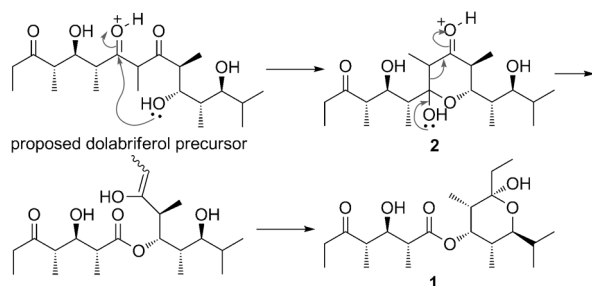


In Silico Inspired Total Synthesis of (–)-Dolabriferol**

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Dolabriferol (**1**) is a noncontiguous polypropionate isolated from the anaspidean mollusc *Dolabrifera dolabrifera*.^[1] Ever since its initial discovery in 1996 by Gavagnin and co-workers, dolabriferol has attracted significant synthetic interest.^[2] The challenging esterification had not been reported in synthetic approaches towards dolabriferol,^[2a,b,d] until the first total synthesis reported by Vogel and co-workers.^[2c]

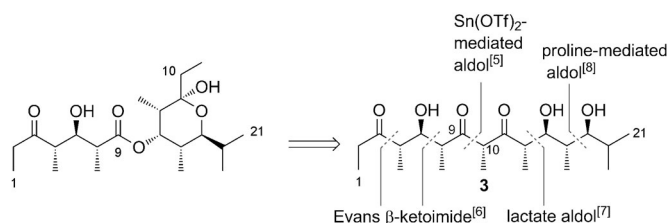
The unusual connectivity of this highly substituted polypropionate ester might originate either biosynthetically^[1] or during isolation^[3] through a mild base- or acid-catalyzed retro-Claisen rearrangement of the intermediate hemiacetal **2** (Scheme 1). Recent computational work in our group has shown this rearrangement to be an energetically favorable pathway.^[4]



Scheme 1. Proposed biosynthetic pathway.

Encouraged by the results of our calculations and the related synthetic achievements of Perkins et al.,^[2c] our retrosynthetic planning (Scheme 2) focused on investigating and replicating the rearrangement of such a linear precursor (**3**). We anticipated that such a route would offer not only a robust construction of the sensitive and hindered ester linkage, but also offer significant insight into the biological construction of noncontiguous polypropionates.

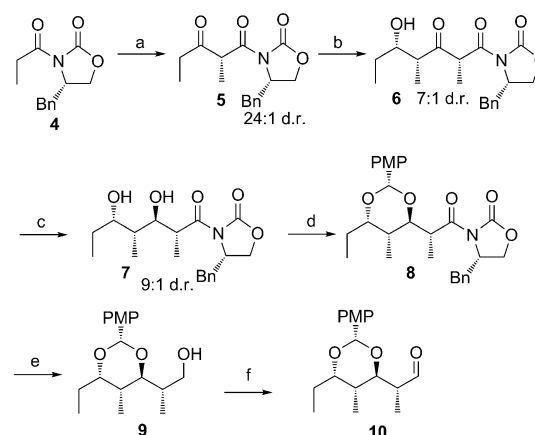
In line with our plan, the linear precursor **3** would be assembled by a Sn(OTf)₂-mediated aldol^[5] coupling of two fragments (C1 to C9 and C10 to C21). These two fragments would be assembled by a combination of robust Evans β-



Scheme 2. Retrosynthesis—main disconnections. Tf = trifluoromethanesulfonyl.

ketoimide,^[6] lactate aldol,^[7] and MacMillan's organocatalytic cross-aldol^[8] methodology.

