 4); Typical Procedure

A solution of DIBAL-H in toluene (5.0 mL, 7.5 mmol) was slowly added (over ca. 7 min) to a solution of dimethyl glutarate (0.50 mL, 3.4 mmol) in Et$_2$O (13.6 mL) at –78 °C under N$_2$. The internal temperature was maintained below –70 °C. The mixture was stirred for 30 min at –78 °C. A solution of allylmagnesium chloride in Et$_2$O (3.7 mL, 7.5 mmol) was added at –78 °C. The reaction mixture was then warmed to r.t. and stirred for 2 h. The mixture was quenched with sat. NH$_4$Cl solution at 0 °C. A saturated solution of Rochelle's salt was added at r.t., and the two-phase mixture was stirred for approximately 8 h. The aqueous layer was extracted with EtOAc (3 ×). The combined organic layers were dried over Na$_2$SO$_4$. The solvent was removed in vacuo, and the resulting material was purified via

Table 1   Results of Sequential Reaction of Starting Diesters with i) DIBAL-H and ii) Either Phosophonate Anion **8** or Allylmagnesium Chloride (**9**)

Entry	Starting diester	Nucleophile[a]	Product	Yield (%)[b]	Comments
1	EtO$_2$C⌁CO$_2$Et	8-Et	EtO$_2$C⌁⌁CO$_2$Et	75	94:6 (E,E:E,Z)
2	EtO$_2$C⌁CO$_2$Et	9	(OH / OH diol)	73	dr ca. 1:1 (^{13}C NMR)
3	MeO$_2$C⌁CO$_2$Me	8-Et	EtO$_2$C⌁⌁CO$_2$Et	91	95:5 (E,E:E,Z)
4	MeO$_2$C⌁CO$_2$Me	9	(OH / OH diol)	71	dr ca. 1:1 (^{13}C NMR)
5	MeO$_2$C⌁(OTES)⌁CO$_2$Me	8-Me	MeO$_2$C⌁(OTES)⌁CO$_2$Me	87	98:2 (E,E:E,Z)
6[c]	MeO$_2$C⌁CO$_2$Me	8-Et	EtO$_2$C⌁⌁CO$_2$Et	18	–
7	MeO$_2$C⌁CO$_2$Me	9	(OH / OH diol)	41	dr ca. 1:1 (^{13}C NMR)

[a] See Scheme 2.

[b] Isolated following purification by silica gel chromatography.

[c] Varying ratios of deconjugated (1,4-) and conjugated (1,3-) dienes were obtained; isomerization to the latter, more stable isomer generally occurred upon handling and storage.

flash chromatography (50% EtOAc–50% hexanes) to provide the desired product (0.44 g, 2.4 mmol, 71%).

(2E,6E)-Diethyl Octa-2,6-dienedioate[6] (Entry 1)

TLC: R_f = 0.6 (25% EtOAc–75% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.87–7.01 (br dt, J = 6.0, 16.0 Hz, 2 H, H3, H6), 5.86 (d, J = 15.0 Hz, 2 H, H2, H7), 4.19 (q, J = 7.0, 7.0, 7.0 Hz, 4 H, CH_2Me), 2.33–2.46 (m, 4 H, H4, H5), 1.29 (t, J = 7.5, 7.5 Hz, 6 H, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.5, 147.0, 122.5, 60.4, 30.6, 14.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{12}$H$_{18}$O$_4$Na: 249.1103; found: 249.1103.

Deca-1,9-diene-4,7-diol[7] (Entry 2)

TLC: R_f = 0.6 (50% EtOAc–50% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): δ = 5.68–5.90 (two overlapping dddd, J = 7.0, 8.0, 10.0, 17.0 Hz, 2 H, H2, H9), 5.11–5.19 (m, 4 H, H1, H10), 3.64–3.76 [br s (W$_{1/2h}$ = 19 Hz) 2 H, H4, H7], 2.38 (br s, OH), 2.30 (two overlapped br ddd, J = 6.0, 6.0, 13.0 Hz, H3b, H3b′, H8b, H8b′), 2.20 (two overlapped app dddd, J = 1.0, 8.0, 8.0, 14.0 Hz, H3a, H3a′, H8a, H8a′), 2.13 (br s, OH), 1.64–1.75 (m, 2 H, H5a, H6a), 1.50–1.62 (m, 2 H, H5b, H6b).

^{13}C NMR (125 MHz, CDCl$_3$, mixture of diastereomers): δ = 135.3, 118.2, 71.5*, 71.0**, 42.6*, 42.3**, 33.8*, 32.9** (*one diastereomer, **the other diastereomer),

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{10}$H$_{18}$O$_2$Na: 193.1205; found: 193.1191.