A rapid and scalable synthesis of the C1 to C9 fragment proceeded through exploitation of Evans β-ketoimide aldol methodology (Scheme 3). Addition of the lithium enolate of *N*-propionyl oxazolidinone (**4**) to propionyl chloride rapidly



Scheme 3. Reagents and conditions: a) EtCOCl, LDA, MgBr₂·Et₂O, –78 °C, THF, 52%; b) TiCl₄, EtN(*i*Pr)₂, CH₂Cl₂, EtCHO, –78 °C, 92%; c) Me₄NBH(OAc)₃, AcOH, MeCN, RT, 83 % over 2 steps from **5**; d) PMP-CH(OMe)₂, TsOH, 1.2 torr, 40 °C, 81%; e) LiBH₄, MeOH, THF, 0 °C to RT, 78%; f) (COCl)₂, DMSO, CH₂Cl₂, –78 °C, then Et₃N. Bn = benzyl, DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, PMP = *p*-methoxy phenyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

afforded the β-ketoimide **5** in high d.r. (24:1). Generation of the titanium enolate of **5**,^[9] and subsequent addition to propionaldehyde smoothly afforded **6** in 92 % yield. Hydroxy directed reduction of the unpurified **6** under Evans–Saksena^[10] conditions afforded the 1,3-*anti*-diol **7** in higher yields than a separate two step procedure.

The highest yielding reaction conditions for the formation of the strained *anti*-PMP acetal **8** were solvent free, thus involving the in vacuo removal of methanol.^[11] LiBH₄

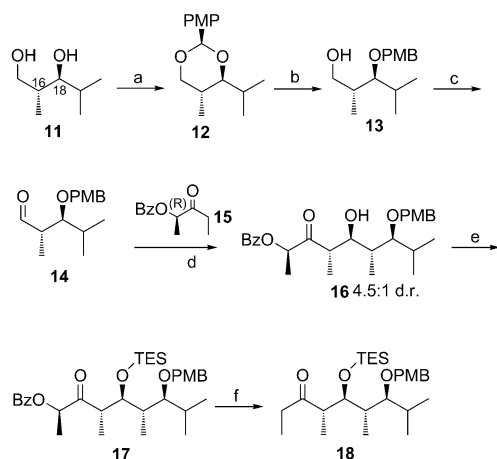
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[**] Financial support for this work was provided by the EPSRC. We wish to thank the EPSRC National Mass Spectrometry Service (Swansea) for mass spectra.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201109080>.

cleavage of the auxiliary using the reaction conditions reported by Li and Hale^[12] cleanly afforded the alcohol **9**. Swern oxidation of **9** afforded the key C1 to C9 coupling partner **10**.

The diol **11**, was derived by modification of the organocatalytic proline aldol protocol reported by Northrup and MacMillan^[8] using a one-pot NaBH₄ reduction^[13] (Scheme 4).

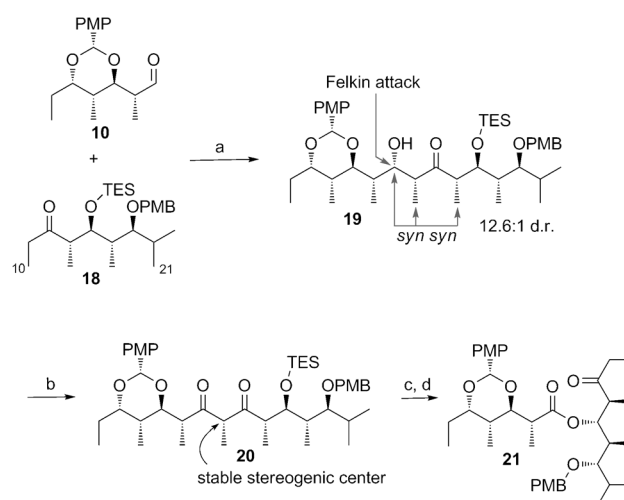


Scheme 4. a) PMP-CH(OMe)₂, cat. TsOH, 1.2 torr, RT, 88%; b) DIBAL, -10°C, CH₂Cl₂, 98%; c) (COCl)₂, DMSO, CH₂Cl₂, -78°C, then Et₃N; d) Cy₂BCl, -78 to -17°C, Et₃N, CH₂Cl₂, 69%; e) TESOTf, 2,6-lutidine, CH₂Cl₂, -78 to 0°C, 92%; f) SmI₂, THF, MeOH, 0°C, 94%. Cy = cyclohexyl, DIBAL = diisobutylaluminum hydride, TES = triethylsilyl.

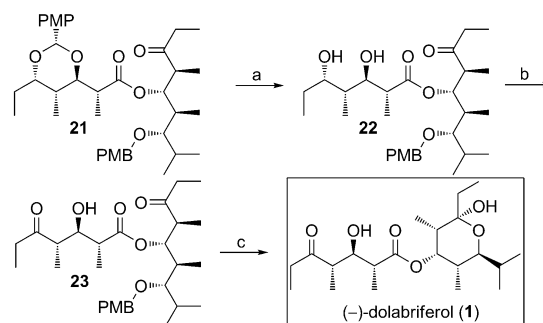
Formation of the PMP acetal **12** under acidic conditions proceeded best when conducted neat and with the removal of methanol. Regioselective cleavage of the PMP acetal with DIBAL afforded the primary alcohol **13**, and subsequent Swern oxidation afforded the aldehyde **14**. Addition of the aldehyde to the *E*-boron enolate of the lactate **15** afforded the aldol adduct **16**, with the auxiliary overturning the inherent Felkin bias of the aldehyde.^[14] Protection of **16** as the silyl ether (**17**), and subsequent SmI₂ cleavage of the benzoate^[15] afforded the C10 to C21 fragment **18**.

Union of the C1 to C9 fragment (**10**) and the C10 to C21 fragment (**18**) was achieved using the tin enolate of **18**, thus affording **19** in excellent yield and high d.r. (12.6:1; Scheme 5).^[5] The stereochemistry of **19** is tentatively assigned based on similar reactions.^[5,16] Oxidation of the C9 hydroxy group afforded the desired linear precursor **20**. There was no evidence of the enol tautomer of the diketone in the ¹H NMR spectrum, and no epimerization at the stereogenic center at C10 was observed. Removal of the silyl ether with HF/Py followed by treatment with DBU^[17a,b] effected the retro-Claisen rearrangement, thus giving the desired connectivity (**21**), whilst leaving the labile PMP acetal intact.

Removal of the PMP acetal under acidic conditions afforded the diol **22** with no observable cleavage of the sensitive ester functionality (Scheme 6). Gratifyingly, selective oxidation of the least hindered secondary alcohol with DMP afforded **23**. The final step of our total synthesis was



Scheme 5. a) Sn(OTf)₂, Et₃N, CH₂Cl₂, -78°C, 83%; b) DMP, NaHCO₃, RT, CH₂Cl₂, 85%; c) HF·Py, Py, THF, RT; d) DBU, PhH, RT, 76%. DMP = Dess–Martin periodinane, DBU = diazabicycloundecane, Py = pyridine.



Scheme 6. a) CSA, MeOH, RT, 80%; b) DMP, NaHCO₃, RT, CH₂Cl₂, 64%; c) DDQ, pH Buffer 7, CH₂Cl₂, RT, 49%. CSA = (±)-10-camphor-sulfonic acid, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

removal of the PMB protecting group in 46% yield to afford the title compound dolabriferol (**1**).

This sequence constitutes the first biomimetic total synthesis of dolabriferol, in 4.0% yield and 15 steps from propionaldehyde. By completing this route, we have demonstrated that a retro-Claisen rearrangement of a 1,3-diketone is a feasible route for the biosynthetic formation of dolabriferol and similar noncontiguous polypropionates.

Received: December 22, 2011
Published online: March 29, 2012

Keywords: aldol reaction · asymmetric synthesis · biomimetic synthesis · natural products · polyketides

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