(2E,7E)-Diethyl Nona-2-7-dienedioate[8] (Entry 3)

TLC: R_f = 0.7 (25% EtOAc–75% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.93 (dt, J = 6.5, 15.5 Hz, 2 H, H3, H7), 5.83 (d, J = 16.0 Hz, 2 H, H2, H8), 4.19 (q, J = 7.0 Hz, 4 H, CH_2Me), 2.24 (dt, J = 7.0, 7.0 Hz, 4 H, H4, H6), 1.64 (p, J = 7.0 Hz, 2 H, H5), 1.29 (t, J = 7.5 Hz, 6 H, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.6, 148.2, 122.1, 60.4, 31.6, 26.5, 14.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{13}$H$_{20}$O$_4$Na: 263.1259; found: 263.1263.

Undeca-1,10-diene-4,8-diol[9] (Entry 4)

TLC: R_f = 0.3 (50% EtOAc–50% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): δ = 5.83 (dddd, J = 7.0, 8.0, 10.0, 17.0 Hz, 2 H, H2, H10), 5.12–5.17 (m, 4 H, H1, H11), 3.64–3.70 (m, 2 H, H4, H8), 2.31 (br dt, J = 6.0, 13.0 Hz, 2 H, H3a, H9a), 2.15 (ddd, J = 7.5, 7.5, 14.5 Hz, 2 H, H3b, H9b), 1.45–1.77 (m, 8 H, H5, H6, H7, OH).

^{13}C NMR (125 MHz, CDCl$_3$, mixture of diastereomers): δ = 135.1 (+), 135.1 (–), 117.9, 117.8, 70.7, 70.6, 42.2, 42.0, 36.7, 36.5, 21.8, 21.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{11}$H$_{20}$O$_2$Na: 207.1361; found: 207.1370.

(2E,7E)-Dimethyl 5-(Triethylsilyloxy)nona-2,7-dienedioate (Entry 5)

TLC: R_f = 0.25 (10% EtOAc–90% hexanes).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.94 (dt, J = 7.5, 15.3 Hz, 2 H, H3, H7), 5.86 (dt, J = 1.5, 15.6 Hz, 2 H, H2, H8), 3.93 (tt, J = 5.7, 11.4 Hz, 1 H, H5), 3.73 (s, 6 H, CO$_2$Me), 2.36 (nfom, 4 H, H4, H6), 0.95 [t, J = 7.8 Hz, 9 H, Si(CH$_2$CH_3)$_3$], 0.59 [q, J = 7.8 Hz, 6 H, Si(CH_2CH$_3$)$_3$]; nfom = non-first-order multiplet.

^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.7, 145.0, 123.5, 70.1, 51.5, 40.1, 6.9, 4.9.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{17}$H$_{30}$O$_5$NaSi: 365.1760; found: 365.1793.

(2E,4E)-Diethyl Hepta-2,4-dienedioate (Entry 6)

TLC: R_f = 0.7 (25% EtOAc–75% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.27 (dd, J = 10.0, 15.0 Hz, 1 H, H3), 6.27 (dd, J = 10.0, 15.0 Hz, 1 H, H4), 6.19 (dt, J = 7.0, 14.0 Hz, 1 H, H5), 5.85 (d, J = 15.0 Hz, 1 H, H2), 4.20 [q, J = 7.5 Hz, 2 H, C(1)(=O)OCH_2Me], 4.16 [q, J = 7.5 Hz, 2 H, C(8)(=O)OCH_2Me], 3.20 (d, J = 7.0 Hz, 2 H, H7), 1.30 [t, J = 7.0 Hz, 3 H, (OCH$_2$CH_3)a], 1.27 [t, J = 7.0 Hz, 3H, (OCH$_2$CH_3)b].

^{13}C NMR (125 MHz, CDCl$_3$): δ = 170.7, 167.0, 143.8, 134.3, 131.5, 121.4, 61.1, 60.4, 38.3, 14.4, 14.3.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{11}$H$_{16}$O$_4$Na: 235.0946; found: 235.0958.

Nona-1,8-diene-4,6-diol[10] (Entry 7)

TLC: R_f = 0.5 (50% EtOAc–50% hexanes).

^{1}H NMR (500 MHz, CDCl$_3$, mixture of diastereomers): δ = 5.82 (dddd, J = 7.0, 7.0, 10.0, 17.0 Hz, 2 H, H2, H8), 5.15 (br d, J = 16.0 Hz, 2 H, H1Z, H9Z), 5.14 (br d, J = 11.0 Hz, 2 H, H1E, H9E), 4.01 (app p, J = 6.0 Hz, 2 H, H4, H6), 2.36 (br s, 2 × OH), 2.28 (ddddd, J = 1.0, 1.0, 7.0, 7.0, 14.0 Hz, 2 H, H3a, H7a), 2.27 (ddddd, J =1.0, 1.0, 7.0, 7.0, 14.0 Hz, 2 H, H3b, H7b), 1.66 (t, J = 6 Hz, 2 H, 2 × H5).

^{13}C NMR (125 MHz, CDCl$_3$, from the mixture of diastereomers): δ = 134.9*, 134.5**, 118.1**, 118.0*, 71.9**, 68.2*, 42.6**, 42.1*, 41.8**, 41.6* (* = anti and ** = syn diastereomer).

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_9$H$_{16}$O$_2$Na: 179.1048; found (from the diastereomeric mixture): 179.1050.

Acknowledgment

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